ORIGINAL ARTICLES

Salicylate kinetics in old age

Salicylate kinetics were determined in 28 subjects 25 to 92 years old who received single, oral doses of sodium salicylate (1 gm/1.73 m²). The serum AUC_∞ of total salicylate did not correlate with age. There was a weak positive correlation between the AUC_∞ of free (unbound) drug and age, but there was no apparent difference between the AUC_∞ values of the 15 women and 13 men. Seven of the 16 subjects >70 years of age cleared salicylate at about the same rate as the younger subjects. A comparison of these seven subjects with the nine >70 years old who were slow eliminators of salicylate revealed that the latter group consisted of more bedridden patients and that these patients had somewhat lower serum albumin concentrations, but they did not differ from the more rapid eliminators with respect to serum creatinine or urea nitrogen levels, SGOT, average age, female/male ratio, and average body weight. The serum protein binding of salicylate decreased with increasing age, apparently due mainly to decreasing serum albumin concentrations. (CLIN PHARMACOL THER 38:6-11, 1985.)

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The proportion of the elderly in the population is increasing. About one of every three elderly people has arthritis or rheumatism[1] and is therefore a candidate for chronic salicylate therapy. Because the therapeutic salicylate plasma or serum concentration range in the treatment of inflammatory diseases is relatively narrow,[7,8] salicylate dosage regimens must be carefully adjusted on the basis of kinetic characteristics of the individual patient. Advanced age is associated with various physiologic changes that can alter the absorption, distribution, metabolism, and excretion of drugs. These changes include decreases in renal function, cardiac output, lean body mass, total body water, serum albumin concentration, and drug metabolizing enzyme activity.[3,6,13] It is desirable, therefore, to assess the effect of age on salicylate kinetics.

Salicylic acid is eliminated from the body by biotransformation to salicyluric acid, salicyl acyl and phenolic glucuronides, and gentisic acid and by renal excretion of unmetabolized drug. Two of these parallel pathways (the formation of salicyluric acid and salicyl phenolic glucuronide) are of limited capacity in man and exhibit Michaelis-Menten kinetics.[10] The serum protein binding of salicylic acid is concentration dependent in the usual therapeutic concentration range, which introduces an additional type of nonlinearity into the kinetics of salicylic acid. To facilitate interpretation of data in our comparative study, the test dose of salicylate was normalized on the basis of estimated body surface area and the effect of age was assessed on the basis of the concentration-time profile of free (unbound) drug.

METHODS

Our subjects were 15 women and 13 men ranging in age from 25 to 92 years. Most were hospitalized for various reasons but had no gastrointestinal, hepatic, renal, or inflammatory disease. None had received sa-

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licylates for at least 1 week before the study. Four were smokers and six drank alcohol regularly. Their serum creatinine concentrations were ≤1.5 mg/dl, the serum urea nitrogen level was <27 mg/dl, and the serum albumin concentration ranged from 2.50 to 4.57 gm/dl.

A single oral dose of sodium salicylate (1 gm/1.73 m^2; body surface area determined by nomogram[4]) was taken as an aqueous solution (100 ml and a rinse) in the morning on an empty stomach. Food was permitted after 1 hour. Blood samples were collected in glass syringes before dosing and about 0.5, 1, 2, 4, 6, 8, 10, and 12 hours thereafter. Serum was separated and stored in a freezer or in dry ice. Salicylic and salicyluric acid concentrations in serum were determined by HPLC after extraction. A mixture of 0.5 ml serum and 0.5 ml 6N hydrochloric acid was extracted with 6 ml ethyl ether. Four milliliters of the ether phase was then extracted with 0.5 ml 0.13 mol/L phosphate buffer at pH 7.4 containing *o*-methoxybenzoic acid as internal standard. The concentration of the internal standard was between 0.02% and 0.05%, depending on the anticipated concentration of salicylate. An aliquot (20 to 30 μl) of the buffer phase was injected onto a C-18 μ-Bondapak column (Waters Associates). The mobile phase consisted of methanol and 1.6% acetic acid (22/78, v/v). Flow rate was 2.5 ml/min and the effluent was monitored spectrophotometrically at 254 nm.

Salicylate serum protein binding was determined by equilibrium dialysis. Serum from blood drawn before dosing was dialyzed at 37° C for 4 hours against an equal volume of 0.13 mol/L isotonic phosphate buffer at pH 7.4 that contained 5 or 30 mg salicylic acid per deciliter. A part of the serum phase was then deproteinized by adding three parts absolute alcohol containing *o*-methoxybenzoic acid, mixing on a vortex, and centrifuging. The salicylic acid concentration in the supernatant was determined by HPLC. The buffer phase was assayed in a like manner, but the internal standard was dissolved in water rather than ethanol and the centrifugation step was omitted. A serum sample drawn after dosing containing about 5 mg/dl salicylic acid, constituted by combining in appropriate proportion serum containing salicylic acid in concentrations above and below 5 mg/dl, was also subjected to equilibrium dialysis. Results are reported as percent free fraction values (i.e., 100 × drug concentration in buffer phase divided by drug concentration in serum phase). Total protein concentrations in serum were determined by the method of Gornall et al.[5] with crystalline human albumin as the standard. The albumin fraction was quantitated by electrophoresis. Determinations were made from the zero-time and 12-hour serum samples and results were averaged. The same pairs of serum samples were assayed for urea nitrogen with a commercial kit.

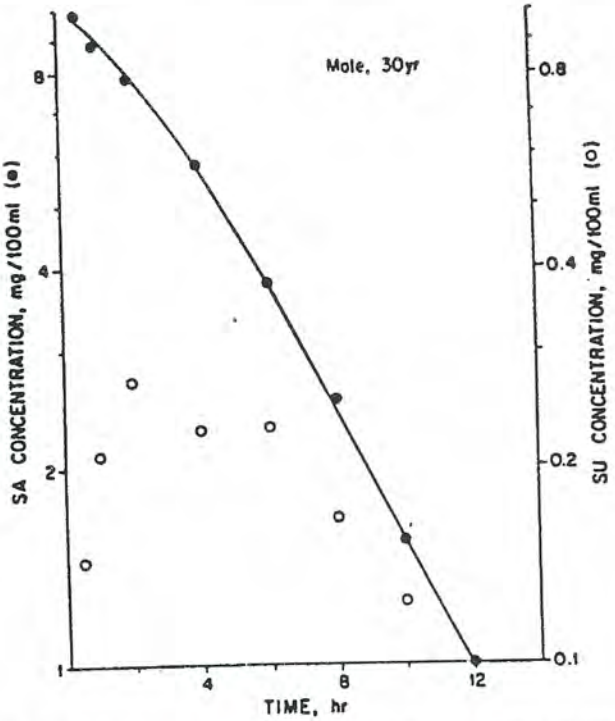

Fig. 1. Serum concentrations of salicylic acid *(SA)* and salicyluric acid *(SU)* in a 30-year-old man after a single, oral dose of sodium salicylate, 1 gm/1.73 m^2 body surface area.

The total serum salicylate and free serum salicylate AUCs from zero to 12 hours were determined by the trapezoidal method; the AUC from zero to infinity was estimated by adding to the $AUC_{0\text{-}12}$ value the remaining area, calculated by dividing the salicylate concentration at 12 hours by the apparent terminal elimination rate constant. The concentrations of free (unbound) salicylate (C_f) used for the area calculations were the product of total concentration (C_t) and free fraction. Free fraction values at different salicylate concentrations were calculated by use of individual estimates of the constants a and b of the empiric equation of Behm and Wagner,[1] who found a linear relationship of the type $(C_f/C_t) = a + bC_t$ for salicylate protein binding determined by equilibrium dialysis. We confirmed this linearity over a salicylate concentration range of at least 5 to 30 mg/dl. Values of a and b for individual subjects were calculated from C_f/C_t ratios and C_t obtained by equilibrium dialysis of zero-time serum samples against

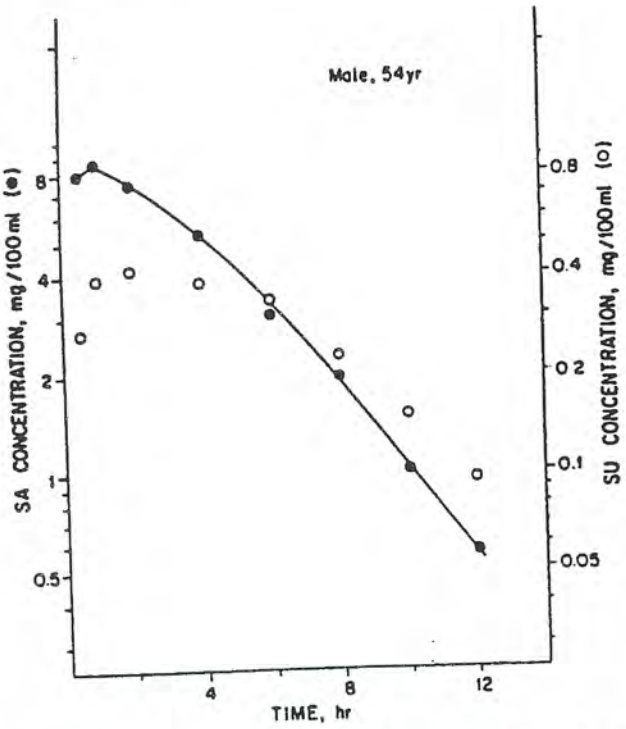

Fig. 2. Serum concentrations of salicylic acid *(SA)* and salicyluric acid *(SU)* in a 54-year-old man after a single, oral dose of sodium salicylate, 1 gm/1.73 m^2 body surface area.

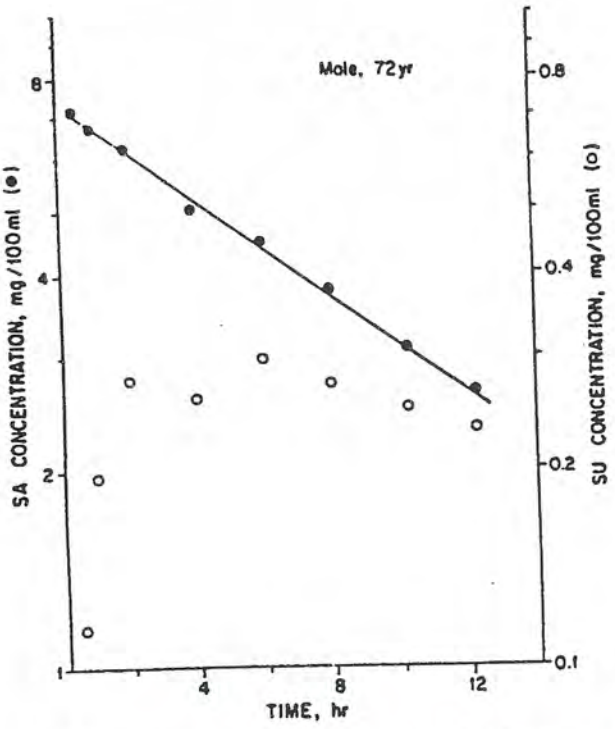

Fig. 3. Serum concentrations of salicylic acid *(SA)* and salicyluric acid *(SU)* in a 72-year-old man after a single, oral dose of sodium salicylate, 1 gm/1.73 m^2 body surface area.

buffer solutions containing 5 and 30 mg/dl salicylic acid, respectively.

RESULTS

Typical serum salicylic acid and salicyluric acid concentration-time curves over the age range of our subjects are shown in Figs. 1 to 4. Because the drug was taken in solution on an empty stomach, absorption was rapid, such that the first (30-minute) serum sample usually had the highest salicylic acid concentration. The salicylate concentration profile of the younger subjects exhibited the typical downward curve characteristic of Michaelis-Menten kinetics (Figs. 1 and 2), while most of the elderly subjects showed exponentially declining concentrations (Figs. 3 and 4), sometimes with an initial distribution phase (Fig. 4). Salicyluric acid concentrations were very low and tended to be higher in older subjects.

The relationship between the serum AUC, for total (free plus protein bound) salicylic acid and age is shown in Fig. 5. There was no discernible difference between women and men and no apparent correlation between AUC, and age, but AUC, values for subjects >70 years of age varied more than those of the younger subjects. The mean (± SD) estimated AUC values from 12 hours (the time of the last blood sample) to infinity were 22% ± 12% (n = 28) of AUC,.

The relationship between the AUC, for free (unbound) salicylate and age is shown in Fig. 6. There is a weak but significant ($r = 0.36$; $P < 0.03$) positive correlation between these AUC, values and age. Seven of the 16 subjects >70 years of age had AUC, values in the same range as those of the younger subjects, whereas nine of the subjects >70 years of age had significantly higher AUC, values indicative of slower salicylic acid clearance. Characteristics of these two groups are compared in Table I. There were no significant differences between the groups with respect to serum creatinine and urea nitrogen levels, SGOT, female/male ratio, age, and body weight, but the relatively slow eliminators of salicylic acid had somewhat lower serum albumin concentrations and a larger proportion of these subjects were bedridden.

Salicylate serum protein binding was variable and concentration dependent, with no significant difference in the free fraction at comparable concentrations of total salicylate between serum samples drawn after dosing and the zero-time serum samples with salicylate added

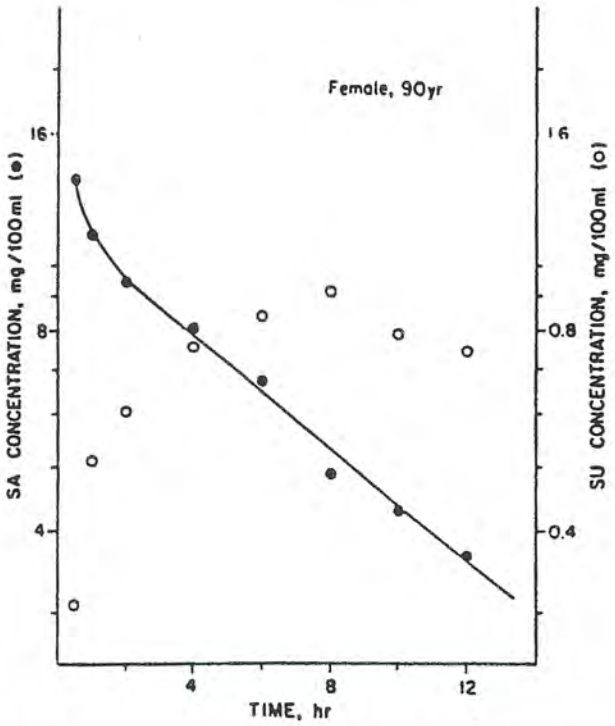

Fig. 4. Serum concentrations of salicylic acid *(SA)* and salicyluric acid *(SU)* in a 90-year-old woman after a single, oral dose of sodium salicylate, 1 gm/1.73 m² body surface area.

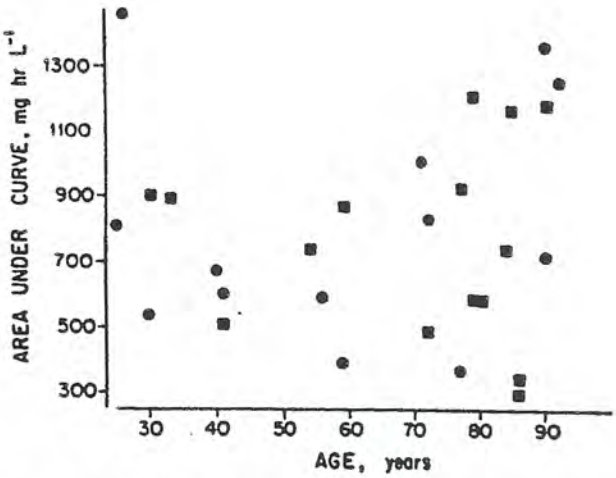

Fig. 5. Relationship between total salicylic acid serum AUC, and age in subjects receiving a single, oral dose of sodium salicylate, 1 gm/1.73 m² body surface area. ■ = Women; ● = men.

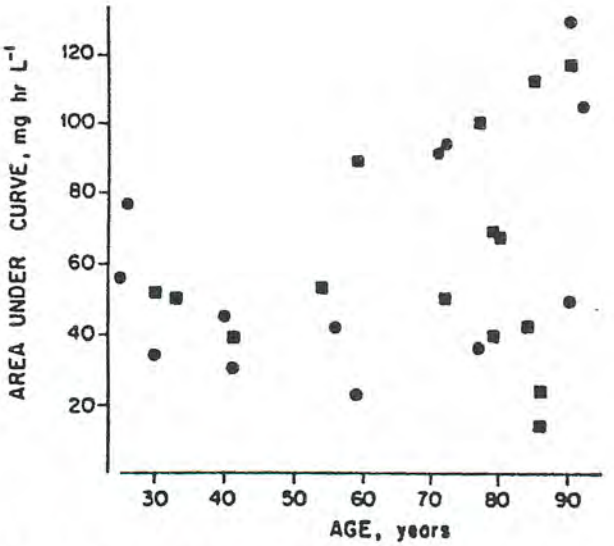

Fig. 6. Relationship between free (not protein bound) salicylic acid serum AUC, and age in subjects receiving a single, oral dose of sodium salicylate, 1 gm/1.73 m² body surface area. ■ = Women; ● = men.

in vitro (Table II). The free fraction at an initial serum salicylate concentration of 5 mg/dl rose with increasing age ($r = 0.533$; $P < 0.005$) and the serum albumin concentration decreased with increasing age ($r = -0.528$; $P < 0.005$). In the elderly (>70 years of age), the slow eliminators of salicylate tended to have higher serum free fractions of the drug than did the more rapid eliminators, but the differences were not significant (Table I). The constants a and b of the equation relating the free fraction to total salicylate concentration in serum (see Methods) negatively correlated with serum albumin concentration and age and were independent of serum levels of creatinine and urea nitrogen (Table III).

DISCUSSION

Because of the capacity-limited kinetics of salicylate, its body clearance decreases with increasing concentration or dose.[9,10] To permit direct comparison of salicylate serum concentration–time profiles, we used doses normalized on the basis of estimated body surface area. The relative contributions of the five important pathways of salicylate elimination (see Introduction) to its body clearance change with dose or concentration. Relatively small single doses, including the dose we used, are eliminated mainly by conjugation of salicylic acid with glycine to yield salicyluric acid.[14] Renal excretion of salicylate and formation of salicylic acid glucuronides become relatively more important elimination pathways for large single doses and for multiple doses that produce high plasma salicylate concentrations. Because age may have different effects on each of these

Table I. Comparison of elderly (>70 years of age) subjects with relatively small and large serum free salicylate AUC_∞ after sodium salicylate, 1 gm/1.73 m² body surface area

	AUC, <60 mg · hr/L	*AUC, >60 mg · hr/L*
No. of subjects	7	9
AUC_∞ of free drug (mg · hr/L)	37.0 ± 13.5	99.3 ± 20.9
AUC_∞ of total drug (mg · hr/L)	505 ± 181	1070 ± 246
Age (yr)	82 ± 6	82 ± 8
Female/male	5/2	5/4
Ambulatory/bedridden	6/1	3/6*
Serum creatinine (mg/dl)	1.1 ± 0.3	1.3 ± 0.2
BUN (mg/dl)	18.9 ± 3.8	17.6 ± 5.6
Serum albumin (gm/dl)	3.43 ± 0.44	3.00 ± 0.35†
SGOT (mU/ml)	19 ± 4	21 ± 6
Body weight (kg)	51 ± 13	50 ± 11
Serum salicylate free fraction (%)		
50 mg/L initial concentration	8.22 ± 1.95	9.59 ± 3.00
300 mg/L initial concentration	27.3 ± 5.3	30.9 ± 7.5

Data are $\bar{X}$ ± SD.
*P < 0.05 by a test comparing two success probabilities.
†P = 0.05 (two-tailed t test).

Table II. Serum free fraction of salicylate in 28 subjects

	Free fraction (%)	
Predialysis concentration (mg/dl)	$\bar{X}$ ± *SD*	*Range*
5 (added in vitro)	7.76 ± 2.55	4.34-14.1
5 (in vivo after dosing)	7.46 ± 2.80	3.77-15.5
30 (added in vitro)	25.2 ± 7.2	13.9-40.6

Table III. Correlation coefficients (r) for the relationship between various characteristics of 28 subjects and the constants a and b for serum protein binding of salicylate*

Correlate	*a*	*b*
Serum albumin concentration	−0.651†	−0.861†
Serum creatinine concentration	0.094	0.133
Serum urea nitrogen concentration	0.094	0.003
Age	0.420‡	0.637†

*$C_f/C = a + bC$, (see Methods).[1]
†P < 0.002, ‡P < 0.02.

pathways, the relationship between salicylate elimination and age is likely to be concentration or dose dependent. A comprehensive characterization of the interrelationship between dose or concentration, age, and salicylate elimination kinetics requires determination of the effect of age on the enzyme kinetic parameters of salicylurate and salicyl phenolic glucuronide formation processes and on the kinetic constants of the other, apparently linear parallel elimination processes. Such studies necessitate intensive blood and urine sampling, which is very difficult in elderly subjects. Our investigation was designed to assess the need for such comprehensive studies by determining the magnitude of the effect of age on the elimination of a single salicylate dose. The size of the dose was such that most of it (about 90%) would be expected to be metabolized rather than excreted unchanged.[14]

As expected, the older subjects in our study had lower serum albumin concentrations, which probably accounted in large part for the decreased serum protein binding of salicylate with increasing age. Because the pharmacologic activity of salicylate appears to be a function of free drug concentration,[12] the effect of age on salicylate kinetics will be discussed relative to the free salicylate concentration data summarized in Fig. 6. It is evident that there is no strong distinct relationship between AUC, (an index that is inversely proportional to body clearance) and age, nor is there any apparent sex difference. However, salicylate kinetics were more variable in the elderly. About half of the 16 subjects >70 years of age had AUC, values of the same order as those of the 25- to 70-year-old subjects. The other half had much higher AUC, values, reflecting a lower time-averaged body clearance of salicylate.

The two groups of subjects >70 years of age showed no evidence of differences in biochemical indices of renal and liver functions, but on the average the slow eliminators of salicylate had lower serum albumin concentrations, and relatively more of these subjects were

bedridden. Bedridden subjects included those with cancer, tuberculosis, and hypertension, but the study group was too small to assess the effects of specific diseases and concurrent drug therapy.

Our results suggest that a substantial percentage of individuals >70 years of age may be relatively slow eliminators of salicylate. This conclusion is limited by the relatively small number of subjects and by the possibility that they may not be representative of the general elderly population. It appears, however, that advanced age per se does not have a pronounced effect on salicylate kinetics. It is more likely that certain pathophysiologic perturbations that affect salicylate kinetics are more frequent or become more severe in old age. These considerations indicate a special need for clinical and kinetic monitoring of salicylate therapy in the elderly.

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