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Pharmacokinetics of Moclobemide in Male, Virgin Female, Pregnant and Nursing Rats

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Abstract—The disposition of moclobemide, a reversible inhibitor of monoamine oxidase isoenzyme A was studied in male, virgin female, pregnant and nursing rats. The average clearance in control rats (male and female) was 36 mL min^{-1} kg^{-1}, the initial volume of distribution 1·4 L kg^{-1}, the volume of distribution at steady state 2·3 L kg^{-1} and the terminal half-life 59 min. The blood-to-plasma concentration ratio of moclobemide was 0·84 giving rise to an average blood clearance of 30 mL min^{-1} kg^{-1}. The clearance values in rats were higher than in man but as a fraction of hepatic blood flow were similar (36 vs 45%). The volume of distribution at steady state was approximately twice as high as in man while the half-life was similar. Pregnant and nursing rats showed no statistically significant differences in their disposition parameters for moclobemide compared with virgin female rats. Nursing rats had statistically significantly lower concentrations of the moclobemide *N*-oxide metabolite than did pregnant and control rats. Generally lower concentrations of the lactam metabolite were also found in this group although the differences did not reach statistical significance. Moclobemide as well as the *N*-oxide and lactam metabolites were found in the amniotic fluid suggesting that moclobemide is capable of crossing the placental barrier.

Moclobemide (4-chloro-*N*-[2-(4-morpholinyl)-ethyl]benzamide) (Fig. 1) is a new reversible inhibitor of the monoamine oxidase isoenzyme A (Da Prada et al 1983). It is largely metabolized before elimination from the body with < 1% of the dose being excreted unchanged in human urine (Schoerlin et al 1987). In man, 19 metabolites accounting together for about 64% of the dose have been isolated from urine (Jauch et al 1990a). The major metabolic degradation occurs via oxidation involving mainly the morpholino moiety of the molecule. While not found in urine, the lactam derivative of moclobemide (M-O) (Fig. 1) is the most prominent degradation product in plasma but is inactive. The morpholine-*N*-oxide (M-NO) (Fig. 1) is quantitatively less important in plasma than in urine but is the only metabolite detectable in human plasma which retains some of the parent drug's activity. However, this activity is less than that of moclobemide (Da Prada et al 1989).

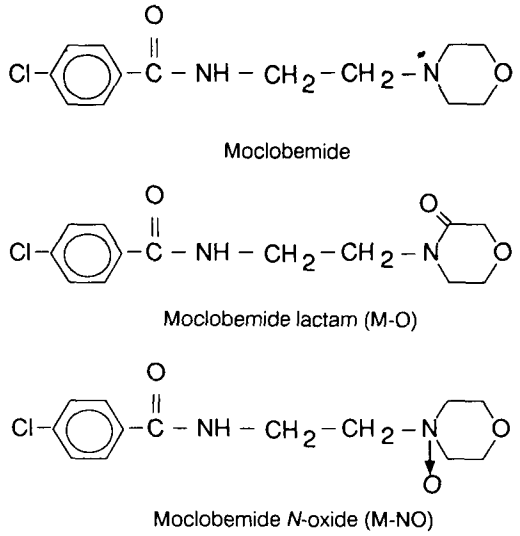

Fig. 1. Structural formulae of moclobemide, the lactam and morpholine-*N*-oxide metabolites of moclobemide.

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Moclobemide has a relatively short half-life with values ranging usually from 1 to 3 h (Schoerlin et al 1987, 1988; Guentert et al 1990). The clearance observed after single doses in two different studies was 0·50 and 0·76 L h^{-1} kg^{-1} (Raaflaub et al 1984; Schoerlin et al 1987) and is not affected by renal impairment (Schoerlin et al 1990). The steady-state volumes of distribution in the same two studies were 1·1 and 1·0 L kg^{-1}. The bioavailability has been reported to be 0·55 (Schoerlin et al 1987) and 0·66–0·69 on average (Guentert et al 1990) after single oral 100 and 150 mg doses. The oral clearance of moclobemide (clearance divided by bioavailability) is approximately 0·7–1·0 L h^{-1} kg^{-1} (Schoerlin et al 1987, 1988; Guentert et al 1990). In a preliminary report on moclobemide in nursing mothers the oral clearance of moclobemide was found to be 27·6 L h^{-1} (Pons et al 1990). Using an average weight of 55·5 kg (range 48–63 kg) the oral clearance was approximately 0·5 L h^{-1} kg^{-1}, lower than found in other groups. However, a control group in the study consisting of non-lactating female volunteers did not reveal a difference between lactating and non-lactating females (Schoerlin, personal communication).

The present study in the rat was undertaken for two reasons. First to determine if the disposition of moclobemide was altered during pregnancy and in the nursing stage. The second purpose was to determine the disposition of moclobemide in rats. To date, no studies of moclobemide disposition in this animal species have been published. Because rats often show sex-related differences in P450 metabolism, moclobemide disposition was determined in both male and female rats.

Materials and Methods

Animals

Virgin female rats (170–200 g), nursing rats (230–275 g) from first time pregnancy, first time pregnant rats (240–310 g) and male rats (250–275 g) were used throughout the studies. For all experiments Sprague-Dawley rats were obtained from Bantin and Kingman (Fremont, CA, USA). The animals (six to seven in each group) were anaesthetized by intramuscular administration of ketamine (22–44 mg kg^{-1}) and acepromazine (10% w/w of total ketamine dose) to the hind leg. Booster doses of the anaesthesia were administered at doses equal to 50% of the original administration using corneal reflex as a guide. The body temperature was monitored using a rectal thermometer probe and maintained at approximately 37°C by placing the animals on a temperature-regulated heating pad. The neck area was shaved, a midline neck incision made and the carotid artery and jugular vein were cannulated with silastic polymer tubing (0·02 in. i.d., 0·037 in. o.d.). The carotid catheter was used for blood collection, and the jugular catheter for bolus dose administration, fluid replacement and packed cell infusion.

Pharmacokinetic studies

A 15 mg kg^{-1} intravenous bolus dose of moclobemide was administered to all animals. Blood samples of 0·3 mL were obtained just before moclobemide administration and again at approximately 2, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 210, 240, and 300 min after administration. The samples were collected in tuberculin syringes containing 3 μL of a 1 USP unit μL^{-1} heparin solution. The tubing was subsequently rinsed with 0·1 mL 0·9% NaCl (saline). The samples were centrifuged, the haematocrit measured and the plasma separated from the packed cells, and stored at −20°C until assayed. Additional samples of 0·3 mL whole blood were collected at 2 and 300 min to measure the whole blood/plasma moclobemide concentration ratio. To prevent hypovolaemia, the packed cells from each collection (with the exception of samples for whole blood determination) were resuspended with 6% dextran 70 to a total volume of 0·3 mL and reinfused within 5 min. At the conclusion of the experiment the rats were exsanguinated and the resulting plasma stored frozen. In the pregnant rats the following additional procedure was carried out: immediately after exsanguination a midline incision was made and the amniotic sac with the foetuses removed. A volume of 1·5 to 3 mL amniotic fluid was aspirated using 25G injection needles and the foetuses immediately killed. The obtained fluid was stored frozen until assayed.

Protein binding

Protein binding was determined using an equilibrium dialysis technique in 1 mL plexiglass equilibrium dialysis cells. The dialysis membrane was a Spectra/por II (Spectrum Medical Instruments Inc., Los Angeles, CA, USA) with a mol. wt cut-off of 12 000 Da. The membranes were rinsed with distilled water and soaked in distilled water for 5 min. The membranes were subsequently soaked in methanol for at least 15 min, rinsed with distilled water, and soaked in 0·13 M phosphate buffer pH 7·4, overnight. Seven hundred μL 0·13 M phosphate buffer, pH 7·4 containing 10 μg mL^{-1} moclobemide was dialysed against 700 μL plasma or serum at 37°C in a water bath shaker for 6–7 h. At the end of the dialysis the volumes in the two half-cells were measured and the samples stored frozen at −20°C until assayed.

The unbound fraction, f_u, was calculated from the buffer and plasma (or serum) concentration ratio from each dialysis cell corrected for volume flux when the flux exceeded 10% of the total buffer volume as described by Øie & Fiori (1985).

Effect of heparin on protein binding

Four virgin rats were cannulated as described above. Two to three mL blood from each rat was drawn from the carotid artery and allowed to clot; the serum was subsequently harvested. Sixty units of heparin (USP) were administered via the jugular vein catheter. Ten min later 6·5 mL blood was withdrawn, centrifuged, and the plasma collected. The serum and plasma collected were pooled separately and used to determine the moclobemide binding in rats as well as to assess the effect of heparin on the binding.

Plasma/whole blood concentration ratio

A sample of the whole blood obtained from all study groups at the first and last sampling time was haemolysed by freezing. The concentration of moclobemide was determined in the haemolysed blood as described for plasma. In addition, heparinized whole blood was obtained from one nursing rat and one female control rat. To the blood [^{14}C]moclobemide (103 μCi mg^{-1}) as well as non-radioactive moclobemide was added to achieve concentrations of 2, 6, and 15 μg mL^{-1}. The samples were incubated for 30 min at room temperature (21°C) and divided into two parts. Half the samples were centrifuged and the resulting plasma was measured for moclobemide using a scintillation counter. The remaining blood, haemolysed by freezing, was measured for moclobemide concentration by scintillation counting. From these results the plasma/whole blood concentration ratio as a function of concentration was determined.

Analysis

Moclobemide and metabolite stock solutions were obtained by dissolving 1 mg moclobemide, 1 mg metabolite M-NO or 1 mg metabolite M-O in 35 μL 0·1 M HCl and diluting with saline to yield concentrations of 400 μg mL^{-1} moclobemide, 100 μg mL M-NO and 100 μg mL M-O. These stock solutions were subsequently used to yield working standards containing mixtures of moclobemide and its metabolites by diluting with control rat plasma. Resulting moclobemide standard concentrations were in the range of 0·31–20 μg mL^{-1} of M-NO in the range of 0·125–8 μg mL^{-1}, and of M-O in the range of 0·19–12 μg mL^{-1}.

One hundred μL of the plasma samples, amniotic fluid samples, standards or quality controls were mixed with 100 μL internal standard solution (6·6 μg mL^{-1} iodinated moclobemide analogue in distilled water), 80 μL saturated Na_3PO_4, and 4 mL methylene chloride. The mixture was vortexed for 1 min and centrifuged at 1000 *g* for 15 min. The aqueous phase was discarded and the organic phase transferred to clean borosilicate glass tubes and evaporated by a gentle stream of nitrogen using an analytical evaporator at room temperture (Organomation N-EVAP). The residue was reconstituted with 150 μL mobile phase (see below),

Table 1. Pharmacokinetic parameters of moclobemide in rats after an intravenous bolus dose of 15 mg kg^{-1} (mean ± s.d.).

	n	CL (mL min^{-1} kg^{-1})	Vd_1 (L kg^{-1})	Vd_{ss} (L kg^{-1})	$t_{\frac{1}{2}}$ (min)	MRT (min)
Male	7	45 ± 16	1·4 ± 0·2	2·4 ± 0·3	54 ± 16	59 ± 17
Female	12	31 ± 8	1·3 ± 0·4	2·3 ± 0·8	62 ± 21	75 ± 24
Pregnant	6	23 ± 8	1·2 ± 0·5	2·1 ± 0·5	108 ± 120	100 ± 39
Nursing	6	32 ± 12	1·5 ± 0·3	2·2 ± 0·7	61 ± 26	72 ± 24

vortexed for 1 min and transferred into HPLC injection vials for assay.

Seventy five μL of the reconstituted sample was injected onto a C6 Spherisorb custom-packed column (5 μm, 150 × 4·6 mm, Alltech) using an autoinjector (Waters WISP 710B). The mobile phase was acetonitrile/0·22 M dipotassium phosphate buffer in water adjusted to pH 3·9 with 0·1 M HCl, 7/31, and the flow rate 1·3 mL min^{-1}. The absorptivity of the mobile phase was monitored at 240 nm using a variable wavelength UV detector (Waters Model 481 LC spectrophotometer). The output was recorded on an integrator (model 3390A, Hewlett-Packard).

Two quality control samples in rat plasma were assayed with each analytical run. One quality control contained 4·53 μg mL^{-1} moclobemide, 1·86 μg mL^{-1} M-NO, and 3·54 μg mL^{-1} M-O, and the other a concentration of 1·01 μg mL^{-1} moclobemide, 0·44 μg mL^{-1} M-NO and 1·77 μg mL^{-1} M-O. If the quality control samples during the assay of plasma concentrations in individual animals deviated more than 3 times the standard deviation for between days from their expected values, the assay was considered to be in error and the results were discarded. Five animals from a total of 36 animals studied had to be excluded from the data treatment as not meeting this criterion.

Pharmacokinetic analysis

The plasma concentrations were fitted to a two-compartment model using the computer program by Huang et al (1984). Area under the curve (AUC) was calculated using the trapezoidal rule to the last observed time point and adding the residual obtained by dividing the last concentration-time point by the terminal slope. Clearance (CL) was obtained by dividing dose by total AUC. The steady-state volume of distribution (Vd_{ss}) was obtained by the method described by Benet & Galeazzi (1979). The initial volume of distribution (Vd_1) and the terminal half-life were obtained from the fitted data. The mean residence time (MRT) was calculated using the relationship.

$$MRT = \frac{Vd_{ss}}{CL}$$

Statistics

Student's *t*-test was used for comparison of different groups. Probabilities < 0.05 were considered to indicate significant differences.

Results

Originally two groups of virgin control animals were studied, one together with the nursing rats and the other with the pregnant rats and male rats. As no statistically significant differences could be found between the two virgin control groups they were treated in the data analysis as one single group ($n = 12$).

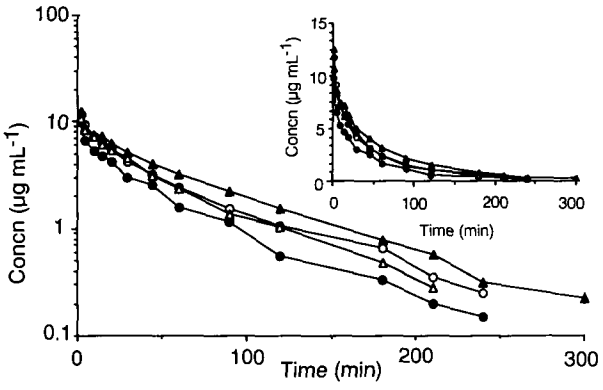

FIG. 2. Average temporal plasma concentrations of moclobemide after an intravenous bolus dose of 15 mg kg^{-1} in male (●), female (○), pregnant (▲) and nursing (△) rats. Insert: Cartesian plot of data.

Moclobemide showed a short initial distribution phase in all groups of animals with a subsequent longer terminal phase. The initial distribution phase was variable among the individual animals and generally not very distinct, being both shallow and of short duration which is expressed in the small differences between the steady-state volume of distribution values, Vd_{ss}, and the initial volume of distribution, Vd_1 (Table 1). The geometric means of plasma concentrations of moclobemide in the various groups are given in Fig. 2, and the pharmacokinetic parameters are given in Table 1. The plasma-to-blood concentration ratio was approximately 0·8 in all groups (Table 2) giving blood clearance values

Table 2. Plasma blood concentration ratios and blood clearances (mean ± s.d.).

	n	Plasma/blood concn ratio	CL_B (mL min^{-1} kg^{-1})
Male	7	0·86 ± 0·08	39 ± 15
Female	12	0·83 ± 0·10	25 ± 6
Pregnant	6	0·82 ± 0·07	19 ± 6
Nursing	6	0·81 ± 0·07	26 ± 11

Table 3. Unbound fraction of moclobemide in plasma of rats.

	Male	Female	Pregnant	Nursing
Mean	0·81	0·86	0·89	0·88
s.d.	0·05	0·06	0·02	0·05
n	7	12	6	6

Table 4. Unbound fraction of moclobemide in serum and plasma from female rats*

	Serum	Plasma
Mean	0·68	0·82
s.d.	0·04	0·05
n	9	9

* Values are from pooled serum and plasma samples in 4 animals. Serum was collected before and plasma 10 min after an intravenous injection of 60 units (USP) heparin.

(Table 2) approximately 20% lower than the plasma clearance values (Table 1).

Few statistically significant differences were observed between the individual groups: the plasma and blood clearance values in the male rats were significantly larger than those in the female control animals ($t=2{\cdot}53$ $P<0{\cdot}05$ and $t=2{\cdot}80$ $P<0{\cdot}02$, respectively) and in pregnant rats ($t=2{\cdot}97$ $P<0{\cdot}02$ and $t=3{\cdot}06$ $P<0{\cdot}02$, respectively; Tables 1, 2). Although the clearances in male rats tended to be larger than in nursing rats (Tables 1, 2) the differences did not reach statistical significance in this case ($0{\cdot}10>P>0{\cdot}05$). The mean residence time in male rats was generally shorter than in female control, nursing and pregnant rats with statistically significant differences being reached only when compared with pregnant rats ($t=2{\cdot}53$ $P<0{\cdot}05$; Table 1). No other differences in the pharmacokinetic parameters of moclobemide based on total concentrations were discernible.

The protein binding of moclobemide was low in all animals. The unbound fraction was on average 0·86, with small differences between the groups (Table 3). In these studies no heparin lock was used. However, administration of residual heparin associated with the red blood cells when they were reinjected to maintain normal haematocrit values and prevent hypovolaemia could not be avoided. The administration of this residual heparin may explain the higher unbound fraction in the study animals when compared with the unbound fraction in serum of virgin control rats with no heparin load (Table 4) as administration of heparin increased the unbound fraction from 0·68 to 0·82 (Table 4). However, even after large amounts of heparin (60 USP units) the increase was relatively small (20%) and is not likely to alter any of the conclusions of the study.

The average concentrations of M-NO and M-O with time for the individual groups are given in Figs 3 and 4, respectively. The metabolite concentrations demonstrated a large variation in the individual animals and the ratio of M-NO to M-O using the area under the plasma concentration-time curve to the last sampling time varied from 0 to 6·22 indicating significant individual variation in the synthesis and elimination of the individual metabolites. However, in general, similar patterns in the two metabolite areas were found in male and female controls as well as in pregnant rats (Table 5). No statistically significant differences in the areas could be seen between these groups with the exception of the nursing group. In this group, only trace amounts of M-NO and largely reduced amounts of M-O were seen. Because added M-NO and M-O could be readily detected in blank plasma from nursing rats, the low concentration is probably not due to factors interfering with the assay of these

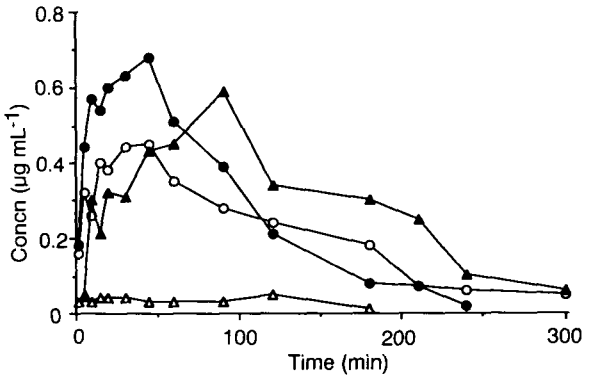

FIG. 3. Average temporal plasma concentrations of metabolite M-NO after an intravenous bolus dose of 15 mg kg^{-1} in male (●), female (○), pregnant (▲) and nursing (△) rats.

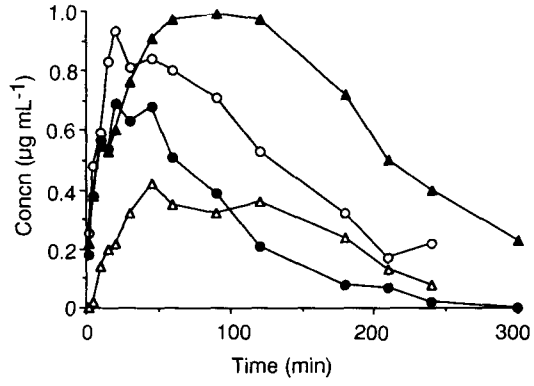

FIG. 4. Average temporal plasma concentrations of metabolite M-O after an intravenous bolus dose of 15 mg kg^{-1} in male (●), female (○), pregnant (▲) and nursing (△) rats.

compounds in nursing rats. The area under the curve of M-NO was statistically significantly lower in nursing rats than in control female and male rats as well as in pregnant rats ($t=2{\cdot}61$ $P<0{\cdot}02$, $t=2{\cdot}88$ $P<0{\cdot}02$, $t=4{\cdot}73$ $P<0{\cdot}001$, respectively; Table 5). The areas of M-O were also lower than in the other groups, but the difference reached statistical significance only with the female control rats ($t=2{\cdot}69$ $P<0{\cdot}02$) probably due to the large interindividual variability seen in the other groups.

Moclobemide, M-NO and M-O were found in the amniotic fluid of pregnant rats (Table 6). This suggests that moclobemide can cross the placental barrier. Whether M-

Table 5. Areas under the curve for the moclobemide metabolites M-NO and M-O.

	n	M-NO (μg min mL^{-1})	M-O (μg min mL^{-1})
Male	7	61±48	112±79
Female	12	55±42	160±78
Pregnant	6	77±37	202±209
Nursing	6	3·7*	26±11

* In four of six animals only trace amounts were observed. The values in the two remaining animals were 3·1 and 19 μg min mL^{-1}.

Table 6. Concentration of moclobemide and metabolites M-NO and M-O in the amniotic fluid of pregnant rats 5 h after the start of the experiment.

	Moclobemide ($\mu g\ mL^{-1}$)	M-NO ($\mu g\ mL^{-1}$)	M-O ($\mu g\ mL^{-1}$)
Mean	0·43	0·25	0·23
s.d.	0·13	0·18	0·16
n	6	6	6

NO and M-O can also cross the placental barrier or whether moclobemide is metabolized in the foetus is, however, not clear from these data.

Discussion

Pregnancy and nursing had no apparent effect on the distribution and elimination of moclobemide in the rat. However, in nursing rats the concentrations of both M-NO and M-O were substantially decreased in comparison with control and pregnant rats although the decrease reached statistical significance only for M-NO. As the result is not an analytical artefact (see Results), the differences are probably related to altered kinetics of the metabolites. Because the areas under the curve of the metabolites are composites of formation as well as of elimination, it is difficult to determine if it is the formation or elimination rate (or both) that is altered. As no change in the overall elimination of moclobemide took place, the smaller areas under the curve of the two metabolites in nursing rats are suggestive of a substantial increase in the elimination clearances of these metabolites. On the other hand, if the formation rate of the metabolites is affected one has to surmise that alternative important elimination pathways for the drug exist. In rat urine hardly any unchanged drug has been found while at least 14 different metabolic products have been detected (Jauch et al 1990b). Although M-NO was the main metabolite in urine it accounts for only 13% of the dose administered. M-O was, on the other hand, hardly detectable in urine (<3%). Because pregnant rats showed no changes, the decreased level in the nursing rats is not related to physiological and hormonal changes during pregnancy with an ongoing post-partum effect as has been reported for theophylline clearance in man (Gardner et al 1987). Sex hormones are known to alter the oxidation of various drugs in the rat (Kato & Kamataki 1982; Kamataki et al 1982). In man, changes in metabolite levels during lactation occurred only with M-NO and not with M-O. The changes seen were much smaller than in the rats: M-NO levels in lactating women were approximately half those in non-lactating females (Schoerlin, personal communcation); this change did not affect the plasma concentration-time curve of the parent compound.

The clearance of moclobemide is relatively high in rats. Because the elimination is mainly hepatic (Schoerlin & Da Prada 1990) and the hepatic blood flow is approximately 90 $mL\ min^{-1}\ kg^{-1}$ (Ohnhaus & Locher 1975; Andersen et al 1987; Sato 1987) the extraction ratio ranges from approximately 20 to 45%. This indicates that moclobemide in rats, as in man, may be considered an intermediate extraction ratio compound and that the drug may show some sensitivity to changes in both hepatic blood flow and hepatocellular enzyme activity.

Male rats had, in general, higher clearance values than female rats. In terms of observed clearance values, the difference is small (31%). However, because moclobemide is an intermediate extraction ratio compound, real differences in hepatocellular activity will to some extent be masked by the partial dependency of clearance on hepatic blood flow. The data suggest that male rats may have an intrinsic hepatic clearance approximately twice that of female rats (107 vs 42 $mL\ min^{-1}\ kg^{-1}$) using the well-stirred model (Pang & Rowland 1977). Gender differences in metabolic rates of drugs involving the P450 system are well known in the rat (Pyörälä 1968; Kato 1974; Vodicnik et al 1981; Billings 1983; Trenk et al 1988) and are often attributed to sex-hormone-dependent P450 isoenzymes (Kato & Kamataki 1982; Kamataki et al 1982). At present there is no indication of a gender-related difference in man.

The moclobemide concentration in the amniotic fluid generally exceeded the concentration found in plasma of the mother at the time of measurements. This could point to a rapid equilibration between plasma and amniotic fluid where the concentrations parallel each other as well as to a slow equilibration where the concentration in the amniotic fluid reaches that in plasma only after 5 h. However, only a single measurement of the amniotic fluid was made and it is difficult to assess whether these results indicate a significant exposure of the foetuses to moclobemide or not. A rapid equilibration between plasma and amniotic fluid would suggest a significant exposure upon administration of high doses. A slow equilibration would, on the other hand, indicate a much lower acute exposure with a potential for rising levels of drug in the amniotic fluid upon chronic drug administration.

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