meaningful observations were made. Converting the mean terminal elimination rate constants generated in this study to half-lives results in values of 3.6 and 4.3 hr for the intravenous and oral treatments, respectively. In contrast, chronic congestive heart failure patients who received oral amrinone had a mean terminal elimination half-life of 8.3 hr (7). Since these patients all had symptoms that were sufficient to place them in class III or IV of the New York Heart Association classification, it is not surprising that their low cardiac output should result in a relatively long half-life for amrinone. Therefore, from the pharmacokinetic considerations discussed above, it would seem that an oral dosage regimen involving medication every 8 hr should be adequate for the treatment of patients with congestive heart failure.

REFERENCES

(1) A. A. Alousi, A. E. Farah, G. Y. Lesher, and C. J. Opalka, Jr., *Fed. Proc. Fed. Am. Soc. Exp. Biol*, **37**, 914 (1978).

(2) A. A. Alousi, A. E. Farah, G. Y. Lesher, and C. J. Opalka, Jr., *Circ. Res.*, **45**, 666 (1979).

(3) A. A. Alousi and J. Edelson, in "Pharmacological and Biochemical Properties of Drug Substances," vol. 3, M. E. Goldberg, Ed., American Pharmaceutical Association, Washington, D.C., 1981, p. 120.

(4) A. E. Farah and A. A. Alousi, *Life Sci.*, **22**, 1139 (1978).

(5) J. R. Benotti, W. Grossman, E. Braunwald, D. D. Davolos, and A. A. Alousi, *N. Engl. J. Med.*, **299**, 1373 (1978).

(6) J. R. Benotti, W. Grossman, E. Braunwald, and B. A. Carabello, *Circulation*, **62**, 28 (1980).

(7) J. Edelson, T. H. LeJemtel, A. A. Alousi, C. E. Biddlecome. C. S. Maskin, and E. H. Sonnenblick, *Clin. Pharmacol. Ther.*, **29**, 723 (1981).

(8) J. Wynne, R. F. Malacoff, J. R. Benotti, G. D. Curfman, W. Grossman, B. L. Holman, T. W. Smith, and E. Braunwald, *Am. J. Cardiol.*, **45**, 1245 (1980).

(9) T. H. LeJemtel, E. C. Keung, W. J. Schwartz, C. S. Maskin, M. A. Greenberg, R. S. Davis, R. Forman, H. S. Ribner, and E. H. Sonnenblick, *Trans. Assoc. Am. Physicians*, **92**, 325 (1979).

(10) M. P. Kullberg, B. Dorrbecker, J. Lennon, R. Rowe, and J. Edelson, *J. Chromatogr.*, **187**, 264 (1980).

(11) J. T. Helwig and K. A. Council, Eds., "SAS User's Guide," SAS Institute, Raleigh, N.C., 1979, p. 317.

(12) M. P. Kullberg, G. B. Freeman, C. Biddlecome, A. A. Alousi, and J. Edelson, *Clin. Pharmacol. Ther.*, **29**, 394 (1981).

Influence of Food on Aspirin Absorption from Tablets and Buffered Solutions

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Abstract □ After a standard meal, 12 normal volunteers received three aspirin dosage forms in a single-dose, complete crossover study. The three dosage forms were an unbuffered tablet, an effervescent solution with 16 meq of buffer, and an effervescent solution with 34 meq of buffer. Plasma and urine aspirin, salicylic acid, and salicyluric acid were measured for 10 hr. Significant differences in the absorption kinetics of aspirin were observed, with aspirin from the two solutions being absorbed faster than from the tablet. Urine pH and renal clearance for all three acid compounds were influenced by the buffer during the first 2 hr only. Area under the curve (AUC) and urine accumulation comparisons suggest that 15–20% more aspirin reaches the general circulation after the tablet, but that the total salicylate absorbed is not different. Comparison with an earlier study indicates the solution with 34 meq of buffer is virtually unaffected by the presence of the meal while the solution with 16 meq buffer and the tablet are more slowly absorbed in the nonfasted state.

Keyphrases □ Aspirin absorption—influence of food, comparison of tablets and buffered solutions □ Absorption—aspirin, influence of food

Aspirin is the drug of choice when a mild analgesic–antipyretic is required, and it is also a primary agent used in the chronic management of rheumatoid arthritis and osteoarthritis. After oral administration, rapid absorption is desirable to provide the rapid onset of effects and to reduce contact time with the gastric mucosa. The potential influence of food on the absorption kinetics of aspirin from two different buffered effervescent solutions and an unbuffered tablet dosage form is the subject of this report.

BACKGROUND

A recent report (1) from this laboratory describes the kinetics of aspirin absorption after oral administration of a tablet and two buffered solutions in fasting subjects. It was noted that while the solution with 16 meq of buffer was absorbed more rapidly than the one with 34 meq of buffer, both provided more rapid and less variable absorption than the tablet dosage form. Because the formulation with 34 meq of buffer is frequently used to treat the combined symptoms of headache and upset stomach associated with overindulgence in food and drink, the absorption kinetics of the same three formulations in nonfasted subjects were evaluated.

A recent review (2) describes the effects of food on drug bioavailability in general. Aspirin absorption from two conventional tablet dosage forms is clearly delayed and slowed when administered after a meal (3). Studies of salicylic acid kinetics suggest dispersed dosage forms such as granules (4) and effervescent solutions (5) are less subject to delayed absorption when food is present in the stomach.

Clearly the composition, quantity, and time of aspirin dosing relative to a meal can be significant factors (2, 3) in evaluating the effects of food on drug absorption kinetics. The meal chosen for the present study was previously evaluated (6) to characterize the associated physiological responses of the stomach including emptying rate, pH, and total acid production. Because the titratable acid reaches a maximal plateau between 1 and 2 hr after eating, a dose time 1 hr postcibus should provide a maximal test of the buffered solutions. The study described herein is identical to the one reported previously (1) in all aspects except the subjects in the present study ate a standard meal 1 hr prior to dosing. Two subjects were used in both studies.

EXPERIMENTAL

Dosage Forms—Three commercially available dosage forms were used to provide approximately equal doses of aspirin: two unbuffered tablets[1], each containing 325 mg of aspirin (T); one effervescent tablet[2] containing 640 mg of aspirin, 1.825 g of sodium bicarbonate, and 1.079 g of citric acid (16 meq of buffer) (S-16); and two effervescent tablets[3], each containing 324 mg of aspirin, 1.904 g of sodium bicarbonate, and 1.0 g of citric acid (34 meq of buffer) (S-34).

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

[2] Aspirvess, Miles Laboratory, Inc., Elkhart, Ind.

[3] Alka-Seltzer, Miles Laboratories, Inc., Elkhart, Ind.

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Table I—Mean Plasma/Urine Aspirin Data and Computed Parameters

Parameter	Mean ± SD, mg/liter[a] T	S-16	S-34
Time, min			
5	0.51 ± 0.57 b	3.32 ± 2.64 c	3.09 ± 1.79 c
10	1.24 ± 0.95 b	6.91 ± 2.14 c	6.17 ± 3.41 c
15	1.90 ± 1.31 b	9.12 ± 3.71 c	8.66 ± 3.14 c
20	2.77 ± 1.92 b	9.41 ± 2.03 c	9.70 ± 2.12 c
30	3.65 ± 3.27 b	7.07 ± 1.28 c	7.47 ± 2.17 c
45	4.42 ± 2.37 b	4.22 ± 1.09 b	4.82 ± 1.66 b
60	4.33 ± 1.52 b	2.95 ± 1.01 c	2.90 ± 1.05 c
90	3.24 ± 1.27 b	1.33 ± 0.52 c	1.25 ± 0.61 c
120	2.29 ± 0.86 b	0.54 ± 0.30 c	0.51 ± 0.29 c
AUC to 120 min, (mg min)/liter	380 ± 124 b	434 ± 60.0 bc	460 ± 70.8 c
Time of maximum concentration, min	60.6 ± 28.2 b	18.6 ± 6.0 c	22.8 ± 5.4 c
Maximum concentration, mg/liter	5.47 ± 2.60 b	10.36 ± 3.13 c	10.0 ± 2.18 c
AUC to infinity, (mg min)/liter	545 ± 101 b	462 ± 61.8 c	479 ± 78.0 c
MRT[b], min	85.2 ± 20.0 b	44.4 ± 10.0 c	41.3 ± 8.4 c
MAT[b], min	62.7 ± 20.0 b	21.9 ± 10.0 c	18.8 ± 8.4 c
VRT, hr	50.7 ± 26.8 b	16.6 ± 8.7 c	16.6 ± 8.7 c
Urine pH 0–2 hr	5.90 ± 0.54 b	6.14 ± 0.45 b	6.70 ± 0.57 c
Renal Clearance 0–2 hr, liter/hr	1.19 ± 0.45 b	1.67 ± 0.60 c	1.76 ± 0.43 c
Terminal log-linear half-life, min	39.0 ± 13.8 b	30.6 ± 14.4 c	23.4 ± 5.4 c

[a] A common letter following the standard deviation indicates no significant difference ($p < 0.05$) (*i.e.*, for AUC to 120 min T and S-16 do not differ and S-16 and S-34 do not differ; however, T and S-34 do differ). [b] MRT is the mean residence time and MAT is the mean absorption time per refs. 7 and 8. MAT computation assumes MRT_{IV} to be 15.6 min for all subjects.

Subjects—Twelve healthy male volunteers, 21–27 years old and weighing 56.9–88.6 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 GI disease or surgery. All were free of any active disease process and none had any medication for 14 days prior to the study.

Methods—A Latin-square design for three treatment in 12 subjects over three consecutive weekends was employed. A 10-hr fast (overnight) was followed by a standard meal (6) consisting of 90 g (uncooked weight) of tenderloin steak, 0.1 g of salt, 25 g of white bread, 8 g of butter, 60 g of vanilla ice cream, 35 g of chocolate syrup, and 240 ml of water. The total caloric value was 458 with approximately 40% fat, 40% carbohydrate, and 20% protein. If blended, the meal provided 540 mosmoles at pH 6.0.

One hour after completing the meal, which was eaten evenly over 30 min, predose blood and urine samples were collected and the aspirin doses administered. A total volume of 240 ml of water, as described previously (1), was given with each dose. After dosing, 100 ml of water was administered at 1, 2, and 3 hr, and each subject ate a uniform meal after the 4-hr blood sample. Subjects remained standing or sitting throughout the day, and exercise was limited to walking about the room. Blood and urine collection and the method of analysis were identical to those used in the preceding study (1).

RESULTS

The mean plasma concentrations and computed parameters for aspirin and salicylic acid are presented in Tables I and II, respectively. The rank order and profile projected in the tables was the same in all 12 subjects except the tablets frequently showed two or three maxima. Urine pH, flow rate, and drug recovery were almost identical to that reported without the meal (1) and, therefore, are not presented in detail herein. From the accumulation as aspirin, salicylic acid, and salicyluric acid in the urine over 10 hr the recovery (projected to infinity) ranged between 65 and 71% for the 36 doses, with no differences among the three dosage forms. Also, the renal clearance of aspirin, salicylic acid, and salicyluric acid agreed with the previously reported fasting study (1), with the salicylurate clearance between 33 and 38 liter/hr for all treatments.

Statistical moments as described by Yamaoka *et al.* (7) and Riegelman and Collier (8) were used and computed as in the previous report (1), with one change. Comparison of the terminal log linear half-lives for aspirin (*i.e.*, 39 ± 13.8, 30.6 ± 14.4, and 23.4 ± 5.4 min) in Table I are longer than previously reported: 14.9 min by Rowland and Riegelman (9) and 15.6 min by Mason and Winer (1), for the elimination half life of aspirin, thus indicating a flip-flop model. Therefore the terminal half-life cannot be used to estimate the elimination rate for aspirin or be used to compute the mean absorption time (MAT). The MAT values in Table I were computed by assuming that each subject has an aspirin elimination half-life of 15.6 min (*i.e.*, MRT_{IV} = 22.5 min), which was the mean estimate in the previous study (1). Computed in this manner the MAT values are estimates of the actual MAT values and represent the differences among the three dosage forms if the total aspirin clearance is constant over the 3 weeks.

DISCUSSION

Although the urine recovery shows the total salicylate absorbed to be about the same for all three dosage forms, there are significant differences in the rate and extent of bioavailability. After the meal, the plasma aspirin curves produced by the two effervescent solutions are almost identical, while the tablets produced later and lower maximum concentrations. The maximal aspirin concentrations for two effervescent solutions are nearly twice that for the tablet dosage form with higher aspirin concentrations by the 5-min sampling time. In addition, the maxima occurs in approximately one-third the time for the effervescent solutions compared with the tablets. These differences and the greater area under the curve (AUC) for the first 2 hr indicate the delaying effect of food on the rate of aspirin absorption from tablets but not on aspirin absorption from effervescent solutions. The areas under the aspirin and salicylic acid curves (when extrapolated to infinity) are ~15% greater for the tablets than for either of the solutions. Consistent with the earlier report (1), greater salicylic acid areas for the tablet dosage form can be attributed to the higher renal clearance with the buffered solutions. The larger aspirin area for the tablet suggests more drug has undergone gastric absorption, thus escaping intestinal metabolism. This hypothesis is supported by the fact that only a small proportion (1–2%) of aspirin clearance is renal, and thus even the observed twofold changes cannot significantly alter the plasma time curve.

Aspirin absorption kinetics can be complex with tablet dissolution, gastric absorption, and gastric emptying all being rate-determining processes. The statistical moment approach makes no assumption concerning the absorption kinetics and treats aspirin kinetics as a purely stochastic process. The MRT values for the tablet are almost twice those for the two solutions and reflect the longer residence time for aspirin in the body after the tablets. If the total aspirin clearance is constant for the three treatments then the greater MRT for the tablets is due to its remaining in the GI tract longer. The MAT values show that a longer time interval (about 40 min) is required for 63.2% of the aspirin to be absorbed after administration of the tablets than after administration of the solutions. These results primarily reflect the rate at which aspirin leaves the stomach and enters the intestine and/or the continued dissolution of the tablets. As noted above, the acid gastric contents and longer residence in the stomach result in some absorption occurring through the gastric mucosa and less intestinal metabolism.

In the fasting subjects S-16 was absorbed more rapidly than S-34 and

Table II—Mean Plasma/Urine Salicylic Acid Data and Computed Parameters

Parameter	Mean ± *SD*, mg/liter[a]		
	T	S-16	S-34
Time			
5 min	0.55 ± 0.45 b	4.09 ± 3.66 c	4.46 ± 1.69 c
10 min	1.29 ± 0.91 b	9.55 ± 4.83 c	10.21 ± 3.97 c
15 min	2.82 ± 1.91 b	17.42 ± 6.38 c	18.16 ± 5.66 c
20 min	4.36 ± 2.70 b	21.07 ± 5.78 c	24.61 ± 6.99 c
30 min	8.19 ± 5.97 b	27.02 ± 5.38 c	31.83 ± 5.58 d
45 min	13.91 ± 8.54 b	30.78 ± 4.12 c	35.64 ± 5.78 d
1 hr	19.11 ± 9.05 b	32.78 ± 3.41 c	37.14 ± 5.32 d
1.5 hr	26.81 ± 10.55 b	33.35 ± 3.94 c	37.36 ± 5.11 c
2 hr	31.57 ± 10.58 b	30.84 ± 4.09 b	35.01 ± 5.46 b
3 hr	33.26 ± 6.30 b	26.34 ± 3.40 c	29.71 ± 4.55 d
4 hr	32.01 ± 3.92 b	22.87 ± 3.60 c	25.52 ± 4.71 d
6 hr	21.97 ± 3.74 b	14.83 ± 2.75 c	16.94 ± 5.63 d
8 hr	15.39 ± 4.49 b	9.02 ± 2.49 c	9.92 ± 3.19 c
10 hr	10.38 ± 4.18 b	5.42 ± 1.95 c	6.11 ± 2.38 c
AUC to 2 hr, (mg hr)/liter	34.58 ± 14.00 b	56.82 ± 6.39 c	62.72 ± 8.22 c
Time of maximum concentration, hr	3.00 ± 0.74 b	1.25 ± 0.32 c	1.15 ± 0.34 c
Maximum concentration, mg/liter	36.79 ± 5.38 b	34.17 ± 3.72 c	38.35 ± 4.91 b
AUC to infinity, (mg hr)/liter	275.17 ± 61.46 b	218.52 ± 49.39 c	233.65 ± 45.76 c
Urine pH, 0–2 hr	5.90 ± 0.54 b	6.14 ± 0.45 b	6.70 ± 0.57 c
Renal Clearance[b] 0–2 hr, liter/hr	0.11 ± 0.14 b	0.19 ± 0.12 b	0.39 ± 0.25 c
Terminal log-linear half-life, hr.	3.55 ± 1.06 b	2.76 ± 0.63 c	2.76 ± 0.62 c

[a] A common letter following the standard deviation indicates no significant difference ($p < 0.05$) (*i.e.*, at the 4-hr salicylate concentration all three means are significantly different as none share a common letter). [b] Although the renal clearance for S-16 and T do not differ significantly at $p < 0.05$ one can reject the null hypothesis if the willingness to accept a Type I error is increased to about 10% (*i.e.*, $p < 0.1$).

had a greater AUC (1). The presence of a meal has eliminated these differences. The more highly buffered solution (S-34) has the same profile and almost identical estimated kinetic parameters (MAT_{meal} = 18.8 min; $MAT_{fasting}$ = 19.81 min) for absorption with and without a meal, while the S-16 solution is absorbed more slowly with a meal present (MAT_{meal} = 21.9 min, $MAT_{fasting}$ = 15 min).

The report by one group (3) that very little aspirin is bioavailable (*i.e.*, 5–8% nonfasting and 16–18% fasting) is not consistent with the 68% estimated by Rowland and Riegelman (9). The difference probably results from the application of a compartment model (3) to estimate elimination and absorption rate constants when delayed and/or continued absorption rendered such modeling inappropriate (flip-flop model). As discussed previously (1) the bioavailability of aspirin is influenced by the ratio of gastric emptying rate to gastric absorption rate, with the absolute bioavailability in the ~50–60% range.

In summary, the absorption of aspirin from tablets after a meal is significantly slower than from buffered effervescent solutions. Both 16 and 34 meq of soluble buffer produce relatively rapid absorption with similar peak aspirin plasma concentration. Comparisons with an earlier work show the 34 meq of buffer to provide plasma aspirin and salicylate profiles which are the same for fasted and nonfasted subjects. These data suggest that for occasional therapy intended to produce high plasma aspirin concentrations rapidly in both fasted and nonfasted individuals, buffered effervescent solutions are significantly better than nonbuffered aspirin tablets.

REFERENCES

(1) W. D. Mason and N. Winer, *J. Pharm. Sci.*, **70**, 262 (1981).

(2) R. Toothaker and P. Welling, *Annu. Rev. Pharmacol. Toxicol.*, **20**, 173 (1980).

(3) P. Koch, C. Schultz, J. Wills, S. Hallquist, and P. Welling, *J. Pharm. Sci.*, **67**, 1533 (1978).

(4) C. Bogentoft, I. Carlsson, G. Ekenved, and A. Magnusson, *Eur. J. Clin. Pharmacol.*, **14**, 351 (1978).

(5) G. Volans, *Br. J. Clin. Pharmacol.*, **1**, 137 (1974).

(6) J. Malagelada, G. Longstreth, W. Summerskill, and V. Go, *Gastroenterology*, **70**, 203 (1976).

(7) K. Yamaoka, T. Nakagawa, T. Uno, *J. Pharmacokinet. Biopharm.*, **6**, 547 (1978).

(8) S. Riegelman and P. Collier, *J. Pharmacokinet. Biopharm.*, **8**, 509 (1980).

(9) N. Rowland and S. Riegelman, *J. Pharm. Sci.*, **57**, 1313 (1968).