Short Communication

Characterization of Ebastine, Hydroxyebastine, and Carebastine Metabolism by Human Liver Microsomes and Expressed Cytochrome P450 Enzymes: Major Roles for CYP2J2 and CYP3A

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ABSTRACT:

Ebastine undergoes extensive metabolism to form desalkylebastine and hydroxyebastine. Hydroxyebastine is subsequently metabolized to carebastine. Although CYP3A4 and CYP2J2 have been implicated in ebastine N-dealkylation and hydroxylation, the enzyme catalyzing the subsequent metabolic steps (conversion of hydroxyebastine to desalkylebastine and carebastine) have not been identified. Therefore, we used human liver microsomes (HLMs) and expressed cytochromes P450 (P450s) to characterize the metabolism of ebastine and that of its metabolites, hydroxyebastine and carebastine. In HLMs, ebastine was metabolized to desalkyl-, hydroxy-, and carebastine; hydroxyebastine to desalkyl- and carebastine; and carebastine to desalkylebastine. Of the 11 cDNA-expressed P450s, CYP3A4 was the main enzyme catalyzing the N-dealkylation of ebastine, hydroxyebastine, and carebastine to desalkylebastine [intrinsic clearance (CLint) = 0.44, 1.05, and 0.16 μl/min/pmol P450, respectively]. Ebastine and hydroxyebastine were also dealkylated to desalkylebastine to some extent by CYP3A5. Ebastine hydroxylation to hydroxyebastine is mainly mediated by CYP2J2 (0.45 μl/min/pmol P450; 22.5- and 7.5-fold higher than that for CYP3A4 and CYP3A5, respectively), whereas CYP2J2 and CYP3A4 contributed to the formation of carebastine from hydroxyebastine. These findings were supported by chemical inhibition and kinetic analysis studies in human liver microsomes. The CLint of hydroxyebastine was much higher than that of ebastine and carebastine, and carebastine was metabolically more stable than ebastine and hydroxyebastine. In conclusion, our data for the first time, to our knowledge, suggest that both CYP2J2 and CYP3A play important roles in ebastine sequential metabolism: dealkylation of ebastine and its metabolites is mainly catalyzed by CYP3A4, whereas the hydroxylation reactions are preferentially catalyzed by CYP2J2. The present data will be very useful to understand the pharmacokinetics and drug interaction of ebastine in vivo.

Ebastine, a potent and selective histamine H1-receptor antagonist, belongs to a second generation of non-sedating antihistamines but with negligible anticholinergic and antiserotonergic properties (Llupia et al., 2003). Ebastine undergoes extensively sequential metabolism in the liver (Hashizume et al., 1998, 2001). The major primary metabolites identified in humans are hydroxy- and desalkylebastine, and hydroxyebastine is further metabolized to carebastine. In vitro studies indicate that the formation of desalkyl- and hydroxyebastine from ebastine is catalyzed by CYP3A4 and CYP2J2, respectively (Hashizume et al., 2002). The specific hepatic cytochrome P450 (P450) enzymes involved in hydroxy- and carebastine metabolism have not been identified so far, despite some information which could be obtained from the previously published pharmacokinetics of ebastine. After oral administration to experimental animals and humans, ebastine is almost completely metabolized to the pharmacologically active principle, the carboxylated metabolite (carebastine), and other inactive metabolites (desalkylebastine) (Yamaguchi et al., 1994; Rohatagi et al., 2001). The Cmax value of hydroxyebastine, the major metabolite of ebastine in vitro, was approximately 50-fold lower than that of carebastine in vivo (Kang et al., 2004). A recent study by Chaikin et al. (2005) has reported that ketoconazole, a potent inhibitor of CYP3A4-mediated metabolism, decreases the clearance of ebastine, leading to an accumulation of the ebastine, with little effect on the pharmacokinetics of carebastine. However, since they did not measure the change of the intermediate metabolite, hydroxyebastine, it is still open to question which P450 isoforms may contribute to the formation of carebastine.

The objective of this study was to identify and kinetically characterize in vitro the P450 isoforms responsible for the metabolism of ebastine and its metabolites. The information from these studies will allow better understanding of the factors affecting ebastine pharmacokinetics and drug interaction.

ABBRICATIONS: P450, cytochrome P450; HLM, human liver microsome; thio-TEPA, triethylenethiophosphoramide; LC/MS/MS, liquid chromatography-tandem mass spectrometry; CLint, intrinsic clearance.
cose-6-phosphate dehydrogenase were purchased from Sigma-Aldrich (St. Louis, MO). Solvents were high-performance liquid chromatography-grade (Fisher Scientific Co., Pittsburgh, PA) and the other chemicals were of the highest quality available. Pooled (H161) or single-donor (H003, H056, and HK34) human liver microsomes (HLMs), and 11 different human reconstituent P450 isoforms, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2F2, 3A4, and 3A5 (Supersomes), were purchased from BD Gentest (Woburn, MA). Human P450s 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, 2F2, 3A4, and 3A5 are coexpressed with human P450 reductase and cytochrome b5; however, P450s 1A2 and 2D6 are only coexpressed with human P450 reductase. The manufacturer supplied information regarding protein concentration and P450 isoform content.

**Metabolism of Ebastine and Its Metabolites in Human Liver Microsomes or Expressed P450s.** The optimal conditions for microsomal incubation were determined in the linear range for the formation of metabolites of ebastine, hydroxyebastine, and carebastine. The rates of formation of metabolites were proportional to incubation times up to 60 min and protein concentrations up to 1.0 mg/ml at 30 min. In all experiments, ebastine, hydroxyebastine, and carebastine were dissolved and serially diluted with methanol to the required concentrations; the solvent was subsequently removed by evaporation to dryness, under reduced pressure with an AES2010 SpeedVac (Thermo Electron Corporation, Waltham, MA).

The incubation mixtures, containing either 25 μl of microsomes (2.5 mg of protein/ml of stock, prepared from three different human liver microsomal preparations) or 25 μl of cDNA-expressed P450 (diluted to 200 pmol/ml with phosphate buffer, pH 7.4) and various concentrations of ebastine, hydroxyebastine, or carebastine (0–100 μM) was reconstituted in 100 μM phosphate buffer (pH 7.4) and prewarmed for 5 min at 37°C. The reaction was initiated by adding the NADPH-regenerating system (1.3 mM β-nicotinamide adenine dinucleotide phosphate, 3.3 mM glucose 6-phosphate, 3.3 mM MgCl₂, and 1.0 U/ml glucose 6-phosphate dehydrogenase) and further incubated (final volume of 250 μl) for 30 min at 37°C in a shaking water bath. The reaction was terminated by placing the incubation tubes on ice and by immediately adding 100 μl of acetonitrile. After adding the internal standard (terfenadine, 1 μM), the mixture was centrifuged at 1000 g for 5 min at 4°C and aliquots of the supernatant were injected into an LC/MS/MS system.

**Chemical Inhibition Studies with Human Liver Microsomes.** Pooled HLMs (H161, pooled from 27 individual microsomes) and a P450-selective inhibitor were added to an incubation mixture similar to that described above. Ebastine, hydroxyebastine, and carebastine concentrations were 5 μM. The P450 isoform-selective inhibitors used were furafylline (10 μM) for CYP1A2, coumarin for CYP2A6 (100 μM), thio-TEPA for CYP2B6 (5 μM), sulforaphenezol for CYP2C9 (10 μM), S-benzylvinylcarn for CYP19 (1 μM), quinidine for CYP2D6 (10 μM), diethyldithiocarbamate for CYP2E1 (10 μM), and ketocoumarol for CYP3A (1 μM). Astemizole (50 μM), a substrate of CYP3A4 and CYP3A5, was used as competitive inhibitor. Except for the addition of P450 isoform-selective inhibitors, all other incubation conditions were identical to those described previously by our group (Shan et al., 1999, 2002). After adding the internal standard and centrifugation as described above, aliquots of the supernatant were analyzed on an LC/MS/MS system.

**Analytical Procedures.** The concentrations of desalkyl-, hydroxy-, and carebastine were measured by LC/MS/MS as described elsewhere (Kang et al., 2004). The system consisted of an API 3000 LC/MS/MS system (Applied Biosystems, Foster City, CA) equipped with an electrospray ionization interface used to generate positive ions [M + H]⁺. The compounds were separated on a reversed-phase column (Luna C18, 2.0 mm i.d. × 50 mm, 3-μm particle size; Phenomenex, Torrance, CA) with an isocratic mobile phase consisting of acetonitrile and water (40:60 v/v) containing 0.1% formic acid. The mobile phase was eluted using an HP 1100 series pump (Agilent, Wilmington, DE) at a flow rate of 1.04 l/min; auxiliary gas flow, 4.0 l/min; curtain gas flow, 1.44 l/min; orifice voltage, 40 V; ring voltage, 350 V; collision gas (nitrogen) pressure, 3.58 × 10⁻³ Torr. The mass transitions used for quantification of hydroxyebastine and carebastine were m/z 486.7 → 167.1, 500.6 → 167.1, and 472.7 → 436.0 respectively (collision energy 40 eV); that for desalkylebastine was m/z 268.4 → 167.1 (collision energy 15 eV). The analytical data were processed by Analyst software (version 1.2; Applied Biosystems).

**Data Analysis.** Results are expressed as means ± S.D. of estimates obtained from three different liver microsome preparations in duplicate experiments. The apparent kinetic parameters of ebastine, hydroxyebastine, and carebastine metabolism were determined by fitting the unweighted kinetic data from HLMs and expressed P45Os to a one-enzyme Michaelis-Menten equation or a sigmoidal (Hill) equation model [V = Vmax /[1 + Ke/[S + [S]₀]], or a substrate inhibition model [V = Vmax/[1 + Ke/[S + [S]₀]]]. Calculated parameters were maximum rate of metabolite formation (Vmax), Michaelis constant (Ke), intrinsic clearance (CLint = Vmax/Ke), Hill coefficient (n), and substrate inhibition constant (Ks). The percentages of inhibition were calculated by the ratio of the rate of metabolite formation with and without the specific inhibitor. Calculations were performed using WinNonlin software (Pharsight, Mountain View, CA).

**Results and Discussion**

We present here a detailed characterization of the in vitro metabolism of ebastine and its metabolites using human liver P450 enzymes as summarized in Fig. 1. We have demonstrated that: 1) ebastine undergoes primary oxidative hydroxylation of the methyl groups of the tert-butyl moiety of ebastine to hydroxyebastine and dealkylation at the alicyclic bond attached to the piperidine nitrogen to form desalkylebastine, and secondary metabolism to carebastine; 2) the major route(s) of ebastine metabolism is mainly catalyzed by CYP2J2, CYP3A4, and CYP3A5; and 3) CYP2J2 exhibits atypical kinetics. These data should provide a scientific base upon which to build focused clinical studies that will help in understanding the pharmacokinetics and pharmacogenetic factors influencing ebastine therapeutic efficacy, drug interactions, and safety.

The formation of metabolites followed simple Michaelis-Menten kinetics with 0–100 μM ebastine, hydroxyebastine, or carebastine, suggesting the involvement of a single enzyme or more than one enzyme with similar affinity (Fig. 2). A similar kinetic profile has been observed with ebastine hydroxylation in human intestinal microsomes (Hashizume et al., 2002) and CYP2J2-mediated terfenadine hydroxylation in recombinant CYP2J2 (Parikh et al., 2003). The kinetic parameters are summarized in Table 1. The formation of carebastine from hydroxyebastine by cCYP2J2 exhibited substrate inhibition (Fig. 3), unlike the kinetic data obtained in HLMs, which were characterized by a hyperbolic Michaelis-Menten equation (Fig. 2). Comparison of the goodness-of-fit values generated from these data indicates that a substrate inhibition enzyme kinetic model provided a better fit than did other models. The corresponding Eadie-Hofstee plot indicated a “hook” in the upper region of this plot (Fig. 3B, inset), which is characteristic of substrate inhibition. The Kₐᵣᵣ was 436.0, respectively (collision energy 40 eV); that for desalkylebastine was m/z 268.4 → 167.1 (collision energy 15 eV). The analytical data were processed by Analyst software (version 1.2; Applied Biosystems).

**Fig. 1.** Proposed metabolic pathway of ebastine in human liver microsomes.
EBASTINE METABOLISM BY CYP2J2 AND CYP3A

CYP3A4, and slightly inhibited by ketoconazole, a potent CYP3A-selective inhibitor (Fig. 4A). Second, expressed human CYP2J2 metabolized ebastine to hydroxyebastine, whereas other P450 isoforms did not (Fig. 5A). We also noted that recombinant human CYP3A4 formed hydroxyebastine from ebastine, but the contributions of this isofom to ebastine metabolism appear minor: 1) the CLint for hydroxyebastine formation by CYP3A4 was 22.5-fold lower than that obtained in recombinant human CYP2J2 (Table 2); and 2) a CYP3A-specific inhibitor (ketoconazole) slightly inhibited (~25%) the rates of formation of hydroxyebastine in HLMs (Fig. 4A). These qualitative findings are consistent with the earlier work which had reported that CYP2J2 is the predominant ebastine hydroxylase in human intestinal microsomes (Hashizume et al., 2002).

The specific hepatic P450 enzymes involved in hydroxy- and carebastine metabolism have not been identified so far. Both ketoconazole (CYP3A inhibitor) and astemizole (substrate of CYP2J2 and CYP3A4) (Matsumoto et al., 2003) markedly inhibited (>82%) car- and desalkylebastine formation (Fig. 4, B and C). Human recombinant CYP2J2 and CYP3A4 formed carebastine from hydroxyebastine (Fig. 5B). Similar to desalkylebastine formation from ebastine, desalkyle- bastine formation from hydroxy- and carebastine was mediated by CYP3A enzyme only (Fig. 5). These results suggest that desalkyle- bastine formation from hydroxy- and carebastine was clearly mediated by CYP3A, and hydroxyebastine was oxidized to carebastine by CYP2J2 and CYP3A4. It would be interesting to consider the enz-ymes responsible for metabolism of terfenadine alcohol, which posses- ses chemical structural similarities to hydroxyebastine. Terfenadine alcohol also has two similar major metabolic pathways of carboxylation and N-dealkylation. Unlike hydroxyebastine, carboxyla-

**TABLE 1**

*Kinetic parameters for the metabolism of ebastine, hydroxyebastine, and carebastine in human liver microsomes*

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<td>Ebastine Dealkylation</td>
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<td>Hydroxylation</td>
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\( V_{\text{max}} \) and \( K_{\text{m}} \) estimated from these data, respectively, were 0.75 \( \mu \)M, 9.86 pmol/min/pmol P450, and 5.55 \( \mu \)M (Table 2). Similar substrate inhibition profiles have been observed previously with CYP2B6-mediated 8,14-dihydroxyefavirenz formation (Ward et al., 2003) and CYP3A-mediated triazolam hydroxylation (Schrag and Wienkers, 2001), which are suggestive of multiple substrate-binding sites (or multiple regions within a single active site). To our knowledge, this is the first report of CYP2J2-mediated substrate inhibition. Although this observation may have no clinical relevance because the expected concentrations of the hydroxyebastine in human plasma after taking the usual dosage of ebastine (Kang et al., 2004) are much lower than the substrate inhibition constants we obtained here, it may offer insight into the characteristics of the enzyme.

We provide evidence that ebastine hydroxylation is predominantly catalyzed by CYP2J2. First, formation rates of hydroxyebastine were potently inhibited (~70%) by astemizole, a substrate of CYP2J2 and

**FIG. 2.** Kinetics for the metabolite formation from ebastine (A), hydroxyebastine (B), and carebastine (C) in three human liver microsomes. An increasing concentration of substrates (0–100 \( \mu \)M) was incubated with human liver microsomes and an NADPH-generating system at 37°C for 30 min. The velocity (pmol/min/mg protein) versus substrate concentration was fit to a Michaelis-Menten equation (see “Data Analysis” under Materials and Methods). Each point represents the average obtained from three different human liver microsomes.

**FIG. 3.** Kinetics for the metabolite formation from ebastine (A) and hydroxyebastine (B) in recombinant human CYP2J2. An increasing concentration of substrates (0–100 \( \mu \)M) was incubated with recombinant human CYP2J2 and an NADPH-generating system at 37°C for 30 min. The velocity (pmol/min/pmol P450) versus ebastine or hydroxyebastine concentration was fit to a Michaelis-Menten equation or substrate inhibition equa-

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we performed an in vitro metabolism study of ebastine as well as its metabolites, hydroxy- and carebastine, using human liver microsomes. The intrinsic clearance of hydroxyebastine was much higher than that of ebastine and carebastine (Table 1). The ratio of maximum dealkylation rate ($V_{\text{max}}$) of hydroxyebastine was also higher than that of ebastine and carebastine. In contrast to hydroxyebastine, carebastine showed low enzyme affinity and metabolic rate, thus resulting in relatively low metabolic clearance. In expressed P450s, the formation of hydroxy- and desalkylebastine from ebastine was catalyzed predominately by CYP2J2 and CYP3A4, respectively (Table 2). When hydroxyebastine was used as a substrate, we concluded that CYP2J2 and CYP3A4 isoforms were responsible for oxidation of hydroxyebastine, whereas CYP3A4 and CYP3A5 were responsible for desalkylebastine formation. Kinetic analysis indicated that the intrinsic clearance of hydroxyebastine was much higher than that of ebastine and carebastine (Table 1). These results provide evidence that once the hydroxyebastine is formed, it undergoes a rapid biotransformation to yield car- and desalkylebastine. Carebastine seems to be relatively metabolically stable to ebastine and hydroxyebastine, supporting the in vivo findings that carebastine is a major metabolite of ebastine. In addition, it is important to note, however, that CYP2J2 is also expressed in the extrahaepatic tissues such as heart, intestine, and kidney. Therefore, in vitro metabolism study using extrahaepatic tissues such as intestinal microsomes is necessary to determine the contribution of extrahaepatic tissues in the metabolism of ebastine and its metabolites.

The identification of CYP2J2 as the catalyst of hydroxylation of ebastine and hydroxyebastine (Fig. 1) may allow us to use ebastine to probe this enzyme system. Despite the identification of a growing list of clinically important drugs (Hashizume et al., 2001; Matsumoto et al., 2003; Parikh et al., 2003) and endogenous substances (Wu et al., 1996; Hashizume et al., 2002) as substrates of CYP2J2 in vitro, it remains difficult to determine or predict its clinical consequences because of the unavailability of a specific and safe probe to measure by CYP3A4 (Ling et al., 1995). However, the previous study did not evaluate CYP2J2-mediated metabolism. Based on recent results (Parikh et al., 2003), which reported that CYP2J2 is a major enzyme involved in terfenadine (structural analog of ebastine) hydroxylation, we can speculate that CYP2J2 as well as CYP3A4 may be involved in terfenadine acid formation from terfenadine alcohol.

After oral administration to humans, ebastine is almost completely metabolized to car- and desalkylebastine (Kang et al., 2004; Lasseter et al., 2004). It is inconsistent with the in vitro findings, which reported that ebastine is predominantly metabolized to hydroxy- and desalkylebastine (Hashizume et al., 1998, 2001, 2002). To clarify this,
the activity of the enzyme in vivo. Our data indicate that ebastine hydroxylation is a specific in vitro reaction marker of CYP2J2 and may have utility as a phenotyping tool to study the role of this enzyme in human drug metabolism.

Department of Pharmacology and PharmacoGenomics Research Center, Inje University College of Medicine, Busan, Korea (K.-H.L., M.-G.K., D.-J.L., Y.-J.Y., M.-J.K., J.-H.S., J.-G.S.); Department of Surgery, Busan Paik Hospital, Busan, Korea (C.S.C., Y.K.C.); Frontier Inje Research for Science and Technology, Inje University, Busan, Korea (K.-H.L., M.-G.K., D.-J.L., J.-H.S., M.-J.K., J.-G.S.); and Technology, Frontier Inje Research for Science and Technology, Inje University, Busan, Korea (C.S.C., Y.K.C.); and Pharmacology, Departments of Medicine and Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana (Z.D.)

References


Address correspondence to: Dr. Jae-Gook Shin, Dept. of Pharmacology and PharmacoGenomics Research Center, # 633–165, Gaegum-Dong, Busanjin-Gu, Busan 614–735, South Korea. E-mail: phshinjg@inje.ac.kr