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Gender Differences in Pharmacokinetics of Maintenance Dosed Buprenorphine*

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Abstract

Aims—Gender differences are known to occur in the pharmacokinetics of many drugs. Mechanisms may include differences in body composition, body weight, cardiac output, hormonal status, and use of different co-medications. Recently subtle gender-dependent differences in cytochrome P450 (CYP) 3A-dependent metabolism have been demonstrated. Buprenorphine N-dealkylation to norbuprenorphine is primarily performed by CYP3A. We therefore asked whether gender-dependent differences occur in the pharmacokinetics of buprenorphine.

Methods—A retrospective examination was made of control (buprenorphine/naloxone-only) sessions from a number of drug interaction studies between buprenorphine and antiretroviral drugs. Twenty males and eleven females were identified who had a negative cocaine urine test prior to participation in the control session and were all on the same maintenance dose (16/4 mg) of sublingual buprenorphine/naloxone. Pharmacokinetic data from their control sessions (buprenorphine/naloxone only) were sorted by gender and compared using the two-sample t-test.

Results—Females had significantly higher area under the plasma concentration curve (AUC) and maximum plasma concentrations for buprenorphine, norbuprenorphine and norbuprenorphine-3-glucuronide. AUCs relative to dose per body weight and surface area were significantly higher for only norbuprenorphine. AUCs relative to lean body mass were, however, not significantly different.

Conclusions—Gender-related differences exist in the pharmacokinetics of buprenorphine; differences in body composition appear to have a major impact; differences in CYP3A-dependent metabolism may also contribute.

Keywords

buprenorphine; buprenorphine pharmacokinetics; buprenorphine metabolism; gender differences; norbuprenorphine; buprenorphine-3-glucuronide; norbuprenorphine-3-glucuronide

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1. Introduction

Gender differences exist in the pharmacokinetics and pharmacodynamics of some drugs (Franconi et al., 2007; Gandhi et al., 2004; Soldin and Mattison, 2009). Evaluation of these gender differences is of national and international concern (United States Food and Drug Administration, 1993; World Health Organization, 2002). In humans, unlike the rat (Waxman and Holloway, 2009), no gender specific drug metabolizing enzymes have been identified; other differences including body weight and composition have been cited as causes. Recent clinical and in vitro evidence points to subtly higher expression of cytochrome P450 (CYP) 3A4 in females (Hu and Zhao, 2010; Lamba et al., 2010; Parkinson et al., 2004; Yang et al., 2010).

Buprenorphine is a mu-receptor partial agonist (Cowan et al., 1977) used in substitution therapy to treat opioid dependence (Johnson et al., 2000; Ling et al., 1998; McCance-Katz, 2004) and as an analgesic. Buprenorphine is metabolized by N-dealkylation to norbuprenorphine, and glucuronidation of both (Cone et al., 1984). CYP3A4 was first shown to be responsible for the N-dealkylation (Iribarne et al., 1997; Kobayashi et al., 1998), with a minor role for CYP2C8 subsequently established (Moody et al., 2002; Picard et al., 2005). UDP-glucuronosyltransferases (UGT) 1A1, 1A3 and 2B7 glucuronidate buprenorphine; UGT1A1 and 1A3 glucuronidate norbuprenorphine (Chang and Moody, 2009; Rouguieg et al., 2010). CYP3A4- and 2C8-mediated hydroxylation of the alkoxy side chain and ring structure also occurs (Chang et al., 2006; Picard et al., 2005). While the relative concentration of these metabolites is responsive to CYP inducers and inhibitors (Moody et al., 2009a), the contribution of these pathways to buprenorphine clearance is considered minimal.

Due to the co-morbidity of injection drug use and HIV infection, we have recently performed a series of drug interactions studies between buprenorphine and antiretroviral medications (Baker et al., 2010; McCance-Katz et al., 2006a; McCance-Katz et al., 2007; McCance-Katz et al., 2010a; McCance-Katz et al., 2006b). In the course of these studies a large number of control (buprenorphine/naloxone-only) pharmacokinetic sessions were performed. An initial retrospective review of these data showed that subjects with positive cocaine urine tests prior to the session had significantly different pharmacokinetics from those with negative tests (McCance-Katz et al., 2010b). We have now examined the data from those, and additional subjects, with cocaine negative tests to see if a gender difference existed in the pharmacokinetics of buprenorphine.

2. Methods

2.1. Procedures

Buprenorphine pharmacokinetic data were retrospectively analyzed from a larger data-set in which opioid-dependent, buprenorphine/naloxone-maintained individuals participated in previously described studies examining drug interactions of buprenorphine with antiretroviral medications (Baker et al., 2010; McCance-Katz et al., 2006a; McCance-Katz et al., 2007; McCance-Katz et al., 2010a; McCance-Katz et al., 2006b). Briefly, opioid-dependent individuals, stable for at least 2 weeks on daily sublingual buprenorphine/naloxone participated in a 24-hour blood sampling study to determine baseline buprenorphine pharmacokinetics, followed by up to 15-day treatment with an antiretroviral medication and a second 24-hour blood sampling study. The data used in this current analysis were from baseline (control) studies done prior to administration of the antiretroviral medication, and were limited to subjects that had a negative cocaine urine test result just prior to the study, and had received buprenorphine/naloxone 16/4 mg. Blood was collected in heparinized tubes, and plasma was prepared and stored frozen until shipment for

analysis. Protocols were approved by appropriate Institutional Review Boards. All subjects signed consent forms prior to enrollment and were compensated for their participation in the study.

2.2 Buprenorphine and metabolite determinations

Buprenorphine and metabolite concentrations were determined using solid-phase extraction and liquid chromatography-tandem mass spectrometry as previously described (Huang et al., 2006).

2.3 Pharmacokinetic analyses

The original analytical results were reevaluated so that blood collection time-points uniform to all studies (i.e., 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours) were used. Values below the lower limit of quantitation, 0.1 ng/mL, were treated as zero. Non-compartmental analyses were used. The maximal plasma concentration (C_{max}), pre-dose concentration (C_0), 24-hour post-dose concentration (C_{24}) and the time to C_{max} (T_{max}) were determined by observation of the data. The area under the plasma concentration versus time curve (AUC) was determined by the trapezoidal rule using an Excel:mac 2001 spreadsheet (Microsoft®, Redmond, WA), where t is time of blood draw and C is plasma concentration:

$$AUC = \sum (t_{n+1} - t_n)(C_n + C_{n+1})(0.5)$$

Buprenorphine clearance adjusted for bioavailability (Cl/F) was determined as dose/AUC. Lean body mass (LBM) (Hallynck et al., 1981) and body surface area (BSA) (Mosteller, 1987) were calculated as described with weight in kilograms and height in centimeters:

$$\begin{aligned} \text{LBM males} &= (1.10 \times \text{weight}) - 128 (\text{weight}^2 / \text{height}^2) \\ \text{LBM females} &= (1.07 \times \text{weight}) - 148 (\text{weight}^2 / \text{height}^2) \\ \text{BSA} &= [(\text{weight} \times \text{height}) / 3600]^{1/2} \end{aligned}$$

2.4 Statistical analyses

All male versus female data, except T_{max} , were compared using the Excel data analysis tools two-tailed t-test, assuming equal variances. Male and female T_{max} were compared using the non-parametric Mann-Whitney test with GraphPad Instat for Macintosh (version 3.0b, GraphPad Software, San Diego, CA). For all comparisons $p < 0.05$ (two-tailed) was considered significant.

3.0 Results

3.1 Demographics

Tabulation of subject demographics appears in the Supplementary Materials. Twenty males and eleven females participated in an initial buprenorphine only session that was associated with a negative urine test for cocaine; all were on a sublingual dose of buprenorphine/naloxone 16/4 mg daily. For males versus females (means $\pm$ SD), neither age (35.7 ± 9.2 vs. 41.5 ± 10.3 years), nor total body weight (84.6 ± 22.3 vs. 73.6 ± 17.9 kg) differed significantly; LBM (62.1 ± 8.1 vs. 46.8 ± 5.9 kg, $p = 5.43 \times 10^{-6}$), BSA (2.03 ± 0.27 vs. 1.81 ± 0.24 m², $p < 0.05$), and height (1.78 ± 0.08 vs. 1.62 ± 0.06 m, $p = 3.89 \times 10^{-6}$) did. The males were 13, 6 and 1 African Americans, Caucasians and other ethnic background, respectively; the females were 5, 4 and 2. Eleven males and ten females participated in multiple control sessions (up to 10) after an adequate washout period.

3.2 Evaluation of average versus initial pharmacokinetics

The participation of a number of subjects in multiple control sessions raised the following question. Should comparisons be made using the initial controls session data, or include an average of the multiple control sessions? Our evaluation of this is further described in the Supplementary Materials. Because all subjects had an initial control session and not all had multiple sessions to average, the results presented in Table 1 and Figure 1 are from the initial control sessions. Table 1 also presents statistical comparison results (p value) from inclusion of averages.

3.3 Comparison of male and female pharmacokinetics

Figure 1 shows the mean 24-hour inter-dose time-course of buprenorphine (Fig. 1A), norbuprenorphine (Fig. 1B), buprenorphine-3-glucuronide (Fig. 1C) and norbuprenorphine-3-glucuronide (Fig. 1D) in males and females. Pharmacokinetic parameter comparisons are shown in Table 1. Females were exposed to higher plasma concentrations of buprenorphine with significantly higher AUC, C_{max} , C_0 and C_{24} ; Cl/F was reduced (Table 1). Females were exposed to higher concentrations of norbuprenorphine (Fig. 1B) and norbuprenorphine-3-glucuronide (Fig. 1D); the increases were associated with significantly higher AUC and C_{max} . No differences were seen with buprenorphine-3-glucuronide (Fig. 1C). Individual AUC results were divided by dose per kg body weight, per BSA and per LBM (Table 1). When adjusting for weight and BSA, only the differences between female and male norbuprenorphine AUC remained significant (Table 1). When adjusting for LBM, there were no longer significant differences in AUCs (Table 1). Both the combined male and female AUC of norbuprenorphine and norbuprenorphine-3-glucuronide had significant (negative slope) correlations (r^2) with body weight (0.211, 0.202), LBM (0.351, 0.267) and BSA (0.275, 0.237).

4.0 Discussion

Gender differences in drug pharmacodynamics and pharmacokinetics are of concern (Franconi et al., 2007; Gandhi et al., 2004; Soldin and Mattison, 2009), with special attention recently drawn to potential gender differences for buprenorphine (Unger et al., 2010). This retrospective study demonstrates that females exposed to the same doses of buprenorphine as males have higher concentrations of circulating parent drug and the metabolites norbuprenorphine and norbuprenorphine-3-glucuronide. To the best of our knowledge this is the first demonstration of a gender difference in buprenorphine pharmacokinetics. The significance of this difference depends in part on the impact of the higher exposure per dose in females and the lesser exposure per dose in males on the adverse and beneficial effects of buprenorphine.

Buprenorphine is a relatively safe opioid in part due to the ceiling effect of this partial mu agonist (Walsh et al., 1994). Fatalities associated with buprenorphine use occur, but have been associated with high intravenous doses and/or co-administration of benzodiazepines (Kintz, 2001; Pirnay et al., 2004). As these fatalities have involved a much higher number of males than females (Kintz, 2001; Pirnay et al., 2004), the lower exposure we see per dose in males strongly suggests gender-related differences in buprenorphine pharmacokinetics play little or no role in these fatalities. The primary use of buprenorphine is in the treatment of opioid dependence; only a single study has indicated that buprenorphine is more effective at preventing illicit opioid use in treated females (Schottenfeld et al., 1998). Therefore, the gender difference in exposure to circulating buprenorphine does not appear to be related to detrimental treatments effects at therapeutic doses in either gender.

This retrospective study was not designed to address mechanisms of gender differences in the buprenorphine pharmacokinetics. We did assess the impact of adjusting the AUC for dose per different measures of body composition. The loss of significant differences when adjusting with LBM is suggestive that differences in body composition (i.e., higher body fat in females) plays a significant factor in the observed gender difference. As addressed in more detail in the Supplemental Materials, it was not possible to reliably follow up this finding by testing for gender differences in volume of distribution. Buprenorphine undergoes enterohepatic recirculation (Cone et al., 1984). This is not readily apparent in Fig. 1 since the graphs are the means of subjects, and the latter hours of the buprenorphine dosing interval are sparsely sampled. We previously presented representative figures showing the fluctuations of buprenorphine concentrations at times where terminal half-lives would be calculated (Bruce et al., 2006), and now present more detailed findings in the Supplementary Materials. The involvement of body composition cannot be just a change in volume of distribution, as the highly lipophilic buprenorphine would be expected to have a lower plasma concentration in the population with higher volumes of distribution.

The loss of significant changes in the AUC per dose per body weight or BSA for buprenorphine and norbuprenorphine-3-glucuronide, with retention of the significant difference in norbuprenorphine, allows speculation that CYP3A4 metabolism of buprenorphine is a contributing factor to the gender difference (Franconi et al., 2007; Gandhi et al., 2004; Soldin and Mattison, 2009). We did not perform concurrent CYP3A4 phenotyping studies and cannot directly prove that the activity of CYP3A4 was higher in the females who participated in these studies, as suggested from clinical and in vitro studies that have shown subtle but significantly higher CYP3A4 activity in females (Hu and Zhao, 2010; Lamba et al., 2010; Parkinson et al., 2004; Yang et al., 2010). Alternatively, as buprenorphine has a high extraction ratio (Iribarne et al., 1997; Kobayashi et al., 1998), its hepatic clearance would be blood flow limited. As total blood flow to the liver is higher in males (Williams and Leggett, 1989), this may contribute to the gender difference. The fact that a corresponding increase in norbuprenorphine was not seen with the decreased buprenorphine in males, may be related to our proposal that buprenorphine N-dealkylation occurs primarily in the small intestine (Moody et al., 2009b).

With equivalent doses of buprenorphine females are exposed to higher concentrations of buprenorphine and its metabolites norbuprenorphine and norbuprenorphine-3-glucuronide. Current evidence suggests this is not a critical concern for normal therapy, but it might need to be taken into consideration when low or high doses of buprenorphine are used. Gender differences in body composition, hepatic blood flow and CYP3A may all play a role.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Time course of plasma concentrations of A) buprenorphine (Bup), B) norbuprenorphine (Nor), C) buprenorphine-3-glucuronide (B3G) and D) norbuprenorphine-3-glucuronide (N3G) for male (○) and female (■) subjects who were on maintenance dosing with 16/4 mg buprenorphine/naloxone, and had negative cocaine urine tests just prior to the pharmacokinetic session. Values are the mean $\pm$ SEM for 20 males and 11 females. Values were from the initial pharmacokinetic session for subjects who participated in more than one study.

Table 1

Comparison of male and female pharmacokinetics for buprenorphine and metabolites.

Analyte/Parameter	Male	Female	p	With Averages p
Buprenorphine				
AUC (ng*h/mL)	41.9 ± 14.5	58.4 ± 24.8	< 0.05	< 0.01
C _{max} (ng/mL)	5.15 ± 1.94	6.97 ± 2.98	< 0.05	< 0.05
C ₀ (ng/mL)	0.83 ± 0.32	1.53 ± 0.86	< 0.005	< 0.001
C ₂₄ (ng/mL)	0.96 ± 0.43	1.49 ± 0.84	< 0.05	< 0.005
T _{max} (h)	1.20 ± 0.50	1.00 ± 0.45	NS	NS
Cl/F (L/min)	7.72 ± 4.72	5.18 ± 1.72	NS(0.097)	< 0.05
AUC/(dose/body weight)	220 ± 92	266 ± 125	NS	NS
AUC/(dose/BSA)	5.29 ± 1.89	6.58 ± 2.89	NS	NS
AUC/(dose/LBM)	162 ± 58	171 ± 76	NS	NS
Norbuprenorphine				
AUC (ng*h/mL)	57.5 ± 30.1	95.1 ± 43.7	< 0.01	< 0.05
C _{max} (ng/mL)	3.87 ± 1.85	5.89 ± 2.49	< 0.05	< 0.01
C ₀ (ng/mL)	2.10 ± 1.61	3.20 ± 1.51	NS(0.074)	< 0.05
C ₂₄ (ng/mL)	1.93 ± 1.20	3.29 ± 1.47	< 0.01	< 0.05
T _{max} (h)	3.38 ± 5.20	1.73 ± 0.79	NS	NS
AUC/(dose/body weight)	284 ± 114	425 ± 188	< 0.05	< 0.05
AUC/(dose/BSA)	7.03 ± 3.15	10.6 ± 4.6	< 0.05	< 0.05
AUC/(dose/LBM)	215 ± 96	275 ± 121	NS	NS
Buprenorphine-3-Glucuronide				
AUC (ng*h/mL)	44.7 ± 38.7	53.7 ± 75.4	NS	NS
C _{max} (ng/mL)	6.71 ± 4.22	10.3 ± 9.0	NS	NS
C ₀ (ng/mL)	1.02 ± 1.27	0.96 ± 1.06	NS	NS
C ₂₄ (ng/mL)	1.11 ± 1.26	1.34 ± 1.87	NS	NS
T _{max} (h)	1.62 ± 2.49	1.14 ± 0.45	NS	NS
AUC/(dose/body weight)	227 ± 205	275 ± 413	NS	NS
AUC/(dose/BSA)	5.54 ± 4.85	6.46 ± 9.48	NS	NS
AUC/(dose/LBM)	170 ± 151	168 ± 249	NS	NS
Norbuprenorphine-3-Glucuronide				
AUC (ng*h/mL)	278 ± 179	426 ± 198	< 0.05	NS(0.079)
C _{max} (ng/mL)	19.6 ± 10.5	29.8 ± 13.5	< 0.05	NS(0.10)
C ₀ (ng/mL)	8.96 ± 8.73	12.7 ± 8.0	NS	NS
C ₂₄ (ng/mL)	9.57 ± 8.62	14.6 ± 8.5	NS	NS
T _{max} (h)	2.15 ± 1.34	2.27 ± 1.17	NS	NS
AUC/(dose/body weight)	1360 ± 680	1910 ± 960	NS	NS
AUC/(dose/BSA)	33.8 ± 18.9	47.6 ± 22.7	NS	NS
AUC/(dose/LBM)	1030 ± 570	1240 ± 610	NS	NS

Values are the mean $\pm$ SD for 20 males and 11 females who were on maintenance dosing with 16/4 mg buprenorphine/naloxone, and had negative cocaine urine tests just prior to the pharmacokinetic session. Values are from the initial control pharmacokinetic session for subjects who participated in more than one study. Comparisons were also made when the average plasma concentrations were first determined for those subjects with multiple control sessions; significance for these comparisons is shown in the right column (with averages). NS – not significant, $p \geq 0.05$.