CLINICAL PHARMACOLOGY GRAND ROUNDS

Altered pharmacokinetics and excessive hypotensive effect of candesartan in a patient with the *CYP2C9*1/*3* genotype

An 89-year-old man with severe hypertension (190/82 mm Hg) and chronic heart failure (New York Heart Association class II) despite treatment with benidipine, doxazosin mesylate (INN, doxazosin), and furosemide was given oral candesartan cilexetil (4 mg/d), an angiotensin II type 1 receptor blocker metabolized via cytochrome P450 (CYP) 2C9. Two days later, he started to have severe dizziness and returned to the hospital on the fourth day without taking any of his medications. The blood pressure 30 hours after the last dose of candesartan was 126/64 mm Hg. Polymorphism analysis revealed the heterozygous poor metabolizer genotype *CYP2C9*1/*3*. The area under the concentration-time curve and the mean residence time of candesartan were both increased 2.5-fold, and the oral clearance of candesartan was 48% lower than that of the average elderly Japanese patient with hypertension. These results suggest that the *CYP2C9*1/*3* genotype could be associated with decreased clearance and increased plasma concentration of candesartan, potentially enhancing its hypotensive effect. (Clin Pharmacol Ther 2003;74:505-8.)

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Candesartan is a long-acting angiotensin II type 1 receptor blocker (ARB) that is widely used to treat patients with hypertension. The oral form is candesartan cilexetil, which is completely converted during enteric absorption to the active form, candesartan. Candesartan is metabolized in the liver by cytochrome P450 (CYP) 2C9 to the inactive metabolite CV15959 and is excreted as such through renal and biliary routes.[1] The existence of genetic polymorphisms in CYP2C9 has been recognized to influence the enzyme's activity. The most common variants of CYP2C9 alleles are *CYP2C9*2*, a 430C<T polymorphism that results in the amino acid exchange Arg144Cys, and *CYP2C9*3*, a 1075A<C polymorphism that causes an Ile359Leu exchange.[2-4] In vitro studies have suggested that the *CYP2C9*3* variant markedly reduces catalytic activity and binding affinity of the enzyme.[2,5] In addition, studies in humans have demonstrated that this variant is associated with poor metabolism of classic CYP2C9 substrates such as tolbutamide,[2] phenytoin,[6] and warfarin.[7] Nonetheless, it is not clear whether the *CYP2C9*3* allele affects pharmacokinetics and therapeutic effects of candesartan. Here we describe a clinical case in which the heterozygous poor metabolizer genotype of CYP2C9 (*CYP2C9*1/*3*) is associated with decreased clearance and increased plasma concentration of candesartan, manifesting clinically by severe dizziness and hypotension.

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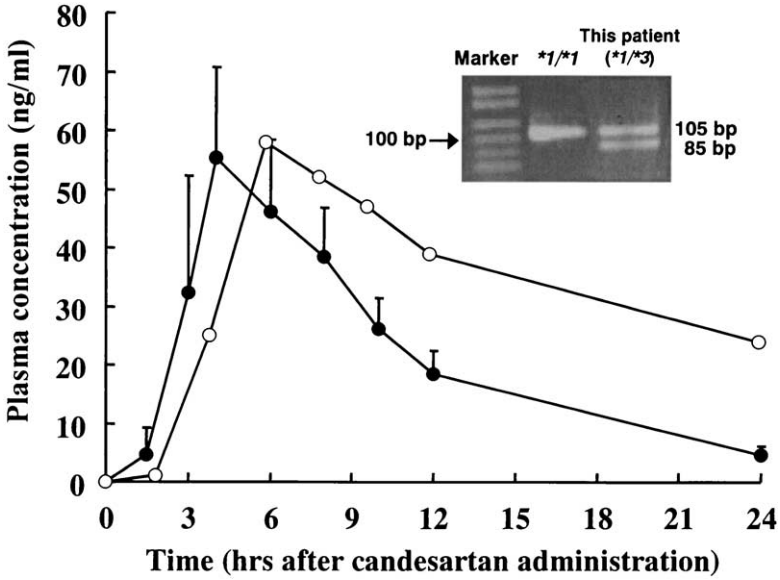

Fig 1. Plasma concentration–time curves of candesartan after oral administration of candesartan cilexetil in our *CYP2C9*1/*3* patient (*open symbols*) and in hypertensive elderly patients (from reference 9) (*solid symbols*, n = 6). *Bars* represent mean ± SD. *Inset*, Polymerase chain reaction (PCR)–restriction fragment length polymorphism analysis of the CYP2C9 gene in a *CYP2C9*1/*1* patient (*lane 1*) and our *CYP2C9*1/*3* patient (*lane 2*). PCR products were digested with *Kpn*I before electrophoresis. The PCR product containing the **1* allele remained uncut, whereas the other produced 85– and 20–base pair (bp) fragments. Only the 85-bp fragment was visible.

CASE REPORT

An 89-year-old man was seen at the outpatient clinic of Hamamatsu University Hospital, Hamamatsu, Japan, with severe hypertension and chronic heart failure (New York Heart Association functional class II). The blood pressure was uncontrollable (190/82 mm Hg) despite treatment with benidipine (4 mg/d), doxazosin mesylate (INN, doxazosin) (2 mg/d), and furosemide (40 mg/d). The ARB candesartan cilexetil, 4 mg/d orally, was thus added for better control of blood pressure. The first day passed without the patient having any symptoms of severe hypotension such as dizziness and syncope. From the second day, he started to have severe dizziness and had to return to the hospital on the fourth day without taking any of his medications. The blood pressure 30 hours after the last intake of candesartan was found to be only 124/64 mm Hg. Candesartan was withdrawn and the symptoms were rapidly alleviated. Serum aspartate aminotransferase and alkaline aminotransferase levels were 17 IU/L and 13 IU/L, respectively. Serum electrolyte levels were as follows: sodium, 142 mEq/mL; potassium, 3.9 mEq/mL; and chloride, 103 mEq/mL. The ratio of blood urea nitrogen to serum creatinine was 14.8, and creatinine clearance was 88.7 mL/min. There was no evidence of significant hepatic or renal dysfunction or dehydration. These results suggest that the metabolism of candesartan was significantly reduced in this patient. Polymerase chain reaction–restriction fragment length polymorphism analysis[8] then revealed that the CYP2C9 genotype of the patient was heterozygous of the wild-type (**1*) and Leu359 (**3*) allele (*CYP2C9*1/*3*) (Fig 1).

To determine whether the pharmacokinetic properties of candesartan were altered in this patient, we obtained written informed consent for an in-hospital readministration of 4 mg candesartan cilexetil. This study was approved by the Ethical Committee of Hamamatsu University School of Medicine. The pharmacokinetic parameters of candesartan in this patient were compared with published values from 6 Japanese patients with hypertension (mean age, 67.2 years).[9] Blood samples were taken at 2, 4, 6, 8, 10, 12, and 24 hours after the administration of candesartan, and plasma concentrations of the drug were determined by use of HPLC.[10] Fig 1 shows the plasma concentration–time curves of candesartan after oral administration of candesartan cilexetil (4 mg) in our patient and the 6 elderly patients with hypertension previously de-

Table I. Pharmacokinetics of candesartan after oral administration of candesartan cilexetil in our *CYP2C9*1/*3* patient and published data from hypertensive elderly patients (from reference 9)

Pharmacokinetic parameter	*CYP2C9*1/*3 patient*	*Other hypertensive elderly patients*
CL_{oral} ($mL \cdot kg^{-1} \cdot h^{-1}$)	52.6	109
MRT (h)	27.8	11.2
AUC(0-∞) ($h \cdot ng/mL$)	1382	549

The area under the concentration-time curve [AUC(0-∞)] and the area under the first moment (plasma concentration multiplied by time)–time curve (AUMC) were calculated by use of the trapezoidal rule for the observed values and with subsequent extrapolation to infinity. The mean residence time (MRT) was determined by dividing AUMC by AUC(0-∞). The oral clearance (CL_{oral}) was calculated as dose divided by AUC(0-∞).

scribed.[9] Peak plasma concentrations (C_{max}) were similar in our patient and the other 6 patients (58.0 ng/mL versus 55.4 ng/mL), whereas the time to reach C_{max} was 4 hours in our patient and 2 hours in the 6 elderly patients. Candesartan in our patient was more slowly eliminated than in the other patients. The area under the concentration-time curve extrapolated to infinity [AUC(0-∞)] and the mean resident time (MRT) of candesartan in our patient were both increased 2.5-fold, and the oral clearance (CL_{oral}) was 48.3% lower than that of the 6 elderly patients (Table I). After a single dose of the drug, the blood pressure of our patient was slightly decreased (from 139/63 mm Hg before dosing to 123/58 mm Hg at 6 hours, 118/66 mm Hg at 10 hours, and 110/62 mm Hg at 24 hours), but he had no significant symptoms of severe hypotension.

DISCUSSION

The patient described in this case report, who carried the *CYP2C9*1/*3* genotype, was found to have a markedly higher plasma drug concentration and significantly lower clearance in comparison with values in other elderly patients. Although renal impairment could alter the pharmacokinetics of candesartan,[11] both renal and hepatic functions were normal in our patient. Our data are consistent with previous reports that the *CYP2C9*3* allele, even when heterozygous with the wild-type allele, alters the pharmacokinetics of its substrates. Lee et al[12] have recently reported that the oral clearance of tolbutamide is reduced by approximately 50% in individuals carrying the *CYP2C9*1/*3* genotype in comparison with those carrying the *CYP2C9*1/*1* genotype. In a group of Japanese patients with the *CYP2C9*1/*3* genotype, the maximal elimination rate of phenytoin was 33% lower than in a *CYP2C9*1/*1* group.[6] There appears to be no significant difference between *CYP2C9*1/*1* and *CYP2C9*1/*3* in human liver microsomes with regard to the kinetics of candesartan. However, expression of the *CYP2C9*3* variant in yeast has been shown to change the metabolism of the drug.[13] It is, therefore, very likely that the *CYP2C9*1/*3* genotype is an important factor that disturbed candesartan pharmacokinetics in our patient. Given that the patient's plasma concentration of candesartan remained high even at 24 hours after candesartan administration, it is likely that the concentration was very high on later days of treatment, which would explain the patient's severe dizziness from the second day and the markedly reduced blood pressure (126/64 mm Hg) when he returned to the hospital on the fourth day. These results suggest that the *CYP2C9*1/*3* genotype could be associated with decreased clearance and increased AUC(0-∞) and MRT of candesartan in humans, resulting in an excessive hypotensive effect. In this context, additive effects of other factors affecting drug disposition in geriatric patients, such as changes in plasma protein binding, hepatic blood flow, and enzyme activity, cannot be ruled out.[14]

This report is the first to suggest an association between CYP2C9 genomic polymorphism and altered pharmacokinetics of candesartan. Previous reports have shown a link between the *CYP2C9*3* allele and deficient conversion of losartan, another ARB, to its metabolite E-3174.[15,16] Because E-3174 is more potent than losartan, the lowered concentrations of the metabolite in association with the *CYP2C9*3* allele may somewhat reduce the blood pressure–lowering effect of losartan. However, in a recent study, healthy subjects with the *CYP2C9*1/*1* and *CYP2C9*1/*3* genotypes did not show any difference in blood pressure after a single dose of losartan.[17] Consistent with this finding, our patient was treated with losartan after the episode of severe dizziness that occurred with candesartan and he did not have any symptoms of hypotension. In the case of candesartan, however, the metabolite is inactive and the decreased metabolism of the drug associated with the *CYP2C9*3* allele may thus be responsible for the observed excessive hypotensive effect. Therefore this report is also the first to demonstrate the potential pharmacodynamic consequences of the *CYP2C9*1/*3* genotype with an ARB, candesartan.

Although the incidence of the *CYP2C9*3* allele is relatively low among white subjects (0.06)[3] and Japanese populations (0.02),[8] the pharmacokinetic disturbance of candesartan in *CYP2C9*1/*3* patients may be important because approximately 4% of Japanese sub-

jects compared with 10% of white subjects are known to express this heterozygous genotype.

In conclusion, this case report suggests that reduced CYP2C9 activity associated with the *CYP2C9*1/*3* genotype may be clinically meaningful in patients receiving candesartan cilexetil. Larger studies on the pharmacokinetic and pharmacodynamic characteristics of candesartan are necessary to confirm the increased drug exposure and hypotensive effect of the drug in *CYP2C9*3* carriers. However, from a practical point of view, determination of the patient's genotype for CYP2C9 should be considered at the first sign of severe hypotension after candesartan administration so that the treatment regimen can be adjusted in a timely manner and further deleterious effects avoided.

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