Ranitidine does not alter pethidine disposition in man

D. R. P. GUAY, R. C. MEATHERALL, J. L. CHALMERS, G. R. GRAHAME & R. J. HUDSON
Departments of Pharmacy, Laboratory Medicine, Internal Medicine and Anaesthesia, St Boniface General Hospital, Winnipeg, Manitoba, Canada R2H 2A6 and Faculties of Pharmacy and Medicine, University of Manitoba, Winnipeg, Manitoba, Canada R3T 2N2

- 1 The effect of concurrent ranitidine administration on the disposition of pethidine was investigated in eight healthy male volunteers (19–33 years).
- 2 The subjects received 70 mg i.v. pethidine HCl doses before and during ranitidine treatment (150 mg p.o. twice daily).
- 3 Ranitidine therapy was not associated with significant alterations in pethidine elimination rate constant, volume of distribution at steady state, total body clearance, and 24 h urinary excretion.
- 4 No alteration in pethidine oxidation to norpethidine was noted, as suggested by nonsignificant changes in lag time to appearance of quantifiable norpethidine in serum, time to peak concentration, peak concentration, area under the curve from time 0–24 h, and 24 h urinary excretion.
- 5 It would appear that, unlike cimetidine, ranitidine does not interact pharmacokinetically with pethidine. Further studies are necessary to evaluate the potential clinical advantages of ranitidine vs cimetidine therapy in patients also receiving pethidine.

Keywords ranitidine pethidine norpethidine pharmacokinetics metabolism

Introduction

Ranitidine, a potent H_2 -receptor antagonist, is in general use for the treatment and prophylaxis of peptic ulcer disease (Brogden *et al.*, 1982; Helman & Tim, 1983; Zeldis *et al.*, 1983). In contrast to cimetidine, ranitidine infrequently has been associated with drug–drug interactions, probably secondary to its lower binding to cytochromes P-450 and P-448 (Knodell *et al.*, 1982; Bell *et al.*, 1981; Rendic *et al.*, 1982; Mihaly *et al.*, 1982). No significant ranitidine-associated alterations in the disposition of phenytoin, warfarin, propranolol, theophylline, diazepam, ethanol, lignocaine, atenolol and chlormethiazole have been reported (Gaginella & Bauman, 1983). Recently, we documented a pharmacokinetic interaction between cimetidine and i.v. pethidine, resulting in a reduction in pethidine clearance and volume of distribution at steady state.

A cimetidine-induced reduction in pethidine oxidation to norpethidine was suggested by reductions in norpethidine area under the serum concentration–time curve and peak norpethidine serum concentrations (Guay *et al.*, 1984).

Accordingly, we undertook to study in normal volunteers the pharmacokinetic interaction of ranitidine with i.v. pethidine. The results of this study demonstrated that, unlike cimetidine, ranitidine does not alter the disposition of pethidine.

Methods

Patients

The subjects studied comprised eight male volunteers judged to be healthy by medical

history, physical examination and laboratory criteria. Ages ranged from 19–33 years and body weights ranged from 55.5–107.5 kg. None was receiving oral medications and none was a smoker. The protocol was approved by the Faculty Committee on the Use of Human Subjects in Research, University of Manitoba.

Protocol

Subjects participated in a two way, single dose, cross-over study with at least 1 month between study days. A single i.v. pethidine dose was given on two occasions. One study day served as the control trial without other drugs. The other study day served as the ranitidine interaction trial. Pethidine administration was preceded by a 1 week course of ranitidine 150 mg p.o. twice daily. On the study day, ranitidine was taken just prior to pethidine administration and continued until the end of the blood sampling schedule. The sequence of the two study days was randomly assigned. Subjects fasted overnight before each pethidine dose.

Each 70 mg i.v. pethidine HCl dose was administered over 2 min. Using an indwelling heparin lock in a forearm vein in the arm contralateral to the pethidine injection site, 5 ml blood samples were collected into additive-free Vacutainer® (Becton-Dickinson, Rutherford, New Jersey, USA) tubes before the dose was given and at 5, 10, 20, 30, 45, 60, and 90 min and 2, 3, 4, 5, 6, 8, and 11 h after the end of the bolus injection. Individual venepunctures were used to collect blood samples 24 and 48 h after the end of the injection. Blood samples were allowed to clot and the serum was separated and frozen at -20°C until the time of analysis. Subjects were instructed to empty the bladder just prior to pethidine administration and subsequently 24 h urine samples were collected. Total volumes were measured and aliquots were separated and stored as above until the time of analysis. Although the urinary excretion of pethidine and norpethidine are pH-dependent (Edwards *et al.*, 1982), control of urinary pH during the study was not attempted. Variations in urinary excretion of pethidine and norpethidine due to urinary pH changes exert negligible effects on pethidine and norpethidine serum pharmacokinetics (Verbeeck *et al.*, 1981).

Compliance with the prescribed ranitidine regimen was assessed by tablet counts and measurements of serum ranitidine concentrations by h.p.l.c. (modified from Vandenberghe *et al.*, 1981). Food was allowed 5 h (lunch) and 10 h (supper) after pethidine administration and was standardized in terms of quantity and fat/

protein/carbohydrate partitioning. As well, subjects rested in a seated position on each study day until after the 11 h blood sample was drawn. These food and posture/exercise restrictions were done to eliminate, as much as possible, these factors as potential study interferences secondary to their effect on hepatic blood flow (Wilkinson, 1975).

Analytical methods

Biological samples were assayed for pethidine and norpethidine content by a h.p.l.c. procedure (Meatherall *et al.*, 1985). Pethidine HCl and norpethidine HCl were gifts from Winthrop Laboratories, Aurora, Ontario, Canada. Diphenhydramine HCl (purchased from Sigma Chemical Co., St Louis, Missouri, USA) and nordiphenhydramine HCl (gift from Warner-Lambert Pharmaceuticals, Ann Arbor, Michigan, USA) were used as the internal standards for pethidine and norpethidine, respectively. In brief, 0.1 ml of internal standard solution (1 $\mu\text{g}/\text{ml}$ each of diphenhydramine and nordiphenhydramine in 1 mM H_3PO_4) were added to 1 ml of serum or urine sample. After alkalization of these serum and urine samples, with 0.1 ml of 1 N NaOH (serum) or 1 ml of saturated sodium borate solution, pH 10.2 (urine), 5 ml of hexane were added and the contents mixed by gentle rocking (60/min) for 15 min. After centrifugation, 4 ml of the hexane layer were removed and 80 μl of 1 mM H_3PO_4 were added to the organic phase. After vortexing for 30 s followed by a brief centrifugation, 50 μl of the aqueous phase was injected into the chromatograph. A Perkin-Elmer Series 2 pump and Perkin-Elmer LC-85 variable wavelength UV-Vis detector set at 205 nm were used. A Supelcosil® LC-PCN 150 mm $\times$ 4.6 mm i.d. (5 μm particle size) column protected by a Supelguard® LC-CN guard column 20 mm $\times$ 4.6 mm i.d. (Supelco, Bellefonte, Pennsylvania, USA) were used. The mobile phase was acetonitrile: 15 mM K_2HPO_4 , pH 7.0: methanol (55:25:20) pumped at 2.5 ml/min. Retention times for pethidine, diphenhydramine, norpethidine, and nordiphenhydramine were 1.44, 1.93, 2.66 and 2.94 min, respectively. Measurements were made by comparing peak area ratios of unknowns to serum and urine based standards. All samples were analyzed in duplicate. Within run coefficient of variation (c.v.) for 50 ng/ml serum pethidine and norpethidine samples were 5.5 and 7.9%, respectively. Corresponding values for 50 ng/ml urine samples were 5.2 and 5.9%, respectively. Between run c.v. for serum pethidine and norpethidine samples at the same

concentration were 8.1 and 9.6%, respectively, with corresponding urine values of 8.8 and 10.2% respectively. The lower limits of the assay were 2.5 and 5 ng/ml for pethidine and norpethidine, respectively.

Pharmacokinetic analysis

Pharmacokinetic data were analyzed using model-independent methods (Gibaldi & Perrier, 1982; Wagner, 1975; Benet & Galeazzi, 1979). The elimination rate constant (λ_z) was determined by linear regression of the postdistribution phase log serum pethidine concentration vs time curve data. The volume of distribution at steady state (V_{ss}) and total body clearance (CL) for pethidine were calculated using the following equations:

$$V_{ss} = \frac{\text{dose (AUMC)}}{(\text{AUC})^2}$$

$$\text{CL} = \frac{\text{dose}}{\text{AUC}}$$

where dose is the i.v. pethidine dose administered; AUC is the total area under the serum pethidine concentration vs time curve obtained using the trapezoidal rule (from start of bolus to time of last detectable sample) and extrapolated to infinity using λ_z ; AUMC is the total area under the first moment of the serum pethidine concentration vs time curve obtained using the trapezoidal rule (from start of bolus to time of last detectable sample) and extrapolated to infinity using λ_z . Twenty-four hour pethidine urinary excretion (A_e [24]) was also measured.

Figure 1 Serum pethidine (mean $\pm$ s.d.) concentration vs time data during the control trial (●) and the ranitidine interaction trial (○) in eight healthy male subjects.

Generation of norpethidine by oxidative demethylation of pethidine was assessed by measurement of the area under the serum norpethidine concentration vs time curve from 0 to 24 h (AUC[24]), peak norpethidine serum concentration (C_{max}), time to peak norpethidine

Table 1 Effect of ranitidine on pharmacokinetic parameters of pethidine disposition

Subject	λ_z (h^{-1})		V_{ss} (l/kg)		CL ($l\ kg^{-1}\ h$)		Ae[24] (mg)	
	Control	Ranitidine	Control	Ranitidine	Control	Ranitidine	Control	Ranitidine
1	0.131	0.134	5.27	4.75	0.769	0.660	4.66	6.74
2	0.109	0.116	4.13	4.22	0.460	0.509	6.13	9.34
3	0.095	0.127	6.07	4.61	0.657	0.634	3.28	2.88
4	0.128	0.111	4.03	4.43	0.560	0.578	5.21	7.81
5	0.063	0.065	4.20	4.21	0.283	0.289	5.05	3.57
6	0.124	0.103	4.70	5.12	0.629	0.629	— ¹	—
7	0.096	0.106	2.73	3.37	0.301	0.393	4.81	4.44
8	0.148	0.140	3.75	3.83	0.595	0.597	1.20	1.29
Mean	0.112	0.113	4.36	4.32	0.532	0.536	4.33	5.15
s.d.	0.027	0.023	1.01	0.55	0.172	0.132	1.62	2.89
Statistical significance ²	NS		NS		NS		NS	

¹Not included for reasons discussed in text.

²Paired Student's *t*-test (two-tailed).

Table 2 Effect of ranitidine on pharmacokinetic parameters of norpethidine disposition

Subject	t_{lag} (h)		t_{max} (h)		C_{max} (ng/ml)		AUC[24] (ng ml ⁻¹ h)		Ae[24] (mg)	
	Control	Ranitidine	Control	Ranitidine	Control	Ranitidine	Control	Ranitidine	Control	Ranitidine
1	0.33	0.75	5.0	2.0	31.8	18.0	608	192	7.03	5.98
2	2.0	1.5	11.0	8.0	20.7	21.9	389	404	5.94	3.65
3	3.0	3.0	11.0	6.0	11.3	12.8	212	213	3.06	3.33
4	3.0	1.0	11.0	8.0	17.6	22.8	288	435	3.84	3.98
5	4.0	3.0	4.0	8.0	13.1	11.5	141	201	1.80	1.33
6	1.5	0.33	6.0	11.0	23.4	27.9	328	520	— ¹	—
7	2.0	4.0	5.0	5.0	14.4	9.5	238	150	4.07	2.57
8	0.75	3.0	3.0	5.0	15.8	16.5	190	215	2.22	2.71
Mean	2.07	2.07	7.0	6.6	18.5	17.6	299	291	3.99	3.36
s.d.	1.23	1.34	3.4	2.7	6.7	6.3	148	139	1.91	1.44
Statistical significance ²	NS		NS		NS		NS		NS	

¹Not included for reasons discussed in text.²Paired Student's *t*-test (two tailed).

serum concentration (t_{max}), lag time to appearance of quantifiable drug in serum (t_{lag}), and 24 h norpethidine urinary excretion (Ae[24]).

Statistical analysis

Statistical analysis employed Student's *t*-test for paired data (Daniel, 1978). Data in the figures and tables are expressed as mean $\pm$ s.d.

Results

Tablet counts and serum ranitidine concentrations indicated good compliance with the ranitidine treatment regimen. The mean ($\pm$ s.d.) serum ranitidine concentration was 342.4 ± 264.0 ng/ml (range 68.2–755.1 ng/ml). These concentrations are consistent with those achieved during chronic ranitidine therapy.

Figure 1 shows the decline in serum (mean $\pm$ s.d.) pethidine concentration over time for the control and ranitidine interaction trials. Pethidine serum concentrations were below the detection limits of 2.5 ng/ml by the 48 h sample in all but one subject during both trials. Subject 5 exhibited measurable levels even at the 48 h sample during both trials. For the sake of brevity, the mean serum norpethidine concentration vs time curves for the control and ranitidine interaction trials are not illustrated. During the analysis of norpethidine data, only data up to and including the 24 h samples were utilized because norpethidine concentrations at 48 h were close to or below detection limits. The effect of ranitidine on pethidine and norpethidine pharmacokinetic parameters is summarized in Tables 1 and 2, respectively.

Ranitidine therapy was not associated with any significant changes in pethidine λ_z , V_{ss} , CL, and Ae[24]. The absence of a significant ranitidine–pethidine pharmacokinetic interaction was also supported by the nonsignificant changes noted in norpethidine t_{lag} , t_{max} , C_{max} , AUC[24], and Ae[24]. Urinary pethidine and norpethidine excretion data for subject 6 were omitted from analysis because of incomplete urine collection.

Discussion

The purpose of this study was to assess the effect of ranitidine on the pharmacokinetics of pethidine in man, comparing this drug to the more widely-used H₂-receptor antagonist cimetidine, which we have studied previously (Guay *et al.*, 1984). Knodell *et al.* (1982) demonstrated that ranitidine, unlike cimetidine, had no significant

effect on pethidine *N*-demethylase activity *in vitro* in rat and human hepatic microsomes. In our study, therapeutic doses and serum concentrations of ranitidine had no significant effect on the pharmacokinetics of pethidine or its major active metabolite, norpethidine. These data are in direct contrast to our previous findings with the cimetidine-pethidine interaction. Cimetidine therapy reduced pethidine CL and V_{ss} and norpethidine generation as measured by AUC[24] and C_{max} by 22, 13, 23, and 29 percent, respectively (Guay *et al.*, 1984).

As we have discussed previously, the true clinical significance of the cimetidine-pethidine interaction is not established and will not be until the relative contributions of pethidine and norpethidine to efficacy and toxicity are known (Guay *et al.*, 1984). As a result, the potential

clinical advantages of ranitidine vs cimetidine therapy in patients also receiving pethidine are speculative at this time. Further studies will be required to resolve this issue. However, with no significant effects on either parent or metabolite pharmacokinetics, we suggest that ranitidine may be the preferred H_2 -receptor antagonist in selected patients requiring concurrent therapy with pethidine.

We acknowledge the skilled secretarial assistance of Ms Eileen Marek-Moller. This work was supported in part by a grant-in-aid from Glaxo Laboratories. Reprint requests to Dr David Guay, Regional Kidney Disease Program, Department of Medicine, Hennepin County Medical Center, 701 Park South, Minneapolis, MN, USA 55415.

References

- Bell, J. A., Gower, A. J., Martin, L. E., Mills, E. N. C. & Smith, W. P. (1981). Interaction of H_2 -receptor antagonists with drug metabolizing enzymes. *Biochem. Soc. Trans.*, **9**, 113-114.
- Benet, L. Z. & Galeazzi, R. L. (1979). Noncompartmental determination of the steady-state volume of distribution. *J. pharm. Sci.*, **68**, 1071-1074.
- Brogden, R. N., Carmine, A. A., Heel, R. C., Speight, T. M. & Avery, G. S. (1982). Ranitidine: a review of its pharmacology and therapeutic use in peptic ulcer disease and other allied diseases. *Drugs*, **24**, 267-303.
- Daniel, W. W. (1978). *Biostatistics: a foundation for analysis in the health sciences* (2nd edition). New York: John Wiley & Sons.
- Edwards, D. J., Svensson, C. K., Visco, J. P. & Lalka, D. (1982). Clinical pharmacokinetics of pethidine: 1982. *Clin. Pharmacokin.*, **7**, 421-433.
- Gaginella, T. S. & Bauman, J. H. (1983). Ranitidine hydrochloride. *Drug Intell. Clin. Pharm.*, **17**, 873-885.
- Gibaldi, M. & Perrier, D. (1982). *Pharmacokinetics* (2nd edition). New York: Marcel Dekker.
- Guay, D. R. P., Meatherall, R. C., Chalmers, J. L. & Grahame, G. R. (1984). Cimetidine alters pethidine disposition in man. *Br. J. clin. Pharmacol.*, **18**, 907-914.
- Helman, C. A. & Tim, L. O. (1983). Pharmacology and clinical efficacy of ranitidine, a new H_2 -receptor antagonist. *Pharmacotherapy*, **3**, 185-192.
- Knodell, R. D., Holtzman, J. L., Crankshaw, D. L., Steele, N. M. & Stanley, L. N. (1982). Drug metabolism by rat and human hepatic microsomes in response to interaction with H_2 -receptor antagonists. *Gastroenterology*, **82**, 84-88.
- Meatherall, R. C., Chalmers, J. L. & Guay, D. R. P. (1985). Analysis of meperidine and normeperidine in serum and urine by high-performance liquid chromatography. *J. Chromatogr.* **338**, 141-149.
- Mihaly, G. W., Smallwood, R. A., Anderson, J. D., Jones, D. B., Webster, L. K. & Vajda, F. J. (1982). H_2 -receptor antagonists and hepatic drug disposition. *Hepatology*, **2**, 828-831.
- Rendic, S., Alebic-Kolbah, T. & Kajfex, F. (1982). Interaction of ranitidine with liver microsomes. *Xenobiotica*, **12**, 9-17.
- Vandenberghe, H. M., MacLeod, S. M., Mahon, W. A., Lebert, P. A. & Soldin, S. J. (1980). Analysis of ranitidine in serum by high performance liquid chromatography. *Ther. Drug Monit.*, **2**, 379-384.
- Verbeeck, R. K., Branch, R. A. & Wilkinson, G. R. (1981). Meperidine disposition in man; influence of urinary pH and route of administration. *Clin. Pharmac. Ther.*, **30**, 619-628.
- Wagner, J. G. (1975). *Fundamentals of clinical pharmacokinetics*. Hamilton, Illinois: Drug Intelligence Publications.
- Wilkinson, G. R. (1975). Pharmacokinetics of drug disposition: hemodynamic considerations. *Ann. Rev. Pharmac. Tox.*, **15**, 11-27.
- Zeldis, J. B., Friedman, L. S. & Isselbacher, K. J. (1983). Ranitidine: a new H_2 -receptor antagonist. *New Engl. J. Med.*, **309**, 1368-1373.

(Received 11 January, 1985,
accepted March 26, 1985)