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## The effect of antacid on aspirin pharmacokinetics in healthy volunteers\*

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**Itthipanichpong C, Wittayalertpunya S, Sirivongs P, Chaiyos N. The effect of antacid on aspirin pharmacokinetics in healthy volunteers. Chula Med J 1990 Nov; 34(11): 859-870**

*The effect of antacid on aspirin pharmacokinetics and bioavailability was carried out in 10 healthy adult male and female volunteers, age ranging from 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 an antacid. (Aluminium hydroxide and magnesium hydroxide). Plasma aspirin, salicylate and salicyluric acid levels were determined by a specific high performance liquid chromatography analysis. Individual plasma profile was analysed using compartmental and noncompartmental method. The result showed that antacid affected the 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 the difference in the rate or the 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 absorption rate constant ( $K_a$ ) was higher when antacid was given. This may produce the rapid onset of the drug.*

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จันทน์ อธิพานิชพงศ์, สุพิชา วิทยาลัยปัญญา, ไพโรจน์ ศิริวงษ์, นงนุช ไชยยศ. ผลของยาลดกรดต่อเภสัชจลนศาสตร์ของแอสไพรินในคนปกติ. จุฬาลงกรณ์เวชสาร 2533 พฤศจิกายน; 34(11) : 859-870

การศึกษาผลของยาลดกรดต่อเภสัชจลนศาสตร์ (pharmacokinetics) และการเอื้อประโยชน์ในร่างกาย (bioavailability) ของยา aspirin ในอาสาสมัครปกติทั้งชายและหญิง จำนวน 10 คน อายุระหว่าง 20-45 ปี โดยให้อาสาสมัครเหล่านั้นรับประทานยา aspirin 650 มิลลิกรัม และสองสัปดาห์ต่อมาผู้รับการทดลองจะรับประทานยา aspirin ขนาดเท่าเดิม ภายหลังจากที่รับประทานยาลดกรด aluminium และ magnesium hydroxide แล้วเป็นเวลา 10 นาที ทำการเจาะเลือดเพื่อตรวจหาระดับของ aspirin, salicylic acid และ salicyluric acid ใน plasma โดยใช้ High performance liquid chromatography ผลการศึกษาพบว่ายาลดกรดที่ใช้มีผลต่อ bioavailability ของ aspirin เพราะทำให้ค่าเฉลี่ยระดับยาสูงสุดในเลือด (mean peak plasma aspirin concentration, Cmax) มีค่าสูงขึ้นอย่างมีนัยสำคัญทางสถิติภายหลังจากที่ได้รับยาลดกรดร่วมด้วย แต่ค่าเฉลี่ยเวลาที่ทำให้ระดับยาสูงสุดในเลือด (Tmax) และพื้นที่ภายใต้เส้นโค้งที่ถ่วงระหว่างปริมาณ aspirin ใน plasma กับเวลา (AUC) ไม่มีความแตกต่างอย่างมีนัยสำคัญ จึงไม่สามารถสรุปได้ว่าความแตกต่างของ bioavailability ของ aspirin ภายหลังจากที่ได้รับยาลดกรดร่วมด้วย มีสาเหตุจากอัตราการดูดซึมยาที่เปลี่ยนแปลงไป หรือจากปริมาณยาที่ถูกดูดซึมเปลี่ยนแปลงไป และไม่พบความแตกต่างใน pharmacokinetic parameter ของ salicyluric acid และ salicylic acid (Cmax, Tmax, AUC, T1/2, Ka และ Kel) นอกจากค่า Ka ซึ่งเป็นค่าคงที่ที่แสดงถึงค่าคงที่อัตราการดูดซึมยาเข้าสู่ร่างกายของ total salicylate เพิ่มขึ้นอย่างมีนัยสำคัญหลังจากการรับประทานยาลดกรดร่วมกับ aspirin แสดงว่าอัตราการดูดซึม total salicylate เพิ่มขึ้น ซึ่งน่าจะมีผลทำให้ยาออกฤทธิ์ได้เร็วขึ้น

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 others.<sup>(1)</sup> The main therapeutic uses of aspirin are to reduce pain, fever and inflammation and has been known for many years. The optimal analgesic or antipyretic dose of aspirin is less than 0.6 g oral dose and may be repeated every 4 hours. The average anti-inflammatory dose is 4 g daily.<sup>(2)</sup>

Regarding the adverse reactions related to aspirin, gastrointestinal side effect are of primary importance because of their potential severity, (bleeding) thus rheumatoid arthritis patients 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.<sup>(1)</sup> Many factors are known to affect the rate of absorption. One factor is the pH of the stomach content.<sup>(3)</sup> If the pH is increased, salicylate is more ionized and this tends to decrease the rate of absorption; however a rise in pH also increases solubility of salicylate, enhancing the rate of absorption.<sup>(1)</sup> After absorption, aspirin is rapidly metabolized to salicylic acid by esterase activity at the intestinal wall, liver and other tissues. Salicylates are excreted mainly by the kidney as free salicylic acid 10%, salicyluric acid 75%, salicylic phenolic 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, where as in acidic urine this may be as low as 2%. Thus the administration of aspirin with other drugs which alter urinary pH will affect 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.<sup>(4)</sup> It is not realized generally that some widely use non systemic antacid can have similar effect. Therefore it would be very interesting to determine drug interaction of aspirin and the most commonly use antacid (aluminum and magnesium hydroxide) in the view of pharmacokinetics in normal volunteers.

## Objective

1. To develop and standardize the methodology for the determination of aspirin and its metabolites in human plasma by high performance liquid chromatography. (HPLC)

2. To elucidate the effect of a commonly used antacid (aluminum and magnesium hydroxide) on aspirin pharmacokinetics in healthy volunteers.

## Material and Methods

### Materials :

#### Test products :

1. Aspirin tablet (325 mg) from the Government Pharmaceutical Organization. Lot number T109699
2. Aluminium and magnesium hydroxide antacid from the Pharmaceutical division, Chulalongkorn Hospital. Lot number 19432

#### Chemicals and solvents.

1. Standard aspirin (ASA), salicylic acid (SA) and salicyluric acid (SU) were purchased from Sigma (St.Louis.Mo,U.S.A.)
2. Internal standard benzoic acid was purchased from Sigma (St.Louis.Mo,U.S.A.)
3. Potassium dihydrogen phosphate from Fouka.Switzerland
4. Methanol from Fisher Scientific, Fair Lawn, NJ, U.S.A.
5. Perchloric acid reagent from Farmitalia Carlo Erba. Italy.

### Subjects

1. Ten healthy volunteers, five male and five female, participated in this study. Their ages ranged from 20-45 years. (average  $31.6 \pm 6.26$  years) and weighed between 40-70 kg. All subjects had normal physical examination and laboratory test data including fasting blood sugar, blood urea nitrogen (BUN), creatinine, SGOT, SGPT, complete blood count (CBC). The study procedures were explained and written informed consent was obtained from all subjects. They were taking no medication for at least one week before entering this study.

### Method

1. Two 325 mg tablets of aspirin were given orally in a single dose with 250 ml of water to each subject after an overnight fast at 7 am. in the morning. The subjects were allowed to have breakfast 2 hours after dosing.
2. 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 respectively after drug administration.
3. 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  $-20^{\circ}\text{C}$  until sample analysis were performed the next day.
4. Following two weeks of wash out period, all subjects were given 30 ml antacid (magnesium hydroxide and

aluminum hydroxide) 10 minutes before 2 tablets of 325 mg aspirin tablets were administered orally after an over night fast. Blood samples were collected as described in 3. It was a cross over study.

5. Determination 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'Kruk RJ. et al.<sup>(5)</sup>

#### *Preparation of plasma samples*

aliquot plasma sample 400  $\mu$ l

- mixed with 40  $\mu$ l .004% benzoic acid (internal standard) in 30% perchloric acid solution
- add 400  $\mu$ l methanol
- vortex 2 minute
- centrifuge at 2500 rpm for 10 minute
- filter

20  $\mu$ l sample of clear filtrate was injected into the HPLC

6. The following pharmacokinetic parameters of salicyluric acid, salicylic acid, aspirin and total salicylate were determined and compared in aspirin with and aspirin without antacid groups.

Cmax = maximum plasma drug concentration

Tmax = time to reach peak or maximum concentration

$[AUC]_0^{24}$  = area under the plasma concentration-time curve from zero time to 24 hour

T1/2 = elimination half life

Kel = elimination rate constant

Ka = absorption rate constant

(The conversion of aspirin and salicyluric acid to total salicylate were performed by multiplying each compound with its molar equivalence

### **Chromatographic condition**

Apparatus : HPLC

Column :  $\mu$ -Bondapak C18, stainless steel column, Water Associates Pty. Ltd., U.S.A. pre-column 5 cm.  $\times$  2.0 mm.i.d. analytical column 30 cm.  $\times$  3.9 mm.i.d.

Pump : Water Model 510 HPLC Pump

Injector : Water Model U6K

Mobile phase : 25% methanol and 75%, 0.1% potassium dihydrogen phosphate buffer (pH  $3.2 \pm 0.1$ )

UV detector : 235 nm (Water Lambda-Max Model 481)

Flow rate : 1.8 ml/min

Attenuation :  $2^4$  mv/full scale

### **Standard curve**

Certain amount of aspirin (15,7.5,3.75,1.88  $\mu$ g), salicylic acid (60,30,15,7.5  $\mu$ g) and salicyluric acid (10,5,2.5,1.25  $\mu$ g) were added to 1 ml of pooled drug-free plasma. These sample were analyzed following the same procedures as described above.

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

### **Statistical analysis**

Cmax (maximum concentration) and Tmax (peak time concentration) were obtained from the data.

$AUC_0^{24}$  (area under the concentration-time curve from 0 to 24 hour) was calculated by the trapezoidal rule.

Elimination rate constant (Kel) and absorption rate constant (Ka) were obtain by computerized CSTRIP program.

Half life (T1/2) =  $0.693/Kel$

All these pharmacokinetic parameters were presented as mean  $\pm$  standard error of mean and they were analysed using student paired t test.

### **Result**

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

#### **Linearity study**

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

#### **Precision study**

The coefficient 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. The results for the method precision and reproducibility were summarised in table 1.

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

compound	concentration in plasma ( $\mu\text{g/ml}$ )	n	peak area of compound	% CV
			peak area of I.S. Mean $\pm$ SD	
salicyluric acid	10	5	$0.9660 \pm 0.0322$	3.33
	5	5	$0.4885 \pm 0.0313$	6.41
	2.5	5	$0.2171 \pm 0.0107$	4.92
	1.25	5	$0.0858 \pm 0.0039$	4.55
salicylic acid	60	5	$8.1257 \pm 0.2340$	2.88
	30	5	$4.3088 \pm 0.2611$	6.05
	15	5	$2.095 \pm 0.0883$	4.21
	7.5	5	$1.0798 \pm 0.0646$	5.98
Aspirin	15	5	$1.7308 \pm 0.0669$	3.87
	7.5	5	$0.9242 \pm 0.0511$	5.29
	3.75	5	$0.4792 \pm 0.0190$	3.96
	1.38	5	$0.2604 \pm 0.0074$	2.84

I.S. = Internal standard

### % recovery

The recovery of salicyluric acid (SU), salicylic acid (SA) and aspirin at each concentration were found to be in the range of 76-94% and the detection limit of either compound was 1  $\mu\text{g/ml}$ .

The chromatogram of plasma salicyluric acid (SU), salicylic acid (SA) and aspirin (ASA) are shown in figure 1

Retention time 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 internal standard (benzoic acid) was 7.9 minute.

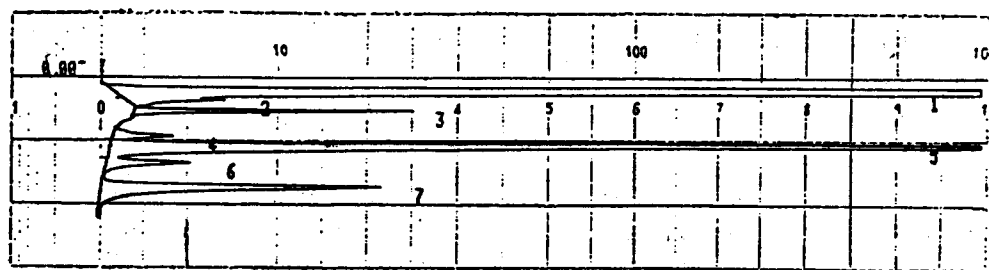
### Effect of antacid on aspirin pharmacokinetics.

Subject data and all the routine laboratory results were normal. (table 2) After oral administration of aspirin 650 mg alone or with aluminum and magnesium hydroxide

antacid, there was no statistical difference in the mean plasma concentration-time profile from 0 to 24 hours as well as the pharmacokinetic parameters of salicyluric acid (SU, figure 2, table 3) and salicylic acid (SA, figure 3, table 4)

The mean peak plasma drug concentration ( $C_{\text{max}}$ ) of aspirin after oral administration of aspirin with antacid was significantly higher than peak concentration after oral aspirin alone ( $C_{\text{max}} = 7.196 \pm 1.240$  and  $4.249 \pm 0.628$   $\mu\text{g/ml}$   $p < 0.05$ , 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. ( $K_a = 2.612 \pm 0.433$  and  $1.376 \pm 0.214$ ,  $p < 0.05$ )

The concentration and time profile of salicyluric acid, salicylic acid, aspirin and total salicylate were fitted with two compartmental kinetic models by using the computerized CSTRIP program analysis.



Peak number	Name	Retention time (min)	Peak area	Concentration (%)
1	plasma peak	1.925	1070826	59.7948
2	plasma peak	2.458	26251	1.4658
3	plasma peak	3.141	51749	2.8896
4	salicyluric acid	4.718	20310	1.1341
5	salicylic acid	5.325	460160	25.6953
6	aspirin	6.411	31796	1.7754
7	benzoic acid	7.921	129739	7.2446

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

**Table 2.** General characteristic 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

1 M = Male  
2 F = Female

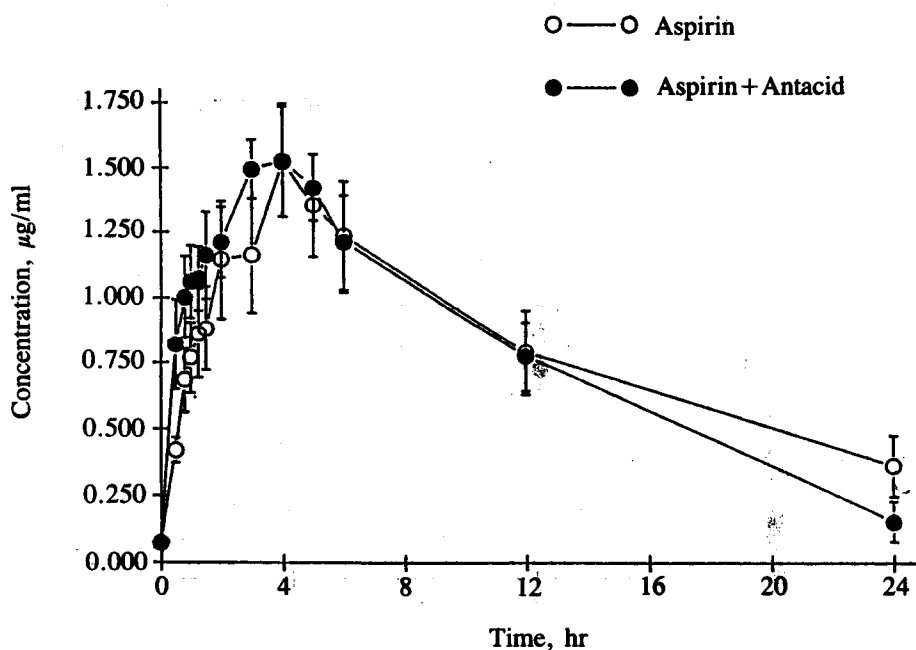


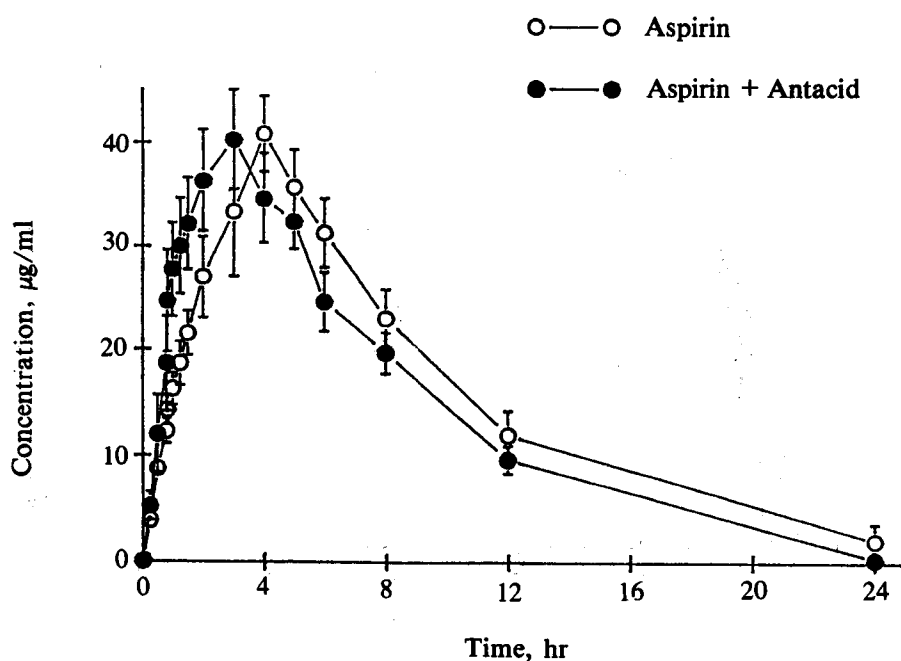
Figure 2. Plasma salicylic acid concentration (Mean  $\pm$  SE) following oral administration of aspirin with and without antacid

Table 3. Plasma pharmacokinetic parameters (mean  $\pm$  SE) of salicylic acid from 10 subjects following oral administration of aspirin (650 mg) and aspirin (650 mg) with antacid.

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

Tmax = Time to reach maximum concentration (min)  
Cmax = Peak concentration ( $\mu$ g/ml)  
[AUC]<sub>0</sub><sup>24</sup> = Area under the plasma concentration-time curve from time zero to 24 hours ( $\mu$ g/ml)  
Ka = Oral absorption rate constant ( $\text{hr}^{-1}$ )  
Kel = Elimination rate constant ( $\text{hr}^{-1}$ )  
T1/2 = Elimination half life (hr)





**Figure 3.** Plasma salicylic acid concentration (Mean  $\pm$  SE) following oral administration of aspirin with and without antacid

**Table 4.** Plasma pharmacokinetic parameters (mean  $\pm$  SE) of salicylic acid from 10 subjects following oral administration of aspirin (650 mg) and aspirin (650 mg) with antacid.

Parameter	Aspirin (650 mg)	Aspirin (650 mg) with antacid
Tmax	204.0 $\pm$ 16.00	168.0 $\pm$ 21.071
Cmax	43.009 $\pm$ 3.76A	43.227 $\pm$ 4.735
AUC	380.940 $\pm$ 42.156	329.801 $\pm$ 31.974
Ka	1.613 $\pm$ 0.155	1.908 $\pm$ 0.457
Kel	0.306 $\pm$ 0.030	0.322 $\pm$ 0.031
T1/2	2.471 $\pm$ 0.265	2.381 $\pm$ 0.315

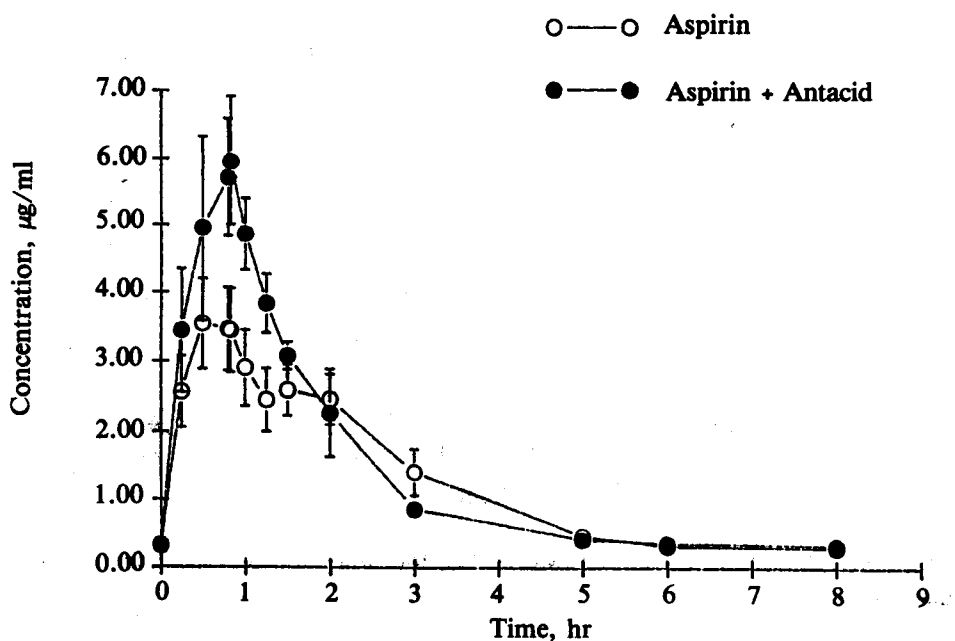
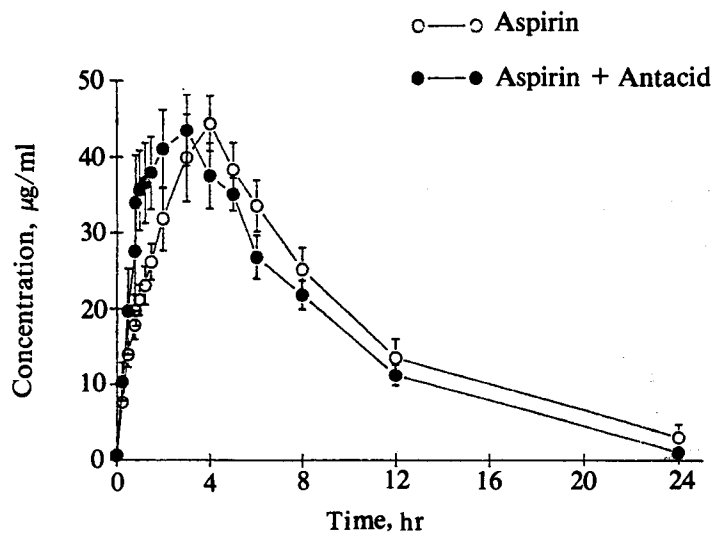


Figure 4. Plasma aspirin concentration (Mean  $\pm$  SE) following oral administration of aspirin with and without antacid

Table 5. Plasma pharmacokinetic parameters (mean  $\pm$  SE) of aspirin from 10 subjects following oral administration of aspirin (650 mg) and aspirin (650 mg) with antacid.

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

\*p < 0.05



**Figure 5.** Plasma total salicylate concentration (Mean  $\pm$  SE) following oral administration of aspirin with and without antacid

**Table 6.** Plasma pharmacokinetic (mean  $\pm$  SE) of total salicylate from 10 subjects following oral administration of aspirin (650 mg) and aspirin (650 mg) with antacid.

Parameter	Aspirin (650 mg)	Aspirin (650 mg) with antacid
Tmax	198.0 $\pm$ 18.0	152.00 $\pm$ 25.113
Cmax	47.566 $\pm$ 3.769	48.568 $\pm$ 5.172
AUC	429.947 $\pm$ 43.593	394.107 $\pm$ 31.167
Ka	1.376 $\pm$ 0.214	2.612 $\pm$ 0.443*
Kel	0.201 $\pm$ 0.015	0.193 $\pm$ 0.013
T1/2	3.622 $\pm$ 0.300	3.740 $\pm$ 0.265

\*p < 0.05

## Discussion

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

The maximum plasma drug concentration (Cmax)

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 (Cmax) after coadministration of antacid with aspirin was higher than mean peak plasma drug concentration after oral aspirin alone ( $4.249 \pm 0.628$ ,  $7.196 \pm 1.240$  µg/ml table 3) but other parameters were not significantly affected (table 5). This includes the absorption rate constant ( $K_a = 4.637 \pm 0.923$  and  $2.908 \pm 0.561$  hr<sup>-1</sup>) which determine the rate of aspirin absorption and the time to reach peak aspirin

concentration. ( $T_{max} = 54.444 \pm 9.761$  and  $53.00 \pm 8.035$  minute) Therefore it cannot be concluded that antacids affect the rate or the amount of aspirin absorption.

Elimination half-life ( $T_{1/2}$ ) of aspirin is approximately 20 minutes in general<sup>(6)</sup> but the present results demonstrates that the elimination half-life of aspirin is as high as  $15.566 \pm 2.358$  and  $21.3718 \pm 9.7628$  hour in aspirin only group and aspirin with antacid group respectively. This is due to subject variations and also the method employed in pharmacokinetic analysis (computerized CSTRIP program). Since elimination half-life is calculated by dividing 0.693 with the value of  $K_{el}$ . The lower the value of  $K_{el}$  the higher value of elimination half-life. This meant that the elimination phase of drug declined very slowly.

The result in table 6 showed that the absorption rate constant ( $K_a$ ) of total salicylate was higher when the combination was administered. ( $K_a = 1.376 \pm 0.214$  and  $2.612 \pm 0.433 \text{ hr}^{-1}$ ) As it is already known that after absorption, aspirin is rapidly hydrolysed to salicylic acid thus from this stage onwards the pharmacokinetics of aspirin and other salicylate hydrolysed to salicylic acid, are predominantly dependent upon the salicylate moiety.<sup>(6)</sup> The mechanism by which antacid (aluminium and magnesium hydroxide) affect the rate of total salicylate absorption may be due to the alteration of gastric pH, as pH rises the dissolution rate of aspirin tablet increases<sup>(6)</sup> and this will facilitate absorption of drug. However no significant difference was 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 drug absorption. Rapid absorption of the drug may be beneficial in providing rapid onset of action and may reduce the contact time with the mucosa and hence decrease the incidence of untoward effects of aspirin ingestion.<sup>(7)</sup>

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 but particularly in the endoplasmic reticulum and the mitochondria.<sup>(1)</sup> The three main metabolites are salicyluric acid (glycine conjugate 75%), salicyl phenolic glucuronide (10%) and salicyl acyl glucuronide (5%).<sup>(8)</sup> Small amount 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.<sup>(9,10)</sup> Since salicyluric acid is the major metabolite of aspirin which can be detected in human plasma, it is found that peak plasma level of salicyluric acid occur at the same time as that of free salicylate.<sup>(8)</sup> The present

result demonstrates the time to reach maximum concentration ( $T_{max}$ ) of salicyluric acid is 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 that reported by Levy et al<sup>(11)</sup> in which antacid (aluminium and magnesium hydroxide) caused serum salicylate concentration to decrease by 30 to 70 percent and an increase in urinary pH after multiple doses of aspirin when administered to three children with rheumatic fever. However the antacid had no effect on the bioavailability of a single oral dose of aspirin in five healthy adult volunteers in the same study. From the study of five different types of commercial antacid suspension performed by Gibaldi et al<sup>(12)</sup> revealed that three caused an appreciable increase in urinary pH and one of these was aluminium and magnesium hydroxide suspension. Thus chronic administration of antacid may cause alteration in urinary pH which may affect the plasma level of salicylate if the two compounds are administered concomitantly but it had no effect when antacid was given as a single dose. The variation in results from one study to another could be due to genetic, race, criteria for inclusion and exclusion of subjects, method of drug analysis and all these factors may apply in this case.

Another study performed by Gaspari et al<sup>(13)</sup> revealed that administration of antacids to uremic patients interfere with the absorption of oral aspirin and the interference can be minimized if aspirin and antacid are given simultaneously. The result obtained in the present study showed that the mean peak aspirin concentration was increase when antacid was given 10 minutes before aspirin. This indicates that the time arrangement for drugs administration would be 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 drug absorption.

## Conclusion

The pharmacokinetic parameters affected by 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 antacid was given. Rapid absorption of drug and higher plasma drug level would assist in providing a quick onset of effect.

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