CIMETIDINE DOES NOT ALTER MORPHINE DISPOSITION IN MAN

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- 1 The pharmacokinetic parameters of morphine were determined in a crossover fashion following 4 days pretreatment with cimetidine, 300 mg every 6 h, or placebo.
- 2 Cimetidine had no apparent effect on the mean morphine plasma clearance, volume of distribution, AUC or half-life ($P > 0.05$; power > 0.80).
- 3 Cimetidine had no apparent effect on the magnitude or duration of morphine induced miosis.
- 4 The absence of a demonstrable effect on the pharmacokinetics of a drug with a high extraction ratio such as morphine suggests that cimetidine did not significantly reduce hepatic blood flow in ambulant normal volunteers.

Introduction

The histamine H₂-receptor antagonist cimetidine has been found to decrease the rate of elimination and raise the serum concentration of various drugs in man including diazepam (Klotz & Reimann, 1980b), chlordiazepoxide (Desmond *et al.*, 1980), theophylline (Reitberg *et al.*, 1981), and propranolol (Feely *et al.*, 1981). The postulated mechanisms for the interaction of cimetidine with these compounds are a direct competition for hepatic enzyme metabolism (Knodell *et al.*, 1982; Puurunen *et al.*, 1980; Puurunen & Pelkonen, 1979), a decrease in hepatic blood flow (propranolol) (Feely *et al.*, 1981) or both.

An apparent toxic interaction between cimetidine and morphine has been postulated in an acutely ill 46 year old male (Find & Churchill, 1981). An evaluation of the effect of cimetidine on morphine metabolism in rats documented a metabolic interaction both *in vivo* and *in vitro* (Mojaverian *et al.*, 1982). The purpose of the present study was to evaluate the effect of cimetidine on the pharmacokinetics and pharmacodynamics of intravenous morphine in healthy volunteers. Since the hepatic clearance of morphine in humans has been reported to be blood-flow limited, this study also provides indirect information on the effect of cimetidine on hepatic blood flow.

Methods

Seven healthy male volunteers (65–98 kg, 20–38 years) gave informed consent to participate in this study. None of the subjects had taken any medication for 2 weeks prior to the study. The volunteers randomly received either oral cimetidine (300 mg) or placebo four times daily for 4 days. Following an overnight fast each volunteer received 10 mg of morphine sulphate (8.5 mg free base) as a 2 min infusion, 1 h after the administration of their morning dose of cimetidine or placebo on day 4. Oral cimetidine and placebo were administered on a 6 hourly schedule throughout the study day. A 20 gauge teflon catheter was placed in a forearm vein, contralateral to the morphine injection site and was kept patent by instillation of heparinized normal saline (3.3 units/ml). One millilitre was withdrawn via the indwelling catheter and discarded prior to collecting each venous blood sample (2 ml). Blood samples were collected prior to and at 2, 5, 10, 15, 20, 30, 60, 90, 120, 180, 240, 360, 480 and 600 min after morphine administration. Plasma was separated and frozen at -20°C until analysis. Subjects remained in a supine position for the first hour following the injection of morphine and subsequently were ambulant. Subjects were allowed to eat lunch approximately 4 h following morphine administration. Pupil diameter

was determined before and 2, 5, 7 and 10 h post-morphine by serial photography (35 mm camera with a fixed focal length lens with one-to-one magnification and electronic flash). The timing of the 2 h photograph was dictated by frequent sampling times and previous published experience regarding the extent of the heroin-induced miosis in the period between 15 min to 2 h post-dose (Tress & El-Sobky, 1979). The pupil diameters were measured directly from contact prints using calipers and a photographed millimeter scale. Blood pressure, heart rate and potential adverse effects were monitored throughout the study. Each volunteer received the alternate treatment in an identical manner following a seven day drug-free period. Morphine concentrations were measured by radioimmunoassay (Roche Diagnostics, Nutley, NJ) according to the method of Spector & Parker (1970); the cross reactivity of cimetidine was negligible. Cimetidine concentrations in whole blood were measured by high-performance liquid chromatography (Randolph *et al.*, 1977) in each subject after cimetidine pretreatment and prior to morphine administration.

Pharmacokinetic analysis of the plasma concentration-time data for each individual was performed using the LAGRAN computer program (Rocci, 1981). This program generates pharmacokinetic parameters using moment analysis and model independent pharmacokinetics. The systemic clearance (CL) of morphine was calculated using Equation (1):

$$CL = \text{Dose}/AUC \quad \text{Equation (1)}$$

where Dose is the intravenous morphine dose and AUC is the area under the morphine plasma concentration-time curve from zero to time infinity.

The elimination half-life ($t_{1/2}\beta$) was computed using Equation (2):

$$t_{1/2} = 0.693/\lambda_z \quad \text{Equation (2)}$$

where λ_z is the absolute value of the terminal slope of a plot of the natural logarithm of morphine plasma concentrations as a function of time. The volume of distribution at steady state of morphine (V_{ss}) was computed via Equation (3):

$$V_{ss} = \frac{\text{Dose} \cdot AUMC}{(AUC)^2} \quad \text{Equation (3)}$$

where AUMC is the first moment of the morphine plasma concentration-time curve (Benet & Galeazzi, 1979).

Pharmacokinetic and pupillometric data for the two treatment periods were tested for differences using a paired Student's *t*-test; $P < 0.05$ was considered significant. In the absence of a treatment effect for a given pharmacokinetic parameter, a power analysis was performed to assess the likelihood of making a Type II error. A power of >0.8 was considered acceptable.

Figure 1 Mean $\pm$ s.d. plasma morphine concentrations (ng/ml) in healthy volunteers ($n = 7$) after single i.v. doses of morphine, with (●) and without (○) cimetidine pretreatment.

Results

Mean morphine concentrations in plasma at various times following morphine administration for each treatment are depicted in Figure 1. No significant difference was observed in the mean morphine concentrations between the two treatments at any time point. Likewise, the mean pharmacokinetic parameters of morphine derived from the individual concentration-time profiles (Table 1) did not differ between cimetidine and placebo pretreatment ($P > 0.05$, power > 0.80). Mean pupil diameters (mm) at selected intervals after morphine administration are shown in Figure 2. Pre-morphine values in the two periods were comparable indicating that cimetidine pretreatment had no significant effect on pupil size. Regardless of the pretreatment, mean pupil diameter was significantly decreased ($P < 0.05$) 2 h after morphine infusion and remained so for up to 10 h; there was no significant difference between the two morphine treatments at any time. Cimetidine serum concentrations prior to morphine administration were in the therapeutic range (0.4–2.5 $\mu\text{g/ml}$). No adverse effects were noted during the entire study with the exception of mild nausea in one subject, which occurred after morphine administration in both periods.

Figure 2 Pupil diameters (mean $\pm$ s.d.) in both treatment groups (cimetidine $\bullet$ — $\bullet$, placebo $\circ$ — $\circ$) were reduced from baseline ($P > 0.05$) but were not different compared to each other at any time point ($P < 0.05$).

Discussion

In this study in normal men, cimetidine had no apparent effect on the pharmacokinetics and pharmacodynamics of morphine. This is supported by the similarity in the mean systemic clearance, volume of distribution, half-life and AUC of morphine after placebo and cimetidine pretreatment. Likewise, the time course of the miotic response to morphine was unchanged by cimetidine. Statistical analysis of the individual pharmacokinetic parameters indicates that our sample size was large enough to detect a cimetidine-induced effect of $\geq 18\%$ with a power of ≥ 0.80 . In other words, the chance of accepting the null hypothesis (i.e. no effect

of cimetidine on morphine disposition) when it in fact should be rejected (Type II error) is small.

The mean plasma clearance of morphine in our ambulant volunteers was 535 ml/min. Mean hepatic blood flow, as determined by ICG clearance, in the supine and sitting positions has been reported to be 1214 ± 146 and 1481 ± 51 ml/min respectively. However, hepatic blood flow in the same study decreased significantly following exercise 716 ± 73 ml/min and in the upright posture 763 ± 81 ml/min (Daneshmend *et al.*, 1981). Morphine clearance as determined in our subjects is therefore consistent with these lower estimates of hepatic blood flow. Based on hepatic blood flow in the upright position, the magnitude of the approximate extraction ratio (morphine clearance/763 ml/min) for morphine was 0.7. This indicates that the systemic clearance of morphine in these normal volunteers is indeed blood flow limited and therefore should be sensitive to changes in hepatic blood flow (Feely *et al.*, 1981; George, 1979; Stanski *et al.*, 1978). That cimetidine did not significantly alter the systemic clearance of morphine implies that cimetidine had little effect on hepatic blood flow in our study.

Plasma morphine concentrations as determined by radioimmunoassay overestimate morphine plasma concentrations when compared with a gas-liquid chromatographic technique (Stanski *et al.*, 1982). The disparity between the assays is believed to be due to crossreactivity of the RIA with morphine-3-glucuronide. The average difference between morphine concentration in plasma samples obtained more than 1 h following an intravenous dose of morphine has been reported to be 27%. Examination of the mean morphine pharmacokinetic parameters derived from the two assays in the same subjects demonstrated a statistically insignificant reduction in volume of distribution at steady state, and systemic clearance as well as a shorter plasma half-life when morphine plasma

Table 1 Effect of cimetidine on pharmacokinetics of morphine in seven healthy volunteers†

Subject	Elimination half-life $t_{1/2}$ (h)		Systemic clearance CL (ml/min)		Steady state volume of distribution V_{ss} (l)		Area under the plasma concentration-time curve AUC (ng h ml ⁻¹)	
	Placebo	Cimetidine	Placebo	Cimetidine	Placebo	Cimetidine	Placebo	Cimetidine
1	2.79	2.94	660	558	152	142	214	254
2	3.83	4.04	520	502	172	185	272	283
3	2.90	3.38	580	434	155	127	244	326
4	3.38	4.79	532	407	159	178	266	348
5	2.86	2.76	582	630	147	162	246	225
6	4.30	3.61	582	543	209	176	243	261
7	2.83	3.03	440	437	104	110	322	324
Mean	3.38	3.51	557	502	157	154	258	289
$\pm$ s.d.	± 0.33	± 0.71	± 68	± 81	± 31.3	± 28.5	± 34	± 45

† No statistical differences were present, power > 0.80

concentrations were determined by RIA (Stanski *et al.*, 1982). The comparative study by Stanski implies that the RIA technique used in the present study may have systematically underestimated systemic morphine clearance. In the present study, the identical RIA method was used for all morphine determinations. Therefore, assay specificity should not have influenced the comparative pharmacokinetic analysis nor the ultimate conclusion that cimetidine did not alter the metabolism of morphine.

Though controversial, other investigators have demonstrated a cimetidine and ranitidine-induced reduction in hepatic blood flow as reflected by reductions in propranolol, lignocaine and indocyanine green clearances (Feely *et al.*, 1981; Lebrech *et al.*, 1981; Jackson, 1981; Feely & Guy, 1982; Knapp *et al.*, 1982). Though the previous reports and the current study may appear to be incongruent, several methodologic differences may have contributed to the disparate conclusions. Hepatic blood flow has been reported to decrease approximately 30–50% when normal subjects stand up; mean hepatic blood flow in the upright position was 763 ml/min (Daneshmend *et al.*, 1981). In the present study, posture-induced decreases in hepatic blood flow may have obfuscated any measurable effect of cimetidine on hepatic blood flow. Cimetidine's ability to alter liver blood flow could be reduced in the upright position. The current investigation more closely mimics cimetidine's action in an ambulatory setting while studies in the supine position may more closely resemble an in-patient setting.

Fine & Churchill (1981) suggested a potentially life-threatening interaction between morphine and cimetidine in a seriously ill patient. A pharmacokinetic interaction between cimetidine and morphine is an unlikely explanation for this patient's clinical course. The exhibited symptoms may have been more likely related to accumulation of morphine, cimetidine (Schentag *et al.*, 1979) and/or phenytoin (Salem, 1981), or a pharmacologic interaction among these agents (Mojaverian *et al.*, 1981).

Animal and human data demonstrate no cimetidine-induced alteration in morphine, oxazepam or lorazepam glucuronidation (Knodell, 1982; Klotz & Rizmann 1980a; Patwardhan *et al.*, 1980). Cimetidine impairs the clearance of morphine *in vitro* and *in vivo* in the rat (Mojaverian *et al.*, 1982). Interspecies variation in morphine metabolism is likely to be responsible for the differences observed in the rat and human experiments (Milthers, 1962; Misra *et al.*, 1961).

In conclusion, in healthy ambulatory men, four days of cimetidine pretreatment neither altered the pharmacokinetics of morphine nor the miotic response to morphine. No increase in adverse effects was noted in those volunteers receiving cimetidine pretreatment.

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References

- BENET, L.Z. & GALEAZZI, R.L. (1979). Noncompartmental determination of the steady state volume of distribution. *J. pharm. Sci.*, **68**, 1071–1074.
- DAHLSTROM, B., TAMSEN, A., PAGLZOW, L. & HARTVIG, P. (1982). Patient controlled analgesia therapy, Part IV: Pharmacokinetics and analgesic plasma concentrations of morphine. *Clin. Pharmacokin.*, **7**, 266–279.
- DANESHMEND, T.K., JACKSON, L. & ROBERTS, C.J. (1981). Physiological and pharmacological variability in estimated hepatic blood flow in man. *Br. J. clin. Pharmacol.*, **11**, 491–496.
- DESMOND, P.V., PATWARDHAN, R.V., SCHENKER, S. & SPEEG, Jr. K.V. (1980). Cimetidine impairs elimination of chlorodiazepoxide (Librium) in man. *Ann. Intern. Med.*, **93**, 266–268.
- FEELY, J., WILKINSON, G.R. & WOOD, A.J. (1981). Reduction of liver blood flow and propranolol metabolism by cimetidine. *New Engl. J. Med.*, **304**, 692–695.
- FEELY, J. & GUY, E. (1982). Ranitidine also reduces liver blood flow. *Lancet*, **i**, 169.
- FINE, A. & CHURCHILL, D.N. (1981). Potentially lethal interaction of cimetidine and morphine, letter. *Can. med. Ass. J.*, **124**, 1434–1436.
- GEORGE, C.F. (1979). Drug kinetics and hepatic blood flow. *Clin. Pharmacokin.*, **4**, 433–448.
- JACKSON, J.E. (1981). Reduction of liver blood flow by cimetidine. *New Engl. J. Med.*, **305**, 99–100.
- KLOTZ, U. & REIMANN, I. (1980a). Influence of cimetidine on the pharmacokinetics of desmethyldiazepam and oxazepam. *Eur. J. clin. Pharmacol.*, **18**, 517–520.
- KLOTZ, U. & REIMANN, I. (1980b). Delayed clearance of diazepam due to cimetidine. *New Engl. J. Med.*, **302**, 1012–1014.
- KNAPP, A.B., MAGUIRE, W., KEREN, G., KARMEN, A., MIURA, D.S. & SOMBERG, J.C. (1982). The effect of cimetidine administration on serum lidocaine levels in man. *Am. J. Cardiol.*, **49**, 1026.
- KNODELL, R.G., 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 H₂-receptor antagonist. *Gastroenterology*, **82**, 84–88.
- LEBRECH, D., GODFORTH, G. & BENHAMOU, J. (1981). Reduction of liver blood flow by cimetidine, letter. *New Engl. J. Med.*, **305**, 100.
- MILTHERS, K. (1962). The *N*-demethylation of morphine in

- rats. Quantitative determination of normorphine and morphine in the urine and faeces of rats given subcutaneous morphine. *Acta Pharmac. Tox.*, **19**, 149–155.
- MISRA, A.L., MULE, S.J. & WOODS, L.A. (1961). *In vivo* formation of normorphine in the rat as a metabolite of tritium nuclear-labelled morphine. *Nature*, **190**, 82–83.
- MOJAVERIAN, P., SWANSON, B.N., DUDASH, M.L., VLASSES, P.H. & FERGUSON, R.K. (1981). Potentially lethal interaction of cimetidine and morphine, letter. *Can. med. Ass. J.*, **125**, 1212.
- MOJAVERIAN, P., SWANSON, B.N., DUDASH, M.L., VLASSES, P.H. & FERGUSON, R.K. (1982). Influence of cimetidine on the pharmacokinetics of morphine in rats. *Res. Comm. Sub. Abuse*, **3**, 1–10.
- PATWARDHAN, R.V., YARBOROUGH, G., DESMOND, P.V., JOHNSON, R.F., SCHENKER, S. & SPEEG, Jr. K.V. (1980). Cimetidine spares the glucuronidation of lorazepam and oxazepam. *Gastroenterology*, **79**, 912–916.
- PUURUNEN, J. & PELKONEN, O. (1979). Cimetidine inhibits microsomal drug metabolism in the rat. *Eur. J. Pharmac.*, **55**, 335–336.
- PUURUNEN, J., SOTANIEMI, E. & PELKONEN, O. (1980). Effect of cimetidine on microsomal drug metabolism in man. *Eur. J. clin. Pharmac.*, **18**, 185–187.
- RANDOLPH, W.C., OSBORNE, V.L., WALKENSTEIN, S.S. & INTOCCIA, A.P. (1977). High-pressure liquid chromatographic analysis of cimetidine, a histamine H₂-receptor antagonist, in blood and urine. *J. pharm. Sci.*, **66**, 1148–1150.
- REITBERG, D.P., BERNHARD, H. & SCHENTAG, J.J. (1981). Alteration of theophylline clearance and half-life by cimetidine in normal volunteers. *Ann. Intern. Med.*, **95**, 582–585.
- ROCCI, Jr. M.L. (1981). *LAGRAN program for area and moments in pharmacokinetic analysis*. Ph.D. Thesis, State University of New York, Buffalo, N.Y.
- SALEM, R.B. (1981). Potentially lethal interaction of cimetidine and morphine, letter. *Can. med. Ass. J.*, **125**, 1212.
- SCHENTAG, J.J., CERRA, F.B., CALLERI, G., DEGLOPPER, E., ROSE, J.O. & BERNHARD, H. (1979). Pharmacokinetic and clinical studies with cimetidine associated mental confusion. *Lancet*, **i**, 177.
- SPECTOR, S. & PARKER, C. (1970). Morphine radioimmunoassay. *Science*, **168**, 1347–1348.
- STANSKI, D.R., PAALZOW, L. & EDLUND, P.O. (1982). Morphine pharmacokinetics: GLC assay versus radioimmunoassay. *J. pharm. Sci.*, **71**, 314–317.
- STANSKI, D.R., GREENBLATT, D.J. & LOWENSTEIN, E. (1978). Kinetics of intravenous and intramuscular morphine. *Clin. Pharmac. Ther.*, **24**, 52–59.
- TRESS, K.H. & EL-SOBKY, A.A. (1979). Pupil responses to intravenous heroin (diamorphine) in dependent and non-dependent humans. *Br. J. clin. Pharmac.*, **7**, 213–217.

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