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Pharmacokinetics of 6-Hydroxybuspirone and its Enantiomers Administered Individually or Following Buspirone Administration in Humans

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ABSTRACT: The objective of this study was to assess the pharmacokinetics of 6-hydroxybuspirone (6OHB) when given orally via three forms: racemate (BMS-528215), S-enantiomer (BMS-442606) and R-enantiomer (BMS-442608), versus following the administration of buspirone. A double-blind, randomized, four-period, four-treatment, crossover study balanced for residual effects in healthy subjects was conducted ($n = 20$). Subjects received single 10 mg doses of each compound in a randomized fashion with pharmacokinetics determined over a 24 h period. There was a 4-day washout between each dosing period. All three forms of 6OHB (racemate, S-enantiomer and R-enantiomer) were well tolerated. There was interconversion between enantiomers. The dominant enantiomer was the S-enantiomer no matter which form of 6OHB was administered. All three forms of 6OHB produced approximately 2- to 3-fold greater exposure to total 6OHB than did buspirone. All three forms produced equal exposure to 1-(2-pyrimidinyl)-piperazine (1-PP) which was approximately 30% less than the 1-PP exposure derived from buspirone administration. All three forms of 6OHB produced approximately 3-fold higher 6OHB:1-PP ratios and approximately 2.5-fold higher total 6OHB exposures than did buspirone administration. All compounds were well tolerated. There seemed to be no advantage of one of the enantiomers of 6OHB over the racemate. Therefore, the racemate was chosen for further clinical development. Copyright © 2007 John Wiley & Sons, Ltd.

Key words: buspirone; 6-hydroxybuspirone; enantiomers; 1-PP; anxiety; pharmacokinetics

Introduction

Buspirone is a potent partial agonist of 5-HT_{1A} receptors and is indicated for the treatment of generalized anxiety disorder (GAD) [1,2]. Buspirone may potentially be beneficial as monotherapy in depression [3,4], but its main use has been as augmentation therapy [5,6] or to decrease sexual dysfunction symptoms from other antidepressants [7,8]. Buspirone has shown positive results in other indications as well [9–12]. After administration, buspirone is completely absorbed [13,14], but undergoes extensive first-pass metabolism, resulting in many metabolites [14,15] and has an oral bioavailability of $<5\%$ [13]. One of the major metabolites identified initially was 1-(2-pyrimidinyl)-piperazine (1-PP) [16]. More recently, further *in vitro* human liver microsomal metabolism studies have identified a metabolite formed by N-oxidation on the piperazine ring and 3-hydroxylated metabolites [17]. One of these hydroxylated metabolites, 6-hydroxy-

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buspirone (6OHB, BMS-528215, 6-hydroxy-8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione), was found to have partial agonist activity at the 5-HT_{1A} receptors [18], and has been identified as a major circulating metabolite of buspirone in human plasma [19].

There has always been much controversy around 1-PP and whether it may diminish the anxiolytic efficacy of buspirone [20–24], but there is also evidence that 1-PP may be anxiolytic itself [25–30]. The goal of the present investigation was to see if any of these forms of 6OHB following oral administration would minimize the exposure to 1-PP and maximize the exposure to 6OHB compared with buspirone administration. Accordingly, the study reported here assessed the pharmacokinetics of 6OHB and 1-PP from three forms of 6OHB: the racemate, S-enantiomer and R-enantiomer, as well as following the administration of buspirone (see Figure 1).

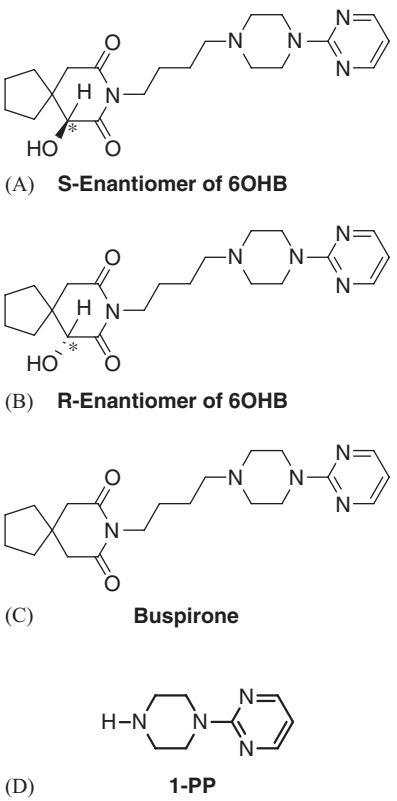

Figure 1. Structures of (A) S-enantiomer (BMS-442606), and (B) R-enantiomer (BMS-442608) forms of racemic 6-hydroxy-buspirone (BMS-528215), (C) buspirone, and (D) 1-(2-pyrimidinyl)-piperazine (1-PP). The asterisk marks the chiral carbon

Materials and Methods

Study design

This study was a double-blind, randomized, four-period, four-treatment, crossover study balanced for residual effects in healthy subjects. The study was conducted at Bristol-Myers Squibb Clinical Research Center, Hamilton, NJ, and was approved by the New England Institutional Review Board prior to subjects signing informed consent.

Normal healthy subjects between the ages of 18–45 years with a body mass index of 18–30 kg/m^2, inclusive, were eligible to participate in the study. The following tests and procedures were done at baseline and at regular intervals during the trial: physical examination, vital signs, clinical laboratory and electrocardiogram (ECG). Subjects were monitored for adverse events throughout the study.

The subjects were administered 10 mg single oral solution doses of buspirone or 6-hydroxy-buspirone (6OHB) as either the racemate (BMS-528215), the S-enantiomer (BMS-442606) or the R-enantiomer (BMS-442608). Doses between 6OHB and buspirone were not adjusted for molecular weight differences since there was only a 4% difference in their molecular weights. Subjects entered the clinic the day before dosing and were kept in the clinic until 24 h after dosing in each dosing period. There was at least a 4-day washout between dosing periods. Pharmacokinetic sample collection was accomplished by collecting venous blood at each of the following time points relative to dosing on day 1 of each dosing period: 0 (prior to dosing), 0.25, 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 10, 12 and 24 h.

Analyte extraction method

After the addition of 100 µl of internal standards ([^{13}C,^{15}N,D_4]buspirone and [^{13}C,^{15}N,D_4]1–PP: 10 ng/ml in methanol/water (30/70 v/v) for buspirone and 1-PP analysis, or MJ-013805: 10 ng/ml in methanol/water (30/70 v/v) for

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R- and S-enantiomers of 6OHB analysis) and 1 ml of phosphate-buffered saline solution to 500 µl of plasma, the samples were loaded onto a preconditioned C18 (EC) solid phase extraction column (International Sorbent Technology LTD, Mid Glamorgan, UK). The loaded samples were first washed with 2 ml of water and then with 1 ml of methanol/water (50/50 v/v). The compounds were eluted with 2 ml of a 3% ammonium hydroxide in acetonitrile solution, and the eluate evaporated to dryness. The residue was reconstituted in 100 µl of 100 mM ammonium acetate/ethanol solution and 10 µl was injected into the LC/MS/MS system (mobile phase delivery pump: Shimadzu, LC-10AD, Shimadzu Corporation, Columbia, MD; Injector: Perkin-Elmer Series 200 autosampler, The Perkin-Elmer Corporation, Norwalk, CT; Mass spectrometer: Quattro LC, Micromass, Inc., Beverly, MA).

Chromatographic conditions

In the 6OHB R- and S-enantiomer assay, chromatographic separation was achieved isocratically on a Chiral AGP analytical column (ChromTech, Sweden: 2.0 × 100 mm, 5 µm). The mobile phase contained 50 mM ammonium acetate in water, and isopropanol (98.5/1.5 v/v). Detection was by positive ion electrospray tandem mass spectrometry (Quattro LC, Micromass, Inc., Beverly, MA). The electrospray positive ion Q1 spectrum of S-enantiomer and R-enantiomer was dominated by the $[M + H]^+$ ion: *m/z* 402 for the S- and R-enantiomers and *m/z* 360 for MJ-013805. For selected reaction monitoring (SRM), the transitions monitored were *m/z* 402 to *m/z* 122 for the S- and R-enantiomers and *m/z* 360 to *m/z* 122 for MJ-013805. The standard curves, which ranged from 0.0500 to 10.0 ng/ml for both enantiomers, were fitted to a $1/\times$ weighted quadratic regression model. The intra-assay precision was within 7.9% CV and the inter-assay precision was within 6.5% CV for both analytes. The assay accuracy was within $\pm$ 9.3% of the nominal values.

In the buspirone/1-PP assay, chromatographic separation was achieved isocratically on a Betasil C18 analytical column (Keystone Scientific, State College, PA: 2.0 × 100 mm, 5 µm). The mobile phase contained 5 mM ammonium acetate in water with 0.1% formic acid, and 5 mM ammonium acetate in methanol/water (90/10 v/v) with 0.1% formic acid (45/55 v/v). Detection was by positive ion electrospray tandem mass spectrometry (Quattro LC, Micromass, Inc., Beverly, MA). The electrospray positive ion Q1 spectrum of the analytes was dominated by the $[M + H]^+$ ion: *m/z* 386 for buspirone, *m/z* 165 for 1-PP, *m/z* 393 for [^{13}C,$^{15}N_2$,D_4]buspirone (IS for buspirone), and *m/z* 172 for [^{13}C,$^{15}N_2$,D_4]1-PP (IS for 1-PP). For SRM, the transitions monitored were *m/z* 386 to *m/z* 122 for buspirone, *m/z* 165 to *m/z* 122 for 1-PP, *m/z* 393 to *m/z* 127 for [^{13}C,$^{15}N_2$,D_4]buspirone, and *m/z* 172 to *m/z* 127 for [^{13}C,$^{15}N_2$,D_4] 1-PP. The standard curves, which ranged from 0.0200 to 10.0 ng/ml for buspirone and from 0.100 to 10.0 ng/ml for 1-PP, were fitted to a $1/\times$ weighted quadratic regression model. The intra-assay precision was within 6.2% CV and the inter-assay precision was within 3.1% CV for both analytes. The assay accuracy was within $\pm$ 5.7% of the nominal values.

Pharmacokinetic analysis

In order to determine the pharmacokinetics of racemic 6OHB, the concentrations of the S-enantiomer (BMS-442606) and R-enantiomer (BMS-442608) at each time point were summed to yield total 6OHB concentration. Pharmacokinetic parameters for 6OHB, 1-PP and the two enantiomers of 6OHB were determined using noncompartmental methods [31,32] using a validated in-house SAS program [33]: peak plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration-time curve from dosing to infinity (AUC_{0-INF}), half-life ($T_{1/2}$), mean residence time (*MRT*), 6OHB:1-PP *AUC* ratio, and S:R enantiomer *AUC* ratio. Geometric means and coefficients of variation for C_{max}, AUC_{0-INF}, 6OHB:1-PP *AUC* ratio, and S:R *AUC* enantiomer ratio were determined. Medians and ranges were calculated for T_{max}. Means and standard deviations were determined for *MRT* and $T_{1/2}$.

Results and Discussion

The study enrolled 20 men and all completed the study. The average age was 32 years (range:

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21–41), with ethnicity being 6 white, 12 black and 2 Hispanic/Latino. The mean weight was 77.6 kg (range: 59.4–103.8), mean height was 175.9 cm (range: 164–191 cm) and the mean body mass index was 25.0 kg/m^2 (range 19.8–30.0).

Although not designed robustly to assess safety, there were no untoward effects seen in ECG or clinical laboratory monitoring, and each compound was generally well tolerated with no compound-related trends in adverse events noted. There were no adverse events different from those already known for buspirone [1].

Tables 1–3 provide the pharmacokinetic parameters for buspirone and 1-PP, the 6OHB R- and S-enantiomers, and total 6OHB, respectively, following administration of the three forms of 6OHB and buspirone. The pharmacokinetic profiles for each of these analytes following the dosing of each treatment are shown in Figure 2. Figure 3 allows one to contrast the concentrations of the same analyte following the dosing of each treatment. Since both enantiomers were observed following the dosing of all forms of 6OHB, interconversion of enantiomers occurred. Because more S-enantiomer was observed following all forms of 6OHB administered, there seemed to be more conversion of R- to S-enantiomer than vice versa.

Following buspirone administration, the rank order of mean exposure [both C_{max} (either as mass units as denoted in Figure 2 or as molar units provided here) and *AUC*(INF)] of analytes was as follows: total 6OHB (4 μM)>S-enantiomer (3 μM)>1-PP (2 μM)>R-enantiomer (1 μM)>buspirone (0.5 μM). In contrast, following either racemate, S-enantiomer or R-enantiomer administration (see Figure 2), the rank order of analyte mean exposure was total 6OHB (~11 μM)> S-enantiomer (~9 μM)>R-enantiomer (~2 μM)> 1-PP (~0.4 μM), with no exposure to buspirone. Therefore, buspirone administration yielded more 1-PP and less R-enantiomer than either form of 6OHB administration. Racemate, S-enantiomer and R-enantiomer each yielded similar exposure to total 6OHB (see Figure 3 and Table 3) which was approximately 2.5-fold greater than that produced by the administration of buspirone. In addition, racemate, S-enantiomer and R-enantiomer administration each yielded equivalent exposure to 1-PP (see Figure 3 and Table 1) which were approximately 30% lower than the 1-PP exposure yielded by buspirone administration.

Table 1. Pharmacokinetic parameters of buspirone and 1-PP following 6OHB and buspirone administration

Pharmacokinetic parameter	Administration of:			
	Racemate 10 mg	S-Enantiomer 10 mg	R-Enantiomer 10 mg	Buspirone 10 mg
Buspirone C_{max} (ng/ml) Geometric mean (CV%)	ND	ND	ND	1.39 (39)
Buspirone T_{max} (h) Median (Min, Max)	ND	ND	ND	0.75 (0.5, 1.5)
Buspirone AUC_{0-INF} (ng h/ml) Geometric mean (CV%)	ND	ND	ND	3.93 (27)
Buspirone *MRT* (h) Mean (SD)	ND	ND	ND	3.31 (0.78)
Buspirone $T_{1/2}$ (h) Mean (SD)	ND	ND	ND	3.17 (1.70)
1-PP C_{max} (ng/ml) Geometric mean (CV%)	2.19 (26)	2.22 (26)	2.18 (30)	4.05 (29)
1-PP T_{max} (h) Median (Min, Max)	2.25 (0.5, 3.0)	2.00 (0.5, 7.0)	2.00 (0.5, 3.0)	1.50 (0.5, 3.0)
1-PP AUC_{0-INF} (ng h/ml) Geometric mean (CV%)	20.86 (44)	22.01 (41)	21.77 (34)	29.9 (46)
1-PP *MRT* (h) Mean (SD)	9.28 (2.40)	9.74 (2.42)	9.56 (2.25)	7.56 (2.50)
1-PP $T_{1/2}$ (h) Mean (SD)	5.98 (1.63)	6.42 (1.61)	6.07 (1.45)	4.86 (1.74)

ND, None detectable or not possible to calculate.

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Table 2. Pharmacokinetic parameters of S- and R-enantiomers of 6OHB following 6OHB and buspirone administration

Pharmacokinetic parameter	Administration of:			
	Racemate 10 mg	S-Enantiomer 10 mg	R-Enantiomer 10 mg	Buspirone 10 mg
S-Enantiomer C_{max} (ng/ml) Geometric mean (CV%)	18.68 (32)	23.18 (30)	14.88 (44)	6.53 (27)
S-Enantiomer T_{max} (h) Median (Min, Max)	1.0 (0.5, 2.0)	0.75 (0.5, 2.0)	0.88 (0.5, 2.0)	0.88 (0.5, 2.0)
S-Enantiomer AUC_{0-INF} (ng h/ml) Geometric mean (CV%)	98.60 (30)	111.53 (29)	87.13 (31)	39.71 (27)
S-Enantiomer *MRT* (h) Mean (SD)	7.12 (1.53)	6.58 (1.40)	7.60 (1.58)	7.63 (1.49)
S-Enantiomer $T_{1/2}$ (h) Mean (SD)	6.25 (1.21)	5.80 (0.90)	6.20 (1.14)	6.14 (1.39)
R-Enantiomer C_{max} (ng/ml) Geometric mean (CV%)	7.00 (32)	5.23 (25)	8.32 (32)	2.60 (31)
R-Enantiomer T_{max} (h) Median (Min, Max)	0.75 (0.5, 1.5)	0.75 (0.5, 2.0)	0.75 (0.5, 2.0)	0.75 (0.5, 1.5)
R-Enantiomer AUC_{0-INF} (ng h/ml) Geometric mean (CV%)	32.88 (27)	26.85 (25)	37.03 (31)	13.28 (31)
R-Enantiomer *MRT* (h) Mean (SD)	7.12 (2.17)	7.19 (1.78)	6.87 (1.98)	7.19 (1.89)
R-Enantiomer $T_{1/2}$ (h) Mean (SD)	6.74 (2.20)	6.31 (1.42)	6.66 (2.25)	6.08 (2.21)
S:R *AUC* Ratio Geometric mean (CV%)	3.00 (10)	4.15 (11)	2.35 (10)	2.99 (12)

Table 3. Pharmacokinetic parameters of 6OHB following 6OHB and buspirone administration

Pharmacokinetic parameter	Administration of:			
	Racemate 10 mg	S-Enantiomer 10 mg	R-Enantiomer 10 mg	Buspirone 10 mg
Total 6OHB C_{max} (ng/ml) Geometric mean (CV%)	25.63 (31)	28.48 (28)	22.98 (40)	9.12 (27)
Total 6OHB T_{max} (h) Median (Min, Max)	0.88 (0.5, 1.5)	0.75 (0.5, 2.0)	0.88 (0.5, 2.0)	0.75 (0.5, 2.0)
Total 6OHB AUC_{0-INF} (ng h/ml) Geometric mean (CV%)	131.52 (29)	138.47 (28)	124.27 (30)	52.93 (28)
Total 6OHB *MRT* (h) Mean (SD)	7.09 (1.64)	6.68 (1.46)	7.36 (1.62)	7.45 (1.60)
Total 6OHB $T_{1/2}$ (h) Mean (SD)	6.33 (1.39)	5.88 (0.97)	6.32 (1.35)	6.05 (1.59)
6OHB:1-PP Ratio Geometric mean (CV%)	6.30 (39)	6.29 (40)	5.71 (34)	1.77 (45)

The mean half-life for 1-PP following buspirone administration was 4.9 h, whereas it was approximately 6 h following either form of 6OHB administered. Therefore, these half-life values of 1-PP following 6OHB administration are reflective of the half-life of the parent drug administration. This fact, and that the T_{max} for 1-PP occurred later following 6OHB administration than following buspirone administration (2.25 h vs 1.50 h) suggest that 1-PP is formed more slowly from 6OHB than from buspirone. The *MRT* values also support this finding.

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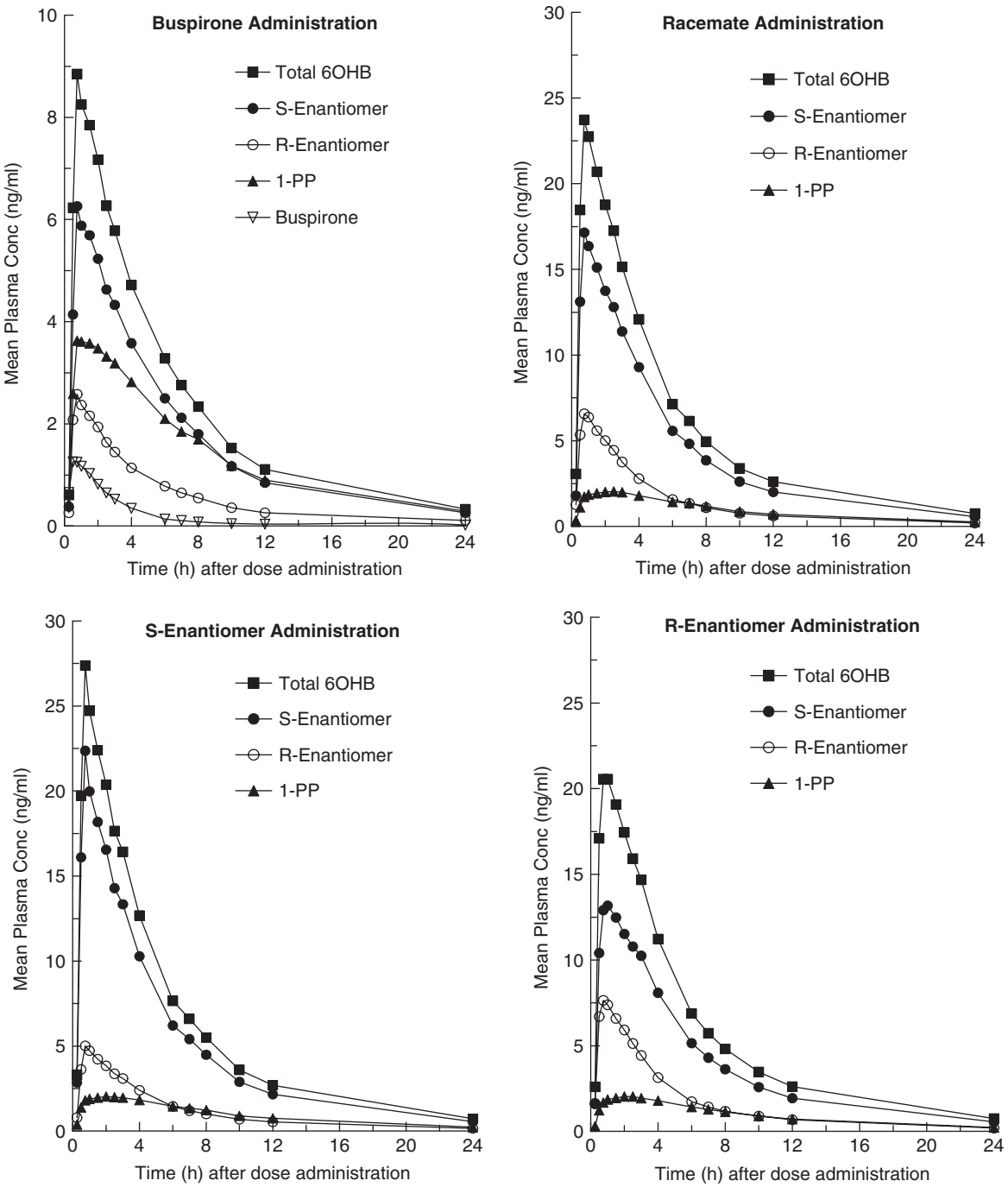

Figure 2. Mean plasma concentration vs time profiles categorized by compound administered

However, it is recognized that the variability around these parameters would not make this difference clinically meaningful.

The S-enantiomer exposure following its oral administration was approximately 4-fold greater than the R-enantiomer exposure following

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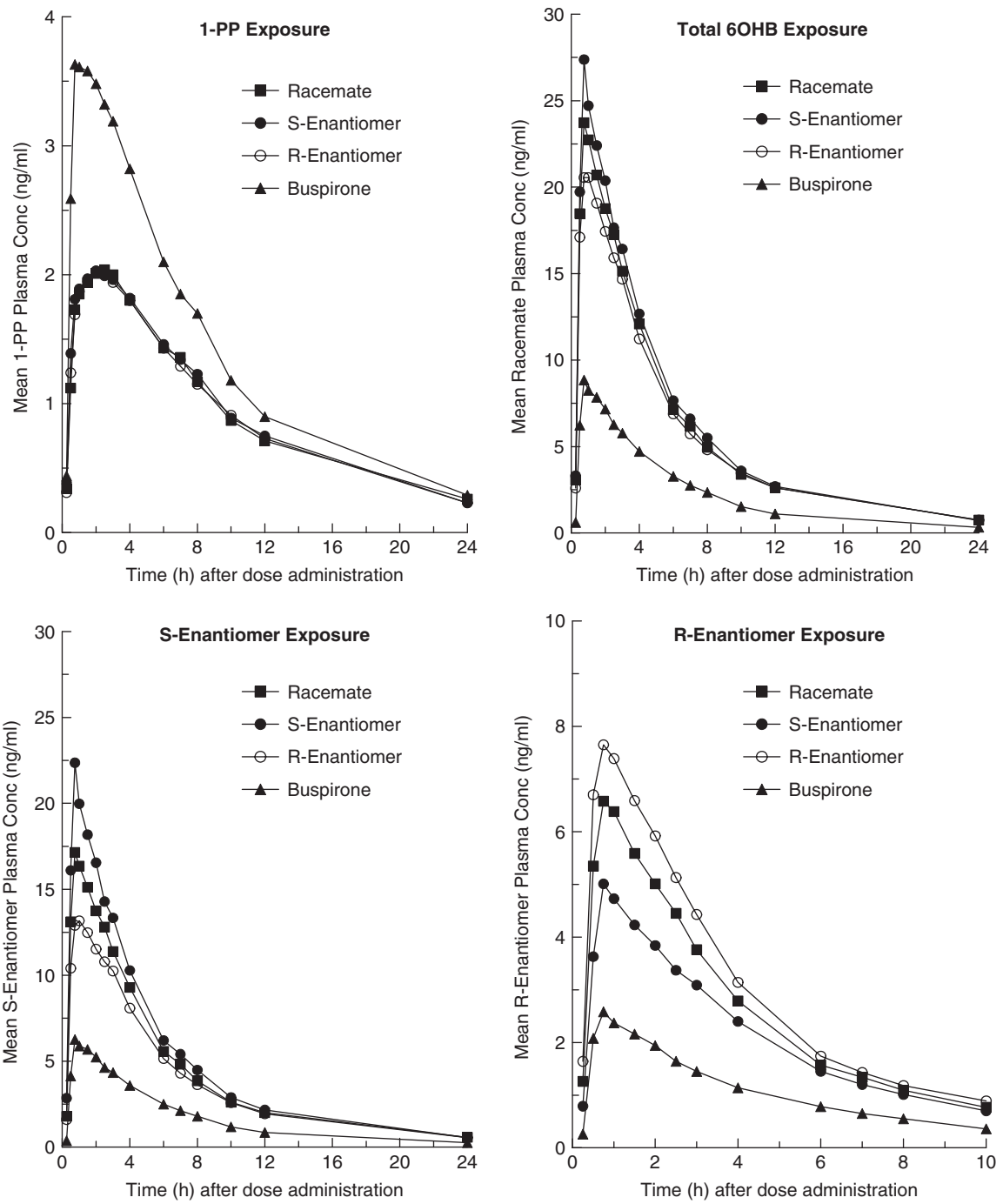

Figure 3. Mean plasma concentration vs time profiles categorized by analyte from each compound administered

R-enantiomer administration (see Table 2 and Figure 2). This, and the fact that the S-enantiomer is the dominant of the two after the administration of either enantiomer, suggest that interconversion is more rapid for the R-enantiomer than for the S-enantiomer. Following racemate dosing, the S-enantiomer exposure (i.e. *AUC*) is approximately 3-fold that of the R-enantiomer exposure

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implying that the clearance of the R-enantiomer is greater than that of the S-enantiomer. Because these compounds were orally administered, differences in bioavailability could also play a part in these observed differences. Enantiomer interconversion could occur presystemically (which would influence enantiomer bioavailability), systemically, or both. There was no major difference in the observed mean half-lives for these two 6OHB enantiomers following their own oral administration (5.8 h for the S-enantiomer and 6.7 h for the R-enantiomer) or following racemate administration (6.3 for the S-enantiomer and 6.7 for the R-enantiomer). It would seem, therefore, that interconversion is achieved rapidly and is not the rate limiting factor in the disposition of these compounds. *In vivo* enantiomeric conversion has been noted for several types of compounds [34–39] and can impact their dispositional pharmacokinetic characteristics [40]. Therefore, the clearance and interconversion of these enantiomers of 6OHB is an area that would warrant further investigation.

The geometric mean S:R enantiomer ratio was similar following racemate administration and buspirone administration (i.e. 3.00 and 2.99, respectively). This geometric mean ratio was 38% higher (4.15) following S-enantiomer administration, and 22% lower (2.35) following R-enantiomer administration (see Table 2 and Figure 2). The mean S:R enantiomer concentration ratio over time is depicted in Figure 4, and shows that the mean ratio was not different between buspirone and racemate administration after about 0.5 h, indicating rapid buspirone conversion to these enantiomers. The mean ratio following R-enantiomer administration followed the same course as that following racemate and buspirone, but more slowly. The ratio following all three of these administrations began to plateau around 5 h, was similar in value, and was fairly constant from 5 h to 24 h. Following S-enantiomer administration, the ratio rapidly declined over the first few time points and then began to plateau. At 8 h after dosing, the ratio

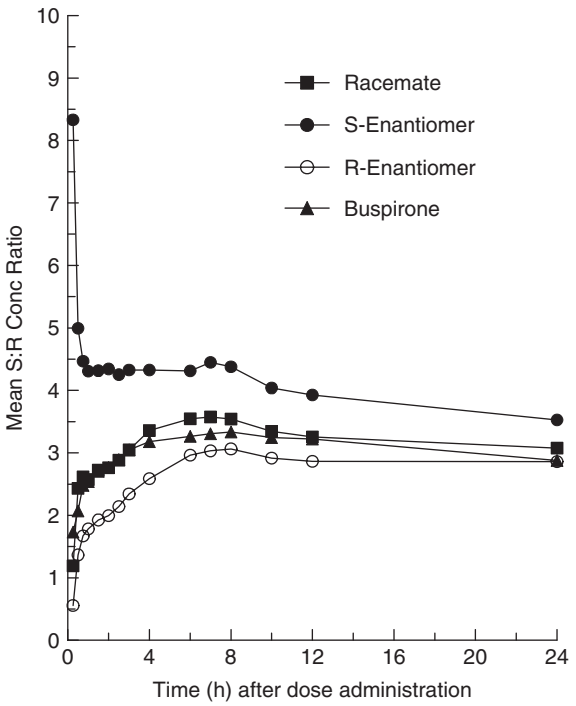

Figure 4. S:R enantiomer ratios over time following administration of 6OHB racemate, 6OHB enantiomers, and buspirone

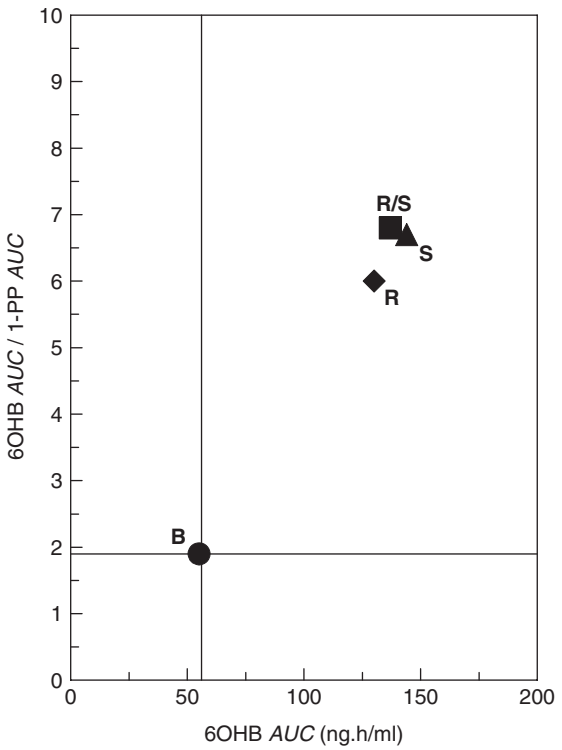

Figure 5. Ratio of 6OHB to 1-PP vs 6OHB exposure following administration of racemate (R/S) and enantiomers (R-, S-) compared with buspirone (B)

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began again to decline slowly until 24 h after dosing when the ratio was similar in value to that following S-enantiomer, racemate and buspirone dosing. Therefore, the S-enantiomer is the dominant enantiomer in plasma following all forms of 6OHB administration and equilibration occurs within a short period of time after dosing.

The geometric mean ratio of total 6OHB *AUC* to 1-PP *AUC* was 3–3.5-fold greater following 6OHB administration compared with buspirone administration (buspirone, 1.77; racemate, 6.30; S-enantiomer, 6.29; R-enantiomer, 5.71). Since one of the objectives of this clinical study was to find which form of 6OHB would maximize total 6OHB exposure (*AUC*) and at the same time maximize the 6OHB:1-PP *AUC* ratio, these two parameters were plotted to visualize which 6OHB form would separate the farthest from buspirone (Figure 5). These values following buspirone administration were plotted and used as the reference point, and parallel lines to the axes were drawn through this point. A compound falling into the upper-right quadrant would meet the criteria for maximizing 6OHB exposure and at the same time limiting the 1-PP exposure. The farther up in this right-hand quadrant, the more ideal the candidate would be for further development. All three forms of 6OHB were found to be in this upper-right quadrant with no clear distinction between racemic 6OHB and either enantiomeric form.

Neither the pharmacokinetics of the three forms of 6OHB nor the safety/tolerability information obtained from this study gave a clear basis for selecting one form over the other. Therefore, for ease of synthesis and development, the racemate was chosen for future clinical trials.

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References

1. Bristol-Myers Squibb Company. BuSpar (buspirone HCl) tablets. *Physicians' Desk Reference* (53rd edn). Thomson PDR: Montvale, NJ, 1999; 823–825.
2. Gorman JM. Treating generalized anxiety disorder. *J Clin Psychiatry* 2003; **64**(Suppl. 2): 24–29.
3. Robinson DS, Rickels K, Feighner J *et al*. Clinical effects of the 5-HT_{1A} partial agonists in depression: a composite analysis of buspirone in the treatment of depression. *J Clin Psychopharmacol* 1990; **10**: 67S–76S.
4. Blier P, Ward NM. Is there a role for 5-HT1A agonists in the treatment of depression? *Biol Psychiatry* 2003; **53**: 193–203.
5. Marangell LB. Augmentation of standard depression therapy. *Clin Ther* 2000; **22**(Suppl. A): A25–A38; discussion A39–A41.
6. Appelberg BG, Syvalahti EK, Koskinen TE, Mehtonen OP, Muhonen TT, Naukkarinen HH. Patients with severe depression may benefit from buspirone augmentation of selected serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. *J Clin Psychiatry* 2001; **62**: 448–452.
7. Rothschild AJ. New direction in the treatment of antidepressant-induced sexual dysfunction. *Clin Ther* 2000; **22**(Suppl. A): A42–A47; discussion A58–A61.
8. Gitlin M. Sexual dysfunction with psychotropic drugs. *Expert Opin Pharmacother* 2003; **4**: 2259–2269.
9. Niederhofer H. An open trial of buspirone in the treatment of attention-deficit disorder. *Hum Psychopharmacol* 2003; **18**: 489–492.
10. Rynn M, Garcia-Espana F, Greenblatt DJ, Mandos LA, Schjweizer E, Rickels K. Imipramine and buspirone in patients with panic disorder who are discontinuing long-term benzodiazepine therapy. *J Clin Psychopharmacol* 2003; **23**: 505–508.
11. Cooper JP. Buspirone for anxiety and agitation in dementia. *J Psychiatry Neurosci* 2003; **28**: 469.
12. Cornelius JR, Bukstein O, Salloum I, Clark D. Alcohol and psychiatric comorbidity. *Recent Dev Alcohol* 2003; **16**: 361–374.
13. Mayol RF, Adamson DS, Gammans RE, LaBudde JA. Pharmacokinetic disposition of ^{14}C-buspirone HCl after intravenous and oral dosing in man. *Clin Pharmacol Ther* 1985; **37**: 210.
14. Gammans RE, Mayol RF, LaBudde JA. Metabolism and disposition of buspirone. *Am J Med* 1986; **80**(Suppl. 3B): 41–51.
15. Gammans RE, Johnston RE. Metabolism, pharmacokinetics and toxicology of buspirone. In *Buspirone: Mechanisms and Clinical Aspects*, Tunnicliff G, Eison A, Taylor D (eds). Academic Press: San Diego, 1995; 223–260.
16. Caccia S, Conti J, Vigano G, Garattini S. 1-(2-pyrimidinyl)-piperazine as active metabolite of buspirone in man and rat. *Pharmacology* 1986; **33**: 46–51.
17. Zhu M, Zhao W, Jimenez H *et al*. Cytochrome P450 3A-mediated metabolism of buspirone in human liver microsomes. *Drug Metab Dispos* 2005; **33**: 500–507.
18. Li Y-W, Wong H, Dockens RC *et al*. 6-OH buspirone, a major active metabolite of buspirone and a high-affinity and highly selective 5-HT_{1A} partial agonist. *Drug Metabolism and Disposition*. DOI: 10.1124/dmd.107.015768
19. Dockens RC, Salazar DE, Fulmor IE, Croop R. Pharmacokinetics of a newly identified metabolite of buspirone

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following administration of buspirone over its therapeutic dose range. *J Clin Pharmacol* 2006; **46**: 1308–1312.
20. Handley SL, McBlane JW, Critchley MAE, Njung'e K. Multiple serotonin mechanisms in animal models of anxiety: environmental, emotional and cognitive factors. *Behav Brain Res* 1993; **58**: 203–210.
21. Kidd EJ, Hajdahmane S, Jolas T *et al*. New methoxychroman derivatives, 4-[-(5-methoxy-chroman-3-yl-)N-propylamino]butyl-8-azaspiro-(4,5)-decane-7,9-dione [(±)-S 20444] and its enantiomers, (+)-S 20499 and (−)-S 20500, with potent agonist properties at central 5-hydroxytryptamine$_{1A}$ receptors. *J Pharmacol Exp Ther* 1993; **264**: 863–872.
22. Simiand J, Keane PE, Barnouin MC, Keane M, Soubrie P, Le Fur G. Neuropsychopharmacological profile in rodents of SR 57746A, a new, potent 5-HT$_{1A}$ receptor agonist. *Fundam Clin Pharmacol* 1993; **7**: 413–427.
23. Matsuda T, Yoshikawa T, Suzuki M *et al*. Novel benzodioxan derivative, 5-(3-[((2S)-1,4-benzodioxan-2-ylmethyl)amino]propoxy)-1,3-benzodioxole HCl (MCK-242), with a highly potent and selective agonist activity at rat central serotonin 1A receptors. *Jpn J Pharmacol* 1995; **69**: 357–366.
24. Cutler NR, Sramek JJ, Kurtz NM. *Anxiolytic Compounds. Perspectives in Drug Development*. Wiley: Chichester, 1996.
25. Gammans RE, Mayol RE, Eison MS. Concentration of buspirone and 1-(2-pyrimidinyl)-piperazine at presynaptic α_2-adrenoceptors in the rat brain. *Eur J Pharmacol* 1983; **180**: 183–186.
26. Gower AJ, Tricklebank MD. α_2-Adrenoceptor antagonist activity may account for the effects of buspirone in an anticonflict test in the rat. *Eur J Pharmacol* 1988; **155**: 129–137.
27. Amano M, Goto A, Sakai A *et al*. Comparison of the anticonflict effect of buspirone and its major metabolite 1-(2-pyrimidinyl)-piperazine (1-PP) in rats. *Jpn J Pharmacol* 1993; **61**: 311–317.
28. De Vry J, Benz U, Schreiber R, Traber J. Shocked-induced ultrasonic vocalization in young adult rats: a model for testing putative anti-anxiety drugs. *Eur J Pharmacol* 1993; **249**: 331–339.
29. Cullen WK, Rowan MJ. Gepirone and 1-(2-pyrimidinyl)-piperazine-induced reduction of aversively evoked ultrasonic vocalisation in the rat. *Pharmacol Biochem Behav* 1994; **48**: 301–306.
30. Cao BJ, Rodgers RJ. Comparative behavioural profiles of buspirone and its metabolite 1-(2-pyrimidinyl)-piperazine (1-PP) in the murine elevated plus-maze. *Neuropharmacology* 1997; **36**: 1089–1097.
31. Gibaldi M, Perrier D. *Pharmacokinetics* (2nd edn). Marcel-Dekker: New York, NY, 1982; 409–417.
32. 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.
33. Statistical Analysis System (SAS). Version 6.12. Cary (NC): SAS Institute, Inc; 1997.
34. Foster RT, Jamali F, Russell AS, Alballa SR. Pharmacokinetics of ketoprofen enantiomers in healthy subjects following single and multiple doses. *J Pharm Sci* 1988; **77**: 70–73.
35. Brocks DR, Jamali F, Russell AS, Skeith KJ. The stereoselective pharmacokinetics of etodolac in young and elderly subjects, and after cholecystectomy. *J Clin Pharmacol* 1992; **32**: 982–989.
36. Oliary J, Tod M, Nicolas P, Petitjean O, Caille G. Pharmacokinetics of ibuprofen enantiomers after single and repeated doses in man. *Biopharm Drug Dispos* 1992; **13**: 337–344.
37. Patel BK, Jackson SH, Swift CG, Hutt AJ. Disposition of flurbiprofen in man: influence of stereochemistry and age. *Xenobiotica* 2003; **33**: 1043–1057.
38. Miura M, Uno T, Tateishi T, Suzuki T. Pharmacokinetics of fexofenadine enantiomers in healthy subjects. *Chirality* 2007; **29**: 223–227.
39. Rippley RK, Yan KX, Matthews ND, Greenberg HE, Herman GA, Wagner JA. Human pharmacokinetics and interconversion of enantiomers of MK-0767, a dual PPARα/γ agonist. *J Clin Pharmacol* 2007; **47**: 323–333.
40. Brocks DR. Drug disposition in three dimensions: an update on stereoselectivity in pharmacokinetics. *Biopharm Drug Dispos* 2006; **27**: 387–406.

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