SALICYLATE ACCUMULATION KINETICS IN MAN

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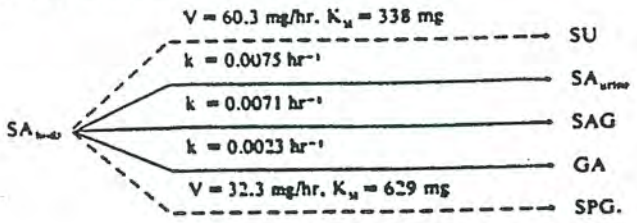
Abstract The plateau level of salicylate in the body attained by repetitive administration of fixed doses of aspirin or sodium salicylate at constant intervals increases more than proportionately with increasing dosages. The time required to attain the plateau increases with increasing dose. These unusual accumulation characteristics account for the pronounced effects of relatively small changes in maintenance dosage on salicylate concentrations in body fluids and on the pharmacologic effects of this drug. It is thus important to make upward adjustments of dosage cautiously, allowing sufficient time for body levels to reach the new steady state before the dosage is increased still further.

SALICYLATE therapy for the treatment of inflammatory disease is intensive and prolonged; optimum salicylate levels are only slightly below the range in which adverse systemic effects are encountered. Under these circumstances it is particularly desirable and appropriate as a guide to therapy to determine the accumulation characteristics of the drug as a function of dose and dosage regimen. That such a determination has not been made rigorously so far is due to the lack of an adequate pharmacokinetic model for salicylate elimination in man and of pharmacokinetic theory for determining the accumulation characteristics of drugs like salicylate that are eliminated in part by saturable processes. The kinetics of salicylate elimination have now been elucidated effectively,[1] and the pharmacokinetic theory for determining the accumulation characteristics of this type of drug as a function of dose and dosage regimen has now been developed.[2] Accordingly, this report deals with the rate and extent of salicylate accumulation during repetitive administration of this drug and thereby serves to rationalize recently reported clinical observations and to identify the special precautions required for the safe and effective use of salicylates in man.

THEORY

Salicylic acid (SA), usually administered as the sodium salt or as its precursor, aspirin, is eliminated from the body by renal excretion and by biotransformation to salicyluric acid (SU), salicyl phenolic glucuronide (SPG), salicyl acyl glucuronide (SAG), and gentisic acid (GA). Two of these processes, the formation of SU and SPG, are easily saturated in man and proceed by the Michaelis–Menten type of kinetics; the other processes follow apparent first-order kinetics in the range studied.[1] Thus,



where the continuous arrows represent apparent first-order rate processes with constants (k), and the discontinuous arrows represent Michaelis–Menten-type processes with in vivo Michaelis constants (K_M)* and theoretical maximum velocities (V). Average values for these constants obtained recently in healthy adult volunteers[1] are shown; the V and K_M values are expressed in terms of salicylic acid. The elimination of salicylate from the body may be described by the following differential equation (Eq. 1):

$$\frac{dSA_{body}}{dt} = -\left(k_{SA}+k_{SAG}+k_{GA}\right) SA_{body} - \frac{V_{SPG}\, SA_{body}}{K_{M,SPG}+SA_{body}} - \frac{V_{SU}\, SA_{body}}{K_{M,SU}+SA_{body}}$$

which can be solved readily by digital computer. A term for gastrointestinal absorption can be added to the equation when appropriate.

When a drug is administered repetitively in a fixed dose at constant intervals, it accumulates in the body until the amount entering the body during each dosing interval (the maintenance dose) equals the amount removed from the body during that time by excretion and biotransformation.[2] At this point, the plateau or apparent steady-state level has been reached. The plateau level of drugs that are eliminated by apparent first-order kinetics is directly proportional to the dose; this relation prevails with many drugs, and dosage adjustments are usually made on the basis of this assumption. Drugs that

Abbreviations Used

GA:	gentisic acid
K_M:	Michaelis constant
SA:	salicylic acid
SAG:	salicyl acyl glucuronide
SPG:	salicyl phenolic glucuronide
SU:	salicyluric acid
V:	theoretical maximal velocity

are subject to nonlinear elimination kinetics have quite different accumulation characteristics.[2] For salicylate, the relation between plateau level and dose is established by setting time equal to the dosing interval and solving equation 1 for various initial values of SA_{body}. The difference in the SA_{body} value at the beginning and end of the dosing interval is the maintenance dose that yields a maximum pla-

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*The Michaelis constant is properly expressed in concentration terms. This is not feasible in in vivo studies because the body, unlike the solutions used in in vitro experiments, is a multiphase system. The in vivo K_M as used in this report is the amount of salicylate in the body when the rate of metabolite formation is ½ of the theoretical maximum rate (V).

teau level equal to SA_{loads} at the beginning of the dosing interval, assuming intravenous administration. A slightly modified approach is used when the drug is given by mouth and absorption is not instantaneous. Details of the mathematics are reviewed elsewhere.[2]

The calculations presented here were carried out with a CDC 6400 digital computer, with use of the MIMIC analogue-digital simulation program. The pharmacokinetic constants for salicylate elimination are average values determined in four healthy adult male subjects in a study described elsewhere in detail.[1]

Results

Figure 1 shows the relation between the maximum plateau/daily dose ratio and the daily dose, assuming intravenous administration of equal doses

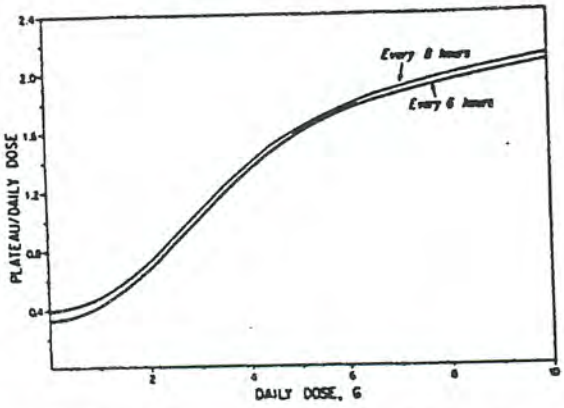

Figure 1. Relation between the Plateau Level/Daily Dose Ratio of SA in Adults and the Daily Dose (Given in Either Three or Four Equal Increments).

The plateau level is the number of grams of SA in the body immediately after intravenous administration of a maintenance dose and thus represents the maximum drug level in the body. Oral administration would change the curves only slightly, depending on the rate of absorption of the drug.

every six or eight hours. Oral administration of the drug would yield only slightly different results, depending on the rate of absorption. The minimum plateau levels can be calculated from the graph by subtracting from the maximum plateau level the amount administered at each dosing. Most important in Figure 1 is the increase in the plateau/dose ratio with increasing dose, which means that an increase in the daily dose will result in a more than proportional increase in the plateau level of salicylate in the body. For example, an increase in daily dose from 2 to 4 g, given in four divided doses per day, will raise the plateau level of salicylate in the body from 1.3 to 5.3 g, a fourfold increase. The same increase in the daily dose of drugs that are eliminated by apparent first-order kinetics would cause only a twofold increase in the plateau level since the plateau:dose ratio of such drugs is constant, independent of dose.

The plateau level calculations shown in Figure 1 represent the magnitude of salicylate accumulation

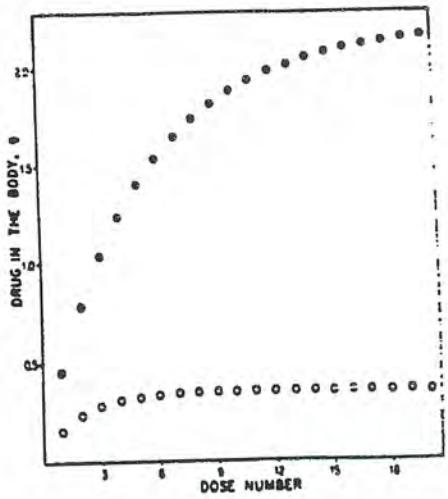

Figure 2. Accumulation of SA in the Body as a Function of Dose Number when 0.5 G (Open Circles) or 1.0 G (Closed Circles) Is Given by Mouth Every Eight Hours to Adults.

The drug is assumed to be absorbed rapidly (absorption half-life of 10 minutes), and the ordinate values are the amounts in the body immediately *before* the next dose.

at the apparent steady state without reference to the rate of accumulation. This rate is shown in Figure 2 for a dosage regimen of 0.5 and 1.0 g every eight hours. It requires only six 0.5-g doses (i.e., two days) to reach steady state, but more than 20 doses (i.e., seven days) are required to reach steady state when 1.0 g is given every eight hours. Doubling the dose also results in a more than sixfold increase in plateau levels under the stated conditions.

Discussion

The simulations presented here are consistent with available experimental data and have important clinical implications. Any increase in the maintenance dose of salicylate will result in a more than proportional rise in the plateau level of salicylate in the body; this level is reached more slowly by repeated administration of large daily doses (irrespective of dosing interval) than with smaller doses. These characteristics must be taken into consideration in the design of dosage regimens and in the monitoring of patients. The maximum response from the usual therapeutic regimen (4 g daily or more) of salicylate or aspirin (which is hydrolyzed rapidly in the body to salicylate[3,4]) cannot be expected to occur in less than one week, and plasma salicylate concentrations are likely to increase up to that time.

The data presented here explain recently reported clinical observations that a 50 per cent increase in the daily dose of aspirin (from 65 to 100 mg per kilogram) produced about a 300 per cent rise in the concentration of salicylate in the serum.[5] In two patients described in that report, serum salicylate concentrations increased from 7 and 14 mg per 100 ml five hours after the last dose of 65 mg of aspirin per kilogram per day for three days to 27 and 41 mg per

100 ml, respectively, five hours after the last dose of 100 mg of aspirin per kilogram per day for three days.[5] The data also help to explain why a relatively small (20 per cent) increase in the daily dose of aspirin can produce a pronounced therapeutic response in patients with rheumatic fever or acute arthritis who have not responded to the lower dose.[6] For the same reasons, the unusual accumulation characteristics of salicylate described here may well account for the relatively high frequency of salicylism in patients who take high doses of salicylates regularly for the relief of arthritis and rheumatism. A small increase in the dose or a seemingly small decrease in the renal clearance or apparent first-order biotransformation rate constants of the drug can cause pronounced rises in body levels of salicylate to the point of intoxication. This rise is due to the fact that the contribution of the saturable processes (SU and SPG formation) to the elimination of salicylate from the body becomes relatively smaller as the amount of salicylate in the body increases. Conversely, the apparently linear processes, including the renal excretion of salicylate, become much more important in that their contribution to the elimination of salicylate from the body increases considerably as salicylate levels in the body rise. For example, the pharmacokinetic model presented here predicts that 6.8 per cent of a 125-mg dose of SA is eliminated as unmetabolized salicylate and SAG whereas 70.4 per cent is converted to SU; this proportion changes to 35.6 and 39.9 per cent respectively when the dose is increased to 8 g.[7] These results, which reflect the increasing importance of the apparent first-order pathways for elimination of salicylate with increasing dose, have been verified experimentally in human volunteers in a more restricted dose range.[1,7]

The quantitative results shown in Figures 1 and 2 are not intended to serve directly as a nomogram and quantitative guide for the design of dosage regimens but rather as a presentation of principles for safe and effective salicylate therapy. The pharmacokinetic constants used in the simulations were derived from four subjects only; other data obtained by us show that there are appreciable inter-subject variations in the rate constants for salicylate biotransformation, and the accumulation kinetics of salicylate are influenced considerably by urinary pH in the high dose range owing to the pronounced effect of urinary pH on the renal clearance of SA. When 1 g of aspirin was given four times a day for seven days to 13 normal adult volunteers, plateau salicylate concentrations in the plasma were 27.0 mg per 100 ml (S.D. 7.9) at a urinary pH of 5.6-6.1; when urinary pH was increased to 6.2-6.9 by concomitant administration of sodium bicarbonate, plasma salicylate concentrations decreased to 15.0 mg per 100 ml (S.D. 4.6).*

The accumulation effects described here will not be reflected fully by plasma salicylate concentrations since the apparent volume of distribution of salicylate increases with increasing dose (as indicated by Swintosky[9] and in unpublished data from this laboratory). The relative magnitude of the dose dependency of salicylate accumulation is also highly dependent on the various rate constants involved and will therefore differ appreciably among subjects. It remains necessary, therefore, to rely on frequent clinical monitoring, as well as on periodic determinations of salicylate concentrations in the plasma* (particularly in patients who cannot recognize or report symptoms of salicylism), and to make upward adjustments of dosage cautiously (in small increments), allowing sufficient time for body levels to reach the new steady state before increasing the dose still further.

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*This recommendation may appear to contradict the preceding statement that the relation between the amount of salicylate in the body and its concentration in the plasma is not linear. However, the direct monitoring of plasma salicylate concentrations makes it possible to determine if drug levels are increasing or decreasing, and if dosage adjustments are necessary.