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# Pharmacokinetics of Salicylate in Man*

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## I. INTRODUCTION

Salicylate, in the form of the natural product willow bark, has been used medicinally since ancient times, and salicylic acid itself has been part of the medical armamentarium for over 100 years [1]. Aspirin (acetylsalicylic acid) is the most widely used medicinal agent today, and its spectrum of therapeutic indications continues to widen. It is amazing, therefore, that the pharmacokinetics of salicylate were elucidated only 5 years ago and that some aspects are still unresolved. What we do know today is enough to paint a fascinating picture of pharmacokinetic complexity which is not only of interest to those concerned with this valuable drug but also to those whose interests focus on pharmacokinetics per se and its clinical implications.

### A. Metabolic Fate

Aspirin is rapidly hydrolyzed in the body to salicylic acid; the biologic half-life of aspirin in man is only about 15 to 20 min [2, 3]. The

drug is subject to first-pass hydrolysis which occurs both in the intestinal wall and in the liver [2, 4]. Salicylic acid is partly excreted as such and partly metabolized to the glycine conjugate salicyluric acid, to the glucuronic acid conjugates salicyl phenolic glucuronide and salicyl acyl glucuronide, and to the oxidation product gentisic acid (2,5-dihydroxybenzoic acid) [5]. The latter is largely excreted as such, i.e., without prior conjugation [6]. Under properly controlled conditions it is possible to recover the administered dose of aspirin or salicylic acid quantitatively in the urine as such and in the form of the several metabolites of salicylic acid, provided that the drug is administered in fully bioavailable form.

## B. Early Evidence of Nonlinear Kinetics

In the early days of pharmacokinetics, the elimination of drugs was viewed as consisting of processes describable by first-order kinetics. Accordingly, the biologic half-life and the fractional composition of urinary excretion products were considered or expected to be independent of dose [7]. This was clearly not the case with salicylate. A review of the literature [8] revealed that the "biologic half-life" of salicylic acid in adult humans increased from about 2.4 to about 19 hr when the dose was increased from 1.6 to 125 mmol (as aspirin or sodium salicylate). Furthermore, the fraction of the dose recovered in the urine during the first 24 hr after drug administration was found to decrease with increasing dose [8]. In 1958, Schachter and Manis [9] reported plasma salicylate and salicylurate concentrations observed in adult humans as a function of time after administration of sodium salicylate, 64 mg/kg. While the plasma salicylate concentrations declined by 74% from 2 to 24 hr after drug administration, the salicylurate concentrations remained essentially constant during this period of time. This plateau would not be expected to occur if the metabolite is formed and eliminated by first-order kinetics, but it is consistent with an essentially constant rate (zero-order) formation and first-order elimination of salicylurate.

## C. Clinical Problems

The therapeutic plasma concentration range of salicylate for treatment of inflammatory diseases is relatively narrow, i.e., from about 15 to about 30 mg/100 ml. Despite this, there are pronounced differences in the literature with respect to the recommended daily therapeutic dose of aspirin, particularly for children. According to one compilation of dosage recommendations from nine literature sources

[10], the daily dose for a 6-year-old child ranged from 70 to 200 mg/kg. It is not surprising, therefore, that salicylate therapy is often less than optimal, particularly if plasma concentrations are not being monitored. According to one author [11], "therapeutic, as opposed to accidental ingestion, plays a major role in the morbidity and mortality of salicylate poisoning." The controversy concerning salicylate dosage regimens is continuing to this date [12] and has recently engaged the efforts of a special Advisory Panel appointed by the FDA Commissioner [13]. Much of this problem is a reflection of the unusual pharmacokinetic characteristics of the drug.

## II. SATURATION OF SALICYLURATE FORMATION

The pharmacokinetic studies of salicylate elimination were facilitated immensely by the discovery, in the early phase of these studies, that 1) the drug and its metabolites can be recovered quantitatively in the urine, and 2) the metabolites do not accumulate in the body of individuals with normal renal function but are excreted as rapidly as they are formed. Evidence for the latter is the linear relationship between serum or plasma salicylate concentration and amount of drug in the body at various times after drug administration calculated as the difference between the amount administered and the amount excreted at various times [14, 15]. Under these conditions it became possible to perform pharmacokinetic studies of salicylate noninvasively, intensively, and over a wide dose range. Moreover, the formation rate of each metabolite could be determined by measuring its excretion rate, and this rate could be related to the amount of salicylate in the body.

### A. Pharmacokinetic Evidence

In 1965 it was found that plots of the logarithm of the amount of salicylate in the body of adults as a function of time after administration of different size doses curved downward and became essentially exponential only when the amount of salicylic acid in the body had decreased to about 200 mg [8]. It was also found that the fraction of the dose excreted as salicyluric acid decreased with increasing dose [8]. The relationship between salicylurate formation rate and amount of salicylate in the body could be described by Michaelis-Menten kinetics [16]. At that time this was a striking discovery which made pharmacokineticists aware of the fact that drug biotransformation processes can become saturated at relatively low, subtherapeutic concentrations. The most dramatic evidence of this

saturability was found in studies of salicylate intoxicated children [14]. In one case the maximum formation rate of salicylurate following accidental ingestion of an amount of aspirin equivalent to more than 140 mg salicylic acid per kg was identical to the maximum formation rate observed upon administration of about one-tenth that dose 8 months later. Other evidence was obtained in 10 normal volunteers who received 2.4 g aspirin daily for 8 days and 7.2 g daily for the next 8 days. While the steady-state plasma salicylate concentrations increased from about 11 to more than 40 mg/100 ml, the steady-state concentration of salicylurate did not increase [17].

### B. Interaction with Benzoic Acid

The major pathway of benzoic acid elimination in man is the same as that of salicylate elimination, i.e., conjugation with glycine. In the case of benzoic acid, the drug is converted to adenyl benzoate, then to benzoyl-coenzyme A, and finally to hippuric acid. It was expected, therefore, that benzoic acid and salicylic acid should have a mutual competitive inhibitory effect on their conversion to glycine conjugates. In fact, administration of benzoic acid in relatively modest doses can cause an essentially complete inhibition of salicylurate formation, but salicylate has no apparent effect on hippurate formation, at least in the dose range investigated [18, 19]. The synthesis blocking experiment with benzoate revealed a useful pharmacokinetic technique for determining the elimination rate constant of a drug metabolite which is not available or suitable for administration as such. This technique consists of administrating the precursor drug, blocking the synthesis of the metabolite some time later, and determining the time course of elimination of the metabolite in the body at the time when the block was applied. In the case of salicylurate, the elimination rate constant thus obtained was essentially identical to that determined upon intravenous administration of this metabolite [20]. On the other hand, oral administration of salicyluric acid yielded potentially misleading results. The metabolite is so slowly absorbed that it resulted in "flip-flop" kinetics, i.e., the terminal exponential phase reflected the rate constant of absorption rather than elimination [20].

### C. Effect of Glycine

Formation of hippurate from benzoate is saturable just like the formation of salicylurate from salicylate. However, the maximum formation rate of hippurate is about 20 times higher than that of salicylurate [5]. The rate limiting factor in the formation of hippurate

is the availability of glycine; oral administration of glycine in effect "unsaturates" the hippurate formation process; i.e., the elimination kinetics of benzoate change from clearly Michaelis-Menten to apparent first-order [18]. It was hoped that glycine might have a similar effect on salicylurate formation and that glycine might become a useful agent for preventing and treating salicylate intoxication. Unfortunately and disappointingly, glycine was found to have no apparent effect on the formation rate of salicylurate in man [21]. Since salicylurate formation is a saturable process also in rats (the in vivo apparent Michaelis constants in man and rat are almost identical but the $V_{max}$ on a body weight basis is substantially lower in rats), glycine was also tried in rats but again without effect [21]. Thus, while the hippurate and salicylurate formation processes follow the same nominal pathway, they differ with respect to the rate-limiting step in the sequence of reactions leading to the production of the respective glycine conjugate. Hippurate formation is rate-limited by the availability of glycine while activation of the substrate (salicylate) is the rate-limiting step in salicylurate formation. This finding and more direct biochemical evidence [22, 23] suggest that the activation of benzoic and salicylic acid is carried out by different enzyme systems. On the other hand, the conjugation of both activated species with glycine is catalyzed by the same glycine N-acyltransferase [23].

### D. Effect of Ethanol

Ethanol inhibits the formation of hippurate from glycine in man but has no apparent effect on the renal excretion rate constant of hippurate [24]. On the other hand, ethanol has no apparent effect on either the formation or urinary excretion of salicylurate following salicylate administration in man [24]. Ethanol prolongs the salicylurate synthesis inhibiting effect of benzoate in man, probably by slowing the elimination of benzoate [24]. These observations suggest that ethanol inhibits the activity of N-acyltransferase or decreases the availability of glycine to the conjugation system. If that is the case, then the selective effect of ethanol would be due to the difference in the rate-limiting step of hippurate and salicylurate formation, respectively. This illustrates the clinical importance of characterizing the rate-limiting step of consecutive drug biotransformation processes in man.

## III. PHARMACOKINETIC MODEL OF SALICYLATE ELIMINATION

Elucidation of the capacity limited nature of the salicylurate formation process in man did not fully explain the pharmacokinetic

characteristics of salicylate elimination. Specifically, a pharmacokinetic model consisting of the in vivo apparent Michaelis-Menten constants for salicylurate formation and apparent first-order rate constants for the parallel processes of renal excretion of salicylate and formation of salicyl phenolic glucuronide, salicyl acyl glucuronide, and gentisic acid was inadequate for describing the time course of elimination of a large dose of salicylate [25]. A more rigorous experimental strategy had to be employed to resolve the problem.

### A. Experimental Strategy

To characterize fully the pharmacokinetics of salicylate in man, each component process had to be studied in detail as a function of dose and time after drug administration. For this purpose, single doses of sodium salicylate were administered and urine was collected at frequent intervals until the excretion of the drug and its metabolites was completed. Every urine sample was assayed for all five excretion products, and the relationship between excretion rate of each of these products and the amount of salicylate in the body at various times after drug administration was examined to determine the type of formation kinetics and the constants by which these kinetics can be described [25]. The elimination (excretion) rate constants of the metabolites were determined directly (following administration of these metabolites) or by the synthesis blocking procedure. Since it was already known that the excretion of the salicylate metabolites is formation rate limited, only reasonable approximation of metabolite elimination rate constants was necessary. A series of differential equations could then be developed to serve as digital computer input for describing the time courses of salicylate elimination and metabolite excretion as a function of dose as well as to calculate the quantitative composition of urinary excretion products of salicylate as a function of dose. A comparison of the computer-generated data with the experimental results permitted an evaluation of the pharmacokinetic model.

### B. Saturation of Salicyl Phenolic Glucuronide Formation and Verification of the Model

The detailed pharmacokinetic study confirmed, as expected, the capacity limited formation kinetics of salicyluric acid and showed that formation of salicyl acyl glucuronide and gentisic acid as well as renal excretion of salicylic acid were apparent first-order processes under the experimental conditions. It revealed, however, that the formation of salicyl phenolic glucuronide was also capacity limited

and, like salicylurate formation, describable by Michaelis-Menten kinetics [25, 26]. This discovery constituted the missing link in the pharmacokinetic characterization of salicylate and yielded a model which describes very well the time course of salicylate elimination, the time courses of excretion of the various metabolites, and the quantitative composition of urinary excretion products as a function of dose. To confirm the capacity limited nature of salicyl phenolic glucuronide formation, the interaction between salicylate and salicylamide was examined in human volunteers. Salicylamide is eliminated by biotransformation to the glucuronide and sulfate conjugates and by oxidation to gentisamide [27]. Concomitant administration of salicylate and salicylamide causes a mutual inhibition of glucuronide formation, consistent with a competitive effect on a capacity limited process [28]. The competition is specific in that salicylamide has no effect on the maximum salicylurate formation rate [28].

## IV. CLINICAL IMPLICATIONS OF NONLINEAR ELIMINATION KINETICS OF SALICYLATE

The potentially most valuable characteristic of pharmacokinetic models is their utility for making predictions. Obviously, these predictions are only as good as the model itself, and one powerful method of model verification is to test its ability to predict the effects of various conditions and factors which can be assessed experimentally. Comparative simulation studies with different potential models of the pharmacokinetics of a particular drug can help to identify the optimum experimental conditions for determining the most appropriate model. One obvious use of the pharmacokinetic model for salicylate elimination derived from single dose studies was for undertaking simulation studies of chronic dosing regimens.

### A. Steady-State Levels

The steady-state or plateau level (concentration or amount) of a drug in the body during continuous or regular intermittent administration of that drug is directly proportional to the dosing rate if the kinetics are apparent first-order [29]. In the case of salicylate, computer simulations showed that the steady-state level increases more than proportionately with increasing dosing rate as a consequence of the limited capacity of two of its biotransformation processes [30]. These predictions are consistent with clinical experience. It has been observed that a 50% increase in the daily dose of

aspirin (from 65 to 100 mg/kg) caused a 300% rise in the serum salicylate concentration [31], and that a relatively small (20%) increase in the daily dose of aspirin produced a pronounced therapeutic response in patients with juvenile rheumatoid arthritis who had not responded to the lower dose [32].

### B. Time to Reach Steady State

It requires a period of time approximately equal to four times the biologic half-life of a drug with first-order elimination characteristics to attain 90% of the steady-state level of that drug if no loading dose is given [33]. In the case of salicylate and other drugs with parallel Michaelis-Menten and apparent first-order elimination processes, the relative elimination rate or metabolic clearance decreases with increasing dose and, therefore, the time required to attain steady state increases with increasing dose [30]. Were there no quantitatively significant parallel apparent first-order processes, the drug would never reach steady state if the dosing rate exceeds $V_{max}$, and drug accumulation would continue until the drug is stopped or the patient dies [34]. That is the case with ethanol. Computer simulations have shown that it takes about 2 days to reach steady state when 1.5 g aspirin per day is given to adults while about a week may be required to reach steady state when the dose is doubled [30]. Clinical studies have shown that it may take longer than 1 week to reach steady state when aspirin in doses of about 100 mg/kg/day is given to children with juvenile rheumatoid arthritis [35].

### C. Effect of Dosing Interval

In view of the narrow therapeutic concentration range of salicylate when used for treatment of arthritic diseases, there has been considerable discussion and concern about the size of, and interval between, fractional doses during a day [12, 13]. Again, the pharmacokinetic model could be used to examine this problem. It was found that there can be a great deal of latitude with respect to the size and interval between fractional doses as long as the total daily dose was properly chosen [36]. The reason for this permissible latitude is the fact that each fractional maintenance dose (whether one-sixth, one-fourth, or one-third the daily dose) adds relatively little to the amount of salicylate already in the body [36]. The available clinical evidence is consistent with these predictions.

## V. INTERSUBJECT VARIATION AND EFFECT OF URINE pH

A review of the literature reveals pronounced intersubject differences in steady-state plasma or serum salicylate concentrations even in normal subjects receiving the same daily dose of aspirin. It is important, therefore, to consider some of the reasons for such differences.

### A. Variables Affecting Steady-State Salicylate Levels

The factors affecting the steady-state plasma or serum salicylate concentration are readily identified. They are relative dosing rate (taking into consideration possible incomplete bioavailability), apparent volume of distribution of salicylate, the Michaelis-Menten constants ($K_M$ and $V_{max}$) for formation of salicyluric acid and salicyl phenolic glucuronide, respectively, the rate constants for salicyl acyl glucuronide and gentisic acid formation and salicylic acid excretion, and (to a relatively minor degree) the rate constant for drug absorption. Thus there are at least 10 variables to be considered. Future research must focus on the elucidation of factors affecting each of these and on means for making quantitative predictions based on individual patient characteristics, if possible. It has been established in twin studies that the $V_{max}$ for salicylurate formation is in part genetically determined, and it appears that salicylate administration may have an induction effect on salicylurate formation by increasing the $V_{max}$ of the process [37]. Females may eliminate salicylate more slowly than do males [38] but the mechanism is not known and there are conflicting reports concerning the existence of such sex difference [37]. One pharmacokinetic variable which has clearly been identified as quantitatively significant and clinically important is the excretion rate constant (or renal clearance) of salicylic acid.

### B. Effect of Urine pH on the Renal Clearance of Salicylate

The renal excretion of salicylate involves glomerular filtration, active renal tubular secretion, and partial, apparently passive renal tubular back-diffusion. Only the nonionic form of salicylic acid is subject to tubular reabsorption. As a consequence, the renal clearance of salicylate is exquisitely sensitive to urine pH. As urine pH is increased from 5 to 8, the renal clearance of salicylate increases more than twentyfold [39]. While this has a relatively small effect on the elimination kinetics of small single doses ($\leq 0.65$ g aspirin in

adults), it has a profound effect on the elimination of larger doses, i.e., when the formation rates of salicyluric acid and salicyl phenolic glucuronide approach saturation. This is particularly apparent when urine pH is increased from below 6 to 7 or higher. Consequently, alkalinization of urine is a commonly employed measure for treating salicylate intoxication.

### C. Effect of Antacids on Urine pH

The alkalinizing effect of sodium bicarbonate on urine pH is well known. Less widely appreciated is the fact that certain "nonsystemic" antacids can also increase urine pH. The term "nonsystemic" is therefore a misnomer. Such widely used antacids as aluminum and magnesium hydroxide and calcium carbonate-glycine mixture can increase urine pH significantly [40]. The lower the baseline urine pH, the greater is the effect of the antacid [40]. Since antacids are frequently taken concomitantly with aspirin (often without knowledge of the physician) to reduce or prevent aspirin-induced dyspepsia, an awareness of this potential interaction is important.

### D. Interaction of Salicylate with Antacids

Administration of sodium bicarbonate, about 4 g/day, to 13 healthy adult volunteers who were taking 1 g aspirin four times a day increased urine pH by less than one unit but decreased the steady-state plasma salicylate concentration from 27 ± 7.9 mg/100 ml to 15 ± 4.6 mg/100 ml (mean ± SD, $p < 0.01$) [41]. Similar effects were observed in children with rheumatic fever who were treated with aspirin, with or without concomitant administration of aluminum and magnesium hydroxide [42]. For example, one 11-year-old boy on 3.2 g aspirin and 150 ml Maalox suspension per day had a serum salicylate concentration of about 10 mg/100 ml and a urine pH of between 7.0 and 8.0. When the antacid was discontinued, urine pH decreased to between 5.0 and 6.4, and the serum salicylate concentration increased to 38 mg/100 ml. The antacid had no effect on the bioavailability of aspirin so that the effect on serum salicylate concentration could be clearly related to the change in urine pH and the corresponding change in the renal clearance of the drug. It is evident that serious salicylate intoxication may be caused simply by withdrawing antacid under certain conditions.

## VI. SERUM PROTEIN BINDING OF SALICYLATE

Serum or plasma protein binding can have pronounced effects on the distribution, elimination, and pharmacologic activity of drugs [43]. The relative importance of this variable in the disposition of salicylate is under intensive investigation in our laboratory, and no definitive information is available at this time. Indirect evidence suggests that the pharmacologic activity of salicylate is a function of the concentration of free (not protein-bound) drug [44].

### A. Intersubject Variations

The serum or plasma protein binding of salicylic acid is drug concentration dependent in the usual therapeutic concentration range; comparative studies must therefore be carried out at similar salicylate concentrations. The drug is bound primarily to albumin. For this reason the free fraction of salicylate in serum (i.e., the ratio of concentrations of free to free plus bound drug) decreases with increasing serum albumin concentration [45]. This is of considerable importance since acute inflammatory diseases are often associated with hypoalbuminemia. Equilibrium dialysis of serum samples from 48 normal human adults against an equal volume of buffer solution containing 30 mg salicylic acid per 100 ml yielded free fraction values ranging from 0.18 to 0.30 [45]. This variation was not entirely due to intersubject differences of serum albumin concentrations. For example, 17 of the subjects had albumin concentrations between 4.1 and 4.3% (the range for all 48 subjects was from 3.5 to 4.8%) and their free fraction values ranged from 0.18 to 0.25 [45]. Endogenous displacing agents and possibly other factors also contribute to intersubject differences in serum protein binding of salicylate in normal human adults.

### B. Effect of Renal Failure

The serum or plasma protein binding of many acidic drugs has been found to be decreased in patients with impaired or absent renal function [46]. We have found that the free fraction of salicylate at a total plasma concentration of about 5 mg/100 ml was about 0.14 in seven normal adults (range, 0.12 to 0.15) and 0.26 (range, 0.19 to 0.34) in six anephric patients [47]. Similar results have been obtained by other investigators. Transplantation of one kidney to an anephric child resulted in a normalization of salicylate binding within 2 days; the free fraction increased again during a subsequent rejection

episode and returned to normal upon successful treatment of that condition [48]. The donor of the kidney exhibited a transient elevation of salicylate-free fraction after removal of the kidney which could have been due to temporarily impaired renal function (pending the compensatory increase in the function of the remaining kidney) or to the surgery per se. There is strong evidence that the decreased protein binding of certain drugs in the plasma or serum of patients with impaired or absent renal function is due to the accumulation of endogenous displacing agents [49].

### C. Effect of Pregnancy and Neonatal State

It has been well established in a number of studies that the serum protein binding of several drugs including salicylate is less extensive in newborn infants than in normal adults. However, the serum protein binding of such drugs is even more decreased in pregnant women at the time of delivery. Consequently, the neonatal: maternal serum concentration ratio of total (free and bound) salicylate is usually above unity at the time of delivery [50, 51]. The decreased drug binding in maternal serum is due partly to the decreased albumin concentration and probably also to the increased fatty acid concentrations during pregnancy. Serum albumin concentrations in neonates are also lower than in normal adults but are usually higher than in maternal serum. Not only are the serum salicylate concentrations usually higher in newborns than in their mothers, newborns also have a larger apparent volume of distribution for salicylate than is found in normal adults [50]. Consequently, maternal serum salicylate concentrations may not reflect adequately the neonatal exposure to the drug.

### D. Effect of Heparin

Recent studies in our laboratory, as yet unpublished, have shown that the plasma protein binding of salicylic acid is decreased by intravenous administration of heparin to rats or humans. This effect can be elicited by therapeutic infusion rates of the anticoagulant and is readily reversible upon discontinuation of heparin. In vitro addition of heparin to plasma or serum has much less effect. Salicylate binding in plasma of patients on i.v. heparin therapy can be increased by treating the plasma with activated charcoal. Apparently, the in vivo heparin effect is due to increased plasma concentrations of fatty acids and or other endogenous compounds which compete with salicylic acid for binding sites on plasma albumin.

## VII. RATIONAL DESIGN OF DOSAGE REGIMENS

Since the therapeutic concentration range of salicylate for the treatment of systemic inflammatory diseases such as rheumatic fever and rheumatoid arthritis is quite narrow, and since a small change of dose can have a much more pronounced effect on steady-state concentrations of salicylate (cf. Section IV.A), dosing rates must be chosen with considerable care. The numerous variables affecting salicylate elimination kinetics cannot be readily evaluated from plasma concentration data obtained after single or during multiple dose administration. Nomograms cannot adequately take into consideration the pronounced interindividual differences in salicylate elimination. Dosing rate adjustments must therefore be made empirically, based on feedback information obtained from plasma concentration monitoring and evaluation of the patient's clinical status. One reasonably conservative approach to individualized therapy is to use 60 mg aspirin per kg body weight per day (in one to six divided doses) for 1 week, obtain a blood sample about 1 to 3 hr after a dose, and increase the daily dose to 80 mg/kg if the plasma salicylate concentration is below 15 mg/100 ml. (Reduction of dosage may be indicated if plasma concentrations exceed 30 mg/100 ml.) Further upward dosage adjustments must be made cautiously in smaller increments and should be carried out only after or in conjunction with thorough clinical pharmacokinetic assessment of the patient [52].

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Author's Note: The literature on the pharmacokinetics of salicylate and related matters is very extensive. No attempt has been made to cover all or most of it in this survey. My purpose has been to review systematically the series of investigations which resulted in the characterization of the pharmacokinetics of salicylate elimination in man and in the elucidation of some of the clinical implications. Emphasis has been placed on research in my laboratory (although only a small fraction of my own publications on salicylates is cited); publications of other investigators were cited mainly to complete the picture. A better appreciation for the important contributions of these other investigators can be obtained by referring to the references in the publications cited in this survey. A complete list of my publications on the salicylates is available upon request.