Aspirin Formulation and Absorption Rate II

Influence on Serum Levels of Tablets, Antacids, and Solutions

By S. V. LIEBERMAN and JOHN H. WOOD

Serum salicylate levels were measured for seven aspirin preparations alone and with a mixture of dihydroxyaluminum glycinate and magnesium carbonate. A twofold increase in serum levels at 10 and 20 minutes after ingestion was observed with the mixture present. With the aspirin preparations, the salicylate serum levels clearly reflected the technology of the aspirin granulation preparation. An optimum level of antacid for rapid absorption was found. A study of the salicylate levels resulting with time from ingestion of solutions and tablets showed that more rapid absorption was accompanied by earlier and higher serum levels.

THE PREVIOUS paper in this series (1) has established criteria for the sensitivity, reproducibility, and range of applicability of a human panel to assess serum salicylate levels accurately after ingestion. It is now possible to apply the human panel to a study of factors involved when aspirin is absorbed from tablets or solutions. Paul and Routh (2) reported that a tablet in which aspirin was combined with a mixture of dihydroxyaluminum glycinate and magnesium carbonate gave a build-up of blood salicylate levels more rapid than a tablet of aspirin alone. Subsequently, there has been disagreement in the literature; some works (3–5) have shown enhanced early absorption, while others (6–8) have questioned this finding. Work dealing with blood levels has not clearly established the reason for the enhancement. Levy (5) has shown a correlation between more rapid dissolution of tablets and early high urinary levels equated to enhanced absorption and has also stated (9) that the added antacid accelerated dissolution. Also it has been suggested (10) that the difference, if real, could be ascribed to aspirin technology rather than to the antacid component of the formulation.

With the sensitivity of the human panel defined by the preceding paper, a valuable tool exists to measure the influence of the antacid combination and of the aspirin technology on the early salicylate blood levels and thus assess the relative roles of each. Additionally, the panel permits a determination of the optimum level of antacid for salicylate absorption enhancement.

Salicylate plasma levels represent the composite result of several discrete and simultaneous processes. The aspirin must dissolve before any absorption can occur in the gastrointestinal tract. After absorption, distribution occurs to the tissues, and the elimination or clearance process begins. The faster the dissolution of the tablet, the larger the concentration gradient, and the faster should be the absorption. Earlier and higher plasma levels must result from higher concentration gradients since absorption and distribution are processes faster than elimination (11).

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EXPERIMENTAL AND RESULTS

Table I lists the panel codes and describes the composition of a series of different aspirin tablets and the corresponding two-layer tablets, with aspirin in one layer and antacid in the other. The aspirin was in each case 5.0 gr. per tablet with 0.56 gr. of cornstarch. The antacid layer was a gelatin granulation (0.16 gr.) containing 0.75 gr. of aluminum glycinate and 1.50 gr. of magnesium carbonate to which 0.23 gr. of cornstarch was added prior to tableting.

Two human panels, identified as panels *1* and *2*, were used concurrently. Aspirin of code N was used in both panels to serve as a link. Each subject received two tablets; the protocol was described previously (1). The data for 10- and 20-minute levels are given in Table II; the pairs are the aspirin alone and its corresponding combination with antacid.

Two different two-layer tablets were prepared using one aspirin granulation with two concentrations of the active antacids—1.5 gr. (code AC) and 3.0 gr. (code AB). These are one-third less and one-third more than the 2.25 gr. antacid used in the previous set of tablets. Using a different aspirin granulation, the relative specificity of the ratio of antacid to aspirin was again examined using 2.25 gr. antacid with 5.0 gr. (code QD) and 6.25 gr. (code QE) of aspirin. The data for these four tablets are given in Table III.

The serum levels from three aspirin preparations—a commercial tablet L, aspirin of code E from the first series, and its corresponding antacid combination, D—were studied as a function of time from 30 to 150 minutes after administration. Since 10- and

20-minute data for D and E were available from panel *1*, L was run separately for these two times. In addition, values for E as EA and ER are also available in the previous paper (1).

Two solutions were used. The salicylate time profile to 90 minutes was determined for a solution prepared by neutralizing salicylic acid with choline so that 100 ml. contained 868 mg. choline salicylate (code NA). This amount is equivalent in salicylate to 10 gr. of aspirin. In addition, the equivalent amount of sodium salicylate, 576 mg. (code NB), was studied for serum levels at 10 and 20 minutes. The results are recorded in Table IV.

DISCUSSION

The data of the two panels in Table I are related through sample N which is common to both. The difference in 10-minute serum salicylate levels between the two panels was small. The difference in 20-minute serum level averages was considerable, although it missed being significant at 95% confidence. This large difference in average was not reflected in the medians which were closer. An examination of the cumulative per cent distribution curves lead to the conclusion that a small number of rapid absorbers in panel *1* were not matched in panel *2*, and the use of larger panels would have eliminated this discrepancy.

This slight possible mismatch between panels does not affect the comparison of the pairs of buffered and unbuffered tablets since each pair involved the same participants. All preparations with the antacid additive show faster acetylsalicylate absorption as reflected in 10- and 20-minute salicylate levels. Except for the comparison B–W at the 10-minute level, all tablet pairs at both 10 and 20 minutes show enhancement, which is statistically significant (95% confidence), for the antacid combination over the aspirin alone. The differences in the averages for the pairs of levels are so great that the ratio of the enhancement in level is approximately twofold.

If one considers median salicylate levels instead of averages, the difference between the pairs is even more striking, showing about a threefold enhancement. As discussed earlier (1), this is a consequence of the asymmetric distribution of levels that occurs during the early absorption. Figure 1 shows median and average levels from early absorption data. The asymmetry of the distribution of level results in a number average appreciably greater than the median level, with a maximum deviation at an average of approximately 20 mcg./ml. of salicylate in the serum. During the early absorptive process, two-thirds of the population may have the average level or less. At low levels and for averages above 40 mcg./ml., the two parameters coincide. The median level is possibly more characteristic than the average for the population and can be treated by nonparametric methods. The average and its statistical significance are the more familiar tools of the investigator.

Figure 2 shows the cumulative per cent distributions for one pair, N and K. This pair is typical of others in the set. It is apparent that the distribution of salicylate levels at 10 minutes with the antacid combination is similar to that of 20 minutes with plain aspirin. The agreement is closer than for the pairs of repeats studied in the previous paper (1). The presence of the antacid has shifted the whole population, not just a small portion of it. Since enhancement of salicylate serum levels was present in every pair, the effect of the antacid layer must be relatively independent of any technology involved in the preparation of the aspirin granulation.

TABLE I.—ASPIRIN DESCRIPTIONS FOR TABLETS USED IN PANELS *1* AND *2*

Aspirin Code	Antacid Combn. Code	Panel	Aspirin Layer Description
B	W	*2*	20-Mesh crystals of manufacturer *A*
E	D	*1*	Aspirin-starch granulation of supplier *A* (1)
N	K	*1*	Aspirin-starch granulation of supplier *B* (2)
S	H	*1*	1/3 (1)–2/3 (2)
T	A	*1*	1/3 (1)–2/3 20-mesh crystals of manufacturer *A*
R	Z	*2*	1/3 (1)–2/3 20-mesh crystals of manufacturer *B*
P	X	*2*	1/3 (1)–2/3 20-mesh crystals of manufacturer *C*

TABLE II.—SERUM SALICYLATE LEVELS OBTAINED WITH THE TABLETS IN TABLE I

Code Designation	Subjects, No.	10-Min. Levels, mcg./ml. Av.	S.D.	Median	20-Min. Levels, mcg./ml. Av.	S.D.	Median
B	28	2.59	1.91	2.0	5.76	5.39	3.7
W	28	3.93	5.11	2.2	18.90	12.28	16.0
E	27	6.13	6.88	2.5	16.76	15.65	12.8
D	27	13.68	10.75	11.0	32.95	17.03	27.5
N (Panel *1*)	27	3.63	4.46	2.0	12.31	11.06	9.0
K	27	10.00	7.69	8.5	30.16	15.56	28.4
S	27	4.31	4.47	1.9	13.52	13.45	7.0
H	27	10.82	9.85	6.0	28.36	17.04	22.2
T	27	3.32	3.44	1.9	9.28	7.15	7.8
A	27	9.49	7.86	6.8	25.64	14.96	23.0
R	28	4.95	5.23	3.4	10.79	10.00	7.0
Z	28	8.69	7.56	7.0	25.91	13.58	26.0
P	28	3.44	4.62	1.8	9.05	12.15	4.0
X	28	7.71	6.61	6.0	24.80	13.11	22.5
N (Panel *2*)	28	3.44	3.77	3.0	7.57	6.83	6.8

TABLE III.—SERUM SALICYLATE LEVELS RESULTING FROM VARIATIONS IN CONCENTRATIONS OF ACTIVE INGREDIENTS WITH BUFFERED TABLETS[a]

Code Designation	Tablet Distinction	10-Min. Levels, mcg./ml. Av.	S.D.	Median	20-Min. Levels, mcg./ml. Av.	S.D.	Median
AC	1.5 gr. antacid	10.11	9.36	6.0	28.24	15.03	20.0
AB	3.0 gr. antacid	11.01	13.74	6.0	29.03	17.28	32.0
QD	Normal	17.3	10.5	15.0	36.5	14.1	36.8
QE	6.25 gr. aspirin	19.8	12.4	17.0	42.8	17.2	40.0

[a] Thirty-eight subjects.

TABLE IV.—SERUM SALICYLATE LEVELS AS A FUNCTION OF TIME FOR TABLET AND SOLUTION PREPARATIONS, mcg./ml.

Sample and Measure		Time Period 10 Min.	20 Min.	30 Min.	40 Min.	60 Min.	90 Min.	120 Min.	150 Min.
D	Av.	...	...	43.56	...	48.05	46.44	43.68	40.33
	No.	...	...	39	...	39	39	40	39
	S.D.	...	...	15.16	...	10.33	9.64	8.99	8.56
	Median	...	...	45.0	...	48.0	46.4	43.8	40.0
E	Av.	...	...	28.36	...	41.53	46.24	45.07	43.11
	No.	...	...	39	...	39	39	39	39
	S.D.	...	...	17.95	...	16.44	13.85	11.96	9.75
	Median	...	...	29.2	...	43.7	48.0	44.3	43.0
L	Av.	6.92	18.14	28.01	...	39.56	42.52	43.72	44.34
	No.	40	40	39	...	39	39	39	39
	S.D.	5.99	11.34	17.98	...	17.20	16.19	12.40	9.85
	Median	5.2	14.3	26.0	...	40.5	44.5	44.0	43.4
NA	Av.	48.01	57.41	...	54.99	52.57	48.22	...	...
	No.	39	38	...	39	38	38	...	...
	S.D.	22.37	11.87	...	10.43	7.41	6.65	...	...
	Median	53.5	64.0	...	55.0	52.0	47.0	...	...
NB	Av.	54.70	63.66	...	...	...	...	...	...
	No.	37	37	...	...	...	...	...	...
	S.D.	20.66	14.81	...	...	...	...	...	...
	Median	49.5	58.5	...	...	...	...	...	...

This technology does, however, contribute to the levels obtainable. The combination B and W, comprising all 20-mesh aspirin crystals, is notably inferior to either of the two commercial granulations. Indeed, the differences for this pair verge on significance with 95% confidence against mixtures of commercial granulation and crystals. Similarly, the differences between the tablets containing only commercial aspirin granulations and the tablets with mixtures border on significance. Thus, the technology of the aspirin preparation is an important factor. Indeed, for the preparations studied, the enhancement possible for the best aspirin, E, compared to the poorest aspirin, B, is more than two-fold—about the same magnitude as the enhancement that aspirin receives in the presence of the antacid combination.

Using urinary salicylate recovery, Levy (5), studying a number of commercial preparations, concluded that aspirin was absorbed more rapidly from the antacid combination. He found lesser differences occurring between different aspirin preparations without antacids.

Table III shows no difference in the average levels between preparations AB and AC which differ in being, respectively, one-third more and one-third less antacid than used in the formulations of Table I. This amount of antacid gives the maximum effect measured by the average level, and no significant additional enhancement was achieved by using additional antacid. The shape of the distribution in the case of AC, the 1.5 gr. of antacid, is somewhat distorted, so that its median is appreciably lower than that of the 3.0 gr. case, AB. This suggests the possibility that 1.5 gr. represents the lower limit for optimal antacid enhancement, an example of the advantage of considering both distributions and medians as well as the statistically based average level in studying differences between tablets.

The traditional aspirin dosage has been 10 gr. The use of additional aspirin should be expected, on a concentration mass action basis, to yield more drug in an absorbable form at any given time. This is confirmed by the serum levels found with the pair manufactured QD–QE, which differ only in the amount of aspirin present (10 *versus* 12.5 gr.) with the antacid layer. The difference for 20-minute serum levels for 12.5 gr. is so great that the method of individual pair difference yields a Student t of 2.6 (99% confidence).

An examination of Table IV and its graphical representation in Fig. 3 shows that, as predicted theoretically, earlier peaking of levels results in higher levels and that the earliest peaking is for the salicylate solutions. Hogben (12) and Smith (13) have shown that salicylate is absorbed faster than acetylsalicylate. Choline salicylate solution (14) has been advocated for extremely rapid absorption. These data give higher levels at 10 and 20 minutes for sodium salicylate (NB) over choline salicylate (NA). The difference is not significant statistically at the 10-minute level, but it is significant statistically with 95% confidence for 20 minutes.

The tablet data show that tablet D, the aspirin with dihydroxyaluminum glycinate and magnesium carbonate, has significant enhancement of salicylate

serum levels over aspirin alone for periods up to and including 60 minutes. The buffered preparation clearly peaks in level in about 45 minutes, while the corresponding aspirin alone, E, reaches its peak in about 90 minutes. The differences in levels between these two at 90, 120, and 150 minutes, although not significant statistically, should be real from the nature of the curves. The commercial aspirin, L, appears to give a peak at 150 minutes or even later, as judged from average levels. The median levels, however, are more in line with tablet E. The average levels at 90 and 120 minutes are not statistically significantly different from those of D. At 150 minutes, the difference is just significant. The set of experimental data confirms the theoretical prediction that earlier peaking leads to higher maximum serum salicylate levels.

In the preceding paper (1), it was shown for aspirin absorption from tablets that the standard deviation of average salicylate serum levels increased almost directly with the level attained. This was true during the early portion of the absorption cycle. It is apparent from Table IV that this does not hold as absorption continues. As the maximum level is approached, the standard deviation decreases markedly and continues to decrease even after the maximum average has been attained.

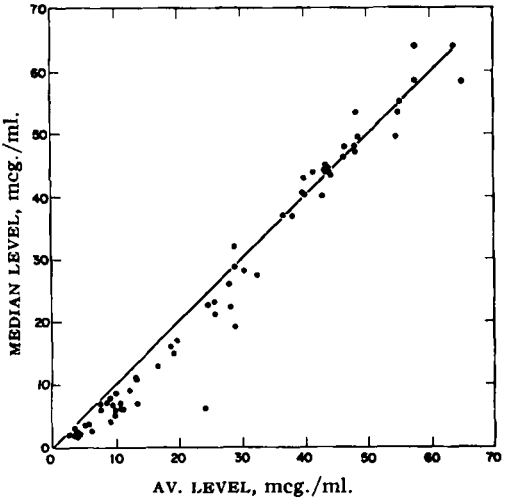

Fig. 1.—Variation of median and average level of serum salicylate during absorption.

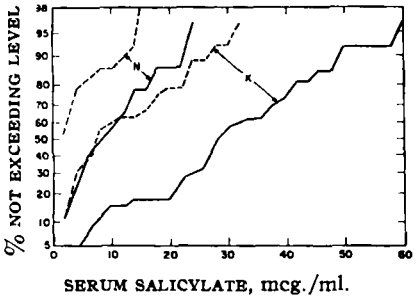

Fig. 2.—Cumulative per cent plot on probability scale of levels obtained with aspirin (N) and its corresponding tablet with antacids (K). Key: - - -, 10-minute levels; ——, 20-minute levels.

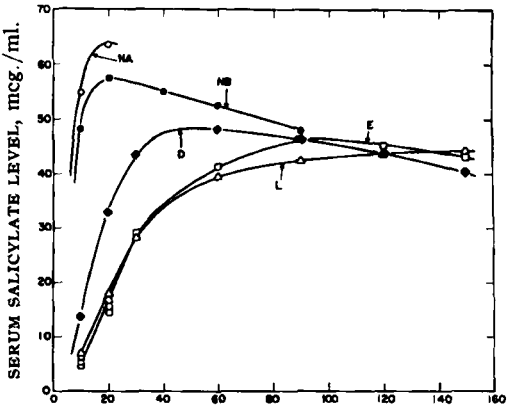

Fig. 3.—Serum salicylate levels resulting from solutions and tablets. Key: NA, sodium salicylate solution; NB, choline salicylate solution; E, aspirin alone; D, with buffer components; L, a commercial aspirin.

This is expected since the fast absorbers have virtually completed their absorption, while the slow absorbers, which contribute notably to the spread of the distribution, begin to build up appreciable levels and the distribution becomes tighter. This is a necessary condition resulting from the fact that the clearance process is slower than the absorption and less variable (11).

SUMMARY

Faster absorption of asprin leads to earlier and higher peak salicylate serum levels. This is shown by tablets of aspirin with a mixture of dihydroxyaluminum glycinate and magnesium carbonate relative to those of aspirin alone. Still earlier and higher peak levels are obtained by a solution. Sodium salicylate solution yields an early level slightly higher than that of choline salicylate solution.

The presence of the cited antacid mixture in an aspirin tablet leads to a twofold enhancement in the average serum salicylate levels attained at 10 and 20 minutes. The median level is increased approximately threefold.

There is an optimum amount of antacid for maximum effect of salicylate serum levels. Variations about this optimum produce no change in levels.

Technology of aspirin granulation can lead to appreciable differences in observed salicylate serum levels.

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