Comparative Plasma Salicylate and Urine Salicylurate Levels following Administration of Aspirin, Magnesium Salicylate, and Choline Magnesium Trisalicylate

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Abstract □ Eighteen healthy volunteers were administered single doses of commercially available solid dosage forms of aspirin, magnesium salicylate (I), and choline magnesium trisalicylate (II), equivalent to ~500 mg of salicylic acid, in a randomized, complete crossover design. Plasma salicylate and urine salicylurate levels were measured by high-pressure liquid chromatography at frequent intervals following dosing; the resultant profiles, areas under the curve (*AUC*), and percentages of dose excreted as salicylurate were statistically analyzed by an analysis of variance. The plasma salicylate levels following the two dosage forms containing I and II were virtually identical when corrected for small differences in the dose. The plasma salicylic acid level following aspirin was ~10% lower during the 1.5–3.0-hr interval due to a portion of unhydrolyzed aspirin, but the dose-corrected *AUC* for the products tested did not differ significantly ($p < 0.05$). During the 24 hr following dosing, 66.5 ± 12.1, 68.4 ± 7.1, and 60.9 ± 14.1% of the salicylic acid were excreted as urine salicylurate for aspirin, I, and II, respectively, with no significant difference ($p < 0.05$). Based on this study, there are no significant differences in the rate and extent of absorption of salicylate following the three dosage forms tested, and the elimination kinetics of salicylic acid are not altered by these dosage forms.

Keyphrases □ Salicylate—comparison of plasma levels following administration of aspirin, magnesium salicylate, and choline magnesium trisalicylate □ Aspirin—plasma salicylate levels following administration of solid dosage form, comparison with magnesium salicylate and choline magnesium trisalicylate □ Magnesium salicylate—plasma salicylate levels following administration of solid dosage form, comparison with aspirin and choline magnesium trisalicylate □ Choline magnesium trisalicylate—plasma salicylate levels following administration of solid dosage form, comparison with aspirin and magnesium salicylate

Relatively high doses of salicylate, primarily as aspirin, frequently are indicated for prolonged periods in the treatment of rheumatoid arthritis. This intensive salicylate therapy commonly is associated with GI disturbances and acute blood loss (1). Recent reports (2–4) suggested that choline magnesium trisalicylate (II) can effectively deliver salicylate without the gastric irritation associated with aspirin. Magnesium salicylate (I) also was reported[1] to be less irritating to the gastric mucosa than aspirin.

If the two salts of salicylic acid are to be used as alternatives to aspirin, it is important to know the rate and extent of their absorption compared to aspirin. Furthermore, because the kinetics of metabolism and excretion of salicylate are complex and serum concentration dependent, the potential influence of the dosage form on elimination also should be evaluated. In the present study, plasma salicylate and urine salicylurate profiles following equivalent single doses of aspirin, I, and II were measured.

EXPERIMENT

Drug Products—Three commercially available products were chosen to provide aspirin[2], magnesium salicylate[3], and choline magnesium salicylate[4]. The salicylate content of each was determined and is reported with the results.

Clinical Protocol—Eighteen male volunteers underwent a comprehensive examination including urine analysis and hematological and blood chemistry determinations to ensure that they were in good health. Volunteers ranged in age from 18 to 24 years and in weight from 62 to 85 kg, and all were within ±20% of ideal body weight. No volunteer had a history of chronic drug use, and none had taken any medications, including salicylate, during the 14 days preceding the study. The three drugs were administered as single doses, equal to ~500 mg of salicylic acid, following a randomized, complete crossover design with a minimum of 3 days between doses.

Following an 8-hr fast, drugs were administered with 240 ml of water; no additional food or water was allowed until a standard meal was given following the 4-hr blood sample. Blood samples were taken *via* an indwelling catheter from a forearm vein, with heparin used to maintain the patency of the catheter. Vacutainer tubes[5] were chilled and samples were handled as described previously (5) to ensure stability. Blood (7 ml) was collected prior to dosing and at 15, 30, 45, and 60 min and 1.5, 2, 3, 4, 8, 12, and 16 hr after dosing. All urine voided was collected 6 hr prior to dosing and for the 0–12- and 12–24-hr intervals following dosing.

Plasma salicylate and urine salicylurate levels were determined by the previously described (5) high-pressure liquid chromatographic method with two modifications. Since the unhydrolyzed aspirin was not to be measured, the retention times of salicylic acid and urine salicylurate were decreased by increasing the amount of acetonitrile in the mobile phase to 22.5%. Only fluorescence detection was employed, with metaanisic acid as the internal standard. A comprehensive evaluation of the method proved its sensitivity, specificity, and reproducibility to be equal or better than published values (5). Samples were stored at −30° prior to analysis.

RESULTS AND DISCUSSION

Table I presents the mean plasma salicylic acid and urine salicylurate levels with the computed parameters and statistical analysis. Estimates of the area under the curves (*AUC*) up to the 16-hr sample [AUC_{0-16} in (micrograms times hours) per milliliter] were computed by the trapezoidal method, and the half-lives were calculated by linear regression of the natural logarithm of the plasma concentration *versus* time for the 4-, 8-, 12-, and 16-hr samples. The *AUC* to infinity [$AUC_{-\infty}$ in (micrograms times hours) per milliliter] was computed as $AUC_{0-16} + 1.44t_{1/2}C_{p16}$, while the maximum plasma concentration, $C_{p\max}$, and the time of $C_{p\max}$, $t_{\max}$, were read directly from the data for each volunteer. The urine salicylurate level is reported as the total milligrams excreted during the 0–12-, 12–24-, and 0–24-hr periods and as the percentage of the dose of salicylate excreted as salicylurate in 24 hr.

As expected, the analysis of variance showed no significant difference in the plasma salicylate level between I and II at any time, while the plasma salicylate level following aspirin was slightly lower during the 1.5–3.0-hr interval. This small difference in the plasma salicylate level probably was due to a portion of the aspirin being unhydrolyzed during the early part of the sampling period. Over the 16 hr, the hydrolysis of aspirin produced more salicylate, with the dose-corrected AUC_{∞},

[1] D. Earnest, Arizona Medical Center, University of Arizona, Tucson, Ariz., personal communication.

[2] Bayer Aspirin, Glenbrook Laboratories, Division of Sterling Drug, New York, N.Y.

[3] Magan, Adria-Warren Teed Pharmaceuticals, Columbus, Ohio.

[4] Trilisate, Purdue Frederick Co., Norwalk, Conn.

[5] Becton-Dickinson 278-069, 7.0 ml containing 14 mg of potassium oxalate and 17.5 mg of sodium fluoride.

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Table I—Mean Plasma Salicylic Acid and Urine Salicyluric Acid Levels following Three Sources of Salicylate

Parameter	Plasma Concentration, μg/ml [Mean[a] ± *SD* (*n* = 18)]		
	Aspirin (494 mg of Salicylic Acid)	Magnesium Salicylate (481 mg of Salicylic Acid)	Choline Magnesium Trisalicylate (500 mg of Salicylic Acid)
0 hr	<0.05 *a*	<0.05 *a*	<0.05 *a*
0.25 hr	10.7 ± 8.94 *a*	11.2 ± 8.71 *a*	7.27 ± 4.81 *a*
0.50 hr	22.7 ± 10.5 *a*	24.5 ± 11.0 *a*	19.0 ± 8.17 *a*
0.75 hr	28.0 ± 9.49 *a*	31.2 ± 12.2 *a*	28.4 ± 10.42 *a*
1.0 hr	30.9 ± 8.98 *a*	33.6 ± 11.5 *a*	35.4 ± 10.42 *a*
1.5 hr	32.9 ± 7.41 *a*	36.5 ± 6.10 *a,b*	37.5 ± 7.97 *b*
2.0 hr	33.1 ± 5.74 *a*	35.0 ± 5.06 *b*	36.5 ± 5.71 *b*
2.5 hr	31.9 ± 5.39 *a*	33.0 ± 4.65 *a,b*	34.4 ± 5.41 *b*
3.0 hr	30.5 ± 5.28 *a*	30.8 ± 4.53 *a*	32.0 ± 5.36 *b*
4.0 hr	26.4 ± 5.35 *a*	25.5 ± 4.88 *a*	27.4 ± 4.65 *a*
8.0 hr	11.0 ± 3.92 *a*	10.5 ± 2.82 *a*	11.1 ± 3.18 *a*
12.0 hr	3.27 ± 2.09 *a*	2.86 ± 1.14 *a*	3.20 ± 1.39 *a*
16.0 hr	0.908 ± 0.786 *a*	0.695 ± 0.322 *a*	0.783 ± 0.388 *a*
AUC_{16}, (μg hr)/ml	224 ± 49.6 *a*	223 ± 40.5 *a*	232 ± 42.1 *a*
$t_{½}$, hr	2.02 ± 0.399 *a*	2.01 ± 0.196 *a*	2.05 ± 0.198 *a*
AUC_{∞}, (μg hr)/ml	226 ± 52.5 *a*	225 ± 41.4 *a*	235 ± 43.2 *a*
$C_{p_{max}}$, μg/ml	35.9 ± 5.87 *a*	39.1 ± 6.21 *b*	41.4 ± 6.75 *b*
t_{max}, hr	1.64 ± 0.698 *a*	1.44 ± 0.670 *a*	1.54 ± 0.583 *a*
$AUC_{\infty}/D \times 10^3$, hr/ml	0.46 ± 0.11 *a*	0.47 ± 0.09 *a*	0.47 ± 0.09 *a*
$C_{p_{max}}/D \times 10^3$, ml^{-1}	0.07 ± 0.01 *a*	0.08 ± 0.01 *b*	0.08 ± 0.01 *b*
SU_{0-12^b}, mg	407 ± 90.5 *a*	393 ± 69.3 *a*	369 ± 77.7 *a*
SU_{12-24}, mg	57.4 ± 33.2 *a*	69.9 ± 68.3 *a*	65.7 ± 48.1 *a*
SU_{0-24}, mg	464 ± 84.7 *a*	465 ± 48.5 *a*	430 ± 99.3 *a*
Percent salicylic acid as salicylurate	66.5 ± 12.1 *a*	68.4 ± 7.1 *a*	60.9 ± 14.1 *a*

[a] A common letter indicates no significant difference ($p < 0.05$) by an analysis of variance and the least-significant difference method (8). [b] Salicylurate excreted.

AUC_{∞}/D, being equivalent to the products containing salicylate salts. Furthermore, the absorption rate as indicated by the time to reach the maximum plasma concentration did not differ significantly among the three products tested.

The percentage of salicylate excreted as salicylurate agreed closely with previous observations (6, 7) and did not differ significantly ($p < 0.05$) among the three treatments. Moreover, the apparent elimination half-life of 2.0 hr was identical for the three treatments and was as expected for a single 500-mg dose. Although chronic administration should produce a longer half-life (6, 7), this result will not be dependent on the dosage form as long as the rate and extent of absorption do not differ substantially.

Based on the present study, the absorption and elimination kinetics and the resultant plasma concentration of salicylate following administration of the commercially available solid dosage forms of I and II are virtually identical. Furthermore, administration of commonly employed aspirin tablets provides a plasma salicylate level that is only slightly lower (10%) at the peak time due to some unhydrolyzed aspirin being present. Over a 16-hr period, and probably on chronic dosing, there would be no significant differences in the plasma salicylate level.

The possible therapeutic implications of these observations depend on the importance of unhydrolyzed aspirin in the body and the possible effects the different forms of salicylate may have on the GI mucosa over time. However, based solely on the plasma salicylate concentration produced, there is no reason to differentiate among the three sources of salicylate evaluated in the present study.

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