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FACTORS INFLUENCING THE PLASMA SALICYLATE CONCENTRATION AND URINARY SALICYLATE EXCRETION AFTER ORAL DOSAGE WITH ASPIRIN

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Abstract—Plasma salicylate concentrations and the rates of total salicylate excretion in the urine were determined at the same time intervals after a single dose and also after multiple doses of aspirin B.P. and aloxiprin. In the single dose study appreciably higher plasma salicylate levels were obtained with the former, but very similar maximum rates of total salicylate excretion were obtained with both aspirin B.P. and aloxiprin. After aspirin B.P. the maximum plasma salicylate level occurred between one to two hours, but the maximum rate of total salicylate excretion occurred three or more hours after dosage. These results are explained by the accrual of metabolites and by a relatively lower rate of total metabolite formation at higher plasma salicylate levels.

In the multiple dose study, a strong inverse relationship was observed between the body weight of an individual and the plasma salicylate concentration. Comparable plasma salicylate levels were obtained with aspirin B.P. and aloxiprin.

THERE appears to have been no detailed study of the salicylate concentration in blood and urine specimens collected at the same time after dosage with aspirin. A number of publications have described the plasma salicylate concentrations obtained[3, 4] and others have described the excretion of salicylate in urine.[5–7] The present paper describes a study of plasma salicylate concentrations and rates of salicylate excretion in the urine at a number of time intervals after a single dose and also after multiple doses of aspirin tablets B.P. or of aloxiprin tablets. The latter provided a form of aspirin which is more slowly absorbed from the gastro-intestinal tract.

Certain factors influencing the plasma salicylate concentration and the rate at which salicylate is excreted in the urine are discussed.

A preliminary account of a part of this work has been previously published.[1, 2]

EXPERIMENTAL

Materials

The forms of aspirin used were aspirin tablets B.P. and aloxiprin tablets ('Palaprin', British Schering Ltd.), each tablet contained the equivalent of 324 mg aspirin. Aloxiprin is a "polymeric condensation product of aluminium oxide and O-acetylsalicylic acid".

Methods

Salicylate determinations. The plasma and urine salicylate concentrations were determined by the method of Brodie *et al.*[8]

Previous experience had shown that keeping the plasma at room temperature for about four hours was sufficient to hydrolyse any aspirin present and this procedure was considered preferable to other methods of hydrolysis. A similar observation has been made by Truitt.[9]

The 'total salicylate' in urine was determined after hydrolysis of the metabolites to salicylic acid. The urine (4 ml) and 12 N H_2SO_4 (2 ml) were heated in an autoclave at 115° for 3 hr and then diluted to 25 ml with water; 2–4 ml of this solution were used for the analysis.

Experimental design

Blood and urine collection procedure.

(*a*) *Single dose study*. Sixteen healthy men were randomly divided into two groups of eight. Each group received 0·65 g aspirin, as aspirin tablets B.P. or as aloxiprin tablets. Blood specimens and total urine collections were obtained at 1, 2, 3, 5 and 7 hr after dosage.

(*b*) *Multiple dose study*. Twenty healthy men were randomly divided into two groups of ten. They were each provided with 21 tablets and instructed to take three (equivalent to 1 g aspirin) at each of the following times—11 p.m. on first day, 7 a.m., 12 noon 6 p.m. and 11 p.m. on second day and at precisely 7 a.m. and 12 noon on the third day. Only the final dose was taken under supervision. One group received their aspirin as aspirin tablets B.P. and the other group as aloxiprin tablets, each subject received seven doses. Blood and urine collections were made 2 hr before and immediately before the final dose and at 1, 2 and 3, or 2, 3 and 4 hr after the final dose.

RESULTS

(*a*) *Single dose study*. The plasma salicylate levels and the corresponding rates of excretion of salicylate in the urine obtained are given in Tables 1 and 2.

The maximum plasma salicylate concentrations of the group which received aloxiprin are only about half those of the group which received aspirin B.P., and the levels did not appear to be longer sustained. These results seem to suggest that not all the aspirin of aloxiprin is absorbed. However, a previous report[10] of separate studies involving the excretion of salicylate in 24-hr urines showed almost equal recovery of salicylate after aspirin B.P. and aloxiprin. The total availability of the aspirin of aloxiprin is also confirmed by the results of the multiple dose experiment (Tables 3 and 4).

There is now a considerable amount of evidence indicating that the rate of absorption of aspirin from a particular dosage form is governed by its rate of solution in the gastro-intestinal fluids.[6, 7, 11] The aspirin of aloxiprin has been shown to dissolve less rapidly than aspirin B.P.[10] and hence it will be less rapidly absorbed. The results presented in Tables 1 and 2 show that lower maximum plasma salicylate concentrations are obtained after a single dose of a slowly absorbed form of aspirin.

Although much lower plasma salicylate levels were obtained after a single dose of aloxiprin, Table 2 shows the maximum rate of salicylate excretion to be very similar to that after aspirin B.P.

After the administration of aspirin B.P. the maximum rates of excretion of salicylate in the urine occur appreciably later than the maximum plasma salicylate concentrations (Table 1). This effect is less marked after aloxiprin administration.

TABLE 1. THE PLASMA SALICYLATE CONCENTRATIONS AND URINE SALICYLATE EXCRETION RATES FOLLOWING THE ORAL ADMINISTRATION OF A SINGLE DOSE OF ASPIRIN (0·65 g) TO 8 MEN

Subject	Body wt.	Serum salicylates (mg/100 ml)					Urine salicylate Excretion rate (mg/60 min)							% of dose excreted in 7 hr
		Time after drug administration (hr)												
	(kg)	1	2	3	5	7	1	2	3	4	5	6	7	
A	67·0	5·2	5·3	4·8	4·1	3·3	11·5	32·5	35·0	31·0	30·0	26·0	28·0	39·0
B	79·5	3·8	4·1	4·4	2·7	1·7	11·5	23·0	48·5	54·0	58·5	40·0	35·0	54·4
C	54·0	6·8	6·0	5·1	3·3	2·0	25·0	38·0	46·5	45·5	47·5	40·5	34·0	55·9
D	77·0	1·1	4·0	3·2	2·7	2·6	18·5	42·0	45·0	38·0	48·0	34·0	36·0	52·6
E	78·0	0·9	1·9	2·5	3·7	2·7	5·5	17·7	27·5	—	25·5	—	37·0	35·4
F	68·5	5·5	4·8	4·0	2·7	2·0	20·3	44·0	48·0	—	37·7	—	38·2	53·4
G	64·5	5·4	4·3	3·5	2·6	2·1	27·5	49·5	55·0	—	55·8	—	40·5	66·4
H	85·0	5·1	—	4·3	3·2	1·8	14·7	32·0	37·0	—	27·5	—	49·2	47·7
Mean		4·22	4·33	4·00	3·11	2·28	16·8	34·8	42·8	—	40·33	—	37·74	50·73

TABLE 2. THE PLASMA SALICYLATE CONCENTRATIONS AND URINE SALICYLATE EXCRETION RATES FOLLOWING THE ORAL ADMINISTRATION OF A SINGLE DOSE OF ALOXIPRIN (≡ 0·65 g ASPIRIN) TO 8 MEN

Subject	Body wt.	Serum salicylates (mg/100 ml)					Urine salicylate Excretion rate (mg/60 min)							% of dose excreted in 7 hr
		Time after drug administration (hr)												
	(kg)	1	2	3	5	7	1	2	3	4	5	6	7	
A	76	1·9	2·5	2·9	2·2	1·7	19·6	33·0	42·2	—	42·8	—	35·7	50·6
B	68	2·1	3·1	3·4	2·7	1·6	18·9	37·2	49·5	—	55·5	—	40·3	59·8
C	90	1·1	2·0	2·3	1·7	1·4	0·3	1·9	21·9	—	23·5	—	32·2	27·4
D	72	1·7	3·1	3·5	3·3	3·1	10·5	26·5	27·6	—	30·3	—	30·0	37·2
E	66·5	1·4	2·7	3·2	2·4	1·7	13·1	30·0	43·6	—	54·0	—	36·0	53·7
F	77·5	2·0	2·6	2·6	2·5	1·8	12·9	27·4	28·4	—	38·3	—	32·0	42·4
G	57·0	0·5	1·9	2·8	3·9	3·4	3·0	11·7	23·6	—	36·8	—	28·8	34·1
H	77·5	1·7	2·3	2·1	1·5	1·2	15·8	34·5	31·4	—	43·8	—	26·7	44·7
Mean		1·55	2·53	2·85	2·53	2·0	11·76	25·28	33·53	—	40·63	—	32·70	43·74

(*b*) *Multiple dose study*. The plasma salicylate concentrations obtained, together with the amount of total salicylate excreted during the 5-hr period studied are given in Tables 3 and 4.

TABLE 3. THE PLASMA SALICYLATE CONCENTRATIONS AND THE URINARY EXCRETION OF SALICYLATE OBTAINED AFTER 7 DOSES OF ASPIRIN B.P., EACH OF 1 g, GIVEN AT APPROXIMATELY 6-hr INTERVALS

Subject	Age	Body wt.	Plasma salicylate (mg/100 ml)						Total*† salicylate excreted (mg)
			Time after final dose (hr)						
	(Years)	(kg)	—2	0	1	2	3	4	
A	20	52·5	24·1	22·2	23·4	23·5	23·1	—	402
B	18	65·0	16·9	15·0	17·4	19·7	19·5	—	367
C	34	87·5	12·7	10·8	13·2	14·4	13·4	—	475
D	30	60·5	20·0	18·6	21·0	21·5	20·6	—	465
E	45	67·0	12·4	10·0	11·2	11·4	12·2	—	478
F	41	90·0	14·7	14·4	—	18·5	18·1	17·7	471
G	29	61·0	18·6	17·1	—	20·6	20·1	19·4	434
H	24	81·0	14·8	14·0	—	17·1	15·9	15·4	—
I	30	81·0	14·9	13·4	—	17·3	16·3	15·6	467
J	22	77·0	14·2	13·0	—	16·6	15·8	15·7	417
Mean		72·25	16·3	14·9	17·2	18·1	17·5	16·8	442

* During the 5-hr period (—2 to + 3 hr).
† Expressed as salicylic acid.

It was initially considered that after 7 doses the subjects would have reached a steady state with respect to their plasma salicylate level, that is, the highest plasma level attainable on this particular dosage regimen would have been reached and salicylate output would equal intake. The results (Tables 3 and 4) show that this was closely approached. The individual plasma salicylate levels obtained varied appreciably, extending over the range of 9–24 mg/100 ml of plasma. In this group of healthy subjects a strong inverse relationship was observed between the plasma salicylate level and body weight (Fig. 1). Such a relationship will not necessarily apply in conditions which alter the plasma protein ratios or the fluid balance. The plasma salicylate concentrations obtained in patients with a low plasma albumen concentration will be lower than those obtained in normal subjects receiving the same dose.[12, 13]

The inverse relationship between plasma salicylate and body weight was observed whether the aspirin was given as aspirin B.P. or aloxiprin. Minimum salicylate levels

TABLE 4. THE PLASMA SALICYLATE CONCENTRATIONS AND THE URINARY EXCRETION OF SALICYLATE OBTAINED AFTER 7 DOSES OF ALOXIPRIN, EACH EQUIVALENT TO 1 g ASPIRIN, GIVEN AT APPROXIMATELY 6-hr INTERVALS

Subject	Age	Body wt.	Plasma salicylate mg/100 ml						Total*† salicylate excreted
			Time after final dose (hr)						
	(Years)	(kg)	− 2	0	1	2	3	4	(mg)
K	31	77·5	12·3	11·6	12·4	12·9	13·0	—	474
L	50	85·0	13·3	11·9	12·8	13·7	14·0	—	525
M	50	69·5	14·5	13·5	14·3	15·0	16·0	—	405
N	36	73·5	15·2	14·3	15·1	16·7	17·0	—	415
O	53	90·0	11·1	10·4	12·0	12·8	13·2	—	363
P	27	102·5	9·6	9·9	—	12·6	12·9	11·8	441
Q	26	95·0	11·9	10·8	—	14·4	14·7	14·2	400
R	19	84·0	13·1	12·7	—	14·1	14·8	14·2	454
S	18	66·0	15·6	15·3	—	17·6	18·0	17·0	300
T	26	57·0	21·5	18·6	—	19·6	21·8	20·4	429
Mean		80·00	13·81	12·90	13·32	14·94	15·54	15·52	421

* Expressed as salicylic acid.
† During the 5 hr period (− 2 to + 3 hr).

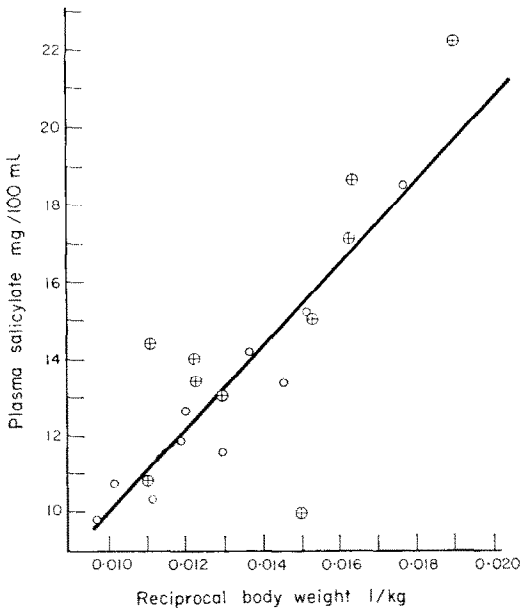

FIG. 1. The relationship between plasma salicylate concentration and body weight in twenty men who received 7 doses each equivalent to 1 g aspirin at approximately 6-hr intervals. 10 men received aspirin tablets B.P. (⊕) and 10 received aloxiprin tablets (○).

of 14·9 mg/100 ml and of 12·9 mg/100 ml were obtained with aspirin B.P. and aloxiprin respectively. However, the group which received aloxiprin were 10% lighter in average weight and when allowance was made for this weight difference, the two plasma levels did not differ significantly.

DISCUSSION

The maximum plasma salicylate level resulting from a single 0·65 g dose of aspirin, is much higher than that obtained after a corresponding dose of aloxiprin. The lower plasma salicylate level attained with aloxiprin is not due to incomplete absorption. On the other hand, the maximum rate of excretion of total salicylate is almost identical in both instances; a similar result was obtained in a previous study.[10] It might have have been expected that the difference in maximum plasma concentrations would have been reflected by a corresponding difference in the maximum rate of excretion.

It may also be observed that the majority of subjects achieved a maximum plasma salicylate concentration one to two hours after the single dose of aspirin B.P., but the rate of total salicylate excretion in the urine of these individuals changes very little from about two to five hours afters after dosage, the maximum rate occurring after three or more hours (Tables 1 and 2). Similar results are discernible in reports in the literature, when the data of plasma salicylate levels of various workers[3, 4] are studied in conjunction with data of salicylate excretion of others.[5–7]

TABLE 5. THE AVERAGE EXCRETION OF TOTAL SALICYLATE BY 5 SUBJECTS WHO ON SEPARATE OCCASIONS EACH RECEIVED 0·16, 0·24, 0·32, 0·64 AND 0·97 g DOSES OF ASPIRIN B.P.

Time of urine collection, (hr after dosage)	Percentage of dose excreted				
	dose (g)				
	0·16	0·24	0·32	0·64	0·97
1½	12·3	11·2	11·4	6·7	7·0
3	16·6	19·3	17·1	11·4	11·2
4½	18·0	17·2	18·2	13·0	11·2
6	14·8	14·2	15·7	14·5	12·2
7½	8·2	8·6	9·2	9·7	10·6
Cumulative total	70·0	70·4	71·5	55·3	52·1

In considering these problems an explanation may be sought either in terms of an anomalous behaviour of the plasma salicylate level or of the rate of excretion in the urine. It may be noted that the difference in plasma concentrations from the two preparations is only apparent after a single dose, for in the multiple dose study, aspirin and aloxiprin gave comparable blood concentrations.

It is suggested that this anomalous behaviour is in part due to the fact that the relationship which exists between the plasma salicylate level and rate of excretion is

not a constant one, but varies according to the plasma salicylate concentration. This can be related to the concentration half-life of salicylate in the body. It may be deduced from the published data[5, 14, 15] that the half-life of salicylate is longer at high plasma concentrations and it has now been shown that a change in the half-life occurs at low plasma concentrations. Evidence for this has been obtained by studying the rate of total salicylate excretion in a group of subjects who on different occasions received 0·16 g, 0·24 g, 0·32 g, 0·65 g and 0·97 g of aspirin B.P. A summary of these findings is presented in Table 5; full details of this study are to be the subject of a separate communication. At the three lowest dose levels, the cumulative percentages of dose excreted at each of the time intervals studied, were almost identical. This is a characteristic of a substance which is eliminated by an apparent first order process. At the higher levels the percentage of dose excreted at each time interval was reduced. This is interpreted as being indicative of a change in the kinetics of the elimination process and that the half-life of salicylate has increased.

These data suggest that there is some additional factor controlling the rate of total salicylate excretion when the plasma salicylate concentration exceeds a low value.This is probably a result of some step in the metabolism of salicylate not complying with first order kinetics, for at least 90% of the ingested salicylate is excreted in the urine as metabolites. Little unchanged salicylate ion is excreted.

The finding that the half-life of salicylate undergoes an appreciable change at a plasma salicylate concentration between that attained from 0·32 g and from 0·64 g of aspirin B.P., may be applied to explain the apparently anomolous excretion of salicylate after aspirin B.P. and aloxiprin administration. This is illustrated by Fig. 2 which

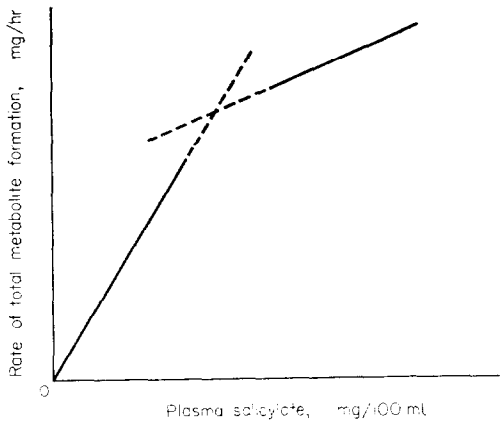

FIG. 2. An illustration of the changing relationship between plasma salicylate concentration and the rate of total metabolite formation.

depicts the changing relationship of the rate of total metabolite formation to the plasma salicylate concentration. The single dose of aloxiprin provides a plasma level (less than 3·5 mg/100 ml) which for most subjects is believed to be below the level at which the rate of formation changes, whereas the higher plasma concentration (5 mg/100 ml) attained with the same dose of aspirin B.P. is above this limiting plasma level and results in a relatively lower rate of excretion.

The above consideration offers a partial explanation of the observed facts. It demonstrates that the rates of excretion derived from the two preparations are not proportional to the respective plasma levels but does not explain why they are almost equal. The accrual of salicylate metabolites in the body may be an additional reason for this apparent anomaly.

Cummings and Martin[16] have pointed out that in respect of drugs which are excreted predominatly as metabolites, the rate of excretion of a metabolite in the urine will only parallel the rate of its formation some time after the attainment of the maximum plasma concentration of the metabolite. The time of maximum metabolite concentration in plasma will not necessarily coincide with the time of maximum drug concentration. This is because the amount of a drug metabolite excreted in the urine in one hour cannot equal the total amount in the body during that hour, but will be some fraction of that amount. The amount of metabolite which is not excreted plus the metabolite formed during the subsequent equal period leads to accrual of the metabolite. This will continue until the rate of excretion of the metabolite equals its rate of formation. Before this time the rate of excretion is less than the rate of formation, after this time the rate of excretion will exceed the rate of formation. This effect will be enhanced when absorption of the drug from the gastro-intestinal tract is rapid and particularly when the formation of the metabolite is rate-limited. Conversely, the magnitude of the effect will be minimized when the drug is slowly absorbed.

The concept of metabolite accrual offers an explanation for the observation that when a single dose of aspirin B.P. is administered the maximum rate of total salicylate excretion occurs some hours after the maximum plasma salicylate concentration. Also, the combined effect of metabolite accrual and of a relatively lower rate of metabolite formation, will be expected to result in anomolously low rates of total salicylate excretion during the first three or more hours after dosage. These effects will be much smaller after aloxiprin administration and the total salicylate excretion will correspond more closely to the plasma salicylate concentration. The net result will be that the observed total salicylate excretion obtained with the two preparations will not differ to the extent expected from the respective plasma salicylate concentrations.

It is considered that the plasma salicylate concentration only provides an accurate assessment of the rate of absorption of aspirin, if measured before metabolism has become appreciable. This applies irrespective of the dosage employed. The rate of total salicylate excretion in the urine is predominantly a measure of the rate of salicylate metabolism and only provides a measure of the rate of absorption when the dose employed does not exceed about 0·3 g. It is considered that had the dose of aspirin B.P. and aloxiprin used in this study been halved, the respective plasma salicylate concentrations and rates of total salicylate excretion would have shown a better proportionality.

In the multiple dose study the rates of total salicylate excretion resulting from aspirin B.P. and aloxiprin are almost identical, because the rate of metabolite excretion parallels the rate of metabolite formation and absorption effects are minimal.

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