Short Communication

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

Received October 2, 2009; accepted March 11, 2010

ABSTRACT:
The impact of the CYP2C19*1 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 (Kel; 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.

This work was supported in part by the National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Human Development [Grant 1U01-HD31313-16 (Network of Pediatric Pharmacology Research Units) (infrastructure and salary support to J.S.L. and G.L.K.); and AstraZeneca, L.P. and Wyeth, who provided funding to support pharmacokinetic studies of omeprazole and pantoprazole, respectively.

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.

Article, publication date, and citation information can be found at http://dmd.aspetjournals.org.

The online version of this article (available at http://dmd.aspetjournals.org) contains supplemental material.

Abbreviations: PPI, proton pump inhibitor; SNP, single nucleotide polymorphism; AUC, area under the plasma concentration versus time curve; ANOVA, analysis of variance; Kel, 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 (α = 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/*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 different 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.

TABLE 1

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

<table>
<thead>
<tr>
<th>Population</th>
<th>n Subjects</th>
<th>Frequency CYP2C19*17</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole cohort</td>
<td>40</td>
<td>0.23</td>
<td>This study</td>
</tr>
<tr>
<td>Omeprazole cohort</td>
<td>37 (23)</td>
<td>0.19 (22)</td>
<td>This study</td>
</tr>
<tr>
<td>Caucasian</td>
<td>107</td>
<td>0.22</td>
<td>This study; DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>repository*</td>
</tr>
<tr>
<td>African American</td>
<td>114</td>
<td>0.21</td>
<td>This study; DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>repository*</td>
</tr>
<tr>
<td>Hispanic</td>
<td>108</td>
<td>0.12</td>
<td>This study; DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>repository*</td>
</tr>
<tr>
<td>Norwegians</td>
<td>332</td>
<td>0.22</td>
<td>(Rudberg et al., 2008)</td>
</tr>
<tr>
<td>Swedish</td>
<td>314</td>
<td>0.18</td>
<td>(Sim et al., 2006)</td>
</tr>
<tr>
<td>Polish</td>
<td>125</td>
<td>0.27</td>
<td>(Kurzawski et al., 2006)</td>
</tr>
<tr>
<td>Greek</td>
<td>283</td>
<td>0.20</td>
<td>(Ragia et al., 2009)</td>
</tr>
<tr>
<td>Ethiopian</td>
<td>193</td>
<td>0.18</td>
<td>(Sim et al., 2006)</td>
</tr>
<tr>
<td>Chinese</td>
<td>384</td>
<td>0.0–0.04</td>
<td>(Chen et al., 2008)</td>
</tr>
<tr>
<td>Japanese</td>
<td>265</td>
<td>0.013</td>
<td>(Sugimoto et al., 2008)</td>
</tr>
</tbody>
</table>

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

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

Discussion

PPIs have been used extensively in both adult (Bardou and Martin, 2008) and pediatric (Tafuri 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 (Kurzawski 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
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.

Acknowledgments. We gratefully acknowledged Jacob Brown for technical assistance.

References


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