Influence of Food and Fluid Ingestion on Aspirin Bioavailability

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Abstract □ The influence of test meals and accompanying fluid volume on aspirin bioavailability from commercial tablets was determined following single oral doses to healthy male volunteers. Plasma aspirin and salicylate levels were determined simultaneously using a GLC end-point. Area analysis indicated that approximately 5–8% of absorbed drug entered the systemic circulation as unchanged aspirin in nonfasted subjects compared to 16–18% in fasted individuals. Food tended to reduce the appearance rate of aspirin into the circulation, resulting in lower and somewhat more sustained levels than with fasting. Plasma salicylate levels were not influenced markedly by the various treatments, although levels were higher in fasted than in nonfasted subjects during the 1st hr after dosing. After this time, fat pretreatment tended to produce higher levels than other treatments.

Keyphrases □ Aspirin—bioavailability in humans, effect of food and fluid volume □ Bioavailability—aspirin in humans, effect of food and fluid volume □ Absorption, GI—aspirin in humans, effect of food and fluid volume □ Analgesics—aspirin, bioavailability in humans, effect of food and fluid volume

Considerable attention has been paid to the absorption characteristics of aspirin from various dosage forms and dosage routes. Studies have concerned aspirin absorption from both oral (1) and rectal (2) routes; the influence of gastric pH, antacids, and buffering agents (3); particle size (4); and interactions with other medicinal agents (5). Other reports have discussed aspirin absorption from sustained-release (6) and conventional (7) tablets and from solutions (8). A bioavailability monograph for aspirin has been published (9).

The objective of this study was to examine the influence of food and fluid volume on the rate and extent of aspirin absorption following single doses to healthy male volunteers. Aspirin absorption is determined in terms of the circulating levels of both unchanged aspirin and salicylate.

EXPERIMENTAL

Protocols—The protocol was similar to that described previously (10). Six healthy males, 21–30 years old and weighing 66–87 kg, took no known enzyme-inducing agents for 1 month and no drugs for 1 week before the study. Subjects took no drugs other than the required doses of aspirin during the study.

Subjects fasted overnight before each dose of aspirin and ate no food, apart from test meals, until 4 hr after dosing. On the morning of a treatment, subjects drank 250 ml of water on arising, at least 1 hr before dosing. Aspirin was dosed at 8 am; blood samples (~5 ml) were drawn from a forearm vein into chilled vacuum tubes containing 50 μl of heparin solution (1000 units/ml) and 50 μl of 50% (w/v) aqueous potassium fluoride immediately before and at 10, 20, and 30 min and 1, 2, 3, 4, 6, 8, and 12 hr after dosing.

As soon as blood samples were drawn, the tubes were gently mixed in ice for 2 min and centrifuged for 3 min at 0°. The plasma was separated and stored at −20° until assayed, usually within 24 hr. This procedure effectively inhibits hydrolysis of aspirin to salicylate after sampling (11).

Treatments—Subjects received single 650-mg doses of aspirin[1] as two 325-mg tablets. Test meals were prepared as described previously (12). Aspirin was administered as follows:

Treatment 1—Two tablets with 250 ml of water immediately following a high carbohydrate meal.

Treatment 2—Two tablets with 250 of ml water immediately following a high fat meal.

Treatment 3—Two tablets with 250 ml of water immediately following a high protein meal.

Treatment 4—Two tablets with 25 ml of water on an empty stomach.

Treatment 5—Two tablets with 250 ml of water on an empty stomach.

All subjects received the same treatment at the same time. Treatments were administered 2 weeks apart, and all subjects received all treatments. Tablets were swallowed whole.

Assay—Plasma aspirin and salicylate were assayed by a GLC method (13) with *m*-toluic acid as internal standard. This method, in association with the described sampling procedure, minimizes hydrolysis of aspirin to salicylate. Any hydrolysis is accounted for by constructing standard curves based on known plasma concentrations of both aspirin and salicylate.

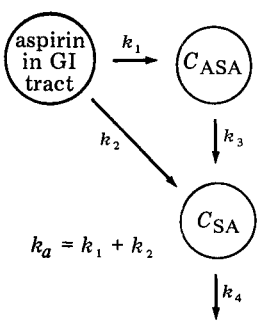
Linear regressions of peak height ratios of compound to internal standard *versus* compound concentration in plasma were $y = -0.007 + 0.159x$ ($r = +0.998$, $n = 14$) for aspirin over a concentration range of 0.5–10 μg/ml and $y = 0.315 + 0.151x$ ($r = +0.997$, $n = 14$) for salicylate over a concentration range of 0.5–100 μg/ml. Average values of peak height ratios divided by known compound concentrations were 0.15 ± 0.02 (*SD*) and 0.19 ± 0.02 for aspirin and salicylate, respectively. Assay reproducibility at the lower limits of the standard curves was ± 10%.

Analysis—The most simple model that may approximate absorption and elimination of salicylate is shown in Scheme I.

In this scheme, "aspirin in GI tract" represents unabsorbed aspirin, while C_{ASA} and C_{SA} represent concentrations of aspirin and salicylate in their respective body distribution volumes. All k's are first-order rate constants. The rate constant k_a represents drug loss from the GI tract due to absorption and hydrolysis. The rate constants k_1, k_2, k_3, and k_4 represent absorption of unchanged drug into the systemic circulation, formation of salicylate during absorption, hydrolysis of aspirin to salicylate once aspirin has entered the systemic circulation, and elimination of salicylate, respectively.

With this pharmacokinetic model, circulating levels of aspirin and salicylate are described by:

$$C_{ASA} = \frac{FDk_1}{V_{ASA}(k_3 - k_a)}[e^{-k_a t} - e^{-k_3 t}] \qquad \text{(Eq. 1)}$$



Scheme I

[1] Bayer Aspirin, lot A6009, Glenbrook Laboratories, New York, NY 10016.

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Table I—Mean Pharmacokinetic Values (±1 *SD*) for Aspirin

Value	Treatment 1	2	3	4	5	Paired *t* Test
k_a, hr^{-1}	1.4 ± 0.5	1.5 ± 0.5	2.9 ± 1.0	4.0 ± 1.4	4.3 ± 2.2	3–5 > 1,2
$t_{1/2(abs)}$, hr	0.55 ± 0.20	0.47 ± 0.10	0.28 ± 0.14	0.20 ± 0.11	0.20 ± 0.10	1,2 > 3–5
k_3, hr^{-1}	0.73 ± 0.23	0.76 ± 0.25	0.71 ± 0.30	1.61 ± 0.73	1.53 ± 0.57	4,5 > 1,2
$t_{1/2(elim)}$, hr	1.0 ± 0.3	0.98 ± 0.21	1.1 ± 0.4	0.55 ± 0.32	0.53 ± 0.29	5 > 2; 4 > 3
FDk_1/Vk_a[a], μg/ml	6.6 ± 3.0	7.2 ± 2.5	6.1 ± 2.1	15.8 ± 5.8	18.6 ± 4.2	4,5 > 1–3
area $^{0\to\infty}_{trap}$[b], μg/hr/ml	13.4 ± 5.5	10.9 ± 4.1	13.9 ± 8.9	9.1 ± 2.6	14.2 ± 6.0	NSD[c]
Peak height, μg/ml	5.0 ± 2.5	4.5 ± 1.3	5.4 ± 1.0	8.1 ± 2.9	11.0 ± 2.6	4 > 2,3; 5 > 1–3
Time of peak, hr	2.2 ± 1.2	1.3 ± 0.6	1.3 ± 1.5	0.44 ± 0.09	0.64 ± 0.67	1,2 > 4; 1 > 5

[a] Fraction of dose absorbed as unchanged aspirin, expressed as a concentration in its distribution volume. [b] Calculated by trapezoidal rule. [c] Not significantly different.

$$C_{SA} = \frac{FD}{V_{SA}}\left[\frac{k_1k_3}{(k_4-k_3)(k_a-k_3)}e^{-k_3t} + \frac{k_a(k_3-k_2)}{(k_4-k_a)(k_3-k_a)}e^{-k_at} + \frac{(k_ak_3-k_2k_4)}{(k_a-k_4)(k_3-k_4)}e^{-k_4t}\right] \quad \text{(Eq. 2)}$$

where F is the fraction of the aspirin dose absorbed as both aspirin and salicylate and V_{ASA} and V_{SA} are the respective distribution volumes.

Individual plasma aspirin levels were fitted graphically to Eq. 1. The small number of data points and the considerable variation in the absorptive phase of plasma aspirin levels made additional curve fitting by computer impractical. Although less variation was observed in plasma salicylate levels, it was not possible to analyze these data in terms of more than two exponents and, therefore, to distinguish further between k_3 and k_a. Salicylate data, therefore, were analyzed in terms of a biexponential expression with an elimination rate constant, k_4, and an appearance rate constant, k', representing the overall contribution of k_3 and k_a. In this case, improved computer estimates of rate constants were obtained (12).

The fraction of absorbed dose entering the systemic circulation as unchanged aspirin and the fraction appearing as salicylate were calculated by area analysis. Integration of Eqs. 1 and 2 yields, respectively:

$$\text{area}^{0\to\infty}_{ASA} = \frac{FDk_1}{V_{ASA}k_ak_3} \quad \text{(Eq. 3)}$$

$$\text{area}^{0\to\infty}_{SA} = \frac{FD}{V_{SA}k_4} \quad \text{(Eq. 4)}$$

The distribution volumes of aspirin and salicylate are similar (14), and FD is common to both equations. Areas under individual plasma level *versus* time curves were calculated by the trapezoidal rule. Residual areas following the last sampling time were obtained by dividing the drug concentration at that time by the appropriate elimination rate constant. Thus, with known values of the respective areas and of the rate constants k_3 from aspirin data and k_4 from salicylate data and with appropriate correction for molecular weights, the ratios k_1/k_a and k_2/k_a are obtained.

Statistical analysis included comparison of plasma aspirin levels, plasma salicylate levels, and all appropriate pharmacokinetic values between treatments by analysis of variance. Differences between individual treatments were examined for significance by a paired t test.

RESULTS

Mean plasma levels of aspirin and salicylate from all treatments are summarized in Figs. 1 and 2. Results of pharmacokinetic analysis are given in Tables I and II.

Plasma aspirin levels tended to be higher and to peak earlier in fasted individuals, while levels were lower and prolonged when aspirin was ingested with food. Prolonged absorption probably accounted for the apparent decrease in the elimination rate constant in nonfasted individuals. The elimination half-life from Treatments 4 and 5, although shorter than from the nonfasted treatments, was larger than values obtained when aspirin was dosed intravenously (14) and may also have been influenced by continued absorption but to a smaller extent than after Treatments 1–3. Although no differences were observed in areas under plasma level–time curves, these values were influenced by varied apparent elimination rates from the different treatments. A better indication of the absorption efficiency of aspirin as unchanged drug was given by FDk_1/Vk_a. This value was significantly higher following Treatments 4 and 5 than from nonfasted treatments.

The various treatments had less influence on plasma salicylate levels than those of aspirin. Fasting treatments tended to yield higher salicylate levels during the 1st hr after dosing. However, after that time, the only consistent trend among treatments was that of higher salicylate levels from the fat treatment compared to those obtained when aspirin was ingested with low fluid volume by fasted subjects.

The overall similarity of salicylate bioavailability characteristics from the five treatments is reflected in the pharmacokinetic values in Table II. No differences were obtained in the apparent appearance rate con-

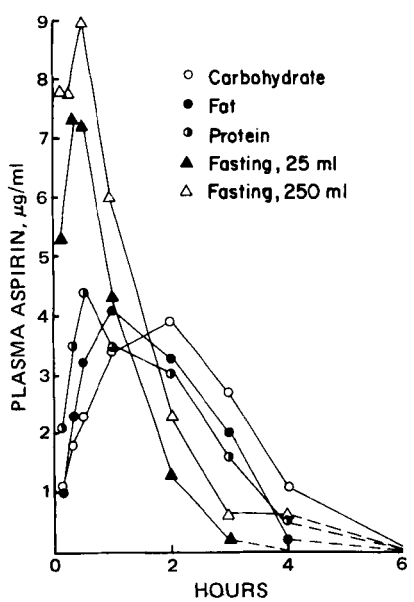

Figure 1—*Average plasma aspirin levels.*

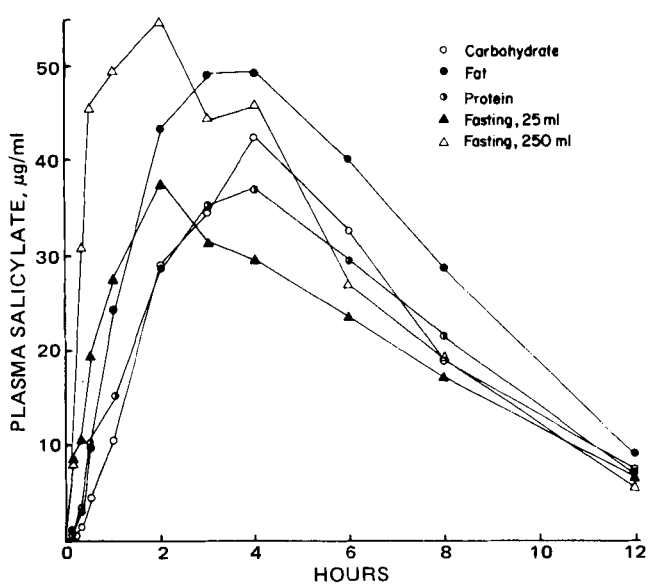

Figure 2—*Average plasma salicylate levels.*

Table II—Mean Pharmacokinetic Values (±1 *SD*) for Salicylate

Value	Treatment 1	2	3	4	5	Paired *t* Test
k', hr^{-1}	0.39 ± 0.14	0.45 ± 0.22	0.43 ± 0.05	0.56 ± 0.23	0.89 ± 0.55	NSD[c]
$t_{1/2}$[a], hr	2.0 ± 0.9	1.9 ± 0.9	1.6 ± 0.2	1.4 ± 0.5	1.1 ± 0.7	NSD
k_4, hr^{-1}	0.31 ± 0.14	0.28 ± 0.06	0.31 ± 0.07	0.25 ± 0.07	0.27 ± 0.10	NSD
$t_{1/2(elim)}$[b], hr	2.5 ± 0.7	2.6 ± 0.6	3.2 ± 0.4	3.0 ± 0.9	3.0 ± 1.3	NSD
FD/V, μg/ml	77 ± 16	109 ± 31	71 ± 11	65 ± 14	98 ± 31	2 > 1,4
area $_{trap}^{0\rightarrow\infty}$[d] μg/hr/ml	310 ± 113	409 ± 98	298 ± 59	289 ± 60	371 ± 68	2 > 1,3
Peak height, μg/ml	46.6 ± 15.2	53.2 ± 10.1	43.6 ± 16.4	46.8 ± 13.7	65.2 ± 16.4	5 > 1,4
Time of peak, hr	3.8 ± 1.3	3.7 ± 0.5	4.3 ± 2.3	1.8 ± 0.9	2.1 ± 1.3	1 > 4; 1, 3 > 5
r^{2e}	0.81 ± 0.19	0.92 ± 0.04	0.86 ± 0.07	0.92 ± 0.05	0.88 ± 0.17	

[a] $t_{1/2} = 0.693/k'$. [b] $t_{1/2(elim)} = 0.693/k_4$. [c] Not significantly different. [d] Area from 0 to 12 hr plus the terminal area, 12 → ∞ hr, calculated from C_{12hr}/k_4. [e] Coefficient of determination $(\Sigma^2_{obs} - \Sigma^2_{dev})/\Sigma^2_{obs}$.

stants or the elimination rate constants between treatments. Treatment 5 yielded the highest mean peak salicylate levels, and both fasting treatments resulted in earlier peak times. However, the overall bioavailability of salicylate from Treatments 2 and 5 tended to be higher than from other treatments. The elimination half-life of salicylate was similar to values previously reported at this dose level (15).

Calculation of the ratios k_1/k_a and k_2/k_a from area analysis and Eqs. 3 and 4 gave the values in Table III. Fasting treatments resulted in a greater percentage of absorbed drug entering the circulation in unchanged form.

DISCUSSION

The simple model utilized in this study is not intended to represent the complex events associated with aspirin pharmacokinetics (15). It is used in a relative sense to determine the influence of fasting and nonfasting treatments on circulating levels of aspirin and salicylate. Although the elimination kinetics of aspirin are saturable, they are essentially linear at the dose level used in this study, so the use of the linear Eqs. 1–4 is justified (15).

The results show that, after all oral treatments, aspirin is absorbed into the circulation predominantly as salicylate. Although circulating levels of aspirin were influenced more by the different treatments than salicylate levels, the latter values are of greater clinical significance.

Comparison of salicylate data among treatments indicates that dosing aspirin on an empty stomach produces higher circulating salicylate levels during the 1st hr after dosing. These levels are increased further if aspirin is taken with a large volume of water. However, the overall bioavailability of salicylate was influenced to only a small extent by food. Since salicylate has a relatively long biological half-life and is chemically stable compared to aspirin, it is not surprising that its overall absorption efficiency is not significantly changed by the delay in stomach emptying due to solid food.

Table III—Percentage (±1 *SD*) of Aspirin Absorbed into the Systemic Circulation as Unchanged Drug (k_1/k_a) and as Salicylate (k_2/k_a)

Treatment	$\frac{k_1}{k_a}$	$\frac{k_2}{k_a}$
1. Carbohydrate	8.6 ± 2.9	91.4 ± 2.9
2. Fat	5.8 ± 2.2	94.2 ± 2.2
3. Protein	5.9 ± 2.1	94.1 ± 2.1
4. Fasting, 25 ml of water	16.0 ± 7.1	84.0 ± 7.1
5. Fasting, 250 ml of water	17.8 ± 10.1	82.2 ± 10.1
Paired *t* test	4,5 > 1–3	2 > 4,5 3 > 5

It is concluded that ingestion of solid food prior to dosing aspirin tablets reduces circulating levels of both aspirin and salicylate during the 1st hr after dosing. This effect is not observed at later times. In fact, fatty meals may increase absorption, perhaps due to greater drug solubilization resulting from increased bile flow.

The absorption rate of aspirin, both as unchanged drug and as salicylate, was optimal when the drug was ingested with a relatively large volume of water on an empty stomach. These conclusions are consistent with observations made with other drugs examined under similar experimental conditions (10, 12).

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ACKNOWLEDGMENTS

Supported by Public Health Service Grant GM 20327 from the National Institute of General Medical Sciences and by a grant from Glenbrook Laboratories.