Pharmacokinetics of mifentidine after single and multiple oral administration to healthy volunteers

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1 The pharmacokinetics of mifentidine, a new long acting histamine H₂-receptor antagonist, were studied using two protocols.

2 In one study, on 5 different days six normal male subjects were given 2.5, 5, 10, or 20 mg mifentidine or placebo orally 60 min before starting a 3 h continuous gastric aspiration during which time blood samples were taken for measurement of mifentidine concentration.

3 The area under the curves of mifentidine plasma levels (AUC) vs time for the four doses was linearly related to the dose for each individual subject ($r = 0.972$, $P < 0.001$). After doses of 2.5, 5, 10 and 20 mg, mifentidine reduced hydrogen ion output by respectively 36, 37, 60 and 75% and secretory volume by 1, 17, 40, and 47%. The effects at the two highest doses were statistically significant. AUC was correlated positively with the percentage reduction in hydrogen ion output ($r = 0.802$, $P < 0.001$) and volume ($r = 0.834$, $P < 0.001$) over a 3 h period.

4 In the second study, the pharmacokinetics were evaluated after once-daily treatment for 14 days in seven subjects given 10 mg and in seven others subjects given 20 mg.

5 After multiple dosing, renal clearance was similar for the two doses (11.6 ± 2.1 l h⁻¹ for the low dose and 17.0 ± 2.0 l h⁻¹ for the high dose). Plasma half-life ($t_{1/2\lambda 2}$) was 16.0 ± 3.0 h after the 10 mg dose and 11.9 ± 1.2 h after 20 mg.

6 These studies indicate that the pharmacokinetics of oral mifentidine are linear in the dose range 2.5 mg to 20 mg.

Keywords mifentidine pharmacokinetics oral administration
H₂-receptor antagonist

Introduction

Recently, a new (imidazolyphenyl) formamidine derivative, mifentidine (Figure 1), has been described as a potent H₂-receptor antagonist (Donetti *et al.*, 1984). *In vivo* and *in vitro* studies have shown the compound is a competitive H₂-receptor antagonist (Bertaccini *et al.*, 1984; Pagani *et al.*, 1985; Poli *et al.*, 1984, 1985; Giachetti *et al.*, 1985; Micheletti *et al.*, 1985) without significant activity at H₁-receptors (Montagna *et al.*, 1982) or at cholinergic receptors (Bertaccini *et al.*,

1985; Scarpignato *et al.*, 1986). In animals, gastric acid secretion stimulated by histamine, pentagastrin or a test meal was inhibited by mifentidine (Bertaccini *et al.*, 1984; Pagani *et al.*, 1985). Evidence suggests that mifentidine is at least three times more potent than ranitidine in inhibiting gastric acid secretion (Pagani *et al.*, 1985; Scarpignato *et al.*, 1985) and longer acting than either cimetidine or ranitidine (Scarpignato *et al.*, 1985, 1986). In addition, the antiulcer

Figure 1 Structural formula of mifentidine

activity against a variety of experimentally-induced gastric and duodenal ulcers was found to be very high (Scarpignato *et al.*, 1986; Del Soldato *et al.*, 1985).

The primary purpose of the studies reported in this paper was to determine the pharmacokinetics of mifentidine after single and multiple oral doses and to correlate its antisecretory activity with plasma mifentidine levels. The secondary aim was to monitor the safety of treatment with mifentidine.

Methods

First study

The pharmacokinetics of mifentidine were studied in six male volunteers, aged 20 to 30 years (mean, 25 years), weight 70 to 81 kg (mean, 75 kg), given single oral tablets of 2.5 mg, 5 mg, 10 mg or 20 mg. Complete medical histories were obtained from each subject before admission to the study and they were given a complete physical examination. A number of laboratory tests were done, including complete blood count, serum chemistry and urinalysis. Subjects were admitted to the Institut für klinische Pharmakologie the night before each dose and stayed there 24 h after. Subjects fasted from 22.00 h of each night before mifentidine administration. The study was approved by the Local Ethics Committee of Freiburg, West Germany. Written informed consent was obtained from all subjects.

Each of the six subjects was given, under double-blind conditions, mifentidine tablets containing 2.5 mg, 5 mg, 10 mg or 20 mg, with a week's interval between them and the placebo randomly introduced into the sequence of drug doses. Each dose was taken with 100 ml water after a 12 h fast. Sixty minutes after ingestion of the drug a nasogastric tube was positioned in the great curvature of the stomach and was checked radiologically. Gastric contents were drawn by a continuous suction pump with frequent manual aspiration to maintain patency of the nasogastric tube. The gastric aspirate was collected and measured every 15 min and portions were frozen

for later determination of hydrogen ion content. Acidity was determined by titration of a 5 ml sample of gastric juice to pH 7 with 0.1 N NaOH in a pH-stat.

Blood samples (5 ml) were obtained in heparin-free Vacutainers just prior to dosing and 1, 1.5, 2 and 3 h after. The plasma was separated by centrifugation and immediately frozen for subsequent assay. Pulse rate and blood pressure were recorded at frequent intervals. A two-lead electrocardiogram was recorded for 1 min periods at regular intervals after the dose.

Standard psychometric investigations were carried out before and 3 and 24 h after drug administration.

Second study

Pharmacokinetics and safety of mifentidine were investigated after daily doses of 10 mg or 20 mg (08.00 h) for 14 days. Twenty males were divided into two groups. In the first group (age 22–34 years, weight 62–87 kg), seven subjects took 10 mg mifentidine and three placebo; in the second group (age 22–32 years, weight 64–78 kg), seven subjects took 20 mg mifentidine and three placebo. Drug treatments were randomly assigned to subjects double-blind.

Blood samples (5 ml) were obtained in heparin-free Vacutainers just prior to the morning dose and 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12 h after the dose on day 1 and just before the morning dose on days 2 to 13. On day 14, blood samples for mifentidine concentrations were obtained immediately before the last morning dose and 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, and 48 h after.

Urine was collected at intervals of 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–24, and 24–48 h on day 1 and day 14. The total volume of urine for each interval was measured and duplicate 10 ml aliquots were frozen for subsequent assay.

In this study blood pressure and heart rate were measured at regular intervals. Haematology, blood chemistry and urinalysis tests were made before the study and on days 1, 7, and 14. Subjects were closely checked every day for any reactions.

Analytical procedures

Liquid chromatography-mass spectrometry detection Plasma samples up to 2 ml were diluted with distilled water to 4 ml final volume and adsorbed on C₁₈ SEP-PAK cartridges, (Millipore, Water Associates) preactivated with methanol and washed with distilled water. The

cartridges were then washed with 3 ml of mixture of water:acetonitrile (90:10, v/v) followed with 3 ml of 1% ammonium acetate and finally eluted with 500 μ l acetonitrile. The acetonitrile eluates containing mifentidine were analyzed by LC/MS (Hewlett-Packard Thermospray) on a Chrompack C₁₈ column (3 mm i.d., 100 mm length). The elution solvent was 100 mM ammonium acetate buffer pH 3.5 and methanol in the ratio of 65:35 v/v containing 100 mg l⁻¹ tetrabutyl ammonium hydrogen sulphate (TBAHS).

The operational temperatures at the tip of the probe and the source were held constant at 30°C and 95°C, respectively. The pressure in the analyzer was kept at 3×10^{-6} Torr at a flow rate of 0.8 ml min⁻¹.

The experimental conditions of the MS detector were on SIM acquisition, ION 1 m/z at 299.25 and Filament in on/positive.

The lower limit of detection was 0.1 ng ml⁻¹ mifentidine.

Liquid chromatography-UV detection Plasma samples up to 2 ml were transferred to tubes containing 200 μ l of a solution of 4-phenyl-1H-imidazole (1 μ g ml⁻¹) as internal standard and, as appropriate, brought to a final volume of 2.2 ml with distilled water. Two ml of 250 mM Na₂HPO₄ buffer pH 8.5 were added to the samples prior to the adsorption on an Extrelut® (Merck) column (18 mm i.d., 70 mm length). After 15 min of equilibration, the column was eluted with ethyl-acetate (2 $\times$ 7.5 ml) and the eluate was evaporated to dryness *in vacuo* at room temperature. The residue was taken up with 4.0 ml of a mixture of 10% methanol in chloroform (v/v).

Mifentidine was re-extracted with 150 μ l of an aqueous solution containing 2.5 mM TBAHS. After mixing and centrifuging at low speed, a suitable amount of the upper aqueous layer was analyzed by LC/UV (Perkin-Elmer Series 4) at 266 nm. The column used was a reversed phase Alltech Solvent Miser C₈ (2.1 mm i.d., 150 mm length) operated at 30°C and the mobile phase was a mixture of acetonitrile, methanol and 10 mM NaH₂PO₄ buffer, (10:20:70 v/v) containing 10 mM of pentane sulfonic acid and 10 mM of triethylamine, adjusted to pH 3 with a solution of 2 M H₃PO₄. The flow rate was 200 μ l min⁻¹. The retention times were 5.2 and 8.5 min, respectively, for mifentidine and the internal standard.

Urine samples up to 1 ml were adjusted to pH 7.0 with 0.33% NH₄OH. 0.5 ml of the solution was added to tubes containing 500 μ l of internal standard (1 μ g ml⁻¹) brought up to 4.0 ml with

250 mM Na₂HPO₄ pH 8.5 and worked up on the Extrelut® column as described for plasma.

The lower limit of detection was 10 ng ml⁻¹ mifentidine.

The data are expressed as mifentidine 2HCl.

Statistical analysis

Data in both studies were analyzed statistically by the BMDP statistical package (Dixon, 1983). Parametric tests for a five-way cross-over design (first study) and for an unbalanced parallel groups design (second study) were applied to normally distributed data. Scores, categorical data and not-normally distributed data were analyzed by non-parametric tests. A *P* value of 0.05 (two-tailed) was considered significant. Pharmacokinetic calculations were done with the SAAM program (Berman & Weiss, 1968). Data are presented as mean $\pm$ s.e. mean.

Results

First study

Mean plasma concentrations of unchanged mifentidine for six subjects after single oral doses of 2.5 mg, 5 mg, 10 mg or 20 mg are plotted in Figure 2. The peak plasma concentration increased with each increase in dose. The area

Figure 2 Mean plasma levels of mifentidine after single oral doses of 2.5 mg (●—●), 5 mg (■—■), 10 mg (▲—▲) or 20 mg (▲----▲).

under the mifentidine plasma concentration-time curve was calculated for each subject after each dose by the linear trapezoidal rule up to the last sampling time (3 h). The AUC 0–3 h was plotted against the dose for each subject. The least-squares linear regression of AUC 0–3 h vs dose for every subject was obtained and pooled according to Fisher's Z-transformation procedure (Davies, 1979). This gave an overall correlation coefficient of 0.972 ($P < 0.001$). Thus, there was a significant linear relationship between AUC 0–3 h and dose.

Mifentidine (2.5, 5, 10 and 20 mg) reduced hydrogen ion output by 36, 37, 60 and 75% and secretory volume by 1, 17, 40 and 47%, the effects of the two highest doses being significant (Table 1). AUC 0–3 h correlated positively with the percentage reduction in hydrogen ion output ($r = 0.802$, $P < 0.001$) and volume ($r = 0.834$, $P < 0.001$).

Heart rate and blood pressure did not change significantly at any dose of mifentidine. Psychometric tests revealed no abnormalities before or after treatments. No clinically significant subjective or biochemical toxic effects of mifentidine were seen after single doses.

Second study

The plasma concentration-time courses during the first and last day of treatment with 10 mg are plotted in Figure 3. Plasma concentrations of mifentidine, measured before the 10 mg doses on days 2–13, did not rise with the number of doses.

The plasma concentration-time courses of mifentidine for the 20 mg schedule during the first and last day of treatment are shown in Figure 4. Plasma concentrations of mifentidine before the 20 mg doses on days 2–13 were not detectable by the LC-UV method used in this series of assays.

Table 1 Secretory volumes and acid outputs after placebo and 2.5, 5, 10 and 20 mg of mifentidine (mean and s.e. mean)

	Secretion volume (ml 3h ⁻¹)	Acid output (mEqH ⁺ 3 h ⁻¹)
Placebo	239.7 (25.7)	16.48 (4.00)
Mifentidine 2.5 mg	237.5 (38.0)	10.58 (1.82)
Mifentidine 5 mg	197.7 (18.2)	10.45 (2.01)
Mifentidine 10 mg	*142.0 (30.1)	*6.51 (1.85)
Mifentidine 20 mg	*126.2 (21.2)	*4.19 (0.83)

* $P < 0.05$ vs placebo

Figure 3 Plasma concentrations of mifentidine (means $\pm$ s.e. mean) after the first (—) and 14th (----) doses of 10 mg.

Since analysis of individual plasma concentration-time courses revealed no significant differences between single and repeated doses (Figures 3 and 4), pharmacokinetic parameters were estimated with simultaneous fitting of post-absorption plasma concentrations and urinary excretion data of the first and last day of administration, according to the following reduced model:

$$C_p \text{ (1st dose)} = A_1 e^{-\lambda_1 t} + B_1 e^{-\lambda_2 t}$$

$$C_p \text{ (14th dose)} = A_2 e^{-\lambda_1 t} + B_2 e^{-\lambda_2 t}$$

$$RU \text{ (1st dose)} = RCl C_p \text{ (1st dose)}$$

$$RU \text{ (14th dose)} = RCl C_p \text{ (14th dose)}$$

in which C_p is the plasma concentration, RU is the rate of urinary excretion, RCl is the renal clearance, t is the time, and A_1 , A_2 , B_1 and B_2 the exponential coefficients.

With the nonlinear regression program SAAM, the equations describing this model were fitted simultaneously by nonlinear least-squares regression to the plasma and urine data for each of the subjects at each dosage level. Data were weighted according to the reciprocals of the calculated values.

The data sets for one subject in the 10 mg group and for two in the 20 mg group were excluded because of technical inadequacies.

The estimated pharmacokinetic parameters for the two doses agree well (Table 2). The drug showed a distribution half-life of 1.5 ± 0.3 h after the 10 mg dose and 1.4 ± 0.3 h after 20 mg.

The half-lives for the λ_2 -phase were 16.0 ± 3.0 h for the low dose and 11.9 ± 1.2 h for the high dose. Renal clearances were about twice the glomerular filtration rate (11.6 ± 2.1 l h⁻¹ for 10 mg and 17.0 ± 2.0 l h⁻¹ for 20 mg).

The amount of mifentidine excreted in the urine was calculated on day 1 as a percentage of the dose for each subject for both dose levels. The mean amount excreted was $12.3 \pm 0.8\%$ of the dose after 10 mg and $13.4 \pm 1.7\%$ after 20 mg. The major part of the dose was excreted in the first 12 h, with the excretion for this interval $9.3 \pm 0.4\%$ for the low dose and $11.3 \pm 1.5\%$ for the high dose (Table 2).

The extent of accumulation R was calculated using the equation Colburn, 1983:

$$R = \frac{AUC(0-\infty) \text{ 14th dose}}{AUC(0-\infty) \text{ 1st dose}}$$

in which $AUC(0-\infty)$ indicates the area under the plasma concentration from time 0 to infinity (extrapolated). The rate of accumulation was 1.2 ± 0.1 after 10 mg and 1.7 ± 0.1 after 20 mg.

Repeated doses of mifentidine were well tolerated. There were no significant changes in blood pressure or heart rate. Haematological tests (ESR, RBC, haemoglobin, haematocrit, WBC, differential blood count, platelets), and biochemical tests (SGOT, SGPT, γ -GT, alkaline phosphatase, total bilirubin, cholesterol, triglycerides, total proteins, electrophoresis,

Figure 4 Plasma concentrations of mifentidine (means $\pm$ s.e. mean) after the first (—) and 14th (----) doses of 20 mg.

Table 2 Pharmacokinetic parameters (mean and s.e. mean) for mifentidine repeated doses (second study)

Parameter	10 mg mifentidine	20 mg mifentidine
Peak concentration (ng ml ⁻¹)		
day 1	23.4 (1.1)	59.3 (5.3)
day 14	21.3 (0.8)	59.7 (6.0)
Time of peak (h)		
day 1	1.8 (0.1)	1.6 (0.1)
day 14	1.8 (0.1)	1.5 (0.1)
$t_{1/2\lambda_1}$ (h)	1.5 (0.3)	1.4 (0.3)
$t_{1/2\lambda_2}$ (h)	16.0 (3.0)	11.9 (1.2)
Renal clearance (l h ⁻¹)	11.6 (2.1)	17.0 (2.0)
% of dose excreted in 12 h (day 1)	9.3 (0.4)	11.3 (1.5)
% of dose excreted in 24 h (day 1)	12.3 (0.8)	13.4 (1.7)

glucose, urea, uric acid, creatinine), electrolytes (K^+ , Na^+ , Ca^{++} , PO_4^-), urinalysis (pH, glucose, proteins, urobilinogen, sediment), were all within the normal range before the study. When repeated on days 1 and 7 of the mifentidine repeated schedule, on day 15 (after the last dose), and 14 days later, the only abnormality was that serum glutamic-pyruvic transaminase (SGPT) was slightly increased (up to 54 U l⁻¹) in two of seven subjects taking 10 mg, in three (up to 34 U l⁻¹) of seven subjects taking 20 mg and in one of six subjects taking placebo. These values had returned to normal 14 days after discontinuing treatment.

Discussion

In the first study, the area under the concentration-time curve increased proportionally with the dose, suggesting that the pharmacokinetics of mifentidine are linear in the 2.5 mg to 20 mg dose range. However, since the blood sampling was limited to only 3 h this assumption needs considerable further verification.

Also in the first study, the areas under the plasma concentration-time curves of mifentidine within the range of 50–60 ng ml⁻¹ h appeared to accompany a 75% inhibition of unstimulated gastric acid output. Similar correlations between plasma drug levels and pharmacodynamic effects have been described for other H₂-receptor antagonists (Henn *et al.*, 1975; Gugler *et al.*, 1981; Pancorbo *et al.*, 1982; Pounder *et al.*, 1976; Lebert *et al.*, 1981 a, b).

The use of multiple rather than separate data sets (plasma and urine) and simultaneous fitting

yields more correct estimates of pharmacokinetic parameters. The half-lives of the λ_1 and λ_2 phases and the renal clearance of mifentidine after repeated dosing were comparable after both 10 mg and 20 mg, confirming the linearity of pharmacokinetics of the drug at these doses. The renal clearance was calculated to be approximately twice the glomerular filtration rate after repeated doses, showing that the drug is actively secreted by renal tubules.

The mean percentage of unchanged mifentidine excreted in 24 h was about 13%. An additional 2–3% of the dose was excreted during the second day after the last dose. The pre-dose plasma concentrations of mifentidine during the 10 mg repeated dose regimen indicate that the drug does not significantly accumulate in this low-dose schedule. The calculated accumulation confirm this for the 20 mg schedule, too.

The main pharmacokinetic property of mifentidine of importance in therapeutic use is its relatively long elimination half-life of 11–16 h after repeated doses, thus differentiating it from other H₂-receptor antagonists with half-lives of about 3 h (cimetidine, ranitidine, famotidine), already in widespread clinical use (Veng Pedersen & Miller, 1980; Garg *et al.*, 1985; Takabake *et al.*, 1985).

Mifentidine was well tolerated after single and repeated doses. The observation that SGPT was slightly increased in five of 14 subjects on the 7th and 14th days may be an artefact. One of these subjects had higher than normal SGPT just before starting the study, although his pre-examination analysis revealed no abnormalities. One subject taking placebo had a similar increase in SGPT values. Nevertheless, these observations merit further investigation.

References

- Berman, M. & Weiss, M. F. (1968). *Users Manual for SAAM*. Bethesda, Md: National Institutes of Health.
- Bertaccini, G., Poli, E. & Coruzzi, G. (1984). Action of the new H₂-antagonist, DA 4577, on different *in vitro* and *in vivo* preparations. *Agents Action*, **14**, 510–515.
- Bertaccini, G., Coruzzi, G. & Poli, E. (1985). Histamine H₂-receptor antagonists may modify dog intestinal motility independently of their primary action on the H₂-receptors. *Pharmac. Res. Commun.*, **17**, 241–254.
- Colburn, W. A. (1983). Estimating the accumulation of drugs. *J. pharm. Sci.*, **72**, 883–834.
- Davies, O. L. (1979). *The design and analysis of industrial experiments*. Second edition.
- Del Soldato, P., Ghiorzi, A., Cereda, E., Donetti, A. (1985). Cimetidine, ranitidine and mifentidine in specific gastric and duodenal ulcer models. *Pharmacology*, **30**, 45–51.
- Dixon, W. J. (1983). *BMDP Statistical Software Manual*, 1983 Revised Reprint. Berkely, University of California.
- Donetti, A., Cereda, E., Bellora, E., Gallazzi, A., Bazzano, C., Vanoni, P., Del Soldato, P., Micheletti, R., Pagani, F. & Giachetti A. (1984). (Imidazolyphenyl) formamidines. A structurally novel class of potent histamine H₂-receptor antagonists. *J. med. Chem.*, **27**, 380–386.
- Garg, D. C., Eshelman, F. N., Weidler, D. J. (1985). Pharmacokinetics of ranitidine following oral administration with ascending doses and with multiple-fixed doses. *J. clin. Pharmac.*, **25**, 437–443.
- Giachetti, A., Pagani, F., Micheletti, R., Brambilla, A., Cereda, E. & Donetti, A. (1985). Pharmacological profile of mifentidine; a novel H₂-receptor antagonists. *Agents Actions*, **16**, 173–175.
- Gugler, R., Fuchs, G., Dieckmann, M. & Somogyi, A. A. (1981). Cimetidine plasma concentration-response relationships. *Clin. Pharmac. Ther.*, **29**, 744–748.
- Henn, R. M., Isenberg, J. I., Maxwell, V. & Sturdevant, R. A. L. (1975). Inhibition of gastric acid secretion by cimetidine in patients with duodenal ulcer. *New Engl. J. Med.*, **293**, 371–375.
- Lebert, P. A., MacLeod, S. M., Mahon, W. A., Soldin, S. J. & Vandenberghe, H. M. (1981a). Ranitidine kinetics and dynamics I. Oral dose studies. *Clin. Pharmac. Ther.*, **30**, 539–544.
- Lebert, P. A., Mahon, W. A., MacLeod, S. M., Soldin, S. J., Fenje, P. & Vandenberghe, H. M. (1981b). Ranitidine kinetics and dynamics II. Intravenous dose studies and comparison with cimetidine. *Clin. Pharmac. Ther.*, **30**, 545–550.
- Micheletti, R., Oliva, D., Belfiore, P., Giachetti, A. & Nicosia, S. (1985). Evaluation of novel compounds interacting with H₂-histamine receptors: effect on histamine-sensitive adenylate cyclase activity in guinea-pig gastric mucosa. *Agents Actions*, **16**, 291–294.
- Montagna, E., Micheletti, R. & Cereda, A. (1982). Interaction of DA 4577, a novel antihistamine (H₂) agent with cardiovascular H₂-receptors. In *Abstracts of the International Symposium on Experimental and Clinical Evaluation of Anti-ulcer Drugs*. Pisa, November 22–23, 1982. (abstract 36).
- Pagani, F., Micheletti, R., Brambilla, A., Schiavone, A., Montagna, E., Ciprandi, C. & Giachetti, A. (1985). Pharmacology of mifentidine, a novel H₂-receptor antagonist. *Arzneim. Forsch. Drug. Res.*, **35**, 451–455.
- Pancorbo, S., Burbrick, M. P., Chin, T. W. F., Miller, K. W. & onstad, G. (1982). Cimetidine dynamics after single intravenous doses. *Clin. Pharmac. Ther.*, **31**, 83–88.
- Poli, E., Coruzzi, G., Bertaccini, G. (1984). Action of mifentidine and ranitidine on the isolated rat uterus. *Pharmac. Res. Comm.*, **11**, 1091–1100.
- Poli, E., Medici, D., Contini, G. A. & Bertaccini, G. (1985). Effect of mifentidine on histamine-stimulated human atrium *in vitro*: comparison with ranitidine and cimetidine. *Arch. int. Pharmacodyn.*, **273**, 221–225.
- Pounder, R. E., Williams, J. G., Russell, R. C. G., Milton-Thompson, G. J. & Misiewicz, J. J. (1976). Inhibition of food-stimulated gastric acid secretion by cimetidine. *Gut*, **17**, 161–168.
- Scarpignato, C., Tramacere, R., Tangwa, M. & Bertaccini, G. (1985). Effect of the new H₂-receptor antagonist mifentidine on gastric acid secretion in the cat: comparison with cimetidine and ranitidine. *Arch. int. Pharmacodyn.*, **276**, 142–151.
- Scarpignato, C., Tangwa, M., Tramacere, R., Del Soldato, P. (1986). The effect of the new H₂-receptor antagonists mifentidine on gastric secretion, gastric emptying and duodenal ulcers in the rat: comparison with cimetidine and ranitidine. *Digestion*, **33**, 7–16.
- Takabake, T., Ohta, H., Maekawa, M., Yamamoto, Y., Ishida, Y., Hara, H., Nakamura, S., Ushiogi, Y., Kawabata, M., Hashimoto, N. & Hattori, N. (1985). Pharmacokinetics of famotidine, a new H₂-receptor antagonist, in relation to renal function. *Eur. J. clin. Pharmac.*, **28**, 327–331.
- Veng Pedersen, P. & Miller, R. (1980). Pharmacokinetics and bio-availability of cimetidine in humans. *J. pharm. Sci.*, **69**, 394–398.

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