Evaluation of the Relationship between Sex, Polymorphisms in CYP2C8 and CYP2C9, and Pharmacokinetics of Angiotensin Receptor Blockers

Teresa Cabaleiro, Manuel Román, Dolores Ochoa, María Talegón, Rocío Prieto-Pérez, Aneta Wojnicz, Rosario López-Rodríguez, Jesús Novalbos, and Francisco Abad-Santos

Service of Clinical Pharmacology, Hospital Universitario de la Princesa, Instituto Teófilo Hernando, Instituto de Investigación Sanitaria Princesa, Madrid, Spain (T.C., M.R., D.O., M.T., R.P.-P., A.W., J.N., F.A.-S.); Liver Unit, Gastroenterology Service, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa, Madrid, Spain (R.L.-R.); and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain (R.L.-R., F.A.-S.)

Received April 17, 2012; accepted November 1, 2012

ABSTRACT

Angiotensin II receptor blockers (ARBs) are used to treat hypertension. Most ARBs are metabolized by CYP2C9. The aim of this study is to evaluate the possible association between sex, polymorphisms in the CYP2C8 and CYP2C9 genes, and the pharmacokinetics of losartan, candesartan, and telmisartan. The study population comprised 246 healthy volunteers from seven single-dose clinical trials: 64 from two candesartan studies, 43 from a telmisartan study, 36 from a losartan study, and 103 from three valsartan studies. DNA was extracted from blood samples and single-nucleotide polymorphisms in the CYP2C8 (CYP2C8*2, CYP2C8*3, CYP2C8*4, CYP2C8*5) and CYP2C9 (CYP2C9*2, CYP2C9*3) genes were evaluated using real-time polymerase chain reaction. Sex only affected telmisartan pharmacokinetics, since women showed a higher telmisartan C\text{max} than men (590.5 ± 75.8 ng/ml versus 282.1 ± 30.8 ng/ml; P ≤ 0.01). CYP2C9 variants were associated only with losartan pharmacokinetics: the half-life of losartan was higher in CYP2C9*3 allele carriers (0.3 ± 0.4 hours) than in volunteers with the wild-type genotype (2.3 ± 0.1 hours) (P ≤ 0.05). CYP2C8 polymorphisms were associated only with valsartan pharmacokinetics, since *2 allele carriers showed faster clearance (1.07 ± 0.57 l/h kg) than those with the wild-type genotype (0.48 ± 0.72 l/h kg; P ≤ 0.01) and carriers of the *3 allele (0.35 ± 0.49 l/h kg; P ≤ 0.001). These results suggest that genotypes for CYP2C9 and CYP2C8 are relevant to the pharmacokinetics of losartan and valsartan, respectively, but not the pharmacokinetics of candesartan or telmisartan.

Introduction

Angiotensin II type 1 receptor blockers (ARBs) are used in the treatment of hypertension (Mori et al., 2006). Losartan (Losartan Alter, Cozaar) was the first selective ARB used in the treatment of hypertension and congestive heart failure (Timmermans et al., 1993). Most ARBs are metabolized by CYP2C9 (Israili, 2000; Schmidt and Schieffer, 2003; Unger, 2003). Losartan, valsartan (Valsartan Alter, Diovan), and candesartan (Candesartan Alter, Atacand) have affinity for the Angiotensin type 1 receptor blockers (ARBs) are used to treat hypertension and congestive heart failure (Timmermans et al., 1993). Losartan, valsartan, candesartan, and telmisartan. The study population comprised 246 healthy volunteers from seven single-dose clinical trials: 64 from two candesartan studies, 43 from a telmisartan study, 36 from a losartan study, and 103 from three valsartan studies. DNA was extracted from blood samples and single-nucleotide polymorphisms in the CYP2C8 (CYP2C8*2, CYP2C8*3, CYP2C8*4, CYP2C8*5) and CYP2C9 (CYP2C9*2, CYP2C9*3) genes were evaluated using real-time polymerase chain reaction. Sex only affected telmisartan pharmacokinetics, since women showed a higher telmisartan C\text{max} than men (590.5 ± 75.8 ng/ml versus 282.1 ± 30.8 ng/ml; P ≤ 0.01). CYP2C9 variants were associated only with losartan pharmacokinetics: the half-life of losartan was higher in CYP2C9*3 allele carriers (0.3 ± 0.4 hours) than in volunteers with the wild-type genotype (2.3 ± 0.1 hours) (P ≤ 0.05). CYP2C8 polymorphisms were associated only with valsartan pharmacokinetics, since *2 allele carriers showed faster clearance (1.07 ± 0.57 l/h kg) than those with the wild-type genotype (0.48 ± 0.72 l/h kg; P ≤ 0.01) and carriers of the *3 allele (0.35 ± 0.49 l/h kg; P ≤ 0.001). These results suggest that genotypes for CYP2C9 and CYP2C8 are relevant to the pharmacokinetics of losartan and valsartan, respectively, but not the pharmacokinetics of candesartan or telmisartan.

This work was partially funded by Fundación Teófilo Hernando, a nonprofit foundation linked to Universidad Autónoma de Madrid, and the Fundación de Investigación Biomédica del Hospital Universitario de la Princesa.

dx.doi.org/10.1124/dmd.112.046292.

This article has supplemental material available at dmd.aspetjournals.org.

ABBREVIATIONS: ARB, angiotensin II receptor blocker; AUC, area under the curve; Cl, total drug clearance; C\text{max}, maximum plasma concentration; C\text{t}, last measured concentration; P450, cytochrome P450; k\text{e}, apparent terminal elimination rate; PK, pharmacokinetics; t\text{1/2}, half-life; T\text{max}, time to reach C\text{max}.
genotype, and less than 2.5% of individuals express the *2/*2, *2/*3, and *3/*3 genotypes (Lee et al., 2002).

The most frequent CYP2C8 variants are *2 (Ile269Phe), *3 (linked polymorphisms Arg139Lys and Lys399Arg), *4 (Ile264Met), and *5 (rare non-synonymous polymorphic allele). CYP2C8*2, CYP2C8*3, and CYP2C8*4 were associated with reduced enzyme activity (Dai et al., 2001; Daily and Aquilante, 2009; Gao et al., 2010), although some studies have shown higher capacity to metabolize repaglinide, rosiglitazone, pioglitazone, and R-ibuprofen in CYP2C8*3 carriers (Niemi et al., 2003; Kirchheiner et al., 2006; Tornio et al., 2008; López-Rodríguez et al., 2008). Allelic frequencies were 80, 2, 11, 7, and 0% for CYP2C8*1, *2, *3, *4, and *5 in a Spanish population, respectively (López-Rodríguez et al., 2008).

Single-nucleotide polymorphisms in CYP2C8 and CYP2C9 that reduce catalytic activity could modify the clinical benefits of ARBs. Therefore, the aim of this study was to evaluate the possible association between polymorphisms in the CYP2C8 and CYP2C9 genes and the pharmacokinetics of the most commonly used ARBs (losartan, valsartan, candesartan, and telmisartan) in Caucasian individuals. We also evaluated the effect of sex on the metabolism of these drugs.

Materials and Methods

Study Design. Our study population comprised 246 Caucasian healthy adult volunteers enrolled in various bioequivalence single-dose clinical trials performed at the Hospital Universitario de la Princesa (Madrid, Spain) between 2006 and 2012. We genotyped 36 subjects receiving losartan (50 mg). 27 of 36 volunteers participating in a candesartan study (32 mg), 37 of 48 enrolled in a valsartan study (160 mg), 34 of 54 participating in another valsartan study (320 mg), and 37 of 48 enrolled in a telmisartan study (80 mg), 32 of 36 enrolled in a valsartan study (160 mg), 34 of 54 in participating in another valsartan study (320 mg), and 37 of 48 enrolled in a valsartan-hydrochlorothiazide study (25–320 mg). All subjects receiving candesartan were excluded from the analysis in the volunteers treated with telmisartan, only one subject had the CYP2C9*2 allele and CYP2C8*4 allele, which were also excluded from the analysis. In the losartan group, only one subject had the CYP2C8*2 allele and CYP2C8*4 allele, which was also excluded from the analysis. In the volunteers treated with losartan, only one subject had the CYP2C8*2 allele, which was excluded from the analysis. CYP2C9 genotypes were classified in three groups: the wild-type genotype (*1/*1), allele *2 carriers (including *2/*4 genotype but not *2/*3), allele *3 carriers (including genotypes *2/*3 and *3/*4), and allele *4 carriers (excluding *2/*4 and *3/*4). Since the *5 allele was present in only one subject, it was excluded from the analysis. In the volunteers treated with losartan, only one subject had the CYP2C9*2 allele and CYP2C8*4 allele, which were also excluded from the analysis. In the losartan group, only one subject had the CYP2C8*2 allele, which was excluded from the analysis. CYP2C9 genotypes were classified in three groups: the wild-type genotype (*1/*1), allele *2 carriers, and allele *3 carriers (including the *2/*3 genotype).

Pharmacogenetics and Pharmacokinetics of ARBs 225

Results

Sample Description and Genotype Frequencies. Sex distribution and age and weight are indicated in Table 1. Weight was higher in men than in women for all of the ARBs studied. CYP2C8 and CYP2C9 genotype frequencies are shown in Table 2; differences in polymorphism distribution between ARBs were established using a χ² test (P < 0.001). Considering all subjects together, allelic frequencies were 76.0, 15.0, and 8.9% for CYP2C9*1, *2, and *3, respectively, and 76.2, 5.3, 14.2, 4.1, and 0.2% for CYP2C8*1, *2, *3, *4, and *5, respectively. CYP2C9*2 and CYP2C8*3 are well established to be in strong linkage disequilibrium (Shintani et al., 2001; Yasar et al., 2002), and the number of subjects carrying both genotypes is included in Table 2. Actually, 77.4% of subjects carrying CYP2C9*2 allele were also carriers of CYP2C8*3; 83.3% in the losartan study, 85% in the case of candesartan, and 72.2% for valsartan. There were no CYP2C9*2 carriers in the telmisartan study.

Effect of Sex on the Pharmacokinetics of ARBs. On average, the AUC and Cmax of all drugs were higher in women than in men (Table 3); this difference could be attributed to the lower body weight of women (who receive a higher dose by weight). Indeed, most differences disappear after adjusting for dose and weight. Consequently, there were no differences between men and women in the pharmacokinetics of losartan, losartan metabolite E-3174, candesartan, and valsartan. However, women showed a higher telmisartan Cmax.
(adjusted for dose and weight) \((P \leq 0.01)\) (Table 3). Women also showed a higher losartan AUC and half-life and a lower clearance, although these differences did not reach statistical significance.

**Involvement of CYP2C8 and CYP2C9 in the Pharmacokinetics of ARBs.** Pharmacokinetic parameters according to CYP2C8 and CYP2C9 polymorphisms are shown in Table 4. No association was found between CYP2C9 and CYP2C8 polymorphisms and the pharmacokinetics of candesartan and telmisartan.

Regarding losartan pharmacokinetics, half-life was longer in subjects with the wild-type CYP2C9*1/*1 genotype (4.6 hours; 95% CI, 4.4–4.8) than in volunteers with the CYP2C9*2 allele (5.7 hours; 95% CI, 5.0–6.3) \((P \leq 0.001)\). The half-life of the losartan metabolite E-3174 was also higher in subjects with the wild-type genotype (2.3 hours; 95% CI, 2.0–2.5) than in volunteers with the wild-type genotype (4.6 hours; 95% CI, 4.4–4.8) \((P \leq 0.001)\). No differences were observed in valsartan pharmacokinetics according to CYP2C8 and CYP2C9 polymorphisms.

On the other hand, carriers of the CYP2C8*2 allele showed higher valsartan clearance (1.07 l/h/kg, 95% CI 0.7–1.5) than subjects with the wild-type genotype (0.48 l/h/kg; 95% CI, 0.3–0.7) \((P \leq 0.01)\). No differences were observed in valsartan pharmacokinetics according to CYP2C9 polymorphisms.

Because CYP2C9*2 is linked to CYP2C8*3, in the valsartan study we compared the subjects carrying both CYP2C9*2 and CYP2C8*3 alleles \((n = 26)\) with the subjects carrying CYP2C9*2 allele and CYP2C8*1/*1 genotype \((n = 10)\), and we found no differences in pharmacokinetic parameters.

**Discussion**

Drug response depends on several factors, including genetics and sex. ARBs are metabolized mainly by P450 enzymes, although other enzymes may be involved. Polymorphisms in genes coding for these P450 enzymes may explain differences in ARB pharmacokinetics, which can in turn affect drug response. Although telmisartan is not metabolized by these enzymes, we included it to confirm that polymorphisms on P450 enzymes do not affect telmisartan pharmacokinetics.

An association was found between the pharmacokinetics of telmisartan and sex, since \(C_{\text{max}}\) was higher in women than in men. Indeed, the drug label indicates that plasma concentrations of telmisartan are generally 2–3 times higher in women, although there are no significant differences in blood pressure. The difference is due to the slower

### Table 1

Characteristics of the subjects genotyped for each drug

<table>
<thead>
<tr>
<th>Study</th>
<th>Genotyped</th>
<th>Sex</th>
<th>Participants</th>
<th>Age</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan ((N = 84))</td>
<td>64</td>
<td>Men</td>
<td>30</td>
<td>25.3 ± 4.3</td>
<td>73.9 ± 9.7</td>
</tr>
<tr>
<td>Telmisartan ((N = 48))</td>
<td>43</td>
<td>Men</td>
<td>19</td>
<td>25.9 ± 5.2</td>
<td>75.4 ± 9.9</td>
</tr>
<tr>
<td>Losartan ((N = 36))</td>
<td>36</td>
<td>Men</td>
<td>18</td>
<td>24.7 ± 3.3</td>
<td>76.6 ± 5.9</td>
</tr>
<tr>
<td>Valsartan ((N = 138))</td>
<td>103</td>
<td>Men</td>
<td>49</td>
<td>23.7 ± 3.4</td>
<td>76.7 ± 10.7</td>
</tr>
</tbody>
</table>

**P < 0.01 versus men in the ARB-matched group; ***P < 0.001 versus men in the ARB-matched group.**

### Table 2

**CYP2C8 and CYP2C9 genotype frequencies for each drug**

Data are expressed as n (%).

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Candesartan ((n = 64))</th>
<th>Valsartan ((n = 103))</th>
<th>Telmisartan ((n = 43))</th>
<th>All ARBs ((n = 246))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP2C8</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*1/*1</td>
<td>25 (69.4)</td>
<td>35 (54.7)</td>
<td>61 (59.2)</td>
<td>146 (59.3)</td>
</tr>
<tr>
<td>*1/*2</td>
<td>1 (2.8)</td>
<td>3 (4.7)</td>
<td>8 (7.8)</td>
<td>9 (20.1)</td>
</tr>
<tr>
<td>*3/*3</td>
<td>1 (0.0)</td>
<td>1 (1.6)</td>
<td>2 (1.9)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td><strong>CYP2C9</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*1/*1</td>
<td>23 (63.9)</td>
<td>31 (48.4)</td>
<td>54 (52.4)</td>
<td>140 (56.9)</td>
</tr>
<tr>
<td>*1/*2</td>
<td>6 (16.7)</td>
<td>20 (31.3)</td>
<td>30 (29.1)</td>
<td>57 (23.2)</td>
</tr>
<tr>
<td>*3/*3</td>
<td>1 (0.0)</td>
<td>1 (1.6)</td>
<td>3 (2.9)</td>
<td>5 (2.0)</td>
</tr>
</tbody>
</table>

Subjects carrying both CYP2C8*3 and CYP2C9*2
Kirchheiner et al., 2002). We did not observe differences in the subjects whose genotypes exhibited the *3 allele, but not the *2 allele. The Cmax of E-3174 is lower in CYP2C9*3 carriers because of the slow formation of the metabolite. Because E-3174 is pharmaco-slower metabolism of losartan. The pharmacokinetics of losartan according to the CYP2C8 polymorphism, possibly reflecting that no losartan metabolite was formed by CYP2C8 in vitro (Babaoglu et al., 2004).

Candesartan cilexetil (cyclohexyl carbonate ester prodrug of candesartan) was identified as a CYP2C8 inhibitor (Walsky et al., 2005); therefore, it is assumed to have affinity for this enzyme. In addition, CYP2C9*3 may change the metabolic activity of candesartan compared with CYP2C9*1 (Hanatani et al., 2001), and the CYP2C9*1/*3 genotype was associated with decreased clearance and increased plasma concentration of candesartan, thus potentially enhancing its hypotensive effect (Uchida et al., 2003). Nevertheless, we did not find any association between the pharmacokinetics of candesartan and any of the polymorphisms studied, maybe because of the low number of subjects and because the effect of CYP2C9 is small, as candesartan is mainly excreted unchanged in urine and feces. Therefore, it is necessary to evaluate this effect in other studies.

Nakashima et al. (2005) studied the association between several P450 enzyme genotypes, including CYP2C9, and valsartan metabolism, and only found involvement of CYP2C9 (Unger and Kaschina, 2003). In addition, no good correlation was observed between the formation rates of 4-OH valsartan and CYP2C8 activity, and CYP2C9 notably catalyzed 4-hydroxylation of valsartan (Nakashima et al., 2005). However, we found that CYP2C8 variants affect the pharmacokinetics of valsartan, since clearance was higher in subjects carrying the CYP2C8*2 allele than in those with the wild-type genotype. This finding cannot be explained on the basis of current knowledge because CYP2C8*2 was previously shown to be associated with decreased enzyme activity with several CYP2C8 substrates (Dai et al., 2001; Daily and Aquilante, 2009; Gao et al., 2010). The effect of CYP2C8*2 on losartan pharmacokinetics could not be evaluated because there was only one subject carrying this allele, but it did not influence the pharmacokinetics of candesartan or telmisartan.

A potential limitation of our study is that no corrections were made for multiple testing and some false positive results could have been obtained. However, some statisticians recommend never correcting for multiple comparisons while analyzing data (Rothman 1990; Savitz and Olshan 1998; Thompson 1998). They instead recommend reporting all of the individual P values and making it clear that no mathematical correction was made for multiple comparisons. They recommend accounting for multiple comparisons when interpreting the results rather than in the calculations. It has also been argued that use of multiple testing corrections is an inefficient way to perform empirical research, since multiple testing adjustments control false positives at the potential expense of many more false negatives (Perneger, 1998; Feise, 2002).

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Sex</th>
<th>Losartan</th>
<th>E-3174</th>
<th>Candesartan</th>
<th>Valsartan</th>
<th>Telmisartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng·h/ml)</td>
<td>Men</td>
<td>455.2 ± 42.5</td>
<td>1807.3 ± 573.6</td>
<td>3258.9 ± 692.0</td>
<td>38803.9 ± 19262.8</td>
<td>2469.9 ± 402.6</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>518.8 ± 43.5</td>
<td>2578.4 ± 1758.1</td>
<td>3814.7 ± 910.6</td>
<td>38588.2 ± 27518.5</td>
<td>3677.2 ± 590.6</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>Men</td>
<td>234.1 ± 23.9</td>
<td>900 ± 67.9</td>
<td>216.3 ± 61.6</td>
<td>4592.2 ± 296.1</td>
<td>282.1 ± 30.8</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>286.5 ± 34.5</td>
<td>301.2 ± 141.4</td>
<td>260.1 ± 63.9</td>
<td>4911.3 ± 294.5</td>
<td>590.5 ± 75.8</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>Men</td>
<td>2.5 ± 0.2</td>
<td>4.9 ± 0.7</td>
<td>11.3 ± 3.3</td>
<td>9.1 ± 0.3</td>
<td>25.1 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>2.4 ± 0.1</td>
<td>4.8 ± 0.5</td>
<td>12.1 ± 3.7</td>
<td>9.4 ± 0.3</td>
<td>33.1 ± 3.2</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>Men</td>
<td>1.2 ± 0.1</td>
<td>3.7 ± 0.8</td>
<td>5.1 ± 1.3</td>
<td>3.2 ± 0.1</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>1.2 ± 0.1</td>
<td>3.7 ± 0.9</td>
<td>4.9 ± 1.2</td>
<td>3.2 ± 0.1</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>Cl (l/h·kg)</td>
<td>Men</td>
<td>1.66 ± 0.5</td>
<td>NC</td>
<td>0.14 ± 0.04</td>
<td>0.4 ± 0.5</td>
<td>17.9 ± 14.7</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>1.82 ± 0.7</td>
<td>NC</td>
<td>0.15 ± 0.04</td>
<td>0.6 ± 0.8</td>
<td>11.7 ± 7.7</td>
</tr>
</tbody>
</table>

NC, not calculated.
*P < 0.01 versus men in ARB-matched group.
Another potential limitation is that sample sizes for some of the drugs are relatively small when they are split up into the various genotypes. Therefore, statistical power could be very low to evaluate differences, especially for the rare polymorphisms (CYP2C9*3 or CYP2C8*4).

Finally, we conclude that the pharmacokinetics of losartan and valsartan, but not of candesartan or telmisartan, is affected by polymorphisms in CYP2C9 and CYP2C8, respectively. In addition, sex affected the pharmacokinetics of telmisartan.

Acknowledgments

This study would not have been possible without the cooperation of the volunteers.

Authorship Contributions


References


Kirchheiner J, Thomas S, Bauer S, Tomalik-Scharte D, Hering U, Doroshyenko O, Jetter A,

Schaefer F, van de Walle J, Zurowska A, Gimpel C, van Hoeck K, Drozdz D, Montini G,

Israili ZH (2000) Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hyper-


Savitz DA and Olshan AF (1998) Describing data requires no adjustment for multiple compar-


Drugs


Kirchheiner J, Bauer S, Meineke I, Rohde W, Meisel C, Roos I, and Brockmoller J

Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the

Frequencies of CYP2C9 variant alleles, including CYP2C9*13 in a Korean population and effect

on glimepiride pharmacokinetics.

P450 oxidoreductase variants on the metabolism of model substrates mediated by CYP2C9.1,

human cytochrome P450 CYP2C9 locus.

Identification of cytochrome P450 forms involved in the 4-hydroxylation of valsartan, a potent

angiotensin system control.


cin etics 44:797–814.


Subramanian M, Agrawal V, Sannee D, Tarn HK, Miller WL, and Tracy TS (2012) Effect of

P450 endoreductase variants on the metabolism of model substrates mediated by CYP2C9.1,


hepatic P450 enzymes by five angiotensin II receptor antagonists. Eur J Clin Pharmacol 56:

135–140.

Thompson JR (1998) Invited commentary: Re: “Multiple comparisons and related issues in the


Tornio A, Niemi M, Neuvonen PJ, and Backman JT (2008) Pharmacokinetics and pharmacody-


pharmacokinetics in cytochrome P450 2C9*1/*1, *1/*2, and *1/*3 individuals. Pharma-


Lee HW, Lim MS, Lee J, Jegal MY, Kim DW, Lee WK, Jang IJ, Shin JG, and Yoon YR (2012)

Frequency of CYP2C9 variant alleles, including CYP2C9*13 in a Korean population and effect


CYP2C9 gene and susceptibility to major depressive disorder. Pharmacogenomics J 3:300–302.


and Ahmad-Santo F (2008) Influence of CYP2C8 and CYP2C9 polymorphisms on pharma-

cokinetic and pharmacodynamic parameters of racemic and enantiomeric forms of ibuprofen


Identification of cytochrome P450 forms involved in the 4-hydroxylation of valsartan, a potent

and specific angiotensin II receptor antagonist, in human liver microsomes. Xenobiotica 35:

589–602.

Niemi M, Leathart JB, Neuvonen M, Backman JT, Daly AK, and Neuvonen PJ (2003) Poly-

morphism in CYP2C9 is associated with reduced plasma concentrations of repaglinide. Clin


Savitz DA and Olshan AF (1998) Describing data requires no adjustment for multiple compar-


Schafer F, van de Walle J, Zurowska A, Gimbel C, van Hoek K, Drozdz D, Montini G,


Investigators (2010) Efficacy, safety and pharmacokinetics of candesartan cilexetil in hyper-

tensive children from 1 to less than 6 years of age. J Hypertension 28:1083–1090.


Generic polymorphisms and functional characterization of the 5′-flanking region of the human


Address correspondence to: Dr. Teresa Cabaleiro, Service of Clinical Pharmacology, Hospital Universitario de la Princesa, C/Diego de León 62, 28006 Madrid, Spain. E-mail: teresa.cabaleiro@salud.madrid.org or fabad.hipr@salud.madrid.org