Value of monitoring plasma salicylate levels in treating juvenile rheumatoid arthritis

Observations in 42 cases

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SUMMARY Plasma salicylate concentration was monitored in 42 children on long-term salicylate therapy for rheumatoid arthritis. A given dose of salicylate per kg resulted in large variations in plasma levels, both between individuals and for a single individual at different times. The factors responsible for such variations were studied; in 6 cases urinary metabolites of salicylate were analysed. The relation between salicylate dosage and plasma half-life accounts for the fact that small changes in dosage can result in large changes in plasma concentration. The addition of corticosteroid or ACTH therapy results in lower plasma levels of salicylate, and necessitates higher dosage of salicylate. After the introduction of routine monitoring of plasma salicylate, the incidence of toxic symptoms fell sharply.

Salicylates are prescribed on a long-term basis in clinical paediatrics, particularly in juvenile rheumatoid arthritis (JRA), but dosage is often incorrect, either so high as to give rise to intoxication, or so low as to be ineffective (Done, 1960; Tschetter, 1963; Pierce, 1974; Buchanan and Rabinowitz, 1974). Individual dosage adjustment for each patient is necessary, firstly because of the narrow margin between therapeutic and toxic plasma levels of salicylate (Brewer, 1970; Calabro, 1970; Mäkelä *et al.*, 1975), and secondly because of the very variable plasma levels which may result from a given dosage, both between patients and even for the same individual (Ansell, 1963; Brewer, 1970). In this paper we wish to show the advantages which may result from systematic monitoring of plasma salicylate levels in children under treatment for rheumatoid arthritis.

Subjects and methods

Forty-two children were observed between 1974 and 1976. The main clinical details are given in Table 1. The total daily dose of salicylate (Table 1) was administered in three divided doses after a meal

over a period of 15 hours, the night hours being excluded. The dose varied widely because the different subtypes of JRA required different dosage of salicylate (e.g. anti-inflammatory effect for acute onset JRA, analgesic effect for poly- or monoarticular JRA).

Table 1 Details of 42 cases of juvenile rheumatoid arthritis treated with salicylates

Clinical form	No. of cases	Sex		Average age (and range) (years)	Drug*		
		F	M		Acetyl-salicylic acid	Sodium salicylate	Micro-encapsulated acetyl salicylic acid
Acute onset	33	15	18	8 (3-13.9)	20	7	6
Polyarticular onset	6	6	—	8 (2.3-14.7)	4		2
Monoarticular onset	3	2	1	3 (1.3-4.5)	3		

*During the period of observation, therapy varied in 7 cases, in 2 cases being changed from acetylsalicylic acid to sodium salicylate; in 2 from acetylsalicylic acid to microencapsulated acetylsalicylic acid; in 1 case from microencapsulated acetylsalicylic acid to acetylsalicylic acid; and in 2 cases from microencapsulated acetylsalicylic acid to sodium salicylate. Dose/kg for each patient is shown in Fig. 1.

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For measurement of plasma salicylate, blood was taken at least 6 days after the beginning of therapy (i.e. after a steady state was reached), 2½–3 hours after the first dose of the day, and thereafter at intervals of 50 ± 25 days (measurements during hospitalisation were often made more frequently). Salicyluric acid, free salicylate, and total metabolites were also estimated in the urine of some of the children. Blood and urinary salicylates were measured by the method described by Shachter and Manis (1958).

Results and discussion

Variation in plasma salicylate levels. Fig. 1a and b shows the plasma salicylate levels related to the dose per kg of salicylate drug; three different preparations of salicylate were used. The results may be interpreted as follows.

(a) *Equivalent doses can give very different plasma levels.* For example, in 14 children taking sodium salicylate as outpatients, a daily dose between 99

Fig. 1 Interindividual variability of (a) outpatients; (b) inpatients. Conversion; Traditional units to SI—Salicylate: $1 \text{ mg}/100 \text{ ml} \approx 0.0724 \text{ mmol/l}$.

and 106 mg/kg (mean 101.2 ± 2.6) yielded plasma salicylate concentrations ranging from 15.6 to $30.6 \text{ mg}/100 \text{ ml}$ (1.1 – 2.2 mmol/l) (mean 22.4 ± 5.1 ; $1.6 \pm 0.37 \text{ mmol/l}$). In 11 cases, a daily dose of acetylsalicylic acid (ASA) between 78 and 83.7 mg/kg (mean 80.1 ± 2), gave plasma salicylate levels varying from 6 to $24 \text{ mg}/100 \text{ ml}$ (0.4 – 1.74 mmol/l) (mean 14.6 ± 5.2 ; $1.1 \pm 0.38 \text{ mmol/l}$). (For the microencapsulated form of ASA mean values were not derived since the few cases treated received widely differing doses.)

The same variability was found in inpatients where the prescribed drug was reliably given; for example 9 cases on a daily dose of ASA between 78 and 88 mg/kg (mean 82.6 ± 4) had plasma salicylate concentrations ranging from 7.9 to $24 \text{ mg}/100 \text{ ml}$ (0.6 – 1.7 mmol/l) (mean 17.4 ± 5.1 ; $1.26 \pm 0.37 \text{ mmol}$). In addition to the inter-individual variation, different salicylate levels are obtained in an individual patient on a uniform dose of drug (Fig. 2).

(b) *The problem of drug plasma level and various commercial salicylate preparations.* Although sodium salicylate seemed to give higher concentrations and microencapsulated ASA lower plasma levels than ASA, these differences were not statistically significant. Thus, when the mean values of the correlations between plasma peak concentrations and dose per kg are compared (i.e. 0.193 ± 0.0096 for ASA in 58

Fig. 2 Intraindividual variability.

cases, 0.202 ± 0.024 for sodium salicylate in 20 cases, and 0.1657 ± 0.0228 for microencapsulated ASA in 14 cases), Duncan test for groups of different number subjects (Kramer, 1956) is not significant (Duncan contrast = 2.104 ; $r = 3$; $df = 89$).

(c) *Corticosteroid therapy lowers plasma salicylate levels.* This observation confirms a previous report by Klinenberg and Miller (1965). ACTH probably has the same effect. This is shown in Fig. 3, where plasma concentrations are shown for a child whose severe symptoms necessitated combined ACTH-salicylate therapy initially. Symptoms failed to improve, and prednisone was later prescribed. Both ACTH and prednisone (dose >15 mg/day) lowered plasma salicylate concentrations.

Incidence of toxic effects and monitoring. Table 2 shows comparative data on the incidence and type of toxic effects observed in both the inpatient and outpatient children during 2-year periods, before and after monitoring became routine. During this 4-year period the quality of clinical care did not change, but the number of intoxications decreased, while the only episode encountered during the second period was very mild. In Case 3 (Table 2) clinical symptoms of toxicity were not accompanied by abnormally raised plasma salicylate levels; hypoalbuminaemia is known to occur frequently in children with polyarthritis (Brewer, 1970), a fact which could be relevant in such cases.

Importance of patient compliance in interindividual variability of plasma concentration. In outpatient

children, no correlation could be found between the per kg dose of salicylate and plasma levels (Fig. 1), but when data from inpatients only were considered, a significant correlation was found both for basal levels (not measured in outpatients) and for peak levels (Table 3). So in outpatients, besides inter-individual variability, an important factor may well be whether the child actually takes the dosage prescribed.

Table 2 Effect of routine monitoring of plasma salicylate levels on incidence of toxic signs

Age (years)	Salicylate dose (mg/kg per d)	Plasma salicylate (mg/100 ml)†	Signs and symptoms
(1) 1972-74, Plasma salicylate monitoring seldom done, $n = 38$; average salicylate dose*: 86.6 ± 15 mg/kg per day			
Case 1 5.7	100	28	Hyperpnoea, coma; hepatomegaly, retinal haemorrhage
„ 6	70	44	Hyperpnoea; high temperature; delirium
Case 2 4.5	100	30	Hyperpnoea; skin vasodilation; rhinorrhagia
Case 3 5	100	20	Hyperpnoea
Case 4 3.9	100	35	Hyperpnoea; vomiting; itching
Case 5 10.2	100	38	Agranulocytosis
(2) 1974-76, Plasma salicylate monitoring routinely done, $n = 42$; average salicylate dose: 85.8 ± 16.8 mg/kg per day			
Case 6 3	100	36	Hyperpnoea

*Maximum doses for each patient were considered.

†See legend to Fig. 1 for conversion factor into SI units.

Fig. 3 Effect of steroids and ACTH on plasma salicylate concentration in a case treated with combined therapy.

Table 3 Correlation for basal and peak levels of plasma salicylate in 11 cases

Case no.	Daily dose (mg/kg)	Basal level* (mg/100 ml)	Peak level† (mg/100 ml)
7	48	2.2	5
8	56.3	—	12.6†
9	67.5	7.2	14.8
10	73.5	—	21.2
11	75.7	15.6	19.3
12	78.4	13.4	18.4
13	80.0	15.7	16.4
14	83.7	—	16.0
15	88.8	16.85	17.6
16	90.9	16.5	28.3
17	93.7	13	17.0
8	93.8	—	32*
8	112.6	26	29†

* $r^2 = 85.4\%$, $P < 0.01$.† $r^2 = 47.6\%$, $P < 0.01$.

All patients were treated only with acetylsalicylic acid except Case 8 who received sodium salicylate or microencapsulated acetylsalicylic acid.

Some kinetic aspects of salicylate therapy in clinical conditions studied.

(a) *Apparent plasma half-life and dose administered* (Fig. 4). Using a graphic method, we calculated the plasma half-life of salicylates in 10 cases. Blood samples were taken at 3.7 and 12 hours (7 cases) or at 2.4 and 7 hours (3 cases) after salicylate administration (dose, 48–108 mg/kg per day). We found a significant correlation between salicylate dose and half-life which is typical of saturation kinetics (Levy, and Yaffe, 1974; Levy, 1968; Levy *et al.*, 1972). This helps to explain the great variation in plasma salicylate levels between individuals in so far as relatively small differences in dose can cause large variations in

Fig. 4 Correlation between salicylate dose and plasma half-life.

apparent half-life and hence in plasma salicylate concentrations (Paulus *et al.*, 1971; Levy and Tsuchiya, 1972). From the practical point of view it is therefore difficult to calculate beforehand the alterations in dose necessary to lower or raise salicylate levels to a desired extent. An empirical approach should therefore be adopted, changing the dose gradually while plasma salicylate concentrations are repeatedly monitored.

(b) *Urinary excretion of salicylates and their metabolites*. When the dose per kg is increased the percentage of the total metabolites excreted as salicyluric acid falls, while that excreted as free salicylate increases (Fig. 5). This could be caused by variations in urinary pH (MacPherson *et al.*, 1955), although in our cases the pH of the urine only ranged between 5 and 6. We interpret our results, obtained on the 24-hour urines of 7 children, as confirming the limited capacity of the liver to conjugate salicylate with glycine, which is likely to be the first process to be saturated (Levy, 1968; Levy *et al.*, 1972; Gibson *et al.*, 1975).

In Fig. 6 plasma salicylate level is related to the urinary excretion (as percentage of the administered dose) of free salicylate, and of total metabolites in 11 patients. There is a clear correlation between plasma salicylate concentration and the urinary excretion of free salicylate, but not of salicyluric acid or total metabolites. These observations agree with those of

Fig. 5 Percentage of the administered dose excreted as salicylate.

Fig. 6 Concentration of blood salicylate at $2\frac{1}{2}$ –3 hours and percentage of the administered dose excreted. Influence of corticosteroids.

Gibson *et al.* (1975). Simultaneous administration of steroids increases the urinary excretion of free salicylate, salicylic acid, and total metabolites, expressed as a percentage of excretion related to the salicylate dose (Fig. 5) or to plasma salicylate level (Fig. 6).

Conclusions

To determine the optimal salicylate dosage in children with rheumatoid arthritis, we consider that the dose should be varied on the basis of the measurements of plasma salicylate levels as well as on the clinical effects. Systematic monitoring of plasma salicylate concentrations may not, however, completely avoid the danger of intoxication because of individual sensitivity to the drug, so that regular clinical checks must be made to detect mild clinical signs of toxicity (such as hyperpnoea).

The relation between salicylate dosage and half-life, typical of saturation kinetics, must also be taken into account when changing the drug dose: small changes of dose can produce large changes in plasma salicylate level. Finally, when corticosteroid or ACTH therapy is used in conjunction with salicylates larger doses of salicylates will be required to attain a satisfactory plasma level.

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