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THE SECOND PEAK IN THE SERUM LEVELS CURVE AFTER ORAL ADMINISTRATION OF A SLOW-RELEASE QUINIDINE DOSAGE FORM: EFFECT OF FOOD

Oral administration of a slow-release dosage form of quinidine gluconate has been reported to lead to two peaks in the serum level curve (Greenblatt *et al.*, 1977; Covinsky *et al.*, 1979). It has been postulated, as suggested for acetaminophen by Clements *et al.* (1978), that this phenomenon could be attributed to a biphasic gastric emptying pattern (Covinsky *et al.*, 1979). We now report that the second maximum could be related to the standard lunch which is provided to subjects in bioavailability studies after a standard fasting period following drug administration.

To investigate the effect of food on the serum level curve of this drug, a clinical study of a fast- and slow-release dosage form of quinidine gluconate (tablets A: Quinate® from Rougier, Chambly, Québec, lot no. 02XD, and B: Quinaglute® from Cooper Laboratories, Cedar Knoll, N.J., lot no. E, 9160, respectively) has been undertaken (Spénard *et al.*, 1982). Two groups of nine healthy volunteers participated in the study after giving informed consent. In two crossover studies (one latin square for

each dosage form) single doses of quinidine gluconate equivalent to 405 mg quinidine base were administered on three separate occasions, 1 week apart. After fasting for 10 h, each subject received in random sequence this single dose according to three modes T of administration: without (T_1), before (T_2) and after (T_3) a standard breakfast. A standard lunch was given after a 4 h fasting period, following the administration of the drug. Venous blood samples were drawn from a heparin lock where the first 1 ml of blood was rejected or by venipuncture. Blood specimens were collected prior to dosing and at 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.5, 15.0, 24.0, 32.0, 48.0 and 72.0 h after drug administration. The serum concentration of quinidine was determined by a modification of the h.p.l.c. method of Drayer *et al.* (1977). Quinine was used as the internal standard. The residue of the extract, obtained from 100 μ l of serum, was reconstituted in 100 μ l of methanol and 10 μ l were injected into the liquid chromatograph (Spénard *et al.*, 1982).

As reported previously (Sirois *et al.*, 1980), the first peak levels were found to be significantly lower and were reached significantly later after administration of tablets B than after tablets A. The second peak serum level was noticeable only with the sustained-release dosage form and for treatment (T_3) only. Figure 1 shows the serum levels of a representative subject (no. 8) on 3 treatments with tablets B.

In order to determine the significance and the time

of the appearance of the second serum peak concentration of quinidine, the difference in serum concentration, ΔC , after the first peak was computed for each corresponding time interval of blood sampling. The values of this parameter were statistically analysed by computer (Table 1) using the SPSS-MANOVA program (Nie *et al.*, 1975). Individual comparisons were made through the use of the Newman-Keul's multiple-range test.

Figure 1 Serum quinidine concentrations after oral administration of a sustained-release quinidine gluconate dosage form in subject 8. T_1 without ($\circ$); T_2 before ($\square$) and T_3 after (∇) a standard breakfast.

Table 1 Mean difference in serum concentration ($\mu\text{g/ml}$) at various time intervals.

Dosage forms of quinidine	Time intervals (h)	Treatments ^a			MANOVA		Newman-Keuls' test ^b
		T_1	T_2	T_3	F	P	
A	3.5-4.0	-0.065 (0.123)	+0.025 (0.188)	-0.071 (0.081)	1.69	0.2	
	4.0-4.5	-0.033 (0.125)	-0.138 (0.077)	-0.104 (0.111)	1.30	0.3	
	4.5-5.0	-0.115 (0.079)	-0.139 (0.147)	-0.020 (0.124)	1.13	0.3	
B	3.5-4.0	-0.002 (0.078)	-0.025 (0.059)	-0.066 (0.125)	0.73	0.5	
	4.0-4.5	-0.015 (0.139)	+0.022 (0.082)	+0.170 (0.114)	5.37	0.01	<u>T_1 T_2 T_3</u>
	4.5-5.0	-0.077 (0.068)	-0.097 (0.315)	+0.015 (0.112)	1.23	0.3	

^aThe value in parentheses is the s.d.; ^bTreatment parameters which are underlined by the same line are not significantly different ($P > 0.05$).

A Quinate $\text{\textcircled{A}}$, B Quinaglate $\text{\textcircled{B}}$.

T_1 without, T_2 before and T_3 after a standard breakfast.

For each dosage form there was no significant difference among treatments in the calculated ΔC between 3.5–4 and 4.5–5 h. However, between 4.0 and 4.5 h, a statistically significant difference was found among treatments with the sustained-release dosage form ($P < 0.02$). When testing for differences between dosage forms, the difference was significant ($P < 0.03$) in the latter interval of time, only.

Since this time interval is just following the standard lunch, it is considered here that this peak must be related to this meal. The fact that the effect is noticeable only with tablets B in treatment (T_3) where the drug is absorbed more slowly suggests that the fraction of unabsorbed drug at lunch time could also be an important factor. In fact, the percentage of absorbed drug after 4 h, as calculated from pharmacokinetic constants (Spénard *et al.*, 1982), was found to be significantly lower in treatment T_3 . An exceptional increase in treatment T_2 could be observed in only two subjects who effectively showed a slow drug absorption (e.g., subject 8 in Figure 1).

In view of the above observations, the effect of lunch on the serum levels could be interpreted in terms of the following mechanisms:

(1) An increase in the mobility of the gastrointestinal tract at the time of the meal taken 4 h after drug administration would favour the deaggregation, dissolution and absorption of residual unabsorbed quinidine. Assuming that quinidine absorption—as postulated for basic drugs in general—occurs at the intestinal level, a meal promoting the evacuation of gastric content containing residual quinidine, could also explain the observed second serum peak. This increased gastrointestinal mobility could be associated with a transient increase in the intestinal and hepatic blood flow as suggested for explaining the effect of food on the absorption of propranolol (Melander *et al.*, 1977) and drugs subject to first-pass metabolism (Maclean *et al.*, 1978) such as quinidine (Ueda *et al.*, 1976).

(2) An increase in serum protein binding of quinidine when the drug is administered with a meal, as reported by Woo & Greenblatt (1980), could also

contribute to the observed peak, but to a lesser extent than the first proposed mechanism since there is no significant serum concentration increase in treatment T_1 and T_2 between 4 and 5 h for tablets B and in all treatments for tablets A. In our study, the use of a heparin lock is inevitably associated with some degree of systematic heparinisation which could influence quinidine binding in blood. This effect of heparin on binding appears to be variable (Ochs *et al.*, 1980) and adds complexity to pharmacokinetic studies (Naranjo *et al.*, 1980).

(3) An enterohepatic circulation of quinidine could also be involved in the occurrence of the second peak. However, this mechanism would not seem to be important if one considers that the increase in serum concentration after the standard lunch is not significant when the slow-release product is administered in a fasting state or before a standard breakfast (Table 1).

From the viewpoint of clinical significance, the average change in concentration of the second peak after food is small. In most patients, for conditions corresponding to those of this study, it is unlikely to be of significance. However, the results of this investigation indicate that the standard meal, taken after drug administration followed by a fasting period, could contribute to observed variations when one is comparing results of different bioavailability studies. Such variations could be influenced by the nature of the meal, the fasting time period following drug administration, the percent of unabsorbed drug at meal time and blood sampling times.

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PROLONGED CONVERTING ENZYME INHIBITION FOLLOWING CAPTOPRIL IN PATIENTS WITH RENAL INSUFFICIENCY

Captopril (Capoten) has been evaluated in the treatment both of hypertension and cardiac failure (Atkinson & Robertson, 1979). However, it is currently indicated only for severe or refractory hypertension because of the relatively high incidence of side effects which include skin rashes and loss of taste, although serious side effects, proteinuria and blood dyscrasias, have been noted especially when captopril is given in high dosage or to patients with renal failure (Lancet, 1980).

A reliable convenient method of analysis for captopril in biological fluids has not been available because of reversible formation of complexes of captopril and endogenous thiol groups. In addition, it is possible that metabolites of captopril may have some inhibiting effect on converting enzyme activity (ACE). However, inhibition of plasma ACE has been shown to be related to haemodynamic responses following single dosing with captopril, and, in these circumstances, measurement of the ACE inhibition may provide an index of plasma captopril concentration (Campbell *et al.*, 1981, 1982).

Captopril (25 mg) or inactive placebo was administered orally on two occasions not less than 7 days apart with random allocation of treatment order to six patients with moderate to severe renal failure and six normal volunteers. Clinical details of the patients with renal failure are shown in Table 1. No alcohol, cigarettes, heavy exercise or caffeine-containing beverages were allowed the day prior to or the day of the study. Patients with renal failure continued to receive their regular medication throughout the study. Those on regular haemodialysis were studied the day following their dialysis. Measurements of blood pressure, heart rate, plasma renin activity, ACE activity and noradrenaline concentration (erect) were made at intervals for up to 72 h following captopril or placebo. Blood pressure and heart rate were measured with a semi-automatic sphygmomanometer (Bosch and Sohn) after 10 min resting supine and after 5 min standing. Supine plasma renin activity

was measured using a commercially available radioimmunoassay kit (REN-K). Noradrenaline was measured using the sensitive radioenzymatic assay of Henry *et al.* (1975). ACE activity must be measured immediately after collection of blood as loss of the inhibitory effect of captopril occurs when stored, even at -20°C , leading to an underestimation of *in vivo* inhibition (Boomsma *et al.*, 1981; Roulston *et al.*, 1980). In this study ACE activity was measured within 4 h of venesection, using a high pressure liquid chromatographic method (Chiknas, 1979) in which ACE activity is calculated by the amount of hippuric acid generated from the substrate hippuryl-L-histidyl-L-leucine. The coefficient of duplicate variation was 5%. Statistical evaluation was by analysis of variance for repeated measures and by Student's *t*-test as appropriate. The protocol was approved by the local Ethical Review Committee and the subjects gave informed written consent to participate.

There were no side effects in either group. ACE activity was similar before treatment on each study day ($42.0 \text{ nmol ml}^{-1} \text{ min}^{-1}$ in the patients and $46.5 \text{ nmol ml}^{-1} \text{ min}^{-1}$ in the normal subjects on Day 1, $40.4 \text{ nmol ml}^{-1} \text{ min}^{-1}$ and $37.2 \text{ nmol ml}^{-1} \text{ min}^{-1}$ on Day 2). ACE activity did not change significantly after placebo. Inhibition of ACE activity, and thus plasma captopril level, was maximal in both normal volunteers and patients between 60 and 90 min after administration of captopril. However, in the normal subjects activity after 12 h did not differ significantly from pre-treatment control values, whereas significant inhibition remained after 48 h in the patients. In both groups reversal of ACE inhibition was mono-exponential with a half-life increased threefold in patients with renal failure ($14.3 \pm 0.8 \text{ h}$, mean $\pm$ s.e. mean) compared with those with normal renal function ($4.6 \pm 0.4 \text{ h}$) ($P < 0.05$). When the extent of inhibition was assessed by the area under the inhibition time curve there was again a significant increase in patients with renal impairment ($1856 \pm 198\%$ inhibition h) compared with normals ($485 \pm 50\%$