THE EXCRETION OF SALICYLATE IN SALICYLATE POISONING

A. G. MORGAN AND A. POLAK

Wessex Renal Unit, Portsmouth

(Received 9 August 1971)

SUMMARY

1. The renal clearance of salicylate has been measured in two groups of patients undergoing treatment by alkaline diuresis for salicylate poisoning. One group received mannitol and sodium lactate, the other acetazolamide and sodium bicarbonate.

2. The relationship between urine pH and salicylate clearance was found to be the same in both groups and similar to that shown at non-toxic concentrations in the blood by previous workers.

3. The influence of the rate of urine flow on the relationship between salicylate clearance and urine pH was also shown to be similar to that found at non-toxic concentrations in the blood.

Although alkaline diuresis is now widely accepted as the most effective method of hastening the renal excretion of salicylate, very little is known about its effect on the clearance of this substance in patients with salicylate poisoning. The observations that form the main basis of alkaline diuretic treatment were made at therapeutic blood concentrations in human volunteers (Macpherson, Milne & Evans, 1955; Gutman, Yu & Sirota, 1955) and in dogs (Weiner, Washington & Mudge, 1959). They revealed a linear relationship between log salicylate clearance and urine pH, with a fourfold increase in clearance for each pH unit. There was also a rise in clearance with increasing urine flow, though this effect was relatively small at high urine pH. These observations were consistent with what has become the accepted theory of the renal excretion of weak acids and bases (Milne, Scribner & Crawford, 1958).

The present paper reports measurements of salicylate clearance in patients undergoing treatment for salicylate poisoning, at blood salicylate concentrations up to five times higher than those in the human volunteers studied by Macpherson et al. (1955). For obvious reasons, the conditions were neither as uniform nor as stable as in planned experiments. The observations are nevertheless noteworthy because they confirm the predicted relationship between salicylate clearance and pH, and because of their relevance to the treatment of salicylate poisoning.

Correspondence: Professor A. Polak, Wessex Renal Unit, Saint Mary's General Hospital, Portsmouth, Hants.
Patients and methods of treatment

Twenty-three adult patients were studied, of whom eleven were treated by a diuretic regime using mannitol and sodium lactate and twelve by a regime using acetazolamide and sodium bicarbonate. The initial serum total salicylate concentration ranged from 44 to 88 mg/100 ml. Further details of the patients are given by Morgan, Bennett & Polak (1968) and Morgan & Polak (1969). The treatment regimes are also described in these papers and will only be summarized here.

Mannitol–lactate regime. Mannitol was used to initiate and, when necessary, to sustain a diuresis. Sodium solutions were used to maintain fluid balance: sodium lactate (1.87%) was given when the urine pH was below 7.0 and sodium chloride (0.9%) when it was above 7.0.

Acetazolamide–bicarbonate regime. Acetazolamide 250 mg was given intravenously to initiate a diuresis of near-maximal alkalinity (pH above 7.5) which was then maintained with an infusion of 1.4% sodium bicarbonate.

Two additional patients were studied in whom 100 g of mannitol was given intravenously during the acetazolamide–bicarbonate regime to obtain limited clearance data at very high urine pH (greater than 7.75) and flow (greater than 7.5 ml/min). Eight such clearance periods were observed and these data are included in Fig. 4. They are omitted from the tables.

Collection and analysis of blood and urine samples

Urine collections (1 h or 2 h) were made anaerobically through an indwelling catheter, and stored at 4° for up to 24 h. Venous blood samples were taken at the start of treatment and then after each urine collection.

Serum salicylate was measured by the method of Trinder (1954) and urinary salicylate by a modification (A. J. Cummings, personal communication) of the method of Brodie, Undenfriend & Coburn (1944), which measures only free salicylate not salicylate metabolites. Serum and urinary creatinine was measured with a Technicon AutoAnalyzer. Urine pH measurements were made at 37° with a Radiometer Capillary pH meter, no. 27.

Derived results

Serum non-protein-bound salicylate concentration was derived from serum total salicylate concentration by using the results of Moran & Walker (1968). Salicylate clearance was calculated by using the non-protein-bound serum salicylate concentration. In calculating the clearance of salicylate or creatinine in any 1 or 2 h period, the arithmetic mean of the serum concentrations at the beginning and end of that period was used.

A value for serum salicylate half-life was derived for each patient from a semi-logarithmic plot of the serum concentration against time: the total serum salicylate, not the non-protein-bound fraction, was used. Mean urine pH was calculated by converting into hydrogen ion concentration, taking an arithmetic mean and then re-converting into pH.

Results

Effect of urine pH on salicylate clearance

The relationship between urine pH and salicylate clearance in the patients treated with mannitol and sodium lactate is shown in Fig. 1. A highly significant correlation exists (r =
Salicylate excretion in poisoning

+0.88; \( P<0.001 \)), and the regression equation is shown in Table 1 to be similar to those obtained by Gutman et al. (1955) and Macpherson et al. (1955) at therapeutic concentrations of serum salicylate. The slightly steeper slope of the regression line obtained from our results may be due to the fact that there was a positive correlation between urine pH and urine flow \( (r = +0.64; \ 0.01 > P > 0.001) \). This correlation was an artifact produced by the treatment protocol, which required that the alkalinizing agent (sodium lactate) should be given only

![Graph showing the relationship between log salicylate clearance and urine pH during mannitol-lactate treatment (x) and acetazolamide-bicarbonate treatment (○).](image)

**Table 1.** Relationship between log salicylate clearance and urine pH by previous workers compared with the results of this study

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regression equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gutman et al. (1955)</td>
<td>( \log (C_{\text{sal}}) = 0.52 \times \text{urine pH} - 2.10 )</td>
</tr>
<tr>
<td>Macpherson et al. (1955)</td>
<td>( \log (C_{\text{sal}}) = 0.52 \times \text{urine pH} - 1.92 )</td>
</tr>
<tr>
<td>Morgan &amp; Polak (this paper)</td>
<td></td>
</tr>
<tr>
<td>Mannitol–lactate treatment</td>
<td>( \log (C_{\text{sal}}) = 0.67 \times \text{urine pH} - 3.21 )</td>
</tr>
<tr>
<td>Acetazolamide–bicarbonate treatment</td>
<td>( \log (C_{\text{sal}}) = 0.63 \times \text{urine pH} - 3.04 )</td>
</tr>
</tbody>
</table>
when a diuresis was established. When allowance is made for this artifact, the relationship between salicylate clearance and urine pH remains highly significant: the partial correlation coefficient (urine flow held constant) is $+0.79; P<0.001$.

In the patients treated with acetazolamide and sodium bicarbonate the urine pH was always higher than in those treated with mannitol and sodium lactate and the mean salicylate clearance was considerably higher (Fig. 1). That the difference in salicylate clearance between the two groups is not due to a difference in urine flow is seen in Table 2, where the ranges and mean values of urine flow are shown to be almost identical. The higher clearance in the acetazolamide–bicarbonate group must, therefore, be largely or entirely an effect of urine pH, and Fig. 2 shows that this effect continues throughout the high pH range obtained in this group,

<table>
<thead>
<tr>
<th>Table 2. The mean and range for urine pH and urine flow for the clearance periods measured during treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine pH</strong></td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Mannitol–lactate regime</td>
</tr>
<tr>
<td>Acetazolamide–bicarbonate regime</td>
</tr>
</tbody>
</table>

though the correlation is less close ($r = +0.44; 0.01 > P > 0.001$) than in the lower pH range obtained in the mannitol–lactate group. The regression equations for the two groups are almost identical (see Table 1), so that the slope of the regression line for the acetazolamide–bicarbonate group is again slightly steeper than those obtained by Gutman *et al.* (1955) and Macpherson *et al.* (1955).

**Effect of urine flow on salicylate clearance**

The relationship between urine flow and salicylate clearance in the patients treated with mannitol and sodium lactate is shown in Fig. 3. A highly significant correlation exists ($r = 0.74; P<0.001$). Though it is partly attributable to the positive correlation between urine flow and urine pH which has already been described, it remains significant when this factor is eliminated. The partial correlation coefficient (pH held constant) is $+0.48 (0.05 > P > 0.01)$.

A similar treatment of the results from the patients receiving acetazolamide and bicarbonate appeared to show no relationship between urine flow and salicylate clearance ($r = +0.21; P>0.1$). However, since it seemed possible that a relatively small effect of urine flow on salicylate clearance might be masked by the large effect of urine pH, the results were re-plotted in a manner previously used by Macpherson *et al.* (1955) with very similar results (Fig. 4). For each collection period the clearance was predicted from the urine pH by using the regression equation $\log(C_{\text{sal}}) = 0.67 \times \text{urine pH} - 3.21$ (Table 1). The difference between the logarithm of the predicted clearance and the logarithm of the observed clearance was then plotted against the urine flow. In this plot (Fig. 4) a positive correlation between flow and clearance can be discerned ($r = +0.36; P<0.005$). It includes eight additional points obtained in the patients to whom mannitol was given in addition to acetazolamide and bicarbonate to induce a diuresis exceeding 7.5 ml/min with a urine pH above 7.75.
Salicylate excretion in poisoning

Fig. 2. Relationship between log salicylate clearance and urine pH during acetazolamide–bicarbonate treatment. ——, Regression line for the points shown; ‒ ‒ ‒ ‒ ‒ ‒, regression line for the results of Macpherson et al. (1955).

Fig. 3. Relationship between salicylate clearance and urine flow during mannitol–lactate treatment.
Relationship between creatinine clearance and salicylate clearance

Creatinine clearance was measured only in the patients who were treated with acetazolamide and sodium bicarbonate. The results for forty-eight clearance periods are plotted against the corresponding values of salicylate clearance in Fig. 5. In thirteen clearance periods salicylate clearance exceeded creatinine clearance confirming tubular secretion of salicylate. The pH of the urine exceeded 7.8 in all of these. Creatinine clearance was below 80 ml/min in ten clearance periods, but salicylate clearance in these periods was not consistently low. No relationship was demonstrated between salicylate clearance and creatinine clearance.

Relationship of urine pH to salicylate half-life

The relationship between serum salicylate half-life and the mean urine pH obtained during the mannitol–lactate or acetazolamide–bicarbonate treatment is shown in Fig. 6. A highly significant correlation exists (r = -0.66; P < 0.001).

DISCUSSION

The accepted view of the excretion of salicylate is that put forward by Weiner et al. (1959) which may be summarized as follows. Salicylate enters the tubular lumen from the plasma by glomerular filtration and tubular secretion. In the filtrate it exists in two forms: salicylate ions and salicylic acid molecules. Salicylate ions are converted into salicylic acid molecules when hydrogen ions are added to the glomerular filtrate, the molecules/ions ratio rising by a factor of 10 with every fall of 1 pH unit: it is approx. 1/100 000 at pH 8, and 1/100 at pH 5. This process, together with the absorption of water from the filtrate, produces a concentration gradient for salicylic acid molecules from filtrate to plasma which favours their rapid reabsorption and so
Fig. 5. Relationship between salicylate clearance and creatinine clearance during acetazolamide bicarbonate treatment.

Fig. 6. Relationship between serum salicylate half-life and the mean urine pH obtained during mannitol-lactate treatment (×) and acetazolamide-bicarbonate treatment (●); the half-life is that of total serum salicylate, not the non-protein-bound fraction.
diminishes their clearance. The tubular epithelium is highly permeable to salicylic acid molecules, but it is much less permeable to salicylate ions. Therefore, any measure that prevents the addition of hydrogen ions to the filtrate will increase clearance by preventing the formation of readily absorbable salicylic acid molecules from the relatively inabsorbable salicylate ions. Diuretic measures also increase clearance, mainly by diminishing the concentration gradient for salicylate reabsorption which results from reabsorption of water.

In the treatment regimes used for these studies all the agents referred to were diuretics and three of them (sodium lactate, sodium bicarbonate and acetazolamide) were agents used to prevent or decrease the addition of hydrogen ions to the glomerular filtrate.

The results show that during the treatment of salicylate poisoning the influence of urinary pH on salicylate clearance is very similar to that previously found in studies at therapeutic blood salicylate concentrations. There was an approximate fourfold increase in clearance for each rise of one unit in urine pH, irrespective of whether the alkaline diuresis was induced with mannitol and sodium lactate or with acetazolamide and sodium bicarbonate. This is substantially less than the tenfold increase with each pH unit which would be the maximum obtainable if the tubular epithelium were as permeable to salicylic acid molecules as to water, and totally impermeable to salicylate ions (Milne et al., 1958). A lesser disparity in permeability to the two forms of salicylate would, however, be consistent with the observed relationship between pH and clearance.

The influence of urine flow on salicylate clearance was also shown to be similar to that found at therapeutic blood salicylate concentrations. Although the effect of diuresis in increasing clearance diminished as urine pH rose, it was still clearly demonstrable when urine pH exceeded plasma pH (Fig. 4). One reason for this became apparent when a rough estimate of the urine-to-plasma concentration gradients was made, since it was found that even in those clearance periods with urine flows in excess of 8 ml/min a positive gradient for salicylic acid molecules, the reabsorbable form of salicylate, still existed. It is, however, theoretically possible that with a progressive increase in urine flow rate the concentration gradient favouring the reabsorption of salicylic acid molecules would be abolished and indeed ultimately reversed, if urine pH remained above plasma pH. Under these conditions more rapid diuresis could only increase clearance by permitting diffusion of salicylic acid molecules from plasma to filtrate, or by decreasing the reabsorption of salicylate ions.

Net tubular secretion of salicylate was demonstrated only in the patients treated with acetazolamide and bicarbonate, since it was only in these patients that the glomerular filtration rate was measured. The fact that it was demonstrated only in clearance periods in which urine pH exceeded 7.8 is not regarded as evidence for pH dependent salicylate secretion, but suggests that at lower urine pH secretion was masked by the increased reabsorption. It is known that acetazolamide may depress tubular secretion of salicylate by competitive inhibition (Weiner et al., 1959), but at the dose employed here this effect was not thought likely to be significant. However, it is possible that salicylate clearance in the acetazolamide-treated patients might have been even higher but for such inhibition, and that it might more often have exceeded the creatinine clearance.

Creatinine clearance itself showed the wide variation expected in such ill patients. It, too, may have been depressed by acetazolamide (Yu & Gutman, 1959), but this aspect of the treatment was not studied. Though no correlation was found between salicylate clearance and creatinine clearance, it is clear that a fall in glomerular filtration rate, and the fall in peritubular
Salicylate excretion in poisoning

blood flow that usually accompanies it, must decrease the rate at which the kidneys can clear salicylate from the plasma.

Clinical aspects of the treatment regimes employed have been discussed elsewhere (Morgan et al., 1968; Morgan & Polak, 1969), but it is appropriate to draw the attention of clinicians to the markedly shorter plasma salicylate half-life obtained with the acetazolamide–bicarbonate regime than with the mannitol–lactate regime. This is shown in Fig. 6, in which the half-life is plotted against mean urine pH during treatment to emphasize the close correlation between them. The very high mean urine pH seen with acetazolamide–bicarbonate treatment is due in part to the promptness with which tubular hydrogen ion secretion is suppressed by intravenous acetazolamide. This allows salicylate clearance to be raised within minutes, a feature which has obvious advantages in severe poisoning. When alkali is given without a carbonic anhydrase inhibitor a comparable effect is seldom seen within the first 2 h.

Although Fig. 6 leaves little doubt that the shorter half-life obtained with the acetazolamide–bicarbonate regime is due predominantly to the higher urine pH, there may have been other relevant differences between the effects of the two treatment regimes. For example, although a rise in blood pH was usual with both regimes, their effect on the pH gradient between cells and extracellular fluid, and hence on the distribution of salicylate, may have been different. Moreover, it seems likely that acetazolamide depressed the gastric absorption of salicylate. Salicylate and acetylsalicylate are known to be retained in the stomach for many hours in cases of poisoning (Matthew, Mackintosh, Tompsett & Cameron, 1966), and their gastric absorption, like their renal tubular reabsorption is strongly influenced by a transepithelial pH gradient (Hogben, Schanker, Tocco & Brodie, 1957) dependent on the activity of carbonic anhydrase.

ACKNOWLEDGMENTS

We wish to thank Dr J. M. S. Knott for allowing us to study patients under his care, and Sister B. G. Johnson and the nursing staff of the Intensive Care Unit, Royal Portsmouth Hospital, for their skilled assistance. A.G.M. was in receipt of a research grant from the Regional Hospital Board.

REFERENCES


