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# Effect of Food on Salsalate Absorption

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**Summary:** To assess the effect of food on salsalate absorption, single 1500-mg oral doses of salsalate were administered to 17 men under fasted and fed conditions according to a randomized open-label crossover design. A 7-day washout separated treatment periods. Blood samples were drawn throughout the 48-h period following dose administration and the resulting plasma samples assayed by high-performance liquid chromatography (HPLC) for unchanged drug, salsalate, and the major metabolite, salicylic acid. When results for the fasted and fed treatments were compared, no significant differences were observed in the pharmacokinetic parameters for the major metabolite salicylic acid or in the extent of absorption of unchanged drug; however, the rate of salsalate absorption was affected. Although the time-to-peak for salsalate was significantly delayed by ~1 h in the presence of food, the peak level was not significantly affected. The lack of difference between the two treatments for the therapeutic moiety, salicylic acid, indicates a lack of a significant food effect on single doses of salsalate. **Key Words:** Salsalate absorption—Presystemic metabolism—Food effect.

The nonsteroidal antiinflammatory agent salsalate (salicylsalicylic acid) is a salicylic acid derivative that provides therapeutic efficacy in the treatment of arthritic conditions, such as rheumatoid arthritis, similar to that provided by aspirin (1) with the advantage of a reduced incidence of occult bleeding and gastric irritation (2,3). The reduction in adverse gastric effects has been attributed to the differences in solubility for the two agents; salsalate undergoes particulate dispersion in the pH of the stomach and is soluble in the pH of the small intestine, while aspirin is soluble in the acidic pH of the stomach.

The unique solubility properties of salsalate combined with its high first-pass metabolism to salicylic acid make salsalate an interesting candidate for an effect of food study. It is well known that the presence of food can affect the absorption and/or solubility of many agents, including aspirin (4–6). The results of a previously reported single-dose salsalate study suggest that there may be a significant effect of food on salsalate absorption (7); however, that study was conducted with minimal blood sampling and only levels of the metabolite, salicylic acid, were measured. The purpose of the present study was to more thoroughly test the effect of food on salsalate absorption by determining plasma levels of both unchanged drug and salicylic acid following single oral doses administered under fasted and fed conditions. Since meals with a high fat content have been demonstrated to prolong gastric retention (8,9), a high-fat meal was chosen as the test meal in order to increase the likelihood of observing a food effect.

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## METHODS

Seventeen healthy male volunteers, aged 20–50 (mean, 33) years and weighing 143–242 (mean, 176) lb, completed the study. All subjects were healthy, as judged by a prestudy medical history, 12-lead electrocardiogram, physical examination, and clinical laboratory tests. Subjects were excluded if they had a prior sensitivity to salicylates; a history of gastrointestinal, cardiovascular, hepatic, or pulmonary disease; a chemical dependency; or if they had consumed any medications, including salicylates, within 1 week of the study start. All subjects gave informed consent prior to receiving the study drug.

Each subject received a single oral 1500-mg dose of salsalate during fasted and fed conditions according to an open-label randomized crossover design. During the fasted treatment, two 750-mg salsalate tablets were administered with 6 ounces of water following an overnight fast. During the fed treatment, two 750-mg salsalate tablets were administered with six oz of water immediately following ingestion of a standardized high-fat breakfast, which consisted of two fried eggs, two strips of bacon, one slice of buttered toast, two oz of hash-brown potatoes, and 8 oz of whole milk. During fasted and fed treatment periods, no food or beverages, except water, were ingested until after the 4-h postdose blood sample. A 7-day washout separated treatment periods.

The actual study design included a third treatment period, which was used to determine the absorption characteristics of a different salsalate formulation given to fasted subjects. Because the performance of this particular formulation is not pertinent to the focus of this paper, results from this treatment will not be discussed.

Venous blood samples (10 ml) were drawn predose, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48 h postdose via direct venipuncture. Plasma was promptly prepared by centrifugation, transferred to capped glass vials, and stored frozen (−20°C) until analysis. The maximum storage time was 36 days, well within the documented stability limits.

Plasma salicylic acid and salsalate (unchanged drug) levels were determined using a high-performance liquid chromatographic (HPLC) technique. The equipment used in this technique included a liquid chromatograph with a Laboratory Data Control (Riviera Beach, FL, U.S.A.) Constametric III delivery system, a WISP 710A automatic sample delivery system (Waters Associates, Milford, MA, U.S.A.), a Shimadzu SPD-2A spectrophotometric detector (Kyoto, Japan), and a Spectra-Physics 4100 computing integrator (San Jose, CA, U.S.A.). Separation was accomplished using a μBondapak C-18 column (Waters Associates). The mobile phase was a methanol and 1% acetic acid (58/42, vol/vol) mixture at a flow rate of 2 ml/min.

Aliquots of plasma (0.5 ml) were acidified with 0.27 *N* hydrochloric acid and extracted with 10 ml ether. The ether fraction was evaporated, and the residue dissolved in 0.5% acetic acid/acetonitrile. Salicylic acid and salsalate were detected at 308 nm and quantitated with α-phenylcinnamic acid as the internal standard. The linear range of the assay for salicylic acid was 2–260 μg/ml plasma; the linear range for salsalate was 2–50 μg/ml plasma. Standard curves were generated daily, and 10% of the unknown samples in each analysis set was randomly repeated. The coefficient of variation for the stated linear ranges of both analytes was ≤6%.

Standard methods of calculating pharmacokinetic parameters were used (10). The peak time ($T_{max}$) was defined as the time of the highest measured plasma salicylic acid or salsalate concentration ($C_{max}$) or, where necessary, as the time between consecutive equal concentrations. Area under the plasma concentration-versus-time curve (AUC) was calculated by the trapezoidal rule from time zero to 48 h, or to the time of the first postdose unquantitatible or zero concentration. The apparent terminal plasma half-life ($t_{1/2}$) values were determined from at least three and usually four or more analytically significant data points in the terminal (postabsorptive) phase of the log plasma concentration-versus-time curves by calculation of the least squares lines. Half-life values were not calculated if fewer than three analytically significant data points fell in the terminal phase of the curve.

An analysis of variance for a three-period crossover, with sequences, subjects within sequences, treatments, and sequence by treatment interaction as factors in the model, was used to compare the mean pharmacokinetic parameters ($C_{max}$, $T_{max}$, AUC, $t_{1/2}$ and plasma levels). Because this experiment was designed to compare three treatments, the difference between the two treatments described in this analysis was declared significant for $p \leq 0.017$ (0.05 divided by 3). This *p*-value was set to avoid the finding of statistical significance occurring by chance alone, as discussed by Yusef et al. (11).

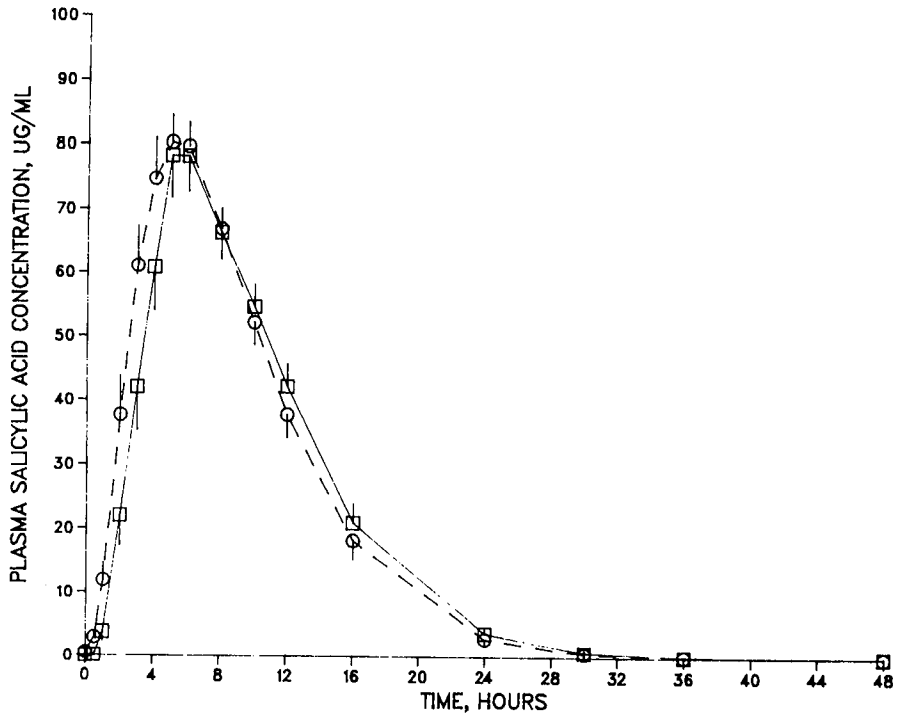


FIG. 1. Mean (± SE) plasma salicylic acid levels following salsalate administration to fasted (○) and fed (□) subjects; n = 17.

The statistical power of the F-test to detect, in the fed AUC mean, a 20% difference from the fasted AUC mean, assuming alpha = 0.017, was >95% for both the salicylic acid parameters and the salsalate parameters. Thus, this study had an adequate sample size to detect a clinically meaningful difference between the two treatments.

## RESULTS

The mean plasma salicylic acid profiles for the two treatments were similar and are depicted in Fig. 1. The lack of any observed differences in mean $C_{max}$, $T_{max}$, AUC values (Table 1), and the mean of the fasted-to-fed AUC ratio (1.05) between the two treatments indicates that a high-fat meal does not affect the appearance of salicylic acid in plasma. The apparent mean half-lives of salicylic acid following a single dose of salsalate averaged ~4 h for both treatments. The 4-h value is in good agreement with half-life values from previously reported studies in healthy subjects (12,13).

Mean plasma salsalate levels for the two treatments were low—much lower than the corresponding salicylic acid levels at most time points—and were less than the lowest standard of 2 μg/ml by 16 h postdose (Fig. 2). Only one difference was observed in the salsalate kinetics between the two treatments (Table 2). The time-to-peak concentration for the fed treatment was significantly longer than that for the fasted treatment. This delay did not affect the peak concentration or the AUC values. The fasted-to-fed AUC ratio was 1.08. Although the apparent plasma half-lives of salsalate could not be calculated for all 17 subjects, those that could be calculated were similar and averaged ~1 h, which is also in good agreement with previously reported results for healthy subjects (10,11).

As indicated by the ranges presented in Tables 1 and 2, outliers occurred in the data for the salicylic acid $C_{max}$ and $T_{max}$ parameters, and for the salsalate $C_{max}$ parameter. In order to determine the effect of the outliers on the outcome of the study, the data were analyzed with and without these data points. Deleting the outliers did not change the statistical conclusion of no difference; in fact, it strengthened the conclusion.

Three adverse experiences were reported, each

TABLE 1. *Mean (±SD) salicylic acid pharmacokinetic parameters (n = 17)*

| Treatment | $C_{max}$ (μg/ml) | $T_{max}$ (hr) | AUC (μg hr/ml) | $t_{1/2}$ (hr) |
|---|---|---|---|---|
| Fasted | 86.0 ± 15.7 | 5.1 ± 1.2 | 870 ± 220 | 3.8 ± 1.0 |
| Range | (62.7–121.2) | (3–8) | (435–1362) | (2.3–6.0) |
| Fed | 85.7 ± 22.1 | 5.6 ± 1.8 | 850 ± 224 | 4.1 ± 1.0 |
| Range | (38.9–118.3) | (3–11) | (447–1355) | (2.6–6.4) |

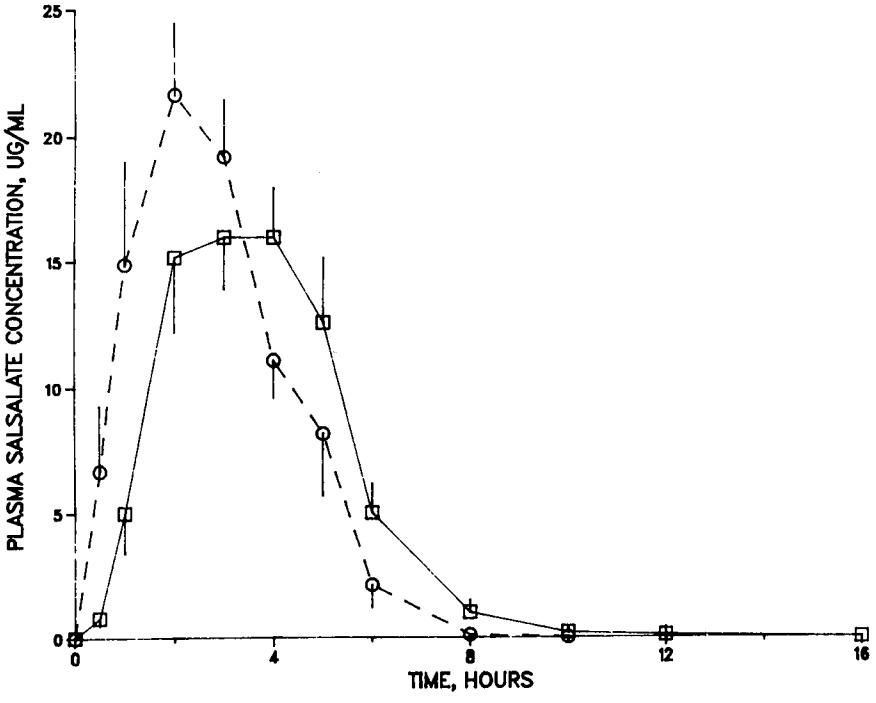


FIG. 2. Mean (± SE) plasma salsalate levels following salsalate administration to fasted (○) and fed (□) subjects; n = 17.

by a different subject, and all occurred during the fasted treatment. One subject reported an ear-ache, one reported a sore throat, and one reported flatus. None of the adverse experiences were considered study-drug related and all resolved without treatment.

## DISCUSSION

The presence of food can affect the presystemic metabolism and actual absorption of many orally administered drugs (4,5). Several studies (12,13), including the present one, have shown that salsalate undergoes extensive presystemic metabolism and is almost completely converted to salicylic acid. The absorption of salsalate has also been shown to be pH- and site-dependent. The unique presystemic metabolism and absorption properties of salsalate made it a likely candidate for a food effect. In this study, a high-fat test meal was administered to increase the likelihood of observing a food effect.

The presystemic metabolism of salsalate appeared to be unaffected by the test meal, based on an analysis of the extents of absorption of the parent drug and the main metabolite, salicylic acid; the presence of food did not significantly affect the mean AUC or half-life values of either compound.

Although the high-fat meal did not have an effect on the extent of salsalate absorption, a significant delay in the rate of salsalate absorption was observed. Since salsalate is soluble in the pH of the small intestine (pH > 6) and not in the acidic pH of the stomach, this delay is probably due to a food-induced delay in gastric emptying. The delay in the rate of salsalate absorption is unlikely to be of any clinical significance, since the appearance of the therapeutic moiety, salicylic acid, in the plasma was unaffected by the presence of food.

The finding that food significantly delayed the time to maximum concentration for salsalate, but not for the metabolite salicylic acid, probably reflects the unique solubility and metabolic characteristics of salsalate. Salsalate begins to slowly dis-

TABLE 2. *Mean (±SD) salsalate pharmacokinetic parameters (n = 17)*

| Treatment | $C_{max}$ (μg/ml) | $T_{max}$[a] (hr) | AUC (μg hr/ml) | $t_{1/2}$ (hr) |
|---|---|---|---|---|
| Fasted | 30.8 ± 9.8 | 2.6 ± 1.3 | 78.1 ± 20.1 | 0.9 ± 0.4[b] |
| Range | (18.0–60.2) | (1–5) | (54.6–115.7) | (0.6–2) |
| Fed | 25.7 ± 9.1 | 3.6 ± 1.2 | 74.6 ± 19.6 | 1.1 ± 0.8[c] |
| Range | (12.4–38.4) | (2–6) | (53.7–126.6) | (0.6–3.3) |

[a] Significant difference ($p \leq 0.017$) between treatments for this parameter.

[b] Half-life values could not be calculated for three subjects due to unquantitatible plasma levels; n = 14.

[c] Half-life values could not be calculated for four subjects due to unquantitatible plasma levels; n = 13.

solve in the duodenum when the pH rises above 5, but the majority of the dose is probably solubilized in the small intestine and then undergoes a rapid and extensive ester hydrolysis to salicylic acid. One can speculate that while food might delay the appearance of salsalate in the small intestine, once the dose is in the small intestine, food might actually increase the solubilization of salsalate and also its ester hydrolysis to salicylic acid. The end result is that the appearance of salsalate in the plasma is delayed but, because of offsetting effects, plasma levels of salicylic acid remain virtually unchanged. The salsalate tablet is designed to disintegrate rapidly, so that drug in the small intestine would be widely dispersed like a granule dose-form, and there is precedent for a similar lack of a food effect on salicylic acid levels with enteric-coated granules of aspirin (14).

The difference in the results between this and the previous single-dose salsalate food-effect study could be due to differences in sampling schedules. In the previous study, blood samples were drawn predose and at 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, and 12 h postdose (7). Blood sampling during this study was more rigorous during the 6–24 h postdose period and was designed to adequately characterize the profile of a twice-a-day product. The expanded sampling schedule proved worthwhile, especially since a substantial portion of the AUCs of salicylic acid concentration-versus-time occurred during the 6–24-h time period. Another procedural difference was the preparation of plasma rather than serum for sample analysis. Plasma was promptly prepared and immediately frozen to avoid the additional hydrolysis of salsalate that occurs during the clotting step of the serum preparation process (15). Other differentiating features of this study include the analysis of both unchanged salsalate and salicylic acid to provide a more complete picture of the effect of food on salsalate absorption, and the inclusion of a larger number of subjects (n = 17) than was included in the previous study (n = 12).

In summary, since there were no significant differences in plasma salicylic acid profiles between the fasted and fed treatments in healthy subjects, it is unlikely that the presence of a high-fat meal would have a clinically significant effect on the absorption of the therapeutic moiety, salicylic acid, for patients on oral salsalate therapy. As a caution, however, this finding does not guarantee that a diseased patient consuming a variant diet would not have different absorption characteristics; additional studies in patients are needed to corroborate these findings.

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