Lack of pharmacokinetic interaction between butorphanol nasal spray and cimetidine

W. C. SHYU & R. H. BARBHAIYA

Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Pharmaceutical Research Institute, Bristol-Myers Squibb Company, Lawrenceville, New Jersey, USA

The potential for a pharmacokinetic interaction between butorphanol nasal spray and cimetidine, under steady state conditions, was evaluated in 16 healthy male volunteers. Subjects received either a 1 mg butorphanol nasal spray every 6 h or a 300 mg cimetidine tablet every 6 h on days 1–4, the combination of two compounds every 6 h on days 5–8 and the original treatment as described in the first segment (days 1–4) on days 9–12. Serial blood and urine samples were collected on days 4, 8 and 12, and additional blood samples were taken immediately, prior to the morning dose on days 3, 7 and 11. Based on the analysis of the $C_{\min}$ samples, the plasma concentrations of cimetidine and butorphanol achieved steady state by the third day of dosing. No statistically significant differences were found in the plasma concentrations of butorphanol or cimetidine (except for $t_{\frac{1}{2}}$ and MRT) between any of the treatment phases. Butorphanol nasal spray and cimetidine can be co-administered without any adjustment of dosage for either drug.

Keywords butorphanol transnasal cimetidine pharmacokinetics

Introduction

Butorphanol tartrate is a synthetic opioid agonist-antagonist analgesic. Although butorphanol is well-absorbed orally, it undergoes extensive first-pass metabolism with an oral bioavailability of approximately 5% (unpublished data). A nasal formulation of butorphanol was developed for convenient administration, avoidance of hepatic first-pass elimination, and rapid absorption. The absolute bioavailability of butorphanol nasal spray in humans is 70% [1–3]. Clinical trials have demonstrated that transnasal butorphanol provides rapid, effective analgesia with side effects comparable with those seen after intramuscular or intravenous injection of the drug [4, 5].

Butorphanol is extensively metabolized with only small amounts of unchanged butorphanol excreted in the urine. The known metabolites of butorphanol are hydroxy-butorphanol, norbutorphanol, and the glucuronide conjugates of butorphanol and its two oxidation products [6]. Following intravenous dosing, about 80% of the dose is recovered in the urine with approximately 30% accounted for by these compounds.

Cimetidine is one of the most commonly prescribed medications for the treatment of duodenal ulcers.

Cimetidine has been reported to inhibit the cytochrome P-450 mediated oxidative metabolism of many drugs [7]. Since both cimetidine and butorphanol undergo oxidative metabolism in humans, it is possible that clearance of one or both drugs may be compromised when the two compounds are administered simultaneously. This study was designed to define the extent of pharmacokinetic interaction between butorphanol nasal spray and cimetidine.

Methods

Subjects

Sixteen healthy male subjects reviewed and signed an informed consent form prior to participation in the study. The study protocol was approved by the Institute Review Board of the clinical site. The key selection criteria were that subjects did not have acute or chronic diseases, subjects had normal nasal anatomy and mucosa, and did not suffer from nasal allergy or viral rhinitis. For Treatment A, the subjects had a mean ($\pm$ s.d.) age of 29 ($\pm$ 6) years (range 20–37 years), a mean

height of 178.0 (± 7.3) cm (range 166.4–191.8 cm), and a mean body weight of 77.7 (± 8.8) kg (range 64.5–88.6 kg). For Treatment B, the subjects had a mean ($\pm$ s.d.) age of 26 (± 6) years (range 20–39 years), a mean height of 176.2 (± 5.1) cm (range 170.2–184.2 cm), and a mean body weight of 72.6 (± 5.2) kgs (range 67.3–83.6 kg).

Drug formulation

Commercially available butorphanol nasal spray (product No. 12097–061–15) and cimetidine (product No. 12097–KXXX–55) were used in the study.

Study design

This was an open label, parallel, multiple dose study. Sixteen male subjects were randomly divided into two treatment groups. Eight subjects (Treatment A) received a 1 mg dose of butorphanol nasal spray every 6 h on days 1–11 and a 300 mg dose of cimetidine every 6 h on days 5–8. On day 12, they received only a single 1 mg dose of butorphanol nasal spray. The other eight subjects (Treatment B) received a 300 mg dose of cimetidine tablet every 6 h on days 1–11 and a 1 mg dose of butorphanol nasal spray every 6 h on days 5–8. On day 12, they received only a single 300 mg dose of cimetidine. Serial blood samples and the total urine output of each subject were collected for 6 h on days 4, 8 and 12 following the 08.00 h morning dose. Additional blood and urine samples were collected for up to 12 h post-dose on day 12. Samples for the measurement of trough concentrations ($C_{\min}$) were also collected on days 3, 7 and 11, immediately before the morning dose.

Drug administration

Each dose of butorphanol nasal spray dose was administered in one spray (approximately 0.1 ml of a 10 mg ml⁻¹ solution) into one nostril. Each subject was instructed and familiarised in the use of the sprayer and during the studies the drug was self-administered. Cimetidine tablets (300 mg) were administered with 200 ml of water. During the co-administration period, cimetidine administration occurred within 5 min of the administration of butorphanol nasal spray. Subjects fasted overnight on days 3, 7 and 11, on the days blood was sampled.

Sample collection

Blood samples were collected at pre-dose, 5, 15, 30, and 45 min, and 1, 1.5, 2, 3, 4, and 6 h after dosing, on days 4, 8 and 12. Additional blood samples were collected at 8, 10 and 12 h after dosing on study day 12. On days 3, 7 and 11, a blood sample was drawn prior to administration of the morning dose. Urine samples were collected over the following time intervals: pre-dose, 0–2, 2–4, and 4–6 h post-dose on days 4, 8 and 12. An

additional urine sample was collected on day 12, 6–12 h post-dose. Plasma and urine samples were stored at –20 °C until analysis.

Sample analysis

Plasma samples were analysed for intact butorphanol by a validated r.i.a. method [8]. The specificity of the assay was confirmed by a GC/MS assay [9]. Urine samples were analysed for intact butorphanol and its metabolites, hydroxybutorphanol, norbutorphanol and their conjugates using a validated h.p.l.c./fluorescence method [10]. Plasma and urine samples were also analysed for intact cimetidine by a validated h.p.l.c./u.v. method [11]. Quality control samples were prepared prior to the initiation of the study, stored and analysed at the same time as the study samples. The performance of the assays was acceptable based on the results of the estimated precision ($<15\%$ coefficient of variation) and accuracy ($<13\%$ deviation) of the quality control samples.

Pharmacokinetic analyses

Noncompartmental pharmacokinetic parameters were calculated as described previously [12, 13]. The highest observed concentration and the corresponding sampling time were defined as $C_{\max}$ and $t_{\max}$, respectively. The absolute value of the slope (λ) of the concentration *vs* time log-linear regression function was used to determine the terminal elimination half-life as using the equation $t_{1/2} = \ln 2/\lambda$. The area under the concentration *vs* time curve ($AUC(0-\tau)$) was calculated using the trapezoidal rule. Mean residence time in the body at steady state (MRT), renal clearance (CL_R) and urinary recovery (%UR) values were calculated using standard methods [12, 13]. The percentage of the dose recovered as metabolites was calculated by correcting for the difference in molecular weight between butorphanol and each metabolite.

Statistical analyses

Repeated measures analysis was conducted on $C_{\max}$, $t_{\max}$, $t_{1/2}$, $AUC(0-\tau)$, MRT, CL_R and %UR within the treatment. For each study treatment, the above parameters were compared at the three sampling periods using the a one-way analysis of variance. In the case of $t_{\max}$, its rank transformation was used for the analysis. $C_{\min}$ values were compared in the same way to demonstrate the attainment of steady state. The subject and day effects were estimated using Type III sums of squares. Significance of the subject and day effects was determined using the mean square error term. If the effect of days was statistically significant, Tukey's procedure was used to make pairwise comparisons based on the means. Additionally, 95% confidence intervals for differences in means were calculated based on the Tukey's procedure. Levene's test was used to check the assumption of

homogeneity of variance among sampling times [14]. A two-sample *t*-statistic was used to compare the treatments with respect to the individual pharmacokinetics of cimetidine and butorphanol obtained from the second sampling (day 8). The value $P=0.05$ was used as the significance level for all tests except Levene's test, where $P=0.001$ was used.

Results

Safety

Butorphanol and cimetidine were well tolerated. A total of 82 adverse experiences were reported by 12 subjects. Sixty-three events were reported by the butorphanol group (Treatment A) and 19 events were reported by the cimetidine group (Treatment B). The most commonly experienced adverse events were lightheadedness (38%), rash (7%), queasy stomach (6%), nausea (5%) and backache (5%). The temperature, blood pressure, pulse, ECG, clinical laboratory and nasal examination results were similar before, during and after the study period. No significant changes were observed at anytime during the study.

Pharmacokinetics

Treatment A The mean (s.d.) values for pharmacokinetic parameters of butorphanol are presented in Table 1. There were no statistical differences observed in the $C_{\min}$ data comparisons, day 3 *vs* day 4, day 7 *vs* day 8, and, day 11 *vs* day 12, suggesting that steady

state was achieved within 3 days of dosing. No statistical difference was found in any of the butorphanol pharmacokinetic parameters before (day 4), during (day 8) or after (day 12) the co-administration of cimetidine. The 95% confidence intervals for differences in means are presented in Table 1. Less than 25% of the administered dose was excreted in urine as either unchanged butorphanol or its metabolites. There was a modest increase (<3%) in the recovery of each analyte after the hydrolysis of the urine samples, suggesting that glucuronidation of butorphanol and its metabolites is minimal. No statistically significant differences in the pharmacokinetics of butorphanol on day 8 were observed between groups assigned to either butorphanol or cimetidine treatment.

Treatment B No statistical difference was found in $C_{\max}$, $T_{\max}$, $AUC(0-\tau)$, CL_R and %UR of cimetidine before (day 4), during (day 8) or after (day 12) the co-administration of butorphanol. The mean $C_{\max}$ and $AUC(0-\tau)$ values in the 3 different days ranged from 1.55–1.83 $\mu\text{g ml}^{-1}$ and 6.60–7.05 $\mu\text{g ml}^{-1} \text{ h}$, respectively. The mean values for CL_R and %UR were about 133–162 ml min^{-1} and 18–21%, respectively. The $t_{\max}$ was usually achieved in 1.5–2.0 h after dosing. The mean values of $t_{\frac{1}{2}}$ and MRT on day 8, during the co-administration of cimetidine and butorphanol, were statistically greater ($P<0.008$) than those observed on days 4 and 12. The mean values of $t_{\frac{1}{2}}$ and MRT increased from 2.47 h to 3.89 h and from 4.23 to 6.57 h, respectively. There were no statistical differences observed in the $C_{\min}$ data comparisons, day 3 *vs* day 4, day 7 *vs* day 8, and, day 11 *vs* day 12, suggesting that steady state was achieved within 3 days of dosing. No statistically significant differences were found in

Table 1 Mean (s.d.) pharmacokinetic parameters for butorphanol in subjects receiving repeated 1 mg dose of butorphanol by nasal spray ($n=8$) with (day 8) or without (days 4 and 12) the coadministration of oral cimetidine (Treatment A). In Treatment B, subjects received butorphanol on day 8

Parameter	Treatment A			Treatment B	Mean (95% confidence intervals) for Treatment A	
	Day 4	Day 8	Day 12	Day 8	Ratio Day 8 <i>vs</i> Day 4	Ratio Day 12 <i>vs</i> Day 4
$C_{\max}$ (ng ml^{-1})	1.57 (0.99)	1.84 (0.83)	2.40 (1.49)	1.43 (0.14)	1.23 (0.63–2.37)	1.47 (0.76–2.85)
$t_{\max}$ (h)#	1.00	1.13	1.25	0.75	–	–
$t_{\frac{1}{2}}$ (h)	4.07 (1.49)	3.90 (1.18)	4.06 (0.91)	3.13 (1.04)	0.96 (0.65–1.27)	1.00 (0.68–1.31)
$AUC(0-\tau)$ (ng $\text{ml}^{-1} \text{ h}$)	4.69 (0.90)	5.58 (1.70)	5.80 (2.23)	5.18 (0.93)	1.16 (0.86–1.57)	1.18 (0.87–1.60)
MRT (h)	6.19 (2.34)	5.92 (1.51)	5.79 (0.66)	5.07 (1.32)	0.96 (0.70–1.22)	0.94 (0.68–1.19)
CL_R (ml min^{-1})	81.40 (25.80)	59.88 ⁺ (19.38)	59.47 (32.74)	50.90 (17.41)	0.74 (0.38–1.09)	0.73 (0.38–1.08)
%UR	2.25 (0.65)	1.99 (0.75)	2.33 (1.82)	1.53 (0.47)	0.86 (0.44–1.68)	0.80 (0.41–1.56)

UR Urine recovery.

NS No statistically significant differences, $P>0.05$.

Median value reported.

+ $n=7$.

Figure 1 Mean plasma concentration – time profiles of butorphanol in subjects who received 1 mg butorphanol by nasal spray before (study day 1), during (study day 8) and after (study day 12) the co-administration of oral cimetidine (300 mg every 6 h).

the pharmacokinetics of cimetidine on day 8 between groups assigned to either butorphanol or cimetidine treatment.

Discussion

The results from this study indicate that the pharmacokinetics of butorphanol are not affected by co-administration of cimetidine. The pharmacokinetics of cimetidine are generally not affected by co-administration of butorphanol, with the exception of a slight increase in $t_{1/2}$ and MRT when butorphanol is co-administered. However, neither C_{max} , %UR nor AUC of cimetidine or butorphanol is altered following concurrent administration of these two drugs. Cimetidine is an inhibitor of oxidative drug metabolism which interacts directly with the haem iron of cytochrome P450 [15]. The lack of a significant pharmacokinetic interaction between butorphanol and cimetidine could be attributed to the involvement of different cytochrome P450 enzymes and/or the lack of competition in metabolism of butorphanol and cimetidine.

In summary, our findings indicate the absence of pharmacokinetic interactions between oral cimetidine and intranasal butorphanol. Thus, dosage adjustment for either butorphanol or cimetidine is not required when these drugs are co-administered by these routes.

The authors sincerely thank the excellent statistical support provided by Ms Rochelle Milbroth and Ms Carol Gleason.

References

- 1 Shyu WC, Mayol RF, Pfeffer M, Gamman RE, Pittman KA, Barbhaiya RH. Pharmaceutical development of transnasal butorphanol. *Biopharm Drug Dispos* 1993; **14**: 371–379.
- 2 Shyu WC, Pittman KA, Robinson DS, Barbhaiya RH. The absolute bioavailability and pharmacokinetics of transnasal butorphanol in patients experiencing rhinitis. *Eur J Clin Pharmacol* 1993; **45**: 559–562.
- 3 Shyu WC, Morgenthien EA, Pittman KA, Barbhaiya RH. The effects of age and sex on the systemic availability and pharmacokinetics of transnasal butorphanol. *Eur J Clin Pharmacol* 1994; **47**: 57–60.
- 4 Hoffert MJ, Couch JR, Diamond S, *et al.* Transnasal butorphanol in the treatment of acute migraine. *Headache* 1995; **35**: 65–69.
- 5 Abboud TK, Zhu J, Longhitano M, *et al.* Efficacy and safety of butorphanol nasal spray for the relief of postepistomy pain. *Curr Ther Res* 1994; **55**: 500–509.
- 6 Gaver RC, Vasiljev M, Wong H *et al.* Disposition of parenteral butorphanol in man. *Drug Metab Dispos* 1980; **8**: 230–235.
- 7 Somogyi A, Muirhead M. Pharmacokinetic interactions of cimetidine. *Clin Pharmacokinet* 1987; **12**: 321–366.
- 8 Pittman KA, Smyth RD, Mayol RF. Serum levels of butorphanol by radioimmunoassay. *J Pharm Sci* 1980; **69**: 160–163.
- 9 Mulvana DE, Duncan GF, Shyu WC, *et al.* Quantitative determination of butorphanol and its metabolites by gas chromatograph-electron capture negative-mass spectrometry. *J Chromatogr* 1996; (in press).
- 10 Willey TA, Duncan GF, Tay LK, Pittman KA, Farmen RH. High-performance liquid chromatographic method for the quantitative determination of butorphanol, hydroxybutorphanol, and norbutorphanol in human urine

- using fluorescence detection. *J Chromatogr B* 1991; **652**: 171–178.
- 11 Kunitani MG, Johnson DA, Upton RA, Riegelman S. Convenient and sensitive high performance liquid chromatography assay for cimetidine in human plasma or urine. *J Chromatogr* 1981; **224**: 156–161.
- 12 Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd Edition, Marcel Dekker, Inc., New York, NY, pp: 409–417, 1982.
- 13 Riegelman S, Collier P. The application of statistical moment theory to the evaluation of *in vivo* dissolution time and absorption time. *J Pharmacokinet Biopharm* 1980; **8**: 509–534.
- 14 Snedecor GW, Cochran WG. *Statistical Methods*, 7th ed., The Iowa State University Press, Ames, IA, pp:253–254, 1980.
- 15 Wilkinson CF, Hetnarski K, Yellin TO. Imidazole derivatives—a new class of microsomal enzyme inhibitor. *Biochem Pharmacol* 1972; **21**: 3187–3192.

(Received 4 December 1995,
accepted 13 June 1996)