Cefoxitin: a hospital study

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Summary

Cefoxitin is a new cephamycin antibiotic that has recently become available for clinical trial. We report here the results of an uncontrolled trial of cefoxitin treatment in 31 hospital patients with various acute infections, 20 of whom were cured. Serum, urine, and bile concentrations of cefoxitin greatly exceeded the minimum inhibitory concentration (MIC) required for clinically important Gram-negative organisms. We conclude that cefoxitin will have a place in the management of serious infections, particularly in the abdominal cavity and renal tracts.

Introduction

Cefoxitin is a semisynthetic cephamycin antibiotic which has recently been made available for clinical trial. Cephamycins differ from the cephalosporins in that they have an α-methoxy group in the 7-position of the structure of the molecule.[1] Cefoxitin also has a carbamoyloxy group in the 3-position of the molecule.[2] While the cephalosporins are labile to the β-lactamases of many Gram-negative organisms, cefoxitin is stable to degradation by these enzymes.[3] Cefoxitin has greater activity than the cephalosporins against most Gram-negative bacilli including indole-producing *Proteus spp* and *Serratia marcescens*, which are normally cephalosporin-resistant, but is less active against Gram-positive organisms.[3-6] Cefoxitin is also active against anaerobic organisms including *Bacteroides fragilis*.[7,8] Pharmacokinetic studies in volunteers have shown that serum and urine concentrations of cefoxitin are higher and more sustained than those obtained after equivalent doses of cephalothin.[3] We studied the toxicological and pharmacological effects of cefoxitin on 31 hospital patients with various acute infections.

Patients and methods

Thirty-one hospital inpatients suffering from various acute infections were selected for treatment with cefoxitin (table I). Ten of the 31 patients suffered from respiratory tract infection, nine from urinary tract infection, eight from septicaemia, and four from intra-abdominal infections. Patients with urinary tract infections were only included in the trial if two consecutive midstream specimens of urine contained a significant growth ($>10^5$/ml) of the same organism before treatment. Cefoxitin was given to patients over five minutes by intravenous bolus injection although eight received several doses intramuscularly. The dose of cefoxitin ranged from 1 g eight-hourly to 2 g six-hourly. The minimum total dose was 8 g and maximum total dose 54 g. In all patients before, during, and after cefoxitin treatment full blood count was taken, Coombs's test, urine analysis, and liver function tests were performed, and serum urea and creatinine concentrations were measured.

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PHARMACOLOGY

Serum cefoxitin concentrations were measured in seven and urine concentrations in four of the 21 patients after intravenous injection of the antibiotic over three minutes. In two patients with postcholecystectomy T-tube drainage cefoxitin concentrations in bile were assayed. Two grams of cefoxitin were given to two patients before lumbar puncture and the cerebrospinal fluid (CSF) was collected one hour after injection and tested for antibiotic activity. One of the patients had meningoencephalitis but the other was subsequently found to have no disease of the central nervous system. Cefoxitin concentration in breast milk was measured in a lactating woman being treated with the drug for a urinary tract infection. Cefoxitin assays were performed using a plate assay method with Penassay media No 1 (Difco) using a *Bacillus subtilis* spore suspension.

Results

Twenty of the 31 patients were cured by cefoxitin, while a further five responded satisfactorily (table I) but the infecting organism either persisted in the sputum (three patients) or reappeared after treatment (two patients). The remaining six patients were considered to be treatment failures. Two of these were elderly women with urinary tract infections, two had respiratory tract infections, and two had septicaemia. In the two patients with chest infections who failed to respond to cefoxitin we could not obtain a bacteriological diagnosis before treatment, although the sputum had been frankly purulent and there were signs of pneumonia. One of the patients with septicaemia who did not respond to treatment proved to have *Enterobacter aerogenes* in the blood for which the MIC of cefoxitin was greater than 80 mg/l. The other had an intra-abdominal abscess associated with biliary sepsis and he remained feverish and unwell with a positive blood culture until the abscess was drained. He died four weeks after this operation and necropsy showed carcinoma of the pancreas with metastases in the liver.

PHARMACOLOGICAL FINDINGS

One gram of cefoxitin given intravenously to two patients produced serum concentrations of 58 and 73 mg/l respectively after five minutes. Five minutes after 2 g cefoxitin was given by intravenous bolus injection peak serum concentrations were measured in five patients and were 130, 140, 230, 305, and 340 mg/l (mean 229 mg/l) (table II). Serum concentrations remained satisfactory one hour after a dose and were adequate at two hours.

Urine cefoxitin concentrations in patients given 2-g doses ranged from 3500 mg/l to 25 000 mg/l in the first hour after administration of the antibiotic (table III). Cefoxitin concentrations in bile were very high (table IV). The cefoxitin concentration in breast milk collected two hours after an intravenous dose of 1 g was 5·6 mg/l milk. Antibacterial activity was not demonstrable in the CSF of two patients given 2 g cefoxitin by intravenous injection one hour before lumbar puncture.

TOXICOLOGICAL EFFECTS

During cefoxitin treatment eight of 31 patients developed transient and slight rises in serum hepatic transaminase concentrations, the maximum concentration being 100 IU/ml (normal range < 35 IU/ml).

TABLE I—*Clinical histories of 31 patients treated with cefoxitin*

Age (years)	Infective diagnosis	Underlying diagnosis	Pathogen	Minimum inhibitory concentration (mg/l)	Outcome
38	Urinary tract infection	Encephalitis	*Escherichia coli*	2·5	Cured
82	Urinary tract infection		*Klebsiella aerogenes*	10	Failed
65	Urinary tract infection	Myxoedema	*E coli*	2·5	Failed (relapsed)
37	Urinary tract infection		*K aerogenes*	2·5	Cured
70	Urinary tract infection	Prostatism; urinary catheter	*K aerogenes*	2·5	Improved
23	Acute pyelonephritis		*E coli*	Not tested	Cured
19	Acute pyelonephritis	Postpartum infection	*E coli*	5	Cured
76	Acute pyelonephritis	Recurrent cystitis	*E coli*	5	Cured
18	Acute pyelonephritis		*E coli*	5	Cured
58	Acute bronchitis	Chronic bronchitis	*Haemophilus influenzae;* pneumococcus	5; 1·25	Improved
65	Acute bronchitis	Chronic lymphocytic leukaemia; emphysema	*H influenzae;* pneumococcus	5; 1·25	Cured
68	Bronchopneumonia		*H influenzae;* pneumococcus	5; 1·25	Cured
55	Bronchopneumonia		None isolated		Cured
62	Lobar pneumonia		None isolated		Failed
58	Lobar pneumonia	Peripheral vascular disease	None isolated		Improved
66	Bronchopneumonia	Squamous-cell carcinoma of lung	*H influenzae*	20	Improved
83	Bronchopneumonia	Dementia	None isolated		Failed
21	Segmental pneumonia		Pneumococcus	1·25	Cured
27	Segmental pneumonia		None isolated		Cured
66	Septicaemia	Intra-abdominal abscess	*E coli*	2·5	Failed
88	Septicaemia	Diverticular disease	*E coli*	5	Cured
44	Septicaemia	Ulcerative colitis; peritonitis	*K aerogenes*	2·5	Improved
62	Septicaemia	Prostatism with urinary catheter	*Enterobacter aerogenes*	80	Failed
56	Septicaemia	Diverticular disease	*E coli*	2·5	Cured
19	Septicaemia	Infectious mononucleosis on prednisolone treatment	*H influenzae*	10	Cured
81	Septicaemia	Prostatism with urinary catheter	*E coli*	5	Cured
25	Septicaemia	Pyelonephritis	*E coli*	5	Cured
66	Peritonitis	Perforated carcinoma of sigmoid colon	Group F streptococcus; *E coli*	5	Cured (plus surgery)
28	Peritonitis	Perforated biliary tree	*Streptococcus viridans;* anaerobic streptococci		Cured (plus surgery)
81	Peritonitis	Perforation of colon	None isolated		Cured (conservative management)
65	Psoas abscess	Psoas abscess	*Staphylococcus aureus*	5	Cured (plus surgery)

TABLE II—*Serum cefoxitin concentrations in two patients after 1 g intravenously, and five patients after 2 g intravenously. Absence of result indicates that no assay was performed*

Minutes after dose	Intravenous dose (g)						
	1	1	2	2	2	2	2
5	73	58	230	305	340	140	
15	44						
30	29		86			52	
45	21						
60	18			52		18	37
120	6		15				11
180			8	5		7	5
240			3	1	3		3

TABLE III—*Urine concentrations of cefoxitin in four patients after 2 g intravenously*

Time after dose (hours)	Urine concentrations (mg l)			
0–1	3500	7000	25 000	5800
1–2	3150	4600	11 000	2800
2–3	2300	1290	5800	1600
3–4	1015	640	1970	720

TABLE IV—*Serum and bile concentrations of cefoxitin (mg/l) after 2 g intravenously*

Minutes after dose:	5	60	120	180	240
Serum concentration	305	52·5	16	5·3	1·5
Bile concentration		217·6	227·6	77·6	32·6

Two patients had proteinuria but there were no unexplained rises in serum urea or creatinine concentrations and no drug-related changes in blood count. One patient developed phlebitis during cefoxitin treatment but recovered rapidly when the intravenous drip site was changed. Five of the eight patients who were given cefoxitin intramuscularly complained of pain at the site of injection and in two of these this was intolerable. None of the patients developed a serious adverse reaction during cefoxitin treatment.

Discussion

With the exception of *Pseudomonas aeruginosa*, cefoxitin is highly active in vitro against most Gram-negative bacilli, and is more active than the "first generation" cephalosporins against these organisms.[9] Cefoxitin has a broader antibacterial activity than most cephalosporins, being active against certain organisms that are resistant to this group of antibiotics, almost certainly because it is extremely stable in the presence of β-lactamases produced by Gram-negative bacilli.[3] The only cephalosporin comparable in this respect is cefuroxime, which also has a high degree of stability to β-lactamases produced by Gram-negative organisms and is also completely stable to degradation by staphylococcal β-lactamase.[10] Cefoxitin, however, is more active than cefuroxime against ampicillin-resistant *Escherichia coli* strains and indole-positive *Proteus spp.*[11]

Cefoxitin has a biological half life of 45 minutes as compared with cephalothin, the cephalosporin to which it is most closely related, which has a half life of only 25 minutes.[3] Our studies in patients have confirmed the findings of Kosmidis and his colleagues[3] in volunteers that mean peak serum concentrations after an intravenous injection of 2 g of the antibiotic are over 200 mg/l, while urine concentrations with the same dose may exceed 20 000 mg/l. Urinary recovery of cefoxitin has been reported as varying between 78%[12] and 90%[3] as compared with 55% with cephalothin. We found that concentrations of cefoxitin in bile greatly exceed the MIC of most Gram-negative bacilli that inhabit the bowel. Hence probably cefoxitin will prove valuable for intra-abdominal and urinary tract infections and biliary sepsis. Cefoxitin was not detected in the CSF of one patient with non-inflammed meninges and one with meningoencephalitis, which accords with the poor meningeal penetration of other β-lactam antibiotics.

In the clinical study cefoxitin cured 20 (64·5%) of a group of 31 patients with infections of the respiratory tract, urinary tract, peritoneal cavity, and septicaemia. Two of the patients with respiratory tract infection failed to respond but in both instances we could not culture an organism from a pretreatment sputum specimen and we cannot therefore assess the importance of this result. Of the two patients with urinary tract infection who failed to respond, one was elderly and had a uterine

prolapse. The second was also an elderly woman with myxoedema who initially responded to cefoxitin but relapsed with the same infecting organism in the urine four weeks later. Both had residual urine in the bladder. All of the patients suffering from pyelonephritis were cured by cefoxitin but two of the eight patients with septicaemia failed to respond. All four patients with intra-abdominal sepsis were cured by cefoxitin treatment, combined in three with surgical drainage.

Cefoxitin appears to share with the cephalosporins and penicillins the property of rarely producing serious adverse reactions. Apart from transient derangement of liver function, and phlebitis in one patient, none of the patients developed untoward reactions to the antibiotic. Furthermore, it has been suggested[13] that cross-allergenicity between the cephalosporins and the cephamycins might not occur because of the differing chemical structures. There was no evidence of nephrotoxicity as demonstrated by increased serum urea or creatinine concentrations, both of which were measured before, during, and after treatment with cefoxitin.

The present uncontrolled study suggests that cefoxitin will have a place in the management of serious infections, particularly in the peritoneal cavity and biliary and renal tracts. Serum, urine, and bile concentrations of the antibiotic greatly exceed the MIC required for clinically important Gram-negative organisms.

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Self-poisoning with barbiturates in England and Wales during 1959-74

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Summary

Hospital admissions due to acute barbiturate poisoning per million population in England and Wales have decreased since 1965 at about the same rate as NHS prescriptions for barbiturates. Admissions due to poisoning with other drugs have increased, but, largely because the benzodiazepine hypnotics and tranquillisers are much less toxic than the barbiturates that they are replacing, deaths from poisoning with all solids and liquids have decreased. The risk of death from self-poisoning associated with each barbiturate prescription has increased two and a half times since 1961, perhaps partly because greater quantities of barbiturate are being dispensed with each prescription and partly because patients for whom these drugs are still being prescribed would, in the event of an overdose, be unlikely to be found and admitted to hospital in time owing to their age and social circumstances. There is now little to justify prescribing barbiturate hypnotics or sedatives for anyone.

Introduction

During 1959-74 over 27 000 people died in England and Wales from acute poisoning with self-administered barbiturates. During that period some 225 million prescriptions for barbiturate hypnotics and sedatives were dispensed within the NHS, apart from those dispensed from hospital pharmacies, for which detailed figures are not available.

My aim was to investigate changes in the overall incidences of death and hospital admission due to self-poisoning with barbiturates in relation to their availability on NHS prescriptions since 1959.

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Methods

The yearly number of deaths in England and Wales from poisoning with all solids and liquids, including medicinal agents and household poisons, and those due to barbiturates were derived from the annual lists of poisonings issued by the Registrar General. Cases in which barbiturates were ingested along with other poisons were listed separately from those caused by barbiturates alone. In 1974 alcohol was specifically mentioned as a contributory cause of death in 15% of barbiturate deaths, but because the contribution of alcohol to deaths in earlier years was uncertain it has been omitted from consideration. Other errors and omissions would undoubtedly arise in the reporting of causes of death and, later, in their classification, but I have assumed that such errors did not appreciably affect the major trends in the years covered by this investigation.

Estimates of the total number of hospital deaths and discharges after poisoning with all medicinal agents (ICD codes N960-N979) and barbiturates alone (coded N971 until 1967, then N967.0) were derived from the *Hospital In-Patient Enquiries* made by the Department of Health and Social Security. The yearly number of prescriptions for barbiturate hypnotics and sedatives (omitting general anaesthetics and anticonvulsants) and average number of doses per prescription were estimated from a 0·5% sample of all NHS prescriptions handled by the Department of Health and Social Security, with the exclusion of those dispensed from hospital pharmacies. These figures underestimate the overall availability of barbiturates in the community but I have assumed that they reflect changes in the latter from year to year with reasonable accuracy.

Yearly death rates and rates of hospital admission were calculated, firstly, per million population in England and Wales, and, secondly, per million NHS prescriptions for barbiturate hypnotics and sedatives.