PAPERS AND SHORT REPORTS

Diuresis or urinary alkalinisation for salicylate poisoning?

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Abstract

Forty-four adults with aspirin poisoning were treated with oral fluids only, standard forced alkaline diuresis, forced diuresis alone, or sodium bicarbonate (alkali) alone. Alkali alone was at least as effective and possibly more effective than forced alkaline diuresis in enhancing salicylate removal. Unlike the diuresis regimens it did not cause fluid retention or biochemical disturbances. The renal excretion of salicylate depends much more on urine pH than flow rate, and forced diuresis alone had little useful effect.

In overdosage aspirin causes sodium and fluid retention and may impair renal function. Attempts to force a diuresis are potentially hazardous and the spurious fall in plasma salicylate concentration caused by haemodilution gives a false impression of efficacy. Further studies are required to determine the optimum treatment for salicylate poisoning.

Introduction

Acute salicylate poisoning is a common medical emergency which still carries a high mortality.[1-3] Treatment is directed at correcting dehydration and metabolic disturbances, while the use of forced alkaline diuresis to enhance salicylate elimination is well established. Forced alkaline diuresis appears effective as judged by the initial fall in plasma salicylate concentrations[4-6] but the recovery of salicylate from urine is disappointing and less than expected. Also the procedure is not without risk. Salicylate intoxication may be complicated by renal failure[1-3 7 8]; pulmonary and cerebral oedema may occur in patients given large volumes of fluid[1 2 8-15]; and biochemical abnormalities are common. All of these problems may be related to the fluid retention and impaired renal function produced by aspirin and other anti-inflammatory analgesics which inhibit prostaglandin synthesis.[16-19]

That renal excretion of salicylate is highly dependent on pH is well documented,[4-6] but such evidence as is available suggests that diuresis alone has relatively little effect.[6 20 21] The unnecessary administration of large amounts of fluid is clearly undesirable, yet the major emphasis in treatment has been placed on diuresis and the effect of alkalinisation of the urine alone on the removal of salicylate does not seem to have been studied in poisoned patients. We have been concerned at the extent of fluid retention after forced alkaline diuresis and have therefore investigated further the effects of diuresis and urinary alkalinisation in patients with aspirin poisoning.

Patients and methods

Forty-four otherwise healthy patients aged 16-65 years with uncomplicated aspirin overdosage were allocated to one of four treatment groups according to the severity of intoxication. Sixteen patients with mild salicylism (plasma salicylate concentrations 250-400 mg/l) served as controls and received oral fluids only. Of the others, 16 received standard forced alkaline diuresis,[6] six forced diuresis without sodium bicarbonate, and six sodium bicarbonate (alkali) alone without diuresis. The study was not intended as a clinical trial, and the numbers of patients in the forced-diuresis and alkali-alone groups were restricted because the safety and efficacy of such treatments had not been established. For similar ethical reasons patients with plasma salicylate concentrations above 700 mg/l were excluded.

Table I summarises the clinical details. Except for one patient who had also taken paracetamol, none had evidence of ingestion of appreciable amounts of other drugs or alcohol. All patients were conscious and recovered uneventfully.

Gastric lavage was performed on patients admitted within 12 hours after taking the aspirin. The regimens of forced alkaline diuresis, forced diuresis, and alkali alone included potassium chloride supplements and were given intravenously over three to four hours. Table I shows the different treatments and the total fluid intakes in each group. Treatment was begun within 30 to 60 minutes after admission, and the start of infusion was taken as zero time.

Investigations—Packed cell volume and plasma concentrations of

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TABLE I—*Clinical details and treatment regimens (mean values ± SD)*

Treatment	Age (years)	Weight (kg)	Ingestion-admission interval (hours)	Admission plasma salicylic acid concentration (mg/l)	Intravenous infusion				Total fluid intake in 16 hours (l)
					Fluid (l)	Bicarbonate (mmol)	Sodium (mmol)	Potassium (mmol)	
Control (n = 16)	29 ± 12	63 ± 14	6·8 ± 5·1	328 ± 57	Oral fluids only				2·72 ± 0·87
Forced alkaline diuresis (n = 16)	29 ± 11	59 ± 10	8·2 ± 5·5	467 ± 102*	6†	225	450	120	8·43 ± 0·92*
Forced diuresis (n = 6)	29 ± 15	64 ± 11	4·3 ± 2·5	463 ± 84*	6†	0	225	120	8·66 ± 0·74*
Alkali alone (n = 6)	27 ± 8	60 ± 6	3·6 ± 3·8	439 ± 86*	1·5	225	225	60	3·90 ± 1·03*‡

*Significantly different from control ($p < 0·05$).
†Containing 150 g dextrose.
‡Significantly different from forced alkaline diuresis ($p < 0·05$).
Conversion: SI to traditional units—Bicarbonate, sodium, and potassium: 1 mmol = 1 mEq.

TABLE II—*Plasma half life and urinary recovery of salicylic acid (mean values ± SD)*

Treatment	Plasma half life (hours)		Urinary recovery (g)	
	Zero time to 4 h	4 h to 16 h	Zero time to 4 h	Zero time to 16 h
Control	19·4 ± 12·2	29·4 ± 7·6	0·16 ± 0·14	0·38 ± 0·32
Forced alkaline diuresis	5·9 ± 4·4*	12·3 ± 9·1*	1·55 ± 0·87*	3·60 ± 0·94*
Forced diuresis	8·0 ± 3·4*	38·6 ± 14·5†	0·44 ± 0·49*†	1·53 ± 1·27*†
Alkali alone	5·0 ± 1·6*	9·0 ± 6·1*	2·44 ± 1·59*	3·87 ± 1·28*

*Significantly different from control ($p < 0·05$).
†Significantly different from forced alkaline diuresis ($p < 0·05$).

TABLE III—*Observed and expected urinary recovery and fall in plasma salicylate concentrations from zero time to four hours in relation to fluid retention (values are means)*

	Urinary recovery (g)*		% Fall in plasma salicylate		Fluid balance at end of infusion (l)
	Observed	Expected	Observed	Expected	
Control	0·33	0·35	13	12	+0·43
Forced alkaline diuresis	1·85	3·64	41	21	+3·57
Forced diuresis	0·60	1·89	30	10	+4·62
Alkali alone	2·67	2·67	39	39	+0·43

*Salicylic plus salicyluric acid.

electrolytes, calcium, phosphate, albumin, urea, and creatinine were estimated at zero time and at four and 16 hours in six patients in each group. Urine pH and sodium, potassium, and creatinine concentrations were also measured and the fluid balance and weight changes recorded. Salicylic and salicyluric acids in serial plasma and spontaneously voided urine samples were estimated by high-performance liquid chromatography.[22] This specific method gives considerably lower values for both plasma and urine salicylate than the simple colorimetric assays in general use. Total (free plus conjugated) salicylic and salicyluric acid concentrations in urine were determined similarly after hydrolysis with β-glucuronidase. The term "salicylate," often used very loosely, is restricted here to salicylic acid only.

Pharmacokinetic and statistical analysis—Renal clearance was determined by dividing the amount of drug or metabolite excreted in the urine by the corresponding area under the plasma concentration time curve, and the apparent volume of salicylate distribution was calculated from the plasma half life and total body clearance.[23] Results are expressed as means ± SD, and comparisons were made using Student's *t* test. Multiple regression analysis[24] was used to evaluate the independent effects of urine flow rate and pH on salicylate elimination.

Results

The three treatment groups consisted of equal numbers of men and women and were comparable in respect of age, weight, ingestion-treatment interval, and initial plasma salicylate concentrations. The control group comprised five men and 11 women with lower plasma salicylate concentrations on admission (table I).

Plasma salicylate—All three treatment groups showed a rapid fall in plasma salicylate concentrations during the infusion, initial half-life values ranging from 5·0 hours with alkali alone to 8·0 hours with forced diuresis. The corresponding value in the control group was 19·4 hours (table II). Once the infusions were stopped there was a pronounced decrease in the rate of fall in plasma salicylate concentrations and major differences between the groups became apparent (fig 1). From four to 16 hours the mean plasma salicylate half life was 9·0 hours with alkali alone, 12·3 hours with forced alkaline diuresis, 38·6 hours with forced diuresis, and 29·4 hours in the control group (table II). Over the same period there was a highly significant negative correlation between the log plasma salicylate half life and mean urine pH ($r = -0·84$; $p < 0·001$). In contrast there was no correlation whatsoever between salicylate half life and urine flow ($r = +0·03$) (fig 2).

Urinary recovery of salicylate—Over the period zero time to four hours the urinary recovery of unchanged salicylate was greatest with alkali alone (2·44 g), intermediate with forced alkaline diuresis (1·55 g), and least in the forced diuresis (0·44 g) and control groups (0·16 g). Over the whole 16-hour period the rank order of recovery was the same (table II). The mean salicylate recovery in the patients given alkali alone and forced alkaline diuresis did not differ significantly, but in both groups the amounts recovered were significantly greater than in the forced diuresis and control groups. The results were similar when the data were normalised for differences in the initial plasma salicylate concentrations. The mean urinary recovery of salicyluric acid was similar in all groups (1·12-1·24 g in 16 hours).

Fluid retention and weight gain—There was a significant positive fluid balance at four hours with a corresponding gain in weight in the patients given forced diuresis and forced alkaline diuresis but not in those given alkali alone or the controls (table III). At 16 hours there was still fluid retention in the first two groups, with mean fluid balances of +3·3 and +4·0 l respectively.

Discrepancy between fall in plasma salicylate values and urinary recovery—Though plasma salicylate concentrations fell impressively during the infusion in all treatment groups (fig 1), this fall was not always matched by a corresponding increase in urinary salicylate excretion. The expected urinary recovery corresponding to the observed fall in plasma salicylate concentration and the expected fall in plasma salicylate concentration corresponding to the observed

urinary recovery were calculated from the volume of distribution, the fall in plasma salicylate concentration, and the urinary recovery of salicylic plus salicyluric acids in each group. With the diuresis regimens there were major discrepancies, which were related to fluid retention. The greatest discrepancy occurred with forced diuresis, where there was a threefold difference between observed and expected values, while agreement was virtually complete in the alkali-alone and control groups (table III). These findings indicate that haemodilution made a large contribution to the initial rapid fall in plasma salicylate concentration during forced diuresis and forced alkaline diuresis.

Effects of urine pH and flow rate on renal salicylate clearance—Table IV shows the mean values for urine pH and flow rate over the first 16 hours. The urine pH exceeded 7·0 in all patients receiving regimens containing sodium bicarbonate and was highest in those given alkali alone (mean pH 8·1). Analysis of the combined data from all groups showed a highly significant correlation between log salicylate clearance and urine pH ($r = +0{\cdot}82$; $p < 0{\cdot}001$; $n = 311$). This relation was reflected in the mean salicylate clearance, which ranged from 1·4 ml/min at pH 6·1 over the first 16 hours in the controls to 23·5 ml/min at pH 8·1 in the alkali-alone group. In contrast, changes in urine flow rate had a variable and much smaller effect on salicylate clearance, particularly at high pH. Multiple regression analysis showed highly significant correlations between log salicylate clearance and both urine pH and log flow rate, correlation coefficients ranging from 0·62 to 0·81 ($p < 0{\cdot}001$). The regression coefficients and constants were similar in all groups (including the controls), and the equations confirmed that pH had a much greater effect on salicylate clearance than flow.

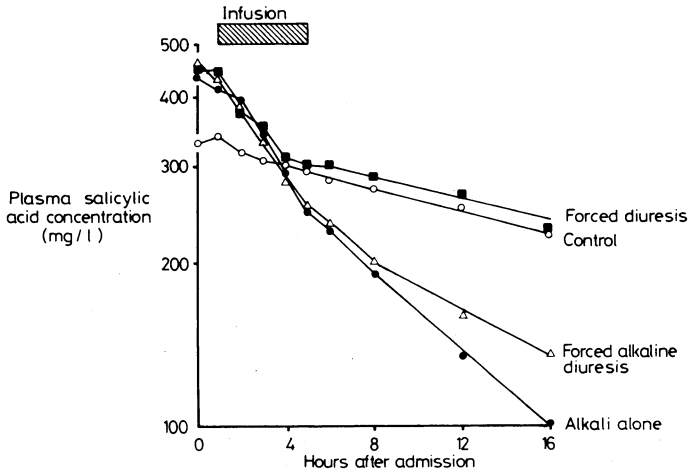

FIG 1—Mean plasma concentrations of salicylic acid in patients with aspirin overdosage receiving different treatment regimens of fluid and alkali.

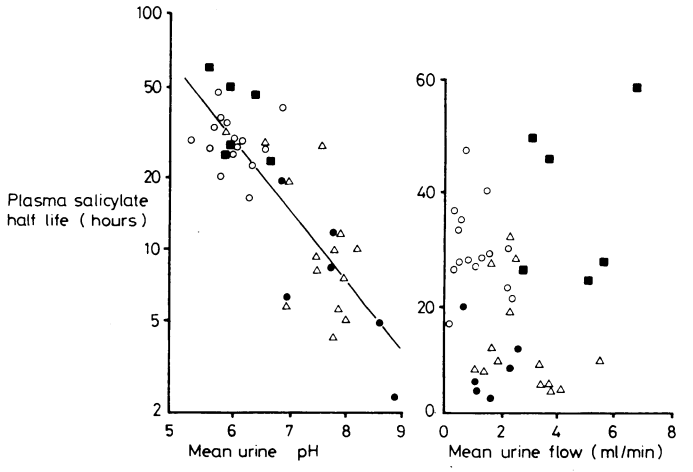

FIG 2—Correlation between log plasma salicylate half life and urine pH from four to 16 hours and lack of correlation between salicylate half life and urine flow over same period.
○ Control. △ Forced alkaline diuresis. ■ Forced diuresis. ● Alkali alone.

TABLE IV—*Urine pH, flow rate, and renal clearance of salicylic acid over the period zero time to 16 hours (mean values ± SD)*

Treatment	Urine pH	Urine flow rate (ml/min)	Renal salicylate clearance (ml/min)
Control	6·1 ± 0·4	1·4 ± 0·8	1·4 ± 1·4
Forced alkaline diuresis	7·3 ± 0·4*	5·1 ± 1·2*	17·5 ± 10·1*
Forced diuresis	6·5 ± 0·3	5·8 ± 1·9*	4·4 ± 1·8*†
Alkali alone	8·1 ± 0·5*†	2·6 ± 0·7*†	23·5 ± 13·7*

*Significantly different from control ($p < 0{\cdot}05$).
†Significantly different from forced alkaline diuresis ($p < 0{\cdot}05$).

Biochemical and haematological changes—In all groups the mean packed cell volume and plasma concentrations of sodium, potassium, calcium, phosphate, and albumin usually decreased during the period of infusion. The changes were minor in the control and alkali-alone groups and most pronounced (and usually statistically significant) during forced diuresis and forced alkaline diuresis. Hyponatraemia and hypokalaemia occurred in 42% and 58% of patients in the second two groups but in none in those treated with alkali alone. The mean creatinine clearance measured in six patients in each group was 91 ± 34 ml/min. In nine patients the creatinine clearance was less than 80 ml/min, and the lowest value was only 18 ml/min in a previously healthy 24-year-old woman. Over the first 24 hours there was a positive sodium balance in the patients given forced diuresis and forced alkaline diuresis. The potassium balance was negative in all treatment groups.

Discussion

Sodium bicarbonate alone was at least as effective and possibly more effective than standard forced alkaline diuresis in enhancing the elimination of salicylate, and unlike the diuresis regimens it did not cause fluid retention or noticeable biochemical abnormalities. Forced diuresis without alkali had very little useful effect, and after treatment there was no correlation at all between urine flow rate and plasma salicylate half life.

Assessing the value of treatment in acutely poisoned patients is never simple. Our different groups were reasonably well matched in most respects, but the controls were only mildly intoxicated; hence comparisons with moderate to severely poisoned patients may not be valid. Furthermore, we excluded patients with plasma salicylate concentrations above 700 mg/l (equivalent to as much as 900 mg/l with the standard colorimetric assay), and our findings cannot necessarily be extrapolated to more severe intoxication. Salicylate absorption after overdosage is often slow and may occasionally continue despite thorough gastric lavage. The intervals between ingestion and treatment varied, and comparisons of half life might be misleading if absorption had been delayed more in some groups than in others. This would not, however, have influenced the renal clearance of salicylate, and the changes in plasma concentrations were entirely consistent with the rates of renal excretion and the increase in the volume of distribution resulting from haemodilution.

Fluid retention is a common problem with forced alkaline diuresis for aspirin poisoning, and deficits of 5 or even 10 l have been recorded.[4 6 13 21 25] This has invariably been attributed to dehydration, though such losses have never been substantiated and are inconceivable except perhaps in the most severe and prolonged intoxications. That aspirin in overdosage should cause sodium and water retention is not surprising, since non-steroidal anti-inflammatory analgesics are potentially nephrotoxic and reduce renal blood flow, impair sodium and water excretion, and antagonise the action of diuretics.[16–19] These effects may be related to inhibition of renal prostaglandin synthesis. Renal function may be impaired in salicylate intoxication,[1–3 7 8] and the creatinine clearance was surprisingly low in some of our patients.

The acute volume expansion produced by attempts to force

a diuresis in such cases is potentially hazardous. Though it is usually tolerated by healthy young adults, water intoxication[9 11] and cerebral[2 8-11] and pulmonary[1 2 12-15] oedema have been associated with vigorous fluid treatment for salicylate intoxication, and deaths have occurred. Dehydration must be corrected, but excess sodium and fluid should clearly be avoided.

The primary object of forced alkaline diuresis is to enhance the removal of salicylate by renal excretion. Nevertheless, efficacy has usually been assessed by the initial decrease in plasma salicylate half life rather than by the amount actually recovered in the urine. Furthermore, recovery has often been inflated by the general use of non-specific analytical methods. The plasma salicylate half life during infusion clearly cannot be used as an index of drug removal with regimens including diuresis. Salicylate has a small, largely extracellular volume of distribution which would be considerably increased by the volume expansion associated with fluid retention. Haemodilution was undoubtedly responsible for the greater initial fall in plasma salicylate concentrations than could be accounted for by the corresponding urinary recovery in the patients treated by diuresis. The discrepancies were related to fluid retention, and the rate of salicylate removal based on plasma half life was grossly overestimated with the diuresis regimens. It might be thought that the problems of fluid and sodium retention could be overcome by using diuretics. We, however, find that although intravenous frusemide (80 mg) reduces the extent of fluid retention, it decreases rather than increases the elimination of salicylate.

In low therapeutic doses salicylate is rapidly eliminated, primarily by conjugation with glycine to form salicyluric acid, which is then promptly excreted by the kidney.[26] After overdosage this pathway is completely saturated, and the maximum rate of removal of salicylate by this route in our patients was only 50 to 60 mg an hour. Renal excretion is an alternative route of elimination, which can be greatly enhanced by making the urine alkaline. Although the correlations between urine flow rate and renal salicylate clearance were statistically significant, the magnitude of the effect was small compared with that produced by changes in pH. This is because the salicylate clearance varies in direct proportion to flow rate, whereas the relation with pH is logarithmic. The influence of pH increased dramatically above pH 7·0, where it completely dominated the elimination kinetics of salicylate. Alkali alone was more effective than forced alkaline diuresis with the same amount of sodium bicarbonate simply because it produced a higher urine pH. The amount of bicarbonate required to produce a strongly alkaline urine in patients with salicylate poisoning varies considerably and the urine may remain acid even in the presence of alkalaemia. Administering 225 mmol (225 mEq) bicarbonate over three hours is unlikely to cause problems in an adult and is usually effective but arterial blood gas analysis should be carried out if larger doses are needed.

Whether or not the relief of symptoms and biochemical improvement are more closely related to reduction in plasma salicylate concentrations or removal of the drug from the body remains an open question. Salicylate can be removed effectively and safely simply by administering sodium bicarbonate, and further studies are required to determine the optimum treatment for salicylate poisoning.

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MEDICINES APPROPRIATED TO THE EYES—Take such medicines as are appropriated to the eyes under the name of (*Ocular Medicines*) I do it partly to avoid multiplicity of words, and partly to instruct my countrymen in the terms of art belonging to physic, (I would have called them [*Ophthalmics*] had not the word been troublesome to the reading, much more to the understanding of a countryman) as I even now called such medicines [*Cephalics*] as were appropriated to the brain. Ocular medicines are two-fold, viz such as are referred to the visive virtues, and such as are referred to the eyes themselves. Such as strengthen the visive virtue or the optick nerves which convey it to the eyes (say Doctors) do it by an hidden virtue, into the reason which no man can dive, unless they should fetch it from the similitude of the substance: And yet they say a Goat's liver conduces much to make one see in the night, and they give this reason, because Goats see as well in the night as in the day. Yet is there no affinity in temperature nor substance between the liver and the eyes: However Astrologers know well enough that all herbs, plants, &c that are under the dominion of either sun or moon, and appropriated to the head, be they hot or cold they strengthen the visive virtue, as Eyebright, which is hot *Lunaria*, or Moonwort which is cold. As for what appertains to the constitution of the eyes themselves, seeing they are exact in sense, they will not endure the least inconvenience, therefore such medicines as are outwardly applied to them (for such medicines as strengthen the visive virtues are always given inwardly) let them neither hurt by their hardness nor gnawing quality, nor be so tough that they should stick to them. Therefore let ocular medicines be neither in powders nor ointments, because oil itself is offensive to the eyes, and how pleasing powders are to them, you may perceive yourself by just going into the dust. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)