Kinetics of Salicyluric Acid Elimination in Man

GERHARD LEVY, LEWIS P. AMSEL, and HOWARD C. ELLIOTT

Abstract □ The kinetics of salicyluric acid (SU) elimination were determined in healthy adult men from urinary excretion and (in one instance) plasma concentration data following intravenous injection of SU or oral administration of salicylate and subsequent blocking of further SU formation by benzoate. Similar results were obtained by the two methods. The elimination of SU is considerably more rapid than is suggested by urinary excretion data obtained after oral administration of SU in aqueous solution. The kinetics of SU formation from salicylate can be characterized adequately by considering the formation process as the rate-limiting step in the excretion of SU after salicylate administration.

Keyphrases □ Salicyluric acid—elimination kinetics □ Benzoic acid inhibition—salicyluric acid formation □ Excretion rates—salicyluric acid, as test drug, as metabolite □ Salicylate excretion—salicyluric acid formation rate effect

Knowledge of the pharmacokinetics of salicyluric acid (SU), the major metabolite of salicylic acid, is desirable for a more complete understanding of the kinetics of salicylate elimination in man. The relatively unusual dose dependency in the elimination kinetics of salicylate is due to the limited capacity of man to form SU (1–4). Urinary excretion data have been used to describe the kinetics of SU formation since there was evidence (4, 5) that the appearance of SU in the urine is rate limited by its formation. The purpose of this study was to determine the kinetics of SU elimination. Since SU is almost completely excreted intact in the urine, its renal excretion rate constant is practically equivalent to the overall elimination rate constant. Presented here are the results of experiments in which SU was administered orally and by intravenous injection. Reported also are data obtained by administering salicylate and blocking SU formation after some time by administration of a competitive inhibitor. The blocking method is of special interest in that it may be useful for assessing the elimination kinetics of certain other types of metabolites, such as glucuronides and sulfates, which are not readily available or cannot be administered as such for other reasons.

EXPERIMENTAL

The subjects were adult men in apparent good health. SU alone or with benzoic acid was administered orally in the morning on an empty stomach. In other experiments, salicylic acid (a direct precursor of SU in man) was given, and 3 hr. later the further formation of SU was blocked by administration of a large dose of benzoic acid. All drugs were given in solution as the sodium salt. SU was administered also by rapid intravenous injection of a solution in pH 7.2 phosphate buffer. Urine collections were made at frequent intervals after drug administration. In one instance, several blood samples were also obtained. SU in the urine and plasma was determined by methods described elsewhere (6–8).

RESULTS AND DISCUSSION

The excretion rate of SU after oral administration of this metabolite decreased exponentially with time and it was not or only slightly affected by concomitant administration of benzoic acid (Figs. 1 and 2; Table I). "Apparent"[1] elimination rate constants determined from the slopes of log excretion rate *versus* time plots ranged from 0.73 to 1.3 reciprocal hr., in good agreement with results reported from another laboratory (2). Ninety percent or more of an oral dose of SU was usually recovered unchanged in the urine and an additional ≃5% was excreted as an acid-labile conjugate. The excretion rate of SU also declined exponentially with time after benzoate administration in experiments where the subjects were given salicylate as a source of SU. However, the elimination rate constants thus obtained were considerably larger than the apparent constants derived from the experiments where SU was administered orally as such (Figs. 1 and 2; Table I). Benzoate served to block the formation of SU (9) rather than its excretion; it may be noted in the experiments with salicylate that there was no rebound or secondary rise in SU excretion after recovery from the effect of benzoate (inset in Figs. 1 and 2). An inhibition of excretory function would have caused accumulation of SU, resulting in higher excretion rates of this metabolite after elimination of the inhibitory agent than prior to its administration.

Data obtained by intravenous injection of SU yielded essentially the same elimination rate constant as was obtained from the experiment with salicylate and benzoate in this subject (Fig. 3). The re-

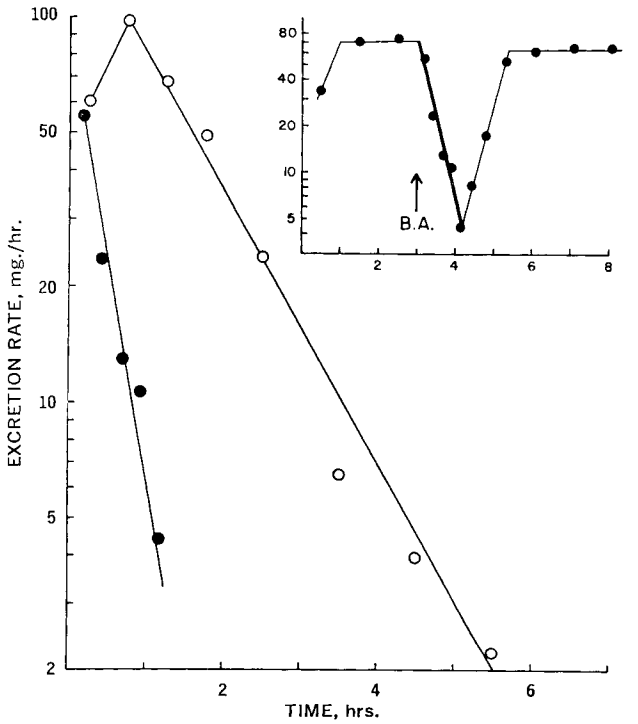

Figure 1—*Excretion rates of salicyluric acid as a function of time (a) after oral administration of 0.2 g. salicyluric acid (○) and (b) after oral administration of 3.2 g. benzoic acid preceded by 1 g. salicylic acid 3 hr. earlier (●). Inset: Time course of salicylurate excretion in experiment (b) starting from the time of salicylate administration. The heavy portion of the curve is identical to the curve shown on the main graph. B.A. = benzoic acid. Data from Subject A.*

[1] In the context of this discussion, the term "apparent" refers to the assumption, subsequently shown to be erroneous, that the slope of the log excretion rate *versus* time plot obtained after oral administration of SU can be used to calculate the elimination rate constant of this metabolite.

Table I—Elimination Kinetics of Salicyluric Acid (SU) When Administered Orally as Such and When Formed *in vivo* from Salicylic Acid (SA)

Subject or Reference	Exptl. Conditions	*Apparent* SU Elimination Rate Constant, hr.$^{-1}$[a]	SU Elimination Rate Constant, hr.$^{-1}$[b]
A[c]	0.2 g. SU	0.80	
A	0.2 g. SU and 5 g. BA[d]	0.73	
A	1 g. SA and 3.2 g. BA 3 hr. later		2.8
A	As above, with glycine[e]		2.8
A	1.5 g. SA and 5 g. BA 3 hr. later, with glycine[e]		2.6
B[f]	0.1 g. SU	1.0	
B	0.5 g. SU	1.3	
B	0.15 g. SU and 5 g. BA	0.78	
B	1 g. SA and 5 g. BA 3 hr. later		4.3
Reference 2 (2 subjects)	0.5 g. SU	≃0.83	

[a] When SU is given. [b] When SA is given. [c] 26 yr., 90 kg. [d] BA = benzoic acid. [e] 5 g. at −1 hr. and 2 g. every hr. thereafter. Glycine has no effect on SU formation in man and was administered in order to determine its effect on BA elimination (9). [f] 40 yr., 81 kg.

covery of intravenously administered SU was 96% of the dose and, contrary to what is observed following oral administration (10), there was no evidence of an SU conjugate. The plasma concentration data, though possibly not very precise due to an unusually high blank (about 0.18 mg./100 ml.), agree well with the urinary excretion data. The similarity of the elimination rate constant for SU obtained by intravenous injection of SU and by administration of salicylate followed by benzoate indicates that the considerably lower *apparent* elimination rate constants obtained in experiments where SU was administered orally are most likely artifacts resulting from slow absorption of SU from the gastrointestinal tract. Assuming that the slope of the line obtained by

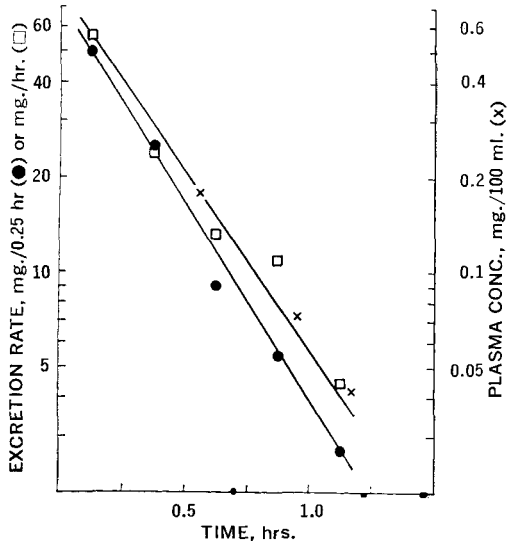

Figure 3—*Excretion rates* (●) *and plasma concentrations* (×) *of salicyluric acid as a function of time after rapid intravenous injection of 97.5 mg. salicyluric acid, Subject A. Shown also are the excretion rates of salicyluric acid after oral administration of 3.2 g. benzoic acid (at zero time) which was preceded 3 hr. earlier by 1 g. salicylic acid* (□).

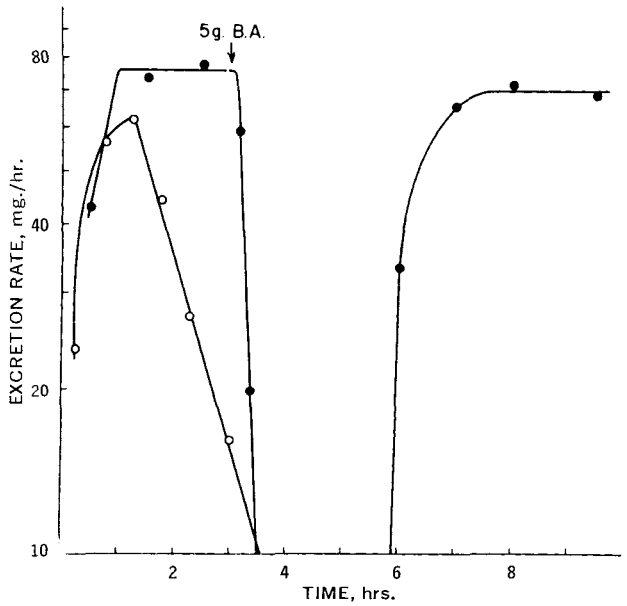

Figure 2—*Excretion rates of salicyluric acid as a function of time (a) after oral administration of 0.15 g. salicyluric acid followed 5 min. later by 5 g. benzoic acid* (○) *and (b) after oral administration of 1 g. salicylic acid followed 3 hr. later by 5 g. benzoic acid* (●). *A total of 11 mg. salicyluric acid were excreted during the 2 hr. when the data points from experiment (b) are below the lower limit of the graph. Data from Subject B.*

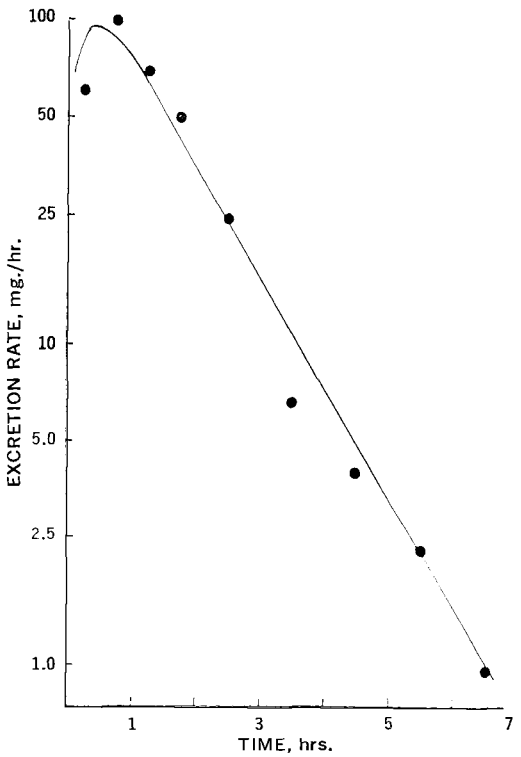

Figure 4—*Theoretical curve for a one-compartment model, assuming first-order absorption and elimination by excretion of orally administered salicylurate. The rate constants for absorption (0.8 hr.$^{-1}$) and elimination (2.8 hr.$^{-1}$) were calculated from the slopes of log excretion rate* versus *time data obtained after oral and intravenous administration of SU to Subject A. The experimental points are the same as in Fig. 1.*

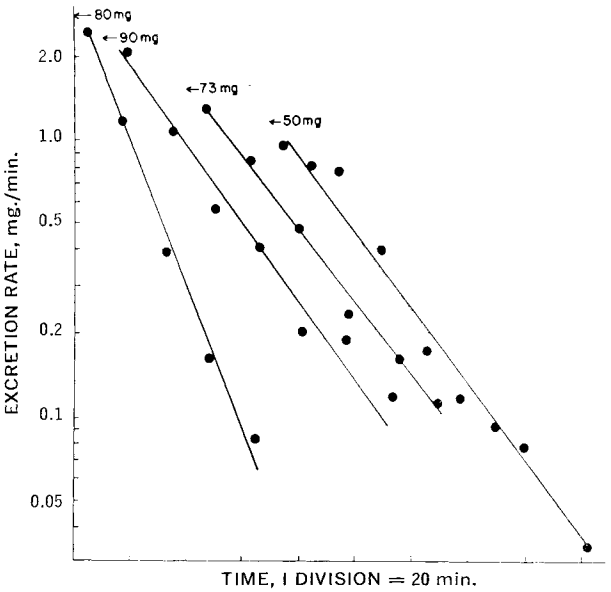

Figure 5—*Excretion rates of salicyluric acid by four healthy men as a function of time after rapid intravenous injection of salicyluric acid. The arrows indicate the time of injection and quantities next to arrows represent the administered dose.*

plotting log excretion rate of SU as a function of time after *oral* administration of this metabolite actually reflects the absorption rate constant (slope $= -k_{abs}/2.3$), and taking the slope of the excretion plot after *intravenous* administration to be a measure of the elimination rate constant, one obtains a theoretical curve which is in good agreement with the experimental data (Fig. 4).

The results of additional experiments with intravenously administered SU are shown in Fig. 5. These data were obtained as described by Elliott (11), but the present pharmacokinetic analysis was based on excretion rates and not, as in the cited paper, on plots of the difference between dose and the cumulative amount excreted at various times. The elimination rate constants for SU in the four subjects, calculated from the slopes of the log excretion rate *versus* time plots, are similar to that for Subject A (Table II). The largest value (3.5 $hr.^{-1}$ in Subject D) was similar to the 4.3 $hr.^{-1}$ value observed in Subject B in the blocking experiment. The observed rate constants for SU elimination exceed by a factor of 10 or more the rate constant for salicylate elimination determined on the basis of a one-compartment model using data from small doses at which the kinetics are apparent first-order (12).

The very high elimination rate constant of SU (half-life approximately 0.3 hr.) found in this study is consistent with other evidence of rapid elimination of this metabolite, such as the existence of a linear relationship between salicylate concentrations in the serum or plasma and the amounts of salicylate in the body as determined from urinary excretion data (4, 5). The elimination (excretion) rate constant for SU is so much larger than the elimination rate constant of salicylate that theoretical considerations based on a one-compartment catenary chain model (13) indicate that SU excretion after salicylate administration is essentially formation rate-limited. This conclusion is even more justified in the case of capacity-limited formation kinetics and makes it possible to use urinary excretion data for the determination of salicylurate formation rates and for establishing the relationship between these rates and the amount of salicylate in the body (5, 14). The use of the much smaller *apparent* elimination rate constant values (derived from experiments where SU was administered orally) for theoretical calculations leads to conclusions (13) which are inconsistent with evidence for saturation effects in salicylate elimination (15).

Table II—Elimination Rate Constants for Salicyluric Acid after Intravenous Injection

Subject	Age, yr.	Wt., kg.	Dose, mg.	Elimination Rate Constant, $hr.^{-1}$
A	26	90	97.5	2.9
C	23	64	90.0	2.0
D	20	73	80.0	3.5
E	26	87	73.0	1.9
F	40	75	50.0	1.9

The synthesis blocking method used to determine the elimination kinetics of SU can also be utilized in principle for certain other types of metabolites. For example, it is feasible to block the formation of salicylic glucuronide with salicylamide (6) and it may be possible also to block the formation of phenolic sulfates with salicylamide (16). This may be particularly useful when a drug metabolite cannot be obtained or synthesized readily, or when it is unstable or poorly absorbed from the gastrointestinal tract and intravenous injection is not feasible. However, the possibility of an effect of the blocking agent on the distribution and/or elimination of the metabolite must be taken into consideration.

REFERENCES

(1) G. Levy, *J. Pharm. Sci.*, **54,** 959(1965).

(2) C. Bedford, A. J. Cummings, and B. K. Martin, *Brit. J. Pharmacol.*, **24,** 418(1965).

(3) G. Levy, A. Vogel, and L. P. Amsel, *J. Pharm. Sci.*, **58,** 721(1969).

(4) G. Levy and S. J. Yaffe, *Clin. Toxicol.*, **1,** 409(1968).

(5) G. Levy, "Importance of Fundamental Principles in Drug Evaluation," Raven Press, New York, N. Y., 1968, p. 141.

(6) G. Levy and J. A. Procknal, *J. Pharm. Sci.*, **57,** 1330(1968).

(7) R. E. Galloway, H. C. Elliott, and A. A. Walker, *Alabama J. Med. Sci.*, **2,** 105(1965).

(8) D. Schachter and J. G. Manis, *J. Clin. Invest.*, **37,** 800 (1958).

(9) L. P. Amsel and G. Levy, *J. Pharm. Sci.*, in press.

(10) G. Levy and L. P. Amsel, *Biochem. Pharmacol.*, **15,** 1033 (1966).

(11) H. C. Elliott, *Proc. Soc. Exptl. Biol. Med.*, **121,** 861(1966).

(12) G. Levy and J. R. Leonards, in "The Salicylates," M. J. H. Smith and P. K. Smith, Eds., Interscience, New York, N. Y., 1966, pp. 5–48.

(13) J. G. Wagner, *J. Pharm. Sci.*, **56,** 586(1967).

(14) E. Nelson, M. Hanano, and G. Levy, *J. Pharmacol. Exptl. Therap.*, **153,** 159(1966).

(15) G. Levy, *J. Pharm. Sci.*, **56,** 1044(1967).

(16) G. Levy and T. Matsuzawa, *J. Pharmacol. Exptl. Therap.*, **156,** 285(1967).

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