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The effects of age and sex on the disposition of acetylsalicylic acid and its metabolites

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1 The disposition of a low dose (600 mg) of acetylsalicylic acid (ASA) and its metabolites (salicylate, salicyluric acid and salicyl glucuronides) was studied in 25 male and female patients of different ages.

2 Plasma levels of ASA and salicylate were found to be significantly higher in the females (young and elderly), whereas plasma levels of salicyluric acid were found to be significantly higher in the elderly (male and female) groups.

3 The higher plasma levels of ASA and salicylate in the females appear to be due to an intrinsically lower metabolic activity in that sex, while the lower clearance of salicyluric acid leads to the accumulation of that compound in the aged.

4 No age and sex effects were found to influence the volumes of distribution of ASA, salicylate and salicyluric acid.

Keywords acetylsalicylic acid age sex metabolism

Introduction

Despite its introduction almost a century ago, acetylsalicylic acid (ASA) is still one of the major drugs used in the treatment of fever, arthritis and headaches, and is now believed to be useful in preventing complications of coronary artery disease. Due to their versatile use, ready availability over the counter and frequent use among the elderly, the pharmacokinetics of the salicylates in the elderly have been evaluated in a number of studies (Castleden *et al.*, 1977; Salem & Stevenson, 1977; Cuny *et al.*, 1979; Roberts *et al.*, 1983). Castleden *et al.* (1977), Cuny *et al.* (1979) and Roberts *et al.* (1983) have shown that most of the pharmacokinetic parameters were not significantly different between young and elderly patients, even though a marked increase in elimination half-life (Cuny *et al.*, 1979) and apparent volume of distribution (Cuny *et al.*, 1979; Roberts *et al.*, 1983) was noted in the elderly group. However, no differences were noted in the area under the curve (AUC) of plasma salicylate concentration in these two age groups. In contrast, Salem & Stevenson (1977) found that the AUC of salicylate for elderly subjects was approximately twice that for young subjects. Recently, Montgomery & Sitar (1981) found higher steady-state plasma levels of salicyluric acid, a major metabolite of salicylate, in elderly patients receiving chronic ASA therapy. In addition, the metabolism of salicylate appears to be influenced by genetic factors (Furst *et al.*, 1977), and plasma concentrations of ASA and salicylate have been found to be consistently higher in female than in male subjects (Coppe *et al.*, 1981; Kelton *et al.*, 1981; Buchanan *et al.*, 1983). Plasma clearance of salicylate has also been found to be greater in male than in female patients (Graham *et al.*, 1977).

In order to discern the age and sex effects on the disposition of ASA, plasma and urinary con-

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centration of ASA and its metabolites were monitored in male and female patients of different ages in the present study.

Methods

The investigation was carried out in 25 hospitalised patients requiring minor analgesics for pain relief (six young male (YM), seven young female (YF), six elderly male (OM) and six elderly female (OF) patients). Since corticosteroids appear to decrease steady-state concentrations of salicylates (Klinenberg & Miller, 1965) as a consequence of metabolic induction (Graham *et al.*, 1977), patients on oral contraceptives or corticosteroids were not included in the present study. Before the study, informed consent was obtained and a blood sample was taken from each patient for routine biochemical analysis (SMA 12). The serum creatinine estimations of all patients were found to be within normal limits, and the patients were free of any significant hepatic disease. Characteristics of the patients are shown in Table 1.

Blood sampling and urine collection

After an indwelling teflon cannula was inserted into an antecubital vein, a blank plasma sample was collected. Each subject took two 300 mg soluble aspirin tablets (Solprin) dissolved in 100–200 ml water. Blood samples (10 ml) were then drawn from the vein at 0.03, 0.08, 0.13, 0.25, 0.33, 0.5, 0.75, 1, 2, 4, 8, 12 and 24 h following administration. Blood specimens were collected in heparinized tubes containing 2×10^{-4} mol/l physostigmine sulphate and centrifuged within 15 min of blood collection. Urine was collected at frequent intervals for 24 h; however, the collections were non-standardised due to inherent difficulties with these patients. Since incomplete urinary recoveries were collected from three out of the seven young female patients, urine samples were collected from two additional young female subjects receiving the same dose of acetylsalicylic acid. The data from this group were utilised only in the comparison of total amount of urinary recovery. The volume and pH of each urine sample was measured and recorded after each collection. Plasma and urine samples were then snap frozen (dry ice in acetone) and kept frozen for subsequent analysis. At no time were samples kept longer than 14 days. Plasma and urinary concentrations of ASA, salicylic and salicyluric acid were measured by the methods described by Cham and coworkers (1979, 1980 a,b). Since authentic samples of glucuronides were not available, the salicyl glucuronides were quantified using a specific enzyme hydrolase (β-glucuronidase). Urine was adjusted to pH 5 with diluted acetic acid and 500 Fishman units of β-glucuronidase were added to each 200 μl of urine sample and whirlmixed for 30 s, stoppered and incubated overnight at 37°C. Analysis for salicylate was then carried out. The amount of salicyl glucuronides present was taken to be the difference in salicy-

Table 1 Characteristics of subjects

Group code	*Number of subjects*	*Age (years)*	*Body weight (kg)*	*Serum creatinine (mg %)*	*Creatinine[a] clearance (ml/min)*	*Albumin (g/l)*
YM	6	20.80 (2.30)[b]	73.50 (26.70)	0.81 (0.12)	128.10 (22.18)	37.00 (5.20)
YF	7	26.70 (13.00)	64.90 (19.50)	0.79 (0.15)	113.17 (44.38)	41.80 (2.60)
OM	6	75.17 (6.50)	74.50 (12.50)	1.11 (0.24)	68.75 (29.81)	31.60 (5.50)
OF	6	78.70 (11.20)	54.50 (9.70)	0.95 (0.42)	49.38 (28.69)	34.80 (4.27)
Analysis of variance						
Source						
Age		**	NS	NS	**	**
Sex		NS	NS	NS	NS	NS
Age × Sex		NS	NS	NS	NS	NS

YM Young-male, Young-female, OM Elderly-male, OF Elderly female
$*P < 0.05$, $**P < 0.01$, NS Not significant
[a]Estimated from serum creatinine by the equation suggested by Cockcroft & Gault (1976)
[b]The number in parentheses is the value of the s.d.

late measured before and after β-glucuronidase treatment.

Data analysis

The areas under the plasma concentration-time curves (AUC) were calculated by the trapezoidal method up to the last data point. The remaining AUC beyond the last data point was estimated using the equation:

$$\int_{t\,\text{last}}^{\infty} Cp.dt = \frac{Cp\ \text{last}}{\lambda} \qquad \text{Equation 1}$$

where λ is the terminal rate constant.

The areas under the first moment of the plasma curve ($AUMC_{0-\infty}$) i.e., the areas under the curves of the product of time and plasma concentration (Benet & Galeazzi, 1979), were also calculated by the trapezoidal method. Residual area following the sampling time was obtained from the equation:

$$\int_{t\,\text{last}}^{\infty} t.Cp.dt = \frac{t\ \text{last}.Cp\ \text{last}}{\lambda} + \frac{Cp\ \text{last}}{\lambda^2} \qquad \text{Equation 2}$$

Presuming complete metabolism of ASA to salicylate (Rowland & Riegelman, 1968) and complete absorption of the formulation (Levy *et al.*, 1972), the apparent volume of distribution of salicylate at steady state (V_{ss}) was calculated by a model-independent method (Benet & Galeazzi, 1979):

$$V_{ss} = \frac{\text{Dose}\ (AUMC_{0-\infty})}{(AUC_{0-\infty})^2} \qquad \text{Equation 3}$$

The apparent volumes of distribution of ASA and salicylic acid were assumed identical at steady state (Rowland & Riegelman, 1968).

Renal clearance (CL_R) of salicylic and salicyluric acid was calculated by dividing the cumulative recovery of the respective compound (Ae) in the urine up to 24 h by the plasma concentration-time curves (AUC) for that compound for 24 h i.e.,

$$CL_R = \frac{Ae}{(AUC)} \qquad \text{Equation 4}$$

The ASA, salicylic and salicyluric acid plasma concentrations and the cumulative urinary excretion of each of the metabolites—salicylate, salicyluric acid and salicyl glucuronides were pooled and fitted to the mathematical model as shown in Figure 1. A weighting of the arithmetic means with their variances, when the subjects were averaged, was employed in the present study. Such a weighting yields the best results for the simultaneous fitting of plasma and urine data (Poland, 1982). The abbreviations used to describe the model are shown in the glossary of symbols.

ASA is rapidly absorbed following oral administration. During the absorption process, the drug is subject to first-pass hydrolysis by esterases in the intestinal wall (Harris & Riegelman, 1969; Rowland *et al.*, 1972; Spenney, 1978) and in the liver (Ali & Kaur, 1983). Only a fraction of the dose approximated to 60% (Rowland & Riegelman, 1967; Rowland *et al.*, 1972) is absorbed as intact ASA. In blood, ASA is rapidly hydrolysed to salicylate mainly by red blood cell aspirin esterase (Costello & Green, 1983). A small fraction of salicylic acid is excreted unchanged in the urine. The rest is metabolised 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 (Levy, 1979).

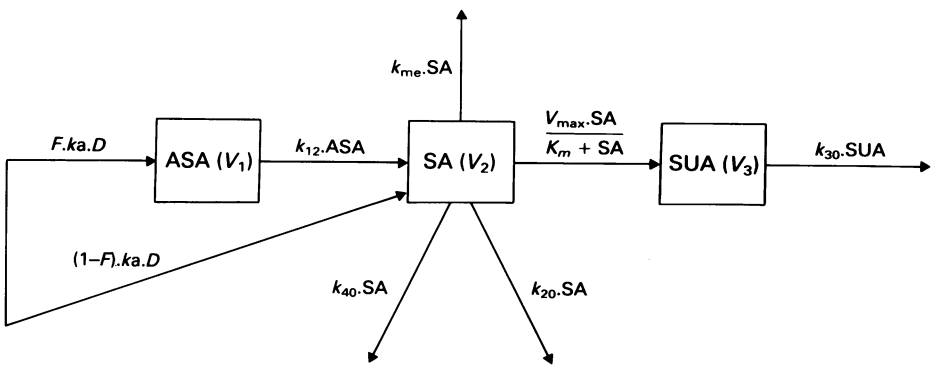

Figure 1 The mathematical model used to describe the plasma concentrations of ASA, salicylate and salicyluric acid, and the urinary excretion of salicylate, salicyluric acid and salicyl glucuronides. The abbreviations used to describe the model are shown in the glossary of symbols.

The formation pathways of salicyluric acid and salicyl phenolic glucuronide are saturable and follow Michaelis-Menten type kinetics (Levy *et al.*, 1969a, 1972). However, the Michaelis-Menten constant (K_M) of salicyl phenolic glucuronide estimated from the urinary excretion rate is double that of salicyluric acid (629 mg *vs* 338 mg) (Levy *et al.*, 1972). Therefore, after moderate doses of 600 mg of ASA as employed in this study, the maximum rate of formation of salicyluric acid is approached, but the formation of salicyl phenolic glucuronide can be incorporated in the model as a linear or first-order process. Since authentic compounds of the two glucuronides were not available to us, they were measured as a single compound after enzyme hydrolysis treatment and their elimination was treated as a single linear pathway.

The model dependent and independent pharmacokinetic parameters were tested statistically using a 2 × 2 factorial analysis of variance which considered the factor age (A) with 1 degree of freedom (df), the factor sex (S) (1 df), and the interaction of both (A × S) (1 df) in order to determine the influence of these factors. Comparison of individual patient group data was performed by Student's *t*-test.

Results

A comparison of the model independent pharmacokinetic parameters among the patient groups is shown in Table 2. The time to reach the peak plasma concentration of salicylate (t_{max}) was slightly faster in the elderly (male and female) groups ($P < 0.05$). Peak plasma concentrations (Cp max) and AUC of ASA and salicylate were found to be significantly higher in the females (young and elderly). The differences were still significant even after the AUCs were normalised to 70 kg for each patient. On the other hand, the AUC of salicyluric acid was significantly higher in the elderly (male and female) groups. When the urinary recoveries of metabolites were compared, that of salicylate was significantly higher in the young (male and female) groups, but no significant differences were found among the groups in the recoveries of salicyluric acid and salicyl glucuronides. However, when the urinary recoveries of salicyluric acid were compared by Student's *t*-test, a significantly greater amount of salicyluric acid was recovered from the urine of young males (YM) than from the other three patient groups (YF, OM, OF) ($P < 0.05$ in all cases). The renal clearances of salicylic and salicyluric acid were significantly lower in the elderly groups and correlated with the creatinine clearance of the patients ($r = 0.71$; $r = 0.86$ and $P < 0.001$ for both cases). No significant differences in the volume of distribution at steady state of salicylate (V_{ss}/kg) were found among the groups.

The computer curve fittings of ASA, salicylic and salicyluric acid plasma levels, and urinary cumulative recoveries of salicylic and salicyluric acid, and salicyl glucuronides are shown in Figure 2. Comparison of the model-dependent pharmacokinetic parameters are shown in Table 3. There was a strong age and sex effect on the maximal metabolizing activity (V_{max}) of salicyluric acid, and an age effect on the renal elimination rates of salicyluric acid and salicyl glucuronides ($k30$, $k40$). There were no significant differences in the volumes of distribution of ASA and salicylic acid among the different age and sex groups, but a slight age effect ($P < 0.05$) was noted for the volume of distribution of salicyluric acid. This was due to a high mean value in the young male patient group. The renal elimination rates of salicylic and salicyluric acid (k_{20}, k_{30}) were found to correlate with the creatinine clearance of the patients ($r = 0.61$, $r = 0.72$; $P < 0.003$, $P < 0.001$ respectively). A weak but still positive correlation was also found for the renal elimination of salicyl glucuronides ($k40$) and creatinine clearance ($r = 0.46$; $P < 0.05$). The volume of distribution of salicylate adjusted for body weight (V_2/kg) correlated with the plasma albumin levels of the patients (Figure 3). The parameters (volume of distribution of salicylate, renal clearance of salicylic and salicyluric acid) estimated by the noncompartmental method (Equations 3 and 4) were found to be comparable to those determined by the compartmental approach.

Discussion

The results of the present study confirm those of previous studies (Coppe *et al.*, 1981; Kelton *et al.*, 1981; Buchanan *et al.*, 1983) in that higher ASA and salicylate plasma concentrations were observed in the female subjects. The differences were still significant after the area under curves (AUC) were normalised to standard body weight. Kelton and coworkers (1981) proposed that higher plasma concentrations of both salicylate and ASA in females than in males were due to a difference in absorption of ASA. A more recent study (Miaskiewicz *et al.*, 1982) indicated that there were sex differences in the time required to attain the peak salicylate concentration after oral administration of sodium salicylate (9 mg/kg). However, in that study, t_{max} was shorter in males than in females ($P < 0.01$); an observation that suggests an oral dose of sodium salicylate would be absorbed from the gastro-

Table 2 Comparison of the model-independent pharmacokinetic parameters

Group code	C_p max (mg/l)		t_{max} (h)		AUC (mg l^{-1} h)			V_{ss} (l/kg)	Urinary recoveries in 24 h (mg)			Renal clearance (l/h)	
	ASA	SA	ASA	SA	ASA	SA	SUA	SA	SA	SUA	SG	SA	SUA
YM	6.17 (1.32)[a]	32.40 (2.23)	0.38 (0.21)	0.94 (0.33)	3.91 (0.88)	160.53 (53.26)	14.95 (5.27)	0.22 (0.069)	14.00 (9.71)	426.90 (34.42)	45.89 (14.00)	0.089 (0.057)	30.90 (8.79)
YF	11.40 (3.69)	40.25 (6.18)	0.31 (0.10)	0.93 (0.12)	8.88 (2.31)	235.42 (52.00)	16.12 (3.72)	0.18 (0.034)	17.57 (9.09)	321.85 (90.48)	26.93 (10.61)	0.088 (0.060)	21.08 (9.57)
OM	6.26 (2.78)	30.35 (8.57)	0.35 (0.10)	0.71 (0.19)	3.83 (2.27)	164.56 (64.11)	34.18 (8.96)	0.24 (0.066)	3.36 (3.75)	319.56 (99.62)	30.29 (10.70)	0.018 (0.018)	9.93 (4.20)
OF	12.25 (5.89)	43.80 (8.83)	0.29 (0.12)	0.72 (0.17)	6.79 (2.42)	339.32 (100.34)	64.40 (31.14)	0.24 (0.11)	6.06 (7.38)	299.29 (97.36)	40.40 (5.65)	0.020 (0.024)	6.19 (4.49)
Analysis of variance													
Source													
Age	NS	NS	NS	*	NS	NS	**	NS	**	NS	NS	**	**
Sex	**	**	NS	NS	**	**	*	NS	NS	NS	NS	NS	*
Age × Sex	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	*	NS	NS

YM Young-male, YF Young-female, OM Elderly-male, OF Elderly-female
*$P < 0.05$, **$P < 0.01$, NS not significant
[a]The number in parentheses is the value of the s.d.

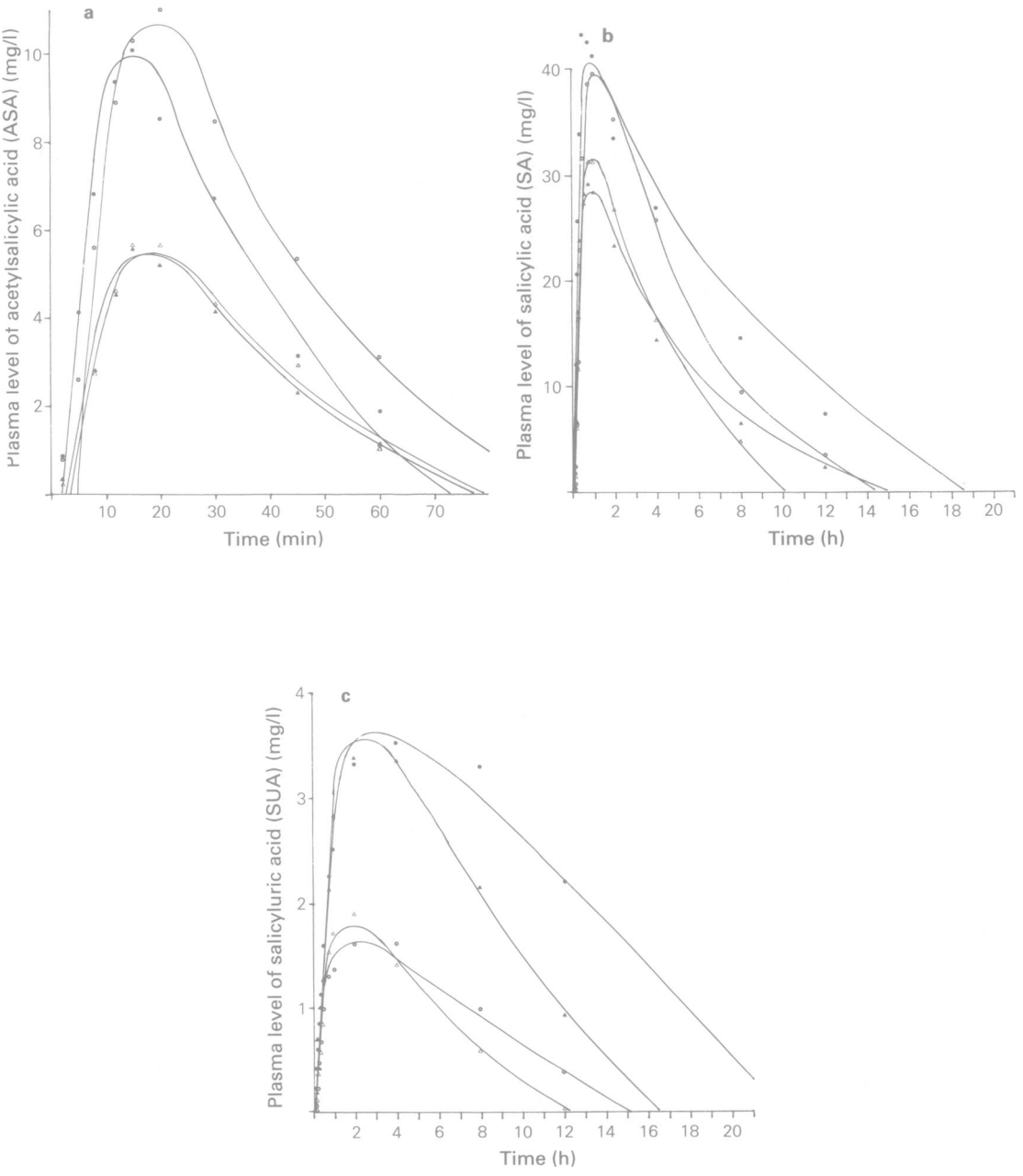

Figure 2 Plasma concentrations of (a) ASA, (b) salicylate and (c) salicyluric acid in young male (△), elderly male (▲), young female (○) and elderly female (●) patients. The symbols are the average values of the individual groups, whereas the curves are predictions from the computer fittings of the mathematical model.

Table 3 Comparison of the model-dependent pharmacokinetic parameters

Group code	ka (h^{-1})	k_{12} (h^{-1})	V_{max} (mg/h)	K_m (mg/l)	k_{20} (h^{-1})	k_{30} (h^{-1})	k_{40} (h^{-1})	k_{me} (h^{-1})	$V_{l/kg/F}$ (l/kg)	$V_{2/kg}$ (l/kg)	$V_{3/kg}$ (l/kg)
YM	5.95 (2.44)[a]	4.14 (2.99)	104.78 (26.52)	16.46 (0.037)	0.0070 (0.0042)	3.82 (1.36)	0.023 (0.0098)	0.073 (0.026)	0.71 (0.14)	0.21 (0.08)	0.15 (0.07)
YF	8.91 (8.31)	3.09 (1.20)	58.59 (21.49)	16.49 (0.016)	0.0071 (0.0040)	3.51 (0.99)	0.011 (0.0019)	0.079 (0.041)	0.47 (0.21)	0.19 (0.04)	0.11 (0.04)
OM	6.46 (2.29)	3.14 (1.91)	60.60 (24.80)	16.48 (0.023)	0.0011 (0.0010)	1.58 (0.67)	0.0081 (0.0025)	0.092 (0.057)	0.69 (0.32)	0.25 (0.08)	0.09 (0.03)
OF	4.75 (1.69)	4.29 (1.29)	36.48 (18.33)	16.50 (0.0086)	0.0081 (0.015)	1.59 (1.04)	0.0092 (0.0039)	0.048 (0.024)	0.60 (0.43)	0.26 (0.09)	0.089 (0.039)
Analysis of variance											
Source											
Age	NS	NS	**	NS	NS	**	**	NS	NS	NS	*
Sex	NS	NS	**	NS	NS	NS	*	NS	NS	NS	NS
Age × Sex	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS

YM Young-male, YF Young-female, OM Elderly-male, OF Elderly female
$^*P < 0.05$, $^{**}P < 0.01$, NS not significant
[a]The number in parentheses is the value of the s.d.

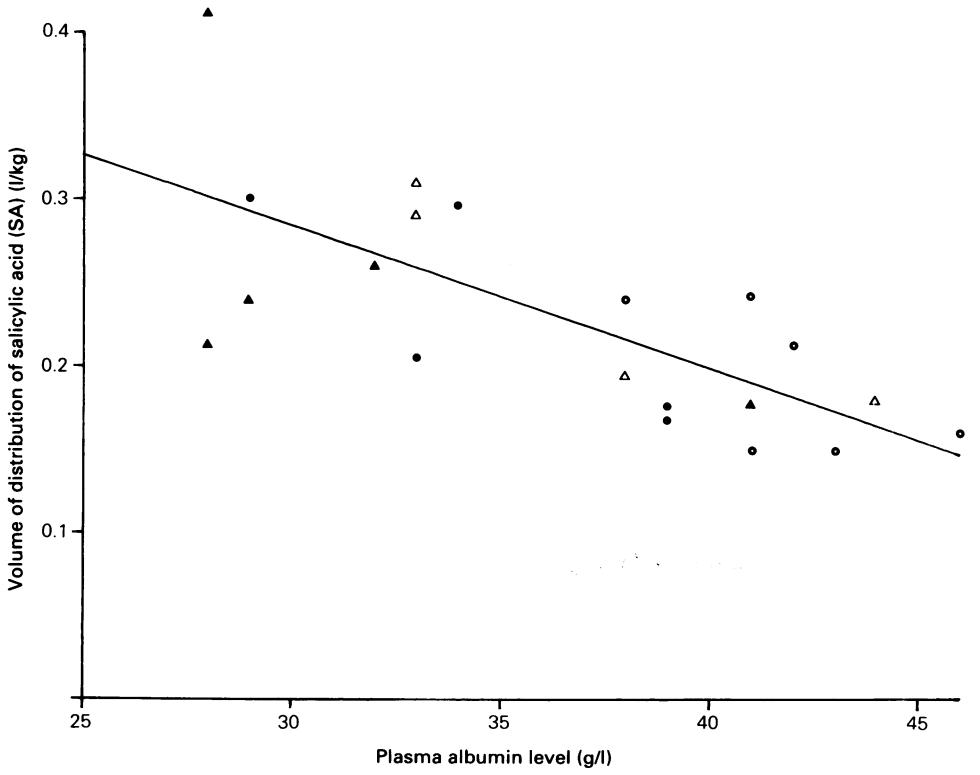

Figure 3 Correlation between the volume of distribution of salicylate and plasma albumin concentration of the patients (elderly male (▲), young female (○) and elderly female (●)) ($r = 0.72$, $P < 0.001$).

intestinal tract at a faster rate in males, the consequence of which would be expected to lead to higher plasma concentrations of salicylate in males than in females. In their study, no sex differences were found in the apparent volume of distribution, plasma salicylate clearance, maximum plasma salicylate concentration (C_{max}) or area under the plasma concentration-time curve. Such results are contrary to those found in this and other studies (Coppe *et al.*, 1981; Kelton *et al.*, 1981; Buchanan *et al.*, 1983). Miaskiewicz and coworkers (1982) administered sodium salicylate in their study, while ASA was given in our own and other studies. It is possible that salicylate derived from ASA differs in its disposition to that of administered salicylate, and that sex differences may emerge only after oral administration of aspirin. The higher ASA plasma concentrations in females are most likely due to an intrinsically lower concentration of aspirin esterase in female blood as suggested by Menguy *et al.* (1972) and Windorfer *et al.* (1974).

No age and sex effects were found to influence the volumes of distribution of ASA, salicylate and salicyluric acid (Tables 2 and 3). However, the volume of distribution of salicylate was found to increase with a decrease in plasma albumin levels (Figure 3). Such a phenomenon was also observed in Larking's study (1979). It is well known that plasma binding of salicylate in man is concentration-dependent (Ekstrand *et al.*, 1979; Borga *et al.*, 1975). Accordingly, its distribution is also expected to be concentration dependent (Rubin & Tozer, 1983), and the concentration of plasma albumin is known to be lower in the aged (Woodford-Williams *et al.*, 1964). Any difference in the volume of distribution of salicylate between young and old subjects will be greatest at higher doses, when the protein binding sites are saturated. Furst and coworkers (1979) have suggested that plasma salicylate concentrations were determined by the clearance of unbound drug and the extent of plasma protein binding. A low dose of 600 mg ASA was, therefore, chosen in the present study to minimize the variation due to differences in the extent of protein binding, and no attempt was made to control urinary pH since urine pH has a relatively small effect on the elimination kinetics of small single doses (Levy, 1979). Any intersubject variation of plasma salicylate concentrations would then be the consequence of variable clearance.

Age *per se* does not seem to have a prominent effect on the plasma concentrations of ASA and salicylate, which is consistent with the results of previous studies (Castleden *et al.*, 1977; Cuny *et al.*, 1979; Salem & Stevensen, 1977; Roberts *et al.*, 1983). On the other hand, salicyluric acid plasma concentrations appeared to be significantly higher in the elderly than in the young subjects, which is in good agreement with the results of Montgomery & Sitar (1981). Similar to the finding of a recent study (Gunsberg *et al.*, 1984), a correlation was found between the renal clearance of salicyluric acid and creatinine clearance. The higher plasma salicyluric acid level in the aged appears to be caused by a lower renal clearance of the compound in that population. A correlation was also found between the renal clearance of salicylic acid and creatinine clearance. However, the lower renal clearance of salicylate in the aged did not lead to higher plasma salicylate levels. This might be due to the small contribution of renal elimination of salicylate to the total elimination of salicylate at low doses.

The renal elimination rate constant (k_{30}) for salicyluric acid was larger than the total elimination rate constant of salicylate in all groups. The decrease in the renal elimination rate constant for salicyluric acid as observed during the ageing process (see Table 3) does not affect the computer calculated time course of salicyluric acid excretion (Levy *et al.*, 1972). Therefore, salicyluric acid excretion after ASA administration was presumed to be formation rate limited (Levy *et al.*, 1969 a,b). Salicyluric acid formation rates were determined from urinary excretion data as described by Levy and coworkers (1972) or derived from plasma concentration of salicyluric acid with the assumption of a constant elimination rate (Bochner *et al.*, 1981). However, Graham and coworkers (1977) have suggested that a small lag in the elimination of salicylurate would cause an overestimate of the calculated volume of distribution. It is therefore desirable as suggested by Levy and coworkers (1972) to computer fit all data simultaneously with appropriate weighting procedures. In the present study, plasma concentrations of aspirin, salicylic and salicyluric acid and cumulative urinary excretion of salicylic and salicyluric acid and salicyl glucuronides were appropriately weighted and simultaneously fitted to the mathematical model (Figure 1).

The parameters (V_2 of salicylate and renal clearance of salicylate and salicyluric acid) determined by the model-dependent approach were found to be comparable with those determined by the model-independent methods and serve to indicate the validity of the model.

Comparision of the model-dependent pharmacokinetic parameters in Table 3 showed the renal elimination rates of salicyluric acid and salicyl glucuronides to be lower in the elderly group, but only the elimination rates of salicylic and salicyluric acid were found to correlate with

creatinine clearance. Strong age and sex effects were found to influence the maximal metabolizing activity of salicyluric acid (V_{max}). Williams (1963) has suggested that glycine conjugation which leads to the formation of salicyluric acid is impaired in man by old age. Results in the present study indicate that females have an intrinsically lower metabolic activity than males and impairment of this activity progresses in both sex groups with age. Gupta and coworkers (1975) found that steady-state serum salicylate concentrations were determined by the apparent rate of salicylurate formation. The age and sex influences on the formation of salicyluric acid might give rise to an explanation for the large inter-individual differences in glycine conjugation of salicylate found in Caldwell *et al.* (1980) study. The present results further confirm the finding of a previous study on animals that higher salicylate concentrations in females is due to an intrinsically lower formation rate of salicyluric acid in this gender (Sechserova *et al.*, 1975). However, it is still not known whether our findings with respect to the effect of age and sex on the disposition of aspirin can be extrapolated to the multiple or chronic dosing situation. If this is the case, then the results in this study may help to explain the clinical observations that toxic salicylate levels are reached at lower dosage in the elderly (Hunt, 1976), and hypersensitivity to aspirin is found mostly in females (Ali Abrishami & Thomas, 1977; Samter & Beers, 1968).

Glossary of symbols

Abbreviations used to describe the model

ASA	acetylsalicylic acid
SA	salicylate
SUA	salicyluric acid
D	dose
F	fraction of dose absorbed as intact ASA
k_a	absorption rate of ASA
k_{12}	decomposition rate of ASA to salicylate
k_{20}	renal elimination rate of salicylate
k_{30}	renal elimination rate of salicyluric acid
k_{40}	renal elimination rate of salicyl glucuronides
k_{me}	renal elimination rate of miscellaneous metabolites
V_{max}	Maximal velocity of conversion of SA to SUA
K_m	Michaelis-Menten constant (the concentration of SA in plasma at which the rate of conversion of SA to SUA is half saturated)
V_1	volume of distribution of ASA
V_2	volume of distribution of SA
V_3	volume of distribution of SUA

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