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, 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_{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 (0.1 ± 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 (Israel, 2000; Schmidt and Schieffer, 2003; Unger, 2003). Losartan, valsartan (Valsartan Alter, Diovan), and candesartan (Candesartan Alter, Atacand) have affinity for the cytochrome P450 (P450) isoenzymes (Unger and Kaschina, 2003), including CYP2C9, and is partially metabolized by glucuronidation (Israel, 2000).

CYP2C8 shares sequence homology with CYP2C9 and can metabolize the same kind of drugs. However, few studies have evaluated the role of CYP2C8 in the metabolism of ARBs (Nakashima et al., 2005). Point mutations or single-nucleotide polymorphisms in the CYP2C8 and CYP2C9 genes have been identified. The common coding mutations in CYP2C9 are CYP2C9*2, and CYP2C9*3 (Stubbins et al., 1996; Lee et al., 2002). CYP2C9*2 and CYP2C9*3 differ from the wild-type CYP2C9 by a single point mutation: CYP2C9*2 is characterized by a 430C>T exchange in exon 3 resulting in an Arg144Cys amino acid substitution, whereas CYP2C9*3 is characterized by a 1075A>C exchange in exon 7 causing an I359L substitution in the catalytic site of the enzyme. Individuals with the *2 or *3 variant alleles could have reduced enzyme activity.

Approximately two-thirds of Caucasians express the wild-type genotype (CYP2C9*1/*1), one-third express either the *1/*2 or *1/*3
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 nonsynonymous 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 reglipinidine, 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-hydrochlorothiazide study (25–32 mg), 43 of 48 participating in a telmisartan study (80 mg), 32 of 36 enrolled in a valsartan study (160 mg), 34 of 54 participating in another valsartan study (320 mg), and 37 of 48 enrolled in a valsartan-hydrochlorothiazide study (25–320 mg). All subjects receiving candesartan (n = 64) and valsartan (n = 103) were analyzed together.

All participants gave their written informed consent for genotyping. These protocols were carried out according to current Spanish legislation on clinical research in humans and were approved by the local clinical investigation ethics committee.

Sample Processing. A peripheral blood sample was taken from each patient and added to a tube with 3 ml of EDTA K3 before being identified with a code and registered. DNA was then extracted from each blood sample in an automatic DNA extractor (MagNa Pure System; Roche Applied Science, Indianapolis, Indiana). The DNA obtained was quantified spectrophotometrically using a NanoDrop ND-1000 Spectrophotometer (Wilmington, DE), and added to a tube with 3 ml of EDTA K3 before being identified with a code and added to a tube with 3 ml of EDTA K3 before being identified with a code and registered. DNA was then extracted from each blood sample in an automatic DNA extractor (MagNa Pure System; Roche Applied Science, Indianapolis, Indiana). The DNA obtained was quantified spectrophotometrically using a NanoDrop ND-1000 Spectrophotometer (Wilmington, DE), and purity was tested using the A260/280 ratio.

Primers and probes used for real-time polymerase chain reaction in a LightCycler 480 (Roche) were previously described (López-Rodríguez et al., 2008).

Drug Determination. Blood samples were collected for analysis before dosing and at different times after dosing. All blood extractions were carried out using a Venoject system (Terumo Europe N.V.) with sterile EDTA tubes. The tubes were centrifuged at 4°C (at room temperature in the case of losartan) for 10 minutes at 3500 rpm (230g). Once centrifuged, plasma was aliquoted in two polystyrene tubes and labeled with the protocol code, the subject number, the period, and the time at which the sample was obtained. The aliquots were stored in two different freezers at −70°C (−30°C in the case of losartan and telmisartan) to prevent the possibility of thawing until their transfer to the laboratory responsible for the analytic determinations. The temperatures of these freezers were registered daily during the storage period. Samples were shipped to the laboratory in dry ice. ARBs and internal standards were measured using validated reversed phase high-performance liquid chromatography and detected by tandem mass spectrometry (see Supplemental Material).

In the case of losartan, the active metabolite E-3174 was measured in the same subjects that were used for the losartan measurements.

Pharmacokinetics. Pharmacokinetic parameters were estimated from the plasma concentration–time data by noncompartmental analysis with WinNonlin Professional software (version 2.0; Pharsight Corporation). The maximum plasma concentration (Cmax) and time to reach the maximum plasma concentration (Tmax) were obtained directly from raw data. The total area under the curve from administration time to infinity (AUCt-t) was calculated as the sum of AUC0-t and the residual area (C divided by k, with C as the last measured concentration and k as the apparent terminal elimination rate, estimated by log-linear regression from the terminal portion of the log-transformed concentration–time plots). The mean of the extrapolated AUC was 2.7% (range, 0.6–8.7). The half-life (t1/2) was calculated by dividing 0.693 by k.

The total drug clearance adjusted for bioavailability (Cl/F) was calculated by dividing the dose by the AUC and later adjusted for weight (Cl/Fwt). In the case of E-3174, total drug clearance was not calculated because we did not know the dose. AUC and Cmax were adjusted for dose and weight and logarithmically transformed for statistical analysis.

Data Analysis. To simplify the analysis and owing to the low number of subjects for some genotypes, we classified CYP2C8 and CYP2C9 genotypes in groups. CYP2C8 genotypes were classified in five 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 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, 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).

The Hardy-Weinberg equilibrium was estimated for all analyzed variants. Deviations from the equilibrium were detected by comparing the observed and expected frequencies using a Fisher exact test based on the De Finetti program (available at http://hq2.helmholtz-muenchen.de/cgi-bin/hw/hw1.pl).

Differences in the genotypic frequencies of variants according to sex were determined using a corrected Pearson χ2 test. The statistical significance of the differences in pharmacokinetic parameters between individuals with different genotypes and sex was calculated using a univariate analysis (t test or analysis of variance). Significant factors were included in a multivariate analysis (multivariate general linear model). SPSS software (version 15; SPSS Inc., Chicago, IL) was used for the statistical analysis. Because this study was designed as an exploratory analysis, we did not adjust P values for multiple testing, which is consistent with prior recommendations (Rothman, 1990; Savitz and Olshan, 1998; Thompson, 1998).

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 an 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 (Shi et al., 2003; Yang 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 telmisartan 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 CYP2C9*3 allele (5.7 hours; 95% CI, 5.0–6.3) than in volunteers with the wild-type genotype (4.6 hours; 95% CI, 4.4–4.8) \((P \leq 0.001)\). The AUC ratio (E-3174 AUC/losartan AUC) was no different between the CYP2C9*3 allele (5.7 hours; 95% CI, 5.0–6.3) and those with the wild-type (291.6 ng/ml; 95% CI, 238.3–345.0) \((P \leq 0.001)\). No differences were observed in the pharmacokinetics parameters.

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 pharmacokinetics 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 valsartan and sex, since \(C_{\text{max}}\) was higher in women than in men. Indeed, the drug label indicates that plasma concentrations of valsartan 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**

<table>
<thead>
<tr>
<th>Study</th>
<th>Genotyped</th>
<th>Sex</th>
<th>Participants</th>
<th>Age</th>
<th>Weight</th>
</tr>
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<tr>
<td>Candesartan ((N = 84))</td>
<td>64</td>
<td>Men</td>
<td>30</td>
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<td>64</td>
<td>Women</td>
<td>34</td>
<td>25.8 ± 5.2</td>
<td>60.3 ± 8.3**</td>
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<tr>
<td>Telmisartan ((N = 48))</td>
<td>43</td>
<td>Men</td>
<td>19</td>
<td>25.9 ± 5.2</td>
<td>74.6 ± 8.9</td>
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<tr>
<td></td>
<td>43</td>
<td>Women</td>
<td>19</td>
<td>25.6 ± 5.6</td>
<td>61.0 ± 9.9***</td>
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<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>
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<tr>
<td></td>
<td>36</td>
<td>Women</td>
<td>18</td>
<td>24.9 ± 4.1</td>
<td>61.3 ± 6.8***</td>
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<tr>
<td>Valsartan ((N = 138))</td>
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<td>49</td>
<td>23.7 ± 3.4</td>
<td>75.7 ± 10.7</td>
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<tr>
<td></td>
<td>103</td>
<td>Women</td>
<td>49</td>
<td>23.4 ± 2.9</td>
<td>58.7 ± 5.0***</td>
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**Table 2**

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

<table>
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<tr>
<th>Polymorphism</th>
<th>Candesartan ((n = 64))</th>
<th>Telmisartan ((n = 43))</th>
<th>Valsartan ((n = 103))</th>
<th>Losartan ((n = 36))</th>
<th>All ARBs ((n = 246))</th>
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<tr>
<td>(<em>1</em>/1)</td>
<td>25 (69.4)</td>
<td>61 (59.2)</td>
<td>25 (58.1)</td>
<td>146 (59.3)</td>
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<tr>
<td>(<em>1</em>/2)</td>
<td>1 (2.8)</td>
<td>3 (7.8)</td>
<td>9 (20.1)</td>
<td>21 (8.5)</td>
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</tr>
<tr>
<td>(<em>1</em>/3)</td>
<td>5 (13.9)</td>
<td>23 (22.3)</td>
<td>5 (11.6)</td>
<td>50 (20.3)</td>
<td></td>
</tr>
<tr>
<td>(<em>3</em>/3)</td>
<td>1 (2.8)</td>
<td>5 (4.9)</td>
<td>1 (2.3)</td>
<td>8 (3.3)</td>
<td></td>
</tr>
<tr>
<td>(<em>2</em>/3)</td>
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<td>0 (0)</td>
<td>2 (4.7)</td>
<td>3 (1.2)</td>
<td></td>
</tr>
<tr>
<td>(<em>1</em>/4)</td>
<td>3 (8.3)</td>
<td>2 (1.9)</td>
<td>1 (2.3)</td>
<td>11 (4.5)</td>
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<tr>
<td>(<em>2</em>/4)</td>
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<td>0 (0)</td>
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</tr>
<tr>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (1.2)</td>
<td></td>
</tr>
<tr>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
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<td>54 (52.4)</td>
<td>32 (74.4)</td>
<td>140 (56.9)</td>
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<td>30 (29.1)</td>
<td>1 (2.3)</td>
<td>57 (23.2)</td>
<td></td>
</tr>
<tr>
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<td>0 (0)</td>
<td>6 (5.8)</td>
<td>0 (0)</td>
<td>6 (2.4)</td>
<td></td>
</tr>
<tr>
<td>(<em>1</em>/3)</td>
<td>6 (16.7)</td>
<td>10 (9.7)</td>
<td>10 (23.3)</td>
<td>37 (15.0)</td>
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</tr>
<tr>
<td>(<em>2</em>/3)</td>
<td>1 (2.8)</td>
<td>3 (2.9)</td>
<td>0 (0)</td>
<td>5 (2.0)</td>
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<tr>
<td>(<em>3</em>/3)</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
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<tr>
<td>Subjects carrying both CYP2C8<em>3 and CYP2C9</em>2</td>
<td>5 (13.9)</td>
<td>17 (26.6)</td>
<td>26 (25.2)</td>
<td>49 (19.9)</td>
<td></td>
</tr>
</tbody>
</table>
clearance in women, although it was not statistically significant in our study. Previous studies have shown that clearance is slower in women for drugs that are metabolized by conjugation or oxidation (Harris et al., 1995).

The pharmacokinetics of losartan, valsartan, and candesartan were not affected by sex. Similarly, Sica et al. (2005) reported no clinically significant effects of age, sex, or race on the pharmacokinetics of losartan. Moreover, candesartan lowered blood pressure regardless of age, sex, body mass index, or cause of hypertension (Hoy and Keating, 2010; Schaefer et al., 2010).

The frequencies of CYP2C9 and CYP2C8 alleles were similar to that found in other studies performed in Spanish subjects (Dorado et al., 2003; Llerena et al., 2003; López-Rodríguez et al., 2008). No association was found between CYP2C9 and CYP2C8 genotypes and the pharmacokinetics of telmisartan, thus confirming previous findings that this ARB is not metabolized by P450 isoforms, since it has no affinity for any of the P450 isoenzymes and is partially metabolized by glucuronidation (Israili, 2000; Unger and Kaschina, 2003).

As expected, the half-life of losartan was longer in subjects with the CYP2C9*3 allele than in volunteers with the CYP2C9*1/*1 wild-type genotype. Losartan is converted to its metabolite E-3174 mainly by CYP2C9 (Israili, 2000; Yasar et al., 2002); therefore, metabolism in vivo is slower and the pharmacokinetics of telmisartan, thus confirming previous results obtained. However, some statisticians recommend never correcting for the potential expense of many more false negatives (Perneger, 1998; Rothman 1990; Savitz and Daily and Aquilante, 2009; Gao et al., 2010). The effect of CYP2C8*2 was previously shown to be 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 CYP2C8, 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 (Permejer, 1998; Feise, 2002).
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
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Authorship Contributions

Participated in research design: Ochoa, Novalbos, Abad-Santos.

Conducted experiments: Cabaleiro, Román, Ochoa, Talegón, Prieto-Pérez, Wojnizc, López-Rodríguez, Novalbos, Abad-Santos.

Performed data analysis: Cabaleiro, Román, Ochoa, Abad-Santos.

Wrote or contributed to the writing of the manuscript: Cabaleiro, Román, Ochoa, López-Rodríguez, Abad-Santos.

References


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