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For oral communications with more than one author, an asterisk(*) denotes the one who presented the work.

COMMUNICATIONS

Diminishing compliance with a hospital formulary in the absence of continuous feedback of information to prescribers

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Hospital Formularies are now widely accepted and there is evidence (Collier & Foster, 1985; Feely *et al.*, 1987) that a Formulary can both improve prescribing habits and reduce drug costs. Little information, however, is available on the long-term effects of a Formulary and the need for continuous input and feeback to prescribers. In a prospective study we observed prescribing habits and drug costs prior to the introduction of a Formulary, for 12 months following a Formulary during which a number of discreet feedback exercises were undertaken and in a subsequent year when no form of feedback or intervention took place.

St James's Hospital is an 800-bed general hospital whose annual drugs bill had been rising at about 20% per annum to approximately £1.7 million in 1985. A minority of prescriptions were written generically, approximately 50% on medical wards and 40% on surgical wards. Following the introduction of a Formulary, prescribers were given regular feedback with regard to their compliance to the agreed list including the use of generic names and adherence to the antibiotic policy by means of individual prescribing information, peer comparison and open discussion at the monthly Medical Committee meeting. During the course of the subsequent 12 months generic prescribing increased by 50% ($P < 0.01$) both in medical and surgical wards. Non-Formulary requisitions counted on a monthly basis initially constituted 5% of all prescriptions and remained static until subjected to intense feedback falling to 2% but when not the subject of any feedback they continued to run in the order of 4–5%. Similarly in the year during which no intervention took place the level of generic prescribing fell to pre-Formulary levels both on surgical and medical sides. The use of a third generation cephalosporin (cefotaxime) was the subject of intense feedback and the cost of the latter fell in the year following the introduction of the Formulary from £112,000 to £75,000. Of particular interest was its use in a series of samples of patients ($n = 35$) receiving cefotaxime. Pre-Formulary it was a drug of first choice in 68% of these patients and in only 42% had appropriate microbiological assessment been made. Following feedback including a Drug Information Note on the use of cefotaxime it was the antibiotic of first choice in only 37% of the sample and appropriate microbiological assessment had been undertaken in 84%. In the year in which there was no active intervention the overall usage of cefotaxime rose to pre-formulary levels and despite a price reduction the annual cost of cefotaxime rose to £94,000 and again its use in uncomplicated respiratory and urinary tract infections and often without appropriate microbiological assessment increased.

In the year following the introduction of the Formulary overall drug expenditure remained static. Drug costs per patient decreased marginally by £1 because of a small increase in patient turnover and bone marrow transplantation. In the subsequent year overall hospital activity showed a small fall and drug retail costs remained static. Nevertheless hospital expenditure on drugs rose by 6%.

While a Hospital Formulary can produce significant savings and improve drug usage, it appears that regular feedback of prescribing habits and continuous educational programmes should be undertaken if this is to be maintained.

Collier, J. & Foster, J. (1985). *Lancet*, **i**, 331.

Feely, J. *et al.* (1987). *Irish med. J.*, **80**, 286.

Adverse drug reactions—incentives to enhance reporting

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The reporting of adverse drug reactions (ADR) through the yellow card system either to the Committee of Safety of Medicine or its Irish counterpart the National Drugs Advisory Board (NDAB) represents the major avenue of detecting the toxicity of drugs in widespread use. Only 30–35 ADR per annum are reported from St James's Hospital, with approximately 800 beds and 15,000 admissions per year. As this voluntary reporting system is obviously under-utilised we undertook a number of initiatives to enhance reporting from our Hospital.

Drug Information Pharmacist: Prescribers were circularised with guidelines on what to report and to do this through the Drug Information Centre and associated pharmacist. In addition nurses were also requested to report adverse drug reactions and a pharmacist surveyed five wards with 136 beds over 6 weeks. These were representative of acute medical and surgical wards. In particular, patient charts were examined and staff were requested to report adverse reactions to the pharmacist. In this study 3,383 drug prescriptions were recorded for 706 patients of whom 38 (5.4%) suffered a suspected ADR. Most ADR involved the gastrointestinal system with nausea, vomiting and drugs commonly implicated were non-steroidal anti-inflammatory drugs, theophylline, potassium, nifedipine, terbutaline, morphine and cytotoxics. Other systems commonly involved were the cardiovascular system and the skin. Only one ADR was described as life-threatening (hypersensitivity reaction). Of particular interest, the majority of reactions (55%) were obtained directly from patient notes and 20% were reported by nurses. Only 7% were reported by medical staff.

Reporting Fee: Prescribers were again circularised and £3 was offered for each ADR yellow card given to a designated doctor. Within 4 weeks 100 adverse drug reactions were reported including two drug-related deaths (pentamidine associated pancreatitis and anaphylaxis with thrombolytic therapy) and 25 serious adverse reactions (e.g. bone marrow suppression, nephrotic syndrome, gastrointestinal haemorrhage, anaphylaxis, jaundice, Stevens-Johnson syndrome, arrhythmias, pseudo membranous colitis). The majority were reporting ADR for the first time and in a questionnaire indicated forgetting to report, unavailability of yellow cards and a lack of familiarity with the reporting system as major constraints in reporting ADR. 78% felt that the reporting fee provided an additional incentive.

This study shows that many ADR go unreported. Whereas a pharmacist may increase reporting the greatest increase and especially in serious ADR has been associated with a fee and involving a doctor. Reporting by nurses may also represent another potential source of ADR reports. The serious nature of 'unreported' ADR occurring in hospital suggests we should re-evaluate the current use of the yellow card system. In this short term study a small fee appeared adequate to establish contact between the prescriber and a recording doctor and stimulate ADR reporting.

Influence of volatile anaesthetics on the potency of tubocurarine and atracurium

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Volatile inhalation agents form the basis of the vast majority of anaesthetics given to children. The degree of potentiation resulting from the administration of inhalation agents during the use of muscle relaxants is not well known, particularly in paediatric anaesthesia. The aim of this study was to evaluate and compare the potentiation by 1 MAC (minimum alveolar concentration) of halothane, enflurane and isoflurane on the dose requirements of tubocurarine and atracurium in children and to contrast this with the corresponding values during narcotic anaesthesia.

One hundred and eight-six fit healthy children aged 4–12 years, undergoing elective surgery requiring ventilation were studied. Following induction of anaesthesia they were randomly allocated to receive halothane, enflurane or isoflurane in 100% oxygen, or fentanyl intravenously with 60% nitrous oxide in oxygen. The patients were intubated and ventilated to normocapnoea and the end-expired concentration of the inhalation agent adjusted to 1 MAC. A Myotest peripheral nerve stimulator was used to stimulate the ulnar nerve with supramaximal square-wave impulses in a train-of-four (TOF) mode at 2 Hz repeated at 10 s intervals. The response of the adductor pollicis muscle was measured mechanically using a force-displacement transducer and a Grass polygraph. Following a stabilisation period of twitch height and end-expired tidal concentration of the volatile anaesthetics for about 10 min the patients were randomly allocated to receive 100, 200, 300 or 400 $\mu g\ kg^{-1}$ of tubocurarine, or 100, 150, 200 or 250 $\mu g\ kg^{-1}$ atracurium to determine potency by the single bolus technique (Gibson *et al.*, 1985). The recordings were continued until maximum neuromuscular blockade had been achieved. Log dose-response curves were constructed after arc-sine transformation of the responses. The ED_{50} (the 50% blocking dose of muscle relaxant) and ED_{95} (95% blocking dose) were then calculated by

substitution in the regression equation. The results are summarised in Table 1.

There was significant potentiation of tubocurarine by both enflurane and isoflurane as shown by significant reduction in ED_{50} and ED_{95}. Although the ED_{50} of atracurium during enflurane and isoflurane anaesthesia and the ED_{95} with all volatile anaesthetics were also lower, the difference was significant only in the case of the ED_{95} under enflurane anaesthesia. It is recommended that lower doses of neuromuscular blocking agents should be used when enflurane and isoflurane are employed in children.

Table 1 Potency of tubocurarine and atracurium ($\mu g\ kg^{-1}$) in children under narcotic and inhalational anaesthesia (95% confidence limits)

	Tubocurarine		*Atracurium*	
	ED_{50}	ED_{95}	ED_{50}	ED_{95}
Narcotic	238.7 (206.3 – 276.3)	527.6 (445.1 – 625.5)	111.8 (89.4 – 139.9)	242.1 (194.2 – 301.8)
Halothane	119.4 (47.4 – 300.4)	532.1 (322.0 – 879.5)	113.1 (97.6 – 130.9)	195.6 (166.2 – 230.3)
Enflurane	135.4** (114.4 – 160.2)	375.2* (306.1 – 455.0)	94.6 (82.8 – 108.2)	177.6* (161.8 – 194.8)
Isoflurane	131.6** (110.2 – 157.2)	323.8** (277.2 – 378.3)	100.4 (81.6 – 123.5)	215.3 (185.7 – 249.7)

* $P < 0.05$, ** $P < 0.001$.

Gibson, F. M. *et al.* (1985). *Anesthesiology*, **62**, 657.

The population pharmacokinetics of lisinopril in hypertensive patients

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Lisinopril (MK 521) is a new ACE inhibitor which is structurally similar to enalapril but does not require hepatic activation on oral administration. The drug is cleared by renal excretion and prolonged elimination half-lives have been observed in patients with renal impairment (Kelly *et al.*, 1986).

This study examines the pharmacokinetics of lisinopril on a population basis, using steady state concentration-time data from two multicentre trials: lisinopril in hypertension in the elderly (40 patients) and lisinopril in hypertension associated with renal impairment (20 patients). The patients were 21–85 years old (mean 65 years) and weighed 51–115 kg (mean 72 kg). Twenty-one patients had a serum creatinine concentration above 120 $\mu mol\ l^{-1}$ and 13 patients had (compensated) cardiac failure. Lisinopril dose was titrated according to response and ranged from 2.5 to 40 mg daily at the time of the study. Blood samples were ideally withdrawn at 1, 2, 4, 6, 8, 12 and 24 h, but additional samples were available in some patients and others only had 2–3 measurements. Serum lisinopril concentrations (total 381) were analysed by radioimmunoassay. Data analysis was by non-linear regression using the program NONMEM (Beal & Sheiner, 1979). An open one-compartment model parameterised to give estimates of clearance/F (CL), volume of distribution/F (V) and absorption rate constant (ka) was fitted to the data and the influence of clinical features such as age, weight, body surface area, sex, serum creatinine and cardiac failure were tested using both linear and non-linear models. Intersubject and residual variability were assumed to conform to a log-additive model.

Serum creatinine was the most important determinant of lisinopril clearance, but weight, age and the presence of cardiac failure were also significant. Lisinopril CL had an intersubject variability of 52% and was best described by the following equation:

$$CL = 0.25 \times wt(kg) \times (creatinine/70)^{-0.89} \times (age/65)^{-0.45}$$

$CL = CL \times 0.65$ in the presence of cardiac failure. Volume of distribution was 371 (intersubject variability > 100%) and was not influenced by any of the clinical features tested. ka was 0.1 h^{-1} with an intersubject variability of 73%. Residual variability was 28%.

This study has quantified the relationship

between lisinopril clearance and various clinical characteristics. Although the relationship between serum concentration, response and toxicity is not yet clear, it would seem prudent to start with lower initial doses in patients with renal impairment or cardiac failure.

Beal, S. L. & Sheiner, L. B. (1979). *NONMEM (User's Guide) Parts I and IV*. Technical Report, Division of Clinical Pharmacology, University of California, San Francisco.

Kelly, J. G. *et al.* (1986). *Br. J. clin. Pharmac.*, **22**, 629P.

Effects of captopril on renal function in a hypertensive population

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The effect of age on the pharmacokinetics of levodopa

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Evans *et al.* (1981) demonstrated a three fold increase in the $AUC_{0-\infty}$ following oral levodopa in elderly compared with young healthy volunteers. However, in the absence of i.v. data no conclusions can be drawn regarding the effect of age on the bioavailability of levodopa. We have studied eight young (age 20–23 years, weight 62–85.5 kg) and nine elderly (age 68–75 years, weight 56.7–93 kg) healthy volunteers following oral (250 mg) and i.v. (50 mg) levodopa after an overnight fast.

We conclude that the oral bioavailability of levodopa is 53% greater in the elderly. However an age related decline in clearance also contributes significantly to the observed increased AUC in elderly compared with young volunteers following oral administration.

Table 1 Pharmacokinetic results (mean ± s.d.)

	Young	*Elderly*	P
Oral (250 mg)			
C_{max} (ng ml^{-1})	1077 ± 577	1842 ± 901	<0.05
t_{max} (h)	0.81 ± 0.65	0.89 ± 84	NS
AUC (ng ml^{-1} h)	1056 ± 282	2512 ± 588	<0.002
$t_{½}$ (h)	1.46 ± 0.36	1.42 ± 0.30	NS
MRT (h)	1.76 ± 0.41	2.25 ± 0.69	NS
MAT (h)	0.56 ± 0.54	0.94 ± 0.66	NS
Bioavailability	0.412 ± 0.161	0.629 ± 0.119	<0.01
Intravenous (50 mg)			
AUC (ng ml^{-1} h)	541 ± 140	806 ± 94	<0.01
CL (ml min^{-1} kg^{-1})	23.4 ± 4.1	14.2 ± 2.8	<0.01
V_{ss} (ml kg^{-1})	1652 ± 385	1014 ± 273	<0.002
$t_{½}$ (h)	1.26 ± 0.28	1.34 ± 0.23	NS
MRT (h)	1.20 ± 0.32	1.19 ± 0.24	NS

C_{max}, maximum plasma concentration; t_{max}, time of C_{max}; AUC, area under plasma concentration-time curve; $t_{½}$, terminal half-life; MRT mean residence time; MAT, mean absorption time; CL, plasma clearance; V_{ss}, volume of distribution at steady state.

Evans, M. A. *et al.* (1981). *Neurology*, **31**, 1288.

Poor compliance appears to be the major cause of unstable anticoagulation with warfarin

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Several factors have been proposed as causes of variable response to warfarin therapy. However, to date, the relationship between patient compliance and intra-individual variability in anticoagulant control has not been fully investigated. Low-dose phenobarbitone (PB) can be used as an indicator of compliance (Feely *et al.*, 1987) and does not appear to induce hepatic microsomal enzymes at doses < 7.5 mg day^{-1} (Prince *et al.*, 1986). In a prospective study, we have given 15 patients with unstable control on warfarin (at least two adjustments in warfarin dose or INR varying $\geqslant 3.0$ over six preceding visits) and 15 patients with stable control on warfarin (INR varying $\leqslant 1.0$ over six preceding visits) study capsules containing their usual daily dose of warfarin and 2 mg PB.

There was no significant change in INR in the group with stable control (Wilcoxon signed-rank test; $P > 0.05$) and no alteration in warfarin dose was required. Thirteen of these patients had PB plasma level to dose ratios (LDRs) within the 'expected range' derived from previously studied age matched normal volunteers (Feely *et al.*, 1987) and two had LDRs just below the range. There was a significant change in INR in the group with unstable control (Wilcoxon signed-rank test; $P < 0.01$), with a reduction in the wide swings in INR which were seen before commencing the study. Five of these 15 patients needed a decrease in their warfarin dose, one required an increase and nine had no overall change in their dose. Three of the 15 'unstable' patients had PB LDRs below the 'expected range'. Of these, one patient with mitral valve disease and atrial fibrillation, whose control did not improve, suffered a fatal stroke during the course of the study.

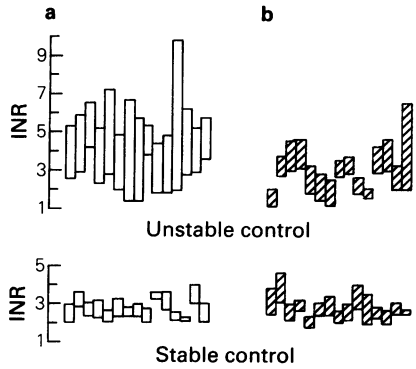

Figure 1 The range of INR for each patient over four consecutive visits before (a) and whilst taking the study capsules (b).

We have shown that the capsules containing 2 mg PB had no effect on the INR in the group with stable control. In the group with unstable control, there was a stabilization in anticoagulant control, while over half the patients remained on the same warfarin dose and a further 33% required a reduction in their dose. It appears that the unstable anticoagulation previously seen in this group was largely due to poor compliance.

Feely, M. *et al.* (1987). *Br. J. clin. Pharmac.*, **24**, 77.

Price, D. *et al.* (1986). *Br. J. clin. Pharmac.*, **22**, 744.

Concentration-dependent metabolism and renal clearance of *p*-aminohippurate

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Measurement of the renal clearance of *p*-aminohippurate (PAH) is a standard method of estimating effective renal plasma flow (ERPF). After an intravenous bolus of PAH, the PAH renal clearance declines with time and approximately 17% of the dose is recovered as the N4 acetyl derivative (AcPAH). The apparent renal clearance of AcPAH is greater than that of PAH (McAuslane *et al.*, 1987). Further investigations into the metabolism and clearance of PAH at three different steady-state plasma concentrations are reported.

Eight healthy male volunteers of mean age 30 years (range 25–42 years) and weight 55–77 kg were studied. PAH was infused at three different rates, 2.5, 5 and 15 mg min^{-1} for three successive 2 h periods. At the start and each time the infusion rate was increased, loading doses were given (200, 200 and 400 mg respectively) to achieve rapid attainment of steady state. At each infusion rate 1 h was allowed for equilibration followed by two accurately timed 30 min urine collection periods. The renal clearance of PAH and AcPAH was calculated from the urinary excretion rate/midpoint plasma concentration (UV/P) and the total body clearance (TBC) of PAH was calculated as the infusion rate/steady state plasma concentration (the mean of estimations after 90 and 120 min at each infusion rate). The percentage of the infused dose of PAH recovered in the urine unchanged and as AcPAH was calculated at each infusion rate. PAH and AcPAH were estimated by h.p.l.c. (McAuslane *et al.*, 1987).

The results are summarised in Table 1.

The renal clearance and % recovery of PAH increased progressively as the plasma concentration increased whilst the opposite effects were observed with AcPAH ($P < 0.01$ by ANOVA). The apparent renal clearance of AcPAH was significantly higher than that of PAH. The metabolism of PAH to AcPAH was greatest at low plasma concentrations. Since the total body clearance of PAH did not differ with a change in plasma concentration the findings raise the possibility of concentration dependent renal acetylation. To avoid significant understimation of ERPF the plasma concentration of PAH should be maintained at 20–30 mg l^{-1} rather than the 10–20 mg l^{-1} generally recommended.

Table 1 Mean (s.d.) renal and total body clearances and % urinary recovery of PAH and AcPAH in eight healthy volunteers

	PAH			*AcPAH*		
Dose rate (mg min^{-1})	2.5	5	15	2.5	5	15
Plasma concentration (mg l^{-1})	4.4(1)	8.5(2)	25.2(5)	0.69(0.3)	1.3(0.4)	2.6(0.8)
Renal clearance	405(48)†	468(108)†	509(100)	1334(478)†*	1069(391)†*	782(219)*
TBC	559(87)	601(136)	590(93)	—	—	—
% recovery	72(6)	78(5)	85(7)	28(5)	20(4)	11(2)

Clearances expressed as ml min^{-1} 1.73 m^{-2}.
† $P < 0.01$ *vs* highest infusion rate, * $P < 0.01$ *vs* corresponding PAH clearance.

McAuslane, J. A. N. *et al.* (1987). *Br. J. clin. Pharmac.*, **24**, 277P.

Caffeine antagonism of the central effects of zopiclone and nitrazepam in man

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Caffeine antagonises certain of the behavioural effects of the benzodiazepines and consumption of large amounts of coffee may attenuate the therapeutic efficacy of these agents (Polc *et al.*, 1981). Zopiclone, a cyclopyralone, is a novel hypnotic/sedative which, although it binds to the benzodiazepine receptor, differs in some of its actions from the benzodiazepines (Nicholson *et al.*, 1983) and may show less interaction with caffeine.

In a randomised, double-blind, cross-over study, 12 volunteers received zopiclone 7.5 mg

+ placebo (ZP), zopiclone 7.5 mg + caffeine 250 mg (ZC) and matching placebos (PzPc) (group 1), or nitrazepam 5 mg + placebo (NP), nitrazepam 5 mg + caffeine 250 mg (NC) and placebo (PnPc) (Group 2). Caffeine was administered in decaffeinated coffee, 1 h after administration of zopiclone or nitrazepam. Psychomotor tests including critical flicker fusion (c.f.f.), digit symbol substitution (DSST), simple reaction time (SRT) and verbal memory (VM) were administered at 2 and 8 h after initial dosing. Compared with placebo, ZP significantly impaired performance on c.f.f., DSST, VM and SRT at 2 h and on c.f.f. and SRT at 8 h. NP had little effect on psychomotor function but did significantly impair memory (VM) at 2 h. Following ZC, no significant impairment was found on any measure at either 2 or 8 h. The amnesic effect of nitrazepam was still apparent following combination with caffeine (NC). In conclusion, caffeine blocked the psychomotor effects of zopiclone but not the amnesic effects of the benzodiazepine, nitrazepam.

Table 1 Mean (+) change from baseline at 2 h on psychomotor performance following treatments

	C.f.f. (Hz)	*DSST (score/90 s)*	*SR (ms)*	*VM (learning sum)*
ZP	−3.8 + 1.3*	−9.7 + 2.4*	−56.5 + 8.5**	9.0 + 0.45*
ZC	−1.4 + 0.7	−6.2 + 4.3	−14.0 + 16.0	9.5 + 0.17
PzPc	+0.1 + 0.4	−0.5 + 2.6	−7.7 + 10.1	9.7 + 0.23
NP	−2.0 + 0.7	−0.8 + 1.9	−9.7 + 5.8	9.1 + 0.53*
NC	−1.7 + 0.9	−3.3 + 2.4	+10.2 + 11.1	9.0 + 0.43*
PnPc	−1.5 + 0.6	−0.3 + 1.4	−0.9 + 7.0	9.6 + 0.24

* $P < 0.05$; ** $P < 0.01$ for ANOVA comparisons with placebo.

Nicholson, A. N. *et al.* (1983). *Int. Pharmacopsychiat.*, **17**, Suppl 2.

Polc, P. *et al.* (1981). *Life Sci.*, **25**, 2265.

Patients' knowledge of their drug therapy and its possible risks

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The recording of a drug history and previous adverse drug reactions (ADRs) in the case notes is standard clinical practice. We have compared the knowledge of general medical outpatients of their drug therapy, its possible risks and the prevalence of any previous ADR with the knowledge of their clinic doctor. Patients were also asked if they were satisfied with the information they had been given regarding their drug therapy. In a further study, the same information was sought from patients attending a specialist anticoagulant clinic and from their clinic doctor. Patients completed their questionnaires from memory; doctors completed theirs by reference to the hospital notes. The questionnaires were completed before the clinic consultation.

One hundred and four consecutive general medical outpatients attending for review and their doctors completed questionnaires. There was doctor/patient agreement on drug therapy in 53% patients. 7% patients knew the indications for none of their drug therapy; 63% knew the indications for all of their treatments. 12% were unable to name or identify any drug they were taking; 56% named all their drugs correctly.

61% of patients were thought to have had a previous ADR, either by themselves ($n = 39$), or by their clinic doctor ($n = 41$): patient/doctor agreement was limited to 11 cases. No patients taking warfarin ($n = 16$) or oral hypoglycaemic agents ($n = 4$) knew of any potential ADR. Of those taking non-steroidal anti-inflammatory drugs ($n = 13$) only one patient knew of any risks of treatment. 67% of patients were satisfied with their level of knowledge of their drug therapy and 40% with their knowledge of ADRs. More data about treatment was sought by 28% and about ADRs by 41% of the patients.

All patients receiving warfarin had been given written and verbal information about their treatment and its risks. To determine if the poor

understanding of their therapy was a feature of the practice of the general medical clinic a further study was undertaken in an anticoagulant clinic where all attending patients were taking warfarin.

One hundred and three consecutive review patients and their clinic doctors completed the questionnaire as before. Patient/doctor agreement on drug therapy occurred in 48% of patients. The risk of bleeding and bruising was known by 5% of patients; 8% knew not to take aspirin with warfarin but did not know why.

In both clinics the patients' knowledge of their drug therapy was inadequate, but no more so than that of their doctors. The clinical case notes provided incomplete drug and ADR data. The failure of written and verbal advice concerning warfarin treatment to inform patients suggests that the inclusion of comprehensive package inserts with medicines may have little impact on patients' knowledge. Since at least one million adults in the United Kingdom have a reading age of less than 9 years (HMSO, 1975) the use of diagrams or cartoons may provide a better method of patient education.

HMSO. (1975). A language for life. London: HMSO.

Enigmatic properties of (±)-thalidomide; an example of a stable racemic compound

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(±)-Thalidomide displays a number of enigmatic physico-chemical and biological properties which suggests that it is not simply a mixture of the two enantiomers but rather a distinct molecular compound or association with properties quite disparate from these of the two optical isomers. Thus, the solubilities of (+)- and (−)-thalidomide in a range of solvents, including water, ether, hexane, ethanol, chloroform and acetone are some 5–9 times greater than those of the (±)-form. The rate of spontaneous hydrolysis of the (±)-form at 23° C in Tris buffer (pH 7.4) is only half that of the two enantiomers while molecular weight determination (Rast Camphor method) gave values of 284 and 273 for the (+)- and (−)-forms and a value of 555 for the racemic form. Estimates of the acute oral toxicity in male ICI SAS strain mice (LD_{50} in g kg^{-1}) for the (±), (+)- and (−)-forms were > 5.0, 0.7, and 1.5 respectively. When given intraperitoneally the values were > 3.0, 0.3 and 0.5 g kg^{-1} respectively for the three thalidomide forms.

Most remarkable was the ability of a single oral dose of (−)-thalidomide (1 g kg^{-1}) to protect male ICI SAS mice against the lethal effects of an oral dose of the (+)-isomer (1 g kg^{-1}). This effect was uninfluenced by route of administration since an oral dose of the (−)-isomer (0.75 g kg^{-1}) also protected mice against the lethal effects of an intraperitoneal dose of (+)-thalidomide (0.5 g kg^{-1}). Thus, the two enantiomers of thalidomide are able to interact to reduce each other's intrinsic toxicity.

It is suggested that the racemic form of thalidomide exists in both the solid state and under physiological conditions as a distinct racemic compound or association. Such associations are not unknown and have been described for a number of racemic substances (Beck, 1904; Matsumoto & Amaya, 1968, 1980) but not as far as we are aware for a drug substance. Bearing in mind the large number of drugs that are used in the racemic form then these observations have major implications. Firstly, it cannot be assumed that the biological properties of a racemate necessarily approximate to the mean of the two enantiomers. Secondly, a racemic compound because of the association, may have distinctly different biological properties from those of the individual enantiomers. This might be ascribed to a difference in molecular volume of the racemic association and secondly because the polarities of those functional groups involved in the association may as a consequence be altered: these two factors may thereby influence a difference in 'receptor fit' of the racemic association compared with the individual enantiomers.

Beck, R. (1904). *Z. Phys. Chem.*, **49**, 682.
Matsumoto, M. & Amaya, K. (1968). *J.C.S. Chem. Comm.*, **480**.
Matsumoto, M. & Amaya, K. (1980). *Bull. Chem. Soc. Japan*, **53**, 3510.

The detection of anti-amodiaquine antibodies by ELISA

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Amodiaquine (AQ) is a 4-aminoquinoline antimalarial which has been associated with liver damage and agranulocytosis in man (Neftel *et al.*, 1986). It has been shown to be readily oxidised to a protein-reactive quinoneimine, (AQQI), which reacts rapidly and spontaneously with protein *in vitro* (Maggs *et al.*, 1988). We have therefore developed assay systems to determine whether AQ is immunogenic.

A specific enzyme-linked immunosorbent assay (ELISA) was developed in which unconjugated metallothionein (MT, a sulphur rich protein, Kojima *et al.*, 1976), or MT conjugated with AQ (AQ–MT), was coated (1 μg ml^{-1}), onto microtitre plates. The ELISA was then performed as previously (Christie *et al.*, 1988). AQ-MT was prepared by reacting [^{3}H]-AQQI (68 mg; 0.5 μCi) prepared by silver oxide oxidation of [^{3}H]-AQ in chloroform, and MT (10 mg) in water, for 30 min at room temperature. The protein-conjugate was purified by exhaustive equilibrium dialysis, and was found to have a ratio of 5.2:1 (AQ:MT).

AQ (0.27 mmol kg^{-1}) or AQQI (27 μmol kg^{-1}) were administered intramuscularly to separate groups of eight rats, for 4 consecutive days. Serum obtained prior to immunization and 14 days after the last injection was tested for IgG anti-AQ activity by ELISA. Antibody activity is expressed as that activity which was inhibitable by AQ-mercapturate (5 μM), which is structurally related to the adduct produced when AQQI reacts with sulphydryl groups in protein.

There was a significant increase ($P < 0.05$) in the specific antibody binding activity following AQ administration (pre-immune, 0.111 ± 0.028; day 14, 0.596 ± 0.155) and after AQQI administration (pre-immune, 0.078 ± 0.018; day 14, 0.584 ± 0.018). These antibodies were shown to be specific for AQ by hapten inhibition experiments, in which antibody binding to AQ-MT was inhibited by the inclusion of a range of structurally related compounds. The antibodies recognised AQ and AQ-mercapturate (Table 1).

AQ and AQQI were shown to give rise to the production of drug specific antibodies in the rat, AQQI being more immunogenic than AQ, suggesting that the immunogenicity of AQ may be a consequence of activation to AQQI. In addition, using this test system we were able to detect specific IgG anti-AQ antibodies in four patients who exhibited agranulocytosis and one patient who exhibited hepatitis whilst receiving AQ, but not in individuals who had not received the drug. Thus, we are now in a position to determine the role of drug-specific antibodies in the pathogenesis of the adverse reactions in prospective studies.

Table 1 Specificity of pooled IgG anti-AQ and anti-AQQI antibodies

Compound	*IC_{50} (nM) anti-AQ*	*anti-AQQI*
MT	>175	>175
AQ-mercapturate	310	180
AQ	250	150

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Effects of a 5-HT_2 antagonist (ICI 169, 369) on human pupillary responses

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Evidence from a number of studies involving the use of 5-HT precursors (e.g. Mantegazzini, 1966), the use of 5-HT releasing agents (e.g. fenfluramine, Kramer *et al.*, 1973) and binding site studies in the iris (e.g. Uusitalo *et al.*, 1984) suggests that 5-HT might have a role in modulating human pupillary responses. ICI 169, 369 is a specific 5-HT_2 antagonist in animal models (Blackburn *et al.*, 1986). In the light of the above evidence ICI 169, 369 might be expected to affect pupillary responses in man.

Six healthy male volunteers (aged 18–37 years) participated in a double-blind, randomised cross-over study comparing the effects of single oral doses of matched placebo, 80 and 120 mg of ICI 169, 369 on pupil responses. The pupillary responses were measured using a portable infrared pupillometer following 15 min dark adaptation (Millson *et al.*, 1988) which assesses resting pupil diameter (RPD), minimally constricted pupil diameter (MPD) and final pupil diameter (FPD). Dosing was separated by at least 1 week and pupil measurements were made before, 3, 5, 8 and 24 h after each dose. The results of RPD are shown in Figure 1.

The results in Figure 1 show that ICI 169, 369 at both doses reduced RPD compared with predose and with placebo 3 and 5 h after dosing. Similar results were obtained with the FPD (e.g. 3 h post dose placebo 6.4 mm, 80 mg ICI 169, 369 3.9 mm $P < 0.01$ and 120 mg ICI 169, 369; 4.0 mm $P < 0.01$). MPD was only affected by the 120 mg dose 5 h after dosing (placebo 5.2 mm, ICI 169, 369 2.7 mm $P < 0.05$).

The results of this study therefore complement the conclusions of previous studies of the involvement of 5-HT in pupillary responses in man.

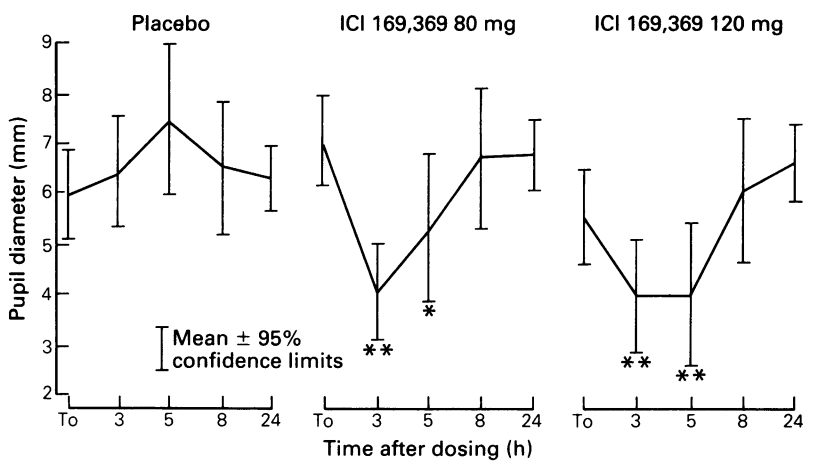

Figure 1 Mean (± 95% CL) of RPD, before (To) and 3, 5, 8 and 24 h after placebo, 80 mg and 120 mg ICI 169, 369. * $P < 0.05$, ** $P < 0.01$ comparing post dose with placebo.

Blackburn, T. P. *et al.* (1986). *Br. J. Pharmac.*, **90**, 256, 277P.

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The biochemical effects of cumulative doses of inhaled salbutamol in normal subjects

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We have recently shown (Lipworth *et al.*, 1988) dose-dependent biochemical changes in response to cumulative doses of salbutamol given by metered-dose inhaler (MDI) to asthmatic subjects. The aim of the present study was to investigate whether these changes were mirrored in a group of normal subjects given an identical dose-range of inhaled salbutamol. Six normal volunteers were studied on 2 separate days, 1 week apart in a single-blind cross-over design. They were given cumulative doubling doses of inhaled salbutamol (100 μg to 4000 μg) or identical placebo from an MDI. Twelve minutes after each dose increment (made every 20 min) venous blood was taken for analysis of plasma potassium (K), magnesium (Mg), glucose (Glu) and cyclic AMP (cAMP). CV values for the respective assays were: 1.1%, 1.8%, 3.9% and 2.25%. Statistical testing was by analysis of variance (ANOVA) between responses at successive doses. Responses at each dose are expressed as 95% confidence intervals for the mean.

There were no differences between baseline values on placebo and salbutamol days, and no significant changes with placebo. There were linear log dose-responses in all variables. ANOVA showed a significant difference between doses for ΔcAMP ($P < 0.005$), Δ Glu ($P < 0.001$), Δ Mg ($P < 0.005$) and ΔK ($P < 0.001$). The plateau in the dose-response curve was not attained within our dose-range, except for ΔMg (at 500 μg). Maximum responses from baseline (within our dose-range) were as follows: ΔcAMP (nmol l^{-1}) 16.16 (10.64, 21.68) $P < 0.01$; ΔGlu (mmol l^{-1}) 1.75 (1.31, 2.18) $P < 0.001$; Δ Mg (mmol l^{-1}) −0.03 (−0.05, −0.01) $P < 0.05$; ΔK (mmol l^{-1}) −0.96 (−1.1, −0.82) $P < 0.001$. The following correlations were significant: Δ K, Δ cAMP ($r = -0.69$, $P < 0.001$); ΔK, ΔGlu ($r = -0.62$, $P < 0.001$); ΔK, Δ Mg ($r = 0.49$, $P < 0.005$); Δ Mg, Δ cAMP ($r = -0.49$, $P < 0.005$); Δ Mg, ΔGlu ($r = -0.36$, $P < 0.05$). There was a greater response in ΔK in normal subjects compared with a previously reported group of asthmatics (Lipworth *et al.*, 1988): Δ K (mmol l^{-1}) at 4000 μg −0.38 (−0.64, −0.12) in asthmatics, compared with −0.96 (−1.1, −0.82) in normal subjects ($P < 0.001$). Furthermore there was also a lower baseline K (mmol l^{-1}) in asthmatics 3.56 (3.41, 3.71) compared with 3.77 (3.61, 3.93) in normals ($P < 0.05$). There were no differences between the two groups for other biochemical parameters.

In conclusion, there were dose related biochemical responses to inhaled salbutamol in normal subjects. These changes were similar to those seen in a group of asthmatics except for a lower baseline K and depressed hypokalaemic response in the latter. This may reflect β-adrenoceptor subsensitivity from chronic salbutamol therapy in the asthmatic group.

Lipworth, B. J. *et al.* (1988). *Br. J. clin. Pharmac.*, **25**, 667P.

Pharmacokinetics of cyclosporin in the early-post operative period following renal transplantation

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Cyclosporin pharmacokinetics are variable following renal transplantation due to changes in absorption and clearance. Overall, there appears to be some improvement in cyclosporin absorption over time after renal transplantation (Kahan *et al.*, 1983). This investigation was designed to quantify changes in the pharmacokinetics of cyclosporin in the first 2 months after renal transplantation.

Ten renal transplant patients aged 17–52 years were studied. Each patient received an oral dose of 15 mg kg^{-1} cyclosporin on the day before transplantation. Immediately after surgery, a 6 h intravenous infusion of 5 mg kg^{-1} cyclosporin was given. All subsequent cyclosporin therapy was given orally once per day.

During the hospital stay 24 h trough blood

samples plus at least one additional sample during each dosing interval were collected. After leaving hospital a trough sample was collected at each outpatient visit over a total period of 60 days. An average of 50 blood samples was obtained from each patient. Cyclosporin concentrations in whole blood were measured by h.p.l.c. Estimates of apparent clearance (CL/*F*) were obtained for each patient at 35 time points using a Bayesian parameter estimation program (Kelman *et al.*, 1982): no information on bioavailability (*F*) was available.

The relationship between CL/*F* and time was investigated by non-linear regression using the program NONMEM (Beal & Sheiner, 1980). CL/*F* declined exponentially from an initial value of 0.70 l h^{-1} kg^{-1} (intersubject CV = 49%) at a rate of 0.127 day^{-1} (intersubject CV = 108%, mean half-life = 5.5 days). The final value of CL/*F* was 0.31 l h^{-1} kg^{-1} (intersubject CV = 28%). The corresponding equation was

$$CL/F\ (l\ h^{-1}\ kg^{-1}) = 0.39e^{-0.127t} + 0.31$$

The decline in CL/*F* could either be due to a decrease in CL or an increase in *F*, the latter being more likely. It could however be due to a combination of both factors. The exponential decay with a half-life of 5.5 days indicates that CL/*F* stabilises within 3 weeks.

In summary, the change in pharmacokinetics which has been reported to occur after renal transplantation has been characterised. This information will now be incorporated into a Bayesian procedure (Kelman *et al.*, 1982) designed to improve the control of cyclosporin therapy following renal transplantation.

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Kahan, B. D. *et al.* (1983). *Transplant Proc.*, **15**, 446.

Kelman, A. W. *et al.* (1982). *Br. J. clin. Pharmac.*, **14**, 247.

Assessment of L-657, 743 (MK-912), an α_2-adrenoceptor antagonist, using intravenous clonidine in man

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MK-912, a benzofuroquinolizine, is a potent and competitive α_2-adrenoceptor antagonist *in vitro* and *in vivo* in animals. Initial volunteer studies are consistent with MK-912 being an α_2-adrenoceptor antagonist (Pettibone *et al.*, 1987). The present study assessed the α_2-adrenoceptor antagonist activity of MK-912 *in vivo* in man by measuring its inhibition of the response to the α_2-adrenoceptor agonist clonidine.

Six normal male volunteers received either 0.2 or 2 mg of MK-912 or a placebo in a randomized, double-blind, cross-over design. One hour after dosing, 200 μg of clonidine were given intravenously over 10 min. Heart rate, blood pressure, salivary flow, sedation, anxiety and physical symptom scores were measured throughout and for 8 h after the clonidine infusion. Venous blood was sampled for plasma growth hormone, plasma insulin and glucose.

In the first hour after ingestion, 2 mg of MK-912 caused an average 10 mm Hg increase in systolic pressure ($P < 0.05$) and some increased anxiety, but was otherwise well tolerated. On the placebo day, the clonidine-induced hypotension averaged (calculated from the area under the curve) a change from baseline of -14.3 ± 6.9 mm Hg systolic and -13.4 ± 4.3 mm Hg diastolic over the 8 h period. This was abolished by pretreatment with 2 mg of MK-912, being $+3.9 \pm 3.4$ mm Hg and -1.6 ± 2.6 mm Hg respectively ($P < 0.01$). Clonidine caused marked xerostomia, sedation and an increase in mean blood glucose of 0.8 ± 0.6 mM after placebo which were all inhibited by 2 mg of MK-912 ($P < 0.05$ in each case). Plasma insulin levels were not significantly different between the 3 days. Plasma growth hormone increased from a mean baseline value of 1.17 ± 0.36 mU l^{-1} to a peak of 12.70 ± 7.52 mU l^{-1} 45 min after the end of clonidine infusion. The 2 mg dose inhibited the peak elevation in growth hormone by an average of 87% ($P < 0.01$). The 0.2 mg dose of MK-912 had no significant effect for most parameters except for a 59% inhibition of the average clonidine induced elevation of plasma growth hormone ($P < 0.05$). Data are mean ± s.d., significance tested by ANOVA compared with placebo.

MK-912 almost entirely inhibited the effect of 200 μg of intravenous clonidine in man consistent with it being a specific α_2-adrenoceptor

antagonist. A dose as low as 0.2 mg is capable of suppressing clonidine induced growth hormone secretion. MK-912 may be a suitable drug to test the possibility that α_2-receptor antagonism attenuates depression.

Pettibone, D. J. *et al.* (1987). *Naunyn-Schmiedeberg's Arch. Pharmac.*, **336**, 169.

Cardiovascular disease and quality of life

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For chronic disorders such as cardiovascular disease, improvement in quality of life is now considered to be an important aspect of treatment. We have previously reported on the usefulness of the Sickness Impact Profile (SIP) in measuring quality of life in angina patients (Shayegan-Salek *et al.*, 1988). The purpose of the present study was to test the ability of a general health status measure, the SIP, to differentiate between the degree of patient impairment associated with hypertension, angina pectoris and cardiac failure and to determine whether the SIP is capable of identifying physical, as well as psychosocial dysfunctions associated with these cardiovascular problems.

Patients with hypertension (HY, $n = 52$), angina (AN, $n = 50$) and cardiac failure (CF, $n = 53$) were recruited sequentially. A group of healthy age and sex matched controls ($n = 93$) were also included. The SIP questionnaire together with a global rating scale of overall health (i.e. patient-rated overall health, PRH; using a 5-point scale) was completed by each patient. The SIP is a self-administered questionnaire of 136 health-related statements, covering 12 areas of daily activity. Three areas represent a physical dimension (body care and movement, mobility, ambulation), four a psychosocial dimension (emotional behaviour, social interaction, alertness behaviour, communication) and five form independent categories (sleep and rest, home management, recreation and pastime, work, eating).

Scores in all areas were higher for patients than for matched controls (Table 1). Work was particularly impaired, reflecting the substantial number of patients who were unemployed due to their illness. Psychosocial functions appeared to be the most impaired in patients with hypertension. In contrast, patients with cardiac failure were the most physically impaired. The overall SIP score and those for physical and psychosocial dimensions correlated well ($P < 0.001$) with global rated health. These results demonstrate that the SIP may be used to monitor PRH and quality of life in the clinical assessment of cardiovascular diseases.

Table 1 Mean percentage (± s.d.) impairment in HY, AN, CF and controls

Category or dimension	*Items*	*HY*	*AN*	*CF*	*Controls*
Overall SIP score	136	7.0(7.7)	8.2(7.4)	10.4(8.1)	2.0 (3.36)
Physical dimension	45	3.7(6.0)	5.0(6.4)	7.7(8.3)	0.75(2.25)
Psychosocial dimension	48	8.9(11.0)	7.6(9.5)	8.3(9.9)	2.90(5.90)
Independent categories	43				
Sleep and rest	7	8.4(11.1)	13.2(14.9)	14.1(12.6)	3.37(6.30)
Home management	10	7.3(12.2)	10.3(15.2)	18.5(19.2)	1.26(4.38)
Work	9	17.4(28.5)	27.3(32.6)	31.6(33.4)	4.04(13.11)
Recreation and pastime	8	13.0(16.5)	14.0(16.0)	18.7(19.0)	5.33(11.25)
Eating	9	2.7(3.7)	3.6(5.1)	4.0(4.7)	0.78(2.62)

Shayegan-Salek, M. S. *et al.* (1988). *Br. J. clin. Pharmac.*, **25**, 99P.

Propafenone therapy: relationship between plasma concentrations and clinical effect

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Propafenone is an orally effective antiarrhythmic drug of the class 1c type. Three metabolites—5-hydroxy (5-OHP), *N*-depropyl and 4-methoxy-5-hydroxypropafenone have been identified. There is evidence that the metabolism of propafenone to 5-OHP is genetically linked.

We have examined the relationship between plasma concentrations of propafenone and its clinical efficacy in six patients (5M/1F) mean (s.d.) 64.3 years (12.7) with frequent ventricular extrasystoles ($> 1000\ day^{-1}$). Patients received a single 10 mg dose of debrisoquine to determine their hydroxylator phenotype. The propafenone was given at a starting dose of 150 mg twice daily and increased, incrementally at weekly intervals, to 300 mg three times daily or until at least a 90% reduction of daily ventricular extrasystoles was demonstrated by 24 h ECG monitoring. Subsequently, propafenone was stopped and frequent blood samples were collected for 72 h during continuous ECG monitoring. The study was approved by the Ethics Committee of Hammersmith Hospital.

Plasma propafenone and 5-OHP were measured by a selective h.p.l.c. method which resolved the remaining metabolites from the compounds of interest. The reproducibility (CV) of the method was < 7% at 100 $\mu g\ l^{-1}$. After modelling the plasma concentration-time data, the plasma concentration and clinical effect (hourly ventricular extrasystole) data, for the 72 h following cessation of therapy, were fitted to a sigmoid Emax model using non-linear regression.

Propafenone was effective in all cases but the plasma concentrations associated with efficacy (EC_{90}) varied widely, range 64–3824 $\mu g\ l^{-1}$ (median 1282 $\mu g\ l^{-1}$). The mean (s.d.) elimination half-life of propafenone was 7.9 h (3.1), range 5.5–14.0 h. The patient with the longest propafenone half-life, patient 2 (Table 1) was a poor hydroxylator of debrisoquine and had the highest ratio, 36, of plasma propafenone to 5-OHP, whereas in the remaining 5 patients this ratio had a median value of 5 and ranged between 2 and 10.

Thus, propafenone is an effective antiarrhythmic agent. Concentration effect modelling shows a wide variability between subject sensitivity to propafenone similar to that seen for other antiarrhythmics, for example tocainide.

Table 1 Propafenone half-life, EC_{50} and EC_{90} in six patients

Patient	*Propafenone half-life (h)*	*EC_{50} ($\mu g\ l^{-1}$)*	*EC_{90} ($\mu g\ l^{-1}$)*
1	6.9	1178	1760
2	14.0	522	940
3	7.9	1251	1624
4	5.5	1026	3824
5	6.8	402	659
6	6.8	4	64

The effect of age on platelet angiotensin II and ANP receptor density

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The activity of the renin-angiotensin-aldosterone system (RAAS) declines with age while plasma atrial natriuretic peptide (ANP) increases with age. Receptors for both angiotensin II (AII) and ANP have been characterised on the human platelet. This study was conducted to investigate the effect of age on these receptor systems in man.

Young, middle aged and elderly healthy volunteers were studied. Following 60 min supine rest

blood was collected for hormone and platelet receptor analysis. PRA and plasma ANP were measured by radioimmunoassay. AII and ANP receptor density was measured using iodinated AII and ANP respectively. Results are expressed as mean ± s.e. mean. Group size is given in parentheses and data were analysed by one way ANOVA.

A negative correlation between age and PRA was observed ($r = -0.49$, $P < 0.05$). Platelet AII receptor density was higher in the elderly (Table 1). There was a positive correlation between age and AII receptor density ($r = 0.41$, $P < 0.05$). Plasma ANP rose with age ($r = 0.49$, $P < 0.05$). ANP receptor density did not change with age.

This study demonstrates raised platelet AII receptor density with age, which may be related to the decline in RAAS activity with age. Despite the rise in plasma ANP with age, there was no change in platelet ANP receptor density.

Table 1

	Young (13)	*Middle age (7)*	*Elderly (8)*
Age (years)	27.2 ± 1	52.1 ± 2.2	66.8 ± 1.4
PRA (ng ml^{-1} h^{-1})	1.05 ± 0.2	0.92 ± 0.3	0.46 ± 0.1
Plasma ANP (pmol l^{-1})	16.9 ± 2.3		27.1 ± 3.9*
AII receptors	(16)	(7)	(9)
B_{max} (fmol/10^9 cells)	2.7 ± 0.6	3.7 ± 1.1	7.4 ± 2.1*
K_d (pM)	69.0 ± 9.0	76.0 ± 7.0	73.0 ± 7.0
ANP receptors	(14)	(7)	(9)
B_{max} (fmol/10^9 cells)	10.5 ± 1.3	10.6 ± 1.5	15.9 ± 3.8
K_d (pM)	3.4 ± 0.3	3.4 ± 0.3	4.1 ± 0.7

Exercise performance related to debrisoquine oxidation phenotype after single doses of metoprolol and atenolol

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The disposition of metoprolol is related to debrisoquine oxidation phenotype so that poor metabolisers (PMs) have high plasma concentrations and prolonged elimination half-lives when compared with extensive metabolisers (EMs) whereas the disposition of atenolol is unrelated to oxidation phenotype (Lennard *et al.*, 1986). We have examined the influence of oxidation phenotype on exercise performance and fatigue during a standardized exercise test in healthy subjects after single doses of metoprolol and atenolol.

Twelve healthy subjects (9EMs, 3PMs) completed a standardized exercise test on four occasions after single oral doses of (1) placebo, (2) metoprolol 50 mg, (3) metoprolol 100 mg, and (4) atenolol 100 mg, in a double-blind balanced cross-over design. The end-points measured were heart rate, time to complete the exercise test (exercise time), and fatigue measured using a 10 cm visual analogue scale. The statistical methods used were Friedman's non-parametric analysis of variance, Wilcoxon's signed rank test, and the Mann-Whitney U test.

When compared with placebo, treatment with the β-adrenoceptor antagonists reduced exercise heart rate, increased the time to complete exercise and increased subjective fatigue. When comparing atenolol treatment with placebo PMs did not differ from EMs, so that PMs did not appear more susceptible to the effects of β-adrenoceptor blockade. When comparing metoprolol 100 mg with atenolol 100 mg, PMs took significantly longer than EMs to complete the exercise ($P < 0.05$, Table 1) and felt greater fatigue ($P < 0.1$ absolute, $P < 0.05$ proportionate; Table 1). Similar but non-significant differences between PMs and EMs were observed when comparing metoprolol 50 mg with atenolol 100 mg. When compared with atenolol, PMs treated with metoprolol experience substantially greater fatigue than do EMs.

Table 1 Mean responses, compared with atenolol 100 mg, in EMs (n = 9) and PMs (n = 3)

	Metoprolol (50 mg)		*Metoprolol (100 mg)*	
	EM	*PM*	*EM*	*PM*
Δ heart rate (beats min^{-1})	+24.6	+8.3	+11.1	+1.7
Δ exercise time (s)	−7.7	+2.0	−14.1	+6.7***
% Δ exercise time	−2.9	+1.4	−6.5	+4.5***
Δ fatigue (mm)	−14.9	+7.0*	−9.9	+8.7*
% Δ fatigue	−22.1	−6.1	−17.1	+60.6**

* $P < 0.1$, ** $P < 0.05$, *** $P < 0.02$ for differences between PMs and EMs.

Lennard, M. S. *et al.* (1986), *Xenobiotica*, **16**, 435.

Effects of pindolol and xamoterol on plasma creatine kinase in healthy subjects

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Muscle pain has been reported during treatment with β-adrenoceptor antagonists and this appears to be more frequent with drugs with substantial partial agonist activity (PAA) such as pindolol which may be associated with a relatively high incidence of muscle symptoms (Yamaoki *et al.*, 1983). Elevation of serum creatine kinase (CK) levels appears more frequent than muscle symptoms in patients receiving pindolol (Imataka *et al.*, 1981). This has also been described with salbutamol and may be due to agonist effects at β_2-adrenoceptors in skeletal muscle. Xamoterol is a new drug with considerable PAA at β_1-adrenoceptors, which is being investigated for the treatment of heart failure and this study was undertaken to see if this drug might also produce muscle symptoms or elevations in CK levels in comparison with pindolol.

Nine healthy male subjects (aged 20 to 60 years) completed the study. Plasma CK levels were measured on 4 separate days during a 1 week placebo run-in period and provided that three levels were within the normal range (24–195 iu l^{-1}) they entered a randomised double-blind period of active treatment with xamoterol 200 mg twice daily or pindolol 10 mg twice daily for 3 weeks. Plasma CK levels were measured at weekly intervals whilst taking active medication and then on alternate days until normal levels were obtained on two consecutive visits during a placebo washout phase. Cycle exercise and muscle strength tests were performed prior to and after 3 weeks active treatment. Subjects were asked to refrain from strenuous physical activity during the course of the study. Subjects crossed over to receive the alternative drug in a similar manner.

CK levels became elevated during treatment with pindolol ($P < 0.05$) compared with the baseline levels on placebo and compared with levels on xamoterol which were not elevated (Friedman analysis of variance and Wilcoxon test). Median (and range) values on placebo and at 1, 2 and 3 weeks of treatment were respectively 91 (53–178), 197 (52–267), 132 (74–380) and 119 (57–297) for pindolol and 93 (56–232), 85 (59–106), 98 (58–115) and 94 (54–150) iu l^{-1} after xamoterol. CK levels for some subjects peaked at 2 [173 (112–637)] or 4 [168 (83–443)] days after the withdrawal of pindolol and were higher ($P < 0.05$) than after stopping xamoterol [94 (59–137) and 89 (67–251)].

With xamoterol BP and HR tended to increase (NS) at rest (supine, sitting and standing) but after 4 min cycle exercise there was a reduction in HR (mean ± s.e. mean 129.0 ± 4.1, placebo 144.4 ± 3.3 beats min^{-1}, $P < 0.01$, paired t-test) but not systolic BP (168.2 ± 8.0, placebo 178.9 ± 7.6 mm Hg, NS). With pindolol diastolic BP tended to fall (NS) in all positions at rest and HR tended to be lower sitting and standing and was reduced during exercise (117.0 ± 4.5, placebo 146.1 ± 4.9 beats min^{-1}, $P < 0.01$) as was systolic BP (151.4 ± 8.9, placebo 169.2 ± 6.7 mm Hg, $P < 0.01$). Whilst the final values for HR on exercise differed for the two drugs this was largely because HR prior to exercise was higher with xamoterol and the percentage reduction in the rise compared with placebo (xamoterol 29.8 ± 3.2%, pindolol 33.0 ± 3.6%) was not

different indicating similar degrees of β_1-adrenoceptor antagonism.

CK levels were elevated in normal subjects during and for a few days after taking pindolol but not xamoterol. This effect may be due to specific partial agonist activity at β_2-adrenoceptors.

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What is the best treatment strategy for patients whose hypertension is not controlled by enalapril 20 mg once daily?

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Treatment with enalapril maleate may be expected to control essential hypertension in approximately 60% of patients. In patients uncontrolled despite 20 mg enalapril daily, we have conducted two separate single-blind studies to address the question—is there further benefit to be gained from increasing the enalapril to 40 mg once daily or is it better to add a β-adrenoceptor blocker (atenolol 50 mg) or a small dose of thiazide (hydrochlorothiazide 12.5 mg)?

One hundred and twenty-three moderate to severe hypertensive patients with supine blood pressure (BP) of 174 ± 24/105 ± 9 mm Hg (mean ± 1 s.d.) after 2 weeks treatment with enalapril 20 mg once daily were randomised to receive enalapril 40 mg (E40) once daily (n = 58), enalapril 20 mg plus hydrochlorothiazide 12.5 mg (E20 + HCTZ) once daily (n = 48) or enalapril 20 mg plus atenolol 50 mg (E20 + A) once daily (n = 17) for 4 weeks. The groups were well matched with regard to age and baseline BP. The results of the studies are shown in Table 1.

There was no significant intergroup difference for the change in either DBP or SBP, however, in the E20 + A group the fall in SBP was not statistically significant compared with baseline. Patients treated with E20 + HCTZ showed a greater tendency to achieve the target DBP of 90 mm Hg or less (33%) as compared with E40 (22%) and E20 + A (24%) although these differences were not significant. The E20 + A group only showed a significant change in the mean PR. There was no significant intergroup difference in the percentage of patients reporting adverse events; E40 (28%), E20 + HCTZ (31%), E20 + A (35%). Routine haematological and biochemical parameters overall were unchanged.

The results of these studies suggest that further lowering of BP is obtained by doubling the dose of enalapril from 20 mg to 40 mg once daily and that this is at least as well tolerated and effective as adding a small dose of thiazide or a β-adrenoceptor blocker.

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Table 1 Change in mean supine systolic BP (SBP) (mm Hg) and diastolic BP (DBP) (mm Hg) and pulse rate (PR) (beats min^{-1})

			After 4 weeks	
Group	*Baseline BP*	*Baseline PR*	*Change in BP*	*Change in PR*
E40	SBP 175 ± 21	81 ± 15	−10 ± 14**	−1 ± 10 (NS)
	DBP 106 ± 9		−7 ± 11**	
E20 + HCTZ	SBP 174 ± 26	79 ± 10	−12 ± 18**	+7 ± 27 (NS)
	DBP 105 ± 8		−7 ± 11**	
E20 + A	SBP 174 ± 28	85 ± 11	−3 ± 20 (NS)	−14 ± 8**
	DBP 107 ± 12		−9 ± 10**	

Change from baseline ** $P < 0.001$, (NS) not significant.

Nifedipine dose titration in primary Raynaud's phenomenon

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POSTER COMMUNICATIONS

The interaction between neuropeptide Y and noradrenaline in reduction of forearm blood flow

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The vasoconstrictor neuropeptide Y (NPY) coexists with noradrenaline (NA) in mammalian perivascular sympathetic neurones including those of man (Wharton & Gulbenkian, 1987). *In vitro* it has direct pressor effects and may modulate both the release and the post-synaptic action of NA (Edvinsson *et al.*, 1987). We have previously shown this peptide to cause myocardial ischaemia when infused directly into coronary arteries in man (Clarke *et al.*, 1987) and reduce coronary blood flow by small vessel constriction after intracoronary infusion in the open chest greyhound (Larkin *et al.*, 1988).

In the present study we have examined the effects of locally infused NPY in forearm resistance vessels in man. Further, using low doses of NPY, we studied its influence on constriction resulting from simultaneously infused NA and reflex sympathetic forearm arteriolar constriction provoked by lower-body negative pressure (LBNP).

In six male volunteers NPY (50, 200 and 1000 pmol min^{-1}) was infused into the left brachial artery and forearm blood flow was measured using venous occlusion plethysmography and mercury in silastic strain-gauges (Whitney, 1953). Blood flow in the infused arm fell in a dose-dependent fashion from 3.8 ± 1.5 (mean ± s.d.) to 3.5 ± 1.4, 2.7 ± 0.8 and 1.8 ± 0.5 ml 100 ml^{-1} min^{-1} respectively (a reduction of 9, 31 and 53%, $P < 0.01$).

In a further study in six subjects we established a dose-response for infused NA (25, 50 and 100 ng min^{-1}) where forearm blood flow fell 48% at the highest dose. This response was unaltered (51% reduction) during co-infusion of NPY at 50 pmol min^{-1}.

In a further six subjects LBNP of 20 cm H_2O resulted in a reduction in forearm blood flow of 13% in the infused arm and 12% in the control arm during saline infusion. When NPY (50 pmol min^{-1}) was infused LBNP produced a 16% reduction in flow in the infused arm compared with a 20% reduction in the control arm. These small differences suggest that NPY does not alter the reflex sympathetic constriction.

While we have shown that NPY has a marked constrictor effect in forearm resistance vessels, we conclude that low doses of NPY do not influence constriction whether induced by exogenous NA or reflex sympathetic activity.

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Comparison of the haemodynamic and hormonal effects of low and conventional dose cyclopenthiazide in normal volunteers

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Despite their widespread use in clinical practice over the past 30 years, the means by which thiazide diuretics lower arterial blood pressure remains uncertain. Proposed mechanisms of action include contraction of plasma and extracellular fluid volumes, attenuation of the pressor responsiveness to angiotensin II and noradrenaline, a direct vasodilator effect and increased production of endogenous vasodepressor substances (Struyker-Boudier *et al.*, 1983). We have demonstrated that low (125 μg) and conventional (500 μg) doses of cyclopenthiazide produce comparable reductions in blood pressure but only the 500 μg dose increased plasma renin activity (McVeigh *et al.*, 1988). Therefore by comparing the effects of low and conventional doses of cyclopenthiazide on the renin angiotensin system, plasma and extracellular fluid volumes and the pressor responsiveness to angiotensin II, we sought to shed further light on the contribution of these mechanisms to the antihypertensive effect of thiazide diuretics.

After an initial 2 week placebo controlled run-in period, eight healthy male volunteers entered a double-blind two-part cross-over study. Each active treatment period lasted 4 weeks. Subjects received either 125 μg or 500 μg of cyclopenthiazide with treatment periods separated by a 4-week placebo phase. Volunteers attended the Department of Therapeutics for study on each of 2 study days at the end of each treatment phase. On the first study day serum potassium, plasma renin activity and plasma angiotensin II levels were measured after 1 h supine rest. Plasma volume using 4 μCi I^{125} and extracellular fluid volume using 16 μCi Br^{88} were measured after appropriate equilibration times. On study day 2, heart rate and blood pressure were recorded before and after 10 min infusion of 4, 8, 16 and 32 ng angiotensin II kg^{-1} min^{-1}. Statistical analysis was performed using paired *t*-tests. Results are expressed as mean ± s.d. and the level of significance chosen at the 5% level.

Low and conventional dose therapy reduced serum potassium concentration by 0.6 mmol l^{-1} and 0.9 mmol l^{-1} respectively ($P < 0.01$). Plasma renin activity increased from 1.0 ± 0.5 to 2.7 ± 1.1 ng Al ml^{-1} h^{-1} ($P < 0.01$) and from 1.1 ±0.6 to 4.5 ± 2.3 ng Al ml^{-1} h^{-1} ($P < 0.01$) with the 125 μg and 500 μg doses and represented a significant treatment difference between doses ($t = 3.44$, $P < 0.02$). Conventional dose cyclopenthiazide alone increased plasma angiotensin II from 5.6 ± 2.0 to 9.6 ± 3.0 ($P < 0.05$). Plasma volume was unaffected by cyclopenthiazide after 4 weeks' therapy. The 125 μg preparation did not contract extracellular fluid volume. The 500 μg dose reduced extracellular fluid volume by 1103 ml (95% CI from 108 ml to 2098 ml, $P < 0.02$). The increases in blood pressure to infused angiotensin II were unaffected by cyclopenthiazide therapy.

Cyclopenthiazide 125 μg produced less stimulation to the renin-angiotensin system than the 500 μg dose. It would appear that mechanisms other than contraction of body fluid volumes and attenuation of vascular reactivity contribute to the long term antihypertensive effect of thiazide diuretics.

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High dose inhaled beclomethasone dipropionate increases bone resorption in normal men

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Six healthy males (mean age 29 years) were treated with inhaled beclomethasone dipropionate (BD), 1 mg twice daily via a 'volumatic' device for 4 weeks (days 8 to 35 of study). Following a 12 h overnight fast, uncuffed blood was drawn for estimation of calcium, phosphate, creatinine, alkaline phosphatase and parathyroid hormone. Urine produced in the 2 h after initial voiding was collected for estimation of hydroxyproline/creatinine ratio (OH-Pr/creat ratio) and calcium/creatinine ratio. Samples were collected before treatment—days 1 and 7; during treatment—days 21 and 35; and after stopping treatment on day 42.

Mean OH-Pr/creat ratio rose steadily through-

out the treatment period to a maximum after 4 weeks (35 days), and promptly returned to pre-treatment levels 1 week after discontinuing BD (Table 1).

There was a significant rise in urinary OH-Pr/creat ratio after 4 weeks treatment (Day 1 *vs* Day 35: $P < 0.05$, CI: 0 to −9.9, and Day 7 *vs* Day 35: $P < 0.02$, CI: −1.6 to −11.2). The changes in urinary OH-Pr/creat ratio after 2 weeks treatment (Day 21) and 1 week after stopping BD (Day 42) were not significantly different from pre-treatment levels. There were no statistically significant changes in serum calcium, phosphate, creatinine, alkaline phosphatase, parathyroid hormone or urinary calcium/creatinine ratio.

Urinary OH-Pr/creat ratio is an accurate measure of bone resorption (Nordin, 1978). We have demonstrated that short term administration of high dose BD causes a reversible increase in bone resorption in normal men.

Inhaled corticosteroids are widely used in the treatment of asthma, and prescriptions for these drugs have risen fourfold in the 10 years since 1975 and continue to rise (Higginbottam & Hay, 1987). Our findings indicate that longer term studies are required to define the effects on bone resorption and bone mass during chronic treatment.

Table 1 Mean hydroxyproline/creatinine ratio (μmol $mmol^{-1}$)

	Day 1	7	21	35	42
Mean OH-Pr/creatinine ratio (μmol $mmol^{-1}$)	17.32	15.85	18.38	22.28	17.4
s.d.	4.9	4.7	4.36	2.6	5.9

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The effect of labour and epidural analgesia on plasma concentrations of drug binding proteins

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α_1-acid glycoprotein (AAG) is the main binding protein in blood for many of the basic drugs, including pethidine, bupivacaine and lignocaine (Piafsky, 1980). Changes in AAG concentration will alter the bound and unbound fractions of these drugs. AAG is also an acute phase reactant, which increases in response to stress (Schmid, 1975). Surgery causes a rise in plasma concentrations, beginning 6 h after skin incision, peaking at 48 h and beginning to decline after 120 h (Colley *et al.*, 1983). The purpose of our study was to investigate the effect of labour and of epidural analgesia during labour on plasma concentrations of AAG.

The subjects studied were healthy women, at term presenting for induction of labour. Patients with pre-eclampsia or those taking any medication were excluded. Approval was obtained from the local University Medical Research Ethics Committee. Consent was given by all patients.

Venous blood samples were taken on the evening before induction, during early labour, during established labour, at delivery and on the first day post partum. The samples were centrifuged and the supernatant serum stored at −20° C until analysis. AAG estimations were by Beckman Array Protein Analysis using a rate methylometer. Statistical analysis was by Student's *t*-test.

Thirty-one patients were studied. Twenty-one received narcotic analgesia, 10 received epidural analgesia.

Patients receiving narcotic analgesia had a significant rise in mean serum AAG concentrations during labour ($P < 0.001$) while levels remained constant in patients receiving epidural analgesia. Mean AAG concentrations were higher in the narcotic group than the epidural

group at delivery but the difference was not statistically significant ($P = 0.07$). On day 1 post partum both groups had a significant rise in concentrations of AAG ($P = 0.02$).

The rise in AAG during labour reduces the risk of toxicity at a given blood concentration of a drug by decreasing the free (unbound) fraction of the drug. This protective effect is reduced by epidural analgesia.

Table 1 Mean (s.d.) AAG levels over the course of the study

	Epidural n = *10*	*Narcotic* n = *12*
Pre-labour	41.2 (10.3)	41.1 (7.8)
Early labour	43.4 (10.4)	43.4 (7.9)
Established labour	40.2 (10.6)	44.9 (7.8)
Delivery	40.0 (11.3)	47.0 (8.9)*
Post partum	56.8 (16.6)*	60.0 (12.0)*

* Significant rise in AAG ($P < 0.05$).

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Role of the flash VEP in the diagnosis and assessment of elderly patients with mild to moderate Alzheimer's disease

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The diagnosis of Alzheimer-type dementia is by exclusion, and its diagnosis and the monitoring of changes in clinical trials may be especially difficult in mild to moderate cases (Henderson & Huppert, 1984). Several measures have been proposed as potential markers for the illness; the flash visual evoked potential (VEP) has been suggested as a specific indicator (Wright *et al.*, 1984; Visser *et al.*, 1985). This has been disputed by Cohen (1983) and there are differences between the studies in terms of age, diagnostic criteria and the inclusion of depression. As AD is an age-related disease, any diagnostic aid must be valid in more elderly groups than tested heretofore. We present a study of the flash (VEP) in an elderly population with mild to moderate Alzheimer's disease (AD) and in elderly controls.

Twenty-eight patients with mild to moderate AD (McKhann *et al.*, 1984) age 78.3 ± 5.4 (mean ± s.d.) years were compared with 25 healthy controls, age 78.7 ± 5.9 years. Depression and reduced visual acuity were among the exclusion criteria for the study, and all the AD patients were able to comply with the test itself. Using Ag/AgCl electrodes, the VEP was measured across Oz referenced to Fz, and Pz and Oz referenced to linked mastoids, N2 and P2 latencies were measured, and the results obtained are shown in Table 1.

The above results indicate that there is statistically significant increased latency of both the N2 and P2 waves at Oz/Fz in elderly patients with mild to moderate AD; however there is a large overlap between the populations, and its value as a diagnostic test is less clear. The presence of this difference may suggest that clinical status in elderly AD patients may be monitored with the flash VEP, as has already been documented with the presenile form of the disease (Orwin *et al.*, 1986).

Table 1 Mean values (and standard deviation) for N2 and P2 latency (ms) in the AD group and the control group

	Oz/Fz	*Pz/Az*	*Oz/Az*
N2			
AD patients ($n = 28$)	127.1 ± 21	135.7 ± 22.7	123.9 ± 18.9
Controls ($n = 25$)	115.1 ± 13.6	131.9 ± 15.7	123.3 ± 19.2
P	< 0.05	NS	NS
P2			
AD patients ($n = 28$)	187.4 ± 35.0	211 ± 39.7	198.9 ± 28.0
Controls ($n = 25$)	155.1 ± 24.7	186.3 ± 23.8	181.7 ± 34.5
P	< 0.01	< 0.05	NS

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Pharmacokinetics of ranitidine syrup in children

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H_2-receptor antagonists are increasingly used in paediatric practice for the treatment of gastro-oesophageal reflux, cystic fibrosis and for rarer conditions such as Job's syndrome. Ranitidine has no hepatic microsomal enzyme inhibiting, anti-androgen or significant prolactin stimulating effects (Brogden *et al.*, 1982) and may now be considered as the drug of choice.

The oral dose to achieve concentrations of 40–60 ng ml^{-1} giving a greater than 90% suppression of gastric acid secretion has been reported to be 1.25–1.9 mg kg^{-1} in older children given tablets (Blumer *et al.*, 1985). This study was designed to determine the pharmacokinetics of ranitidine in syrup form given twice daily in young children. A dose of 2 mg kg^{-1} was chosen to achieve maximal acid production suppression. Eight children aged 7 months—14 years were studied. All had normal hepatic and renal function and no child received any other form of concomitant acid suppressant therapy.

Following the first 2 mg kg^{-1} (ranitidine syrup) dose of proposed continuing medication, blood (1–2 ml) was collected via an indwelling venous catheter at 0, 30, 45, 60, 90, 120 150 min and 3, 4, 5, 6, 8 and 12 h post dose. Plasma was separated and stored at −20° C before assay by radioimmunoassay (Jenner *et al.*, 1981). Each child was again studied in steady state and samples taken at similar times throughout the 12 h dose interval.

The median and range results for selected pharmacokinetic parameters following a single dose and in steady state are shown in Table 1.

No accumulation of ranitidine was observed in keeping with relationship between measured half-life dose interval. Wide variation in all kinetic parameters was observed.

Although concentrations sufficient to provide 90% suppression of gastric acid secretions were observed in all children for the first half of the dose interval, these were maintained at 8 h in four, and in only one of the children at 12 h. If continuous gastric acid suppression is considered necessary, a more frequent dosage regimen would be indicated.

Table 1

	Single dose		*Steady-state*	
	Median	*Range*	*Median*	*Range*
C_{max} (ng ml^{-1})	246	150–452	263	111–649
t_{max} (h)	1.80	0.75–2.50	1.75	0.67–3.00
$AUC_{12\,h}$ (ng ml^{-1} h)	1076	780–1616	1274	720–2357
$t_{½}$ (h)	3.9	2.2–8.4	—	—

The median (and range) ratio of AUC_{12} (steady-state) to AUC_{∞} (single dose) was 1.02 (0.74–2.30).

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Estimating plasma concentrations of desipramine in Chinese depressed patients using the repeated one-point method

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Using the repeated one-point method, Fant and co-workers (1984) predicted steady-state nortriptyline plasma concentrations. Similarly we succeeded in predicting the plasma elimination half-lives ($t_{½}$) and concentrations of bupivacaine after epidural administration (Chan, 1987). We now report a pilot study of 12 depressed Chinese patients to test if this method could be used for desipramine (D).

In-patients with a diagnosis of depression were recruited into the study according to strict selection criteria. The local Ethics Research Committee had read and approved the protocol. The patients received for 14 consecutive days at exactly a fixed time (usually 21.00 h) 50 mg of D (2 × 25 mg Pertofran, supplied by Ciba Geigy Ltd). Blood samples were withdrawn at 24 h after the first dose and the second dose, and on day 4 and day 14. The samples were collected into heparinised, plasticizer-free tubes. Plasma was removed and stored at −20° C until analysis of D by high performance liquid chromatography with electrochemical detection. Table 1 summarises patient data and D kinetic parameters. C_1 and C_2 are plasma concentrations of D after first and second dose respectively while C_0, the derived intercept, is obtained from the derived elimination rate constant, k. Regression analysis of the predicted (C_{pred}) and observed (C_{obs}) plasma concentrations shows a high correlation (r = 0.9572) and the linearity could be described by y = 1.497 + 0.806x. The mean $t_{½}$ was 26.0 ± 12.5 h which is comparable with the reported value (23.2 ± 7.9 h) on healthy Chinese by Rudorfer *et al.* (1984). It concluded that the repeated one-point method is useful for monitoring D disposition in our depressed patients.

Table 1 Patient data and kinetic parameters of desipramine

Patient	*Age (years)*	*Sex*	C_1 (ng ml^{-1})	C_2 (ng ml^{-1})	k (h^{-1})	$t_{½}$ (h)	C_0 (ng ml^{-1})	C_{pred} (ng ml^{-1})	C_{obs} (ng ml^{-1})
FKW	19	M	9.2	14.6	0.0222	31.5	15.7	22.3	15.6
CKF	52	M	8.3	20.4	0.0259	26.8	15.5	17.9	24.7
AH	67	F	18.3	23.7	0.0509	13.6	62.1	25.9	25.3
WWK	23	M	14.9	17.1	0.0209	33.2	24.6	37.7	20.7
YTL	21	M	9.6	9.9	0.1335	5.2	236.5	10.0	10.2
CSY	35	F	33.0	53.0	0.0209	33.2	54.5	83.7	80.0
CSC	18	M	19.0	32.0	0.0158	43.8	27.8	60.2	45.0
YCM	50	M	23.4	29.5	0.0560	12.4	45.3	48.5	46.0
NT	50	M	18.6	30.2	0.0197	35.2	29.8	49.4	38.6
WCT	55	M	11.3	17.4	0.0257	26.9	20.9	24.6	19.2
CTY	56	F	30.5	50.5	0.0176	39.4	46.5	88.5	67.8
YMF	34	F	14.7	17.7	0.0662	10.5	72.0	18.5	17.7

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Excretion of famotidine in breast milk

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Famotidine is a potent H_2-receptor antagonist that has recently been introduced for the treatment of gastric and duodenal ulceration. At therapeutic dose, 40 mg once daily, famotidine inhibits basal gastric acid secretion for 10–12 h but has a shorter plasma elimination half-life of approximately 2.8 h (Chremos, 1987). Although the pharmacokinetic profile of famotidine has been well documented, data on the excretion of this drug in human breast milk are lacking. Previous studies have shown that both cimetidine and ranitidine readily pass into breast milk and the concentration of drug in milk is generally greater than corresponding plasma concentrations. Reported milk:plasma concentration ratios range from approximately 3 to 12 with cimetidine (Somogyi & Gugler, 1979) and 1 to 7 with ranitidine (Riley *et al.*, 1981).

We have measured whole breast milk and plasma famotidine levels during three 'feeding' intervals following a single dose of 40 mg famotidine. Eight women aged 23–37 years, weight 52–120 kg, who had recently given birth but did not plan to breast feed gave informed consent to take part in the study. The women were given a 40 mg tablet of famotidine with 100 ml of water at 10.00 h on the day of testing. Blood samples were withdrawn 15 min pre-dose, and at 15, 30 min, 1, 2, 4, 6 and 24 h post dose. Following centrifugation plasma was separated and frozen at −20° C until analysis. Breast milk samples were extracted by standard breast pump at 2, 6 and 24 h post dose. At each sampling time three aliquots of milk each representing 5 min collection were taken initially from the right and then the left breast. pH was measured immediately and the milk samples were stored at −20° C. All samples were assayed for famotidine concentration by h.p.l.c. following solid phase extraction, using a modification of the method of Vincek *et al.* (1985).

The concentration of famotidine was similar in milk collected from the right and left breasts. The mean of the six milk aliquots was compared with the corresponding plasma concentration at the same time point, and the milk:plasma ratio was determined.

Time after dosing (h)	*Milk:plasma ratios* (mean s.d.)
2	0.41 (0.17)
6	1.78 (0.55)
24	1.33 (0.86)

Median pH of breast milk samples was 7.14 (range 6.77–7.64). The concentration of famotidine in breast milk appeared to lag behind that measured in plasma by 2–4 h. The observed peak breast milk concentration (mean 72 ± 21 ng ml^{-1}) 6 h after dosing was not significantly different from the peak concentration of famotidine in plasma (mean 75 + 22 ng ml^{-1}) measured 2 h post dose.

In conclusion, the present findings indicate that after oral dosing famotidine is detectable in human breast milk. However comparison with historical data suggests that famotidine is less extensively excreted in breast milk than either cimetidine or ranitidine. This should be taken into consideration when prescribing H_2-receptor antagonist therapy for nursing mothers.

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Acute haemodynamic effects of cromakalim, a novel vasodilator, in patients with ischaemic heart disease

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Cromakalim is a novel anti-hypertensive agent which is chemically unrelated to existing cardiovascular drugs. It activates potassium channels in vascular smooth muscle, promotes the efflux of potassium ions and thereby hyperpolarises the smooth muscle cell membrane reducing available calcium for contraction (Hamilton *et al.*, 1986).

We investigated the acute resting haemodynamic effects of cromakalim in eight male patients, aged 40–65 (mean 53.4 years) with ischaemic heart disease during routine cardiac catheterisation. All patients had stable angina pectoris with no evidence of heart failure. All cardioactive drugs, except for short acting nitrates, were stopped 24 h prior to the study. All patients gave informed written consent and the study was approved by the hospital ethics committee.

Under local anaesthetic a femoral arterial sheath was inserted for systemic arterial pressure recording and through it a micromanometer-tipped catheter (Sentron) was introduced into the left ventricle for measurement of left ventricular pressure and dP/dt. A thermodilution Swan-Ganz catheter was introduced into the pulmonary circulation via a femoral vein for measurement of pulmonary pressures and cardiac output. Heart rate was taken from a simultaneous ECG. Baseline recordings were taken and cromakalim was then infused (15 $\mu g\ kg^{-1}$) over 10 min into a peripheral vein. Haemodynamic recordings were made at 5, 10, 15, 20, 25 and 30 min following the onset of the infusion. No adverse effects were reported.

The effects of cromakalim on mean arterial pressure (MAP), systemic vascular resistance (SVR), cardiac output (CO) and heart rate (HR) are shown in Table 1; values are mean ± s.e. mean and all comparisons are made with the baseline values using Student's paired *t*-test. There was no significant effect on mean pulmonary artery pressure and total pulmonary vascular resistance. Left ventricular dP/dt rose slightly in all patients but did not reach significance, the rise perhaps reflecting the trend in heart rate.

These findings indicate that cromakalim acts primarily on arteriolar smooth muscle, reducing systemic vascular resistance with resulting decrease in mean systemic arterial pressure and increase in cardiac output. The increase in heart rate may reflect reflex sympathetic activation. Further work is needed to investigate a possible inotropic effect of the drug.

Table 1

	MAP (mm Hg)	*SVR (dyn s cm^{-5})*	*CO (l min^{-1})*	*HR (beats min^{-1})*
Baseline	101.0 ± 5.3	1438.8 ± 126.2	5.87 ± 0.5	58.0 ± 2.5
5 min	94.4 ± 4.2*	1062.4 ± 77.1***	7.36 ± 0.6*	62.4 ± 2.9**
10 min	88.8 ± 3.9***	1001.1 ± 112.5****	7.75 ± 0.9*	66.5 ± 2.3****
15 min	96.6 ± 6.7	1022.3 ± 118.1***	7.96 ± 0.7***	64.9 ± 3.5**
20 min	100.3 ± 7.0	1154.1 ± 141.3***	7.60 ± 0.7***	61.0 ± 3.0
25 min	99.8 ± 8.4	1273.7 ± 219.8	7.11 ± 0.7	62.4 ± 2.0*
30 min	97.6 ± 8.9	1184.7 ± 197.7	7.54 ± 1.0	63.8 ± 2.8*

*$P < 0.05$, ** $P < 0.01$, *** $P < 0.005$, **** $P < 0.0005$.

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Oxcarbazepine in the management of intractable trigeminal neuralgia

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Currently, the drug of choice in the management of trigeminal neuralgia is carbamazepine (CBZ; Cambell *et al.*, 1966; Tomson *et al.*, 1980). CBZ's onset of action is rapid (within 24 h) but is often associated with toxicity such as confusion, nausea, ataxia and nystagmus necessitating discontinuation of medication. Additionally 20% of patients responding initially to treatment may subsequently become refractory (Taylor *et al.*, 1981). Oxcarbazepine (OXC), a keto derivative of carbamazepine, has recently been shown to have antineuralgic properties in the absence of significant side effects (Ferago, 1987).

In the present study we have assessed the efficacy, tolerability and kinetics of OXC in a series of six patients (two males, four females; mean age 61 years, range 42–77), with trigeminal neuralgia refractory to CBZ therapy, over a period of 6 months.

Patients were clinically evaluated as outpatients and OXC (300 mg tablets; Ciba Geigy Pharmaceuticals, UK) administered according to a dose schedule comprising 600 mg daily of OXC initially, rising up to 2400 mg daily in two patients in order to get optimal control. All patients kept daily pain diaries and underwent regular biochemical and haematological investigation. Rationalization of drug management was achieved by therapeutic drug monitoring by h.p.l.c. of serum steady state concentrations of OXC and its primary pharmacologically active metabolite 10,11-dihydro-10-hydroxy-carbamazepine (OXC-OH; Elyas *et al.*, 1988).

An excellent response to OXC was seen in all patients with pain control correlating well with total serum drug concentrations of OXC and OXC-OH. An overall total serum therapeutic range, in the six patients, of 60–120 μmol l^{-1} of OXC-OH corresponding to a daily range of 1200–2400 mg day^{-1} OXC was observed. Both OXC and OXC-OH total serum concentrations correlated, $r = 0.957$ and $r = 0.645$ respectively, with OXC dose. In one patient OXC-OH was found to be 47% bound to serum proteins and that free and total concentrations of OXC-OH correlated significantly ($r = 0.960$). No significant side effects were observed during the 6 month treatment period, though a mild hyponatraemia was observed during high doses of OXC.

It is concluded that OXC has potent antineuralgic properties in the absence of significant side effects and therefore may be the drug of choice in the management of intractable trigeminal neuralgia.

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Assessing compliance: is return tablet count worthwhile?

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Many clinical trials employ return tablet count (RTC) as their sole measure of compliance. This method assumes that tablets removed from the container are ingested. We have recently assessed compliance over 4 weeks in three separate studies using RTC and low-dose phenobarbitone, a pharmacological indicator of compliance (Feely *et al.*, 1987). The results of two of these individual studies have already been reported (Pullar *et al.*, 1988a, b). Using data from these studies we compare here the two methods of assessing compliance. RTC is calculated as the ratio of actual:expected number of tablets removed from the bottle and expressed as a percentage. The weight-corrected phenobarbitone level to dose ratio (LDR) is calculated and expressed as a percentage of the lowest LDR found in age related volunteers (Feely *et al.*, 1987). The LDRs for volunteers > 50 years are higher than in younger volunteers. However, the values in the older group are based on small numbers. We have therefore also expressed the LDR as a

percentage of the lowest volunteer value irrespective of age. Data were available on 216 patients (194 > 50 years).

Depending on the controls used between 32% and 48% of patients with 'good' compliance (90–109%) by RTC had evidence of poor compliance by phenobarbitone LDR. If patients appeared to have excessive compliance by RTC the LDR indicated that approximately half had poor compliance with similar results for patients who failed to return their container. However LDR confirmed poor compliance in most patients who had poor compliance by RTC (if the age related lowest volunteer value is used LDR confirmed poor compliance in all those with ≤ 80% compliance by RTC).

The use of the lowest normal volunteer value makes it likely that LDR will overestimate compliance. Despite this, compared with the indicator, RTC grossly overestimates compliance. This could affect the conclusions of clinical trials which use RTC as a measure of compliance.

Table 1 Number of patients with various levels of compliance as assessed by RTC and phenobarbitone LDR

		% compliance by tablet count					
		29%≤ n = *1*	*30–59%* n = *10*	*60–89%* n = *22*	*90–109%* n = *161*	*≥110%* n = *10*	*Failed to return container* n = *12*
LDR as % of lowest volunteer value	>90%	0	0	7	110	6	8
LDR as % of lowest age related volunteer value	>90%	0	0	4	84	4	6
	60–89%	0	0	9	66	5	4
	30–59%	0	6	8	9	0	2
	≤29%	1	4	1	2	1	0

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Acute effects of diuretics in heart failure

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In normal man, the acute (< 30 min) vascular effects of frusemide and bumetanide differ (Johnston *et al.*, 1986). Frusemide reduces forearm bloodflow (FBF) and increases venous capacitance (VC) and mean arterial pressure (MAP); these effects are not observed after bumetanide. In addition, plasma renin activity (PRA) increases after frusemide, and it is probable that the vascular effects observed relate to this. In patients with chronic cardiac failure (CCF) PRA also increases after frusemide (Francis *et al.*, 1985) but the vascular responses are variable (Dikshit *et al.*, 1973). Similar variability of response has been observed after bumetanide, despite accurate invasive methodology (Ziacchi *et al.*, 1981; Verma *et al.*, 1987). We wished to compare the effects of frusemide and bumetanide in CCF using non-invasive techniques.

Nine men in stable CCF, age range 55–77 years, were admitted for study. All had normal renal function, and were being treated with diuretics. In addition, some patients were receiving digoxin (3) and some flosequinan, a vasodilator (5). A 12 h urine collection was made on the day prior to study for volume and Na^+ content. On the day of the study, the morning diuretic dose was omitted. A venous cannula was inserted, and the patient rested for 1 h in the supine position. Heart rate (HR, radial pulse), blood pressure (Hawksley random-zero sphygmomanometer), and FBF and VC (venous occlusion plethysmography) were measured at the end of this period, and blood withdrawn for measurement of PRA and aldosterone by radioimmunoassay. Subjects were then given frusemide 20 mg, bumetanide 0.5 mg or water i.v. according to a randomised double-blind pattern. Observations were repeated at 5, 10 and 15 min after drug administration, and a further blood sample

obtained at 12 min. A urine collection was made at 35 min. The study was repeated at weekly intervals.

No change was observed in HR. MAP tended to increase after both placebo and drug administration, but no significant changes were observed. No change in FBF was observed after placebo or bumetanide. A small reduction in FBF was observed after frusemide, from 2.59 ± 0.57 ml min^{-1} 100 ml^{-1} prior to drug administration to 2.18 ± 0.47 ml min^{-1} 100 ml^{-1} at 5 min thereafter, but this difference was not significant. VC was unchanged by either drug. A significant increase in PRA was observed after frusemide, from 3.91 ± 1.4 to 4.65 ± 1.6 ngA1 ml^{-1} h^{-1} ($P < 0.05$, Wilcoxon's test) but not after bumetanide. Aldosterone levels were unchanged.

From this study it would appear that the acute vascular responses to diuretics are attenuated in patients with CCF when compared with normals. No significant difference could be detected between frusemide and bumetanide except that PRA release by frusemide was confirmed.

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Influence of rifampicin and ranitidine on circadian blood pressure and pharmacokinetics of tertatolol in hypertensives

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Tertatolol is a new β-adrenoceptor blocker without intrinsic sympathomimetic activity or β_1/β_2-adrenoceptor subtype selectivity. In contrast to other β-adrenoceptor antagonists tertatolol does not appear to decrease renal plasma flow and it even slightly increases glomerular filtration rate as well as sodium and potassium excretion (Walker *et al.*, 1985). From the pharmacokinetic point of view about 98% of this β-adrenoceptor blocker are biotransformed by the liver, whereby sulphoxidation, hydroxylation and conjugation appear to be the major pathways. Rifampicin is known to be a strong enzyme-inducing drug, ranitidine initially has been claimed an 'interaction free drug', in the meantime this H_2-receptor antagonist is used very frequently and subsequently quite a number of drug interactions with ranitidine have been described (Kirch *et al.*, 1984).

The interaction of tertatolol with rifampicin and ranitidine was investigated in 10 patients with arterial hypertension (WHO stage I–II; four male, six female subjects; mean age 60.9 ± 14.8 years; mean body weight 68.5 ± 14.6 kg; mean ± s.d.). All had given their informed consent to participate in the investigation. The study protocol was approved by a local hospital ethics committee. They were treated orally with tertatolol 5 mg once daily alone and after randomized allocation with ranitidine 150 mg twice daily or rifampicin 600 mg once daily for 1 week each (tertatolol 5 mg were concurrently administered on seventh day of the treatment phases). Following each therapy phase circadian blood pressure values as well as kinetic parameters were obtained. Maximum plasma concentrations were 123.67 ± 32.38 ng ml^{-1} on treatment with tertatolol alone, they were reached after 1.95 ± 1.77 h, whereby the elimination half-life was 9.2 ± 7.09 h. Co-administration of ranitidine did not significantly alter kinetic parameters and the antihypertensive effect of tertatolol. Rifampicin, however, decreased maximum plasma levels of tertatolol to 80.61 ± 18.47 ng ml^{-1} and considerably shortened elimination half-life to 3.38 ± 2.58 h ($P < 0.01$ compared with tertatolol alone). Urinary excretion of parent tertatolol and 4-hydroxy tertatolol was decreased under rifampicin and a tendency to a reduction of the effect of tertatolol on circadian blood pressure values was observed. 24 h after administration heart rate on tertatolol alone (67.7 ± 5.9 beats min^{-1}) was lower than that on tertatolol plus rifampicin (73.5 ± 7.3 beats min^{-1}). In conclusion, a pronounced pharmacokinetic interaction of tertatolol with rifampicin, but not with ranitidine was found in the present study.

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The felodipine/digoxin interaction. A placebo-controlled study in patients with heart failure

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In contrast to verapamil or quinidine dihydropyridine derivates like nifedipine, nitrendipine or nisoldipine only cause slight elevations of digoxin serum levels by about 15 to 20% (Kirch *et al.*, 1986a, b, c; Kleinbloessem *et al.*, 1985). As felodipine is a newer dihydropyridine the question arose if it would interact with digoxin.

In a placebo-controlled double-blind cross-over study 14 patients with congestive heart failure (NYHA stage II-III; mean age 64 ± 11 years; body weight 81 ± 19 kg; mean ± s.d.) were treated after randomized allocation for 1 week each with placebo, 10 mg felodipine as slow release tablet or 10 mg felodipine as plain tablet. All patients were on steady state therapy with digoxin 0.375 mg day^{-1}. Patients had given their informed consent to participate in the investigation. The study protocol was approved by a local hospital ethics committee. Digoxin concentrations in plasma and urine were measured by a commercially available radioimmunoassay (Diagnostic Products Corporation).

Mean trough levels of digoxin in plasma were 1.3 ± 0.5 ng ml^{-1} on placebo, 1.2 ± 0.4 ng ml^{-1} on felodipine as slow release tablet and 1.2 ± 0.4 ng ml^{-1} on the plain tablet of felodipine. Corresponding mean peak plasma concentrations were 2.7 ± 0.8 ng ml^{-1}, 2.6 ± 0.7 ng ml^{-1} and 3.0 ± 0.6 ng ml^{-1}, the areas under the plasma concentration-time curves were 19.9 ± 6.4 ng ml^{-1} h, 18.8 ± 6.2 ng ml^{-1} h and 18.2 ± 4.5 ng ml^{-1} h. Plasma clearance as well as renal clearance of digoxin were not changed on administration of both formulations of felodipine. Systolic time intervals as non-invasively measured haemodynamic parameters were not significantly altered following the slow release tablet, while the plain tablet significantly decreased the PEP/LVET ratio compared with placebo. Heart rate was slightly increased by both formulations of felodipine tablets. In conclusion felodipine as slow release tablet did not increase digoxin plasma levels in patients with congestive heart failure.

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Study of the potential pharmacokinetic interaction between ciprofloxacin and cyclosporin in man

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Ciprofloxacin is a quinolone antibiotic which has been reported to decrease theophylline clearance (Wijnands *et al.*, 1986). Inhibition of theophylline metabolism has been suggested as the mechanism of the interaction. Cyclosporin is a potent immunosuppressive agent with a narrow therapeutic index. Since theophylline and cyclosporin are both metabolized by cytochrome P-450 drug metabolizing enzymes (Robson *et al.*, 1987; Maurer *et al.*, 1984), we have performed a study to investigate whether ciprofloxacin alters the pharmacokinetics of cyclosporin in healthy volunteers.

Ten healthy male volunteers (age 28.9 ± 3.7 years and weight 73.4 ± 11.1 kg (mean ± s.d.)) were studied. The study was undertaken according to a randomized two-period cross-over design with a 6 day washout period. Each subject received oral cyclosporin (5 mg kg^{-1}) on two occasions, after no treatment or on the day 7 of an 8 day course of oral ciprofloxacin 500 mg 12 hourly. After an overnight fast, subjects were given cyclosporin in a standard chocolate drink and a standard lunch 3.5 h later. Blood samples (1 ml) were collected at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 32 and 48 h after cyclosporin administration. Whole blood cyclosporin was measured by a specific monoclonal antibody radioimmunoassay (Quesniaux *et al.*, 1986).

The cyclosporin blood concentration data was fitted to a two-compartment model. Statistical

analysis was performed using Student's *t*-test for paired data. There was no significant difference ($P > 0.05$) in the pharmacokinetic parameters estimated for cyclosporin without and during ciprofloxacin administration (Table 1).

The results of this study suggest that ciprofloxacin 500 mg twice daily would not affect the pharmacokinetics of cyclosporin to a clinically important degree.

Table 1 Pharmacokinetic parameters for cyclosporin without and during ciprofloxacin treatment (mean ± s.d.; $n = 10$)

	Cyclosporin alone	*Cyclosporin + ciprofloxacin*
Cl/F ($l\,h^{-1}\,kg^{-1}$)	0.84 ± 0.20	0.77 ± 0.15
$AUC_{(0-\infty)}$ ($\mu g\,l^{-1}\,h$)	6456 ± 1306	6704 ± 1199
t_{max} (h)	1.77 ± 0.95	1.60 ± 0.52
C_{max} ($\mu g\,l^{-1}$)	1027 ± 175	1051 ± 138
$t_{½}$ (h)	13.8 ± 6.2	13.7 ± 6.4

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Tolerance and kinetic study of intravenous medifoxamine in healthy human volunteers

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Medifoxamine is a monoamine re-uptake inhibiting antidepressant drug undergoing clinical evaluation (Randhawa *et al.*, 1987). Animal studies have shown that it undergoes extensive first pass extraction and metabolism. It is necessary, therefore, to determine its absolute bioavailability in man by giving both oral and intravenous doses. Because the drug had not been given intravenously to man, a dose-finding tolerance study was carried out to find a dose which is well tolerated and gives measurable plasma levels.

Twelve normal healthy volunteers (3M/9F) received intravenous doses of medifoxamine. Increasing single doses (5 to 100 mg) were administered to pairs of subjects. Plasma medifoxamine concentrations measured using high performance liquid chromatography (h.p.l.c.).

The results showed that single intravenous doses of medifoxamine, up to 100 mg, had no effect on heart rate, systolic or diastolic blood pressure. No subjective side effects were reported. There were no changes in vital signs or in routine laboratory tests. Medifoxamine was detected in the plasma of all subjects. The drug had a short elimination half-life which was independent of the dose, and the area under the curve (AUC) was directly proportional to the dose. The means of half-life, clearance, area under the curve and volume of distribution (V) for each dose are given in Table 1.

Table 1 The results of the study

Dose (mg)	*AUC ($\mu g\,l^{-1}\,h$)*	*AUC/mg*	*Clearance ($ml\,min^{-1}$)*	*Half-life (h)*	V *(l)*
5	73	14.5	2402	—	—
10	187	18.7	967	—	—
25	228	11.1	1625	0.68	68
50	680	13.6	1193	1.16	118
70	875	12.5	1384	1.05	123
100	1462	14.6	1322	1.37	156

Randhawa, A. *et al.* (1987). *Br. J. clin. Pharmac.*, **24**, 267P.

Topical salbutamol in atopic eczema

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β-adrenoceptor agonists suppress inflammation by a variety of mechanisms, including functional antagonism of endothelial cell contraction induced by inflammatory mediators, inhibition of mast cell disruption and suppression of leucocyte activity. In animal studies salbutamol applied topically appears to have similar potency to hydrocortisone as an anti-inflammatory agent (Sapra & Green, 1985) and might thus be useful as an alternative to corticosteroids in the treatment of some inflammatory skin conditions. However, Archer & MacDonald (1987) reported that salbutamol administered either orally or topically in white soft paraffin was ineffective in treating atopic eczema. They suggested that the lack of efficacy of topical salbutamol might be due to poor percutaneous penetration. The percutaneous absorption of salbutamol from various vehicles has been shown to be much lower from white soft paraffin than from aqueous cream (Sapra, 1986.) We have therefore compared the efficacy of topical application of 1% w/w salbutamol in aqueous cream with a matched placebo in patients with chronic atopic eczema. The study was a double-blind, within-patient comparison, of 3 weeks duration.

Children, aged 5–13 years with chronic eczema of symmetrical distribution on the limbs were admitted to the study, with informed parental consent. A full history was taken and the eczema assessed clinically on a 0–6 point scale. All previous topical medication was stopped and 1% hydrocortisone and emulsifying ointment supplied for use as required. After 1 week the eczema was reassessed and salbutamol therapy randomly allocated to one limb and placebo to the contralateral limb. Up to 1 g salbutamol cream, measured using templates, was applied twice daily and the eczema assessed 1 and 2 weeks later.

Fifteen patients completed the study, there being three withdrawals, one with a mild exacerbation. The average weekly amount of salbutamol cream used was 7.6 g, and of placebo 8.0 g. Usage of 1% hydrocortisone on other areas averaged 12.3 g weekly and did not vary significantly ($P > 0.05$) throughout the study.

As assessed by the clinician, the mean score for eczema at the start of therapy was 2.3 for both the salbutamol and the placebo treated limbs. After 2 weeks therapy it was 2.1 for the salbutamol treated limb and 1.9 for the placebo. These values were not significantly different when analysed by the Wilcoxon matched pairs signed ranks test. Patients' assessment on diary cards also showed no significant differences between salbutamol and placebo treated limbs. We conclude that topical salbutamol had no obvious beneficial effect on atopic eczema over the 2 week period.

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Patients' knowledge of and attitudes to medicines: an Irish perspective

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It is generally held that increased patient knowledge of drug therapy including methods of administration would facilitate improved compliance. A recent postal survey in Southampton (Ridout *et al.*, 1986) and a survey of patients attending Boots Pharmacies (Busson *et al.*, 1986) revealed an unsatisfactory state of knowledge about prescription medication. To determine the situation in Ireland 50 representative patients (56% female and 44% male) attending St James's Hospital were interviewed by a pharmacist.

The patients had received a mean of 3.6 (range 1 to 14) medicines dispensed by a community pharmacist. On questioning 76% indicated

that they 'always' took their medicines as directed 20% 'usually', 2% 'sometimes' and 2% 'rarely'. Although 88% of patients knew the indication for the therapy (informed in most instances by their doctor) only 40% knew the actual name of the medication. Knowledge of drug name was higher (66%) in those on monotherapy.

Only one-third of patients had been made aware of the possibility of adverse drug reactions and almost invariably by the prescriber rather than the dispensing pharmacist. Only 45% of patients had received information on the expected duration of therapy. Similarly patients only occasionally were given instructions on the storage or safe disposal of medicine left over (12%) or what to do in the event of missing a dosage (4%). In relation to possible drug interaction only 34% received information with regard to alcohol ingestion. Over half (58%) indicated that they would inform their prescriber of non-prescription medication but only 25% would inform the pharmacist.

Four out of ten patients were taking non-prescription therapy at the time of interview. A wide variety of therapy including oral hypoglycaemics, anti-epileptic and anti-hypertensive drugs had been prescribed. The majority of patients indicated that they would prefer additional information with regard to drug therapy but 30% felt that the pharmacist would not be the appropriate source. There was a greater preference for verbal discussion with the prescriber rather than written instructions and also for practical demonstration of drug use for example inhalers, eye drops.

The results of this survey suggest considerably more information could usefully be given to patients particularly in relation to drug names, method of taking medication and possible interactions. The role of the dispensing pharmacist in this regard needs to be enhanced.

Busson, M. *et al.* (1986). *Pharmaceut. J.*, **236**, 624.

Ridout, S. *et al.* (1986). *Br. J. clin. Pharmac.*, **21**, 701.

Use of the P300 event related potential in the assessment of early hepatic encephalopathy

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In recent years, event related potentials have been used in the diagnosis and grading of hepatic encephalopathy (HE). Somatosensory (Sien-Sing *et al.*, 1985), brainstem auditory (Sien-Sing *et al.*, 1986) and visual evoked responses (VER) (Zeneroli *et al.*, 1984) have all been used. The most useful has been considered to be the latency of the N3 (the 3rd negative peak in the waveform) of the VER but it is subject to great variability and is most effective in defining and interpreting the higher grades of HE. This study assessed the value of the P300 (a positive event related potential component occurring between 200 and 700 ms) in early HE.

Twenty-six patients, ranging in age from 33 to 72 years, were assessed clinically and psychometrically (star-scores and trail times). Star-scores were derived by assessing a 5 pointed star drawn by the patient as described by Zeegan *et al.* (1970); the time taken to complete standard number connection tests constituted the trail times. The control patient group consisted of 15 non-encephalopathic, biopsy proven cirrhotics and the test group was composed of 11 early encephalopathic cirrhotics (Grades 1–2; U.S., 1976). Each patient had a VER, using the flashing light mode and an auditory P300, using the odd-ball two-tone discrimination paradigm, performed. The latencies of the VER N3 and the P300 were measured. There was a significant difference between the latency of the P300 in stable and encephalopathic patients as shown in Table 1.

It is concluded that the P300 latency was more sensitive in HE than the VER N3. It appears that the P300 may have a use as a quantitative aid in the assessment of the early stages of hepatic encephalopathy.

Table 1 Psychometric and event related potential measures in cirrhotic patients (mean ± s.e. mean)

	Non-encephalopathic	*Encephalopathic*
Star-score (max 20)	14.1 ± 0.6	8.6 ± 1.2
Trail time (s)	47 ± 3.5	142 ± 23.1*
VER N3 (ms)	220 ± 17	246 ± 22
P300 (ms)	342 ± 7	409 ± 8*

* $P < 0.05$ (Student's *t*-test).

Sien-Sing, Y. *et al.* (1985). *Hepatology*, **6**, 1352.
Sien-Sing, Y. *et al.* (1986). *Gastroenterology*, **89**, 625.
U.S. D. H. E. W. (1976). *Fogarty International Centre Proceedings* 22 No. 76-725.
Zeegan, R. *et al.* (1970). *Br. med. J.*, **2**, 633.
Zeneroli, M. L. *et al.* (1984). *Gut*, **25**, 291.

Plasma protein binding of lignocaine and warfarin in non-insulin dependent diabetes mellitus

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Alterations in the plasma protein binding of drugs may influence the amount of free drug available to sites of drug action and biotransformation. Two studies in Type 1 insulin-dependent diabetic patients (Ruiz-Cabello & Erill 1984; Barry *et al.*, 1986) have demonstrated reduced binding of both acidic drugs, diazepam, sulphasoxazole (Ruiz-Cabello & Erill, 1984) and warfarin (Barry *et al.*, 1986) and the basic drug lignocaine (Barry *et al.*, 1986). We therefore examined plasma protein binding of warfarin and lignocaine in maturity onset diabetics (Type II non-insulin dependent).

We determined plasma protein binding in 15 maturity onset diabetics (aged 59 ± 3 years, mean ± s.e. mean) treated with diet alone (n = 7) and diet plus oral hypoglycaemics (n = 8) and 10 controls (age 58 years ± 5 years) patients. Glycosylated haemoglobin HbA1 was 9.6 ± 0.7% in the former and 6.6 ± 0.4% in the latter ($P <$ 0.05).

Drug binding was performed by equilibrium dialysis. ^{14}C-radiolabelled drug solutions were added to serum to yield concentrations of 2.5 μg ml^{-1} of warfarin and 1 μg ml^{-1} of lignocaine. Protein binding was determined at 37° C following 4 h equilibrium dialysis against Na_2HPO_4 buffer pH 7.45, using semi-macrocells and a semipermeable membrane, molecular weight cut off of 10,000.

The results are shown in Table 1. There was no statistically significant difference in protein binding of warfarin or lignocaine in maturity onset diabetics compared with controls.

In contrast with our earlier finding of a 37% increase in free lignocaine and a 20% increase in free warfarin in insulin dependent diabetics (Barry *et al.*, 1986) the binding of these drugs does not appear to be altered in Type II diabetes mellitus.

Table 1 Protein binding (mean % ± s.e. mean) of lignocaine and warfarin in non-insulin dependent diabetics

	Control (n = *10*)	*Diabetic* (n = *15*)	P
Lignocaine	68 ± 2	70 ± 1	NS
Warfarin	98.9 ± 0.05	99.0 ± 0.03	NS

Ruiz-Cabello, F. & Erill, S. (1984). *Clin. Pharmac. Ther.*, **36**, 691.
Barry, M. *et al.* (1986). *Br. J. Pharmac.*, **89**, 719.

Indocyanine green estimated liver blood flow in chronic liver disease: bolus *vs* steady-state infusion

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Indocyanine green (ICG) is highly extracted by the liver and its systemic clearance is widely used to estimate liver blood flow (LBF). The two commonly used methods for measurement of clearance are the continuous infusion technique employing the Fick principle and clearance calculated from the monoexponential decay in ICG levels following a single intravenous injection (Caesar *et al.*, 1961). The latter is attractive because it is less time consuming and does not involve hepatic vein catheterization. However, it has not to date been adequately compared with the standard continuous infusion technique. Furthermore, the one compartmental monoexponential model may not represent the best fit of plasma concentration-time data (Christie *et al.*, 1986).

The aims of our study were to compare single ICG bolus with steady state clearance in patients with chronic liver disease (CLD) and also to identify the model that would best fit the plasma ICG concentration-time curve.

We studied 14 patients with established CLD (seven female, seven male, mean age ± s.d., 50 ± 4 years). ICG was administered as a rapid intravenous bolus (0.25 mg kg^{-1}) and peripheral blood samples obtained at intervals up to 40 min. Immediately after this a continuous infusion of ICG was begun at a rate of 0.45 mg min^{-1}. After an equilibration period steady state samples were obtained. In 11 patients the extraction ratio of ICG was determined following hepatic vein catheterisation. ICG plasma concentrations were measured by a spectrophotometric method (Caesar *et al.*, 1961).

In the single injection technique ICG kinetics were analysed by linear regression analysis and 11 patients' data were best fitted by a monoexponential curve. There was a strong positive correlation ($r = 0.94$, $P < 0.001$) between clearance values obtained from the monoexponential curve and those obtained using non-compartmental area under the concentration-time curve (AUC) analysis. In three patients data was best fitted by a biexponential curve. However the % difference in fitting this data monoexponentially in calculating clearance was less than 5%. There was no significant difference between the clearance values obtained using single injection (209 ± 40 ml min^{-1}, mean ± s.d.) and continuous infusion (194 ± 36 ml min^{-1}) and there was a close correlation ($r = 0.95$, $P < 0.001$) between both methods. Where extraction ratio was measured LBF estimates by both techniques were in good agreement ($r = 0.8$, $n = 11$, $P < 0.05$) and again single injection data tended to overestimate LBF. Omission of extraction ratio led to inaccurate estimates of LBF as the extraction ratio was only 20% in many patients.

Although there is some controversy concerning the most appropriate method of assaying ICG (Christie *et al.*, 1986) and it is possible that h.p.l.c. analysis would facilitate the accurate detection of low levels of plasma ICG the contribution of such data to AUC assessment of clearance is small. In practical terms this data suggests that sampling up to 20 min following single injection and calculation of clearance using a non-compartmental AUC method reliably estimates ICG clearance (and LBF provided extraction ratio is measured) in patients with chronic liver disease.

Caesar, J. *et al.* (1961). *Clin. Sci.* **21**, 43.
Christie, J. P. *et al.* (1986). *Br. J. clin. Pharmac.*, **21**, 568 P.

Inhibition of drug metabolism by allopurinol

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Allopurinol, an analogue of hypoxanthine, is an effective drug used in the treatment of both the primary hyperuricaemia of gout and that secondary to haematological disorders or antineoplastic therapy. It inhibits the enzyme xanthine oxidase by both competitive and non-competitive mechanisms. Allopurinol may also interfere with hepatic microsomal enzymes resulting in inhibition of metabolism of other drugs. However the effect is reported as variable and the clinical significance unclear (Vessel *et al.*, 1970).

Recently we observed a patient on long term warfarin treatment demonstrate a 42% increase in prothrombin ratio after 2 days of allopurinol therapy and a second patient on concomitant theophylline treatment showed a 38% increase in peak plasma levels of theophylline after a similar duration of allopurinol treatment. Although isolated case reports of such interactions have been described before we wished to determine the effect of allopurinol on hepatic drug metabolism.

Using the [^{14}C]-aminopyrine breath test (Henry *et al.*, 1979) as an index of oxidative drug metabolism we studied five patients (five male, mean age 57 years) with hyperuricaemia. Each patient was studied before and 2 days after commencing allopurinol 100 mg day^{-1}. Following intravenous administration of 2 μCi [^{14}C]-aminopyrine 2 mmol of exhaled $^{14}CO_2$ were collected in a liquid scintillation vial containing 4 ml of 1M hyamine-ethanol 1:1 (vol/vol) with phenolphthalein as indicator. Breath samples were collected at 30 min intervals over 4 h. The half-life of $^{14}CO_2$ was calculated from a semilogarithmic plot of the breath specific activities, beyond 2 h. Allopurinol treatment resulted in an increase in the mean [^{14}C]-aminopyrine half-life by 44% (Table 1).

These results indicate that allopurinol impairs hepatic *N*-demethylation of aminopyrine. It is possible that the effect of allopurinol on oxidative metabolism is greater than hitherto appreciated.

Table 1 [^{14}C]-aminopyrine half-life (min) in hyperuricaemic patients following allopurinol treatment (mean ± s.e. mean, $n = 5$)

Pretreatment	*Post-treatment*	
72 ± 12.9	104 ± 16.5	$P < 0.05$

Henry, D. *et al.* (1979). *Br. J. clin. Pharmac.*, **8**, 539.

Vessel, E. S. *et al.* (1970). *New Engl. J. Med.*, **283**, 1484.

Intravenous pentoxifylline increases tissue oxygenation in the treatment of established ischaemic rest pain

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It may be possible to achieve symptomatic relief of rest pain and improvement in tissue nutrition by increasing oxygen delivery to ischaemic tissue. Ehrly (1979) has proposed that tissue oxygenation may be improved by pentoxifylline. We carried out an open pilot study to evaluate the role of intravenous pentoxifylline in the management of ischaemic rest pain.

Twenty patients (four diabetics) with a mean age 68.4 years, and suffering from established rest pain for at least 4 weeks were enrolled into the study; each had Fontaine stages 3 or 4 disease and had angiographic evidence of two or more limb arterial segments occluded and were therefore candidates for limb salvage surgery which is usually necessary in the vast majority of such patients. Each member of the study received 600 mg pentoxifylline by slow i.v. infusion twice daily for 3 weeks. Systolic pressure measurements and transcutaneous oxygen tension (tc Po_2) measurements were made before, during and after the study period, the technicians being blind to clinical results. Pain evaluation was performed by self assessment using a linear analogue scale.

Pain was significantly reduced after treatment (mean score 53.2 and 28.1; $P < 0.001$). Ten patients obtained sufficient pain relief to avoid surgical intervention and seven of these had complete or near complete resolution of rest pain. In those patients with symptomatic improvement mean tcPo_2 values on the dorsum of the foot were 22.3 ± 16.8 mm Hg (pre-study) and 30.9 ± 17.1 mm Hg (post-study); $t = 2.9$, $P < 0.02$ using two tailed paired *t*-test. Pain relief correlated well with the observed increase in mean tcPo_2 values ($r = 0.839$). Those who required surgical intervention showed no improvement in either tcPo_2 values or pain indices. There was no significant change in ankle systolic pressures in any of the patients. Significant side effects were found in six patients

necessitating early withdrawal from the study due to nausea and vomiting. Ten patients required operation because of insufficient or no response to medication.

These preliminary results suggest that i.v. infusion of pentoxifylline was associated with a significant increase in tissue oxygen availability in many ischaemic limbs thus obviating the need for surgery. The 50% avoidance rate for surgery is notable. The improvement in tissue oxygenation may provide a possible explanation for the improvement in symptomatology seen in this study. A double-blind controlled trial is now under way to examine this relationship in more detail.

Ehrly, A. M. (1979). *J. Med.*, **10**, 331.

Effects of intravenous and oral nifedipine on *ex vivo* platelet function

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Platelets are important in the pathophysiology of myocardial ischaemia by forming thrombi and releasing thromboxane A_2. Ca^{2+} channel blockers have an antiplatelet effect *in vitro* and *ex vivo* which may be of additional benefit to their haemodynamic effects in patients with acute myocardial ischaemia. We studied the *ex vivo* antiplatelet effect of an intravenous (i.v.) nifedipine (N) preparation in normal subjects compared with oral dosing, using single platelet counting in whole blood.

i.v. trial: six subjects (aged 39 ± 5 years, mean ± s.e. mean) were given i.v. N (10 mg% in 15% polyethylene glycol, 15% ethanol and 70% water), the vehicle alone or saline in a double-blind randomised cross-over fashion on separate days at least 1 week apart. The dose of N (0.75 mg bolus and 1.2 mg h^{-1} for 2 h, or equivalent volumes of vehicle alone or saline) was chosen because it causes modest haemodynamic changes and can be safely given to patients with acute myocardial infarction (Walley *et al.*, 1987). Blood was taken for platelet function assay before N and after 2 h, and for plasma N level at 2 h.

Oral trial: In a similar study, 12 subjects (aged 31 ± 3 years) were given 20 mg oral slow release N or identical placebo. Blood was taken for platelet function assay before treatment and again at 2 and 8 h, and for plasma N level at 2 and 8 h.

Platelet function was measured by counting the number of platelets lost from whole blood using an Ultra Flo 100 platelet counter, 2 min after the addition of ADP 2, 5 and 10 μM or collagen 1 and 2 μg ml^{-1}, and 10 min after the addition of adrenaline 1, 5 and 10 μM. Results were analysed by Kruskal Wallis analysis of variance and Wilcoxon signed rank test.

I.v. N, its vehicle alone or saline had no effect at the doses studied on platelet aggregation by any of the agonists. Oral N in contrast inhibited aggregation to collagen at 2 h (maximum inhibition 17 ± 6%, $P \leq 0.05$) and 8 h (maximum 19 ± 8%, $P \leq 0.05$), but not to ADP or adrenaline.

The plasma N level at 2 h on infusion was 18.5 ±1.9 ng ml^{-1}, and on oral N 21.5 ± 3.8 and 8.1 ± 1.1 ng ml^{-1} at 2 and 8 h respectively. These 2 h levels do not differ significantly, and therefore the lack of effect of i.v. N is probably due to the vehicle. The vehicle alone has an *in vitro* antiplatelet effect similar to that of N itself (Walley *et al.*, 1988). However *in vivo* the vehicle causes thrombophlebitis (Walley *et al.*, 1987), which may increase platelet aggregability and overcome any direct antiplatelet effect. The effect *ex vivo* at plasma N levels of 21 ng ml^{-1} (= 0.05 μM) contrasts with the level needed for an effect *in vitro* (20–30 μM). This study confirms the preferential effect of N in inhibiting collagen induced aggregation. I.v. N given in haemodynamically appropriate doses to patients with acute coronary syndromes is unlikely to have a significant antiplatelet effect.

Walley, T. *et al.* (1987). *Clin. Cardiol.*, **10**, 800.
Walley, T. *et al.* (1988). *Br. J. clin. Pharmac.*, **26**, 642P.

Effects of calcium channel blockers on *in vitro* platelet function in whole blood using single platelet counting

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Calcium (Ca^{2+}) is important in platelet activation. Ca^{2+} channel blockers have an antiplatelet effect, although drug concentrations required to demonstrate this effect are much higher *in vitro* than *in vivo*. Whole blood techniques may be more sensitive in detecting this antiaggregatory effect than optical aggregation in platelet rich plasma (Jeremy *et al.*, 1985). We therefore studied the effects of diltiazem (D), verapamil (V) and the dihydropyridines nifedipine (Nif) and nimodipine (Nim) and their solvents on *in vitro* platelet aggregation in whole blood measured by single platelet counting (Bevan & Heptinstall, 1985).

D and V were dissolved in normal saline, and Nif and Nim in 15% polyethylene glycol, 15% ethanol and 70% water (this solvent is the vehicle for the intravenous preparation of nifedipine), all to a concentration of 1 mg ml^{-1}. Drugs were added to blood (taken from six normal drug-free subjects aged 21–31 years) to give end concentrations of 3, 30 and 90 μM. The appropriate solvents were used in equivalent volumes as controls. The blood was then incubated at 37° C for 30 min. Platelet aggregation was measured by counting the number of platelets lost from whole blood 2 min after the addition of ADP 5 μM and collagen 2 μg ml^{-1}, and 10 min after the addition of adrenaline 5 μM using an Ultra Flo 100 platelet counter. Results were analysed by Kruskal Wallis analysis of variance and non-parametric comparisons between groups.

30 μM and 90 μM D and V inhibited platelet aggregation induced by collagen in a concentration dependent fashion compared with the saline control (maximum inhibition by D 61 ± 13% $P < 0.02$ and V 52 ± 14% $P < 0.05$). D and V similarly inhibited the response to adrenaline (maximum inhibition by D 19 ± 4% $P < 0.01$, and V 22 ± 4% $P < 0.01$). Nif and Nim also inhibited aggregation by these agonists in a concentration dependent fashion (maximum inhibition to collagen by Nif 97 ± 7% and Nim 87 ± 2% and to adrenaline by Nif 70 ± 1% and Nim 70 ± 4%). This inhibition did not differ significantly from that caused by the PEG/ethanol/water solvent alone, which also inhibited aggregation to these agonists in a concentration dependent manner (maximum inhibition to collagen 78 ± 5% and to adrenaline 69 ± 8%). No drug or solvent affected ADP induced aggregation.

Aggregation inhibition by nifedipine is more readily shown in whole blood than in platelet rich plasma (Jeremy *et al.*, 1985), perhaps because it is closer to the physiological situation. Despite using a sensitive whole blood technique in this study, high concentrations of V and D were still needed to show an effect *in vitro*.

No independent antiplatelet effect of the dihydropyridines has been shown in this study. The antiaggregatory effect of the PEG/ethanol/water solvent may be due to the resulting whole blood ethanol concentrations of 12, 122 and 367 mg dl^{-1}, as ethanol inhibits aggregation to adrenaline and collagen at plasma concentrations greater than 200 mg dl^{-1} (Mikhailidis *et al.*, 1983).

Bevan, J. & Heptinstall, S. (1985). *Thrombosis Res.*, **38**, 189.

Jeremy, J. Y. *et al.* (1985). *Drugs exp. clin. Res.* **9**, 645.

Mikhailidis, D. P. *et al.* (1983). *Br. med. J.*, **287**, 1495.

The pre-eminence of nicotine *N*-oxidation and its diminution after carbimazole administration

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Despite the social, economic and clinical importance of the principal tobacco alkaloid nicotine, its quantitative metabolic disposition in man has not been fully elucidated. That the C-oxidation product cotinine is the major human metabolite is accepted dogma and this forms the basis of its use as a 'biomonitor' of tobacco exposure. In addition to cotinine, various *N*-oxides of nicotine have been detected. In the light of our recent discovery of a rare inherited defect of *N*-oxidation of both trimethylamine and nicotine (Al-Waiz *et al.*, 1987; Ayesh *et al.*, 1988), the aim of the present study was to obtain a more complete

metabolic profile for nicotine in man and to determine the effect of the *N*-oxidation inhibitor carbimazole upon its metabolism.

Six healthy non-smoking male volunteers, aged 22–29 years consented to the study which was approved by the local Health Authority ethics committee. Each individual was studied on three separate occasions as follows: (i) with nicotine alone, (ii) with a single oral dose of carbimazole (20 mg) 1 h before nicotine, and (iii) with nicotine alone. At least 72 h elapsed between each dose of nicotine which was given as a chewing gum preparation (Nicorette) containing nicotine (4 mg), chewed over 20 min. Urine samples were collected 0–8 and 8–24 h post-dose and were analyzed for their nicotine and cotinine content by capillary gas chromatography with nitrogen selective detection, with and without reduction of *N*-oxides with titanium (III) sulphate. The following were thereby determined: nicotine, continine, nicotine *N*-oxides (NNOs) and cotinine *N*-oxide. Results for the two control days were averaged.

There was no significant difference between the % dose (± s.d.) excreted on control (16.7 ± 18.4) and carbimazole pretreatment (6.7 ± 3.5) days. The pattern of metabolites on control and pretreatment days respectively, expressed as relative % dose (± s.d.), was nicotine (13.3 ± 7.7; 15.6 ± 11.0), cotinine (14.5 ± 9.6; 26.5 ± 15.3), NNOs (60.2 ± 5.9; 50.4 ± 24.7) and cotinine *N*-oxide (12.1 ± 6.7; 7.5 ± 7.8). None of the differences seen after carbimazole administration was statistically significant; however, a strong negative correlation emerged between the carbimazole associated fall in NNOs excretion and the concomitant rise in cotinine excretion ($r = 0.916$, $P = 0.01$).

The above findings suggest that after administration of 4 mg nicotine, approximately 60% of the elimination occurs as NNOs compared with only 14.5% as cotinine. In addition, the coefficient of variation of NNOs excretion was low (<0.1), compared with 0.55–0.66 for the other metabolites. The data show that the pre-eminent route of urinary excretion of nicotine is as nitrogen oxidation products and that a minor but significant metabolic switching from *N*- to C-oxidation can occur after carbimazole administration.

Both the quantitative importance of the NNOs as urinary metabolites and their low coefficient of variation relative to cotinine illustrate the potential utility of determining collective urinary nicotine *N*-oxides in the biomonitoring of tobacco exposure.

Al-Waiz, M. *et al.* (1987). *Clin. Pharmac. Ther.*, **42**, 588.

Ayesh, R. *et al.* (1988). *Br. J. clin. Pharmac.*, **25**, 664P.

The effect of age on platelet intracellular free calcium concentration

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Judgment analysis (JA) as a technique for providing individualized assessments of quality of life (QOL)

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Increasingly therapeutic interventions are evaluated by their impact on patient QOL (e.g. hypertensive medication; Croog *et al.*, 1986). Most QOL measures however impose an external value system rather than seeking to measure QOL in terms important to each individual. The present pilot study examined individual QOL assessments and examined JA as a method of obtaining meaningful, quantifiable and individualized assessment of QOL. JA is a technique whereby the relative influence of a number of factors on a choice or decision can be estimated (e.g. clinical judgment in arthritis; Kirwan *et al.*, 1983). Normal individuals ($n = 10$) were asked to nominate the five most important aspects of their

lives. Possible life scenarios (40 cases) involving these five aspects were then presented and individuals asked to judge what their QOL would be given a particular life scenario. Analysis provided a profile of the relative weighting (range 0.0–1.0) of each of the five factors in judgments about QOL. This exercise was repeated using five life aspects drawn from current QOL measures (i.e. physical, social and emotional functioning, living conditions and general health).

A total of 11 different aspects of life were considered important by various individuals in assessing their QOL; health (10), work (8), finances (6), relationships (5), social life (5), family (4), religion (4), living conditions (3), contentment (3), independence (1) and education (1). Health was the only QOL aspect considered important by every individual. Its relative weighting in QOL decision making averaged 0.25 (range 0.09–0.34). In all the five nominated aspects explained two-thirds of the QOL decision making variability on average (r^2 = .67). When individuals were provided with five life aspects considered important in QOL research generally and asked to make QOL decisions using these, the relative weighting of each aspect differed considerably between individuals. No two individuals provided even the same rank ordering of importance of the five aspects. In all use of the five provided aspects accounted for 64% of QOL decision making variability.

Results illustrate the widely differing values given by individuals to a variety of life aspects when evaluating their QOL. Given such variability the validity for pharmacology of QOL measures with the provision of both standard lists and standard weightings of life aspects is questionable. As seen here the JA method can be used to improve QOL assessment since it allows both individual nomination of relevant life aspects and individual weighting of life aspects in QOL measurement.

Croog, S. H. *et al.* (1986). *New Engl. J. Med.*, **314**, 1657.

Kirwan, J. R. *et al.* (1983). *Ann. Rheum. Dis.*, **42**, 648.

Effects of SK&F 101468, a novel dopamine D_2-receptor agonist, on supine plasma prolactin and haemodynamics in normal man

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SK&F 101468 (4-[2-(dipropylamino)ethyl]-1, 3-dihydro-2H-indol-2-one, monochloride) has been characterized in animal studies as a potent and highly selective agonist at dopamine D_2-receptors (Gallagher *et al.*, 1985), therefore offering potential advantages over existing dopamine agonists. In a single-blind, placebo-controlled, rising-dose study, fourteen healthy male volunteers received oral doses of SK&F 101468 solution ranging from 10 μg to 2500 μg. Measurements of plasma prolactin concentrations were made at intervals between 0 to 4 h and at 6, 8 and 24 h post treatment. Measurements of supine pulse rate and blood pressure were made at 15 min intervals for 6 h post treatment. Subjects were given a standard meal at 4 h.

SK&F 101468 produced a statistically significant dose dependent lowering of basal plasma prolactin concentrations when the area under the plasma prolactin-time curves were compared for treatment in the range 80 μg to 2500 μg and for placebo from 0–4 h (Table 1).

In addition, doses of 640 μg to 2500 μg consistently inhibited meal-induced stimulation of prolactin secretion as shown when the area under the plasma prolactin-time curves were compared for treatment and placebo from 4–6 h. There were no clinically significant changes in supine heart rate or blood pressure due to treatment, although there were small statistically significant increases in heart rate at higher doses of SK&F 101468. Short lasting nausea was apparent in some subjects at doses of 1250 μg and above, but otherwise the drug was well tolerated and there were no clinically significant effects on routine laboratory screening.

SK&F 101468 demonstrates potent dopamine D_2-receptor agonism in healthy man and is about to enter clinical trials to evaluate the CNS activity of the compound.

Table 1 Model derived differences from placebo in mean AUC, 0–4 h

Dose of SK&F 101468 (μg)	Number of subjects	Mean AUC, 0–4 h difference from placebo (μiu ml^{-1})	Approximate 95% confidence interval	
			Upper	Lower
10	2	−4.40	47.2	−56.52
20	2	−9.50	42.01	−61.01
40	4	−19.40	14.46	−53.26
80	5	−47.90	−16.91	−78.89
160	5	−45.00	−15.66	−74.34
320	7	−68.70	−43.26	−94.14
640	8	−86.90	−62.28	−111.52
1000	2	−117.40	−70.00	−164.80
1250	4	−86.20	−51.93	−120.47
1850	1	−68.00	−5.21	−130.79
2500	1	−77.00	−13.39	−140.61

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The kinetics of oxidation of metoprolol enantiomers by human liver microsomes

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Metoprolol (M) is oxidized by the form of cytochrome P450 responsible for the polymorphic oxidation of sparteine and debrisoquine (P450-SP/DB). Inhibition by the quinidine/quinine isomer pair as an *in vitro* marker of the activity of P450-SP/DB has indicated that this enzyme catalyses the α-hydroxylation of M, but is only partly responsible for M *O*-demethylation (Otton *et al.*, 1988). These studies have been extended to investigate the kinetics of the oxidation of M enantiomers by human liver microsomes.

Microsomes prepared from the livers of three renal transplant donors (HL3, HL4 and HL9) were incubated with 20 concentrations of (S)-M or (R)-M lying between 5 μM and 2000 μM. α-Hydroxymetoprolol (HM) and *O*-demethylmetoprolol (ODM) were assayed by h.p.l.c. The data were fitted by both one- and two-site enzyme activity models using the method of extended least squares.

The kinetics of HM formation by microsomes from livers HL4 and HL9 were described adequately by a one-site model. The Michaelis-Menten constants calculated for microsomes from HL4 were: K_m = 41 μM, V_{max} = 0.80 nmol mg^{-1}microsomal protein 20 min^{-1} when (R)-M was the substrate, and K_m = 69 μM, V_{max} = 1.19 nmol mg^{-1} 20 min^{-1} when (S)-M was the substrate. For microsomes from liver HL9, the values were K_m = 69 μM, V_{max} = 1.15 nmol mg^{-1} 20 min^{-1} and K_m = 67 μM, V_{max} = 1.32 nmol mg^{-1} 20 min^{-1} for (R)-M and (S)-M, respectively. Microsomes from liver HL3 did not produce detectable amounts of HM and nor did those from HL4 and HL9 when incubations were repeated in the presence of 100 μM quinidine. The *O*-demethylation of M by microsomes from livers HL4 and HL9 was biphasic, whereas the kinetics of this reaction in HL3 microsomes were best fitted by the one-site model (Table 1). When the incubations of HL4 and HL9 microsomes were repeated in the presence of 100 μM quinidine, the kinetics of ODM formation were monophasic and the Michaelis constants were similar to those for the low affinity/high capacity site observed in the absence of quinidine.

The biphasic kinetics of M *O*-demethylation *in vitro* are compatible with the formation of ODM at more than one enzyme site. Cytochrome P450-SP/DB appears to catalyse the high affinity/low capacity component. This component can be further distinguished by its sensitivity to inhibition by quinidine and its absence in microsomes from a putative poor metaboliser liver (HL3).

Table 1 Apparent K_m (μM) and V_{max} (nmol mg^{-1} 20 min^{-1}) values for the *O*-demethylation of M by human liver microsomes

Liver specimen	*(R)-Metoprolol*				*(S)-Metoprolol*			
	K_{m_1}	V_{max_1}	K_{m_2}	V_{max_2}	K_{m_1}	V_{max_1}	K_{m_2}	V_{max_2}
Control								
HL4	645	18.9	10.8	1.3	1378	28.1	63.1	3.1
HL9	2843	29.3	42.6	4.3	836	20.8	46.1	2.4
HL3	1899	20.4	—	—	1164	17.1	—	—
With quinidine								
HL4	956	20.8	—	—	943	29.3	—	—
HL9	1211	17.5	—	—	1530	26.1	—	—

Otton, S. V. *et al.* (1988). *Br. J. clin. Pharmac.*, **25**, 644P.

Influence of pH on the buccal absorption of captopril

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When given perorally captopril takes 1–2 h to achieve a maximal therapeutic effect. This delayed onset time may be unacceptable in the treatment of hypertensive crisis or severe heart failure. It has been suggested that absorption of captopril across the oral mucosa would lead to a more rapid onset of pharmacological effect. Two recent studies have shown that if the normal captopril tablet is used sublingually there is a marked decrease in systolic and diastolic blood pressure, beginning at 2–5 min (Tschollar & Belz, 1985; Hauger-Klevene, 1986). These findings have recently been disputed (Dessi-Fulgheri *et al.*, 1987). Most reently McMurray & Struthers (1988) have reported a significant increase in plasma renin activity after use of sublingual captopril. The present study was designed to examine the influence of pH on the buccal absorption of captopril. Such information would be of value in the development of a formulated product of captopril for buccal/sublingual administration.

Six healthy male volunteers (age range 21–31 years) took part in this randomised, double-blind study which was approved by the Ethics Committee, The Queen's University of Belfast. The buccal partitioning model of drug absorption, first reported by Beckett & Triggs (1967), was used to examine the absorption of captopril (2 mg) at seven different pHs namely 3,4,5,6,7,8 and 9. This method involved placing a buffered captopril solution in the mouth and circulating it for 5 min. After this absorption period the solution was collected and the amount of drug remaining was quantified using reverse phase h.p.l.c. with u.v. detection.

The absorption results are pesented graphically in Figure 1.

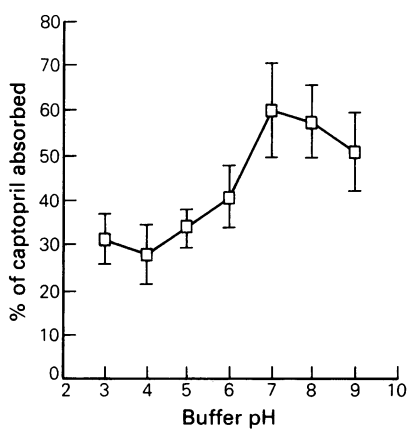

Figure 1 Influence of pH on captopril buccal absorption (mean of six volunteers ± s.e. mean).

From the results it can be seen that captopril was well absorbed between pH 6 and 9. Since this range incorporates the normal salivary pH and since captopril is soluble in saliva, the drug in its current formulation should be readily absorbed across the buccal membranes after sublingual administration.

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An examination of the possible pharmacokinetic interaction of trimetazidine with theophylline, digoxin and antipyrine

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Trimetazidine (TMZ), 1-(2,3,4-trimethoxybenzyl) piperazine dihydrochloride is an anti-anginal drug used in the treatment of various vascular ischaemic diseases. It improves performance capacity in angina pectoris as shown by duration of exercise, total work performance and improvement in ECG signs of ischaemia (Sellier *et al.*, 1987). TMZ has a novel mode of action, different from the β-adrenoceptor-blocker, nitrate and calcium antagonist group of drugs. The cardioprotective role of TMZ in cardiac ischaemia is due to its antioxidant action in preventing the damage induced by oxygen free radicals (Maridonneau-Parini & Harpey, 1985). The purpose of the present study was to investigate the possible pharmacokinetic interaction between TMZ, theophylline (TH) and digoxin (DG). The opportunity was also taken to examine the effect of TMZ on antipyrine (AP) pharmacokinetics to determine if it could act as either an inducer or inhibitor of drug hydroxylation reactions.

Thirteen male subjects aged 19–35 years took part in the study which lasted 39 days, during which they had TMZ tablets (20 mg twice daily) from day 15 till day 39. Blood samples were collected up to 24 h for oral TH (375 mg) pharmacokinetics on day 1 and 29 and up to 48 h on day 3 and 31 for oral DG (0.5 mg) pharmacokinetics. AP (500 mg) was administered orally as a solution on days 8 and 36 and saliva collected at intervals up to 33 h after dosing. TH and AP concentrations were measured by h.p.l.c. and DG by radioimmunoassay.

The pharmacokinetics of each of the drugs determined by iterative weighted least squares regression using BIOV (Ings *et al.*, 1980) before and after TMZ treatment were compared by two-way ANOVA and 95% confidence intervals.

The half-life of AP in saliva before and after TMZ treatment was not significantly different with 95% confidence for half-life after TMZ ranging from between 9.5% less than to 35.4% greater than before TMZ.

It was concluded, therefore, that there was no pharmacokinetic interaction between repeated doses of TMZ and both TH and DG. In addition, it would appear from the AP half-life that TMZ is neither an inducer nor inhibitor of drug hydroxylation.

Table 1

	Treatment					
	Theophylline			*Digoxin*		
Parameter	*Before TMZ*	*During TMZ*	P	*Before TMZ*	*During TMZ*	P
Cp_{max} (μg ml^{-1})	9.66 ± 1.7	9.7 ± 1.2	NS	0.0023 ± 0.008	0.0023 ± 0.008	NS
t_{max} (h)	1.2 ± 0.5	1.1 ± 0.5	NS	1.3 ± 0.5	1.0 ± 0.4	NS
Terminal $t_{½}$ (h)	6.5 ± 1.8	6.8 ± 1.8	NS	30.8 ± 17.3	41.0 ± 35.3	NS
AUC (μg ml^{-1} h)	98.8 ± 31.7	107.2 ± 31.7	NS	0.022 ± 0.010	0.026 ± 0.015	NS

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Stereospecific pharmacokinetics of cromakalim enantiomers at various oral dose levels, in healthy male subjects

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Cromakalim, BRL 34915, (±) 6-cyano-3,4-dihydro-2,2-dimethyl-trans-4- (2-oxo-1-pyrrolidinyl)-2H-benzo-[b]-pyran-3-ol, is a structurally novel orally active antihypertensive agent which acts via potassium channel activation (Hamilton *et al.*, 1986). Chemically, cromakalim is a racemate consisting of an equal mixture of its (+)- and (−)-enantiomers, BRL 38226 and BRL 38227, respectively. We have recently shown, in six healthy male subjects, that the pharmacokinetics of the enantiomers of cromakalim following a repeat dose study are similar to those which would have been predicted using single dose data (Gill *et al.*, 1988a). The purpose of this investigation was to extend these initial findings and determine the pharmacokinetics of the enantiomers following the oral administration of cromakalim at several dose levels.

Four healthy male subjects were each administered single oral doses of 0.5, 1.0, 1.5 and 2.0 mg of cromakalim, at 7 day intervals. The plasma from multiple blood samples collected up to 96 h, following each cromakalim dose, was assayed for BRL 38226 and BRL 38227 content by chiral capillary gas chromatography-mass spectrometry (Gill *et al.*, 1988b). The pharmacokinetic parameters for each enantiomer were calculated using standard methodology and are presented in Table 1.

These data are consistent with the pharmacokinetics of BRL 38226 and BRL 38227 being independent of dose over the range 0.5–2 mg, and the terminal phase half-life values support a once daily dosing regimen for cromakalim.

Table 1 Pharmacokinetic parameters (mean ± s.d.) of BRL 38226 and BRL 38227 in four healthy male subjects following the oral administration of cromakalim at four dose levels

Cromakalim dose (mg)	C_{max} *(ng ml^{-1})*		t_{max} *(h)*		$t_{1/2}$ *(h)*		*AUC (ng ml^{-1} h)*	
	BRL 38226	*BRL 38227*	*BRL 38226*	*BRL 38227*	*BRL 38226*	*BRL 38227*	*BRL 38226*	*BRL 38227*
0.5	1.2 ± 0.1	3.1 ± 0.6	5.0 ± 1.4	3.5 ± 1.0	28.4 ± 6.3	18.1 ± 1.1	45.3 ± 12.6	64.4 ±14.5
1	2.3 ± 0.4	6.3 ± 2.0	4.5 ± 1.3	3.0 ± 0.8	27.4 ± 7.2	19.2 ± 1.5	87.9 ± 22.3	131 ± 35.9
1.5	4.7 ± 1.0	9.5 ± 1.5	6.5 ± 2.5	4.8 ± 3.6	19.8 ± 4.2	18.6 ± 4.4	156 ± 56.9	251 ± 89.3
2	6.0 ± 1.0	13.2 ± 1.8	4.0 ± 1.4	2.5 ± 0.6	22.0 ± 3.5	19.1 ± 2.1	186 ± 49.8	305 ± 68.6

Gill, T. S. *et al.* (1988a). *Br. J. clin. Pharmac.*, **25**, 669P.
Gill, T. S. *et al.* (1988b). *Br. J. clin. Pharmac.*, **26**, 227P.
Hamilton, T. C. *et al.* (1986). *Br. J. Pharmac.*, **88**, 103.

Effect of captopril on intraocular pressure (IOP) in healthy human volunteers

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Angiotensin-converting enzyme activity has been found to be present in aqueous humour (Vita *et al.*, 1981), in the choroid and ciliary body (Igic & Kojovic, 1980) of human eyes and in homogenates of the retina and retinal vessels of swine (Ward *et al.*, 1979). Its role in regulation of IOP is not yet clear.

Angiotensin (15–20 μg), injected into the vitreous body, decreased IOP in rabbits without change in aqueous humour outflow facility (Eakins, 1964). In another study, angiotensin II given intravenously, reduced IOP in intact cats and in perfused enucleated cat eyes (Macri, 1965). On the other hand, it has been shown that angiotensin II decreased aqueous humour outflow facility in monkeys (Kaufman & Barany, 1981). In rabbits, eye drops of angiotensin-converting enzyme inhibitors, including captopril, have been shown to reduce IOP with magnitude and duration comparable to that of 0.5% timolol (Watkins *et al.*, 1987).

Captopril 50 mg, timolol (a positive control) 20 mg or matched placebo, in a single oral dose, were given to nine healthy volunteers on three occasions, at least 1 week apart, in a randomised double-blind cross-over design based on three three-by-three latin squares. IOP was measured using the non-contact tonometer just before and at 1, 2, 3 and 4 h after drug administration.

The data were analysed using multiple regression analysis with the base line IOP value included as a continuous independent variable together with treatment, time of measurement and subjects using the dummy variable technique.

Considering all the post-treatment measurements compared with placebo, captopril 50 mg had no significant effect on IOP in both right (+ 0.4 mm Hg) ($F(1,93) = 1.4$) and left (+0.4 mm Hg) ($F(1,93) = 2.6$) eyes. Timolol 20 mg decreased IOP significantly in both right (−2.6 mm Hg) ($F(1,93) = 64.0$, $P < 0.0001$) and left (−2.4 mm Hg) ($F(1,93) = 90.1$, $P < 0.0001$) eyes.

The result of this study shows that a single 50 mg oral dose of captopril had no significant effect on IOP of healthy human volunteers.

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Ward, P. E. *et al.* (1979). *Life Sci.*, **24**, 1419.
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Effect of captopril on skin blood flow following intradermal bradykinin measured by laser Doppler flowmetry

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Skin response to intradermal bradykinin and the effect of angiotensin converting enzyme inhibitors on this response can be quantified by measuring the size of the induced weal (Ferner *et al.*, 1987; Fuller *et al.*, 1987). Intradermal bradykinin increases skin blood flow. It is suggested that laser Doppler flowmetry may provide an alternative objective measurement of this response.

Six healthy volunteers, three males and three females aged 22 to 34 years, received 25 mg captopril or matched placebo, at least 1 week apart, according to a double-blind, randomised, balanced cross-over trial design. Doses of bradykinin of 0, 1 and 2.5 μg in 0.1 ml of 0.9% NaCl solution were injected intradermally into the flexor aspect of the forearms between 1 and 2 h ($t1$) and between 3 and 4 h ($t2$). Laser Doppler flowmeter (LDF) output, expressed in volts (v), was recorded at a fixed distance from the site of each injection (predetermined from previous studies to lie outside the induced weal) at 10 min after injection and computer analysis yielded a mean LDF value for a 5 min period. Weal and flare outlines were traced onto transparent acetate sheets and weal thickness measured by modified Holtain calipers at 15 min. Areas were measured from the tracings using a digitizing

tablet linked to a microcomputer. Weal volume was calculated from weal area and thickness.

Two-way ANOVA showed no significant difference between treatments in LDF values following intradermal normal saline (mean of all values ± s.e. mean = 0.45 ± 0.08 V). The LDF values (mean ± s.e. mean) following 1 and 2.5 μg bradykinin were respectively 0.63 ± 0.15 v and 1.34 ± 0.22 v at $t1$, 0.95 ± 0.32 v and 1.45 ± 0.34 v at $t2$ on placebo days; 1.53 ± 0.23 v and 1.77 ± 0.25 v at $t1$, 1.49 ± 0.25 v and 1.50 ± 0.18 v at $t2$ on captopril days. Multiple regression analysis using subjects, concentrations of bradykinin and treatments as independent variables, using the dummy variable technique, showed that pre-treatment with captopril significantly increased LDF output following intradermal bradykinin at $t1$ (B = 0.45 v, $F(1,27) = 11.09$, $P < 0.005$) but not at $t2$. At both $t1$ and $t2$, captopril significantly increased weal thickness (B = 0.11 mm, $F(1,27) = 7.29$, $P < 0.025$ at $t1$, B = 0.10 mm, $F(1,27) = 4.93$, $P < 0.05$ at $t2$), area (B = 57 mm^2, $F(1,27) = 22.94$, $P < 0.0001$ at $t1$, B = 41 mm^2, $F(1,27) = 11.09$, $P < 0.005$ at $t2$) and volume (B = 33 mm^3, $F(1,27) = 18.32$, $P < 0.001$ at $t1$, B = 29 mm^3, $F(1,27) = 9.06$, $P < 0.01$ at $t2$). After each treatment, there was no significant difference in LDF output, weal thickness, area and volume between the two times. There was no significant difference between treatments in flare sizes.

This study shows that laser Doppler flowmetry can be used to detect skin blood flow changes induced by intradermal bradykinin and the potentiation of this effect by captopril. This was not demonstrated by flare size measurements. Contrary to the findings of Ferner *et al.* (1987), captopril was found to enhance significantly the weal response induced by bradykinin.

Ferner, R. E. *et al.* (1987). *Br. med. J.*, **294**, 1119.
Fuller, R. W. *et al.* (1987). *Br. J. clin. Pharmac.*, **23**, 88.

Effects of antimalarial drugs on the growth of granulocyte-monocyte colonies in cultures of normal human bone marrow

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Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene after Co-Proxamol dosage in young and elderly volunteers

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Dextropropoxyphene (D) is used as an analgesic often in combination with paracetamol (Co-Proxamol). Preliminary findings suggested that the elimination half-lives of both D and its principal plasma metabolite nordextropropoxyphene (ND) were prolonged in elderly hospital inpatients as compared with published data in younger subjects (Crome *et al.*, 1984).

In order to study this further we gave two tablets Co-Proxamol (65 mg D) to 12 young and 12 elderly healthy volunteers (six male, six female in each group) and measured plasma D and ND for up to 7 days using high-performance liquid chromatography with electrochemical oxidation detection. These measurements were repeated after 2 weeks Co-Proxamol, two tablets 3 times daily. Some of the results are summarised in Table 1.

The only significant difference in half-lives within the groups was that the mean D half-life was longer in the young on chronic dosing ($P <$

0.05, paired *t*-test). The mean single and chronic dose D and ND half-lives were all significantly longer in the elderly ($P < 0.02$, Mann-Whitney U-test). In addition, the mean D areas under the curve for both single (young 543 ± 283, elderly 1629 ± 1087 mg l^{-1} h) and multiple (young 784 ± 360, elderly 1446 ± 753 mg l^{-1} h) doses were significantly higher in the elderly ($P < 0.01$ and $P < 0.05$, respectively). Finally, on chronic dosing the mean maximum concentrations (C_{max}) of both D (young 118 ± 51, elderly 280 ± 131 mg l^{-1}) and ND (young 664 ± 131, elderly 1105 ± 257 mg l^{-1}) were higher in the elderly ($P < 0.01$) although there were no significant differences in the time taken to reach C_{max}. There were no significant differences between the male and female subjects in either group. No side effects were reported.

Thus, as with many other compounds which undergo hepatic oxidation, the rate of metabolism of D is reduced in the elderly.

Table 1 Age, weight and D and ND half-lives after single and multiple D dosage mean ± s.d.

	Age (years) (Median, Range)	*Weight (kg)*	*D half-life (h)*		*ND half-life (h)*	
			Single	*Multiple*	*Single*	*Multiple*
Young	26 (21–28)	67 ± 4.8	13.2 ± 5.2	23.7 ± 11.3	22.4 ± 3.8	23.0 ± 4.9
Elderly	75 (70–79)	68 ± 7.6	33.2 ± 21.0	40.4 ± 24.4	45.6 ± 20.1	43.1 ± 9.2

Crome, P. *et al.* (1984). *Human Toxicol.*, **3**, 41S.

Value of a pill box with a concealed monitoring device in a clinical trial and in routine practice

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A single large dose of antimicrobial can be effective in urinary infection. During conventional courses, motivation may decline. The course may be stopped when symptoms abate or because they persist. Poor compliance has been blamed for failure of antibacterial therapy in tuberculosis. A pill box, whose openings are recorded by a concealed electronic device (Dickins *et al.*, 1986), was used to study the effect of compliance on the outcome of treating urinary tract infections with 7 day courses of cephalexin or trimethoprim, and to monitor routine anti-tuberculous therapy. Information stored in the memory of the monitor is read out and edited by a microcomputer. Tablet taking habits can be assimilated at a glance. Totality of compliance was assessed by the number of box openings, expressed as a proportion of the numbers expected, were compliance perfect. The proportion of dosage intervals of 'ideal' length was taken as an index of consistency. Patients were ignorant of the monitor.

Eighty patients, in the community, (mean age (s.d.) 69(9) years) with urinary tract infections sensitive to either or both antibacterials were studied. Three dropped out. Ninety-three percent of urinary infections were cured by trimethoprim, 200 mg twice daily, 67% by cephalexin, 250 mg four times daily ($P < 0.006$). Cure did not depend on age, gender, genitourinary history or infecting organism. Totality of compliance was worse for cephalexin ($P = 0.01$) but both totality and consistency index were similar in those cured and not cured by it. Totality correlated with consistency ($P < 0.05$) only for cephalexin. There were five residual tablets: given the number of box openings less than that required for perfect compliance, there should have been 171. Rigid adherence to a conventional course of cephalexin did not promote cure. Poor compliance may establish over exacting regimens.

Compliance with once daily 'Rifinah' (Merrell Dow Pharmaceuticals) was monitored successfully between successive clinic visits (interval 26 (5) days) in all but one of twenty three consecutive outpatients (age 42 (12) years). Two patients were undercompliant by tablet counting. Seven more under used their boxes but several opened them excessively. Both totality and consistency of compliance were greater ($P < 0.02$)

in those studied in the first 2 months of treatment. Patients may have taken reduction in dose at the end of the intensive phase as signalling cure. In routine practice, knowledge of the presence of the monitor may improve compliance and discussion of the compliance data prove useful in counselling.

Dickins, J. *et al.* (1986). *Br. J. clin. Pharmac.*, **22**, 246P.

Evaluation of the vascular thromboxane A_2 receptor blocking activity of GR32191 in man

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GR32191 is a potent thromboxane A_2 (TP) receptor blocking drug which is active upon both platelet and vascular smooth muscle TP-receptors *in vivo* in animals (Lumley *et al.*, 1988) and *in vitro* on human isolated tissue (Lumley *et al.*, 1987). Following oral dosing to man the drug produces a marked and long lasting antagonism of the platelet TP-receptor (Thomas *et al.*, 1987) but we have as yet no measure of the ability of GR32191 to block the vascular TP-receptor *in vivo*. We have therefore compared the effect of chronic oral dosing with GR32191 upon U-46619-induced platelet aggregation *ex vivo* and prostaglandin (PG)$F_{2\alpha}$-induced constriction of a superficial hand vein *in situ*. Prostaglandin $F_{2\alpha}$ was used as the vasoconstrictor agent since studies have indicated that it contracts human vascular smooth muscle via stimulation of TP-receptors (Uski *et al.*, 1984) and unlike other TxA_2 mimetics can be administered safely to man.

A double-blind, placebo-controlled, cross-over study was performed in eight healthy male subjects (30–39 years). GR32191 20 mg, or placebo, was administered orally 12 hourly for 15 days (29 doses) and the effect upon the hand vein and platelets determined 12 h after the first and final doses. Increases in hand vein diameter (HVD) in mm, were monitored using an optical wedge pressure transducer (Harvard-Bio-Science) whilst maintaining a congestion pressure of 40 mm Hg through a cuff placed on the upper arm (Nachev *et al.*, 1971). On each occasion triplicate determinations of HVD were first performed, followed by a further determination 13–15 min into a $PGF_{2\alpha}$ infusion (0.15 or 1.5 μg for 15 min). Platelet aggregation to U-46619 up to a highest concentration of 30 μM was monitored in whole blood using a platelet counting method. Results were expressed as the concentration of U-46619 required to produce 50% aggregation (EC_{50}).

Compared with placebo GR32191 was found to antagonise both $PGF_{2\alpha}$-induced vasoconstriction and U-46619-induced platelet aggregation. Thus 12 h after the first dose of placebo the mean increase in HVD was 2.22 mm before and 1.48 mm during infusion of $PGF_{2\alpha}$, representing a 33% constriction by the prostaglandin. Similarly, 12 h after dose 29 the corresponding values were 1.85 and 1.20 representing a 35% constriction. In contrast 12 h after the first dose and 29th doses of GR32191, values of 1.87 and 1.86 and 2.06 and 2.16 mm were obtained. Therefore, following dosing with GR32191 no vasoconstriction was observed to $PGF_{2\alpha}$. In the case of platelet aggregation, the U-46619 mean EC_{50} values prior to dosing with GR32191 or placebo were comparable, being 0.23 and 0.3 μM. However following dosing with GR32191 a marked rightward displacement of the U-46619 aggregation concentration-effect curve was observed with increases in the mean EC_{50} value to 11 μM following the first dose and a still further increase to > 30 μM following the final dose, i.e. 50% aggregation to U-46619 could not be obtained at this time. The corresponding EC_{50} values after placebo were 0.29 and 0.36 μM.

In summary, orally administered GR32191 appears to effectively block both platelet and vascular smooth muscle TP-receptors in man. Such a profile is desirable in a TP-receptor blocking drug since, in addition to its platelet aggregating activity, TxA_2-induced vasoconstriction may also play a key role in the pathology of ischaemic vascular disease.

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Preliminary investigations of the effect of 4-pyridylglutethimide on aromatase in breast carcinomas

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Breast cancers have the ability to convert partially formed precursors into active steroids and certain tumours may aromatise androgens into oestrogens (Abul-Hajj, 1982; Miller & Forrest, 1976). Inhibitors of the aromatase system have been used to treat hormone-dependent breast cancer and rely on effective inhibition of oestrogen biosynthesis. The present work investigates the ability of 4-pyridylglutethimide (PyG) (Foster *et al.*, 1985) an analogue of aminoglutethimide (AG) to inhibit *in vitro* aromatisation in human breast carcinoma. Initial screening studies with PyG were performed using human placental aromatase measuring the release of tritiated water from 1β, 2β-[^{3}H]-testosterone (Graves & Salhanick, 1979). The IC_{50} values for AG and PyG were 7.5 μM and 49 μM respectively.

Breast cancer tissue was obtained from seven female patients (34–60 years) at mastectomy and stored at −20° C until assayed. The turnover tissue was carefully excised from adhering fat, minced and divided into equal portions of about 500 mg. The tissue was sonicated and incubated in Krebs-Ringer phosphate buffer pH 7.4 containing 7α-[^{3}H]-testosterone and a NADPH-generating system for 2 h at 37° C in the presence and absence of the inhibitor (50 μM). The reaction was terminated by the addition of 70% methanol. Cold steroid (500 μg) was added to the incubate to assess losses during separation and purification. Fractions of both testosterone and oestradiol were purified by t.l.c. and characterisation was performed by derivative formation (Miller *et al.*, 1974). The amount of cold steroid remaining was measured by either u.v. spectrophotometry or GC mass spectrometry. Radioactivity was determined by liquid scintillation counting. The method detects conversions in excess of 0.02% (Miller & Forrest, 1976).

Evidence for oestrogen synthesis from testosterone was obtained in five of the seven tumours and conversion ranged from 0.02 to 1.86%. In all five tumours showing oestradiol synthesis, the levels of conversion were reduced by the presence of PyG (Table 1). In those in which PyG was compared with AG the latter was found to be a more potent inhibitor in the human carcinoma preparation. This supports the above data obtained with the human placental aromatase. However, unlike AG, the PyG derivative does not inhibit cholesterol side chain cleavage (Foster *et al.*, 1985). In view of this and the present findings, PyG appears to be worthy of further investigations as a potential agent for the management of advanced breast cancer.

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Table 1 Percentage conversion of testosterone to oestradiol by breast carcinoma

Patient	M.W.	D.G.	O.R.	A.S.	L.T.	V.J.	W.W.
Control	0.31	<0.02	<0.02	0.02	0.02	0.03	1.86
PyG (50 μM)	0.07	<0.02	<0.02	<0.02	<0.02	0.02	1.43
AG (50 μM)	<0.02	–	<0.02	–	–	–	0.55

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A single blind placebo controlled crossover safety study of 42068RP in healthy volunteers

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42068RP is a new tetrazole 5-carboxamide shown to possess anti-allergic effects *in vitro* and in a variety of animal species. It is hoped that this compound would be effective as an oral drug for the prophylactic treatment of asthma. The present study was performed to investigate the safety, tolerability and haemodynamic profile of different doses of 42068RP in healthy volunteers.

The study was approved by the ethics committee of the South Glamorgan Area Health Authority. Five groups of eight healthy male volunteers (age range 18–40 years) were included in the study after giving their written informed consent. Each volunteer underwent a full medical examination including routine biochemical and haematological screening. Each group received both drug and placebo in a single-blind, cross-over design separated by an interval of at least 1 week, each volunteer undertaking the study once only. Doses used were 12.5 mg, 25 mg, 50 mg, 100 mg and 150 mg in ascending order, the higher dose administered only after safe completion of the previous dose level. Blood pressure (lying and standing), heart rate (lying and standing), respiration rate were measured and an ECG rhythm strip monitored at regular intervals for up to 14 h after drug administration. All side effects were recorded throughout the study. Venous blood was sampled at regular intervals for measurement of drug levels. The data were analysed using analysis of variance and Student's *t*-test for paired data.

No significant dose-related changes were observed in any of the parameters measured with doses up to 150 mg when compared with placebo. No abnormal cardiac rhythms were observed and no consistent side effects were noted though occasional headaches were reported which were inconsistent and not dose related, occurring in both placebo and active groups.

The limited pharmacokinetic data indicate that the t_{max} was about 1.5 h, Cp_{max} was proportional to the dose given and the elimination half-life was about 6 h. Furthermore there was little subject to subject variation in the kinetic data.

42068 RP in doses up to 150 mg is well tolerated in healthy volunteers with a good side-effect profile. Further evaluation of its efficacy as an oral anti-asthmatic agent would therefore be appropriate.

Biperiden pharmacokinetics in young healthy volunteers and elderly parkinsonian patients

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Biperiden is a synthetic anticholinergic agent used in the treatment of Parkinson's disease and drug induced extrapyramidal side effects (Kline *et al.*, 1974). We have compared the pharmacokinetics of biperiden in elderly parkinsonian patients and young healthy volunteers.

Ten young healthy volunteers (three male, seven female, mean age 24 ± 4.7 years) and eight elderly parkinsonian patients (three male, five female, mean age 77.4 ± 4.8 years), received a single oral dose of biperiden 4 mg (day 1) and 7 days later biperiden 2 mg twice a day for 6 days (days 8 to 14) with a single dose of 2 mg on day 15. Concomitant medication was permitted in patients only. Serial blood samples were taken on days 1 and 15 for assay of plasma biperiden concentrations (Le Bris & Brode, 1985).

Estimates of Cp_{max} and t_{max} were extracted directly from raw data. Elimination half-life ($t_{½Z}$) was calculated using a two compartment elimination model and least squares log linear regression. Estimation of $t_{½}z$ was only appropriate in six of the young volunteers as plasma biperiden concentrations were below the detection limit of the assay in the remaining four. $AUC_{0-\infty}$ was estimated by the trapezoidal rule with extrapolation to infinity using the elimination rate constant. Results were analysed by the non parametric Mann Whitney U Test for unpaired data. $P < 0.05$ was taken as the minimum level of statistical significance.

Side effects reported during this study were consistent with the administration of biperiden. In young volunteers side effects were mild in nature (e.g. dry mouth, blurred vision) whilst elderly parkinsonian patients were more suscep-

tible to the CNS effects of the drug (e.g. mental confusion, mood change, hallucinations).

The results indicate that biperiden was eliminated less efficiently in elderly parkinsonian patients when compared with young healthy volunteers. Caution should therefore be exercised when prescribing this drug to such patients.

Table 1 Mean pharmacokinetic parameter estimates ± s.d.

	Day 1		*Day 15*	
	Young volunteers	*Elderly patients*	*Young volunteers*	*Elderly patients*
Cp_{max} (ng ml^{-1})	4.3 ± 2.6	7.2 ± 4.4	2.5 ± 1.4	*4.2 ± 2.2
t_{max} (h)	0.9 ± 0.4	*1.6 ± 0.7	0.8 ± 0.3	**1.6 ± 0.3
$t_{½}$ z (h)	14.2 ± 3.2	*30.2 ± 6.4	24.5 ± 8.8	*38.5 ± 12.2
AUC (ng ml^{-1} h) (0–∞)	28.6 ± 13.5	***78.7 ± 36.6	20.9 ± 36.6	***98.01 ± 36.7
	*$P < 0.05$	**$P < 0.01$	***$P < 0.001$	

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Stereoselective metabolism and irreversible binding of mianserin by human liver microsomes

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Mianserin is a tetracyclic antidepressant drug that has been implicated in a number of adverse drug reactions (Chaplin, 1986). The role of metabolism in these side effects has not been fully elucidated. It has previously been reported that human liver microsomes are capable of metabolizing mianserin to an electrophilic species which binds irreversibly to sulphydryl groups (Lambert *et al.*, 1987). In this study we have examined the stereoselective metabolism of mianserin to both stable and chemically reactive metabolites and have investigated the nature of the reactive metabolite formed.

Human liver microsomes (8 mg) were incubated with [^{3}H]-R-or S-mianserin (10 μM; 0.5 μCi) and NADPH (1 mM) in a total volume of 4 ml phosphate buffer (0.1 M; pH 7.4) at 37° C for 30 min. In other incubations [^{3}H]-mianserin (1 μM or 10 μM; 0.5 μCi), [^{3}H]-desmethylmianserin (1μM; 1.61 μCi) or [^{3}H]-8-hydroxymianserin (1 μM; 0.87 μCi) were used and in one experiment, sodium cyanide (0.1 to 5 mM) was added. Irreversibly bound material was measured by exhaustive solvent extraction of methanol precipitated protein. Stable metabolites were identified by co-chromatography with authentic standards.

For each of the livers the NADPH-dependent irreversible binding, hydroxylation and *N*-oxidation occurred to a significantly ($P < 0.05$) greater extent with the S stereoisomer (Table 1). In contrast demethylation occurred to a significantly ($P < 0.01$) greater extent with the R stereoisomer. In a separate experiment the irreversible binding of desmethylmianserin (5.97%) was shown to be significantly greater ($P < 0.05$) than for both racemic mianserin (3.96%) and 8-hydroxymianserin (4.17%). When cyanide was included in the incubation with [^{3}H]-mianserin significant ($P < 0.05$) inhibition of irreversible binding was observed, but there was no reduction in total metabolism.

The metabolism of mianserin to both stable and reactive metabolites by human liver microsomes has been shown to be stereoselective. In addition the results obtained with cyanide suggest the formation of a chemically reactive iminium ion metabolite, similar in nature to that reported for phencyclidine (Ward *et al.*, 1982).

Table 1 The NADPH-dependent metabolism of mianserin

Liver		*Binding (%)*	*Total (%)*	*8-hydroxy (%)*	*desmethyl (%)*	*N-oxide (%)*
I	R	2.4	81.4	4.8	40.0	2.2
	S	4.9	63.8	6.2	16.0	5.6
II	R	2.4	59.1	6.5	16.7	1.2
	S	3.1	74.5	19.5	8.9	6.4
III	R	3.6	79.8	12.8	25.7	3.3
	S	5.4	80.3	18.0	12.0	6.9
IV	R	2.0	58.2	5.6	15.2	1.5
	S	2.3	62.1	11.8	7.2	5.1
Mean	R	2.6	69.6	7.4	24.4	2.1
	S	3.9	70.2	13.9	11.0	6.0

Values are means of either three experiments (IV) or four determinations (I–III).

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The effect of hepatic enzyme induction on the *in vitro* cytotoxicity of phenytoin and mianserin

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Phenobarbitone-induced mouse liver microsomes and human mononuclear leucocytes (MNL) have been used to study the metabolic basis for the predisposition of certain individuals to various drug adverse reactions (Spielberg, 1984). Such studies have suggested that inherited deficiences in detoxication enzymes may be responsible for the toxicity of certain compounds. We have extended this *in vitro* test system by using human as well as mouse liver microsomes (Maggs *et al.*, 1988) and have suggested that variation in drug activation may also play a crucial role in drug toxicity. In order to examine this possibility, we have studied the effects of hepatic enzyme induction on the *in vitro* cytotoxicity of phenytoin and mianserin.

Microsomes were prepared from the livers of untreated and phenobarbitone (PB; 60 mg/kg/day × 3), β-naphthoflavone (BNF; 75 mg kg^{-1} day × 3) or vehicle (saline or corn oil)-treated male mice. The cytochrome P-450 content of the microsomes was measured according to Omura & Sato (1964). MNL (1×10^6) isolated from freshly drawn human blood were incubated with either phenytoin (150 μM) or mianserin (10 μM) in a HEPES-buffered medium, along with a metabolising system (0.5 mg microsomal protein and 1 mM NADPH) at 37° C for 2 h. NADPH was omitted from control incubations. Cells incubated with phenytoin were pretreated with the epoxide hydrolase inhibitor trichloropropane oxide (TCPO; 30 μM for 10 min). Cell death was assessed by trypan blue exclusion, following a further 16 h incubation in drug-free medium (Spielberg, 1984).

Neither vehicle (0.9% saline or corn oil) had a significant effect on the P-450 content compared with the level in untreated animals (0.63 ± 0.10 nmol mg^{-1} protein). Both PB and BNF significantly increased hepatic microsomal P-450 levels ($P < 0.05$) (Table 1). Microsomes from vehicle-treated animals were not capable of metabolising either phenytoin or mianserin to a cytotoxic species. However, microsomes from both PB and BNF-treated animals activated both drugs to metabolites which produced significant death of MNL. Cell death was dependent upon the presence of NADPH. Cytotoxicity resulting from the metabolism of mianserin by induced mouse microsomes was not as great as that previously found with human liver microsomes (Riley *et al.*, 1988).

In conclusion, the cytotoxicity of phenytoin and mianserin is dependent upon cytochrome P-450 enzymes which are inducible in mice by both PB and BNF. The adverse reactions observed with phenytoin and mianserin may therefore be influenced by inter-individual variation in the levels of such activating enzymes.

Table 1 Effect of enzyme induction on phenytoin and mianserin toxicity

Treatment	*P-450* (*nmol mg^{-1} protein*)	*Cytotoxicity (% cell death)* *Mianserin* −NADPH	+NADPH	*Phenytoin* −NADPH	+NADPH
Saline	0.61 ± 0.11	3.3 ± 0.5	3.1 ± 0.2	4.0 ± 0.3	4.1 ± 0.3
PB	1.34 ± 0.14	3.4 ± 0.4	7.3 ± 3.3*	4.3 ± 0.4	18.9 ± 2.0*
Corn oil	0.68 ± 0.08	2.6 ± 0.3	2.6 ± 0.3	3.9 ± 0.3	3.9 ± 0.2
BNF	0.98 ± 0.12	3.2 ± 0.3	5.5 ± 0.6*	4.4 ± 0.4	15.9 ± 1.8*

Values are mean ± s.d. for four animals. $P < 0.05$ (Mann-Whitney U Test)

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Metabolism of ciamexon by human liver microsomes

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Ciamexon (BM 41.332), a derivate of the immunomodulant 2-cyano-aziridine series, is effective in a rat model of adjuvant arthritis and suppresses spontaneous insulin-dependent diabetes in BB rats (Bicker & Usadel, 1986). The metabolism of [^{14}C]-ciamexon has not been elucidated although the drug is cleared rapidly from plasma in the rat (Isert *et al.*, 1987). In this study we have investigated the *in vitro* metabolism of [^{14}C]-ciamexon by human liver microsomes.

Four histologically normal livers from renal transplant donors were used (microsomal cytochrome P450 contents between 0.29 and 0.83 nmol mg^{-1} protein). [^{14}C]-ciamexon (10 μM, 0.2 μCi) was incubated with washed microsomes (8 mg protein) and NADPH (1 mM; omitted from controls) in 0.1 M phosphate buffer pH 7.4 (4 ml final volume) at 37° C for 15 min. The reaction was stopped by the addition of diethyl ether (2 × 5 ml) and irreversibly bound material was determined after exhaustive solvent extraction of methanol-precipitated protein. Ether and methanol extracts were pooled and assayed by reversed-phase h.p.l.c. (C_{18} column, methanol-ammonium phosphate buffer gradient).

The metabolism and irreversible binding of [^{14}C]-ciamexon were found to be NADPH dependent. The major metabolite was isolated by h.p.l.c. and analysed by LC-MS using a VG TS-250 spectrometer and yielded $[M + 1]^+$ for the alcohol (M = 219) formed from the oxidation of the 6-methyl group of ciamexon (M = 203). A further product of oxidation, the carboxylic acid, was identified by co-chromatography with an authentic standard (Table 1). A third, polar metabolite was not identified.

These studies indicate that the major route of metabolism by human liver microsomes for ciamexon is the oxidation of the aromatic methyl group to yield the alcohol, which may be further metabolised to the carboxylic acid derivative. Only low levels of radioactivity became irreversibly bound to liver microsomes, indicating that the drug undergoes little or no oxidative bioactivation.

This work was supported by Boehringer Mannheim GmbH, West Germany.

Table 1 The metabolic profile of [^{14}C]-ciamexon with human liver microsomes in the presence of NADPH

Liver	*Unknown*	*6-OH*	*6-COOH*	*Irreversibly bound*
1	10.61 ± 5.03	57.02 ± 3.47	0.80 ± 0.21	0.34 ± 0.03
2	14.88 ± 0.42	63.56 ± 0.43	8.00 ± 0.77	0.57 ± 0.04
3	11.03 ± 0.18	67.23 ± 4.87	0.00 ± 0.00	0.95 ± 0.38
4	13.50 ± 0.70	65.80 ± 0.39	5.11 ± 4.44	0.08 ± 0.01

Data are mean % ± s.d. (n = 3) of incubated radioactivity.

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The quantitative assessment of ethanol pharmacodynamics by eye movement analysis

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Ethanol is a socially acceptable and widely available sedative-hynotic which has numerous interactions with other drugs (Weller & Preskorn, 1984). Saccadic eye movements have been shown to be affected by a variety of sedative drugs, including ethanol, and have been used to investigate the interactions between drugs and ethanol (Ali *et al.* 1986; Griffiths *et al.*, 1984, 1986; Seppala, 1979). Saccadic movements are the most common movements of the eye and are used to centre the fovea on different parts of the visual field rapidly. Interference with the speed or accuracy of saccades is therefore likely to lead to a degradation of the quality of visual information gathered and to impair or delay judgement.

This study has made a detailed investigation of the time course of the effects of a single oral dose of ethanol on reaction time (ms), peak saccade velocity (° s^{-1}), peak acceleration (° s^{-1} s^{-1}), peak deceleration (° s^{-1} s^{-1}), mean acceleration velocity (° s^{-1}) and mean deceleration velocity (° s^{-1}).

Eight healthy male volunteers received a single oral 75 g dose of ethanol (187.5 ml vodka [40% vol/vol]) in an equal volume of orange juice or placebo (orange juice alone). Blood samples were collected pre-dose and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 3.0, 4.0 and 6.0 h after dosing. Saccadic eye movements were measured pre-dose and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0 h after dosing. The Cardiff Saccade Generation And Analysis System (CSGAAS) was used to generate, collect and analyse the saccades. Eighty saccades (20 each at target displacements of 20, 25, 30 and 35°) were collected and analysed at each measurement point. The data were analysed by two-way repeated measures analysis of variance followed by Student's t-test at each time point.

Mean whole blood ethanol concentrations reached 100 ± 8 (mean ± s.e. mean) mg dl^{-1} after 1 h and exhibited zero order elimination (V_{max} = 15.43 mg dl^{-1} h^{-1}). Reaction time in the presence of ethanol was significantly different from placebo between 0.5 and 2.5 h after dosing ($P < 0.05$), although this was superimposed on declining trend after both treatments. Ethanol treatment significantly decreased peak saccade velocity when compared with placebo after 0.5 h ($P < 0.001$), an effect which continued up to 4 h. Peak acceleration, peak deceleration and mean deceleration velocity exhibited a similar time course to that of peak saccade velocity but peak deceleration and mean deceleration velocity appeared to be more sensitive during the declining phase of the drug effect. Peak saccade velocity and peak acceleration showed significant differences of $P < 0.01$ 2–4 h post dose but those of peak deceleration and mean deceleration velocity were more significant ($P < 0.001$). Mean deceleration velocity remained significantly different ($P < 0.05$) from placebo 6 h after dosing with ethanol. Mean acceleration velocity was a poor indicator of ethanol effect.

We have demonstrated that saccadic eye movement parameters, other than the widely quoted peak saccade velocity, may be employed to describe the time course of ethanol effects. Mean deceleration appears particularly useful in this respect due to its sensitivity during the declining phase of the drug effect.

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Haemodynamic and dose related efficacy and tolerance of orally administered MCI-154 in patients with chronic heart failure

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Single dose tolerance and pharmacokinetics of oral UK-61,260, a novel inotrope/vasodilator

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UK-61,260 is a potent, oral, force selective inotrope/vasodilator in preclinical studies (Ellis *et al.*, 1987, 1988; Alabaster & Rance, 1987).

Single dose pharmacokinetics of UK-61,260 were defined in three studies approved by independent ethics committees. All subjects were healthy adult males, aged from 18 to 44 years and gave written informed consent. UK-61,260 was given as the mesylate dihydrate salt and doses are given as base equivalents. Plasma concentrations were measured by h.p.l.c. and mean pharmacokinetic parameters are summarised in Table 1.

Groups of four fasting male subjects received weight-adjusted single oral doses of UK-61,260 in solution, or similar placebo at random. Peak plasma concentrations were linearly proportional to dose. The mean plasma elimination half-life was 5.2 h, first order kinetics being apparent in all subjects. There was no evidence of dose dependent kinetics.

A two-way randomised crossover study compared an aqueous solution and a capsule formulation of 2.5 mg UK-61,260 in a group of 12 subjects. The relative bioavailability of the capsule was 1.14 using the solution as the reference formulation. Urinary recovery of unchanged drug up to 48 h after dosing represented 27% and 32% of the solution and capsule doses respectively.

A two-way randomised crossover study assessed the effect of food on pharmacokinetic parameters of 2.5 mg capsules of UK-61,260 in a group of 12 healthy subjects. Peak plasma concentrations were similar on each occasion, but the mean time to peak was slightly longer in the fed condition.

Side-effects (headache; postural dizziness) were those expected from the pharmcological activity of the compound and were most marked in the three subjects whose peak plasma concentrations of UK-61,260 exceeded 50 ng ml^{-1}. Side-effects were more frequent in the fasting condition. These results support the use of single oral doses of UK-62,260 up to 2 mg which have already been shown to produce beneficial haemodynamic changes in patients with chronic heart failure (Hornung *et al.*, 1988).

Table 1

Study	n	*Formulation*	*Condition*	*Dose*	k_{el} (h^{-1})	$t_{1/2}$ (*h*)	t_{max} (*h*)	C_{max} (*ng ml*$^{-1}$)
201	2	Solution	Fasting	10 μg kg^{-1}	0.1650	4.20	1.0	5.5
	4	Solution	Fasting	20 μg kg^{-1}	0.1594	4.35	1.5	10.5
	2	Solution	Fasting	40 μg kg^{-1}	0.1254	5.53	1.5	23.0
	6	Solution	Fasting	80 μg kg^{-1}	0.1312	5.28	1.6	51.0
202	12	Capsule	Fasting	2.5 mg	0.1429	5.12	1.7	17.7
	12	Solution	Fasting	2.5 mg	0.1576	4.92	1.2	16.6
203	12	Capsule	Fed	2.5 mg	0.1156	7.23	2.6	14.6
	12	Capsule	Fasting	2.5 mg	0.1179	7.68	1.6	16.1

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The pharmacokinetics and tolerance of single doses of UK-61,260 in healthy elderly subjects

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UK-61,260 has positive inotropic and vasodilator properties in animals (Alabaster & Rance, 1987; Ellis *et al.* 1987) and is undergoing Phase II study in patients with heart disease. As many patients with such conditions are elderly, this pharmacokinetic and tolerance study was deemed appropriate.

Twenty healthy elderly subjects received either 1 mg UK-61,260 or placebo. The study was stratified so that subjects were divided into four equal groups: men 65–70, men >70, women 65–70, women >70 years. In each group three subjects received active drug and two placebo. Blood was taken for 12 h and urine for 48 h for drug measurement. Pulse and BP were recorded lying and standing. UK-61,260 was measured by GC-MS and the pharmacokinetic parameters obtained by conventional methods. Informed written consent and Ethics Committee approval were obtained.

After weight correction, women had higher C_{max} 7.8 *vs* 5.9 ng ml^{-1} and larger AUCs 72.8 *vs* 64.0 ng ml^{-1} h. Those aged > 70 years had larger AUCs than those aged 65–70 years; 73.5 *vs* 63.3 ng ml^{-1} h. Other parameters showed no changes between sub-groups. At 12 h 11.3% and at 48 h 22% of the dose had been excreted unchanged in the urine. The mean urinary clearance was 41.3 ml min^{-1}. At 6 h mean ± s.d. supine BP had fallen by 16.0 ± 13.5/10.7 ± 8.1 on drug and 21.2 ± 14.4/6.8 ± 12.5 on placebo. The standing BP falls at 6 h were 27.0 ± 22.6/11.7 ± 17.7 and 15.3 ± 19.7/3.7 ± 12.4. Two subjects both taking UK-61,260 developed side-effects: dizziness and headache in one case each. There were no withdrawals. These results are broadly similar to those obtained in younger subjects (Collier *et al.*, 1988).

We would like to thank BCO-Analytical Services for the drug assay and Dr J. K. Faulkner and Dr J. Collier of Pfizer Central Research for their help. This study was supported by Pfizer Central Research.

Table 1 Pharmacokinetic results in 12 subjects

		AUC (*ng ml*$^{-1}$ *h*)	k_{el} (h^{-1})	C_{max} (*ng ml*$^{-1}$)	t_{max} (*h*)
Men		61.7	0.1154	5.7	3.8
n = 6	s.d.	14.3	0.0245	0.9	1.2
Women		71.6	0.1172	7.6	3.2
n = 6	s.d.	10.8	0.0179	1.2	0.8

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The use of intravenous ranitidine in stressed children

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Severely stressed children are at risk of developing gastro-duodenal ulcers which have a significant morbidity and mortality. The stress may be caused by infection, hypoxia, hypovolaemia or severe injury, particularly head injury. The primary defect is decreased gastro-duodenal mucosal protection, but attempts at correcting this with prostaglandins, have met with limited success. Because it is gastric acid which erodes the defective mucosa, another approach is to reduce gastric acid output. We have studied the effect of ranitidine, a specific H_2-receptor antagonist on subjects likely to develop stress ulcers.

Twenty children with ages ranging from 1 day to 12 years were studied. Ten were under 1 year and 10 over. They were all patients on ITU and the stress event was cardiothoracic surgery in 16 cases, severe heart failure in three and asthma in one. Each child was intensively studied immediately before and for 6 h following the first 1 mg kg^{-1} intravenous dose of ranitidine. Gastric pH was recorded pre dose and hourly thereafter. Blood samples were collected at 5, 10, 15, 30, 45, 60, 120 and 150 min and 3, 4, 5 and 6 h post dosing and separated plasma assayed by radioimmunoassay (Jenner *et al.*, 1981) after storage at −20° C. All urine passed within each hour was collected and aliquots stored and later assayed for ranitidine. Any alteration in the child's status was recorded for consideration as to possible side effects.

Ten children had a gastric pH $\geq$ 5 prior to dosing and throughout the 6 h study period. The remaining 10 patients had a gastric pH = 3 at the onset. Of these, six achieved pH $\geq$ 5 within 2 h of dosing but this was not maintained for the whole of the study period in two patients.

For seventeen patients for which kinetic data are available, the mean (± s.d.) post distributive volume of distribution was 2.2 ± 1.2 l kg^{-1}. The mean (± s.d.) plasma clearance was 11.7 ± 5.6 ml min^{-1} kg. The mean (± s.d.) plasma terminal half-life was 2.39 ± 0.89 h. Urine kinetic data are available on 13 children. The mean (± s.d.) fractional urine recovered was 0.44 ± 0.28; the renal clearance was 5.8 ± 3.6 ml min^{-1} kg^{-1}; and the non renal clearance 6.2 ± 5.1 ml min^{-1} kg^{-1}.

The use of intravenous ranitidine in a dose of 1 mg kg^{-1} 6 hourly in children liable to severe stress ulceration appears to be safe but may be insufficient to maintain alkalinity of gastric juice over the period of risk in some patients. However, in this study, no ulceration was seen in any child on this dose frequency regime. Further investigation to determine whether an increased dose or more frequent dosing would maintain alkalinity in all children is probably indicated.

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Side effects of long-term amiodarone therapy at low maintenance doses

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Although amiodarone (AD) is an effective antiarrhythmic agent, long-term therapy may be associated with unwanted effects (Mason, 1987). In a prospective study we assessed the incidence of side effects associated with long-term AD therapy at low maintenance doses.

One hundred patients, 52 women and 48 men, 26 to 75 years old (mean 59 ± 13) receiving AD, for refractory arrhythmias, were followed up by a protocol. Only patients taking AD 200 mg day^{-1}, 5 days per week, without previous pulmonary, thyroid gland or hepatic dysfunction were included. The protocol was applied before starting AD therapy (group A, 32 patients) and also in patients receiving the drug chronically (group B, 68 patients) between 1 and 12 years (mean 3.5 ± 5). The protocol was reapplied in both groups 1, 3, 6 and 12 months after starting the study. The protocol included a clinical history and physical examination, blood count, haematic biochemistry, clotting factors activity, antithyroid antibodies, triiodothyronine (T3), thyroxine (T4), free T4 (FT4), thyrotropin (TSH), chest roentgenograms, spirometry and diffusion capacity measured by single breath carbon monoxide dilution.

The results are summarised in Table 1.

The results of this study indicate that when AD is used at low maintenance doses, the incidence of severe complications is lower than that referred by others using high doses (Fogoros *et al.*, 1983; McGovern *et al.*, 1983). Namely, only in 3% was AD discontinued. Nevertheless, our study shows a higher percentage of skin photosensitivity, probably due to the greater sun exposure encountered by Spanish patients.

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Table 1 Clinically significant unwanted effects of AD 200 mg day^{-1} (5 days per week)

	Group A[1]	*Group B*[1]	*Total*[2]
Bradycardia	0	2	2%
Pneumonitis (a)	0	0	0%
Hepatitis (b)	0	0	0%
Neurologic effects	0	4	4%
Impaired vision (c)	0	0	0%
Skin photosensitivity	3	20#	23%
Facial pigmentation	2	7	9%
Hypothyroidism (d)	1	2	3%
Hyperthyroidism (e)	0	1	1%
AD withdrawal	0	3	3%

#$\chi^2 = 3.87$, $P < 0.05$ (group A *vs* group B); 1 = number of patients, 2 = percentage of patients (a) = restrictive defects were found in 11%, with reduced diffusing capacities in 4%, without any clinical or radiological features consistent with interstitial pneumonitis; (b) = there were transitory alterations in liver function test in 8% (4 in group A, 4 in group B); (c) = corneal deposits were not considered; (d) = all of them had high antithyroid microsomal antibodies; (e) = 51% show increase of FT4 (30 in group A, 21 in group B), T4 increased transitory in 21% (9 in group A, 12 in group B) and T3 in 3%.

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The pharmacokinetics and pharmacodynamics of a new class III antiarrhythmic UK66,914 – results of a phase I study

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A comparison of plasma concentrations observed following repeat oral administration of zopiclone or flurazepam in the elderly

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Zopiclone, a cyclopyrrolone which has the pharmacological profile of a non-barbiturate hypnotic, has been compared pharmacodynamically and kinetically against flurazepam, a commonly-prescribed member of the benzodiazepine family of hypnotics. The study design employed a double blind, randomised placebo-controlled strategy, involving repeated oral administration for 7 nights of 7.5 mg of zopiclone, or 15 mg of flurazepam of placebo. Blood samples were taken 12 h after the 1st and 7th doses.

Subjects considered for inclusion in this study, were elderly in-patients of either sex, over 65 years but in a stable medical condition, who in the preceding 10 days had not undergone surgery or received sedative agents. Resulting plasma from these subjects was assayed (depending on drug administered) for either zopiclone or flurazepam and its *N*-hydroxyethyl- and desalkyl-metabolites, by new, specific h.p.l.c. methods.

No statistically significant difference ($P > 0.05$) was observed between plasma zopiclone levels on day 1 (27 ± 10.4 ng ml^{-1}) and day 7 (24 ± 9.0 ng ml^{-1}). However, analysis of plasma from subjects who had received flurazepam only, revealed the presence of quantifiable levels of the major pharmacologically active desalkyl-metabolite. A highly statistically significant difference ($P < 0.001$) was observed between plasma desalkylflurazepam levels on day 1 (15 ± 16 ng ml^{-1}) and day 7 (80 ± 68 ng ml^{-1}).

Zopiclone would not appear to accumulate to any great extent in the elderly over 7 days of dosing, while the active metabolite of flurazepam does to a very high degree. These differences are probably attributable to the marked disparity in the plasma elimination half-lives of the two products in the elderly; approximately 8 h for zopiclone (Gaillot *et al.*, 1983) and 40–100 h for desalkylflurazepam (Detti, 1983; Greenblatt *et al.*, 1981). Consequently any 'hangover' sedative effect which occurs on repeat administration of zopiclone, should be no greater than that observed after a single dose. However, there would appear to be every likelihood of a marked increase in this 'hangover' effect on repeated administration of flurazepam.

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Influence of the timing of glipizide dosage on post-prandial hypoglycaemia in healthy volunteers

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Since previous studies (McEwen *et al.*, 1982; Edwards *et al.*, 1988) have indicated an additive effect of sulphonylurea plasma concentration and glucose level on insulin release, more effective hypoglycaemia may be achieved by timing dosage in relation to meals, so that circulating drug levels are well established by the time of the metabolic impact of food.

Six healthy male volunteers completed a balanced two-way crossover study with an identical standard breakfast on each occasion. In one session, 5 mg oral glipizide was given with food: in the other session, 5 mg oral glipizide was given 30 min before breakfast. Blood samples were collected via an indwelling cannula at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3.5 and 4.5 h after breakfast, for analysis of glucose (oxidase method), insulin (RIA) and glipizide (h.p.l.c.) concentrations.

In comparison with the response to dosage at breakfast time, treatment 30 min before breakfast resulted in a marked attenuation of the post prandial rise in blood glucose (Table 1, ANOVA: $P < 0.001$), maximal at 1 h, with a 40% reduction in mean glucose. Insulin responses were brisker after pre-prandial treatment. Glipizide AUC and C_{max} were similar following the two regimens, although pre-prandial treatment tended to give a more rapid absorption phase.

These data suggest that morning glucose control in type II diabetes might be improved if glipizide were given 30 min before breakfast, rather than with food.

Table 1 Mean (s.d.) plasma glucose (mmol l^{-1}): breakfast at 0 h

Time (h)	*Dosage 30 min before food*	*Dosage with food*
0	5.98 (0.63)	6.03 (0.80)
0.25	5.85 (0.76)	5.93 (0.86)
0.5	5.60 (0.61)	5.90 (0.43)
0.75	5.60 (0.96)	6.68 (0.48)
1	4.68 (0.97)	7.98 (1.24)
1.25	3.96 (1.42)	5.38 (1.20)
1.5	2.98 (1.20)	4.45 (1.42)
2	3.75 (0.93)	3.78 (1.40)
2.5	3.95 (1.43)	3.93 (0.83)
3.5	4.12 (0.46)	4.17 (1.02)
4.5	4.85 (0.67)	4.78 (0.99)

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Pharmacokinetics of benorylate in young volunteers and elderly patients with arthritis

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Benorylate is readily absorbed after oral administration and hydrolyses in the blood to aspirin and paracetamol. After biotransformation in the liver, these agents are excreted principally as urinary metabolites. As a consequence of the reduced hepatic and renal function commonly found in elderly patients, plasma concentrations may be elevated. On the administration of more than 4 g of benorylate daily in the elderly, there is a disproportionate increase in the risk of toxicity due to salicylate, because of the dose-dependence of its elimination (Beringer, 1984). Therefore, intoxication may be occurring in some old people being treated for arthritis with the standard regime of 8 g daily in a divided dose.

In order to provide information about the handling of this schedule of treatment with benorylate, we compared the chronic dosing pharmacokinetics of salicylic acid and paracetamol in six patients with osteoarthritis (median age 81; range 66–90 years; weight 54; range 48–65 kg), six patients with rheumatoid arthritis (median age 79; range 70–84 years; weight 50; range 49–64 kg) and 12 normal subjects (median age 22; range 19–28 years; weight 65; range 53–80 kg). Benoral suspension (10 ml, 40% w/v, twice daily) was given at intervals of 12 h for 14 days and a single dose administered on day 15. Plasma specimens were collected on days 4, 8 and 12 at 0 h (trough) and 3 h (peak) and at appropriate intervals on days 15 to 17 to obtain the disposition profiles after the final dosage. During this period, urinary specimens were obtained from 0–8, 8–24 and 24–30 h and the drugs and their metabolites, *viz.* salicyluric acid and the glucuronide, sulphate, cysteine and mercapturate conjugates of paracetamol, were estimated. Extents of protein binding of salicylic acid were determined and free drug levels calculated. No significant difference existed between the arthritic groups in any of the parameters, except that the median half-life of free salicyclic acid was greater ($P = 0.041$) in patients with osteoarthritis (10.6 h) than in those with rheumatoid arthritis (7.7 h). The median excretion of salicylic acid was reduced in patients (3.6% of dose) by comparison with normal subjects (5.3% of dose) and this was reflected in values of renal clearance of 0.14 and 0.34 ml min^{-1}, respectively, which were significantly different ($P = 0.003$). Total excretion of salicyclic and salicyluric acids was also decreased and was significant ($P = 0.027$) in comparison with the control (74.2% of dose) and osteoarthritic (54.9% of dose) groups. Large differences in the average concentrations at steady-state of free and total salicylic acids were evident between controls (24.6 and 157.2 mg l^{-1}, respectively) and patients (71.9 and 241.4 mg l^{-1}, respectively), but this discrimination reduced

when values were normalised to a body weight of 70 kg (free, 23.2 and 49.4 mg l^{-1} and total salicylic acid, 161.1 and 168.8 mg l^{-1}, in the respective groups). Similarly, the average steady-state concentration of paracetamol was significantly greater ($P = 0.037$) in arthritics (10.6 mg l^{-1}) than in normal subjects (6.6 mg l^{-1}), but it was not when the normalised values (7.9 and 6.6 mg l^{-1} respectively) were compared. Many differences between groups were observed in peak and trough levels of salicylate and paracetamol and generally these values declined with increasing time of dosage.

It is concluded that the salicylate toxicity experienced by elderly arthritics associated with benorylate treatment may be partly a result of reduced clearance, but a major factor at least in this group of patients appears to be the lack of adjustment of dosage for body weight.

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Comparison of the effects of propranolol, metoprolol and ICI 118,551 on the CVS and finger tremor in hyperthyroidism

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β-adrenoceptor antagonists have been shown to reduce the peripheral manifestations of hyperthyroidism including finger tremor (McDevitt & Nelson, 1978). The purpose of this study was to study the receptors involved in the increased amplitude of finger tremor in thyrotoxicosis by comparing the effects of the selective β_2-adrenoceptor antagonist, ICI 118,551 (Bilski *et al.*, 1983) (ICI) with those of propranolol (Prop), metoprolol (Met) and placebo (Pl) in thyrotoxic patients.

Six newly diagnosed untreated female hyperthyroid patients, (mean free T4 73 ± 39 pmol l^{-1}) received single oral doses of Prop 40 mg, Met 100 mg, ICI 40 mg and placebo (Pl) according to a randomised double-blind cross-over design with at least 24 h between doses. On each study day 2 h after drug administration and after resting for 30 min, heart rate, blood pressure, FEV_1 and finger tremor were measured and Gibson's Spiral Maze completed (Gibson, 1965). The patient then performed an exercise step test at the end of which heart rate and blood pressure were measured. Heart rate was measured using a direct writing electrocardiogram, blood pressure using a Hawksley random zero sphygmomanometer and finger tremor using a piezo electric accelerometer, attached to the dorsum of the middle finger of the left hand. The results (± s.d.) were compared by analysis of variance. A P value of < 0.05 was considered significant.

Supine heart rate was reduced by Prop (90 ± 16 beats min^{-1}), Met (85 ± 13 beats min^{-1}) and ICI (101 ± 13 beats min^{-1}) compared with Pl (106 ± 18 beats min^{-1}). Supine systolic blood pressure was reduced by Met (106 ± 11 mm Hg), Prop (111 ± 8 mm Hg) and ICI (119 ± 13) compared with Pl (125 ± 19 mm Hg). Diastolic blood pressure was not altered by any treatment. Exercise heart rate was reduced by Met (119 ± 15 beats min^{-1}), Prop (128 ± 24 beats min^{-1}) and ICI (164 ± 27 beats min^{-1} compared with Pl (174 ± 35 beats min^{-1}). Met caused a greater reduction in exercise heart rate than Prop.

Met (11 ± 8 mv^2) and ICI (10 ± 8 mv^2) reduced finger tremor compared with Pl (21 ± 17 mv^2). Prop (16 ± 12 mv^2) caused no significant change. No treatment affected performance on Gibson's Spiral Maze. FEV_1 was unaffected by any treatment.

These results confirm that β-adrenoceptor antagonists reduce the cardiovascular manifestations of hyperthyroidism. Met, a β_1-selective antagonist and ICI, a selective β_2-adrenoceptor antagonist, both reduced finger tremor, suggesting that both β_1 and β_2- receptors are mediators in thyroid tremor.

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The effect of fenoterol and its enantiomers on cyclic AMP production by human lymphocytes

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It is generally accepted that the (−)-enantiomers of β-adrenoceptor agonists and antagonists are more potent than the (+)-enantiomers. However it has been shown for the β-adrenoceptor partial agonist pindolol that the racemate, (−), and (+)-enantiomers have equipotent partial agonist activity at the human lymphocyte β_2-adrenoceptor (Milligan *et al.*, 1985). It has also been shown that the racemate, (−), and (+)-enantiomers of the selective β_2-adrenoceptor agonist terbutaline have equipotent agonist effects at the human lymphocyte β_2-adrenoceptor (Anderson *et al.*, 1987). We have investigated the agonist activity of racemic fenoterol and its enantiomers by measuring cyclic AMP production in human lymphocytes. Blood (30 ml) was obtained by venepuncture from young healthy adults (males and females) mean age 27 years (range 19–35). Lymphocytes were isolated by Boyum's method (1968) and incubated for 15 min at 37° C in Hank's balanced salt solution containing 10^{-13} M theophylline and either racemic, (−) or (+)-fenoterol at concentrations of 10^{-8}, 10^{-6}, 10^{-5}, 10^{-4} M. As a control 10^{-5} M (−)-isoprenaline was included in all experiments. At the end of the incubation time the cells were killed by heating to 95° C for 7 min. The lymphocytes were lysed by freezing and thawing four times. Cyclic AMP production was measured by radioimmunoassay (Amersham International PLC). The observations were repeated in the presence of 10^{-6} M propranolol. Analysis of results was by the Wilcoxon matched-pairs signed-rank test and the unpaired Student's *t*-test. A P value < 0.05 was considered significant. Racemic and (−)-fenoterol produced dose-dependent increases in cyclic AMP which were significantly reduced by 10^{-6} M propranolol at the 10^{-6}, 10^{-5} and 10^{-4} M concentrations. There was no significant reduction of the (+)-fenoterol response by propranolol except at the 10^{-4} M concentration. The (+)-fenoterol response was significantly less than either the racemic or the (−)-enantiomer response. The results for the 10^{-5} M concentrations of fenoterol are shown in Table 1 ($n = 10$).

In contrast to terbutaline where the (−) and (+)-enantiomers were approximately equipotent, (−)-fenoterol is much more potent than (+)-fenoterol at the human lymphocyte β_2-adrenoceptor.

Table 1 Cyclic AMP production expressed as a percentage of that produced by 10^{-5} M (−)-isoprenaline (± s.e. mean)

	(±)-Fenoterol	*(−)-Fenoterol*	*(+)-Fenoterol*
Drug only (10^{-5} M)	112.6 ± 28.8*	104.3 ± 23.4*	4.6 ± 2.4
Drug + propranolol	19.3 ± 10.2†	3.8 ± 2.0†	0.3 ± 0.3

* $P < 0.05$ compared with (+)-fenoterol.
† $P < 0.05$ compared with 'drug only' levels.

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Backtracking booze with Bayes

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A knowledge of population estimates of pharmacokinetic parameters and the application of Bayes Theorem to sparse plasma drug concentration data has been used to adjust drug dosage in individual patients (Whiting *et al.*, 1986). For medico-legal purposes the problem is different in that sparse plasma drug concentration data may be available from which either estimates of the original dose (drug OD) or of earlier concentrations above a legal limit (alcohol) may be requested. We have applied Bayes Theorem to illustrate the uncertainties involved in 'back-

tracking' blood alcohol concentrations. Rather than using the approximation derived by Sheiner *et al.* (1979) the required integrations were performed numerically to accommodate non-normal prior distributions.

Solutions to equation 1 were calculated using standard multi-dimensional Gaussian integration (NAG algorithm D01FCF). A simple pharmacokinetic model with first order input and zero order elimination was used to describe the fate of alcohol after an oral dose taken prior to $t(0)$. The size of the dose was unknown up to a limit determined by the physical capacity of the stomach and the typical alcohol content of spirits. Using population estimates of the first order absorption (0.13 min^{-1}), zero order elimination rate constants (0.2 g l^{-1} h^{-1}) and volume of distribution of alcohol (37.5 l) probability distributions of the blood alcohol concentration at $t = -3$ h given a concentration at $t(t(0) + 4$ h)of 60 mg dl^{-1} were calculated for the following conditions:- a) Instant absorption; variability only due to the assay. ---- b) Instant absorption; variability in both assay and rate of elimination. - - - c) Full model. —

The direct application of Bayes Theorem is feasible for a simple model of drug absorption and elimination using standard methods of integration. However backtracking of alcohol concentrations is unreliable if absorption continues after the time for which the estimate is required. Improved estimates may be possible if prior information on the amount of alcohol ingested is available, but in this case the model must incorporate a description of saturable first-pass metabolism.

Equation 1

$$p(\theta|x) = \frac{l(x;\theta)p\theta}{\int l(x;\theta)p\theta d\theta}$$

x data p probability
θ parameters l likelihood

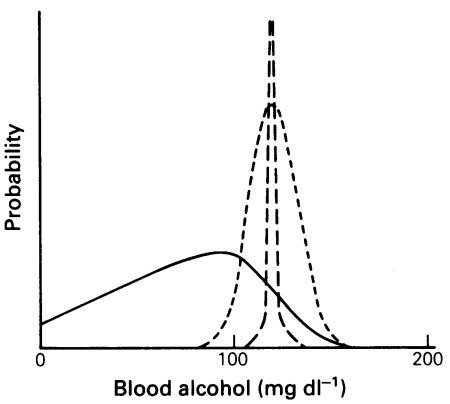

Figure 1 Reasonably precise estimates of the initial blood alcohol concentration are possible only under conditions (a) or (b).

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Effects of an inhaled leukotriene (LT) antagonist, SK&F 104353-Z_2 on LTD_4 and histamine induced bronchoconstriction in normal man

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The cysteinyl-containing leukotrienes (LTs) are potent broncho-constrictors when inhaled by man, and may have a fundamental role in the pathogenesis of asthma. Before specific LT-receptor antagonists are evaluated in clinical asthma, it is first essential to determine their LT-antagonist activity in human subjects.

SK&F 104353-Z_2 (the disodium salt of 2(S)-hydroxy-3(R)-[(2-carboxyethyl)thiol]-3-[2-(8-phenyloctyl)phenyl]-propanoic acid)—a potent antagonist of cysteinyl-LTs in guinea pig and human airways *in vitro* (Hay *et al.*, 1988) has been formulated as a solution for nebulisation. To assess the activity of this antagonist in man, we have investigated the acute effect of pre-inhalation of a single dose of SK&F 104353-Z_2

(D) (800 μg) on LTD_4 and histamine-induced bronchoconstriction in healthy male volunteers, in a randomised, placebo (P) controlled, double-blind, two-part, crossover study.

Each of the eight subjects (mean age: 30 years; range: 24–36 years) was studied on 4 separate days. On a study day, measurements of: FEV_1, specific airways conductance (sGaw), ar d flow at 30% vital capacity above residual volume ($V_{max_{30}}$), were made pre- and post-dosing. Solutions of P or D were nebulised using an ultrasonic nebuliser and the aerosol inhaled for 10 min. At 15 min post-dosing, a single concentration of LTD_4 or histamine was inhaled from a Wright nebuliser for 2 min—the nebuliser concentration of agonist had been previously found to reduce sGaw to at least 50% for each subject, by a previously described method (Barnes *et al.*, 1984). At 1 min post-challenge, lung function was measured by sGaw and $V_{max_{30}}$, and repeated at 5 min intervals until sGaw had recovered to 90% or more of post-dosing values.

SK&F 104353-Z_2 significantly reduced LTD_4-induced bronchoconstriction: mean minimum percentage of post-dosing values (mean ± s.e. mean)

(1) sGaw: 44.5 ± 3.9% (P) *vs* 85.7 ± 2.1% (D) $P < 0.001$;

(2) $V_{max_{30}}$: 52.0 ± 1.6% (P) *vs* 89.9 ± 1.2% (D) $P < 0.001$;

and shortened the time to sGaw recovery [sGaw 90% post-dosing values]: 35.9 ± 4.6 min (P) *vs* 1.9 ± 0.8 min (D) $P < 0.001$. In contrast SK&F 104353-Z_2 had no significant effect on histamine-induced bronchoconstriction: mean minimum percentage of post-dosing values (mean ± s.e. mean)

(1) sGaw: 40.8 ± 4.1% (P) *vs* 42.9 ± 4.5% (D);

(2) $V_{max_{30}}$: 53.4 ± 1.7% (P) *vs* 54.4 ± 3.5% (D);

and did not significantly alter the time to sGaw recovery: 30.2 ± 3.0 min (P) *vs* 31.5 ± 4.8 min (D). SK&F 104353-Z_2 had no effect on baseline lung function and no side effects were found.

These results demonstrate that inhaled SK&F 104353-Z_2 is an active LT-antagonist in man, producing significant protection against LTD_4-induced bronchoconstriction. The lack of effect on histamine-induced bronchoconstriction suggests that SK&F 104353-Z_2 is a specific LT-antagonist in man. Since SK&F 104353-Z_2 is well tolerated, and is active in man by the inhaled route, it has great potential for use in elucidating the actual role of LTs in asthma.

Barnes, N. C. *et al.* (1984). *Thorax*, **39**, 500.
Hay, D. W. P. *et al.* (1988). *J. Pharmac. exp. Ther.*, **243**, 474.