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Moclobemide excretion in human breast milk

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1 Six lactating white women, aged 24–36 years, received a single oral dose of 300 mg moclobemide, between 09.00 h and 11.00 h, 3 to 5 days after the delivery of a full term neonate.

2 Complete milk collections were obtained before, 3, 6, 9, 12 and 24 h after drug administration by means of a breast pump. Venous blood samples were drawn before, and 0.5, 1, 3, 4.5, 6, 9, 12, 24 h post-dosing.

3 Moclobemide, and its major metabolite (Ro 12-8095) were measured in milk and plasma samples using h.p.l.c. The active metabolite (Ro 12-5637) could only be detected in plasma.

4 Moclobemide and its metabolites were not detectable in 24 h plasma samples. C_{max}, t_{max} and $t_{½}$ for moclobemide were (mean ± s.d.) 2.70 ± 1.24 mg l^{-1}, 2.03 ± 1.19 h and 2.26 ± 0.26 h, respectively.

5 The concentrations of moclobemide and Ro 12-8095 in milk were highest at 3 h after drug administration and the drug and metabolite were not detectable after 12 h. Ro 12-5637 was not detected in any milk sample. The percentages of the dose excreted as moclobemide and Ro 12-8095 were (mean ± s.d.) 0.057 ± 0.020% and 0.031 ± 0.011%, respectively. An average 3.5 kg breast-fed neonate would therefore be exposed to only a 0.05 mg kg^{-1} moclobemide dose (approximately 1% of the maternal dose on the mg kg^{-1} basis). The low amount of moclobemide excreted into breast milk is unlikely to be hazardous to suckling infants.

Keywords breast milk antidepressant monoamine oxidase inhibitor moclobemide

Introduction

Moclobemide, a benzamide derivative, is a new reversible monoamine oxidase-A inhibitor (Keller *et al.*, 1987). It possesses an antidepressant efficacy comparable with that of clomipramine, amitriptyline and imipramine (Larsen *et al.*, 1984; Norman *et al.*, 1985; Stabl *et al.*, 1989) and superior to that of placebo (Casacchia *et al.*, 1984; Stabl *et al.*, 1989). Most patients tolerate moclobemide better than tricyclic antidepressants (Larsen *et al.*, 1984; Stabl *et al.*, 1989). Moclobemide might be useful in the management of postnatal depression. The advantages of breast feeding in this condition are well recognized and physicians are often reluctant to advise discontinuation of breast feeding because of potential risks to the infant posed by the presence of an antidepressant drug in mother's milk. The purpose of this study was to measure the time course of moclobemide and its metabolites in human milk and to determine the exposure of breast-fed neonates after a single 300 mg oral dose.

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Moclobemide is a weak base (pKa 6.3) with an *n*-octanol/water distribution coefficient of 62 at a pH of 7.4 and a molecular weight of 269. It is 50% bound to plasma proteins (Schoerlin *et al.*, 1989). Data in normal healthy volunteers indicate a short terminal half life (1 to 2 h), an intermediate clearance (39 l h^{-1}) and a large volume of distribution (1 to 1.5 l kg^{-1}) after a 150 mg intravenous dose. The drug is eliminated primarily by metabolism and exhibits non linear kinetics. The absolute bioavailability averages about 60% after a 100 mg oral dose (Schoerlin *et al.*, 1987).

Ro 12-8095, the main metabolite, produced by hydroxylation of the morpholine ring, is inactive while Ro 12-5637 produced by *N*-oxidation of the same ring is active.

Methods

Six lactating white women, ranging in age from 24 to 36 years, in height from 158 to 172 cm and in weight from 48 to 63 kg were recruited to the study. Each subject was in good health as assessed by medical history, physical examination and routine laboratory tests. The study was performed on day 3 to 5 after delivery of a full term neonate. Mothers nursing twins were excluded. The subjects had not used any medication known to induce or inhibit drug metabolism, for at least 2 weeks before drug administration and during the study. Written informed consent was obtained from all subjects prior to the study. The protocol was approved by the UER Cochin Port-Royal Ethics Committee. Before the study each mother agreed to stop nursing her infant for 24 h after drug administration.

Each mother received a single oral dose of 300 mg moclobemide as three 100 mg tablets with 120 ml of water between 09.00 h and 11.00 h after a low-fat breakfast. A lunch was served 4 h after drug intake. During the entire blood sampling period, the subjects were allowed light meals which were low in fat. Breast milk was collected using an Egnell SMB breast electric pump (AMEDA AG, Zug, Switzerland). The working cycle of the breast pump is divided into three phases: a short suction phase, during which the pressure decreases from atmospheric pressure to 520 mm Hg (negative pressure of 240 mm Hg); a short relief phase, back to atmosphere pressure; a resting phase under slight overpressure of about 10 mm Hg. The suction rhythm is of 48 periods min^{-1}. Milk samples were collected immediately before dosing and 3, 6, 9, 12, 24 h after drug administration. Available milk was collected as completely as possible from each breast. Blood samples were drawn, immediately before, 0.5, 1, 3, 4.5, 6 and 9 h after drug administration in the first two patients. Two additional blood samples were taken, 12 and 24 h post-dosing in the remaining four. Plasma and milk samples were stored at −20° C until analysis.

The concentrations of moclobemide and its metabolites (Ro 12-5637) and (Ro 12-8095) in plasma were measured by h.p.l.c. (Geschke *et al.* 1987). Moclobemide and Ro 12-8095 were measured in milk using the same h.p.l.c. method after a two step extraction with butylchloride and an acetonitrile/hexane (1 : 1 v/v) mixture. The detection limits were as follows: 20, 30 and 30 ng ml^{-1} in 0.5 ml of plasma for moclobemide, Ro 12-5637 and Ro 12-8095; and 0.025 and 0.030 mg l^{-1} in 0.5 ml of milk for moclobemide and Ro 12-8095, respectively. The interassay reproducibility was as follows: 1.8 to 7.9% and 3.3 to 9.0% for moclobemide and Ro 12-8095 over the concentration range in plasma (0.15 to 2.50 mg l^{-1}) and in milk (0.035 to 0.700 mg l^{-1}), respectively. The apparent elimination half-life ($t_{½}$) was calculated by linear regression from the slope of the log linear decay of the 4.5 to 12 h concentration-time points. The area under the moclobemide plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule with extrapolation to infinity using the ratio of the concentration calculated at the last time point divided by the terminal elimination rate constant. The oral clearance (CL_O) was calculated as the ratio of the oral dose/AUC.

The results are expressed as means and standard deviations (s.d.). For $t_{½}$, values of the mean and s.d. are the harmonic mean and the 'pseudo' standard deviation (Lam *et al.*, 1985).

Results

Milk yield was 440 ± 103 ml 24 h^{-1} and 82.6 ± 37.5 ml/time-point.

Mean plasma moclobemide and metabolite plasma concentration-time curves are shown in Figure 1a. Moclobemide, Ro 12-5637, Ro 12-8095 were not detectable in 24 h plasma samples. The maximum plasma concentration of moclobemide (C_{max}) was observed between 0.58 and 3.17 h after drug administration (t_{max}) and ranged from 1.47 to 4.93 mg l^{-1} (Table 1). The mean $t_{½}$, AUC and oral plasma clearance (CL_O) values of moclobemide were 2.27 ± 0.26 h, 11.66 ± 3.30 mg l^{-1} h and 27.61 ± 8.28 l h^{-1}, respectively (Table 1).

The concentrations of moclobemide and its main metabolite Ro 12-8095 excreted in breast

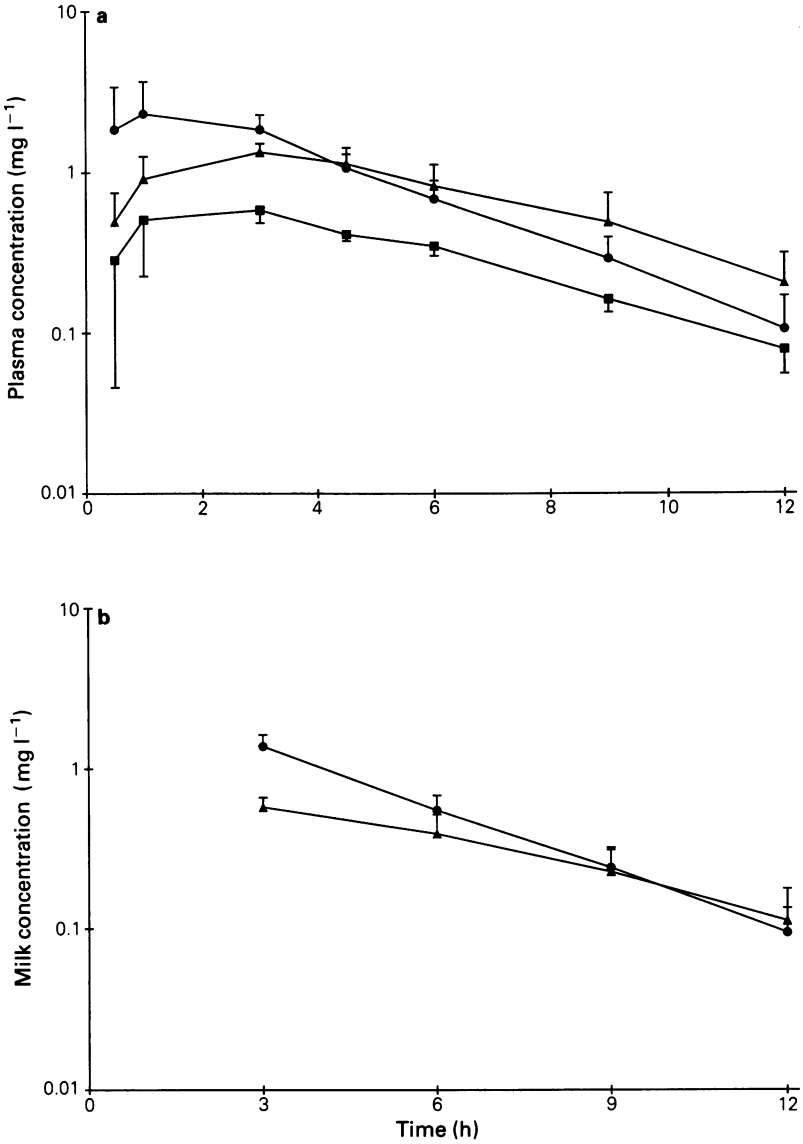

Figure 1 a) Plasma concentration-time profiles (mean ± s.d.) of moclobemide (●), Ro 12-8095 (▲) and Ro 12-5637 (■) following a 300 mg oral dose of moclobemide in six lactating mothers. b) The mean (± s.d.) concentration of moclobemide (●) and Ro 12-8095 (▲) in breast milk as a function of time following a 300 mg oral dose of moclobemide in six lactating mothers.

Table 1 Parameters describing the pharmacokinetics of moclobemide following a 300 mg oral dose in six lactating mothers

Subject	t_{max} (h)	C_{max} (mg l^{-1})	$t_{1/2}$ (h)	AUC (mg l^{-1} h)	CL_O (l h^{-1})
1	3.17	1.88	2.43	9.66	31.05
2	1.10	3.14	2.42	13.39	22.41
3	3.08	1.47	1.98	7.40	40.56
4	0.58	4.93	2.28	16.33	18.37
5	1.20	2.14	2.00	9.66	31.06
6	3.03	2.63	2.63	13.49	22.25
Mean	2.03	2.70	2.27	11.66	27.62
s.d.	1.19	1.24	0.26	3.30	8.16

Table 2 Breast milk excretion of moclobemide and Ro 12-8095 following a 300 mg oral dose in six lactating mothers

	Moclobemide			*Ro 12-8095*	
Subject	*Cumulative amount excreted in milk (0–24 h)* (mg)	*% of dose excreted in milk* (%)	*Cumulative amount/ plasma AUC ratio* (l h^{-1})	*Cumulative amount excreted in milk (0–24 h)* (mg)	*% of dose excreted in milk* (%)
1	0.1059	0.035	0.01096	0.0500	0.106
2	0.1948	0.065	0.01455	0.1285	0.041
3	0.1483	0.049	0.02005	0.0950	0.030
4	0.1408	0.047	0.00862	0.0772	0.024
5	0.1576	0.053	0.01631	0.1445	0.046
6	0.2833	0.094	0.02101	0.0841	0.027
Mean	0.1718	0.057	0.01525	0.0966	0.031
s.d.	0.0617	0.020	0.0049	0.0347	0.011

milk were highest 3 h after drug administration and were no longer measurable after 12 h. The milk concentration-time curves paralleled the plasma concentration-time curves (Figure 1b). The concentration of moclobemide in milk correlated with its plasma concentration ($y = 45.118 + 0.71892x$; $r = 0.986$): the slope of this equation indicates that the concentration of drug in milk is, on average, 72% of that in plasma. The percentage of the administered dose excreted in 24 h was 0.057 ± 0.020 and 0.031 ± 0.011% for moclobemide and Ro 12-8095, respectively (Table 2). Ro 12-5637, an active metabolite, was not detected in breast milk.

Discussion

The experimental design took into consideration the significant changes, previously described (Wilson *et al.*, 1980), in milk composition and yield, which depend on the time of sampling during a feeding, the side of collection, the time of the day, the stage of lactation and the nutritional state. The sampling protocol was standardized to allow interpatient comparisons and also for the measurement to be relevant to clinical practice. Milk was sampled from each breast as completely as possible in order to obtain samples representative of a complete feed. The time interval between consecutive milk collections was similar to that of a regular schedule of breast feeding. In all patients the study was performed during the fourth to the sixth days postpartum and at the same time of the day. All of the lactating mothers were well nourished and had given birth to a full term neonate.

Drug excretion in breast milk is primarily by passive diffusion across the mammary membranes leading to rapid equilibration of drug between plasma and milk (Wilson *et al.*, 1980). Breast milk can, therefore, be considered as a

compartment with bidirectional transfer across a blood-milk barrier rather than a bladder with milk accumulation between two consecutive collections. We thus chose to consider each milk sample as instantaneous, at the mid-point of the milk collection interval, rather than to consider the amount of drug recovered as the result of drug accumulation in breast during the time elapsed since the previous milk collection. The parallel decline of milk and plasma moclobemide concentrations (Figure 1a and 1b) support the hypothesis of rapid equilibration of drug between plasma and milk. The kinetic parameters describing the time course of moclobemide in plasma in the lactating mothers following a 300 mg dose are consistent with those observed in previous studies in healthy male volunteers (Data on file Hoffmann La Roche).

We have shown that breast-fed neonates from mothers treated with a single 300 mg oral dose of moclobemide would be exposed to only a small amount of the drug and its major and inactive metabolite Ro 12-8095 when fed as early as 3 h after drug administration. Using the total amounts of compounds recovered in breast milk over the period of the study, a child weighing 3.5 kg is estimated to receive, on average, about 0.050 mg kg^{-1} moclobemide (approximately 1% of the maternal dose on the mg kg^{-1} basis) and 0.028 mg kg^{-1} Ro 12-8095, assuming that such a 3–5 day old infant would be able to ingest the relatively large amount of milk collected. The amount of moclobemide transferred into milk is not expected to be very much higher after the 6th day post-delivery due to changes in milk yield and composition which occur during maturation.

During multiple dosing, accumulation of the compounds in plasma and breast milk may occur. Accumulation in plasma has been demonstrated in healthy volunteers. Furthermore, moclobemide exhibits non linear kinetics when given as a 100 mg dose three times daily for 15 days, the steady-state area under the plasma drug concentration-time curve being two times higher than after a single 100 mg dose (Schoerlin *et al.*, 1987). The dosage used in the present study is two to three times higher than a single therapeutic dose. Thus, the AUC obtained in the present study in lactating mothers receiving a single 300 mg dose was similar to that, at steady-state, in healthy volunteers receiving 150 mg three times daily (Data on file Hoffmann La Roche). The dosage used in the present study might, therefore, be considered as representative of steady-state conditions, suggesting that exposure of breast-fed neonates during a dosing interval of a 150 mg three times daily therapeutic chronic dose is not expected to be different to that following a single 300 mg dose. The low amount of moclobemide excreted into breast milk is unlikely to be hazardous to suckling infants.

References

Casacchia, M., Carolei, A., Barba, C., Frontoni, M., Rossi, A., Meco, G. & Zylberman, M. R. (1984). A placebo-controlled study of the antidepressant activity of moclobemide, a new MAO-A inhibitor. *Pharmacopsychiatry*, **17**, 122–125.

Geschke, R., Korner, J. & Eggers, H. (1987). Determination of the new monoamine oxidase inhibitor moclobemide and three of its metabolites in biological fluids by h.p.l.c. *J. Chromatogr.*, **420**, 111–120.

Keller, H. H., Kettler, R., Keller, G. and Da Prada, M. (1987). Short-acting novel MAO inhibitors: *In vitro* evidence for the reversibility of MAO inhibition by moclobemide and Ro 16-6491. *Naunyn-Schmiedebergs Arch. Pharmac.*, **335**, 12–20.

Lam, F. C., Hung, C. T. & Perrier, D. G. (1985). Estimation of variance for harmonic mean half-lives. *J. pharm. Sci.*, **74**, 229–231.

Larsen, J. K., Holm, P. & Mikkelsen, Ph. (1984). Moclobemide and clomipramide in the treatment of depression. *Acta Psychiatr. Scand.*, **70**, 254–260.

Norman, T. R., Ames, D., Burrows, G. D. & Davies, B. (1985). A controlled study of a specific MAO-A reversible inhibitor (Ro 11-1163) and amitriptyline in depressive illness. *J. affective Disord.*, **8**, 29–35.

Schoerlin, M. P., Mayersohn, M. & Korn, A. (1987). Disposition kinetics of moclobemide, a mono amine oxidase-A enzyme inhibitor: single and multiple dosing in normal subjects. *Clin. Pharmac. Ther.*, **42**, 395–404.

Schoerlin, M. P. & Guentert, T. W. (1989). Pharmakokinetik und Metabolismus reversibler MAO-A Hemmer beim Menschen. *Psychiatr. Prax.*, **16**, 11–17.

Stabl, M., Bizière, K., Schmid-Burgk, W. & Amrein, R. (1989). Review of comparative clinical trials: moclobemide *vs* tricyclic antidepressants and *vs* placebo in depressive states. *J. Neural. Transm.*, suppl 28, 77–89.

Wilson, J. T., Brown, R. D., Cherek, D. R., Dailey, J. W., Hilman, B., Jobe, P. C., Manno, B. R., Manno, J. E., Redetzki, H. M. & Stewart, J. J. (1980). Drug excretion in human breast milk: principles, pharmacokinetics and projected consequences. *Clin. Pharmacokin.*, **5**, 1–66.

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