Pharmacokinetics of butorphanol nasal spray in patients with renal impairment

W. C. SHYU¹, E. A. MORGENTHIEN² & R. H. BARBHAIYA¹

¹Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Pharmaceutical Research Institute, Bristol-Myers Squibb Company, Lawrenceville, NJ, ²Department of Biostatistics and Data Management, Bristol-Myers Squibb Company, Syracuse, NY, USA

- 1 The pharmacokinetics of butorphanol were evaluated in 18 female volunteers with varying degrees of renal function following a single, 1 mg transnasal dose of butorphanol tartrate. The creatinine clearance (CL_{CR}) values for subjects in the normal (NOR), moderately impaired (MI), and severely impaired (SI) groups were $\geq 70 \text{ ml min}^{-1}$, $30\text{--}60 \text{ ml min}^{-1}$, and $\leq 30 \text{ ml min}^{-1}$, respectively.
- 2 Serial blood and urine samples were collected immediately after dosing for 48 h. Plasma concentrations of butorphanol were determined using a specific radioimmunoassay. Urine concentrations of butorphanol and its metabolites (hydroxy-butorphanol, norbutorphanol and their glucuronide conjugates) were determined using h.p.l.c. with fluorescence detection.
- 3 There was no significant difference between the three treatments for peak plasma concentration of butorphanol and time to peak. Statistically significant differences were detected among the study groups for AUC, $t_{1/2}$, MRT, and CL_R with the mean values for severely impaired subjects significantly different from those of normal renal subjects; mean values for moderately impaired subjects were not significantly different from either the normal or severely impaired groups for all respective parameters.
- 4 The elimination half-life of butorphanol increased from 5.75 h in NOR to 10.48 h in SI. A similar trend was observed for MRT. Creatinine clearance (CL_{CR}) significantly correlated with CL_R ($r=0.563$, $P=0.019$), CL_T/F ($r=0.505$, $P=0.033$), $t_{1/2}$ ($r=-0.554$, $P=0.017$) and λ ($r=0.606$, $P=0.008$).
- 5 Although the exposure of butorphanol was greater in subjects with renal impairment, there was no trend for an increase in the number of adverse experiences reported by subjects with renal dysfunction.
- 6 Patients with less than 30 ml min^{-1} creatinine clearance may require less frequent administration of transnasal butorphanol as compared with subjects with normal or moderately impaired renal function.

Keywords butorphanol transnasal renal impairment pharmacokinetics

Introduction

Butorphanol tartrate is a synthetic opioid agonist-antagonist analgesic which undergoes extensive first-pass metabolism when given orally, resulting in a bioavailability of only 5% (unpublished data). A transnasal formulation of butorphanol was developed to bypass hepatic first-pass elimination, to achieve rapid absorption, and to provide a convenient mode of administration

to patients with moderate to severe pain. The absolute bioavailability of transnasal butorphanol is 70% [1–3].

In normal subjects, transnasal butorphanol exhibits linear pharmacokinetics in the dose range of 1–4 mg [4]. The maximum plasma concentrations after administration of 2 mg transnasal butorphanol are approximately 2.7 ng ml^{-1} and occur around 0.25–0.75 h. The plasma elimination $t_{1/2}$ is about 4–6 h. The serum protein binding for butorphanol is about 80%.

Correspondence: Dr Wen Chyi Shyu, Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Pharmaceutical Research Institute, Bristol-Myers Squibb Company, PO Box 4000 Princeton, New Jersey 08543-4000, USA

Butorphanol is extensively metabolized by the liver and only small amounts (<10% of the dose) of the intact drug is recovered in the urine after parenteral administration [5]. However, the elimination and disposition of butorphanol and its metabolites (nor-butorphanol, hydroxy-butorphanol, and their glucuronide conjugates) may be altered in patients with renal impairment. *In vitro*, the opioid receptors binding affinity for the metabolites is less than 1/100th of that for butorphanol. Although parenteral butorphanol has been used in the clinic for over 17 years, there are no data on the effects of renal impairment on the pharmacokinetics of this drug. The present study was designed to evaluate the safety, tolerance, and pharmacokinetics of transnasal butorphanol in female subjects with varying degrees of renal impairment.

Methods

Subjects

Eighteen females with varying degrees of renal function were enrolled in the study after they reviewed and signed an informed consent form at Applied Clinical Research Center, under the direction of Dr D. Weidler (Miami, FL, USA). In order to evaluate rigorously the safety of butorphanol in this populations, females were recruited to the study since female subjects tend to tolerate butorphanol less well than males. Subjects did not have any acute or chronic diseases, allergies or viral rhinitis; they had normal nasal anatomy and mucosa. Subjects were placed into three groups according to the status of their renal function as judged by creatinine clearance (CL_{CR}) which was experimentally determined. The volunteers with normal renal function, moderately-impaired, and severely-impaired renal function had creatinine clearances of $\geq 70 \text{ ml min}^{-1}$, $30\text{--}60 \text{ ml min}^{-1}$, and $\leq 30 \text{ ml min}^{-1}$, respectively. The mean (s.d.) age, height, weight, and CL_{CR} values for the normal renal function group were 49 (7) years, 163 (4) cm, 67 (9) kg and $86 (19) \text{ ml min}^{-1}$, respectively. The corresponding values were 51 (15) years, 163 (6) cm, 78 (14) kg and $48 (10) \text{ ml min}^{-1}$, respectively, for the moderately-impaired patients and 52 (8) years, 163 (5) cm, 83 (22) kg and $13 (7) \text{ ml min}^{-1}$, respectively, for the severely-impaired patients. Subjects with renal impairment requiring therapy with either haemodialysis or peritoneal dialysis were excluded from the study. No statistical significant differences in the demographic data were detected among the three groups.

Physical examinations, medical history, and clinical laboratory analysis were conducted prior to and after completion of the study. Subjects had no evidence or history of: chronic infectious disease, cardiovascular disease, hepatic disease, pulmonary obstructive disease, bronchial asthma, hypertension, or glaucoma. Heavy smokers were excluded from the study. Subjects were screened for drugs of abuse and instructed to refrain from alcohol for 24 h and medications for 1 week prior to initiation of the study and for the duration of the

study. Subjects refrained from alcohol, smoking and beverage containing caffeine during the study period.

Study design

This was an open, parallel-group study designed to determine the effect of renal impairment on the pharmacokinetics of butorphanol following a single, 1-mg transnasal dose to subjects with normal, moderately-impaired, or severely-impaired renal function. Eighteen female subjects ($n=6$ per group) were assigned to one of the three groups based on their creatinine clearance. Each subject received a single, 1 mg transnasal dose of butorphanol tartrate using a metered-dose spray pump. Serial blood samples and total urine output were collected for 24 h for the normal renal function group and for 48 h for the renally-impaired groups following dosing for the determination of butorphanol plasma levels and butorphanol and its metabolites in urine for subsequent pharmacokinetic analysis.

Drug formulation and administration

The transnasal butorphanol formulation was prepared and packaged by Bristol-Myers Squibb Company, Evansville, IN, USA (product No. 12097-061-15). The butorphanol 10 mg ml^{-1} solution was packaged in an amber, screw-cap glass bottle. A Valois metered pump (Vp 3/100 mcl) and a Valois nasal adapter with a dust overlap (Valois of America, Greenwich, CT, USA) were used as the nasal spray device. A transnasal placebo (product No. 12097-M00-22) was supplied for subjects to practice the spray technique prior to dosing.

Each dose was administered in one spray stroke, delivering approximately 0.1 ml of the 10 mg ml^{-1} butorphanol tartrate solution into one nostril. Each subject was instructed in the use of the sprayer by the study personnel and practiced with the placebo prior to initiation of the study. The drug was self-administered with the head tilted slightly forward and the opposite nostril closed. The sprayer was pumped firmly and quickly while sniffing gently. The sprayer was then removed and the head tilted back. The exact dose administered was calculated from the weight of the sprayer immediately before and after dosing. The pump delivers $0.10 \pm 0.01 \text{ mg}$ of butorphanol tartrate in each spray. The subject remained in the ambulatory condition for at least 4 h after dosing.

Sample collection

Approximately 7 ml blood samples were collected from each subject immediately before (predose), and at 3, 6, 9, 15, 30, and 45 min, and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h after drug administration. Two additional blood samples were taken from the renally-impaired subjects at 36 and 48 h after dosing. The blood was collected into a vacutainer containing K_3EDTA as the anticoagulant. The plasma was separated and immedi-

ately frozen and stored at -20°C pending analysis for intact butorphanol.

Total urinary output was collected just before dosing (predose), and from 0 to 2, 2 to 4, 4 to 6, 6 to 12, 12 to 16, and 16 to 24 h after dosing. In addition, samples were collected from 24 to 36 and 36 to 48 h after drug administration from the renally-impaired subjects. The volume and pH of each collection were recorded and the urine specimens were refrigerated throughout the collection period. Exactly 50 ml of each urine sample were transferred to a storage bottle and stored at -20°C pending analysis for butorphanol and its metabolites.

Sample analysis

Plasma samples were analysed for intact butorphanol by a validated radioimmunoassay method [6]. Two metabolites of butorphanol, hydroxy-butorphanol and nor-butorphanol, do not cross-react with the specific butorphanol antibody used in this assay which was confirmed by a GC/MS assay [7]. Urine samples were analysed for intact butorphanol, hydroxy-butorphanol, nor-butorphanol, and their conjugates using a validated h.p.l.c. method using fluorescence detection [8]. Plasma quality control (QC) samples containing butorphanol were prepared prior to initiation of the study. Urine QC samples were prepared prior to initiation of the study containing three levels of butorphanol, hydroxy-butorphanol, and nor-butorphanol. All QC samples were shipped to the clinical site and returned with the study samples. The QC samples were assayed with each study sample group to verify accuracy, precision, and reproducibility of the assay and stability of the analytes during storage and shipment. Plasma standard curves were linear over the range of $0.013\text{--}1\text{ ng ml}^{-1}$ for butorphanol. Urine standard curves were linear from 1 to 100 ng ml^{-1} for butorphanol and hydroxy-butorphanol and from 2 to 200 ng ml^{-1} for nor-butorphanol. The percent of relative standard deviation (%RSD) for plasma QC samples (0.13, 0.20 and 0.60 ng ml^{-1}) was less than 16.4% for between-day and within-day analysis. The %RSD for urine QC samples (10, 85 and 1000 ng ml^{-1}) was less than 13% for between-day and within-day analysis. The deviation of mean predicted concentrations of all analytes from the corresponding nominal concentrations was less than 11%.

Pharmacokinetic analysis

The plasma concentration-time data for butorphanol were analysed by non-compartmental methods [9,10]. The highest observed plasma concentration and the corresponding sampling time (t) were reported as C_{max} and t_{max} , respectively. The elimination half-life ($t_{1/2}$) was calculated from the slope (λ) of the best fit terminal log-linear portion of the plasma concentration-time curve (C vs t). The slope was estimated for the C vs t profile by performing linear least-squares regression analysis of

the linear segment of the log C vs t data. The data were fitted to the function: $\ln C = \ln B - \lambda t$, starting with the last three nonzero data points, where B is the intercept. The procedure continued, adding preceding data points one at a time, until C_{max} was reached. The terminal log-linear portion was defined by the data set for which the mean square error term from the regression was minimized. The area under the C vs t curve (AUC) and the area under the first moment C vs t curve (AUMC) were calculated from t_0 to t_m using the linear trapezoidal rule, where t_m is the time at which C appeared to decline in a log-linear manner [10]. From t_m to t_n , the last non-zero data point, the log trapezoidal rule was used. AUC and AUMC were extrapolated to infinity and reported as AUC and AUMC, respectively.

The estimated mean residence time (MRT) in the body was estimated from $\text{MRT} = \text{AUMC}/\text{AUC}$. The total urinary recovery, %UR, was calculated as the cumulative amount of compound excreted within the collection period, and was expressed as a percentage of the administered dose. The percent of dose recovered as metabolites was calculated by correcting for the difference in molecular weight between butorphanol and each metabolite. Renal clearance (CL_R) of butorphanol was calculated as UR/AUC , where UR is the cumulative amount of butorphanol recovered in the urine.

Statistical analyses

The single-dose pharmacokinetic parameters for butorphanol (AUC, C_{max} , $t_{1/2}$, MRT, CL_R , and %UR) were compared between the three study groups using a one-way analysis of variance (ANOVA) model. The analyses were also performed for hydroxy-butorphanol, nor-butorphanol, total (free + glucuronide conjugate) butorphanol, total hydroxy-butorphanol, and total nor-butorphanol %UR data. If significant differences were detected among the study groups, pairwise comparisons were performed using the Tukey procedure [11]. Levene's test was used to check the assumption of homogeneity of variance [12]. t_{max} data was compared among the groups using the Kruskal-Wallis test [11]. If significant differences were detected, pairwise comparisons were performed with pairwise Wilcoxon rank sum tests [11]. C_{max} and AUC values were normalized to a 1 mg dose level prior to analysis. All statistical calculations were performed at a level of significance of $\alpha = 0.05$ with the exception of Levene's test ($\alpha = 0.001$) and the Wilcoxon tests ($\alpha = 0.017$, Bonferroni [12]). Linear regression analyses were performed for creatinine clearance (CL_{CR}) vs CL_T/F , CL_R , $t_{1/2}$, and λ (elimination rate constant).

Results

Butorphanol nasal spray was safe and well-tolerated by all normal and renally-impaired subjects. A total of 23 adverse events were reported by the subjects, of which 11 were reported from the normal renal function group,

six were reported from each of the renally impaired patients. Mild dizziness (26%), sleepiness (13%) and drowsiness (9%) were reported most often by subjects in the current study, as was found in other clinical studies with transnasal butorphanol [3]. There was no increase in the frequency, duration, or severity of side effects with increasing renal impairment. All subjects recovered untreated and completed the study.

The mean plasma butorphanol concentration *vs* time profiles for normal renal function, moderately-impaired and severely-impaired groups are shown in Figure 1. The mean (s.d.) butorphanol pharmacokinetic parameters are presented in Table 1 for normal renal function, moderately-impaired and severely-impaired groups. The %UR data for free and total (free + glucuronide-conjugated) butorphanol, hydroxy-butorphanol, and nor-butorphanol are shown in Table 2. There were

Figure 1 Mean butorphanol plasma concentrations following transnasal administration of 1 mg butorphanol to normal and renally-impaired subjects ● normal; ◆ moderately impaired; ■ severely impaired.

Table 1 Mean (s.d.) pharmacokinetic parameters for normal renal function, moderately-impaired and severely-impaired subjects following 1 mg transnasal butorphanol

Renal function	C_{max} (ng ml ⁻¹)	t_{max*} (h)	AUC (ng ml ⁻¹ h)	$t_{1/2}$ (h)	MRT (h)	CL_R (ml min ⁻¹)
Normal (1)	1.19 (0.72)	0.38 (0.25–1.00)	4.32 (1.63)	5.75 (1.42)	6.50 (1.02)	35.37 (20.82)
Moderately-impaired (2)	1.24 (0.43)	0.38 (0.25–1.00)	6.49 (1.32)	8.55 (3.38)	9.54 (3.45)	31.87 (13.99)
Severely-impaired (3)	1.17 (0.51)	0.50 (0.25–2.00)	7.41 (2.64)	10.48 (3.56)	12.21 (3.27)	9.0 (7.35)
Statistical comparison†	NS	<u>1 2 3</u>	<u>1 2 3</u>	<u>1 2 3</u>	<u>3 2 1</u>	<u>1 2 3</u>

*, Median (range) is reported. †Means not connected by a common underline are significantly different, $P \leq 0.05$, Tukey test. NS, Not significant.

statistically significant differences among the subject groups for AUC ($P=0.041$), $t_{1/2}$ ($P=0.043$), MRT ($P=0.011$), CL_R ($P=0.020$), and for butorphanol, total butorphanol, hydroxy-butorphanol, and total hydroxy-butorphanol %UR ($P \leq 0.044$). Based on Tukey's procedure, the mean values of dose-normalized AUC, $t_{1/2}$, MRT, and CL_R for subjects with severe renal impairment were significantly different from those of the normal subjects. The 95% confidence interval on differences in mean values for the corresponding parameters are (167, 6007), (0.3, 9.2), (1.5, 9.9) and (–49, –3), respectively. The corresponding mean values for the moderately-impaired did not significantly differ from those of either the normal renal function or severely-impaired subjects. Moderately-impaired subjects had significantly greater mean %UR values than those of severely-impaired subjects for butorphanol, total butorphanol, hydroxy-butorphanol, and total hydroxy-butorphanol. The mean %UR values for normal renal function subjects were also greater than those for severely-impaired subjects for total butorphanol, hydroxy-butorphanol, and total hydroxy-butorphanol. There were no significant differences among the groups for dose-normalized C_{max} , t_{max} , or %UR for nor-butorphanol or total nor-butorphanol.

Creatinine clearance (CL_{CR}) significantly correlated with CL_R ($r=0.563$, $P=0.019$), CL_T/F ($r=0.505$, $P=0.033$), $t_{1/2}$ ($r=-0.554$, $P=0.017$) and λ ($r=0.606$, $P=0.008$).

Discussion

The pharmacokinetic parameters for normal renal function subjects in the present study were similar to those previously reported for young females [3]. The absorption rate of transnasal butorphanol was not affected by renal function, based on the comparison of C_{max} and t_{max} values among normal renal function, moderately-impaired and severely-impaired subjects. With decreasing renal function, there was a slight increase in butorphanol plasma concentrations, $t_{1/2}$ and MRT and a slight decrease in CL_R . The increase of AUC in the renally impaired patients was probably associated with decrease of non-renal clearance.

Table 2 Mean (s.d.) % urinary excretion of butorphanol and its metabolites following 1 mg transnasal butorphanol to normal and renally-impaired subjects

Analyte	%UR*			Statistical comparison†
	NOR	MI	SI	
Butorphanol	0.8 (0.5)	1.1 (0.6)	0.4 (0.3)	MI NOR SI ⁺
Total# butorphanol	1.7 (0.6)	1.9 (0.4)	0.8 (0.6)	MI NOR SI ⁺
HO-butorphanol	6.1 (1.6)	6.3 (2.7)	2.0 (1.0)	MI NOR SI ⁺
Total# HO-butorphanol	7.3 (1.7)	9.9 (3.3)	2.9 (1.8)	MI NOR SI ⁺
Nor-butorphanol	1.1 (0.6)	1.4 (1.2)	0.6 (0.5)	—
Total# Nor-butorphanol	3.2 (2.6)	5.5 (3.5)	5.0 (4.7)	—

*, % Urinary excretion up to 24 h for normal renal function subjects and to 48 h for renally-impaired subjects. †, Means not connected by a common underline are significantly different, $P \leq 0.05$, Tukey test.

⁺, NOR = Normal renal function, MI=moderately-impaired, and SI=severely-impaired. #, Total = Free and conjugated.

The results of this study are similar to a number of other drugs and analgesics which are subject to first-pass metabolism in humans. The pharmacokinetics of these types of compounds are not greatly affected by impairment of kidney function. For example, the plasma $t_{1/2}$ of meperidine for subjects with end-stage renal disease is the same as that for subjects with normal renal function [13] and no dose adjustment is recommended for subjects with renal impairment when naloxone [14], or pentazocine [14] is administered. On the other hand, for subjects with glomerular filtration rate less than 10 ml min^{-1} , it is recommended that the dose of propoxyphene [15] be reduced by 50% of the recommended dose for subjects with normal renal function. Similarly, it is recommended that the dosing interval of methadone [14] be increased from 6 to 8 h to 8 to 12 h in patients with glomerular filtration rate less than 10 ml min^{-1} . For morphine [16] and codeine [14], the pharmacokinetics of the parent compounds were not significantly altered in renal impairment patients, however, prolong respiratory depression was observed in this population which might be attributed to the accumulation of the morphine-6-glucuronide conjugate.

Due to lack of complete metabolic elucidation of butorphanol, only butorphanol, hydroxy-butorphanol, nor-butorphanol, and their glucuronide conjugates were identified in the urine which accounted for less than 15% of the administered dose. The extent of glucuronide conjugation was minimal for butorphanol and its two oxidative metabolites, hydroxy-butorphanol and nor-butorphanol. The %UR of butorphanol and its metabolites was lower in subjects with severely impaired renal function than in subjects with normal or moderately impaired renal function. However, the metabolite/parent ratios remained relatively the same for all five metabolites regardless of renal function. Dose-adjusted AUC values increased with decreasing renal function. While statistically significant correlations of CL_{CR} with CL_{R} , CL_{T}/F , $t_{1/2}$, and λ were found in this study, all correlation coefficients were less than 0.61. Therefore, prediction of the pharmacokinetic parameters of butorphanol nasal spray can be only approximated based on the creatinine clearance of the patients. Based on the

prolonged $t_{1/2}$ and increased exposure to patients with severe renal impairment ($\text{CL}_{\text{CR}} < 30 \text{ ml min}^{-1}$), it is recommended that transnasal butorphanol be administered less frequently to severely impaired patients than to those with normal renal function ($\text{CL}_{\text{CR}} > 70 \text{ ml min}^{-1}$).

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