Alkaline Diuresis in Treatment of Aspirin Poisoning

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Brit. med. J., 1964, 2, 1033–1036

The rate at which salicylates are removed from the body is augmented by making the urine alkaline (Morris and Graham, 1931). MacPherson, Milne, and Evans (1955) have shown that the production of an alkaline polyuria ensures a rapid removal of salicylate and suggest this as a method of treatment in patients with salicylate intoxication.

Such a method has been widely used in children poisoned with salicylates, the serum salicylate level undergoing a 50% reduction in two to five hours without untoward side-effects. These results compare favourably with those obtained with exchange transfusion and haemodialysis (Oliver and Dyer, 1960 ; Whitten, Kesaree, and Goodwin, 1961).

Children usually have a low blood *p*H when they present for treatment, and the administration of bicarbonate to make the urine alkaline presents no difficulty. Adults who have taken salicylates usually have a high blood *p*H and a low Pco_2, due to hyperventilation, and the administration of bicarbonate may further disturb the acid/base balance and have undesirable clinical results.

This hypothesis may account for the reluctance to treat adults who have taken salicylates by any method involving the administration of bicarbonate. The data available on the magnitude of *p*H change to be expected and its clinical effects are not clearly documented. The therapeutic gain obtained in making the urine alkaline is clear, and we decided to treat adult patients with moderate to severe aspirin poisoning by the method of forced alkaline diuresis, observing the clinical and biochemical changes during treatment.

We have taken as an index of efficiency in treatment the rate at which the serum salicylate concentration fell, and agree with Whitten *et al.* (1961) that this is the most satisfactory measurement with which to compare different methods of treatment.

In a previous paper (Dukes, Blainey, Cumming, and Widdowson, 1963) we compared the relative efficiency of haemodialysis and forced alkaline diuresis in the treatment of aspirin poisoning, and it is our present purpose to report upon the biochemical changes induced by alkaline diuresis and to offer evidence on the clinical effects of administering sodium bicarbonate.

Methods

We have treated five cases. On admission their clinical status was evaluated, with particular reference to the symptoms and signs shown in Table I, and the results were recorded.

On their admission the stomach contents were removed by aspiration, but lavage with large volumes of water was avoided, following the precepts of Clemmesen (1959). Aspirin may be particularly difficult to remove by lavage, and Rushton (1964) has shown that tablets may adhere firmly to gastric mucosa after lavage.

A sample of venous blood was taken for the determination of salicylate by the method of Trinder (1954). *p*H was measured using capillary blood, and Pco_2 and standard bicarbonate were determined as described by Astrup (1961).

A catheter was placed in the bladder and the urine collected hourly. Its volume, *p*H, and salicylate concentration (Trinder, 1954) were determined. Treatment was by the intravenous infusion of 0.9% NaCl, 5% dextrose, and 2% $NaHCO_3$ in rotation, at an initial rate of about 2 litres an hour. This produced a diuresis in excess of 5 ml./min. at a *p*H of about 7.5. Subject to the absence of signs of circulatory overload and the establishment of a satisfactory diuresis this rate of infusion can be maintained for about three hours, as indicated in the results.

Results

The value for serum salicylate as determined is not a reliable index of the severity of poisoning, as is indicated below. Two other indices have been derived—namely, the total absorbed salicylate and the circulating salicylate. The former is retrospective and denotes the total quantity recovered in the urine. plus a correction for the quantity remaining in the body after clinical recovery. The circulatory salicylate is calculated by multiplying the serum concentration by the " salicylate space " (see Appendix) for that particular patient. This abstraction of a salicylate space is open to some objection, but is advanced as having a value in predicting the degree of poisoning which is borne out by the retrospective measurements.

Smith, Gleason, Stoll, and Ogorzalek (1946) have shown that in animals poisoned with salicylates the concentration in the various body tissues differs, bearing some relation to their protein content. It is therefore difficult to make a measurement which adequately reflects the mean tissue concentration. Nevertheless, the value obtained for the normal salicylate space makes an approximation which has clinical value.

Serum salicylate concentration at zero time, designated S_0, has been described by Done (1960) and is found in retrospect from the curve plotting serum salicylate against time in an untreated patient. An extrapolation of this curve to the moment in time when ingestion occurred intersects the ordinate at the value of S_0. This is the concentration of salicylate which would have resulted had absorption been immediate and complete. It is possible to compute this value in another way. If the total absorbed salicylate is divided by the calculated salicylate space a second value of S_0 results which should agree closely with the first if the assumptions about salicylate space are valid. Comparison between the two values is shown in Table I.

Clinical Signs

Table I shows the clinical signs seen on admission, and the serum salicylates, circulating salicylates, and salicylate at zero time. As an index of severity of poisoning any of these criteria may be chosen, but perhaps S_0 is the most satisfactory, since it takes account of body size and total dose.

Correlation between this value and the clinical signs produced is not apparent. All patients complained of deafness and tinnitus, and overbreathing was present in all as evidenced by

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the low P_{CO_2}. Sweating, vomiting, tachycardia, and restlessness had no prognostic value ; in fact, the highest value for S_0 showed the fewest of these symptoms.

TABLE I.—*Correlation of Clinical Signs with Indices of Severity of Poisoning in Five Patients*

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	F	M	F	M	M
Age	16	43	41	58	18
Time between ingestion and serum salicylate determination (hours)	4	14	3	6	12
Serum salicylate (mg /100 ml.)	76	88	55	84	63
Clinical signs :					
Deafness	+	+	+	+	+
Tinnitus	+	+	+	+	+
Overbreathing	+	+	+	+	+
Sweating	+	+	−	+	+
Vomiting	+	−	+	−	+
Tachycardia	+	+	−	+	+
Restlessness	+	+	−	−	−
Impaired conscious level	−	−	−	−	−
Circulating salicylates (g.)	11·8	14·1	5·8	11·8	9·5
Recovered salicylate (g.)	15·6	14·3	13·6	11·7	9·9
Zero-time serum salicylate (mg./100 ml.) (predicted from excretion curve)	143	130	132	105	90
Zero-time serum salicylate (mg./100 ml.) (predicted from body size)	148	126	126	113	91

No patient had an impaired level of consciousness and no opinion can be offered on this symptom, but the remaining symptoms appear to offer no help in assessing severity of poisoning.

The clinical effects of salicylates are modified by the lapse of time, so that identical serum levels in two patients would result in different clinical signs if one level was three hours and the other 12 hours after ingestion.

Individual susceptibility to aspirin may account for the lack of correlation in this small series, but we have shown that a patient may present with few clinical signs and yet be severely poisoned, using the criteria outlined.

Rate of Removal of Aspirin

The rate of diminution of serum salicylate with time is shown in the curves of Fig. 1. These curves represent the resultant of

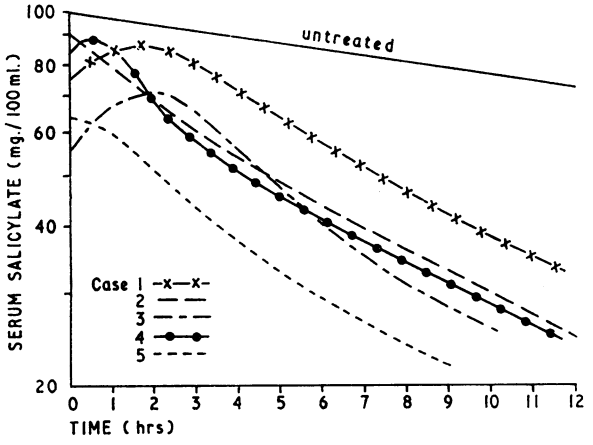

FIG. 1.—Serum salicylate concentration in five cases.

absorption and excretion. Excretion occurs by loss into the urine, loss by chemical transformation, and loss by movement between body compartments.

As indicated in the Appendix, the rate of equilibration between the blood and the extracellular space is rapid and probably contributes little to the diminution of serum salicylate.

The rate of biotransformation is low compared with renal excretion in the presence of an alkaline urine (Schachter and Manis, 1958), and the curves therefore show predominantly the resultant between alimentary absorption and renal excretion.

In two of the patients absorption was still occuring on admission, but was complete in three. Fig. 1 indicates that absorption continued in those cases of more recent ingestion, and it is possible to say from these curves that absorption continues in excess of excretion for about five to six hours after the dose.

This observation is important in assessing the value of a single estimate of serum salicylate made on admission. Such an estimate is best used in the following way. If the aspirin was taken six or more hours before the determination, absorption may be considered complete and S_0 can be predicted by drawing a line with half excretion time of 24 hours passing through the value determined and finding the intercept on the ordinate at zero time. In such a case the value for circulating salicylate agrees well with the total recovered salicylate and with S_0, as seen in Cases 2, 4, and 5.

If the aspirin was taken less than six hours before the determination of serum salicylate there will be an underestimate of S_0 and the circulating salicylate will be markedly different from the recovered salicylate and from S_0, the difference being the quantity remaining unabsorbed.

Some correction may be made for this underestimate if it is assumed that the absorption rate is such as to double the serum salicylate concentration in about four hours. Thus in Case 3 the initial concentration was 55 mg./100 ml. at three hours. At seven hours, therefore, the concentration would be 110 mg./100 ml. but since absorption ceases at six hours the level will be in the region of 100 mg./100 ml. The seriousness with which one would regard this latter level points to the importance of considering the unabsorbed drug. The institution of treatment modifies the peak level a great deal, and the highest level seen in this patient was 69 mg./100 ml.

The mean half excretion time of salicylate for all five patients was 7.5 hours. The half excretion time in untreated cases as quoted in the literature has a mean value of 22 hours with a spread of values from 6 to 40 hours. Oliver and Dyer (1960) give mean values of 6.1 hours with treatment and 17.2 hours without treatment in children.

In patients treated by haemodialysis we have observed that in the period of two to three hours which elapsed before treatment started the half excretion times are about 30 to 40 hours. These values are probably high, since absorption may occur during this time. We have therefore assumed a mean half excretion time of 24 hours, and this time is shown in Fig. 1.

Fig. 2 shows how treatment modifies the pattern of excretion of salicylate and indicates the importance of early and vigorous treatment. The starting level of serum salicylate in Fig. 2 is that predicted at zero time.

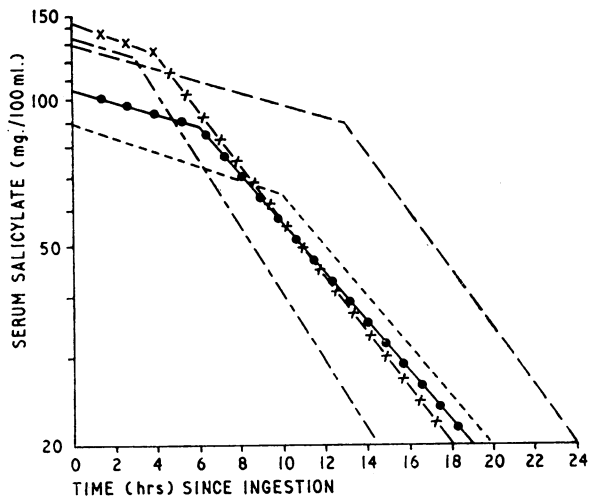

FIG. 2.—Rate of decline of serum salicylate from predicted initial level S_0. Patient identification as in Fig. 1.

Metabolic Changes

Water

Fig. 3 shows a histogram of the water balance in Case 3. This pattern was seen in all the patients, and the period of water retention lasts for several hours, the volume retained being up to 5 litres. The reason for this water retention is in part a restoration of water deficit consequent upon vomiting, hyperventilation, and sweating. Retention may also be due to

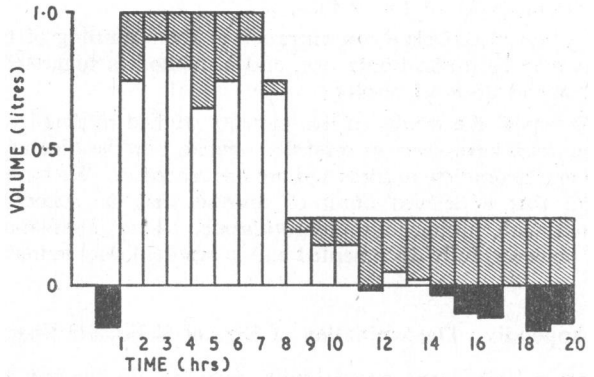

FIG. 3.—Water balance during forced diuresis. Water intake is plotted upwards from the base line. Urine output is plotted downwards from this level and is shown hatched. White blocks thus represent net water retention and black blocks net water loss. No correction applied for insensible loss.

other causes about which we have no data, the important practical point being that this period of water retention usually occurs and should not deter adequate water-infusion. The dangers of overinfusion were not prominent in our patients, but careful observation of the venous pressure and for the appearance of basal crepitations is a wise precaution.

The quantity of urine excreted rose to a peak after four to five hours and then fell, and it is at this time that problems with water overload might be expected to appear. It has been our practice to diminish the infusion rate when the urine excretion falls, since by this time the serum salicylate is usually at a safer level and the requirement for diuresis has diminished.

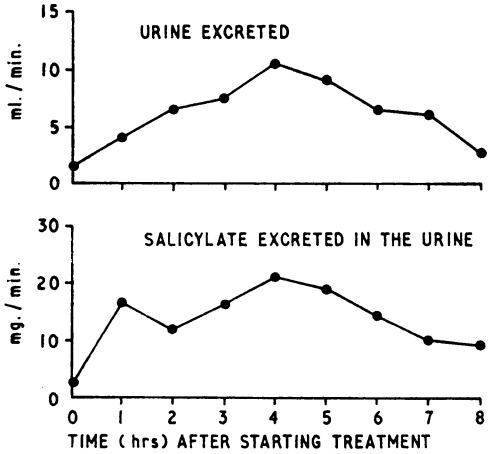

FIG. 4.—Mean results in five cases.

The mean values of urine-flow for all the patients is shown in Fig. 4. The urine-flow during treatment rose to a peak of 10 ml./min. after four hours, and the mean flow over the eight-hour period was 6.9 ml./min. The curve showing salicylate excretion in the urine (Fig. 4) has a similar shape, with a peak of 22 mg./min. after four hours and a mean of 13.4 mg./min. The mean content of each millilitre of urine was thus 2.19 mg. This rate of excretion is similar to that observed by Oliver and Dyer (1960) in children. The results of Whitten *et al.* (1961) show that with urine flows of 3.8–11.4 ml./min., the mean total salicylate excretion was 5.0 mg./min. These results are in children; we have obtained higher urine-flows in adults and achieved a more rapid urinary excretion of salicylate. It is of interest to note that in this series the half excretion time varied from two to five hours, the more rapid fall in serum concentration with a lower urinary excretion reflecting the smaller size of the salicylate space in children.

Table II shows the value for each patient and the mean value for all patients of the urine flows over the treatment period of eight hours.

TABLE II.—*Urine Flow (ml./min.) During the First Eight Hours of Treatment*

Case No.	Hours								Mean
	1	2	3	4	5	6	7	8	
1		18·6	7·0	16·8	11·5	5·2	5·8	6·8	8·9
2	12·0	12·0	11·0	12·8	13·2	12·2	10·8	2·5	10·8
3	2·3	4·2	1·7	3·3	5·5	4·2	1·7	1·0	3·0
4	2·3	5·2	3·1	15·6	7·4	4·5	4·2	3·7	7·0
5	2·9	2·9	3·7	3·7	4·6	4·6	8·3	7·2	4·7
Mean ..	4·9	8·6	7·3	10·4	8·4	6·1	6·1	4·2	6·9

pH Changes

Fig. 5 shows the mean *p*H of blood and urine in the five patients over the treatment period. Mean *p*H was computed by converting to hydrogen-ion concentration, taking an arithmetic mean, and converting this value back to *p*H. The urine *p*H

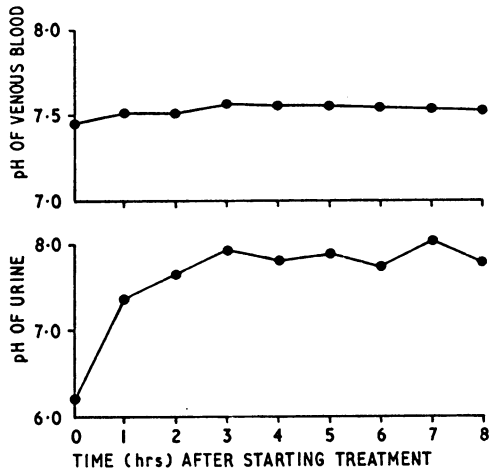

FIG. 5.—Mean *p*H of blood and urine in five cases.

graph shows that after the first hour of treatment the value is high enough to produce rapid excretion but that it continues to rise over several hours. The change in urinary *p*H was used to control the administration of bicarbonate, the mean quantity being about 300 mEq over eight hours.

Blood *p*H before treatment gave a mean value of 7.48, and during treatment this rose to 7.51. The highest level attained was 7.69 in Case 2; the pretreatment level was 7.59. The Pco_2 was 18.9 mm. Hg and standard bicarbonate 22.5 mEq/l. These figures are in accord with those published by Oliver and Dyer (1960) and by Whitten *et al.* (1961).

No untoward clinical features were observed in any of the patients, and the man with the *p*H of 7.69 was quite comfortable. In our patients at least the artificial creation of a metabolic alkalosis superimposed on an existing respiratory alkalosis had no clinically deleterious results.

Changes in Pco_2

Pco_2 was diminished in all patients, reflecting their increased alveolar ventilation. This observation as an index of salicylate intoxication is unfortunately unreliable since hysterical over-

breathing, which may occur in patients with drug overdose, will produce the same results. The mean pretreatment value for P_{CO_2} was 26 mm. Hg, rising to normal levels after six hours. Thus the *p*H change in the urine and the extracellular fluid occurs several hours before restoration of P_{CO_2} to normal.

Changes in Electrolytes

A fall in serum potassium and an increase in serum sodium have been reported when children have been treated with bicarbonate. We have not observed a significant change in serum sodium, but serum potassium has usually fallen, the mean values being 5.1 mEq/l. before treatment and 3.2 mEq/l. after treatment.

We have not thought it necessary to administer potassium with the bicarbonate to prevent intracellular potassium loss, since urinary excretion of potassium over the treatment period has not been large—of the order of 80 mEq.

Further work might indicate the place of potassium supplements in therapy.

Discussion

The treatment of aspirin poisoning suggested in this paper differs in two important respects from that in current general use. The first difference is in the avoidance of large volumes of water in gastric lavage. In this we follow the precepts of Clemmesen (1954), who has shown that the avoidance of such lavage results in a marked fall in mortality and morbidity in a large series of patients suffering from the effects of poisoning of all types. We have, however, aspirated the stomach contents to avoid vomiting with possible inhalation of vomitus.

The second point of difference is the use of alkalis in treatment. The attitude to the use of alkalis appears to have been determined on the basis of the raised blood *p*H, and their use has therefore been avoided.

We use a different criterion—namely, what is the most effective means of removing circulating salicylate—and the use of alkalis then becomes necessary to achieve maximum excretion. The deliberate production of a metabolic alkalosis appears to have had no harmful clinical effects, and the advantages conferred by rapid removal of the aspirin are manifest.

Summary

The treatment of aspirin poisoning by the administration of sodium bicarbonate is not widely practised because of the possible deleterious effects of raising blood *p*H.

This paper discusses the possible advantages in the production of an alkaline diuresis by the administration of fluids and sodium bicarbonate, and describes the treatment in five cases of aspirin poisoning.

Intravenous administration of dextrose, sodium chloride, and sodium bicarbonate solutions produced an average urine-flow of 6.9 ml./min. at mean *p*H of 7.5. This treatment resulted in a diminution of the serum salicylate to one-half of its original value in a mean time of 7.5 hours.

The clinical signs in patients with severe aspirin poisoning who are seen early offer little prognostic assistance, and the value of the various clinical signs is discussed.

Blood *p*H was increased to a mean value of 7.51 and no untoward effects were noted, all the patients recovering without incident. Blood potassium concentrations fell during treatment from a mean of 5.1 to 3.2 mEq/l.

The serum salicylate concentration at the beginning of treatment may be misleadingly low, and a method is suggested for the interpretation of results.

We report the results in five patients studied in detail. Ten other cases have been successfully treated, but the biochemical data are incomplete in these and are not recorded. We have also found that a delayed onset of diuresis may be successfully treated with intravenous chlorothiazide. This observation is not, however, fully documented and is reported only tentatively.

Appendix: Determination of Size of Salicylate Space

Serum salicylate concentration may be diminished by a movement of ions from the serum into some larger space, and if the movement were slow would make an important contribution to the curves of serum salicylate diminution with time. If equilibration were rapid, however, this effect could be ignored. A knowledge of the size of the space at the time of equilibrium would be helpful to assess the total dosage in the body.

Method.—Four normal subjects were investigated. Into each was injected 1 g. of buffered sodium salicylate, using a forearm vein. The serum salicylate concentration was then followed for four hours. Results showed that equilibration in the salicylate space was complete within two minutes, the salicylate ion being freely diffusible. A very slow decrease was observed over the four hours as salicylate was excreted in the acid urine.

The size of the salicylate space was 0.22 l. $\pm$ 0.023 l./kg. of body weight, so that an average male would have a salicylate space of approximately 15 l.

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