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ACKNOWLEDGMENTS

The authors thank Dr. M. Aylward and his Clinical Staff for their help in the recruiting and dosing of the human volunteers, Mr. P. Ho for his technical assistance, and Miss A. Jones and Miss D. A. Protheroe for their secretarial assistance.

Comparative Aspirin Absorption Kinetics after Administration of Sodium- and Potassium-Containing Buffered Solutions

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Received March 28, 1983, from the *Pharmacokinetics Laboratory, University of Missouri-Kansas City, Schools of Pharmacy & Medicine, Kansas City, MO 64108.* Accepted for publication June 29, 1983.

Abstract □ Twelve fasting normal volunteers received three aspirin dosage forms in a single 325-mg dose in a complete crossover study; the plasma aspirin and salicylic acid levels and the urine salicylic acid and salicyluric acid levels were measured over 10 h. The three dosage forms included an unbuffered tablet and two effervescent solutions, one with sodium bicarbonate-citrate buffer and the other with potassium bicarbonate-citrate buffer. A significantly faster absorption rate was observed with the sodium bicarbonate-citrate buffer, when compared with the potassium bicarbonate-citrate buffer and the unbuffered tablets, which were equivalent. These differences were attributed primarily to gastric emptying rate differences. Urine pH and salicylate renal clearance were significantly affected by the single dose of antacid buffer. The area under the curve and urine accumulation comparisons suggested that ~25% more aspirin reaches the general circulation intact after administration of the unbuffered tablet than the two solutions, but that the total salicylate absorbed is equivalent for all three dosage forms. This difference in aspirin bioavailability is probably due to the fact that the two buffered solutions are predominantly absorbed through the intestine, in which presystemic hydrolysis occurs, whereas a significant portion of the tablet dose is absorbed through the gastric mucosa.

Keyphrases □ Aspirin—absorption kinetics after administration of sodium- and potassium-containing buffered solutions □ Salicylic acid—absorption kinetics after administration of sodium- and potassium-containing buffered solutions □ Absorption kinetics—aspirin after administration of sodium- and potassium-containing buffered solutions

Aspirin is the drug of choice when a mild analgesic-antipyretic effect is required. It is also a primary agent used in the chronic management of rheumatoid arthritis and osteoarthritis. After oral administration for pain, rapid absorption is desirable to provide the rapid onset of effects and to reduce contact time with the gastric mucosa. The potential influence of potassium ion *versus* sodium ion on the absorption kinetics of aspirin from two different effervescent solutions is the subject of this report.

BACKGROUND

A recent report (1) from this laboratory compared the absorption kinetics of aspirin from three commercially available dosage forms. Two of the dosage forms were extemporaneously prepared effervescent solutions containing either 1.825 or 3.808 g of sodium bicarbonate as a component of the buffer. It was concluded that a primary mechanism for the more rapid absorption of the solutions than the unbuffered tablet was more rapid gastric emptying. Also, the lower area under the aspirin curve for the solutions was attributed to a greater portion of the aspirin being absorbed through the intestine (*i.e.*, rather than through the stomach wall) and thus being subjected to a greater presystemic hydrolysis.

Patients on sodium-restricted diets may wish to take aspirin as a buffered effervescent solution. Absorption kinetics of the commercially available buffered effervescent solution was compared with that of a solution in which the sodium was replaced with potassium. A commercially available unbuffered tablet was also studied for comparison.

EXPERIMENTAL SECTION

Dosage Forms—Three dosage forms were used to provide equal doses of aspirin: a plain tablet containing 325 mg of aspirin[1]; an effervescent tablet containing 324 mg of aspirin, 1,904 g of sodium bicarbonate, and 1 g of citric acid[2]; and a prepared effervescent tablet containing 324 mg of aspirin, 2.26 g of potassium bicarbonate, and 1 g of citric acid.

Subjects—Twelve healthy volunteers (eight males and four females; ages 21–37 years; weight, 53.6–94.5 kg) were evaluated by a comprehensive physical examination, blood chemistry profile (including blood count and differential), and complete urinalysis. None of the subjects had a history of gastrointestinal disease or surgery. All subjects were free of any active disease process, and none had used any medication for 14 d before the study.

Method—A Latin-square design for three treatments in 12 subjects was employed. A 10-h fast preceded dosing and continued for 4 h postdose. At ~7 a.m., predose urine and blood samples were obtained, and a single dose of aspirin with 240 mL of water was administered. The effervescent tablets were dissolved in 140 mL of water 3 min before dosing and the mixture was then swallowed. The glass was rinsed with 100 mL of water, which also was swallowed. After dosing, 100 mL of water was administered at 1, 2, and 3 h, and a uniform meal was served after the 4-h sample was obtained, after which water was allowed *ad libitum*. Subjects remained standing or sitting through the day, and exercise was limited to walking about the room.

Blood was drawn into chilled vacuum containers[3] *via* an indwelling catheter at 5, 10, 15, 20, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, and 10 h. Plasma was separated by centrifugation at 1764×*g* at 4°C within 20 min of collection. All urine was collected at 2-h intervals over 10 h, the pH and volume were measured, and an acidified aliquot was saved for analysis. All samples were frozen at −30°C and assayed within 2 weeks of collection by the HPLC method described previously (2).

RESULTS

As shown in Tables I and II, both plasma aspirin and salicylic acid levels rise more rapidly after administration of the solution with sodium than the potassium solution or the tablet. This rank order and profile reflect the values for 11 of the 12 subjects and is statistically significant ($p < 0.05$). Plasma aspirin levels rise rapidly to a mean peak of 7.20 μg/mL at 17.5 min with the single 324-mg dose in a sodium-containing effervescent solution, whereas the potassium-substituted solution reaches only 5.26 μg/mL at 30.4 min, which is not significantly higher ($p < 0.05$) than for the tablet. The ultimate exposure

[1] Bayer Aspirin; Glenbrook Laboratories -Division of Sterling Drug Inc., New York.
[2] Alka-Seltzer; Miles Laboratories, Inc., Elkhart, Ind.
[3] Vacutainer BD, 278-069, 7.0 mL, containing 14 mg of potassium oxalate and 17.5 mg of sodium fluoride.

0022-3549/84/0700-0998$01.00/0

Table I—Mean Plasma Aspirin Levels and Kinetic Parameters [a]

Parameter	Na^+ solution	K^+ solution	Tablet
Mean conc, μg/mL			
5 min	1.04	0.71	0.94
10 min	4.17	1.84	2.17
15 min	6.43	2.97	3.42
20 min	6.27	3.56	3.98
30 min	4.41	4.34	4.22
45 min	1.99	2.65	3.34
60 min	1.10	1.56	2.70
90 min	0.36	0.52	1.28
120 min	0.30	0.30	0.80
Maximum conc., μg/mL	7.20*	5.27†	4.76†
Time of maximum conc., min	17.5*	30.4†	36.7†
Area under curve to 120 min, (μg·min/mL)	228.1*	211.4*	276.3†
to infinity, (μg·min/mL)	231.7*	216.6*	290.8†
$t_{1/2}$, min	19.6*	18.7*	24.7†

[a] A common symbol beside the mean indicates no significant difference ($p < 0.05$) by three-way analysis of variance and least significant difference.

to aspirin, as indicated by the area under the curve to infinity, is higher by ~25% for the tablet than for the two buffered solutions, which are equivalent.

Parameters that indicate the rate of absorption, maximum concentration, and time to maximum concentration for salicylic acid show the sodium-containing solution to be faster, with the potassium-containing solution being intermediate, and the tablet slowest. For salicylic acid, however, only the maximum concentration differs significantly ($p < 0.05$), whereas the renal clearance of salicylate is higher for the two buffered solutions (Table III). The overall contribution to total clearance is not sufficient to lower the area under the salicylate plasma curve over 10 h (Table II).

In Table III, the data obtained from urine samples are summarized, and the small differences in urine pH and salicylate renal clearance resulting from the buffered solutions are shown. Although urine pH was measured for 10 h, only during the first 2 h was there a significant difference between buffered and unbuffered dosages. Over a 10-h period, ~70% of the 325-mg dose was recovered in urine as salicylurate and salicylate, which demonstrates the equivalence of the extent of aspirin and/or salicylate absorption for all three dosage forms.

Table II—Mean Plasma Salicylic Acid Levels and Kinetic Parameter [a]

Parameter	Na^+ solution	K^+ solution	Tablet
Mean conc., μg/mL			
0.08 h	1.03	0.71	0.73
0.16 h	6.17	3.13	2.04
0.25 h	12.3	6.18	4.39
0.33 h	18.1	9.87	6.62
0.50 h	20.8	16.6	10.6
0.75 h	20.2	19.5	13.9
1.0 h	19.0	19.1	14.8
1.5 h	17.1	16.8	15.6
2 h	15.3	15.7	16.1
3 h	12.0	12.5	13.4
4 h	9.94	10.1	11.2
6 h	5.86	6.51	6.92
8 h	3.23	3.51	3.96
10 h	1.86	2.06	2.28
Maximum conc., μg/mL	21.8*	20.2*	17.2†
Time of maximum conc., h	0.59*	0.75*	1.50†
Area under curve to infinity, μg·h/mL	94.9*	95.6*	98.1*
$t_{1/2}$, h	2.42*	2.60*	2.91*

[a] A common symbol beside the mean indicates no significant difference ($p < 0.05$) for three-way analysis of variance and least significant difference.

Table III—Mean Urine Salicylate and Salicylurate Levels [a]

Parameter	Na^+ solution	K^+ solution	Tablet
Urine volume (0 → 2 h), L	0.131*	0.186*	0.170*
Urine pH (0 → 2 h)	6.63*	6.87*	6.11†
Salicylic acid renal clearance (0 → 2 h), L/h	0.31*	0.43*	0.14†
Urine volume (0 → 10 h), L	0.845*	0.918*	0.874*
Salicylic acid renal clearance (0 → 10 h), L/h	0.334*	0.353*	0.204†
Accumulation of salicylic acid (0 → 10 h), mg	28.7*	29.2*	17.1†
Accumulation of salicyluric acid (0 → 10 h), mg	214*	206*	221*
Percent aspirin dose (equivalent) recovered as salicylic acid and salicylurate to 10 h, %	72.3*	70.4*	69.9*

[a] A common symbol beside the mean indicates no significant difference ($p < 0.05$) for three-way analysis of variance and least significant difference.

DISCUSSION

Two significant results were obtained from this study. First, the rapid absorption rate of aspirin from a buffered solution is, in part, related to the sodium content, and potassium is not equivalent to sodium in this regard. This observed difference in absorption rate is most probably from the comparative effects of these two ions on gastric emptying kinetics. Before mixing with gastric secretion, the solutions are each ~100 mM in sodium or potassium ion with a total milliosmolarity of ~120[4]. In this concentration range, sodium has been shown to accelerate gastric emptying, whereas potassium inhibits gastric emptying (3, 4). Thus, although both solutions can raise gastric pH, which would speed gastric emptying, the inhibitory effect of potassium nullifies the pH effect, and the potassium-containing solution is emptied at about the same rate as the unbuffered tablet.

A second and more subtle observation is the extent to which aspirin reaches the general circulation unhydrolyzed, which is the same for both the sodium- and potassium-containing buffered solutions. Both are ~25% less bioavailable than the unbuffered tablet. This is consistent with the previously stated hypothesis (1) that the aspirin administered in a buffered solution is ionized in the stomach and little or no absorption occurs until it is emptied into the intestine. Intestinal absorption is associated with greater presystemic hydrolysis and, thus, a lower portion is bioavailable. These observations are consistent with the hypothesis that the potassium-containing solution is retained longer in the stomach and the antacid buffering is sufficient to reduce or inhibit gastric absorption.

It would appear that the replacement of sodium in extemporaneously prepared effervescent solutions of aspirin may slow absorption to equal that of a conventional tablet. However, the protection afforded the gastric mucosa by the elevated pH may be the same for both the sodium and potassium buffers.

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