Gastrointestinal Absorption of Aspirin Anhydride

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The gastrointestinal absorption of aspirin anhydride by humans has been found to be slow and incomplete. This explains and is consistent with a reported lack of therapeutic efficacy of this drug. It is concluded that aspirin anhydride is less satisfactory for salicylate therapy than aspirin itself.

CONTINUOUS ATTEMPTS have been made to develop new derivatives and dosage forms of salicylic acid having greater effectiveness, better absorption characteristics, and less tendency to cause gastrointestinal irritation and bleeding than presently used salicylate preparations. It has been suggested (1) that (based on physical-chemical evidence) aspirin anhydride should be a superior form for the oral administration of aspirin. While aspirin anhydride has been studied recently with respect to its tendency to cause gastrointestinal bleeding (2, 3), no information concerning the gastrointestinal absorption and physiological availability of this substance has yet appeared in the literature.

There has been particular reason to question the absorption efficacy of aspirin anhydride since its solubility in aqueous media is extremely low, namely 3.2 mg. per 100 ml. at 37.5° (1), which is less than one-hundredth the solubility of undissociated aspirin itself. Another poorly soluble and slow-dissolving salicylate, aluminum acetylsalicylate, recently has been found to be absorbed not only very slowly but even incompletely (4). In the present communication the results of our absorption studies with aspirin anhydride are reported and related to available pharmacologic and physical-chemical data.

EXPERIMENTAL

Materials.—Micronized acetylsalicylic acid U.S.P. and micronized aspirin anhydride were utilized. Both compounds were assayed colorimetrically in terms of salicylic acid (9) after alkaline hydrolysis. One gram of acetylsalicylic acid was found to be equivalent to 0.96 Gm. aspirin anhydride (theoretical: 0.95 Gm.) on the basis of the salicylic acid assay. The drugs were handfilled into hard gelatin capsules, size 00, which were weighed individually before and after filling to obtain exact dosage. The specific surface area of each drug was determined by the nitrogen adsorption method and was found to be 1.22 M.²/Gm. for micronized aspirin and 2.24 M.²/Gm. for micronized aspirin anhydride.[1]

Absorption Tests.—Male adults in apparent good health served as test subjects. Their weights and ages are listed in Tables I and II. In the study of early absorption, each subject received two capsules containing a total of either 1 Gm. aspirin or 0.96 Gm. aspirin anhydride about 1 hour after a light noon meal. The medication was administered together with 100 ml. of water, and another 100 ml. water was given exactly 1 hour later. The two drugs were administered in crossover fashion, 1 week apart. One-half the group received aspirin first, while the other half received aspirin anhydride first. All subjects were instructed to observe similar dietary habits on the two days scheduled for the studies. A small urine sample was collected immediately prior to drug administration to obtain blank values and to make certain that the subjects had not inadvertently ingested a salicylate-containing medication during the 24 hours preceding the test. Exactly 2 hours after drug administration, total urine was collected from each subject.

The total absorption study was initiated in the morning after an overnight fast. The subjects were instructed to empty their bladder of overnight urine and to drink one glass of water. One hour later, after collection of a small urine sample, either 1 Gm. of aspirin or aspirin anhydride in two hard gelatin capsules was administered, together with 100 ml. of water. Total urine was collected exactly 2 hours after drug administration and from then on at 2–3 hour intervals (except for a greater night-time interval) for at least 36 hours. The subjects did not eat until 1 hour after drug administration.

The urinary excretion method for measuring salicylate absorption has been employed previously in our laboratory (4, 5) and by other workers cited in a previous publication (6). Urinary salicylate excretion data correlate well with plasma salicylate levels (5) as can be expected, although excretion data are possibly more accurate since they represent cumulative rather than transitory values.

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[1] We thank Mr. E. L. Rowe, Pharmacy Research Section, Product Research and Development, The Upjohn Co., for the surface area measurements.

TABLE I.—URINARY EXCRETION OF APPARENT SALICYLATE[a] 2 HOURS AFTER ORAL ADMINISTRATION OF EQUIVALENT DOSES[b] OF ASPIRIN AND ASPIRIN ANHYDRIDE

Subject	Age, yrs.	Wt., lbs.	Aspirin Amount, mg.	Aspirin Urine Vol., ml.	Aspirin Urine pH	Aspirin Anhydride Amount, mg.	Aspirin Anhydride Urine Vol. ml.	Aspirin Anhydride Urine pH	Ratio[c] ASA/AA
N	21	130	49.8	107	7.0	16.7	267	6.4	3.0
B	21	160	6.9	168	5.6	2.8	185	6.9	2.5
C	24	177	16.2	106	6.6	8.3	74	5.9	1.9
S	22	155	39.3	59	5.6	17.9	211	5.5	2.2
Go	22	150	14.6	31	5.6	7.3	64	5.6	2.0
F	21	185	7.6	153	5.6	10.1	206	5.2	0.75
Cl	21	125	25.4	64	5.6	12.5	69	5.5	2.0
A	23	173	36.8	55	5.7	8.4	67	5.7	4.4
Average			24.6	93	5.7	10.5	143	5.6	2.3

[a] Expressed as salicylic acid. [b] 1 Gm. aspirin and 0.96 Gm. aspirin anhydride. [c] ASA = mg. salicylate excreted after administration of aspirin. AA = mg. salicylate excreted after administration of aspirin anhydride.

TABLE II.—SECOND-HOUR AND TOTAL URINARY EXCRETION OF APPARENT SALICYLATE[a] AFTER ORAL ADMINISTRATION OF 1 GM. ASPIRIN

Subject	Age, yrs.	Wt., lbs.	Amount Excreted After 2 Hr., mg.	Total Amount Excreted, mg.	Total Urine Vol., ml.	Av. Urine pH	Total Amount Excreted in Previous Test
L	33	170	73.2	555	1340	5.9	538
R	21	190	59.5	683	1830	5.9	...
G	22	200	27.9	374	3420	5.5	399
Average			53.5	537	2197	5.7	

[a] Expressed as salicylic acid.

Urine pH.—The pH of each urine sample was determined with a Leeds and Northrup pH meter, model 7664. The salicylate excretion rate increases rapidly when urinary pH exceeds 7.0 (7, 8), and an unusually high urinary pH during one test period but not during the other could distort significantly the comparative data. These considerations caused the elimination of one subject participating in the early absorption test since the pH of his urine exceeded 7.0 in one instance.[2]

Analytical Methods.—Salicylate in the urine was determined colorimetrically according to Trinder (9) with a Bausch and Lomb Spectronic 20 colorimeter. All readings were corrected for blank values. Zero-hour blank values were used for second-hour urine samples, and average blank values obtained from previous 24-hour urine collections were used in the assay of all other samples.

RESULTS AND DISCUSSION

Table I shows the results of the study of early absorption. On the basis of the amounts of salicylate excreted 2 hours after drug administration, it is apparent that aspirin anhydride is absorbed considerably less rapidly than aspirin. The difference in amounts of excreted salicylate is statistically significant ($p < 0.05$), although there is considerable variation within each group. This is quite usual since our previous salicylate absorption studies and those of others indicate that subjects can be classified on a fairly consistent basis as either rapid, average, or slow absorbers.[3] This is evidenced in the present study by the much more consistent results obtained when the data are expressed as a ratio of salicylate excreted from aspirin to salicylate excreted from aspirin anhydride (see Table I). As shown in the tabulation, average urinary pH was essentially the same in both groups. Since the pH scale is nonlinear, and therefore nonadditive as such, the individual pH values were first converted to molar terms, then averaged, and finally the average molar concentration was reconverted to pH units. There may be some question as to the propriety of averaging pH values even in this manner, but it was done here as an aid in summarizing the data.

Urine flow rate has been found to have a small though noticeable effect on salicylate excretion (8, 10). It is unlikely that the small differences in urine flow noted in the present study had a significant effect on salicylate excretion, but even if they did, it could only be in favor of the aspirin anhydride results.

Results of the total absorption study are listed in Table II for aspirin and in Table III for aspirin anhydride. Average urinary pH and volume did not differ significantly after administration of the two substances. Since the subjects who participated in this study took the drugs on empty stomachs, absorption as evidenced by second-hour salicylate excretion was faster than in the other group of subjects who took the drug after a light meal. The average ratio of salicylate excreted from aspirin to salicylate excreted from aspirin anhydride was, however, essentially the same in both groups, namely 2.3 and 2.2. The total amount of apparent salicylate excreted after aspirin anhydride administration was considerably less than after aspirin administration. This shows that aspirin anhydride is not absorbed completely. It

[2] Similar precautions are appropriate in the case of blood level studies, since drug concentrations in the blood are a function of both absorption and elimination rates.

[3] This phenomenon is apparently related to differences in gastric emptying rates.

TABLE III.—SECOND-HOUR AND TOTAL URINARY EXCRETION OF APPARENT SALICYLATE[a] AFTER ORAL ADMINISTRATION OF 1 GM. ASPIRIN ANHYDRIDE

Subject[b]	Amount Excreted After 2 Hr., mg.	Total Amount Excreted, mg.	Total Urine Vol., ml.	Av. Urine pH	Physiologic Availability, %[c]
L	36.4	412	2440	6.1	71
R	14.7	428	3910	5.7	60
G	22.9	184	2315	5.8	47
Average	24.7	341	2888	5.8	61

[a] Expressed as salicylic acid. [b] Ages and weights are listed in Table II. [c] Calculated according to a method described in the text.

has been established previously that the effect of absorption rate on the ratio of the principal metabolites of salicylic acid appearing in the urine is negligible at the dosage used in this study (4). Of interest is the fact that the total amount of apparent salicylate excreted after a given dose differed significantly among the subjects. This is apparently due to quantitative differences in the biotransformation of salicylate, causing different degrees of formation of metabolites not identifiable by the colorimetric method. These differences reflect the biochemical individuality of each subject. Total excretion data from a previous aspirin absorption study were available for two subjects and are listed in Table II. It can be seen that the values are very similar to those obtained in the present study, suggesting that these individual biotransformation patterns are quite stable.

The physiologic availability of aspirin anhydride was calculated according to the method used in the human bioassay procedure of Melnick, *et al.* (11), which has been applied previously to salicylates by Morrison and Campbell (12) and by the authors (4). Thus, upon administration of equal doses, by weight, of the two salicylates

$$\% \text{ physiologic availability} = \frac{\text{amount excreted after aspirin anhydride}}{\text{amount excreted after aspirin}} \times 100 \times 0.96,$$

the latter term being a correction factor for the slightly higher salicylate content of aspirin anhydride. The data in Table III show that physiologic availability ranged from 47 to 71%, indicating that a significant portion of orally administered aspirin anhydride was not absorbed. It should be pointed out that the drug was used in this study in a physical form highly favorable for absorption, namely as the micronized powder, and that the physiologic availability may be even less when aspirin anhydride is administered in the form of compressed tablets containing drug solids of conventional particle size. The particle size of the aspirin anhydride used in this study was considerably smaller than that of aspirin. Had the specific surface areas of the two drugs been the same, it is likely that the absorption rate of aspirin anhydride would have compared even less favorably with that of aspirin.

Our findings explain the observation by Wood, *et al.* (2), that, in a significant portion of their patients, aspirin anhydride did not produce such satisfactory relief of symptoms as did aspirin. Our data, indicating poor and incomplete gastrointestinal absorption of aspirin anhydride, are also consistent with the toxicologic data reported by Gray, *et al.* (13). These workers found that the LD_{50} of aspirin anhydride in rats was about 50% higher than the LD_{50} of aspirin. Furthermore, death after administration of aspirin anhydride occurred much later than after administration of aspirin.

The gastrointestinal absorption of salicylates, when administered in solid form, is rate-limited by the dissolution process (6, 14), and the slow and incomplete gastrointestinal absorption of aspirin anhydride can be attributed to its extremely low dissolution rate in aqueous media (15). This factor was not taken into account in earlier work by others (1). Moreover, it appears in the light of present knowledge that the theoretical calculations presented in the early work (1) resulted in an underestimation of the absorption rate of aspirin from solution, partly because absorption of this drug from the stomach (16, 17) was neglected in the calculations, but primarily because the absorption rate of aspirin was assumed to change with pH of the gastrointestinal fluids exactly according to theory. Subsequently, it has been established, however, that the decrease in absorption rate of weak acids with increasing pH of intestinal fluids is much less than predicted by the Henderson-Hasselbalch equation, because the pH directly at the site of absorption remains lower than that of the intestinal fluids (18).

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