Letter to the Editors

Different accumulation of temocapril and enalapril during repeated dosing in elderly patients

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Angiotensin-converting enzyme (ACE) inhibitors, temocapril and enalapril, are prodrugs that are converted to the active metabolites, temocaprilat and enalaprilat, respectively. Temocaprilat is eliminated by renal and biliary routes, while enalaprilat is mainly excreted in urine [1, 2]. This difference explains a 2-fold increase in plasma temocaprilat and a 13-fold increase in plasma enalaprilat in patients with renal insufficiency [3]. Because renal function is physiologically decreased with age, it is hypothesized that, compared with temocaprilat, accumulation of enalaprilat during repeated dosing is greater and blood pressure (BP)-lowering effect is enhanced in elderly hypertensive patients. In this study, temocapril or enalapril was given once daily for 14 days to elderly hypertensive patients. Pharmacokinetic profiles and BP-lowering effects after single and repeated dosings of these drugs were determined.

Seven elderly patients (four men, three women) with essential hypertension were included. Their mean (+ range) age, body weight and 24 h creatinine clearance were 70 (65–77) years old, 56 (44–64) kg and 78 (58–117) ml min⁻¹. They did not take any antihypertensive drugs for at least 1 week before the treatment with temocapril or enalapril. Informed written consent was given by all patients after the protocol was approved by the review board of Moka Hospital.

Low initial dose (2 mg day⁻¹ of temocapril, 5 mg day⁻¹ of enalapril) was recommended for the treatment of hypertension in elderly people in Japan. One 2 mg-tablet of temocapril or one 5 mg-tablet of enalapril was given orally at 08.00 h for 14 days. Patients received the drug after an overnight fast on day 1 and day 14. These

trials were performed by a randomized, cross-over design with 14 days-washout period. Blood samples for plasma temocaprilat or enalaprilat were obtained for the 24-h period after the 1st and 14th dosings of each drug. Supine BP was measured automatically for the 24-h period on days 1 and 14 after dosing of each drug and also on day-1 (control). Plasma concentrations of active metabolites (temocaprilat and enalaprilat) were measured by an inhibitor-binding assay using high-performance liquid chromatography [4]. The coefficient of variation was 4.3–6.0% (5–70 ng ml⁻¹) for intra-assay and 3.9–12.3% (5–90 ng ml⁻¹) for inter-assay. The limit of quantification was 1.0 ng ml⁻¹. Area under the plasma concentration–time curve from 0 to 24 h (AUC_{0–24}) was calculated using the linear trapezoidal rule. Accumulation ratio was determined by AUC_{0–24} after 14th dosing/AUC_{0–24} after 1st dosing. Relationship between creatinine clearance and log e (accumulation ratio) was analysed by linear regression.

During the repeated dosing, the AUC_{0–24} of temocaprilat did not increase (ng h⁻¹ ml⁻¹; 170 ± 66 (1st dosing) → 168 ± 63 (14th dosing)) and that of enalaprilat tended to increase (487 ± 167 (1st dosing) → 642 ± 300 (14th dosing), *P* = 0.06 (Student's *t*-test)). Accumulation ratio of temocaprilat was significantly (*P* = 0.02) smaller than that of enalaprilat (temocaprilat 1.0 ± 0.3, enalaprilat 1.3 ± 0.3: mean difference –0.3 (95% CI –0.5 to –0.1)). Accumulation ratio of enalaprilat negatively depended on creatinine clearance in each patient (Figure 1). BP significantly (ANOVA: *P* = 0.02) decreased after the 1st dosing of temocapril, and the effect was not enhanced after the 14th dosing. On the other hand, BP did not decrease after the 1st dosing and significantly (ANOVA: *P* = 0.04) decreased after the 14th dosing of enalapril. One patient had excessive BP drop and experienced hypotensive episodes (dizziness and tachycardia) at 8 h after 14th dosing of enalapril [SBP/DBP (mmHg): control 148/101 → enalapril 102/73, temocapril 145/98, PR (beats min⁻¹): control 74 → enalapril 93, temocapril 76]. The value of creatinine clearance in this patient was lowest (58 ml min⁻¹), and

Figure 1

Relationship between creatinine clearance and drug accumulation ratio during a repeated dosing. Temocaprilat (○), enalaprilat (●)

accumulation ratio was 1.8 for enalaprilat and 1.0 for temocaprilat.

Because renal function decreases with age, elimination of a drug that is mainly excreted by the renal route may be reduced. Consequently, drug accumulates in the elderly if they receive the standard dose. In this study, enalaprilat accumulated in plasma during repeated dosing, which negatively depended on renal function in elderly patients. However, temocaprilat has a dual pathway of excretion: renal and biliary [1]. Potential mechanism of biliary excretion is as follows: temocaprilat is uptaken into hepatocytes by organic anion-transporting polypeptide 1, and then excreted in bile by canalicular multispecific organic anion transporter [5,6]. These findings led us to speculate that plasma accumulation of

temocaprilat is relatively small in the elderly, which is confirmed in this study. As expected, BP lowering-effect of enalapril was enhanced during the repeated dosing in this study. In addition, one patient with very low creatinine clearance, had hypotensive episodes after the last dose of enalapril. Therefore, to prevent an excess BP drop, a lower maintenance dose of enalapril might be appropriate in elderly patients, especially with very low creatinine clearance.

References

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