# THE TIME REQUIRED FOR ABSORPTION AND URINARY EXCRETION OF ACETYLSALICYLIC ACID AND METHYL SALICYLATE

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*The two salicylates (acetylsalicylic acid and methyl salicylate) are well absorbed. The time required to be eliminated into urine after oral administration and dermal application of these two drugs was compared in female and male. The renal elimination time after skin application of methyl salicylate was shown to be longer than that after oral administration of acetylsalicylic acid ($P<0.025$) in an empty stomach (without food). When administer with meal, it took longer time to eliminate the oral salicylate into urine than that of the empty stomach ($P<0.001$). No difference in absorpion and excretion time of the two salicylates was observed between female and male ($P>0.05$).*

*It is suggested, therefore, that the gastrointestinal absorbable form of salicylates (acetylsalicylic acid) enters and leaves the body faster than topically applied as methyl salicylate. No sex difference was observed on the three phenomena. Presence of food in the stomach delays the body entry and leaving time of oral acetylsalicylic acid in both sexes.*

## INTRODUCTION

Inspite of the introduction of many new analgesic drugs, acetylsalicylic acid (ASA) is still one of the widely prescribed analgesic-antipyretic and anti-inflammatory agents. It is also the standard drug employed for the comparison and evaluation of others.[1] Regarding, the cardiovascular disorders in elderly patients such as thromboembolic diseases, this drug is used for both preventive and curative purposes. Acetylsalicylic acid and other derivative such as methyl salicylate are known to be extensively metabolized in the liver and excreted by kidneys. Salicylic acid is an active metabolite of both drugs in blood. The detection of salicylic acid in urine is simple. The extent and time-

course of absorption and excretion of per oral ASA or topical application of methyl salicylate in Thais have not yet been reported. Therefore, an experiment on the oral administration of acetysalicylic acid and skin application of methylsalicylate was performed with a view to estimate and compare the length of times of the drugs in human body.

**Table 1** The time required to detect salicylic acid in the urine after orally-administered acetylsalicylic acid in empty stomach ; stomach with meal and topical application of methyl salicylate.

| Salicylates | Routes of Administration | Length of time required for the presence of salicylic acid in urine (minute) | | |
|---|---|---|---|---|
| | | Female n | Male n | Both sex N |
| Acetylsalicylic Acid | Per oral with empty stomach | 33.00 ± 2.99 5 | 31.36 ± 1.36 11 | 32.65 ± 1.43 16 (A) |
| | Per oral after a standard meal | 47.50 ± 2.49 6 | 45.00 ± 2.24 11 | 45.88 ± 1.56 17 (B) |
| Methylsalicylate | Per cutaneous | 36.25 ± 2.33 12 | 36.75 ± 2.25 20 | 38.44 ± 1.64 32 (C) |

The results were expressed as mean ± standard error of the mean

*Note:* 1. n=number of subjects either male or female
2. N=number of both sexes (male and female)
3. (A)is significant different from (B)($P<0.001$)
4. (A)is significant different from (C)($P<0.025$)
5. (B)is significant different from (C)($P<0.025$)

**Table 2** The data of age and body weight of male and female volunteers.

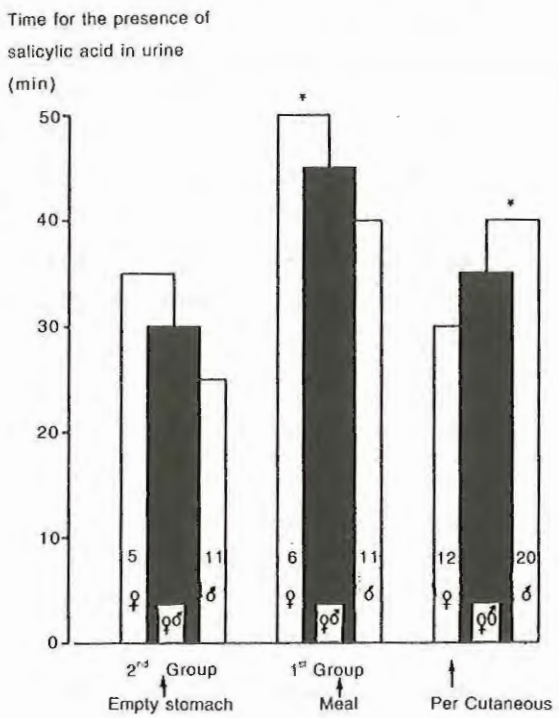
| Subject | Male | | Female | | Female (cont). | | |
|---|---|---|---|---|---|---|---|
| | Age(Yr) | Weight(Kg) | Age(Yr) | Weight(Kg) | Subject | Age(Yr) | Weight(Kg) |
| 1 | 22 | 44.0 | 23 | 41.5 | 32 | 20 | 55.5 |
| 2 | 22 | 62.0 | 19 | 55.0 | 33 | 21 | 47.0 |
| 3 | 21 | 65.5 | 22 | 40.5 | 34 | 22 | 46.5 |
| 4 | 21 | 62.0 | 22 | 46.5 | 35 | 22 | 41.7 |
| 5 | 21 | 61.0 | 22 | 49.0 | 36 | 20 | 64.5 |
| 6 | 22 | 52.5 | 21 | 46.0 | 37 | 21 | 39.5 |
| 7 | 21 | 58.0 | 22 | 50.0 | 38 | 22 | 53.5 |
| 8 | 22 | 63.0 | 22 | 48.0 | 39 | 23 | 44.0 |
| 9 | 21 | 47.5 | 21 | 44.5 | 40 | 21 | 42.0 |
| 10 | 21 | 54.5 | 22 | 38.5 | 41 | 21 | 43.5 |
| 11 | 22 | 64.5 | 22 | 50.0 | 42 | 21 | 44.0 |
| 12 | 21 | 51.2 | 22 | 46.5 | 43 | 20 | 41.5 |
| 13 | 21 | 65.5 | 22 | 52.0 | 44 | 22 | 46.0 |
| 14 | 21 | 53.0 | 22 | 44.5 | 45 | 22 | 45.0 |
| 15 | 22 | 71.5 | 21 | 41.5 | 46 | 21 | 49.5 |
| 16 | 22 | 59.0 | 22 | 43.0 | 47 | 21 | 51.0 |
| 17 | 22 | 57.0 | 22 | 48.5 | 48 | 21 | - |
| 18 | 26 | 63.0 | 21 | 42.5 | 49 | 22 | 49.0 |
| 19 | 21 | 59.5 | 21 | 51.5 | 50 | 21 | 60.0 |
| 20 | 20 | 56.5 | 20 | 55.5 | 51 | 21 | 41.5 |
| 21 | 21 | 58.5 | 22 | 51.5 | 52 | 22 | 46.0 |
| 22 | 20 | 54.5 | 21 | 45.0 | 53 | 21 | 46.0 |
| 23 | 22 | 61.0 | 21 | 44.5 | 54 | 22 | 47.5 |
| 24 | 21 | 61.0 | 21 | 62.0 | 55 | 22 | 41.5 |
| 25 | 21 | 73.0 | 22 | 47.5 | 56 | 21 | 52.0 |
| 26 | 21 | 68.5 | 21 | 44.5 | 57 | 21 | 45.0 |
| 27 | 21 | 59.0 | 22 | 37.5 | 58 | 21 | 43.5 |
| 28 | 22 | 61.0 | 23 | 48.0 | 59 | 22 | 42.5 |
| 29 | 22 | 64.0 | 21 | 56.0 | 60 | 20 | 41.5 |
| 30 | 22 | 59.0 | 21 | 46.5 | 61 | 21 | 43.0 |
| 31 | 19 | 66.0 | 22 | 41.5 | 62 | 21 | 44.0 |

**Table 3** The mean age and body weight of the volunteers with standard error of the mean.

| | Mean ± Standard error of the mean | |
|---|---|---|
| Sex | Age(year) | Weight (kilogram) |
| Male | 21.42 ± 0.02 (n=31) | 59.90 ± 1.50 (n=31) |
| Female | 21.39 ± 0.10 (n=62) | 46.85 ± 0.72 * (n=61) |
| Both male and female | 21.39 ± 0.094 (n=93) | 51.24 ± 0.89 (n=92) |

*Note:* 1. An asterisk(*)means statistically significant difference from the mean weight of male subject (P<0.001)

2. n in the brackets represents number of volunteers




*Note:*
1. The asterisks(*) show the statistical difference from each other (P<0.05 upto 0.005).
2. The numbers present in the bar graph represents the number of volunteers.
3. The solid columns are the averages of males and females.
4. ♀♂ represents male and female average; ♀=female average; ♂= male average.

**Fig. 1** The lengths of time commencing from either the ingestion of acetylsalicylic acid (empty or stomach with meal) and per cutaneous application of methyl salicylate until salicylic acid appearance in urine.

## MATERIALS AND METHODS

Human volunteers of either sex, weighing 51.24 ± 0.89 Kg, were fasted 24 hr prior to the commencement of experiment. They never underwent any recent medical treatment within a week. Each volunteer emptied their urinary bladder before drug administration urine samples were tested for the presence of salicylates. If the test was positive, such volunteer will be omitted. The volunteers were randomly divided into groups as follows:

A.Group

After emptying of the bladder with a negative salicylate test, subiects' forearms of either side were rubbed upon with 2 ml of oil of wintergreen B.P. for 3 min until most of the drug was absorbed. Then, timing was started, and the volunteers were allowed to drink water ad libitum. At 15-min intervals, a urine sample was collected and tested for the presence of urinary salicylates by a chemical identification test.[2] The time in minutes from the completeness of skin application to last urine sample with the detectable urinary salicylates was recorded.

B.Group

After a test for the absence of urinary salicylates was performed as in A., the second group of the volunteers was randomly divided into two subgroups of 17 and 16; the first group of volunteers ate about 300 gm of fried rice with pork, whereas the second group was starved; but all of them could drink water freely. The first group served as the stomach with meal; the second was the empty stomach group.

Acetylsalicylic acid (300 mg) in gelatin capsule was taken orally with 250 ml of drinking water by all of the volunteers; then the urine sample was collected at 15-min interval and tested for salicylates as in A.

## RESULTS

The average age of female and of male were 21.39 ± 0.10 years (n=62) and 21.42 ± 0.20 years(n=31), respectively. The average age of both sex was 21.39 ± 0.094 years (n=93). The body weight of female and of male was 46.85 ± 0.72 kilograms (n=61) and 59.90 ± 1.50 kilograms (n=31) respectively. The average weight of both sexes was 51.24 ± 0.89 kilograms (n=92) (table 2 and table 3).

The length of time required to detect urinary salicylic acid after oral and dermal administration was shown in the table1. The average time for the presence of urinary salicylic acid after oral administration in fasting subjects female and male were 33.00 ± 2.99 min (n=5) and 31.36 ± 1.36 min (n=11)respectively. After meal, the time required for excretion of salicylate was 47.50 ± 2.49 min (n=6) for female and 45.00 ± 2.24 min (n=11) for male. The average time of both sexes was 45.88 ± 1.56 min (n=17). The dermal application of methylsalicylate, the excretion time was 36.25 ± 2.33 (n=12) for female and 39.75 ± 2.25 min (n=20) for male; whereas the average time of both sexes was 38.44 ± 1.64 min (n=32).

## DISCUSSION

It has been nearly a century since acetylsalicylic acid has been replaced sodium salicylate

for rheumatic disease and used as an antipyretic. The mechanisms of action as well as its use were extensively reported. [3,4,5,.....11] The side effects and toxicities of acetylsalicylic acid were also revealed. [12,13.....16] The gastro-intestinal absorption and urinary excretion of both acetyl-salicylic acid and methyl salicylate [17,18,19,20] were also studied in man. It is known that food can influence the gastro-intestinal absorption of a number of drugs. [21] However, there has been no report on the effect of Thai food on the absorption and the acetylsalicylic acid and methyl salicylate.

In the present study , no sex difference in the length of time taken from either ingestion (acetylsalicylic acid) or dermal application (methyl salicylate) until its appearance in urine was found in all of the experimental conditions (empty and food stomach) (Table 1, Fig.1). Food delayed gastrointestinal absorption of acetylsalicylic acid. Thus food either by itself might directly affect the rate and extent of absorption and excretion or alter pH in stomach as well as in urine as seen after administration of antacid. [22] Acidic drugs such as salicylic acid (an active form of the salicylates in blood) are less ionized in acidic urine but more ionized in alkaline urine. [23] At present, the dermal dosage form of drug is of great interest; it is not only convenient for use but also is without first-pass drug metabolism. In the contrary, the environmental toxic chemicals and the counter irritants containing methyl salicylate may be absorbed through skin and cause kidney failure which should be taken into a consideration. The slowness of skin absorption in comparing with gastrointestinal absorption might be due to the absorbing surface area upon which the drug was applied (the forearm) is very small comparing with that of the whole gastrointestinal absorbing area.

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