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Inter- and intrasubject variations of multiple saliva peaks of acetaminophen after oral administration of tablets

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Summary

Acetaminophen (AAP) tablets (500 mg) were administered twice orally to five fasted male subjects with a dosing interval of 1 week. Multiple saliva peaks were observed during both trials in all the subjects with considerable inter- and intrasubject variations. The second peaks of AAP in the fasted subjects were evoked irrespective of food intake.

Acetaminophen (AAP) has been reported to show multiple peaks in its plasma (Clements et al., 1978) and saliva (Shim et al., 1990) concentration-time profiles following oral administration to man. Biphasic gastric emptying was suggested as a cause for the multiple peaks of AAP (Clements et al., 1978), based on the correlation between gastric emptying pattern and plasma AAP profiles after oral administration of AAP solution to the fasted subjects. Oberle and Amidon (1987) proposed the hypothesis that variable gastric emptying rate will result in double peaks of drugs with short half-lives such as ranitidine and cimetidine.

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If this suggestion is true, considerably large inter- and intrasubject variations of the peak patterns should be expected, since the gastric emptying patterns show great inter- and intrasubject variations (Mojaverian et al., 1991). Nevertheless, another representative drug showing multiple plasma peaks, ranitidine, showed very little variation in peak patterns among individuals over a period of 1 week (Shim and Hong, 1989).

It is our interest to determine whether the slight intrasubject variations are ranitidine-specific or just a general reaction to drugs showing multiple peaks. With this in mind, AAP tablets were administered twice to five fasted male subjects with a dosing interval of 1 week and the reproducibility of the double-peak patterns was examined. Saliva instead of plasma was sampled for convenience and safety since the concentrations of AAP in saliva and plasma were con-

firmed to be linearly proportional (Shim et al., 1990).

On the other hand, food intake after drug dosing has often been considered to evoke the second peaks of certain drugs such as cimetidine (Pedersen, 1981) and ranitidine (Miller, 1984). We have already reported multiple plasma peaks for AAP after oral administration of AAP tablets (500 mg) to five non-fasted male subjects (Shim et al., 1990). In the present study, the AAP tablets were administered to five fasted subjects to examine the effect of food intake on the appearance of the second AAP peaks.

Acetaminophen tablets (500 mg, Tylenol, Korea Cilag Co. Seoul, Korea) were administered to five healthy Korean male volunteers ranging in

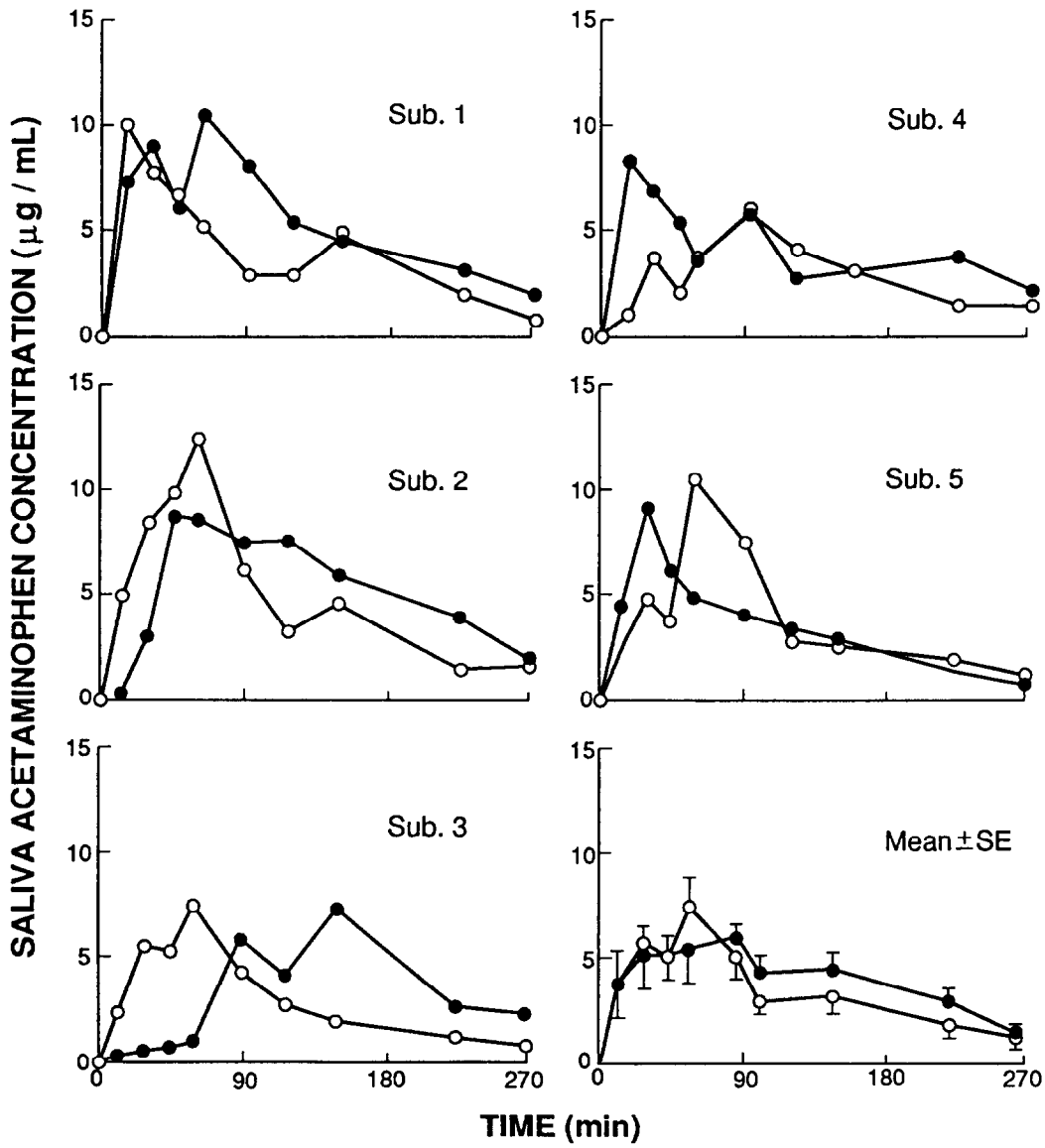

Fig. 1. Saliva concentration-time curves after oral administration of acetaminophen tablet (500 mg) to fasted male subjects at trial I (○) and II (●). The time interval between the trials was 1 week.

age from 20 to 23 years (mean 21.5), in weight from 58 to 70 kg (mean 62.5), and in height from 167 to 174 cm (mean 169.7). The disintegration time of the tablets in pH 1.2 buffer was 4.1 ± 0.8 min ($n = 10$) as determined by the USP XXII method. Subjects 1–3 were smokers, and the other two were non-smokers. Informed consent was obtained from each subject. All subjects were healthy with normal hepatic and renal functions and normal haematological profiles. None was taking any drug or alcohol. They were fasted 12 h after a standard meal during the evening (9 p.m.) before the experiment.

On the next morning (8 a.m.) AAP was administered as 500 mg Tylenol tablets to the five subjects. The oral cavity was then immediately rinsed with 200 ml of water. Standard meal and water (ad libitum) were allowed 2.5 h after the dose. No food or drink was permitted until then, and sleep was not allowed during the experiment. Saliva samples (2 ml) were collected immediately before and 15, 30, 45, 60, 90, 120, 150, 225 and 270 min after dosing. The samples were stored frozen at −20°C until assay for AAP. A small amount (20 mg) of citric acid was put on the tongue and held for 1 min in order to stimulate salivary flow. All the subjects took Tylenol again 1 week after the first dosing in the same fashion.

AAP in saliva samples were assayed modifying the reported HPLC method (Shim et al., 1990). To 1.0 ml of centrifuged ($6000 \times g$, 1 min) saliva, 1 ml of 0.3 N barium hydroxide was added. After vortexing for 2 min, 1 ml of 5% (w/v) zinc sulphate was added and vortexed for 1 min. After centrifugation at $6000 \times g$ for 10 min, 20 μl of the supernatant was injected onto the reversed-phase C_{18} column (10 μm, μ-Bondapak, 30 cm × 0.39 cm i.d., stainless-steel, Waters, P/N 27324). AAP was monitored at 245 nm and the detection limit was 0.1 μg/ml. The mobile phase was a 11:89 (v/v) mixture of acetonitrile and water. The flow rate of the mobile phase was adjusted to 1.0 ml/min and the mean operating pressure was 60 bar. AAP was appropriately separated from other substances in the saliva with a retention time of 4.9 min. The total run time per injection to eliminate any possible interfering peaks was 8 min. The AAP concentrations in the saliva samples were calculated from the peak height ratio of AAP using the standard calibration curve. Recovery of AAP from the saliva samples was 92.5% in the concentration range of 0.5–20 μg/ml, and calibration curves were linear in this concentration range. Intra- and interassay coefficient of variations were 4.5 and 7.8%, respectively.

The area under the saliva AAP concentration-time curve (AUC) and area under the moment of saliva concentration-time curve (AUMC) from time zero to 270 min were calculated by the trapezoidal rule. The mean residence time (MRT) of AAP was calculated based on the AUMC/AUC ratio. Saliva concentrations of the first (C_{max1}) and second (C_{max2}) peaks, and the time to reach the first (T_{max1}) and second (T_{max2}) peaks were read directly from the experimental data. Differences between the parameters were examined for significance by paired t-test. A p value of 0.05 or less was considered to be significant.

The saliva AAP concentration-time curves after oral administration of tablets to five fasted subjects are shown together in Fig. 1. Distinct

TABLE 1

Comparison of multiple-peak parameters of acetaminophen (500 mg) administered orally to human subjects as tablets (n = 5)

Trial	C_{max1} (μg/ml)	C_{max2} (μg/ml)	C_{max2}/C_{max1} ratio	T_{max1} (min)	T_{max2} (min)	AUC (min μg ml^{-1})	MRT (min)
I	7.6 ±3.6	7.0 [a] ±1.8	1.2 [a] ±0.7	33 ±16	102 [a] ±46	1057.1 ±349.1	226.3 ±131.0
II	8.5 ±1.4	8.1 ±1.8	1.0 ±0.2	42 ±29	105 ±39	1570.8 ±402.5	184.8 ±32.2

[a] Expressed as mean ± SD of four experiments except for subject 5 in trial I. Time interval between the first (trial I) and second dosings (trial II) was 1 week.

multiple saliva peaks appeared in all the subjects during both trials except subject 5 in trial II (second dosing). There was no difference between smokers and non-smokers in the peak profiles. This is consistent with our recent work (Shim et al., 1990), where distinct double peaks of AAP were observed in the plasma and saliva profiles after oral administration of tylenol to four fed male subjects. The concentration-time profiles of AAP in the saliva will reflect those of the plasma, since the saliva/plasma ratio of AAP in Korean male subjects was confirmed to be constant at 1.05 ($r = 0.944$, $p < 10^{-6}$) (Shim et al., 1990). Subject 5 in trial II showed a single peak, while subject 4 in trial I showed three peaks. Average saliva concentration-time curves during both trials also showed distinct double peaks.

The effect of a 1 week interval on the peak patterns and bioavailability parameters is summarized in Table 1. There was no significant difference in the parameters between the two trials. T_{max1}, T_{max2}, C_{max1} and C_{max2} were in the range of 15–90, 60–150 min, 4.3–12.5 and 4.9–11.0 μg/ml, respectively, in both trials. The C_{max2}/C_{max1} ratio ranged from 0.4 to 2.1 except for subject 5 in trial II. C_{max1} was much lower than C_{max2} in some cases (subjects 3–5 in trial I, and subjects 1 and 3 in trial II). AUC, AUMC and MRT during both trials were in the range of 508.2–2160.4 min μg ml^{-1}, 136875.2–490316.1 min^2 μg ml^{-1} and 120.1–451.1 min, respectively.

Our recent work on oral ranitidine in man (Shim and Hong, 1989) showed a small intrasubject variation in the multiple-peak patterns over a dosing interval of 1 week. However, its intersubject variation was considerably larger as expected. There were significant linear correlations between the two trials in C_{max1}, C_{max2}, T_{max1} and AUC, indicating high reproducibility of the multiple-peak patterns of ranitidine over 1 week.

In contrast to ranitidine, the multiple saliva peaks of AAP showed a substantial intrasubject variation over a 1 week period. Intersubject variation of AAP was almost comparable to that of ranitidine. There were no significant correlations between the two trials in T_{max1}, T_{max2}, C_{max1} and C_{max2}. The large intrasubject variation of the multiple peak patterns seems to be spontaneous considering the large inter- and intrasubject variabilities in the duration of each phase of the interdigestive migrating motor complex (IMMC) and inter-IMMC interval (Mojaverian et al., 1991). The reason why ranitidine shows limited intrasubject variation remains unknown at present. It would be intriguing to clarify whether the reproducibility of the multiple-peak patterns is dependent on the characteristics of the drug substances or on the gastric emptying patterns of each individual. Further studies including simultaneous administration of multiple-peak drugs would be necessary before a clear conclusion can be drawn.

Additional information on the effect of food intake on the appearance of the multiple peaks was obtained from the present study. The second peaks of AAP in the present study appeared prior to food intake at 2.5 h after drug dosing. The second plasma peaks of ranitidine also appeared prior to food intake in the fasted subjects (Shim and Hong 1989). Moreover, T_{max1} and T_{max2} of AAP in fed subjects (Shim et al., 1990) did not differ from those of the present study. Therefore, multiple peaks of AAP and ranitidine were concluded not to be evoked by food intake in spite of the previously reported assumptions for cimetidine (Pedersen, 1981) and ranitidine (Miller, 1984).

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References

Clements, J.A., Heading, R.C., Nimmo, W.S. and Prescott, L.F., Kinetics of acetaminophen absorption and gastric emptying in man. *Clin. Pharmacol. Ther.*, 24 (1978) 420–431.

Miller, R., Pharmacokinetics and bioavailability of ranitidine in humans. *J. Pharm. Sci.*, 73 (1984) 1376–1379.

Mojaverian, P., Reynolds, J.C., Ouyang, A., Wirth, F., Kellner, P.E. and Vlasses, P.H., Mechanism of gastric emptying of a nondisintegrating radiotelemetry capsule in man. *Pharm. Res..*, 8 (1991) 97–100.

Oberle, R.L. and Amidon, G.L., The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; An explanation for the double peak phenomenon. *J. Pharmacokinet. Biopharm.*, 15 (1987) 529–544.

Pedersen, P.V., Pharmacokinetic analysis of linear system approach I: Cimetidine bioavailability and second peak phenomenon. *J. Pharm. Sci.*, 70 (1981) 32–38.

Shim, C.K. and Hong, J.S., Inter- and intrasubject variation of ranitidine pharmacokinetics after oral administration to normal male subjects. *J. Pharm. Sci.*, 78 (1989) 990–994.

Shim, C.K., Kim, M.A., Lee, M.H. and Kim, S.K., Development of controlled release oral drug delivery systems by membrane-coating technique. II. Correlation between saliva and plasma concentration of acetaminophen in man. *J. Kor. Pharm. Sci.*, 20 (1990) 29–33.