

The Effect of Vitamin C and Antacid Tablets (SDI) on the Pharmacokinetics of Aspirin Tablets (SDI) in Human

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Abstract:

The study explored the effect of vitamin c and antacid on the pharmacokinetics of aspirin in human subjects.

The study was conducted in 12 healthy adults volunteers who were asked to take in the first study, two tablets of aspirin (300 mg) alone. In a second study, the same subjects were given two tablets of aspirin (300 mg) together with one tablet of vitamin c 500 mg. Eventually, in the third study, the subjects were administered two tablets of aspirin (300 mg) and one capsule containing NaHCO₃ (500 mg). The three studies were separated by one week wash out period.

In each study, urine was collected from each individual participated in the study at specific time intervals for up to 24 hours post dosing to calculate the cumulative amount of salicylate excreted in urine. The excretion rate was plotted against the mid-time sampling time to calculate the elimination rate constant (K), and the elimination half-life (T_{0.5}).

It was found from the current investigation that administration of vitamin c tablet with aspirin tablets reduce (K) values and elongate T_{0.5}, whereas, NaHCO₃ intake elevate K values and reduce T_{0.5} in all subjects participated in the study.

It can be concluded from the current investigation that administration of weak acid drugs like vitamin c, or weak base drugs like antacid have considerable effect on the residence of aspirin in the body and consequently its intensity and duration of clinical effect.

Key words: Aspirin, vitamin c, antacid, elimination rate constant, elimination half-life.

تأثير حبوب فيتامين سي والمضادة للحموضة (معمل أدوية سامراء) على الحركة الدوائية
 لحبوب الأسبرين (معمل أدوية سامراء) في جسم الإنسان
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الخلاصة:

تمت دراسة تأثير فيتامين سي وبيكاربونات الصوديوم على حركة حبوب الأسبرين داخل جسم الإنسان. أجريت الدراسة على مجموعة من المتطوعين الذين أبلغوا بتناول 2 حبة من الأسبرين بجرعة 300 ملغم لوحده في الدراسة الأولى ومع حبوب الفيتامين سي بجرعة 500 ملغم في الدراسة الثانية وأخيراً مع ببيكاربونات الصوديوم بجرعة 500 ملغم في الدراسة الثالثة وبفاصل أسبوع بين الدراسات الثلاث كفترة لغسل الدواء من الجسم.

تم جمع الإدرار من قبل كل شخص مشارك في الدراسة في أوقات محددة من وقت تناول الدواء و لمدة 24 ساعة وقياس كمية الساليسيلات المتجمعة في الإدرار وحساب سرعة الإفراز ورسمها مع وقت الوسط لجمع العينات لحساب ثابت معدل الإفراز والعمر النصف للإفراز.

وجد من خلال هذه الدراسة أن استخدام الفيتامين سي قد قلل ثابت معدل الإفراز، وأن عمر النصف للإفراز قد أصبح أطول، بينما مع استخدام ببيكاربونات الصوديوم ارتفعت قيمة ثابت معدل الإفراز وقل عمر النصف للإفراز عند كل الأشخاص المشاركين في الدراسة.

من هذا البحث نستنتج بأن الأدوية الحامضية الضعيفة مثل الفيتامين س والقاعدية الضعيفة مثل مضادات الحموضة لها تأثير مؤثر على فترة بقاء الأسبرين في الجسم وبالتالي على شدة وفترة فاعليته العلاجية.
الكلمات المفتاحية: أسبرين، فيتامين سي، مضادات الحموضة، ثابت معدل الإفراز، عمر النصف للإفراز.

Introduction:

Aspirin (acetyl salicylic acid=ASA) is a weak acid drug usually taken orally as a tablet. Aspirin is used in the treatment of mild to moderate pain, inflammation, and fever [1, 2]. It is also used as an antiplatelet agent to prevent myocardial infarction, stroke and transient ischemic episodes [3, 4].

Aspirin is promptly absorbed by passive diffusion from stomach and intestine. Aspirin is rapidly biotransformed into the active metabolite (salicylate) in the stomach, in the intestinal mucosa, in the blood and mainly in the liver. Therefore, it has short elimination half-life ($T_{0.5}$) of about 20 minutes. Only a small portion of aspirin is excreted unchanged in the urine. Salicylic acid is further metabolized in the liver into its glycine conjugate salicyluric acid and its glucuronic acid conjugates, salicyl phenolic glucuronide and salicyl acyl glucuronide [5, 6]. Ring hydroxylation products of salicylic acid are also formed, although in much smaller amounts; these include gentisic acid (2, 5-hydroxybenzoic acid) and 2, 3-dihydroxybenzoic acid. Additional metabolites, also formed in minor amounts, include gentisuric acid and salicyluric acid phenolic glucuronide [5, 7]. Salicylate is responsible for most anti-inflammatory and analgesic effects.

Urinary excretion of unchanged salicylate accounts for 10% of the total elimination of salicylate. Excretion of salicylate results of glomerular filtration, active proximal tubular secretion through the organic acid transporters and passive tubular reabsorption. Urinary excretion is markedly pH dependant, and as the urinary pH rises from 5 to 8, the amount of free ionized salicylate excreted increases from 3% of the total salicylate dose to more than 80% (by ion trapping in the urine). It was reported

that renal salicylate excretion can be enhanced by alkaline diuretic [8].

Generally, many drugs are reabsorbed from the renal tubules by either an active or a passive process after their filtration through glomerulus. The reabsorption of drugs that are weak acids or weak bases is affected by the pH of the fluid in the renal tubule and the pK_a of the drug. These two factors determine the percentage of ionized and unionized forms of the drug. Generally, the unionized form is more lipid soluble, and thus has higher membrane permeability. The unionized form of drug is easily reabsorbed from the renal tubule back into the body. This process of drug reabsorption can significantly reduce the amount of drug excreted, depending on the pH of the urinary fluid and the pK_a of the drug. The pK_a of the drug is constant; however the normal pH of urine may vary from 4.5 to 8.0, depending on diet, pathophysiology, and drug intake. The pH of urine rises after consumption of vegetables and fruits, or diets rich in carbohydrates. On the other hand, diets rich in protein lower the pH of the urine. Administration of drugs such as vitamin c and antacids like sodium carbonate in large quantities may decrease (acidify) or increase (alkalinize) the urinary pH, respectively. Furthermore, urinary pH is highly influenced after intravenous administration of drug or fluid [9].

The aim of this study is to evaluate the effect of administering weak acid drugs like vitamin C, or weak base drugs like antacid on the pharmacokinetics of aspirin after oral administration to healthy adult subjects.

Materials and Methods:

Study conduct:

Aspirin tablet 300 mg (SDI), vitamin c tablets 500 mg (SDI), antacid (NaHCO₃) 500 mg, colour developing reagent; were used in the study. All the study phases including the clinical, bioanalytical, and pharmacokinetic were conducted in the college of pharmacy, university of Baghdad, Baghdad, Iraq. The study protocol which involve all details of the study was approved by the principal investigator, the clinical investigator, the ethical committee, and the institutional review board (IRB) before study conduct. A written consent was obtained from each subject before starting the study.

Twelve healthy adult eligible subjects were participated in the current investigation. The subjects were considered to be eligible for participation in the study based on; clinical and physical examinations, and routine clinical laboratory tests.

The study was designed as; fasting, single-dose, three-treatment, three-period, three-sequence, randomized crossover design with one week washout period between dosing. As per study design, each subject should receive; single dose of two aspirin tablets of 300 mg (Samarra Drug Industries, Iraq = SDI) alone, two aspirin tablets of 300 mg (SDI) and one tablet of vitamin c 500 mg (SDI), or two aspirin tablets of 300 mg (SDI) and one capsule containing NaHCO₃ 500 mg.

No drug was taken for at least 48 hrs prior the study. After over-night fasting, urine was voided from each subject, and a sample of 50 ml was kept to be used as blank. The subjects were then administered the investigational drug products with 240 ml of water, and remained fasting for three hours after dug products intake. Water was allowed for the next hours (200 ml at hourly intervals). Urine was collected from each subject. The subjects were asked to void

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their bladder completely at each time interval to insure empty bladder and minimize the residual urine. The time of urination was noted and the volume of urine excreted was measured. Urine samples of 50 ml were kept in closed container in refrigerator until all samples were collected. Urine samples were collected for 24 hours after investigational drug products intake.

Chemical analysis of salicylate:

Measurement of salicylate concentration is based on the chemical analysis of the phenolic group which react with the ferric ion (found in color developing agent). To exactly 1 ml of urine sample, 5 ml of colour developing reagent was added. The colour developing reagent is composed of; mercuric chloride 8.0 gm, ferric nitrate 8.0 gm, 24 ml of 1N HCl, and adequate distilled water to complete the volume to 200.0 ml. The mixture was centrifuged, and the supernatant was transferred into kimex tube. The absorbance was determined spectrophotometrically at 530 nm ^[10].

Determination of elimination rate constant (K):

Excretion rate was plotted versus mid point time during urine collection interval on semilog paper. The K value for each subject and in each experiment was obtained from the terminal slope of the plot. The elimination half-life (T_{0.5}) was calculated as 0.693/K^[9].

Result and Discussion:

Figure-1 shows three plots of excretion rate (dA/dt) versus midpoint time profiles of the three experiments conducted in the current investigation.

The first plot demonstrate administration of two aspirin tablets of 300 mg alone, the second plot reflects administration of two aspirin tablets of 300 mg and one tablet of

vitamin c 500 mg, and the third plot shows administration of two aspirin tablets of 300 mg and NaHCO₃ 500 mg.

Table-1 exhibit the calculated elimination rate constants and elimination half-lives obtained in this study. The elimination rate constant was increased and the half live of salicylate was decrease when

aspirin tablets were administered with antacid, whereas administration of vitamin c resulted in reducing the elimination rate constant and elongating the elimination half live, compared to the control elimination rate constant values obtained from administration of aspirin tablets alone; as shown in figure-1 and Table-1.

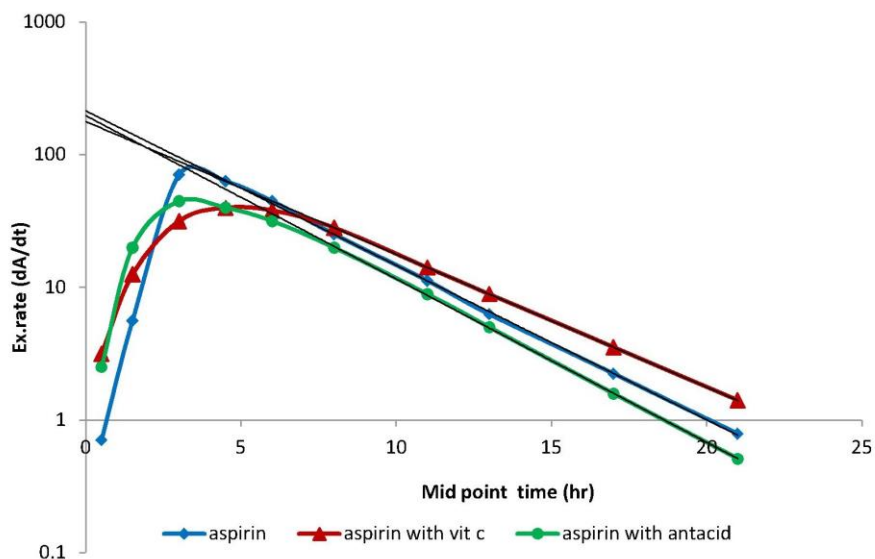


Figure-1: Excretion rate (mg/hr) versus mid point time (hr) plots after administration of aspirin tablets alone, aspirin tablets and vitamin c tablet, or aspirin tablets and antacid.

Table-1: Mean elimination rate constants (K) and the corresponding elimination half-lives (T_{0.5}) of salicylate.

Product	K (hr ⁻¹)	T _{0.5} (hr)
Aspirin tablets alone 2X300 mg	0.268	2.6
Aspirin tablets + vitamin c 2X300 mg + 500 mg	0.230	3.0
Aspirin tablets + NaHCO ₃ 2X300 mg + 500 mg	0.282	2.4

Experimental and clinical studies confirmed that urinary alkalization increases salicylic acid elimination. It was reported that high doses of antacids increase urinary pH, thus increasing urinary excretion of salicylic acid, and consequently leading to decrease its plasma levels^[11].

The effect of ascorbic acid (vitamin c) supplementation (3g/day) on renal clearance and plasma plateau level of salicylate was studied by Hansten, and Hayton (1980) who found that ascorbic acid did not significantly alter urine pH nor did it

affect renal excretion or blood level of salicylate^[12].

In other study it was found that the total oral body clearance of salicylic acid under acidic conditions was significantly lower than that under alkaline urine conditions^[8]. They have reported that there was also a significant difference in percentage of the dose excreted unchanged under acidic and alkaline condition. The percentage of excreted dose was increased from 2.3 +/- 1.5% under acidic conditions to 30.5 +/- 9.1% under alkaline conditions.

However, increase urinary excretion of ascorbic acid (vitamin c) and decrease excretion of aspirin was reported to occur when the drugs are administered concurrently^[13].

Specifically, at low ascorbic acid intake, acetylsalicylic acid increased urinary ascorbic acid, but at high ascorbic acid intake, acetylsalicylic acid instead decreased urinary ascorbic acid^[14].

From pharmacokinetic point of view, it can be suggested that administration of weak acid drugs like vitamin c, or antacid intake together with aspirin could possibly alter the pH of the renal tubules. This change in the pH may have remarkable effect on the reabsorption of aspirin from renal tubules back to the general circulation, and consequently the amount of aspirin excreted in urine and its elimination half life; which in turn have clinical impact in the duration and intensity of effect of aspirin in human.

Conclusions:

From the results of the current investigation, it was found that administration of vitamin c or antacid with aspirin influence the elimination of the aspirin from the body.

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