Influence of Food on the Clinical Effect of Angiotensin I Converting Enzyme Inhibitor (SQ 14,225)

YOICHI IZUMI, MASANOBU HONDA, MICHINOBU HATANO and YUKINORI KAWAHARA*

The Second Department of Internal Medicine, Nihon University School of Medicine, Itabashi-ku, Tokyo 173 and *Product Development Laboratories, Sankyo Company Ltd., Hiromachi, Shinagawa-ku, Tokyo 140

IZUMI, Y., HONDA, M., HATANO, M. and KAWAHARA, Y. Influence of Food on the Clinical Effect of Angiotensin I Converting Enzyme Inhibitor (SQ 14,225). Tohoku J. exp. Med., 1983, 139 (3), 279-286 — In order to clarify the influence of food on the clinical effect of angiotensin I converting enzyme inhibitor (SQ 14,225, captopril), 25 mg of the drug was administered to patients with hypertension using a two-way crossover study design. In the first study (study I), each subject received the drug 30 min after breakfast, and changes in blood pressure (BP), blood concentration of captopril (BCC), plasma renin activity (PRA), plasma aldosterone (PA) and plasma angiotensin I converting enzyme activity (ACE-A) were determined for 3 hr. BP was recorded for 6 hr. Four days after study I, the same subjects received the drug 2 hr after breakfast, and each parameter was again determined (study II), similarly to study I. No significant difference in the hypotensive responses to captopril was observed between both studies during 6 hr of observation. Maximum hypotensive effects were found within 90 min of the treatments in study I and study II, and BP returned almost to baseline levels at 6 hr in both studies. Maximum BCC levels were found 60 and 90 min after the drug administration in studies I and II, respectively, and these approximated to half of each maximum level at 180 min. There were no statistically significant differences in the biological half-life ($T'/2$), maximum concentration ($C_{\text{max}}$), maximum concentration time ($T_{\text{max}}$), and area under the blood concentration curve [$\text{AUC}_{\text{o-3}}$] between both studies. The peak in PRA occurred at 60 and 90 min after the administration of the drug in studies I and II, respectively. In study I, a slightly greater reduction of PA levels was found, but there was no significant difference in the magnitude of the reduction between both studies. The present results indicate that food did not exert any significant influence on the clinical effect of captopril. — — — captopril; food; blood pressure

Recently, a new orally active angiotensin I converting enzyme inhibitor, captopril (SQ 14,225), has been utilized for laboratory and clinical purposes to investigate the pathogenesis of hypertension and for the treatment of hypertension (Ondetti et al. 1977; Vollmer and Boccazno 1977; Ferguson et al. 1978; Gavras et al.

Received for publication, May 25, 1982.
Reprint request: Masanobu Honda, M.D., the 2nd Department of Internal Medicine, Nihon University School of Medicine, Ooyaguchi, Itabashi-ku, Tokyo 173, Japan.

279
1978; Laffan et al. 1978; Millar et al. 1981). However, the most effective method of administration in the clinical application of the drug should be adopted for the clinical use of the drug as an antihypertensive agent. It is well known that one of the important factors influencing the bioavailability of drugs is food intake, which generally reduces the absorption of drugs (Wagner 1977). Contrary to the above concept, however, Melander (1978) has indicated the food-enhanced bioavailability of several antihypertensive drugs; namely, the beta-adrenoreceptor blockers propranolol and metopronol, canrenone, thiazide and hydralazine. We, therefore, investigated whether or not food intake influences the clinical effect of captopril in patients with hypertension.

MATERIALS AND METHODS

Nine patients with essential hypertension (8 male, 1 female) aged 36 to 60 years (43.3 ± 7.9, mean ± s.d.) and one with malignant hypertension (aged 54 years, male) were admitted under an isocaloric diet containing 7-8 g/day of NaCl. In the subjects, except the one with malignant hypertension, antihypertensive medication and medical care were stopped for at least 2 weeks before admission. In the patient with malignant hypertension, antihypertensive medication was stopped for 3 days before the start of the present examination. In study I, the subjects had breakfast at 8 a.m., and were then kept in recumbency. Thirty min after the end of breakfast, venous blood was drawn from the left antecubital vein. Subsequently, they received a 25 mg captopril administration. The supine position was maintained for 3 hr, and venous blood samples were collected 15, 30, 60, 90, 120 and 180 min after the administration of the drug for plasma renin activity (PRA), plasma aldosterone (PA), plasma angiotensin I converting enzyme activity (ACE-A) and blood concentration of captopril (BCC). After the last blood sampling, the subjects took lunch, and were permitted to behave normally. Blood pressure (BP) was recorded for 380 min, starting 20 min before, and ending 6 hr after the drug administration. In the supine period (-20 min to 3 hr), BP was measured at 10 min intervals, and in the casual period (3-6 hr), at 1 hr intervals. In the second study (study II), breakfast was taken at 8 a.m., and the drug was administered 2 hr after the finish of breakfast. Blood sampling and measurements of BP were carried out before and after the drug administration, similarly to study I.

The radioimmunoassay procedure for PRA followed the method of Haber et al. (1969). PA was also determined by the radioimmunoassay technique developed by Nowaczynski et al. (1974). ACE-A was estimated by the spectrophotometric assay of Lieberman (1975). BCC was determined by the high-performance liquid chromatography developed by Kawahara et al. (1981).

The results were expressed as means ± s.e. Statistical analysis was performed by Student’s paired t test, and p values of less than 0.05 were considered as statistically significant.

RESULTS

The responses of systolic BP (SBP), diastolic BP (DBP) and mean BP (MBP) to 25 mg of captopril in studies I and II are shown in Fig. 1. In all parameters including the SBP, DBP and MBP in both studies, significant decreases began within 30 min. Statistical significance was evaluated by comparison with the mean of the pretreatment BP values. The maximum decreases in SBP, DBP and MBP were observed at 90 min, and these were 78.8%, 80.4% and 79.6% of the pretreatment levels, respectively, in study I. In study II also the maximum
decreases in SBP, DBP and MBP were observed in 90 min, being 82.5%, 81.2% and 87.7% of the pretreatment values, respectively. All BP levels in both studies returned gradually from each maximum decrease and almost reached pretreatment levels at 6 hr. There were no significant differences in the magnitude of the decreases in the SBP, DBP and MBP between the two studies. The absolute mean values of the pretreatment BP in study I were 173.8±5.9, 104.6±3.4 and 127.7±3.9 mmHg (mean±s.e.) for SBP, DBP and MBP, respectively. In study II, the values were 167.0±4.5, 100.7±3.4 and 122.8±3.4 for SBP, DBP and MBP, respectively.

The changes in BCC are shown in Fig. 2. Maximum BCC was 121.0±31.0 ng/ml at 60 min in study I, and 169.5±18.1 at 90 min in study II. There was no significant difference in these maximum values between the two studies. Significant differences in BCC levels between the two studies were noted at 60 and 90 min after the drug administration. The biological half-life (T1/2) of 0.80±0.18 hr in study I was not significantly different from that of 1.31±0.37 in study II. The

![Fig. 1. Responses of systolic, diastolic and mean blood pressure to 25 mg of captopril administered 30 min (solid circles) and 2 hr (open circles) after a meal in patients with hypertension. Each point and vertical bar represent mean values±s.e. (n=10). The p values (p<0.05, *p<0.02, **p<0.01) indicate statistically significant changes from pretreatment values.](image)
maximum concentration (C max) was 172.3±18.3 ng/ml in study I and 200.2±19.8 in study II, but the difference between the two studies was not significant. The time to reach maximum concentration (T max) was 1.70±0.31 hr in study I and 1.55±0.14 in study II, and the difference was not significant. The area under the blood concentration curve \( [\text{AUC}]_0 \) of 229.0±29.2 in study I was not significantly different from that of 292.3±31.2 in study II either. Thus, there were no significant differences in the results of pharmacokinetic analysis between the two studies.

The changes in PRA are shown in the upper part of Fig. 3. In study I, PRA increased from 2.81±0.95 ng/ml/hr as the baseline level to 6.05±1.90 as the maximum level 60 min after the drug administration and the elevated PRA then returned to 3.93±1.56 at 180 min. Significant elevations compared to the pretreatment level were noted at all time points. In study II, the maximum PRA level of 8.64±2.31 was reached from a baseline level of 3.58±0.96, at 90 min. At 180 min, the elevated PRA had returned to 5.97±1.41. Significant increases were found 60, 90 and 120 min after the drug administration. There were no significant differences in the increments of PRA at the same time points between the two studies.

As shown in middle part of Fig. 3, maximum reductions (52.4±4.3 pg/ml in study I and 60.6±5.9 in study II) in PA were reached at 90 and 60 min after the treatment from their baseline levels (68.6±8.4 in study I and 72.8±7.4 in study II), respectively. The values had returned almost to each baseline level at 180 min (69.1±9.1 in study I and 82.8±12.7 in study II). Significant reductions were noted at 90 and 120 min in study I, and at 60 min in study II.

![Fig. 2. Changes in blood concentration of captopril following 25 mg oral administration of the drug in a two-way crossover study where the drug was given 30 min (solid circles) and 2 hr (open circles) after a meal. Each point and vertical bar represent mean value±S.E. (n=10). The p values (*p<0.05) indicate statistical significance.](image-url)
Captopril and Food

Fig. 3. Responses of plasma renin activity (PRA), plasma aldosterone (PA) and plasma angiotensin I converting enzyme activity (ACE-A) to 25 mg of captopril administration 30 min (solid circles) and 2 hr (open circles) after a meal. Each point and vertical bar represent mean value±s.e. (n=10). The p values (* p<0.05, † p<0.02, ‡ p<0.01) refer to a comparison with the values before the administration of captopril.

The bottom part of Fig. 3 shows the changes in ACE-A in both studies. ACE-A began to fall within 15 and 30 min in studies I and II, and their maximum reductions were found at 180 and 120 min, respectively. The baseline levels in studies I and II were 37.1±5.0 and 38.6±6.2 U/ml, and the minimum levels were 20.0±3.8 and 21.2±4.5, respectively.
DISCUSSION

Food is one of the important factors which can influence the absorption of drugs because orally administered drugs must first be dissolved in the gastrointestinal fluid. It has generally been considered that food intake exerts a negative effect on the absorption of drugs (Heading et al. 1973; Chasseaud and Taylor 1974). Welling (1977) suggested that drugs should be taken on an empty stomach whenever possible. Contrary to the above concept, however, several investigators have demonstrated that food intake can improve the absorption of several drugs (Melander et al. 1977; Beermann and Groschinsky-Grind 1978; Welling 1980). In addition, it has been reported that components and contaminants of food may also influence the absorption and biotransformation processes (Jaffe et al. 1971; McGilveray and Mattok 1972). The above findings indicate that food-drug interactions are very complex, and that a separate determination of the pharmacokinetic characteristics of each newly developed drug is required.

In the first report concerning BCC by McKinstry and Singhvi (1980), who determined the time course of radioactivity following administration of radioisotope labeled captopril, maximum BCC was observed sooner and higher for human subjects who fasted in comparison with those who were fed. The possibility that the radioactivity after the administration of the radioisotope labeled drug reflected the total activity including the free form and protein binding captopril in the blood, should therefore be considered. In the present study, the blood concentration of the free form of captopril was obtained by a newly developed method (Kawahara et al. 1981), and slightly different results in the time course of BCC and PRA between the two situations were observed. The peaks of BCC and PRA in study I were reached sooner than those in study II; however, the levels were higher in study II than in study I. There was a significant difference in BCC levels at 90 and 120 min between the two studies. However, the results of pharmacological analysis expressed as the T1/2, C max, T max and [AUC]o failed to reveal any statistically significant differences between the two studies. Differences in the time courses of BCC between the two studies could not reflect each time course of BP. Two explanations are considered for these inconsistent findings. One is that only precise analyses expressed as the T1/2, C max, T max and [AUC]o are significant for determining the difference in pharmacokinetics. The other is that more than a certain value of BCC cannot induce a more effective hypotensive action. Nor-motension resulting from a some dose of captopril should not be affected by enhanced doses of the drug. For example, it may be sure that 50 mg of the drug induces a statistically significant high level of BCC; however, this dose of the drug may not be able to show a hypotensive effect in a dose dependent manner. A single administration of 100 mg of captopril revealed no hypotensive action in normotensive human subjects (Kono et al. 1980).

In view of the interrelations between humoral factors and BP, tendencies for reciprocal changes in BP and BCC or PRA were found, however, reductions of ACE-A remained at 180 min in both studies. These discrepant changes between BP,
BCC or PRA and ACE-A render it difficult to determine the precise hypotensive mechanisms of the drug. It is possible that the complex nature of the hypotensive action of the drug could be elucidated by including a search for changes in vasodilators, such as kinin or prostacyclin (Honda et al. 1981). In any case, based on the responses of BP in the two situations, where 25 mg of the drug was given at 30 min and 2 hr after breakfast, the influence of food on the clinical effects of captopril appears insignificant. However, further studies into the problem of the absorption of captopril under various conditions are required.

Acknowledgments

We express thanks to Mr. Seichi Shimada and Sankyo Co. for the supply of captopril, and Mrs. Noriko Izumi for her secretarial help.

References