Short Communication

Impact of the *CYP2C19**17 Allele on the Pharmacokinetics of Omeprazole and Pantoprazole in Children: Evidence for a Differential Effect^S

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ABSTRACT:

The impact of the *CYP2C19**17 allele on the pharmacokinetics of pantoprazole and omeprazole in previously studied children ($n = 40$) was explored. When pantoprazole area under the plasma concentration versus time curve (AUC) was examined as a function of *CYP2C19* genotype, a significantly lower AUC was observed for subjects identified as *CYP2C19**1/*1 and *1/*17. For

pantoprazole, a statistically significant relationship was observed between *CYP2C19* genotype and both dose-corrected AUC ($p < 0.0001$) and the apparent elimination rate constant (K_{el} ; $p = 0.0012$); no significant genotype-phenotype relationships were observed for omeprazole.

*CYP2C19**17 is characterized by $-806C>T$ (rs12248560) in the regulatory gene region and increases transcription levels. Subjects carrying *CYP2C19**17 have higher *CYP2C19* activity toward mephenytoin and omeprazole (Sim et al., 2006). There is limited information regarding the effect of *CYP2C19**17 on the pharmacokinetics of *CYP2C19* substrates in adults (Rudberg et al., 2008), and only a single study assessed the clinical outcome (Kurzawski et al., 2006). The goals of this exploratory study were as follows: 1) to characterize the effect of *CYP2C19* genotype, especially the *CYP2C19**17 allele, on the pharmacokinetics of two proton pump inhibitors (PPIs), omeprazole and pantoprazole, in a pediatric cohort and 2) to determine the frequency of *CYP2C19**17 in population samples that represented different ethnic backgrounds.

Materials and Methods

Clinical Trials. The current investigation was enabled by a reassessment of data and samples available from previous pharmacokinetic studies of omeprazole (Kearns et al., 2003b) and pantoprazole (Kearns et al., 2008) conducted in pediatric populations for the purpose of product labeling. The Institutional Review Boards at participating institutions approved both investigations, and subjects were enrolled by parental permission and patient assent, as appropriate.

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Conflict of Interest: G.L.K. has served as a paid consultant for AstraZeneca, L.P. and Wyeth regarding the development of the pediatric programs for omeprazole and pantoprazole.

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ate. The approvals contained provisions for data reanalysis and expanded genotype analysis of stored DNA specimens. Study designs, complete methods, and results were previously described in detail (Kearns et al., 2003b, 2008), and therefore only pertinent information is recapitulated in this brief communication.

The omeprazole study comprised 37 subjects, 23 of whom yielded evaluable pharmacokinetic data (Kearns et al., 2003b); these subjects were further investigated for *CYP2C19**17. Ten or 20 mg of omeprazole was administered as a single solid oral dose to subjects aged 9.5 ± 3.8 years (mean $\pm$ S.D.; range, 2–16 years) and weighing 26.2 ± 15.1 kg (range, 11–75 kg), and 10 participants were male.

The pantoprazole study (Kearns et al., 2008) reported two cohorts of children, an oral and an intravenous study arm. The orally dosed cohort consisted of 24 subjects (16 male) aged 10.8 ± 3.4 years (range, 5–16 years) and weighing 45.0 ± 19.9 kg (range, 20–90 kg). Subjects received a single oral dose of 20 or 40 mg of pantoprazole. DNA was available for all 24 subjects. The intravenous cohort comprised 16 of the originally enrolled 19 children (three subjects were excluded from pharmacokinetic analysis due to incomplete data). Study participants received a single 0.8 or 1.6 mg/kg i.v. dose of pantoprazole. Subjects were 8.1 ± 4.4 years of age (range, 2–14 years) and weighed 37.1 ± 27.0 kg (range, 11–109 kg). Note that subjects who participated in the omeprazole and pantoprazole studies were not related and participated in only one of the investigations.

Subjects for Allele Frequency Determination. The DNA samples of the ethnic panels (whites, $n = 107$; African Americans, $n = 114$; Hispanics $n = 107$) were isolated from discarded, anticoagulated blood obtained for routine clinical management of hospitalized patients after all identifiers had been removed, as required by our Institutional Review Board exempt protocol.

Genotyping. Genomic DNA was isolated with the QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, CA). Genotyping of *CYP2C19**2–*8, *10, *12, and *17 was performed on the PPI study subjects with polymerase chain reaction-restriction fragment length polymorphism procedures, as detailed in the supplemental table. *CYP2C19**17 testing comprised two single nucleotide polymorphisms (SNPs), $-806C>T$ and $-3402C>T$, which reportedly are in complete linkage (Sim et al., 2006). Subjects were grouped according to their genotype into six groups: *CYP2C19**1/*1, *1/*17, *2/*17, *2/*2, *17/*17, and

ABBREVIATIONS: PPI, proton pump inhibitor; SNP, single nucleotide polymorphism; AUC, area under the plasma concentration versus time curve; ANOVA, analysis of variance; K_{el} , elimination rate constant.

*1/*2 and *1/*4, which were combined into a single group. The DNA samples of the ethnic panels were only genotyped for *CYP2C19**17.

Statistical Analyses. Associations between *CYP2C19* genotype and dose-corrected area under the plasma concentration versus time curve (AUC) and elimination rate constant (K_{el}) for both omeprazole and pantoprazole were determined by analysis of variance (ANOVA). Statistically significant differences ($\alpha = 0.05$) were further investigated by post hoc analysis using Tukey's honestly significant difference test. All statistical analyses were conducted by using JMP software (version 8.0.2; SAS Institute, Inc., Cary, NC).

Results

The allele frequencies for the pantoprazole study cohorts (oral and intravenous combined, $n = 40$) were as follows: *CYP2C19**1, 0.59; *CYP2C19**2, 0.20; *CYP2C19**4, 0.01; and *CYP2C19**17, 0.23. No homozygous *CYP2C19**17/*17 individuals were observed. In the omeprazole cohort ($n = 23$), allele frequencies were 0.52, 0.26, and 0.22 for *CYP2C19**1, *2, and *17, respectively. Frequencies for all subjects enrolled in the original omeprazole study ($n = 37$) are given in Table 1. The frequency of the *CYP2C19**17 allele was also determined in DNA samples from three ethnic populations and was comparable with previously published data (Table 1). Allele frequencies were in Hardy-Weinberg disequilibrium. These observed *CYP2C19**17 allele frequencies predict that 4.8, 4.4, and 1.4% of whites, African Americans, and Hispanics are ultrarapid metabolizers with a homozygous *CYP2C19**17/*17 genotype. The two *CYP2C19**17-defining SNPs were linked in all subjects, with the exception of one African American. This subject carried -806C>T, the SNP believed to increase *CYP2C19* expression levels (Sim et al., 2006), but lacked -3402C>T.

Selected pharmacokinetic parameters, i.e., apparent terminal K_{el} and AUC normalized for drug dose (mg · h/l per 1 mg/kg dose), from the omeprazole and pantoprazole studies (Kearns et al., 2003b, 2008) were examined for their association with *CYP2C19* genotype. The relationships for K_{el} and AUC for pantoprazole are shown in Fig. 1, A and B, respectively. The relationship for omeprazole K_{el} or AUC is shown in Fig. 1, C and D, respectively.

ANOVA revealed a statistically significant relationship between *CYP2C19* genotype and both dose-corrected AUC ($p < 0.0001$) and K_{el} ($p = 0.0012$) for pantoprazole but not for omeprazole. In the case of pantoprazole, neither of the pharmacokinetic parameters was dif-

ferent between the *CYP2C19**1/*1 and *CYP2C19**1/*17 groups, but in both cases, groups with two functional alleles were statistically significantly different from groups that contained only one functional allele, e.g., the *CYP2C19**1/*2 and *CYP2C19**2/*17 groups. In contrast, no statistically significant relationships were observed for omeprazole. Differences between pantoprazole and omeprazole with respect to *CYP2C19* genotype-phenotype relationships were most evident for K_{el} , as can be seen in Fig. 1, B versus D.

Discussion

PPIs have been used extensively in both adult (Bardou and Martin, 2008) and pediatric (Tafari et al., 2009) patients to treat a variety of conditions (e.g., gastroesophageal reflux disease, ulcer disease, Zollinger-Ellison syndrome, *Helicobacter pylori* infection, nonulcer-related dyspepsia, drug-associated gastritis) where increasing intragastric pH is considered to be of therapeutic benefit. Recent data generated from a pediatric cohort suggest that long-term PPI use for time periods up to 11 years is safe, well tolerated, and produces few adverse reactions (Hassall et al., 2007). As previously reviewed (Klotz, 2006; Bardou and Martin, 2008) and reported by others (Hunfeld et al., 2008; Rocha et al., 2008), the pharmacokinetics and pharmacodynamics of the PPIs are primarily dependent upon the activity of the polymorphically expressed *CYP2C19* and, to some degree, on *CYP3A4*.

The quantitative significance of the *CYP2C19**17 allele with respect to the biotransformation of the PPIs has been demonstrated (Kurzwski et al., 2006; Sim et al., 2006; Baldwin et al., 2008; Hunfeld et al., 2008) in adults. Our data from a single-dose pharmacokinetic study of pantoprazole, given as a racemic mixture (Kearns et al., 2008), also suggests this dependence in a population of pediatric patients (Fig. 1, A and B). This finding was not unexpected, given the comparable frequency of the *CYP2C19**17 allelic variant between pediatric and adult populations (Table) and the known ontogenic pattern for *CYP2C19* gene expression (Hines, 2008). However, the data presented in this brief report are not sufficient to attribute a higher level of functional activity in vivo to the *CYP2C19**17 allele relative to the reference *CYP2C19**1 allele.

The apparent absence of a genotype-phenotype relationship for dose-corrected AUC and K_{el} for omeprazole was totally unexpected given previously published data from adults, which suggests [despite a very small ($n = 16$) subject cohort] that the impact of *CYP2C19* allelic variants on the systemic exposure (AUC) of omeprazole and pantoprazole was comparable (Hunfeld et al., 2008). The reasons underlying the discrepant findings between omeprazole and pantoprazole in pediatric patients as presented in the current study are not entirely clear. Variability associated with pharmacokinetic parameters within a genotype group composed of a relatively small number of subjects (a common feature for pediatric pharmacokinetic studies conducted to support product labeling) (Abdel-Rahman et al., 2007) may be one factor that contributed to the lack of association between genotype and omeprazole AUC (Fig. 1C). However, values for omeprazole K_{el} appeared to be completely independent of *CYP2C19* genotype. In addition, our previous study of pantoprazole (Kearns et al., 2008) demonstrated that the pharmacokinetic parameters were not associated with route of administration.

Another possibility relates to differences in the relative contributions of *CYP2C19* and *CYP3A4* to the overall biotransformation of omeprazole compared with pantoprazole (Savarino et al., 2009). The observed genotype-phenotype relationships presented in this report imply that *CYP2C19* is quantitatively more important to pantoprazole elimination than it is to omeprazole elimination, at least within the age range of children included in the original studies. Given that

TABLE 1

*CYP2C19**17 allele frequencies in different ethnic groups and patient populations

Population	n Subjects	Frequency <i>CYP2C19</i> *17	Reference
Pantoprazole cohort	40	0.23	This study
Omeprazole cohort	37 (23)	0.19 (22)	This study ^a
Caucasian	107	0.22	This study; DNA repository ^b
African American	114	0.21	This study; DNA repository ^b
Hispanic	108	0.12	This study; DNA repository ^b
Norwegians	332	0.22	(Rudberg et al., 2008)
Swedish	314	0.18	(Sim et al., 2006)
Polish	125	0.27	(Kurzwski et al., 2006)
Greek	283	0.20	(Ragia et al., 2009)
Ethiopian	190	0.18	(Sim et al., 2006)
Chinese	384	0–0.04	(Chen et al., 2008)
Japanese	265	0.013	(Sugimoto et al., 2008)

^a Frequency for all subjects initially enrolled in the omeprazole study. Kinetic data were obtained on a subset of 23 children.

^b DNA repository refers to samples maintained in the laboratory of the authors; ethnicity was determined by self-report.

FIG. 1. Relationship between *CYP2C19* genotype and the AUC (mg · h/L per 1 mg/kg; A and C), and the apparent terminal K_{el} (B and D) for pantoprazole and omeprazole, respectively. Boxes reflect the interquartile range, whereas the lines in the boxes depict the mean values; whiskers indicate the 10th and 90th percentiles, respectively. Open and closed symbols in A and B represent subjects who received oral and intravenous pantoprazole, respectively. *CYP2C19* genotypes and number of subjects in each genotype group are given at the bottom of the graphs. Horizontal lines above the boxes in A and B join genotype groups that are not significantly different from each other as determined by Tukey's honestly significant difference test after an initial ANOVA. Genotype groups not connected by a line in A and B (pantoprazole) are significantly different from each other (AUC, $p < 0.0001$; K_{el} , $p = 0.0012$). For omeprazole (C and D), no statistically significant differences were detected ($p = 0.099$). Statistical comparisons were conducted by using JMP software (version 8.0.2; SAS Institute Inc.).

CYP2C19 gene-dose effects have been consistently observed in adults, this observation implies that developmental changes in non-*CYP2C19*-mediated pathways (i.e., *CYP3A4*) may result in those alternative pathways being quantitatively more important to omeprazole elimination than *CYP2C19* and thereby obscuring the *CYP2C19* genotype-phenotype relationship. Although speculative at this time, such a hypothesis could be tested by comparing the relative amounts of hydroxylated *CYP2C19*-generated metabolites to *CYP3A4*-mediated sulfone metabolites recovered in the urine of children compared with adults. The potential impact of intestinal *CYP2C19* and *CYP3A4* on the oral bioavailability of omeprazole (Hosohata et al., 2009), the potential impact of multiple (versus single) dosing protocols on PPI biotransformation (Schwab et al., 2005), and, finally, the potential, age-associated differences in the relative activity of the enzymes responsible for the clearance of the two drugs studied (Kearns et al., 2003a) may also be considered. However, the pharmacokinetic data on which the current analysis is based do not allow us to address these issues at the present time.

Despite these potential limitations, our data illustrate that inclusion of the *CYP2C19**17 allele in assessing pharmacokinetic data from a cohort of pediatric patients who received either omeprazole or pantoprazole revealed apparent agent-specific differences in the genotype-phenotype association. These results do not infer information of therapeutic significance. Finally, our findings emphasize

the importance of considering multiple routes of drug biotransformation and their relative quantitative importance when using drug-metabolizing enzyme genotype to infer information about the pharmacokinetics of drugs within a given pharmacologic class.

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