6-Hydroxybuspirone Is a Major Active Metabolite of Buspirone: Assessment of Pharmacokinetics and 5-Hydroxytryptamine$_{1A}$ Receptor Occupancy in Rats

Harvey Wong, Randy C. Dockens, Lori Pajor, Suresh Yeola, James E. Grace, Jr., Arlene D. Stark, Rebecca A. Taub, Frank D. Yocca, Robert C. Zaczek, and Yu-Wen Li

Departments of Metabolism and Pharmacokinetics (H.W., L.P., J.E.G.), Clinical Discovery (R.C.D.), Biotransformation (S.Y.), and Neuroscience Biology (A.D.S., R.A.T., F.D.Y., R.C.Z., Y.W.L.), Pharmaceutical Research Institute, Bristol-Myers Squibb, Wallingford, Connecticut

Received March 16, 2007; accepted May 8, 2007

ABSTRACT:
The pharmacokinetics and in vivo potency of 6-hydroxybuspirone (6-OH-buspirone), a major metabolite of buspirone, were investigated. The plasma clearance (47.3 ± 3.5 ml/min/kg), volume of distribution (2.6 ± 0.3 l/kg), and half-life (1.2 ± 0.2 h) of 6-OH-buspirone in rats were similar to those for buspirone. Bioavailability was higher for 6-OH-buspirone (19%) compared with that for buspirone (1.4%). After intravenous infusions to steady-state levels in plasma, 6-OH-buspirone and buspirone increased 5-hydroxytryptamine (HT)$_{1A}$ receptor occupancy in a concentration-dependent manner with EC$_{50}$ values of 1.0 ± 0.3 and 0.38 ± 0.06 μM in the dorsal raphe and 4.0 ± 0.6 and 1.5 ± 0.3 μM in the hippocampus, respectively. Both compounds appeared to be ~4-fold more potent in occupying presynaptic 5-HT$_{1A}$ receptors in the dorsal raphe than the postsynaptic receptors in the hippocampus. Oral dosing of buspirone in rats resulted in exposures (area under the concentration-time profile) of 6-OH-buspirone and 1-(2-pyrimidinyl)-piperazine (1-PP), another major metabolite of buspirone, that were ~12 (6-OH-buspirone)- and 49 (1-PP)-fold higher than the exposure of the parent compound. As a whole, these preclinical data suggest that 6-OH-buspirone probably contributes to the clinical efficacy of buspirone as an anxiolytic agent.

Buspirone (Fig. 1) is a potent and selective 5-HT$_{1A}$ receptor partial agonist that has been prescribed for the treatment of generalized anxiety disorders (Sramek et al., 2002; Blier and Ward, 2003; Goodman, 2004). Although the onset of action of buspirone is relatively slow and the efficacy is only obtained after chronic treatment, therapy with buspirone is not associated with undesirable side effects such as sedation, cognitive impairment, withdrawal symptoms, and potential abuse liability that can occur with benzodiazepine treatment (Eison and Temple, 1986; Tumincliff, 1991; Argyropoulos and Nutt, 1999). Buspirone has also been suggested to have a role in the treatment of depressive disorders (Thase et al., 1998; Blier and Ward, 2003).

Current hypotheses on the clinical mechanisms of action of buspirone focus on its agonist activities on 5-HT$_{1A}$ receptors (Schreiber and De Vry, 1993; Blier and Ward, 2003). Belonging to the superfamily of G-protein-coupled receptors, 5-HT$_{1A}$ receptors share a high identity (89%) of their transmembrane-spanning amino acid sequences in humans and rats (Albert et al., 1990). They are abundant as presynaptic (somatodendritic) autoreceptors on serotonergic neurons, primarily in the midbrain dorsal raphe nucleus; activation of the 5-HT$_{1A}$ autoreceptors inhibits the neuronal activity and results in a reduction of 5-HT release in terminal synapses of the serotonergic neurons (Blier and Ward, 2003). 5-HT$_{1A}$ receptors are also present as postsynaptic receptors in the forebrain limbic structures; activation of these receptors inhibits activities of postsynaptic neurons innervated by serotonergic axonal terminals. It has been hypothesized that prolonged activation of 5-HT$_{1A}$ autoreceptors in the dorsal raphe with 5-HT$_{1A}$ agonists, such as buspirone and its analogs, results in desensitization of the receptors and consequently increases releases of 5-HT in the limbic regions (Blier and Ward, 2003). The enhanced serotonergic functions are believed to be responsible for anxiolytic and antidepressant effects of these agents. Although behavioral/clinical effects of buspirone and other 5-HT$_{1A}$ agonists are believed to be mediated through occupying and acting on 5-HT$_{1A}$ receptors, the level of 5-HT$_{1A}$ receptor occupancy required for the effects has not been well investigated. In two human positron emission tomography studies, little or no occupancy of 5-HT$_{1A}$ receptors has been observed after administration of clinically efficacious doses of buspirone (Rabiner et al., 2000; Passchier et al., 2001). Preclinically, the requirement of
5-HT$_{1A}$ occupancy for buspirone and its analogs at behaviorally active doses has not been investigated.

In humans and rats, buspirone is extensively metabolized and has low oral bioavailability (<5%) (Caccia et al., 1983; Jajoo et al., 1989). The metabolic disposition is similar in the two species with three major metabolic pathways being N-dealkylation to 1-(2-pyrimidinyl)piperazine (1-PP) and hydroxylation to either 5-hydroxybuspirone or 6-hydroxybuspirone (Fig. 1). Of these metabolites, 1-PP has been the most extensively investigated in its role as an active metabolite (Caccia et al., 1986; Zuideveld et al., 2002). 1-PP behaves as an $\alpha_1$-adrenoceptor antagonist with a low affinity to the 5-HT$_{1A}$ receptor (Caccia et al., 1986; Gobbi et al., 1991) and therefore is unlikely to play an important role in the anxiolytic effects of buspirone. Much less is known about the pharmacological properties of 6-OH-buspirone. Conversion to 6-OH-buspirone has been shown to be the predominant metabolic pathway involved in buspirone elimination in human liver microsomes (Zhu et al., 2005). In addition, plasma levels of 6-OH-buspirone have been recently reported to be 40-fold greater than those of buspirone after oral administration to humans (Dockens et al., 2006). More recently, 6-OH-buspirone has been found to possess anxiolytic activity in rats using the fear-induced ultrasonic vocalization paradigm (A. D. Stark, unpublished observations). The primary aims of the present study were 1) to evaluate the pharmacokinetics of 6-OH-buspirone in rats, 2) to characterize the in vivo potency of 6-OH-buspirone and buspirone at the 5-HT$_{1A}$ receptor by measuring receptor occupancy using in vivo autoradiography, and 3) to investigate the requirement of 5-HT$_{1A}$ occupancy for buspirone at behaviorally active doses.

Materials and Methods

Pharmacokinetic Studies in Rats. Male Sprague-Dawley rats (weighing 250–350 g) (Charles River, Wilmington, MA) with single carotid artery catheterization were used in this study. Rats ($n = 3$ dose group) received either a single 5 mg/kg i.a. dose or a single 10 mg/kg p.o. dose of 6-OH-buspirone or buspirone. The vehicle for both the i.a. and p.o. dosing was 0.2 M sodium acetate buffer, pH 4. Serial blood samples (0.25 ml) were collected at predose and 0.1, 0.2, 0.25, 0.5, 1, 2, 4, 6, 8, and 12 h after i.a. dosing and at predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, and 12 h after p.o. dosing. Immediately upon collection, the blood was mixed with K$_2$EDTA and stored on ice. Within 60 min, blood samples were centrifuged at approximately 1000 g for 15 min at 4°C, and plasma was harvested. The plasma samples were stored at −80°C until use.

Concentrations of buspirone, 6-OH-buspirone, and 1-PP in plasma were quantitated using a liquid chromatography tandem mass spectrometry (LC/MS/MS) method. Briefly, 50 $\mu$l of plasma, 50 $\mu$l of 10 ng/ml internal standard solution, and 0.2 ml of phosphate-buffered saline were mixed. Samples were passed through a conditioned C$_{18}$ (EC) solid phase extraction cartridge, washed with 1 ml of water and 0.5 ml of 50:50 (v/v) methanol/water, and eluted with 2 ml of 5% ammonium hydroxide in acetonitrile. The eluted sample was transferred and evaporated to dryness under nitrogen at 40°C. Residues were reconstituted with 0.1 ml of 10:1 (v/v) 100 mM ammonium acetate/ethanol, and 10 $\mu$l was analyzed using LC/MS/MS. High-performance liquid chromatography separation was achieved using a mobile phase consisting of 50% A [aqueous 5 mM ammonium acetate (0.1% formic acid)] and 50% B [90:10 methanol/water 5 mM ammonium acetate (0.1% formic acid)] on a Betasil-C$_{18}$ column (2 × 100 mm, 5 $\mu$m) (Thermo Electron Corporation, Waltham, MA) at a flow rate of 250 $\mu$l/min with an analysis time of 4 min. Detection was performed in positive, multiple reaction monitoring mode using a Micromass Quattro liquid chromatograph (Waters, Milford, MA) with an electron ionization source as the LC/MS/MS interface.

In Vivo Autoradiography Studies. Male Sprague-Dawley rats (weighing 250–350 g) with dual jugular vein catheterization (Charles River Laboratories, Wilmington, MA) were used in this study. Rats were housed in polycarbonate cages and maintained on a 12:12 h light/dark cycle with free access to standard chow and water. Buspirone (Bristol-Myers Squibb, Wallingford, CT), 6-OH-buspirone (Bristol-Myers Squibb), and $[^3]$HWAY-100635 (a selective 5-HT$_{1A}$ antagonist; GE Healthcare, Chalfont St. Giles, Buckinghamshire, UK) dosing solutions were freshly prepared using sterile saline as vehicle. For buspirone experiments, rats were injected i.v. with a loading dose of buspirone (0.45–12 mg/kg), immediately followed by a continuous infusion of the buspirone at 0.45 to 12 mg/kg/h for 90 min through one jugular vein. For 6-OH-buspirone experiments, rats were injected i.v. with a loading dose of 6-OH-buspirone (2.4–23.7 mg/kg), immediately followed by a continuous infusion of 6-OH-buspirone at 2.4 to 23.7 mg/kg/h for 90 min through one jugular vein. For both groups of rats, blood samples (0.3–0.4 ml) were taken at 0.4, 20, 60, and 60 min postdose through the second jugular vein. In previous pilot experiments, it was determined that steady-state plasma concentrations of buspirone and 6-OH-buspirone were achieved by 40 min after the start of the infusion under the protocol described (data not shown). Steady-state plasma concentrations ($C_{ss}$) of buspirone and 6-OH-buspirone are presented as the mean ± S.D. of the 40-, 50-, and 60-min time points.

Immediately after the last blood sample, 10 $\mu$Ci/100 g b.wt. $[^3]$HWAY-100635 (in 0.6–0.7 ml of saline) was injected i.v. Rats were decapitated 30 min later, the brains were collected, frozen, and sectioned (20 $\mu$m) using a Cryostat, and sections were mounted on Superfrost slides (VWR, Wilmington, DE). Brain sections were exposed to tritium-sensitive phosphor screens (PerkinElmer Life and Analytical Sciences, Shelton, CT) for 2 to 3 weeks, and images of $[^3]$HWAY-100635 binding in the brain were captured and analyzed using a Cyclone Storage Phosphor Imaging System (PerkinElmer Life and Analytical Sciences). The cerebellum, where 5-HT$_{1A}$ receptor density is nominal, was used as a reference region for defining nonspecific binding. The percentage occupancy at 5-HT$_{1A}$ receptors in the region of interest was calculated as 100% − percent $[^3]$HWAY-100635 binding in drug-treated − $[^3]$HWAY-100635 binding in cerebellum). $[^3]$HWAY-100635 binding in vehicle vehicle $[^3]$HWAY-100635 binding in cerebellum.

Concentrations of buspirone and 6-OH-buspirone in the plasma were quantitated using a LC/MS/MS method. Briefly, 0.1 ml of plasma, 50 $\mu$l of 200 mM internal standard solution, and 0.1 ml of 0.1 M Na$_2$CO$_3$ were mixed followed by the addition of 1.0 ml of 1:1 methyl tert-butyl ether/ethyl acetate. Samples were vortexed and centrifuged, and the organic layer was transferred and evaporated to dryness under nitrogen at 60°C. Residues were reconstituted with 0.1 ml of H$_2$O/CH$_3$CN/HCOOH (50:50:0.1, v/v/v, High-performance liquid chromatography separation was achieved using an acetonitrile (0.1% formic acid)/water (0.1% formic acid) gradient on a Zorbax SB-C$_{18}$ column (2 × 50 mm, 5 $\mu$m) (Agilent Technologies, Palo Alto, CA) at a flow rate of 200 $\mu$l/min with an analysis time of 5 min. Detection was performed in positive, multiple resolution mode using a Micromass Quattro Ultima mass spectrometer (Waters) with an electron ionization source as the LC/MS/MS interface.

Data Analysis. Plots of 5HT$_{1A}$ receptor occupancy versus plasma concentration were fitted to a one-site binding model using nonlinear regression according to the following equation: occupancy = $B_{max}$ × $C$/(EC$_{50}$ + $C$), where $B_{max}$ is the maximal binding, $C$ is the drug concentration, and EC$_{50}$ is 

![Chemical structure of buspirone and 6-OH-buspirone.](image)
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Figure 3 shows representative autoradiograms of the inhibitory effect

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The percentage of 5-HT1A receptors labeled by intravenous injections of [3H]WAY-100635 in the rat brain is consistent with that reported previously (Hume et al., 1994; Khawaja, 1995). A high density of [3H]WAY-100635 binding appeared in the cortex, septum, hippocampus, hypothalamus, and raphe nuclei in the brainstem. An intravenous infusion of buspirone or 6-OH-buspirone inhibited [3H]WAY-100635 in all these regions in a dose-dependent manner. Figure 3 shows representative autoradiograms of the inhibitory effect of 6-OH-buspirone on in vivo [3H]WAY-100635 binding in the forebrain areas including the hippocampus from rats receiving various doses of 6-OH-buspirone (Fig. 3, A–C).

The distribution pattern of 5-HT1A receptors labeled by intravenous injections of [3H]WAY-100635 is shown. The occupancy of 5-HT1A receptors increased with increasing steady-state concentrations of buspirone.

Results

The pharmacokinetic parameters of 6-OH-buspirone and buspirone in rats are summarized in Table 1. Plasma clearances for both buspirone and 6-OH-buspirone were high in relation to liver blood flow in rats, being 68.7 ± 8.7 and 47.3 ± 3.5 ml/min/kg, respectively (Table 1). Estimates of volume of distribution at steady-state (Vss), and half-life (t1/2) were also comparable. 6-OH-buspirone had greater exposure after oral administration than buspirone with higher estimates of both bioavailability and the maximum observed concentration achieved after oral dosing (Cmax). (Table 1). Figure 2 shows plasma concentration-time profiles of buspirone, 6-OH-buspirone, and 1-PP in rats after a single 5 mg/kg i.a. or 10 mg/kg p.o. dose of buspirone. Plasma concentrations of both 6-OH-buspirone and 1-PP were noticeably higher than those of the parent compound when buspirone was administered orally. Mean area under the concentration-time profile of buspirone, 6-OH-buspirone, and 1-PP in rats after a single 5 mg/kg i.a. or 10 mg/kg p.o. dose of buspirone. Plasma concentrations of both 6-OH-buspirone and 1-PP were noticeably higher than those of the parent compound when buspirone was administered orally. Mean area under the concentration-time profile (AUC) estimates for the buspirone metabolites were approximately 12 (6-OH-buspirone)- and 48 (1-PP)-fold higher than AUC estimates for the parent compound after oral dosing (Fig. 2; Table 2).

The distribution pattern of 5-HT1A receptors labeled by intravenous injections of [3H]WAY-100635 in the rat brain is consistent with that reported previously (Hume et al., 1994; Khawaja, 1995). A high density of [3H]WAY-100635 binding appeared in the cortex, septum, hippocampus, hypothalamus, and raphe nuclei in the brainstem. An intravenous infusion of buspirone or 6-OH-buspirone inhibited [3H]WAY-100635 in all these regions in a dose-dependent manner. Figure 3 shows representative autoradiograms of the inhibitory effect of 6-OH-buspirone on in vivo [3H]WAY-100635 binding in the forebrain areas including the hippocampus from rats receiving various doses of 6-OH-buspirone (Fig. 3, A–C).

The percentage of 5-HT1A receptor occupancy in two representative brain regions, the hippocampus and the dorsal raphe nucleus, steady-state plasma concentrations, and infusion rates for buspirone and 6-OH-buspirone are summarized in Tables 3 and 4. In rats dosed via an i.v. infusion with buspirone, 6-OH-buspirone Cmax values were ~6- to 20-fold less than buspirone Cmax values. The range of buspirone and 6-OH-buspirone infusion rates resulted in a wide range of steady-state concentrations. Occupancy of 5-HT1A receptors increased with increasing steady-state concentrations of both compounds.

In Fig. 4 the relationship between brain 5-HT1A receptor occupancy in hippocampus and dorsal raphe and plasma concentrations of buspirone and 6-OH-buspirone is examined. The data for each brain region were fitted to a one-site binding model, and the estimated in vivo EC50 values are presented in Table 5. The in vivo affinity of buspirone (or its metabolites) appeared more potent for 5-HT1A receptors in the dorsal raphe than in the hippocampus (Table 5; Fig. 4). Likewise, 6-OH-buspirone exhibited a higher in vivo affinity in the dorsal raphe than in the hippocampus.

Discussion

The clearance of buspirone in rats estimated from the current study is similar to the clearance estimate of 51 ml/min/kg observed by Caccia et al. (1983). 6-OH-buspirone showed pharmacokinetics similar to buspirone in rats with the exception of mean oral bioavailability, which was ~13-fold higher (Table 1). A recent pharmacokinetic study in humans reported a similar range of half-lives for both buspirone (2.8–4.6 h) and 6-OH-buspirone (4.7–4.3 h) after oral administration of buspirone, which is consistent with similar elimination characteristics of both compounds in humans (Dockens et al.,
2006). Currently, there is no literature information on the oral bioavailability of 6-OH-buspirone in humans.

The in vivo affinity/potency of buspirone and 6-OH-buspirone at 5-HT\textsubscript{1A} receptors in the brain was examined after intravenous infusions of both compounds to steady state in the rat. In vivo binding of \[^{[3]}\text{H}\]WAY-100635, a selective 5-HT\textsubscript{1A} antagonist, in the hippocampus and dorsal raphe was dose dependently inhibited by buspirone and 6-OH-buspirone, indicating their interaction with 5-HT\textsubscript{1A} receptors in vivo. The in vivo affinity at 5-HT\textsubscript{1A} receptors for both compounds was 3- to 4-fold higher in the dorsal raphe than in the hippocampus (Table 5). As elucidated in the Introduction, the forebrain regions including the hippocampus express postsynaptic 5-HT\textsubscript{1A} receptors, whereas the dorsal raphe posses 5-HT\textsubscript{1A} somatodendritic autoreceptors. A higher affinity to the autoreceptors relative to that for the postsynaptic receptors has been observed with pindolol, a \(\beta\)-adrenoceptor antagonist with a high 5-HT\textsubscript{1A} affinity, and been postulated to underlie the effect of pindolol for augmentation of the selective serotonin reuptake inhibitor antidepressant efficacy (Raurich et al., 1999; Rabiner et al., 2000; Martinez et al., 2001). The dorsal raphe has also been considered to play an important role in the anxiolytic effects

![FIG. 3. Inhibition of \[^{[3]}\text{H}\]WAY-100635 binding in rat brain after intravenous infusions of 6-OH-buspirone at various infusion rates. A, vehicle; B, 2.4 mg/kg/h; C, 11.9 mg/kg/h. Hip, hippocampus. Scale bar, 2 mm.]

![TABLE 3. Steady-state concentrations of buspirone and 6-OH-buspirone, and 5-HT\textsubscript{1A} receptor occupancy in the hippocampus and dorsal raphe after intravenous infusions of buspirone.]

<table>
<thead>
<tr>
<th>Rat ID</th>
<th>Infusion Rate</th>
<th>Buspirone C\textsubscript{ss}</th>
<th>6-OH-buspirone C\textsubscript{ss}</th>
<th>5-HT\textsubscript{1A} Receptor Occupancy</th>
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|       | mg/kg/h | µM | µM | % setHidden

![FIG. 4. Relationship between 5-HT\textsubscript{1A} receptor occupancy in two brain regions (hippocampus and dorsal raphe) and plasma concentration after intravenous infusions of buspirone (A) and 6-OH-buspirone (B).]

![TABLE 4. Steady-state concentrations and 5-HT\textsubscript{1A} receptor occupancy in the hippocampus and dorsal raphe after intravenous infusions of 6-OH-buspirone.]

<table>
<thead>
<tr>
<th>Rat ID</th>
<th>Infusion Rate</th>
<th>C\textsubscript{ss}</th>
<th>5-HT\textsubscript{1A} Receptor Occupancy</th>
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![TABLE 5. Estimated in vivo EC\textsubscript{50} of buspirone and 6-OH-buspirone to 5-HT\textsubscript{1A} receptors in the hippocampus and dorsal raphe of the rat.]

<table>
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<tr>
<th>Compound</th>
<th>In Vivo EC\textsubscript{50}</th>
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<tbody>
<tr>
<td></td>
<td>Hippocampus</td>
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<tr>
<td></td>
<td>µM</td>
</tr>
<tr>
<td>Buspirone</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>6-OH-buspirone</td>
<td>4.0 ± 0.6</td>
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of 5-HT_{1A} partial agonists, including buspirone, whose effects have been hypothesized to be mediated by desensitizing 5-HT_{1A} autoreceptors in the dorsal raphe (Sim-Selley et al., 2000). Our observation of a higher affinity binding of buspirone and its major metabolite, 6-OH-buspirone, to 5-HT_{1A} autoreceptors in the dorsal raphe supports the hypothesis.

Although 6-OH-buspirone was present in the plasma after buspirone infusions, the levels of the metabolite were 6- to 20-fold less than that of the parent compound. As the in vivo affinity of 6-OH-buspirone at the 5-HT_{1A} receptor is comparable to that of buspirone (Table 5), the contribution of this metabolite in occupying 5-HT_{1A} receptors in the buspirone experiments is probably low. Although 1-PP was not quantitated in this experiment, it has been shown to have low in vitro affinity and selectivity at 5-HT_{1} receptors in rat brain (Caccia et al., 1986; Gobbi et al., 1991) and thus is not likely to contribute significantly to the 5-HT_{1A} occupancy observed in our studies.

To our knowledge, this is the first published report on the activity of 6-OH-buspirone at the 5-HT_{1A} receptor. On the basis of the current study, the in vivo affinity/potency of 6-OH-buspirone appears to be comparable to that of buspirone. Buspirone has been shown to have extensive hepatic first-pass metabolism in both rats and humans with a reported bioavailability of 4% in humans (Caccia et al., 1983; Mahmood and Sahajwalla, 1999). Although we observed relatively low levels of 6-OH-buspirone compared with those of buspirone after intravenous infusions (Table 3) and intra-arterial dosing (Table 2) of the parent compound, it could contribute significantly to the biological activity of buspirone after oral dosing due to the higher circulating levels of metabolites resulting from extensive first-pass metabolism. The current pharmacokinetic study in rats shows oral exposures of 6-OH-buspirone that are ~12-fold higher than those of buspirone after a 10 mg/kg p.o. buspirone dose (Fig. 2; Table 2). In humans, oral exposures of 6-OH-buspirone are even higher, being ~40 fold greater than those for buspirone when oral doses of buspirone over the therapeutic dose range (10–60 mg daily) are given (Dockens et al., 2006).

Receptor occupancy requirements associated with an anxiolytic effect at the 5-HT_{1A} receptor is not well understood. In both the fear-induced and air-puff-elicited ultrasonic vocalization models of anxiety in rats, buspirone has been shown to have anxiolytic effects at an oral dose of 10 mg/kg (Vis et al., 2001; Naito et al., 2003). Based on concentrations of buspirone and 6-OH-buspirone observed in the current study and in vivo EC_{50} estimates presented in Table 5, maximum 5-HT_{1A} receptor occupancies of ~23% in the dorsal raphe and ~7% in the hippocampus occur after an oral dose of 10 mg/kg to rats. In a recent study in humans, buspirone and 6-OH-buspirone concentrations were monitored after 5 days of buspirone administration over the therapeutic dose range (Dockens et al., 2006). At the highest dose used in the study (i.e., oral doses of 30 mg/kg twice daily), mean C_{max} values of 2.0 ng/ml (0.005 μM) and 39 ng/ml (0.097 μM) were reported for buspirone and 6-OH-buspirone, respectively. These concentrations would result in 5-HT_{1A} receptor occupancies of ~10% in the dorsal raphe and ~3% in the hippocampus using in vivo EC_{50} estimates presented in Table 5.

Low levels of 5-HT_{1A} receptor occupancy by buspirone at clinically effective doses have been reported previously in human positron emission tomography studies (Rabiner et al., 2000; Passchier et al., 2001). A single dose of 10 or 40 mg of buspirone occupies ~5% 5-HT_{1A} receptors in healthy human subjects (Rabiner et al., 2000; Passchier et al., 2001). A similar low fraction (<10%) of occupancy in humans has been observed with other selective and nonselective 5-HT_{1A} agonists such as tandospirone, flesinoxan, and EMD 128 130 after single or multiple clinical doses capable of activating central 5-HT_{1A} receptor functions (Nakayama et al., 2002; Rabiner et al., 2002; Bantick et al., 2004). Results of the current study are consistent with these literature observations, suggesting that high levels of 5-HT_{1A} receptor occupancy are not required to elicit an anxiolytic effect either preclinically in rats and clinically in humans.

In summary, the present study demonstrates that 6-OH-buspirone is the major active metabolite of buspirone with similar in vivo potency at the 5-HT_{1A} receptor. 6-OH-buspirone has improved oral exposure in comparison with buspirone and could be an effective anxiolytic agent alternative to buspirone. Finally, results of our current study are consistent with literature reports suggesting that a low 5-HT_{1A} receptor occupancy requirement is needed for anxiolytic activity.

Acknowledgments. We thank our colleagues Vincenzo Calandra, Xiaoxin Yan, Todd Strong, Shelly X. Ren, and Rick Pieschl for contributing to this study.

References


Address correspondence to: Dr. Yu-Wen Li, Neuroscience Biology, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492-7660. E-mail: yu-wen.li@bms.com