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A KINETIC STUDY OF THE ELIMINATION OF 3-METHYLSALICYLIC ACID AND ITS ACETYL DERIVATIVE IN MAN

BY

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A study of the kinetics of the elimination of salicylic acid in man (Bedford, Cummings & Martin, 1965) has indicated that at low plasma salicylate levels, such as result from the administration of 0.3 g of acetylsalicylic acid, the elimination of salicylic acid is by an apparent first-order process. At higher plasma salicylate levels the rate of formation of the major metabolite, salicyluric acid, approaches a limiting value and it is then formed by an apparent zero-order process, and the elimination of salicylic acid is by simultaneous first-order and zero-order processes. Therefore, whereas after a small dose of acetylsalicylic acid the half-life of salicylic acid is 3 to 4 hr, when larger quantities of salicylate are present in the body the half-life is much longer. That is, the elimination of salicylic acid is relatively rapid at low concentrations, but becomes progressively slower when the concentration is increased. This study has now been extended to 3-methylsalicylic acid (*o*-cresotinic acid) (Martin & Cummings, 1962), and its acetyl derivative 3-methylacetylsalicylic acid, which are the respective homologues of salicylic acid and acetylsalicylic acid. Both 3-methylsalicylic acid, in the form of its sodium salt, and 3-methylacetylsalicylic acid have been the subject of clinical evaluation (May, 1909; Stockman, 1912; Serré, 1927; Vienne, 1933; Lightbody & Reid, 1960).

METHODS

Fourteen healthy young men took part in these studies. They were not restricted with regard to diet or fluid intake and pursued their normal occupations during the experiments.

Drugs. 3-Methylsalicylic acid (2-hydroxy-3-methylbenzoic acid, melting point 167 to 168° C) and 3-methylacetylsalicylic acid (2-acetoxy-3-methylbenzoic acid, melting point 113 to 115° C) were administered as fine powders in hard gelatin capsules or as tablets containing 0.324 g of the drug per tablet.

Chemical methods. 3-Methylsalicylic acid in serum and urine hydrolysates was estimated by the method of Brodie, Udenfriend & Coburn (1944) for salicylic acid, with the modifications that carbon tetrachloride was used as the extracting solvent and the extinction of the ferric complex was determined at 570 mμ.

3-Methylsalicylic acid in serum. The serum (1 or 2 ml.) was diluted to 4 ml. with water, 1 ml. of 6 N-hydrochloric acid was added and the whole was extracted with 25 ml. of carbon tetrachloride; 20 ml. of this extract was treated with 5 ml. of a 0.03% ferric nitrate solution.

After the administration of 3-methylacetylsalicylic acid, the sera were kept at room temperature for 15 hr or more to allow any 3-methylacetylsalicylic acid present to be hydrolysed to 3-methylsalicylic acid by enzymes present in the serum.

" *Total 3-methylsalicylic acid" in urine.* The drug metabolites were hydrolysed by heating 3 ml. of urine and 2 ml. of 12 N-sulphuric acid in an autoclave at 115° C for 3 hr. The hydrolysate was diluted to 25 ml. with water and 4 ml. of this solution was used for the determination. The results were expressed in terms of 3-methylsalicylic acid, although under these conditions only 80 to 85% of the 3-methylsalicyluric acid originally present is hydrolysed to this acid.

The isolation of 3-methylacetylsalicylic acid from urine. Four men each received 1 g of 3-methylacetylsalicylic acid and a complete urine collection was made for the following 2 hr. The pooled urine was acidified to *p*H 2 and extracted twice with an equal volume of chloroform.

The combined chloroform-extract was repeatedly washed with one-tenth of its volume of 0.1% ferric nitrate solution to remove the free 3-methylsalicylic and 3-methylsalicyluric acids. The chloroform was evaporated under reduced pressure when a crystalline product was obtained, which was recrystallized from light petroleum (boiling point 80 to 100° C). The product had a melting point of 113 to 116° C, which was unchanged by admixture with authentic 3-methylacetylsalicylic acid (melting point 113 to 115° C). It gave no colour with ferric salts and its infrared spectrum was identical with that of 3-methylacetylsalicylic acid.

The determination of 3-methylacetylsalicylic acid in urine. (1) Immediately after its collection, 5 ml. of urine and 0.5 ml. of 10 N-hydrochloric acid were extracted with 50 ml. of chloroform. The free 3-methylsalicylic acid concentration was determined using 20 ml. of this extract.

The 3-methylacetylsalicylic acid was determined after hydrolysis to 3-methylsalicylic acid by shaking a further 25 ml. of the chloroform-extract with 2.5 ml. of N-sodium hydroxide for 20 min, adding 0.5 ml. of 10 N-hydrochloric acid, shaking for a further 10 min and using 20 ml. of the chloroform solution for the determination. The difference between the two results was considered to give the amount of 3-methylacetylsalicylic acid in the urine.

(2) The amount of 3-methylacetylsalicylic acid in urine was also determined after its separation by thin-layer chromatography on silica gel. The technique used was essentially the same as that described below for the determination of 3-methylsalicyluric acid, but the urine (0.3 ml.) was applied directly to the chromatogram in this instance. After development, the 3-methylacetylsalicylic acid was detected in ultraviolet light as a dark band on a fluorescent background. This was quantitatively transferred into 5 ml. of 5 N-ammonia solution. After 1 hr the 3-methylacetylsalicylic acid had hydrolysed to 3-methylsalicylic acid, which was then determined by measuring its extinction at 298 mμ. Standards and blank urine were treated similarly.

The synthesis of 3-methylsalicyluric acid. Equimolar amounts of glycine ethyl ester and 2-acetoxy-3-methylbenzoyl chloride in benzene were maintained at 25° C for 1 hr in the presence of triethylamine. Evaporation of the benzene and treatment with 2.5 N-sodium hydroxide for 1 hr on a steam bath, followed by acidification, gave 3-methylsalicyluric acid, *N*-(2-hydroxy-3-methylbenzoyl)glycine, melting point 152 to 155° C. (Found: C, 57.4; H, 5.5; N, 6.75%. Calculated for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.3; N, 6.68%.)

The isolation of 3-methylsalicyluric acid from urine. Urine collected from subjects who had received 1 g of 3-methylsalicylic acid was acidified to *p*H 2 and 200 ml. were extracted with chloroform in a liquid/liquid extractor.

The residue obtained on evaporation of the chloroform was extracted with hot carbon tetrachloride, which after concentration and cooling deposited a crystalline product. This was recrystallized from carbon tetrachloride. The product had the infrared spectrum of 3-methylsalicyluric acid.

The determination of total 3-methylsalicyluric acid in urine. (1) The glucuronides of 3-methylsalicyluric and 3-methylsalicylic acids were hydrolysed to their respective acids by heating 6 ml. of urine and 2 ml. of concentrated hydrochloric acid in a boiling-water bath for 1 hr. The two acids were then separated by thin-layer chromatography on silica gel (Merck GF 254).

The hydrolysate was diluted to 10 ml. with water and 0.3 ml. was applied as a narrow band to a thin-layer chromatographic plate (20 × 20 cm). The chromatogram was developed at 20° C with the solvent (benzene, ether, acetic acid and methanol; 60 : 30 : 10 : 1, v/v), until the solvent front had travelled 12 cm. The 3-methylsalicyluric acid was detected in ultraviolet light by reference to a standard.

A band 6 mm wide, containing the 3-methylsalicyluric acid, was quantitatively transferred into 1 ml. of methanol and 4 ml. of water were added. Then, after centrifugation, 0.3 ml. of N-hydrochloric acid was

added to 3 ml. of the supernatant fluid and the extinction of the 3-methylsalicyluric acid solution was measured at 305 mμ. Blank urine and 3-methylsalicyluric acid standards were treated similarly. The results of four analyses on each of three urine samples were as follows: sample 1, 2.56, 2.53, 2.47 and 2.50; sample 2, 1.03, 1.11, 1.16 and 1.12; sample 3, 0.37, 0.47, 0.41 and 0.51.

(2) A method similar to that described for the differentiation of salicylic and salicyluric acids (Brodie *et al.*, 1944) was also used. The urine was hydrolysed as described above and the hydrolysate was diluted to 10 ml. The whole hydrolysate was extracted with 20 ml. of carbon tetrachloride and then 5 ml. was re-extracted with 25 ml. of chloroform. The carbon tetrachloride extract (16 ml.) was used for the determination of 3-methylsalicylic acid and its glucuronides, and the chloroform extract (20 ml.) for that of the total 3-methylsalicyluric acid. Standards containing equivalent amounts of the two acids were treated similarly.

The determination of 3-methylsalicylic acid glucuronide in urine. The 3-methylsalicylic acid concentration was determined before and after hydrolysis with β-glucuronidase at 37° C for 2 hr, or with 3 N-hydrochloric acid at 95° C for 1 hr. The difference was considered to represent the amount of 3-methylsalicylic acid present as glucuronide.

RESULTS

The rate of excretion of total 3-methylsalicylic acid in the urine of two men who received a single oral dose of 3-methylsalicylic acid, and on a subsequent occasion received an equivalent dose of 3-methylacetylsalicylic acid, is given in Figs. 1 and 2. It is apparent that 3-methylsalicylic acid or its metabolites are slowly eliminated from the body. The rate of excretion of total 3-methylsalicylic acid in the first 3 hr is much greater after 3-methylacetylsalicylic acid than after 3-methylsalicylic acid (Fig. 2), but decreases rapidly

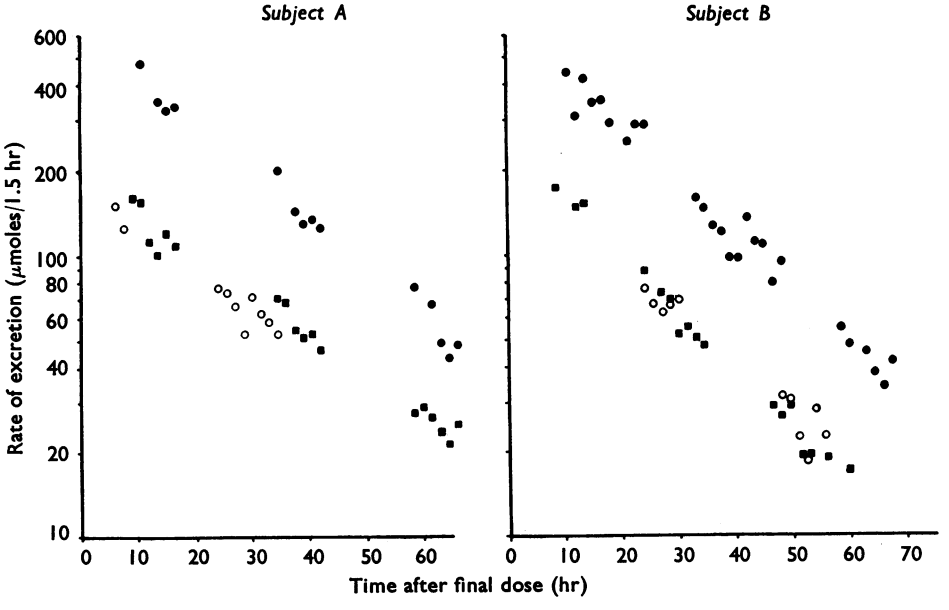

Fig. 1. Plots of the rate of excretion of total 3-methylsalicylic acid in the urine of two men (A, B) against time. On separate occasions the two men received: a single dose of 0.64 g of 3-methylsalicylic acid (■); a single dose of 0.82 g of 3-methylacetylsalicylic acid (O); a dose of 1 g of 3-methylsalicylic acid every 12 hr for 3 days, six doses in all (●). Urine was collected over accurately timed 90-min intervals for 9 or more hr daily, until the excretion had reached a low level.

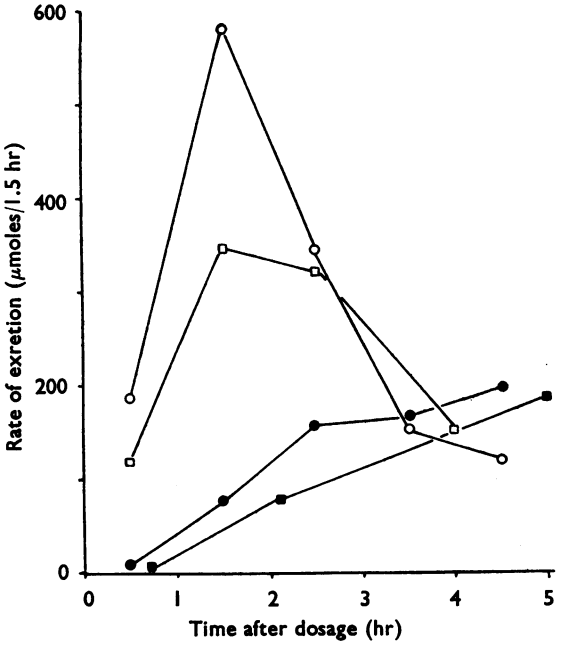

Fig. 2. The rate of excretion of total 3-methylsalicylic acid in two men (A, B) during the first 6 hr after the administration of 0.9 g of 3-methylsalicylic acid (●, ■) and after 1 g of 3-methylacetylsalicylic acid (○, □).

until finally the decline in the log rate of excretion is similar for both compounds (Fig. 1). This was considered to indicate that, whereas in the final stages the same metabolites are excreted after both preparations, there is a short period after the administration of 3-methylacetylsalicylic acid when the unchanged drug is also excreted. Confirmation of this was achieved by the isolation of 3-methylacetylsalicylic acid from urine, and two independent methods of analysis were subsequently designed to estimate it in the urine.

TABLE 1

EXCRETION OF 3-METHYLACETYLSALICYLIC ACID AND ITS METABOLITES

Numbers give the amounts of unchanged 3-methylacetylsalicylic acid (I) and its metabolites (II) excreted in the urine of four men (A, B, N, P) during the first 7 hr after dosage with 1 g of 3-methylacetylsalicylic acid. * Determined by thin-layer chromatographic method in a separate study. The last row of numbers gives the percentages of the doses excreted as 3-methylacetylsalicylic acid

	Cumulative amount excreted (μmoles)								
Time after dosage (hr)	A	A		B		N		P	
	I*	I	II	I	II	I	II	I	II
1	268	112	7	130	57	118	46	415	—
2	680	444	23	554	215	259	165	711	66
3	814	707	53	779	338	—	—	—	—
4	865	817	98	800	472	290	385	758	217
5	889	—	220	—	594	—	—	—	—
6	903	—	—	—	—	293	549	—	355
7	—	—	393	—	765	—	648	—	437
% of dose	17·3	15·7		15·2		5·7		14·6	

The rate of excretion of 3-methylacetylsalicylic acid in the urine (Table 1) rises to a maximum about 2 hr after dosage and then rapidly decreases until after 4 to 6 hr it is negligible. As much as 17% of the dose may be excreted as 3-methylacetylsalicylic acid. These results indicate that after about 6 hr the drug had been completely eliminated from the body by the two processes of hydrolysis and excretion.

The decline of the plasma concentration of 3-methylsalicylic acid was studied in men (C, D, E, F) who received a single dose of 3-methylacetylsalicylic acid and on a subsequent occasion an equivalent dose of 3-methylsalicylic acid. Semilog plots of the plasma concentration against time for both drugs ultimately appear to be linear and to have the same slope (Fig. 3). The results provide values of 13, 14, 16 and 18 hr for the half-life of 3-methylsalicylic acid.

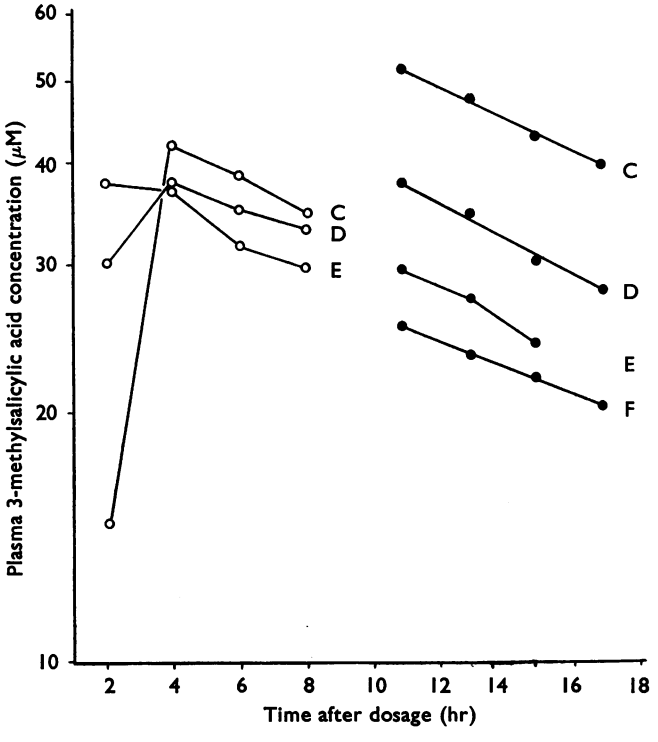

Fig. 3. Plots of plasma concentration of 3-methylsalicylic acid against time after the administration of single doses of 3-methylacetylsalicylic acid (○) and 3-methylsalicylic acid (●). Four men (C, D, E, F) received 0.78 g of 3-methylsalicylic acid and blood collections were made after 12, 14, 16 and 18 hr. Ten days later, three men (C, D, E) received 1 g of 3-methylacetylsalicylic acid and blood collections were made after 2, 4, 6 and 8 hr.

The decline of the plasma 3-methylsalicylic acid concentration in three individuals (G, H, J) was also studied after they had each received six 1-g doses of 3-methylsalicylic acid (Fig. 4). The decline is log-linear over the 48-hr period studied and provides figures for the half-life of 19, 21 and 21 hr.

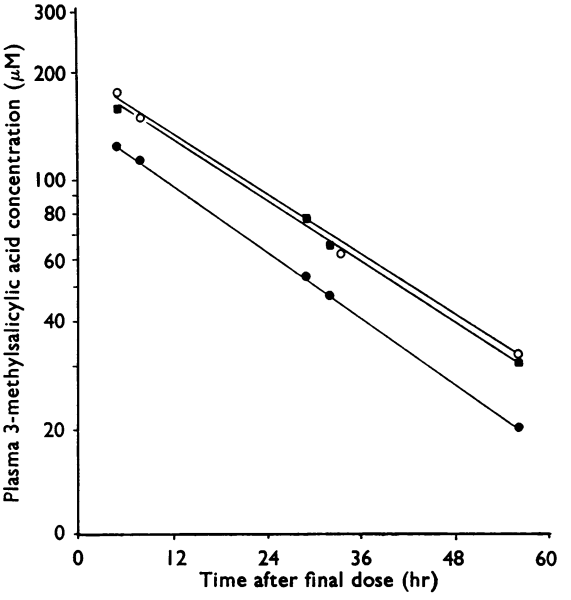

Fig. 4. Plots of the plasma concentration of 3-methylsalicylic acid in three men (G, H, J) who each received a 1-g dose of 3-methylsalicylic acid at approximately 12-hr intervals for 3 days, six doses in all. Blood was collected at 5, 8, 29, 32 and 53 hr after the final dose.

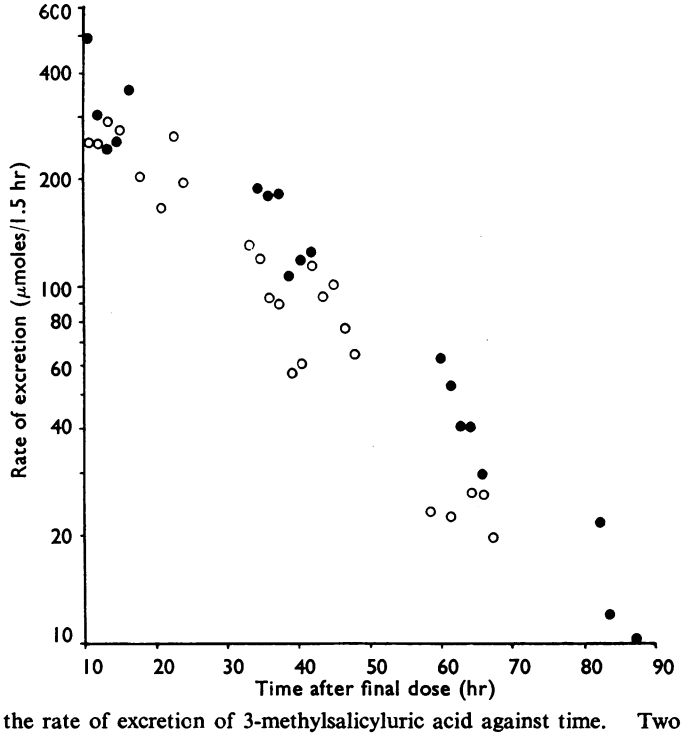

Fig. 5. Plots of the rate of excretion of 3-methylsalicyluric acid against time. Two men (A,●; B,○) received a dose of 1 g of 3-methylsalicylic acid every 12 hr for 3 days. The 3-methylsalicylic acid was determined by the thin layer chromatographic method.

The half-life of 3-methylsalicylic acid in two men (A, B) calculated from excretion values (Fig. 1) is 20 and 16 hr respectively.

A detailed investigation of the qualitative and quantitative aspects of the elimination of 3-methylsalicylic acid was made in two subjects (A, B), urine being collected at a number of equal intervals over 3 days after drug administration. Its elimination qualitatively resembles that of salicylic acid. Small amounts of unchanged drug were detected in the urine and the presence of the glycine conjugate, 3-methylsalicyluric acid, was demonstrated by chromatography and by the isolation of material possessing an infrared absorption spectrum identical to that of the synthetic compound. Semilog plots of the rate of excretion of 3-methylsalicyluric acid with time (Fig. 5), appear to be linear and to have the same slope as corresponding plots of the rate of excretion of total 3-methylsalicylic acid (Fig. 1). Urine specimens collected at various times contained 3-methylsalicyluric acid in amounts corresponding to about 70% of the total 3-methylsalicylic acid present (Table 2).

TABLE 2

THE PERCENTAGE OF THE TOTAL 3-METHYLSALICYLIC ACID IN URINE EXCRETED AS 3-METHYLSALICYLURIC ACID, AT VARIOUS TIMES AFTER THE ADMINISTRATION OF 0·64 G OF 3-METHYLSALICYLIC ACID TO TWO MEN (A, B)

The results were obtained from urines collected for the study of total 3-methylsalicylic acid excretion (Fig. 1)

	3-Methylsalicyluric acid (%) at time after dosage (hr)									
Subject	12	14	17	24	36	42	50	54	60	64
A	73	—	71	—	73	68	—	—	71·5	68·5
B	—	63	—	76	73	—	70	75	—	—

Treatment of the urine with β-glucuronidase increased the amount of free 3-methylsalicylic acid, indicating the presence of glucuronic acid conjugates. For an individual the glucuronides also constitute an almost constant percentage of the total 3-methylsalicylic acid excretion over the 9-hr period studied (Table 3).

TABLE 3

THE PERCENTAGE OF TOTAL 3-METHYLSALICYLIC ACID IN URINE EXCRETED AS GLUCURONIDE BY FOUR MEN (K, L, M, N) WHO RESPECTIVELY RECEIVED 2, 4, 8 AND 12 MG/KG OF 3-METHYLSALICYLIC ACID

Time after dosage (hr)	Glucuronide (%) excreted by			
	K	L	M	N
3	22·3	18·0	34·8	24·6
6	22·7	20·5	31·2	26·8
9	22·8	20·7	33·6	26·0

The *in vitro* rate of hydrolysis of 3-methylacetylsalicylic acid at *p*H 7.4 is appreciably slower than that of acetylsalicylic acid (Fig. 6), the first-order rate constants for hydrolysis being 1.73×10^{-3} hr^{-1} and 6.80×10^{-3} hr^{-1} respectively.

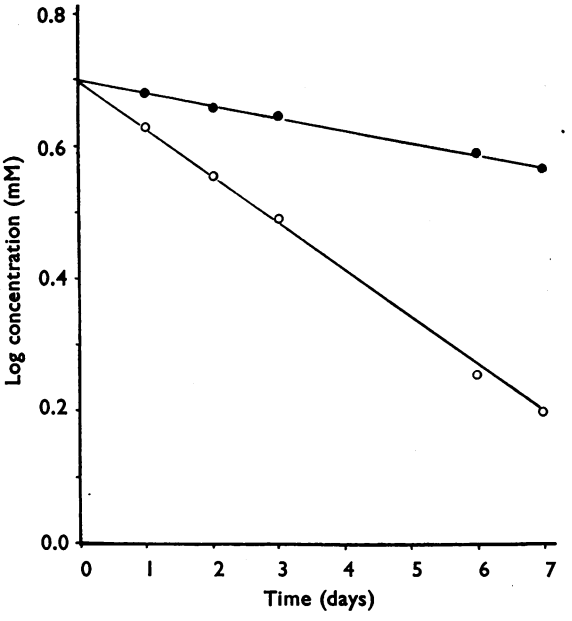

Fig. 6. The rate of hydrolysis of 3-methylacetylsalicylic acid (●) and of acetylsalicylic acid (○) *in vitro*. A 5 mM-3-methylacetylsalicylic acid solution in 0.1 M-phosphate (*p*H 7.4) was kept at 20° C in the dark and its concentration was determined at intervals for 7 days. The rate of hydrolysis of acetylsalicylic acid was determined under the same conditions.

DISCUSSION

The plasma and the urinary excretion results both indicate that 3-methylsalicylic acid is slowly eliminated in man with a half-life of about 18 hr. Its elimination is slower than that of salicylic acid, the difference being particularly marked at low dosage levels. Whereas the half-life of salicylic acid increases progressively when the amount in the body is increased, no such increase in the half-life of 3-methylsalicylic acid has been observed within the dose range studied. (In the multiple dose studies the amount of drug in the body probably exceeded 2 g.)

One factor which probably contributes to the slower elimination of 3-methylsalicylic acid is that it is bound to the plasma proteins more extensively than is salicylic acid (Stafford, 1962), and this will affect its distribution and reduce its concentration at the metabolic sites. The enzymic reaction controlling the rate of metabolism of 3-methylsalicylic acid may also be slower but no evidence is available on this point.

The observed log-linear decline in the plasma concentration of 3-methylsalicylic acid over 48 hr (Fig. 4) suggests that the elimination of this drug may be by an apparent first-order process. This is supported by the observation that the decline in the rate of excretion of 3-methylsalicyluric acid appears to be log-linear (Fig. 5) and also by the finding that the percentage of the total 3-methylsalicylic acid excreted as 3-methylsalicyluric acid remained almost constant throughout the excretion period (Table 2). The plots of rate of excretion of total 3-methylsalicylic acid also appear to be log-linear (Fig. 1), but this does not

constitute proof for a first-order rate of elimination, for Cummings, Martin & Park (1964) have provided theoretical evidence that a log-linear decline can also result from simultaneous zero-order and first-order elimination. This has been observed in respect of the elimination of salicylic acid (Bedford *et al.*, 1965).

The present results provide no evidence to suggest that the formation of 3-methylsalicyluric acid is rate limited at the concentrations of drug achieved in the body in the present studies. However, in all these studies the maximum rate of excretion of 3-methylsalicyluric acid (380 μmoles/90 min) was lower than the observed rate of excretion of salicyluric acid (400 μmoles/90 min) when formation of this acid was apparently rate limited (Bedford *et al.*, 1965).

Limitation in the rate of formation of 3-methylsalicyluric acid may therefore well occur at high levels of 3-methylsalicylic acid. Results which would permit the comparison of the rates of metabolism of the two drugs on the basis of equivalent concentrations of the free drug at the site of the metabolic enzymes have not been obtained.

Whereas the urinary excretion values examined over the whole period of excretion indicate that the overall elimination of drug is a first-order process, the rates of excretion (Figs. 1 and 5) show considerable fluctuations over short periods of time. In some instances consecutive results differ by more than 50% and the variation is frequently greater than the limits of experimental error. This variation is not readily or wholly explicable in terms of the *p*H or the volume of the urine. Moreover, fluctuations in the rate of excretion of total 3-methylsalicylic acid are accompanied by corresponding fluctuations in the rate of excretion

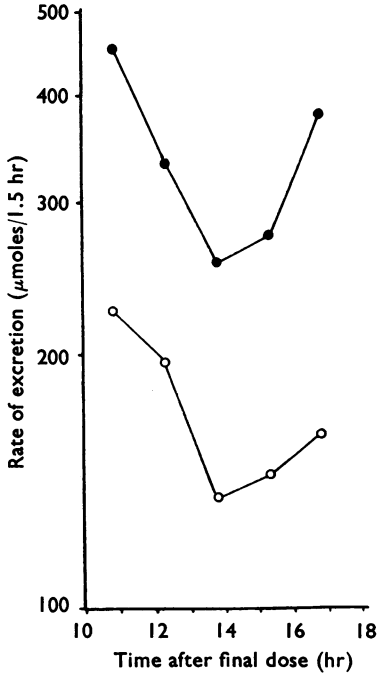

Fig. 7. An example of the fluctuations in the rates of excretion of 3-methylsalicyluric acid (●) and of the other metabolites of 3-methylsalicylic acid (○).

of both 3-methylsalicyluric acid and the other metabolites of 3-methylsalicylic acid (Fig. 7). It is tentatively suggested that this may be due to the biliary excretion of 3-methylsalicylic acid and its entero-hepatic circulation.

Acetylsalicylic acid and 3-methylacetylsalicylic acid are both eliminated from the body by three competitive processes, excretion, hydrolysis and metabolism. It is probable that any metabolites derived directly from these compounds are largely hydrolysed and appear in the urine as salicylic acid or 3-methylsalicylic acid metabolites respectively. After the administration of 3-methylacetylsalicylic acid, an average of 15% of the dose appears in the urine as the unchanged drug. Elimination by hydrolysis therefore proceeds about six-times as fast as the competitive process of excretion. This may be contrasted with acetylsalicylic acid, its elimination by hydrolysis being so rapid relative to that by excretion that little acetylsalicylic acid appears in the urine.

The rate of elimination of 3-methylacetylsalicylic acid may be assessed from the decline in its rate of excretion in the urine. The present studies suggest that the rate constant for elimination is within the range 0.6 to 1.5 hr^{-1}, the results available being insufficient for a more precise determination. The corresponding rate constant for the elimination of 3-methylsalicylic acid, calculated from the plots in Figs. 1 and 4, is within the range 0.033 to 0.053 hr^{-1}.

The maximum rate of total 3-methylsalicylic acid excretion in the urine after the administration of 3-methylacetylsalicylic acid is considerably greater than that after an equivalent dose of 3-methylsalicylic acid. This can be attributed largely to the more rapid excretion of 3-methylacetylsalicylic acid, rather than to any difference which may also exist in their rates of absorption and the following kinetic considerations support this view.

The excretion rate constant (K_e) for a drug may be calculated from a knowledge of the elimination rate constant (K) and the proportion of the total drug which is excreted unchanged in the urine (D_e/D), where D and D_e are respectively the amount of drug absorbed and the amount excreted unchanged in the urine, by the equation: $K_e=KD_e/D$.

For 3-methylsalicylic acid, if 10% is excreted unchanged and taking the maximum observed value of $K=0.05$, then $K_e=0.053\times10/100=0.005$ hr^{-1}.

For 3-methylacetylsalicylic acid, if 14% is excreted unchanged and taking the minimum observed value of $K=0.6$, then $K_e=0.6\times14/100=0.084$ hr^{-1}. The excretion rate constant of 3-methylacetylsalicylic acid is thus appreciably greater than that of 3-methylsalicylic acid.

It has been shown (Fig. 6) that the rate of hydrolysis *in vitro* of 3-methylacetylsalicylic acid ($K_h=1.73\times10^{-3}$ hr^{-1}) is lower than that of acetylsalicylic acid ($K_h=6.80\times10^{-3}$ hr^{-1}). These results agree with those of Bastide (1954), who in addition showed that 3-methylacetylsalicylic acid is more slowly hydrolysed than acetylsalicylic acid in the presence of human serum. Bastide also deduced the presence of acetylsalicylic acid in the urine after oral dosage, but the evidence on which this was based is inconclusive. He assumed that the increase in the amount of salicylic acid in urine after hydrolysis could be attributed to acetylsalicylic acid in the urine and similar reasoning was applied to the excretion of 3-methylacetylsalicylic acid. However, by this procedure an increase in the amount of salicylic acid or 3-methylsalicylic acid will result from the hydrolysis of the ester glucuronides present in the urine. For this reason, the present studies employed a preliminary extraction

of 3-methylacetylsalicylic acid from the urine before hydrolysis to eliminate labile glucuronides.

Bastide (1954) observed a slower rate of excretion after 3-methylacetylsalicylic acid than after acetylsalicylic acid and attributed this to its slower rate of hydrolysis. The present findings conflict with that view, for they indicate that 3-methylacetylsalicylic acid is excreted rapidly and it is only by virtue of its hydrolysis to 3-methylsalicylic acid that its excretion subsequently appears to be slow.

SUMMARY

1. The plasma concentrations and the rates of excretion of " total " 3-methylsalicylic acid in urine have been determined after single and multiple doses of 3-methylsalicylic acid and after single doses of 3-methylacetylsalicylic acid.

2. The rate of elimination of 3-methylsalicylic acid is slow, with an average of 18 hr for its half-life.

3. The rate of excretion of " total " 3-methylsalicylic acid in the first 3 hr is much higher after 3-methylacetylsalicylic acid than after 3-methylsalicylic acid, but thereafter decreases rapidly and the decline in the rate of excretion is finally similar for both drugs.

4. This difference in the rate of excretion for the two drugs was due to the excretion of unchanged 3-methylacetylsalicylic acid. As much as 17% of the dose may be excreted in this form.

5. The rate of excretion of unchanged 3-methylacetylsalicylic acid rises to a maximum about 2 hr after dosage and then rapidly decreases. None could be detected after 7 hr.

6. The results indicate that the elimination of 3-methylsalicylic acid is by a first-order process, at the drug concentrations achieved in these studies.

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REFERENCES

BASTIDE, P. (1954). La désacétylation et l'elimination *in vivo* de quelques dérivés salicylés. *Ann. Biol. Chem.*, **12**, 518–525.

BEDFORD, C., CUMMINGS, A. J. & MARTIN, B. K. (1965). A kinetic study of the elimination of salicylate in man. *Brit. J. Pharmacol.*, **24**, 418–431.

BRODIE, B. B., UDENFRIEND, S. & COBURN, A. F. (1944). The determination of salicylic acid in plasma. *J. Pharmacol. exp. Ther.*, **80**, 114–117.

CUMMINGS, A. J., MARTIN, B. K. & PARK, G. S. (1964). Drug elimination by simultaneous first order and zero order processes. *Nature (Lond.)*, **202**, 779–780.

LIGHTBODY, T. D. & REID, J. (1960). Ortho-cresotinate and diabetes mellitus. *Brit. med. J.*, ii, 1704–1707.

MARTIN, B. K. & CUMMINGS, A. J. (1962). Belgian Patent Specification No. 633620.

MAY, R. (1909). The action of cresotinic and toluic acids. *Brit. med. J.*, ii, 791–793.

SERRÉ, M. (1927). *Sur une Nouvelle Médication Salicylée (La Crésopirine)*. Doctorate Thesis at the University of Lille.

STOCKMAN, R. (1912). The therapeutic action of cresotinic acids. *J. Pharmacol. exp. Ther.*, **4**, 97–102.

STAFFORD, W. L. (1962). The binding by bovine plasma and plasma fractions of salicylic acid and some of its 3-alkyl analogues. *Biochem. Pharmacol.*, **11**, 685–692.

VIENNE, P. L. A. (1933). *La Crésopirine dans le Traitement des Différentes Formes du Rhumatisme.* Doctorate Thesis at the University of Lille.