THE EFFECT OF ANTACID ON ASPIRIN PHARMACOKINETICS IN HEALTHY THAI VOLUNTEERS

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ABSTRACT

The effect of antacid on aspirin pharmacokinetics and bioavailability was determined in 10 healthy adult male and female volunteers, aged 20-45 years old. Each subject received 650 mg of aspirin orally after an overnight fast. The wash out period was 14 days and then all subjects were given 650 mg of aspirin 10 minutes after antacid (aluminium hydroxide and magnesium hydroxide). Plasma aspirin, salicylate and salicyluric acid levels were determined by a specific high performance liquid chromatographic analysis. Individual plasma profiles were analysed using compartmental and non-compartmental methods. The results show that antacid affected the relative bioavailability of aspirin since the mean peak concentration (C_{max}) of aspirin was significantly higher when antacid was given. However, the time to reach peak concentration (T_{max}) and the area under the plasma concentration-time curve (AUC) showed no significant difference between the two treatments. It was, therefore, not possible to conclude that the non-bioequivalence was caused by a difference in rate or amount of aspirin absorption, or both. No significant difference was observed in C_{max}, T_{max}, AUC, $t_{1/2}$, K_a, K_{el} of salicylate and salicyluric acid. However, the rate of total salicylate absorption was increased since the absorption rate constant (K_a) was higher when antacid was given. This may provide a more rapid effect of the drug.

KEY WORDS

salicylate, salicyluric acid, aspirin, antacid, aluminium hydroxide, magnesium hydroxide, pharmacokinetics, bioavailability

INTRODUCTION

Aspirin (acetylsalicylic acid) is the most widely prescribed analgesic-antipyretic and anti-inflammatory agent and it is the standard drug for comparison and evaluation of other similar compounds /1/. The main therapeutic uses of aspirin to reduce pain, fever and inflammation have been known for many years. The optimal analgesic or antipyretic dose of aspirin is less than 0.6 g orally and may be repeated every 4 hours. The average anti-inflammatory dose is 4 g daily /2/.

Regarding the adverse reactions related to aspirin, gastrointestinal side effects are the most important because of their possible severity (bleeding). Thus rheumatoid arthritic patients who are prescribed high doses of aspirin are generally advised to take aspirin with meals followed by a glass of water or antacids in order to minimize the gastric intolerance.

Aspirin is rapidly absorbed from the stomach and upper small intestine /1/. Many factors are known to affect the rate of absorption, one being the pH of the stomach contents /3/. It the pH is increased, salicylate is more ionized and this tends to decrease the rate of absorption; however, a rise in pH also increases the solubility of salicylate, enhancing absorption /1/. After absorption, aspirin is rapidly metabolized to salicylic acid by esterase activity in the intestinal wall, liver and other tissues. Salicylates are excreted mainly by the kidney as free salicylic acid (10%), salicyluric acid (75%), salicylic phenolic glucuronide (10%), acyl glucuronide (5%) and gentisic acid (less than 1%). The excretion of free salicylate is extremely variable and depends upon both the dose and the urinary pH. In alkaline urine, more than 30% of the drug may be eliminated as free salicylate, whereas in acidic urine this may be as low as 2%. Thus the administration of aspirin with other drugs which alter urinary pH will affect the plasma concentration of aspirin. The alteration of gastric and urinary pH and the effect on steady-state serum salicylate by sodium bicarbonate is well known /4/. It is not generally realized that some widely used non-systemic antacid can have a similar effect. Therefore it would be very interesting to determine the interaction of aspirin and the most commonly used antacid from the viewpoint of pharmacokinetics. The aim of this work was to elucidate the effect of a commonly used non-systemic antacid (aluminium and magne-

sium hydroxide) on aspirin pharmacokinetics in healthy Thai volunteers.

MATERIALS AND METHODS

Chemicals

Aspirin tablets (325 mg) were obtained from the Governmental Pharmaceutical Organization (Lot number T109699). Aluminium and magnesium hydroxide antacid was supplied by the Pharmaceutical Division, Chulalongkorn Hospital (Lot number 19432), Bangkok, Thailand.

Standard aspirin (ASA), salicylic acid (SA), salicyluric acid (SU) and benzoic acid were purchased from Sigma (St. Louis, MO, USA). Methanol (HPLC grade) was obtained from Fairlawn, NJ, USA. Potassium dihydrogen phosphate was purchased from Fouka, Switzerland.

Subjects

Ten healthy Thai volunteers, five male and five female, participated in this study. They were aged from 20-45 years (average 31.6±6.26 years) and weighed between 40-70 kg. All subjects had normal physical examinations and laboratory test data including fasting blood sugar, blood urea nitrogen (BUN), creatinine, SGOT, SGPT and complete blood count (CBC). The subjects took no medication for at least one week before entering this study.

Ethical approval was obtained from the Faculty Board of Ethics Committee (Faculty of Medicine, Chulalongkorn University). The study procedures were explained to the subjects and written informed consent was obtained.

Methods

Two 325 mg plain aspirin tablets were given orally in a single dose with 250 ml of water to half of the subjects after an overnight fast at 7 AM. The others were given antacid (30 ml of magnesium and aluminium hydroxide) 10 minutes before the 2 plain aspirin tablets. The subjects were allowed to have breakfast 2 hours after dosing. Blood samples (5 ml) were drawn from the antecubital vein prior to

dosing (0) and at 15, 30, 40, 50, 60 minutes and 1 1/4, 1 1/2, 2, 3, 4, 5, 6, 8, 12, 24 hours after aspirin administration. All blood samples were collected in centrifuge tubes containing heparin and 5 mg/ml of potassium fluoride (25%) to prevent aspirin hydrolysis. After centrifugation (2,500 rpm for 15 minutes), the plasma samples were collected and frozen at -20°C until analysis the next day. Following a two week wash out period, the treatments were repeated in a cross over manner. Determinations of aspirin (ASA), salicylic acid (SA) and salicyluric acid (SU) in plasma were performed using the modified high performance liquid chromatographic method described by O'Krukl *et al.* /5/.

Preparation of plasma samples

Plasma samples were prepared by transferring 400 μl aliquots of plasma into glass test tubes and mixing with 40 μl 0.004% benzoic acid (internal standard) in 30% perchloric acid solution; 400 μl of methanol was then added to this solution. The samples were vortexed for 2 min and centrifuged at 2500 rpm for 10 min. Aliquots (20 μl) of clear supernatant were injected onto the column.

Chromatographic conditions

Reversed phase HPLC was performed using a Water Model 510 solvent delivery system and a U6K universal injector. A C18 μBondapak column 30 cm x 3.9 mm I.D. (10 μm average particle size) and a guard column (50 x 2 mm I.D.) packed with μBondapak C18/Porasil B were used throughout the investigation. The absorbance of the eluent was determined using a Water Model 481 variable wavelength UV absorption detector. Absorbance was monitored at a wavelength of 235 nm. The mobile phase composition was 25% methanol and 75% potassium dihydrogenphosphate buffer (pH 3.2±0.1). The chromatograms were recorded on a Water Model 740 recorder. The flow rate was 1.8 ml/min.

Standard curve

Various amounts of aspirin (15, 7.5, 3.75, 1.88 μg), salicylic acid (60, 30, 15, 7.5 μg) and salicyluric acid (10, 5, 2.5, 1.25 μg) were added

to 1 ml of pooled drug-free plasma. These samples were analyzed following the same procedure as described above.

Standard curves were constructed based on peak area ratio obtained by internal standardization. The line relating the peak area ratios and the concentration of best fit was measured using a least-squares linear regression method.

Statistical analysis

The following pharmacokinetic parameters of salicyluric acid, salicylic acid, aspirin and total salicylate were determined and compared in the aspirin treated group and the aspirin with antacid treated group:

C_{max} (maximum concentration) and T_{max} (peak time concentration) were obtained from the data;

$[AUC]_0^{24}$ (area under the plasma concentration-time curve from 0 to 24 hours) was calculated by the trapezoidal rule;

Elimination rate constant (K_{el}) and absorption rate constant (K_a) were obtained by computerized CSTRIP program;

Elimination half life ($t_{1/2}$) = $0.693/K_{el}$.

All these pharmacokinetic parameters were presented as means±standard error of the mean and they were analysed using Student's paired t-test.

RESULTS

Analysis of salicyluric acid, salicylic acid and aspirin in plasma samples by HPLC method

The standard curve of salicyluric acid was linear in the concentration range 0-10 μg/ml ($y = 0.2966 + 9.9668x$, $r = 0.9996$). For salicylic acid the calibration curve was linear in the concentration range 0-60 μg/ml ($y = -0.8827 + 7.4334x$, $r = 0.9995$). The aspirin calibration curve was linear in the range 0-15 μg/ml ($y = 8.9310x - 0.5480$, $r = 0.9997$).

The coefficients of variation determined from peak area ratio of the compound to the added internal standard in plasma were less than 7% at all concentrations investigated. Results for the method's precision and reproducibility are summarised in Table 1.

TABLE 1
Precision and reproducibility of the HPLC analysis of salicyluric acid (SU), salicylic acid (SA) and aspirin (ASA)

compound	concentration in plasma (μg/ml)	n	peak area of compound / peak area of I.S. Mean ± SD	% CV
salicyluric acid	10	5	0.966 ± 0.0322	3.33
	5	5	0.4885 ± 0.0313	6.41
	2.5	5	0.2171 ± 0.0107	4.92
	1.25	5	0.0858 ± 0.0039	4.55
salicylic acid	60	5	8.1257 ± 0.2340	2.88
	30	5	4.3088 ± 0.2611	6.05
	15	5	2.095 ± 0.0883	4.21
	7.5	5	1.0798 ± 0.0646	5.98
Aspirin	15	5	1.7308 ± 0.0669	3.87
	7.5	5	0.9242 ± 0.0511	5.29
	3.75	5	0.4792 ± 0.0190	3.96
	1.88	5	0.2604 ± 0.0074	2.84

I.S. = Internal standard

The recovery of salicyluric acid (SU), salicylic acid (SA) and aspirin at each concentration was found to be in the range of 76-94% and the detection limit of each compound was 1 μg/ml.

The chromatogram of plasma salicyluric acid (SU), salicylic acid (SA) and aspirin (ASA) is shown in Figure 1.

The retention times for salicyluric acid (SU), salicylic acid (SA) and aspirin (ASA) were 4.7, 5.3 and 6.4 minutes, respectively, and the retention time for the internal standard (benzoic acid) was 7.9 minutes.

Effect of antacid on aspirin pharmacokinetics

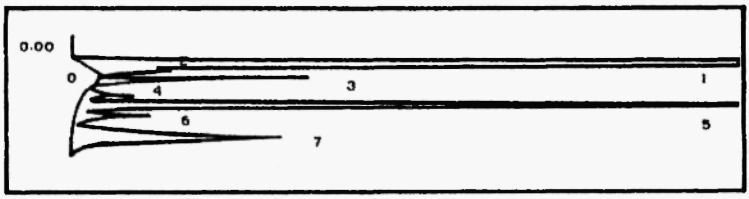
Subject data and routine laboratory results are shown in Table 2. After oral administration of aspirin 650 mg alone or with aluminium and magnesium hydroxide antacid, there was no statistical difference in the mean plasma concentration-time profile curve from 0-24 hours or in the pharmacokinetic parameters of salicyluric acid (SU, Figure 2, Table 3) and salicylic acid (SA, Figure 3, Table 4).

The mean peak plasma concentration (C_{max}) of aspirin after oral administration of aspirin with antacid was significantly higher than peak concentration after oral aspirin alone (C_{max} = 7.196±1.240 and 4.249±0.628 μg/ml, $p < 0.05$, Table 5, Figure 4) and the mean absorption rate constant (K_a) of total salicylate was also higher after concomitant ingestion of aspirin with antacid, as shown in Table 6, Figure 5 (K_a = 2.612±0.433 and 1.376±0.214, $p < 0.05$).

The concentration-time profile of salicyluric acid, salicylic acid, aspirin and total salicylate were fitted to a two compartment kinetic model by using the computerized CSTRIP program analysis.

DISCUSSION

The described method has adequate accuracy and precision for determination of salicyluric acid, salicylic acid and aspirin levels in human plasma after oral administration of aspirin 650 mg, since the coefficients of variation were found to be less than 7% and the percentage recovery of all the compounds was higher than 75%. The detection limit of each compound was 1 μg/ml, and no interference from other substances in plasma was observed in the chromatogram.



Peak number	Name	Retention time (min)
1	plasma peak	1.925
2	plasma peak	2.458
3	plasma peak	3.141
4	salicyluric acid	4.718
5	salicylic acid	5.325
6	aspirin	6.411
7	benzoic acid	7.921

Fig. 1: Chromatogram of salicyluric acid (SU), salicylic acid (SA) and aspirin (ASA) in human plasma 75 minutes after oral administration of aspirin 650 mg.

TABLE 2
General characteristics and laboratory results of 10 healthy subjects

Subject No	Sex	Weight (kg)	Age (years)	Glucose (mg/dl)	BUN (mg/dl)	Creatinine (mg/dl)	SGOT unit	SGPT unit	Albumin (g/dl)	Globulin (g/dl)
1	M	58	29	100	10	0.6	37	33	3.75	2.60
2	M	59	31	87	11	1.0	38	17	4.90	3.20
3	M	63	44	93	10	0.6	26	22	3.55	3.95
4	M	78	33	91	10	0.9	23	20	3.85	2.85
5	M	57	24	93	8	0.8	21	12	4.30	2.80
6	F	44	38	95	10	0.4	23	27	3.25	3.30
7	F	44	31	94	11	0.7	19	14	3.55	3.55
8	F	60	24	79	10	0.8	19	12	3.45	4.05
9	F	50	27	82	12	0.7	25	20	3.95	2.90
10	F	50	35	87	10	0.8	21	16	3.75	3.75

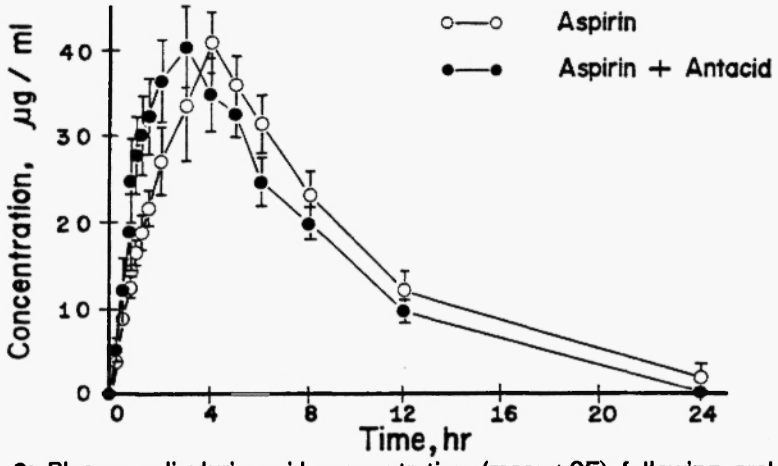


Fig. 2: Plasma salicyluric acid concentration (mean±SE) following oral administration of aspirin with and without antacid.

TABLE 3

Plasma pharmacokinetic parameters (mean±SE) of salicyluric acid (SU) from 10 subjects following oral administration of aspirin (650 mg) and aspirin (650 mg) with antacid.

Parameter	Aspirin(650mg)	Aspirin (650mg) with antacid
Tmax	246.0 ± 30.265	243.0 ± 37.536
Cmax	1.752 ± 0.192	1.878 ± 0.175
AUC	23.307 ± 4.861	17.966 ± 2.139
Ka	5.890 ± 4.446	3.605 ± 1.475
Kel	0.124 ± 0.026	0.155 ± 0.024
T1/2	9.707 ± 3.520	6.422 ± 1.831

Tmax = Time to reach maximum concentration (min)
Cmax = Peak concentration (μg/ml)
$[AUC]_0^{24}$ = Area under the plasma concentration-time curve from time zero to 24 hours (μg/ml)
Ka = Oral absorption rate constant (hr^{-1})
Kel = Elimination rate constant (hr^{-1})
t1/2 = Elimination half life (hr)

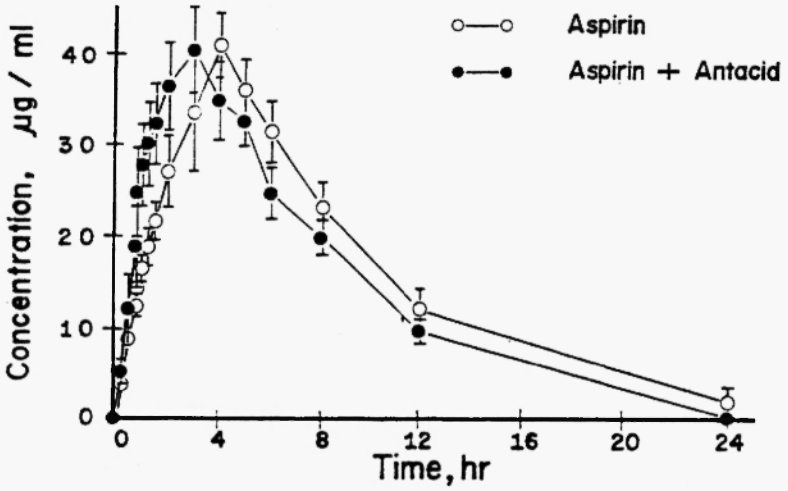


Fig. 3: Plasma salicylic acid concentration (mean±SE) following oral administration of aspirin with and without antacid.

TABLE 4

Plasma pharmacokinetic parameters (mean±SE) of salicylic acid (SA) from 10 subjects following oral administration of aspirin (650 mg) and aspirin (650 mg) with antacid

Parameter	Aspirin(650mg)	Aspirin (650mg) with antacid
Tmax	204.0 ± 16.00	168.0 ± 21.071
Cmax	43.009 ± 3.760	43.227 ± 4.735
AUC	380.940 ± 42.156	329.801 ± 31.974
Ka	1.613 ± 0.155	1.908 ± 0.457
Kel	0.306 ± 0.030	0.322 ± 0.031
T1/2	2.471 ± 0.265	2.381 ± 0.315

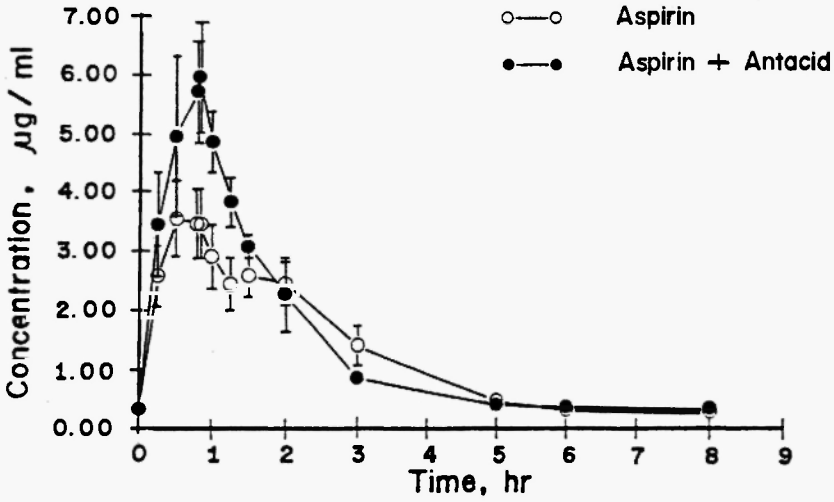


Fig. 4: Plasma aspirin concentration (mean±SE) following oral administration of aspirin with and without antacid.

TABLE 5

Plasma pharmacokinetic parameters (mean±SE) of aspirin (ASA) from 10 subjects following oral administration of aspirin (650 mg) and aspirin (650 mg) with antacid

Parameter	Aspirin(650mg)	Aspirin (650mg) with antacid
Tmax	54.444 ± 9.761	53.00 ± 8.035
Cmax	4.249 ± 0.628	7.196 ± 1.240*
AUC	15.857 ± 1.688	16.744 ± 1.221
Ka	4.637 ± 0.923	2.908 + 0.561
Kel	0.054 + 0.013	0.038 ± 0.011
T1/2	15.566 ± 2.358	21.372 ± 9.763

*$p < 0.05$

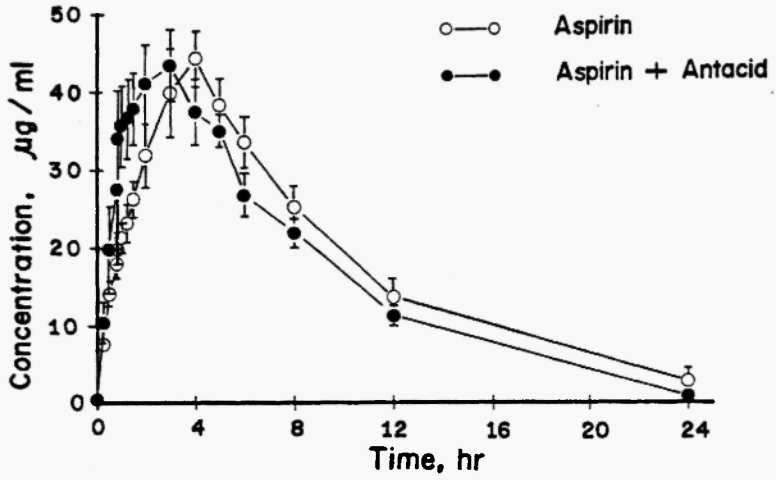


Fig. 5: Plasma total salicylate concentration (mean±SE) following oral administration of aspirin with and without antacid.

TABLE 6
Plasma pharmacokinetic parameters (mean±SE) of total salicylate from 10 subjects following oral administration of aspirin (650 mg) and aspirin (650 mg) with antacid

Parameter	Aspirin(650mg)	Aspirin (650mg) with antacid
Tmax	198.0 ± 18.0	152.00 ± 25.113
Cmax	47.566 ± 3.769	48.568 ± 5.172
AUC	429.947 ± 43.593	394.107 ± 31.167
Ka	1.376 ± 0.214	2.612 ± 0.443*
Kel	0.201 ± 0.015	0.193 ± 0.013
T1/2	3.622 ± 0.300	3.734 ± 0.265

*$p < 0.05$

The maximum plasma drug concentration (C_{max}) represents the highest plasma concentration achieved after drug administration and it also reflects both the rate and extent of drug absorption into the body. The mean peak plasma aspirin concentration (C_{max}) after coadministration of antacid with aspirin was higher than the C_{max} after aspirin alone (4.249±0.628 and 7.196±1.240 μg/ml, Table 5) but other parameters were not significantly affected, including the absorption rate constant (K_a = 4.637±0.923 and 2.908±0.561 hr^{-1}), which determines the rate of aspirin absorption and the time to reach peak aspirin concentration (T_{max} = 54.444±9.761 and 53.00±8.035 minute). Therefore, it cannot be concluded that antacid affects the rate or the amount of aspirin absorption.

The results in Table 6 show that the absorption rate constant (K_a) of total salicylate was higher when the combination was administered (K_a = 1.376±0.214 and 2.612±0.433 hr^{-1}). As it is already known that after absorption, aspirin is rapidly hydrolysed to salicylic acid, from this stage onwards the pharmacokinetics of aspirin and other salicylates hydrolysed to salicylic acid are predominantly dependent upon the salicylate moiety /6/. The mechanism by which antacid (aluminium and magnesium hydroxide) affects the rate of total salicylate absorption may be due to the alteration of gastric pH: as pH rises the solubility of aspirin increases /6/ and this facilitates absorption of the drug. However, no significant differences were observed in the area under the total plasma salicylate concentration-time curve (AUC), the maximum total plasma salicylate concentration (C_{max}) and time to reach peak total salicylate concentration (T_{max}). Thus antacid affects bioavailability of total salicylate by enhancing the rate of absorption. Rapid absorption may be beneficial in providing a rapid onset of action and may reduce the contact time with the mucosa, which might reduce the incidence of untoward effects of aspirin ingestion /7/.

Antacid caused no change in the time course of plasma salicylic acid concentration and the pharmacokinetic parameters (Figure 2, Table 3).

Biotransformation of aspirin occurs in many tissues, and particularly in the endoplasmic reticulum and mitochondria /1/. The three main metabolites are salicyluric acid (glycine conjugate 75%), salicyl phenolic glucuronide (10%) and salicyl acyl glucuronide (5%) /8/. Small amounts undergo oxidation to gentisic acid or gentisuric acid, which may be formed by glycine conjugation of gentisic acid or from

salicyluric acid by microsomal oxidation /9, 10/. Salicyluric acid is the major metabolite of aspirin which can be detected in human plasma, and it was found that the peak plasma level of salicyluric acid occurs at the same time as that of free salicylate /8/. The present result demonstrates the time to reach maximum concentration (T_{max}) of salicyluric acid was about 4 hours (Table 3). There was no significant change in all pharmacokinetic parameters of salicyluric acid when antacid was coadministered (Table 3).

The results of our investigation did not agree with those reported by Levy *et al.* /11/, who found that antacid (aluminium and magnesium hydroxide) caused serum salicylate concentration to decrease by 30 to 70% by increasing urinary pH after multiple doses of aspirin were administered in three children with rheumatic fever. However, in the same study, antacid had no effect on the bioavailability of a single oral dose of aspirin in five healthy adult volunteers. The study of five different types of commercial antacid suspension carried out by Gibaldi *et al.* /12/ showed that three types caused an appreciable increase in urinary pH, among them being aluminium and magnesium hydroxide suspension. Thus chronic administration of non-systemic antacid may cause alteration in urinary pH which would probably affect the plasma level of salicylate if the two compounds are administered concomitantly, but there was no effect when antacid was administered as a single dose. The variations in results from different studies could be due to genetic factors, race, criteria for inclusion and exclusion of subjects, methods of drug analysis, and all these factors may apply in this case.

Another study performed by Gaspari *et al.* /13/ revealed that administration of antacids to uremic patients interferes with the absorption of oral aspirin and the interference can be minimized if aspirin and antacid are given simultaneously. The results obtained in the present study show that the mean peak aspirin concentration increased when antacid was given 10 minutes before aspirin. This indicates that the time arrangement for the drugs' administration is one factor that influences drug absorption. Therefore, in cases where aspirin and antacid are to be given concomitantly, antacid should be given prior to aspirin in order to get better aspirin absorption.

CONCLUSION

The pharmacokinetic parameters of aspirin affected by the coadministration of aspirin with antacid in this study were the mean peak plasma aspirin concentration (C_{max}) and the absorption rate constant (K_a) of total salicylate which were significantly increased after the antacid was given. A more rapid absorption of aspirin and a higher plasma drug level would provide a faster onset of effect.

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