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Acetazolamide and Sodium Bicarbonate in Treatment of Salicylate Poisoning in Adults

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Summary: Ten adults suffering from salicylate overdosage were treated successfully with a combination of sodium bicarbonate and acetazolamide to exploit the increase in salicylate clearance which is known to occur in very alkaline urine. The advantages of the method include the absence of important complications and the small volume of fluid required.

Introduction

More than 20 years ago the renal clearance of free salicylate was shown to increase approximately fivefold when the pH of the urine was raised from 7 to 8 (Smith *et al.*, 1946). Alkaline diuresis has since become an established method of treating salicylate overdosage, but its exponents—for example, Dukes *et al.*, 1963; Beveridge *et al.*, 1964; Matthew and Lawson, 1967—have laid more emphasis on achieving a high urine flow than on a very high urine pH. If this emphasis were reversed some of the hazards of a very rapid throughput of fluid might be avoided.

MacPherson *et al.* (1955) suggested the use of a combination of acetazolamide (Diamox) and sodium bicarbonate to maintain a urine of nearly maximal alkalinity. Either substance alone will have this effect, but with acetazolamide it wears off as the plasma bicarbonate and pH fall (Counihan *et al.*, 1954); with bicarbonate it is sustained, though at the expense of some elevation of plasma bicarbonate and pH (Pitts *et al.*, 1949). The combination should produce a sustained effect with little change in blood pH. However, where there is an initial metabolic acidosis, which makes some elevation of plasma bicarbonate and pH desirable, the effect of acetazolamide in delaying this elevation is likely to be slight (Schwartz *et al.*, 1959). Though treatment with acetazolamide and bicarbonate has had varying success in children (Schwartz *et al.*, 1959; Feuerstein *et al.*, 1960), we feel that the results in a small series of adult patients are sufficiently favourable and consistent to warrant this report.

Material and Methods

Studies were made of 10 patients admitted to the Royal Portsmouth Hospital with moderate or severe salicylate intoxication. Details of the cases are included in Table I. Cases A and B are listed separately because of minor deviations from the treatment regimen (see Results). Treatment was begun if

the serum salicylate level was above 50 mg./100 ml. or if obvious clinical signs of salicylate intoxication were present.

On admission one venous blood sample was taken for salicylate estimation, and a second sample one hour later provided that treatment had not been started. A small-volume gastric lavage was performed. The patient was then catheterized, and closed bladder drainage set up. An intravenous infusion was started and 250 mg. of acetazolamide given intravenously.

Intravenous Infusion.—In the first hour, 1 litre of 1.4% sodium bicarbonate. In the second hour, 1 litre of 1.4% sodium bicarbonate plus 20 mEq KCl. Then if the patient is still clinically dehydrated, 1 litre of 0.9% sodium chloride plus 20 mEq KCl hourly until the patient is rehydrated. If the patient is not clinically dehydrated (or when dehydration has been corrected by 0.9% sodium chloride), 1 litre of 1.4% sodium bicarbonate plus 40 mEq KCl two-hourly for four hours.

If treatment is still required (serum salicylate >40 mg./100 ml.) a further 250 mg. of acetazolamide is given intravenously and the following solutions are infused in rotation every two hours: (1) 1 litre of 0.9% sodium chloride plus 40 mEq KCl, and (2) 1 litre of 1.4% sodium bicarbonate plus 40 mEq KCl.

The infusion should be stopped and this method of treatment abandoned if a positive fluid balance of two litres develops after the correction of dehydration.

On admission one venous blood sample was taken for salicylate estimation, and a second sample one hour later provided that treatment had not been started. A small-volume gastric lavage was performed. The patient was then catheterized, and closed bladder drainage set up. An intravenous infusion was started and 250 mg. of acetazolamide given intravenously.

The following investigations were carried out.

Clinical.—Frequent physical examinations were made, particular attention being given to the state of hydration and to cardiovascular, respiratory, and neurological disturbances.

Blood Samples.—Venous samples were taken on admission and after each litre of intravenous fluid, and the following serum constituents were measured: creatinine, sodium, total CO₂, chloride, potassium, calcium, magnesium, and salicylate. Capillary blood pH measurements (Docrat and Kenny, 1965) were made initially, after two hours, and at the end of treatment.

Urine Samples.—Urine collections were made serially, each ending when a litre of fluid had been given intravenously—that is, after one to two hours. Urine pH and volume were measured and an aliquot was refrigerated for creatinine, sodium, chloride, potassium, and salicylate estimation.

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TABLE I.—Details of Cases Studied

Case No.	Sex	Age	Approx. Dose of Aspirin taken (g.)	Approx. Time before Assessment (Hours)	Pre-treatment Serum Salicylate Level (mg./100 ml.)	S ₀ †	Summary of Clinical State									
							Impairment of Consciousness	Shocked	Convulsion Prior to Treatment	Restlessness	Hyper-ventilation	Vomiting	Sweating	Dehydration	Deafness	Tinnitus
1	F	19	33	8	51	60	—	—	—	—	—	+	—	—	+	+
2	M	35	45	12	54	70	—	—	—	+	+	+	+	+	+	+
*3	F	28	—	12	80	105	+	—	+	—	+	+	+	+	—	—
4	M	33	—	9	52	65	+	—	—	—	+	—	—	—	+	+
5	M	23	26	12	69	91	—	—	—	+	+	—	—	+	+	+
6	F	17	24	4	51	89	—	—	—	—	—	—	—	—	+	+
7	F	39	33	6	77	89	+	—	+	—	+	+	—	—	—	—
8	M	26	45	6	60	70	—	—	—	—	—	—	+	—	+	+
†A	M	41	45	7.5	81	94	+	+	+	—	+	—	+	+	—	—
B	F	21	33	5.5	88	109	—	—	—	+	+	—	+	—	—	—

* Blood barbiturate level 0.9 mg./100 ml. Salicylate intoxication initially overlooked. † Transferred for haemodialysis. ‡ Serum salicylate level which would have resulted if absorption had been immediate and complete (see text).

Laboratory Methods

Serum creatinine, sodium, total CO₂, chloride, potassium, and urinary creatinine were estimated on a Technicon Auto-Analyzer. Urinary sodium, chloride, and potassium were measured in the early part of the study by an E.E.L. flame photometer, and later by a Unicam S.P.90 flame photometer, which was also used to measure calcium and magnesium. All pH measurements were made at 37° C. on a Radiometer capillary pH meter No. 27. Serum salicylate concentration was estimated by the method of Trinder (1954). Urinary salicylic acid concentration was measured by a modification of the method of Brodie *et al.* (1944).

Derived Data

Serum salicylate half-life was derived from semilogarithmic plotting of the serum salicylate level against time.

Salicylate and creatinine clearances were calculated by using the mean of the initial and final serum levels for each clearance period.

S₀.—*S₀*, the serum salicylate level which would have resulted had absorption been immediate and complete was calculated by the method of Done (1960), who took an *S₀* value above 100 as an indication of severe poisoning. His calculation assumed a half-life of 20 hours in the untreated patient.

Cumulative balances for water, sodium, chloride, and potassium were estimated by subtracting the urinary output from the amount infused. No vomiting occurred during treatment.

Mean urine pH was calculated by converting to hydrogen ion concentration, taking an arithmetic mean, and converting this value back to pH.

Results

Clinical.—Complete recovery occurred in all the patients in this study. No cardiovascular or neurological complications were encountered during treatment. The patients in whom there was initial dehydration are indicated in Table I. It will be noted from Table III that these are the patients who were

allowed to accumulate a positive fluid balance in excess of two litres.

Biochemical and Balance Data.—Biochemical and balance data are given in Table II, which contains data relating to the removal of salicylate, and Table III, which contains data relating to freedom from complications. Serum calcium and magnesium did not change significantly, and are therefore not included in Table III. Cases A and B are listed separately in the tables because their treatment included an extra litre of bicarbonate where the treatment regimen prescribed normal saline. Their maximum blood pH was recorded following this deviation from the regimen. These two cases are excluded from the calculation of group averages. The fall in serum salicylate during treatment is depicted in Fig. 1 and the relationship of salicylate and creatinine clearances is shown in Fig. 2.

FIG. 1.—Serum salicylate levels in 10 patients prior to treatment, and the rate of fall during treatment.

TABLE II.—Data Relating to Salicylate Elimination

Case No.	Initial Serum Salicylate (mg./100 ml.)	Salicylate* Half-life (Hours)	Average Urine Flow (ml./min.)	Mean* Urine pH	Maximum Recorded Urine pH	Lowest Recorded Urine pH	Pretreatment Urine pH	Length of Diuretic Treatment (Hours)	Urinary Salicylic Acid Recovered (g.)
1	51	3.2	7.2	7.93	8.0	7.75	6.8	6.25	4.2
2	54	8.5	2.8	7.95	8.0	7.87	7.05	6.5	4.6
3	80	5.8	2.6	7.95	7.99	7.81	7.3	7.0	4.8
4	52	7.4	4.0	7.95	8.0	7.75	6.5	5.25	2.2
5	69	7.8	4.3	7.83	7.92	7.55	6.35	6.0	3.9
6	51	4.2	7.0	7.85	7.95	7.78	6.88	6.0	6.0
7	77	6.4	7.7	7.78	7.87	7.6	6.85	6.25	7.1
8	60	7.3	5.0	7.85	7.92	7.64	6.87	6.25	6.5
Av.		6.3	5.2	7.88	7.96	7.72	6.82	6.2	
A	81	9.8	6.3	7.65	7.9	7.34	5.9	10.5	9.8
B	88	7.0	6.7	7.85	7.98	7.55	6.55	8.0	6.6

* See methods section for details of the values.

TABLE III.—Data Relating to Freedom from Complications

Case No.	Length of Diuretic Treatment (Hours)	I.V. Fluid (Litres)	Maximum Positive Fluid Balance (Litres)	Maximum Cumulative Sodium Balance (mEq)	Minimum Cumulative Potassium Balance (mEq)	Initial Serum Potassium (mEq/l.)	Lowest Serum Potassium (mEq/l.)	Initial Capillary pH	Highest Recorded Capillary pH
1	6:25	4	+1:31	+151	-49	3.7	2.7	—	7.45
2	6:5	4	+2:93	+429	-104	4.0	3.0	7.22	7.54
3	7	5	+3:89	+629	-45	4.2	2.9	7.45	7.45
4	5:25	3.5	+2:17	+415	-43	4.1	2.8	7.45	7.45
5	6	4	+2:46	+446	-113	5.0	2.9	7.27	7.44
6	6	4	+1:32	+269	-18	4.2	3.1	7.45	7.55
7	6:25	4	+1:09	+267	-57	5.2	3.6	7.44	7.54
8	6:25	4	+2:12	+395	-77	4.6	3.0	7.45	7.50
Av.	6:2	4.1	+2:15	+374	-63	4.4	3.0	7.39	7.49
A	10:5	7	+2:75	+593	-96	5.9	2.7	7.54	7.61
B	8	4.9	+1:53	+376	-8	4.7	3.5	7.40	7.59

FIG. 2.—Salicylate clearance and creatinine clearance during treatment. Salicylate clearance (see Discussion) is shown by solid lines, and creatinine clearance by dotted lines. Acetazolamide was given at time zero.

Discussion

It is difficult to compare the effectiveness of the above treatment with that of other methods employed in adult cases of salicylate poisoning. Every report uses different criteria for salicylate removal, and clearances are not given in any, no doubt because of the difficulty of estimating free salicylate in the urine. The "half-life" has the important drawback that it is prolonged by continuous absorption of salicylate, but Cumming *et al.* (1964) and Ghose and Joekes (1964) quote a value of 7.5 hours and 12 hours respectively. By this criterion the present method, with a half-life of 6.3 hours, is satisfactory. An advantage, however, is the small volume of urine, and therefore of infused fluid, which was needed to reach this short

¹ The volumes quoted are those which had been given when the logarithm of the plasma salicylate level had been halved.

half-life: the average input¹ of 4.4 litres, compared with 6.25 litres (Ghose and Joekes, 1964) and approximately 8 litres (Cumming *et al.*, 1964), reduces the likelihood of producing fluid and electrolyte imbalance in patients whose balance is often precarious at the start, and who often have to be treated in busy understaffed units. Table IV summarizes the differences in half-life, urine flow, and pH in our own cases treated by the present method and by a conventional alkaline diuresis regimen (Morgan *et al.*, 1968). It emphasizes the favourable influence of a very high urine pH.

In a small series which included no old patients and none with an initial serum salicylate level above 90 mg./100 ml., the fact that all the patients recovered without clinical complications is not remarkable, but the freedom from neurological complications is reassuring in view of the occurrence of convulsions in children (Schwartz *et al.*, 1959). This difference is the more striking since three of our patients had had convulsions before treatment. It may be due to the dose of acetazolamide per kg., which was approximately half that used in children by Schwartz *et al.* and by Feuerstein *et al.* (1960).

TABLE IV.—Data to Show the Influence of Urine pH on Salicylate Half-life

	No. of Cases Treated	Mean Salicylate Half-life	Mean Urine pH	Range for Urine pH	Average Urine Flow (ml./min.)
Mannitol and alkali treatment*	5	17.8	6.6	6.0-7.05	7.3
Acetazolamide and alkali treatment	4	11.2	7.4	7.2-7.5	7.8
	8	6.3	7.88	7.6-8.0	5.2

* Treatment as described by Morgan *et al.* (1968). The nine patients receiving this treatment are divided into two groups according to the urine pH achieved.

The absence of significant alkalosis in the present series is also reassuring. However, it has not been established that acetazolamide will always ensure that bicarbonate can be given without aggravating severe alkalosis, since only one of the patients (Case A) had an initial blood pH as high as 7.54. It is encouraging that even this patient's pH did not rise above 7.61, though he was one of the two who received more bicarbonate than was laid down in the treatment regimen. Nevertheless it is premature to recommend this treatment without modification either for those few cases whose initial blood pH is above 7.6 or for those with severe metabolic acidosis. Where there is marked hyperventilation our present practice is to give only saline until the blood pH is known: if it is above 7.6 acetazolamide is given and bicarbonate omitted, while if it is below 7.25 the reverse applies.

Bicarbonate and acetazolamide may tend to aggravate the renal potassium wasting which is produced by salicylate (Robin *et al.*, 1959). It was therefore anticipated that hypokalaemia might be more troublesome with this regimen than with previous methods of treatment, but it did not prove to be so. Nevertheless, it may be found that as soon as a diuresis occurs (>2 ml./min.) a rate of potassium infusion of 30 mEq/hour is preferable to that of 20 mEq/hour employed here. In three cases in which this modification was adopted the serum potassium remained within normal limits. Another modification

that might prove advantageous is the substitution of 5% dextrose for 0.9% saline in those patients who are initially hypernatraemic.

The values for salicylate clearance given in Table II and Fig. 2 cannot be compared with those of other authors as they are based on total serum salicylate concentrations—as measured by the method of Trinder (1954)—and not on the unbound fraction only. They are presented, nevertheless, because they provide the clinician with a rough estimate of the rate of salicylate excretion that he may obtain with acetazolamide and sodium bicarbonate infusion at any given serum salicylate level. In Fig. 2 creatinine clearance values are also shown, since the glomerular filtration rate is sometimes low in salicylate overdose and may be further depressed by acetazolamide (Milne, 1963). The effectiveness of the treatment regimen might be limited by this, and also by competition for tubular secretion between acetazolamide and salicylate (Weiner *et al.*, 1959).

Although this paper lays greater emphasis on a very high urine pH than a very high urine flow, it is clear that the rate of flow must still be a factor limiting salicylate clearance. When rehydration is not promptly followed by a brisk diuresis the use of an osmotic diuretic may therefore still be of value. We have unpublished data to show that the addition of mannitol to the present treatment regimen can further increase salicylate clearance. It should, however, be borne in mind that mannitol may cause complications of its own (Morgan *et al.*, 1968).

It is not suggested that acetazolamide and sodium bicarbonate treatment will replace haemodialysis in the severest cases of salicylate intoxication, for in these there may be other indications for dialysis than the serum salicylate concentration. However, the concentration itself may often be brought down to a safer level during the time required to transfer a patient to a dialysis unit. We have recently treated two such patients prior to dialysis, reducing the serum salicylate in one from 136 to 107 mg./100 ml. in two hours, and in the other from 104 to 69 mg./100 ml. in three hours.

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Strontium-85 Scanning of Suspected Bone Disease

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Summary: Strontium-85 scanning of suspected bone lesions in 81 patients has added to the criteria for the diagnosis of malignant and other lesions of bone. Of 46 patients with a previous history of malignant disease and skeletal symptoms negative radiological findings were recorded in 19, but nine of these had positive scans, eight of which when followed up over periods of up to four years proved to be metastatic. A similar prevalence of positive scans occurred in patients without a previous history of malignancy. Because of the anatomical localization of lesions made possible by this technique a tissue diagnosis was made in six patients, while fields of radiotherapy were altered in another seven. This technique can improve the management of patients with suspected bone disease.

Introduction

Patients with back pain present difficulties in diagnosis when the radiological features are normal or show changes which can be interpreted in more than one way. It has been estimated that at least a 30% alteration in bone density must take place before changes can be detected by conventional radiological techniques (Lachman, 1955). Tomography may improve the delineation of the lesion, but some idea of the area involved must be given first.

Normal bones accumulate radioisotopes by a variety of processes which involve simple exchange diffusion, active transport, and incorporation into bone mineral (Bauer, Carlsson, and Lindquist, 1958). Increased uptake in a particular area of bone may be due to increased blood flow, altered exchange processes, or new bone formation. These changes arise in the repair processes involved in traumatic, inflammatory, and neoplastic lesions, micro-fractures probably occurring in most of the vertebral diseases of this nature. In neoplastic lesions a variety of causes may lead to an increased uptake, including osteolysis opening up a large area for exchange, new bone formation in sclerotic deposits, and, on occasion, osteomalacia (Folli, 1950). Bone biopsy of areas which had shown increased ⁸⁵Sr uptake

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