REVIEW ARTICLE

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Does Urine Alkalinization Increase Salicylate Elimination? If so, Why?

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Contents

Abstract

Urine alkalinization is a treatment regimen that increases poison elimination by the administration of intravenous sodium bicarbonate to produce urine with a pH ≥7.5. Experimental and clinical studies confirm that urinary alkalinization increases salicylate elimination, although the mechanisms by which this occurs have not been elucidated. The conventional view is that ionisation of a weak acid, such as salicylic acid, is increased in an alkaline environment. Since the ionisation constant (pKa) is a logarithmic function then, theoretically, a small change in urine pH will have a disproportionately larger effect on salicylate clearance. Hence, elimination of salicylic acid by the kidneys is increased substantially in alkaline urine. However, as salicylic acid is almost completely ionised within physiological pH limits, alkalinization of the urine could not, therefore, significantly increase the extent of ionisation further and the conventional view of the mechanism by which alkalinization is effective is patently impossible. Further experimental studies are required to clarify the mechanisms by which urine alkalinization enhances salicylate elimination.

Much of what we knew about the metabolic fate and elimination of salicylates dates from 1950–70, and was made possible by the development of analytical techniques that allowed separation, identification and quantification of the various end-products of salicylate metabolism in blood and urine. The resulting literature is voluminous and cannot be reviewed in detail here. This review critically assesses relevant literature to determine whether urine alkalinization with sodium bicarbonate increases salicylate elimination and, if so, by what mechanism this is achieved.

1. Salicylate Toxicokinetics

The most commonly encountered salicylate, aspirin (acetylsalicylic acid), is hydrolysed rapidly to salicylic acid by non-specific

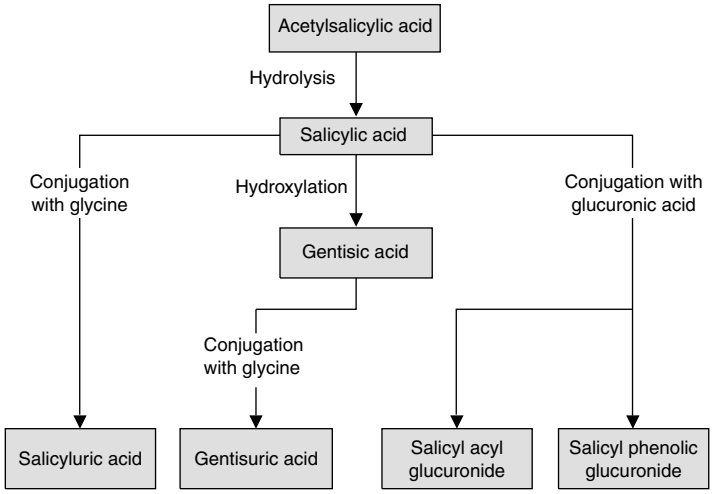

Fig. 1. The metabolism of aspirin (acetylsalicylic acid).

esterases in the intestinal wall and other tissues (figure 1). As much as 35% of a therapeutic dose may be hydrolysed during the course of absorption.[1] While some salicylic acid is then eliminated unchanged, variable amounts are conjugated with glycine to produce salicyluric acid and with glucuronic acid to form salicyl phenolic glucuronide, the major urine metabolites of acetylsalicylic acid after therapeutic doses. In addition, salicyl acyl glucuronide and the ring hydroxylation products of salicylic acid, namely gentisic acid and its glycine conjugation product, gentisuric acid, are all formed in minor amounts and excreted into the urine. The relative proportions of unchanged salicylic acid and salicyl phenolic glucuronide in the urine depend on the body load of salicylate to be eliminated because the formation of salicyluric acid and salicyl phenolic glucuronide is capacity-limited. After a therapeutic dose (aspirin 600mg), unchanged salicylic acid, salicyluric acid and salicyl phenolic glucuronide accounted for 9%, 75% and 11% of urine salicylate, respectively.[2]

In contrast, when plasma salicylate concentrations were very high (>700 mg/L), salicylic acid accounted for 65%, while salicyluric acid and the phenolic glucuronide accounted for 22% and 15%, respectively.[2] Thus, after salicylate overdose, the major metabolic pathways become saturated and renal excretion of salicylic acid becomes increasingly important.

Various studies indicate that salicylate filtered at glomeruli in the physiological range of urine pH undergoes reabsorption, probably in the distal renal tubule.[3,4] The amount reabsorbed decreases with increasing pH.[4-6] Moreover, salicylate is secreted actively from the proximal tubule.[3,6] It is possible, but unproved, that active tubular secretion of salicylate takes place at all pH values within the physiological pH range but that it is masked by the more extensive passive reabsorption from the luminal fluid. It is not known if active salicylate excretion can be affected by urine pH.

2. Definition of Urine Alkalinization

Urine alkalinization is a treatment regimen that increases poison elimination by the administration of intravenous sodium bicarbonate to produce urine with a pH ≥7.5.[7] The term 'urine alkalinization' emphasises that urine pH manipulation rather than a diuresis is the prime objective of treatment. For this reason, the terms 'forced alkaline diuresis' and 'alkaline diuresis' are not employed in this review.

3. Experimental Studies

3.1 Urine Alkalinization in an Animal Model

Three fasting dogs were anaesthetised with pentobarbital.[8] Sodium salicylate 2.0–2.5g was then administered intravenously and renal salicylate clearance was determined. In addition, and subsequently, each dog was administered 100mL of a 10% solution of sodium bicarbonate intravenously to alkalinize the urine. Urine flows were between 2.0–6.2 mL/min. Plasma salicylate concentrations were in the range of 150–400 mg/L The renal salicylate clearance was again determined. Salicylate concentrations were measured by a modification of the method of Brodie et al.[9] The effect of sodium bicarbonate administration on renal salicylate clearance is shown in figure 2. Although the analytical methods employed were not specific for salicylic acid, this very early study is included to demonstrate that 55 years ago urine alkalinization was known to increase salicylate elimination.

Reimold et al.[10] studied the effects of urine alkalinization on salicylate elimination in 18 anaesthetised dogs administered sodium salicylate 700 mg/kg intravenously over 1 hour. Serum salicylate concentrations greater than 1000 mg/L were produced in all the animals, with a maximum concentration of 1220 mg/L. Following the intravenous administration of sodium salicylate, all animals

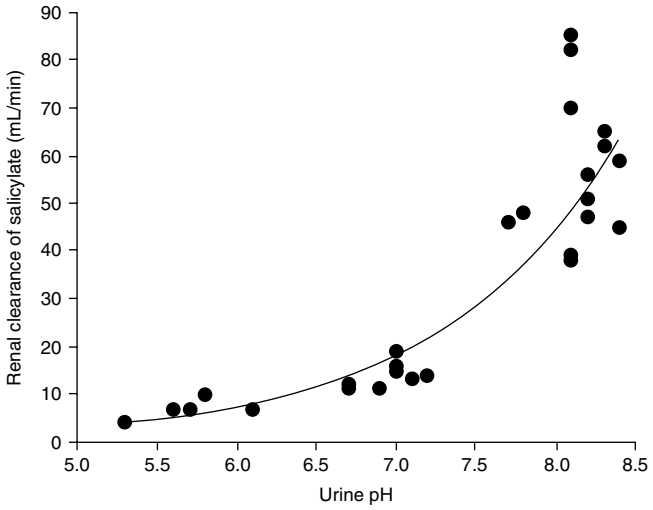

Fig. 2. The effect of sodium bicarbonate on renal salicylate clearance in the dog.[8]

received a solution of saline 0.225% with glucose 2.5% and potassium chloride 20 mmol/L, infused at a rate of 2 mL/min. The infusion rate was doubled for a period of 20–60 minutes if urine flow exceeded fluid administration. In nine dogs, this was the only treatment (water diuresis group). The remaining nine dogs were also administered sodium bicarbonate 1 mmol/min in an attempt to increase the urine pH above 7.5, when the blood pH fell below 7.35 or the plasma bicarbonate fell below 18 mmol/L (water diuresis and bicarbonate group). The administration of sodium bicarbonate was interrupted if the blood pH rose above 7.45 or if the plasma bicarbonate concentration rose above 30 mmol/L.

The urine pH, serum salicylate concentration, serum salicylate half-life, total salicylate excretion and survival rate for the two groups of dogs 9 hours after intravenous administration of sodium salicylate are shown in table I. A urine pH of 7.5 was not reached in the dogs in the water diuresis and bicarbonate group for a mean time of 305 minutes. Furthermore, as seven out of the nine dogs in the water diuresis group and three of the nine in the water diuresis and bicarbonate group died during the study, the data may be subject to bias due to small sample size. In addition, although original data are not given in the published paper,[10] figure 2 in the paper suggests that the mean half-life was similar before and after the urine pH of 7.5 was reached in the water diuresis and bicarbonate group. However, the mean total salicylate excretion over 9 hours of treatment was significantly greater ($p < 0.001$) and survival increased in the group treated with urine alkalinization.

3.2 Urine Alkalinization in Human Volunteers

Four volunteers were fasted for 12–14 hours.[8] Each individual then received, over a period of 3 hours, sodium salicylate 3–4g orally, during which time, three 1-hour salicylate clearances were determined. At the end of this time, volunteers were given sodium bicarbonate 5–7g orally. One hour later, the volunteers received a maintenance dose of sodium salicylate 2g orally and sodium bicarbonate 2–7g orally. Two additional, 1-hour salicylate clearances were then determined. Urine flows were between 2.0–10 mL/min. Plasma salicylate concentrations were in the range 150–280 mg/L. Salicylate concentrations were measured by the method of Brodie et al.[9] The effect of sodium bicarbonate on renal salicylate clearance is shown in figure 3.

Vree et al.[11] conducted a randomised crossover study in six volunteers who were administered sodium salicylate 1.5g orally and were then subjected to urine alkalinization (mean ± standard deviation [SD] urine pH of 7.67 ± 0.65) or urine acidification (mean urine pH 5.54 ± 0.57). The mean peak plasma salicylate concentrations measured by high pressure liquid chromatography were 93.3 ± 18.6 mg/L and 109.8 ± 17.8 mg/L (non-significant difference), respectively. In acidic urine, the renal salicylate clearance was 0.48 ± 0.35 mL/min and when the urine was alkaline 11.9 ± 6.4 mL/min ($p = 0.0014$). Mean total body clearance increased significantly ($p = 0.041$) during urine alkalinization (2.27 ± 0.83 L/h) compared with urine acidification (1.38 ± 0.43 L/h). The mean elimination half-life during urine alkalinization (2.50 ± 0.41 hours) was significantly less ($p = 0.0156$) than the mean elimination half-life during urine acidification (3.29 ± 0.52 hours).

4. Clinical Studies

4.1 Case Series

Prescott et al.[12] studied 16 patients who were mildly intoxicated (mean ± SD plasma serum salicylate concentration of 328 ± 57

Table I. The impact of urine pH on salicylate elimination[10]

Group	Mean urine pH 9h post-dosing	Mean serum salicylate concentration at 9h post-dosing (mg/L)	Mean serum salicylate half-life (h)	Mean ± SD salicylate excretion over 9h (mg)	Mortality at 9h post-dosing (%)
Water diuresis (n = 9)	6.0	330	6.2	2287 ± 141	7/9 (78)
+Bicarbonate (n = 9)	7.8[a]	192	5.2	2512 ± 164[b]	3/9 (33)

a Significantly different from water diuresis group ($p < 0.001$).

b Significantly different from water diuresis group ($p < 0.005$).

SD = standard deviation.

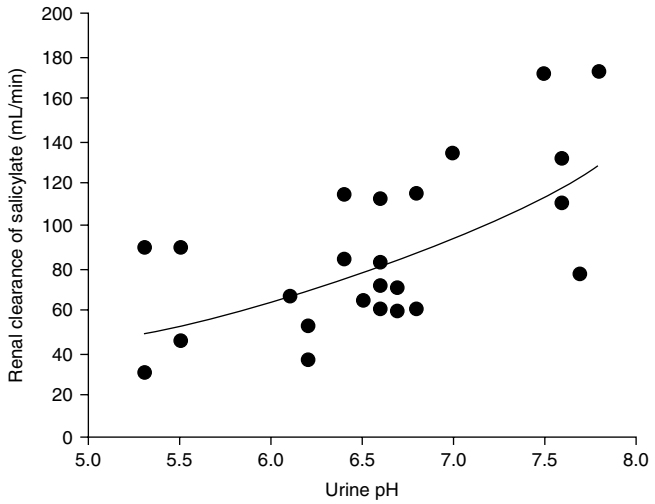

Fig. 3. The effect of sodium bicarbonate on renal salicylate clearance in human volunteers.[8]

mg/L) and who served as controls, receiving oral fluids only. A further six patients with a mean (± SD) plasma salicylate concentration of 439 ± 86 mg/L were given 225 mmol bicarbonate and 60 mmol potassium in 1.5L fluid. The infusions were given over 3–4 hours. Patients receiving urine alkalinization had significantly greater ($p < 0.05$) renal salicylate clearances than controls (pH 6.1 ± 0.3). In addition, a significant ($p < 0.05$) decrease in mean (± SD) plasma half-life compared with the control group was reported (table II). These data show that urine alkalinization enhances salicylate clearance. However, the conclusions of the study are based on only six patients and there were insufficient data to determine if urine alkalinization had an impact on patient morbidity.

Dukes et al.[13] and Cumming et al.[14] reported their findings in five patients with severe salicylate poisoning who were treated with urine alkalinization. All patients received an infusion of 0.9% sodium chloride 500mL, 5% glucose 500mL and 2% sodium bicarbonate 500mL (1/6M sodium lactate in one patient) in rotation, at an initial rate of 2 L/h. The rate of infusion was then adjusted to produce a urine output of approximately 500 mL/h. Urine pH was measured hourly. Alkali was omitted from the infusion when a urinary pH of 8.0 was attained. The mean urine pH was approximately 8 between 3–8 hours after commencement of sodium bicarbonate. Salicylate concentrations in this study were measured by a non-specific method.[15] Urine pH was measured by a pH meter. There are a number of discrepancies in the sex, plasma salicylate concentrations and urine outputs of the patients reported in these two papers (table III), which were stated to relate to the same study participants.

Although the urinary salicylate excretion was clinically significant, this was an observational study that lacked a control group and conclusions regarding the efficacy of urine alkalinization cannot therefore be made. Although the authors reported that clinical improvement occurred as plasma salicylate concentrations declined, no data were presented to confirm this.

Lawson et al.[16] compared the decline in plasma salicylate concentrations in 40 patients with moderate or severe salicylate poisoning who were allocated randomly to one of three treatment groups: (i) forced water diuresis; (ii) forced alkaline diuresis; and (iii) forced cocktail diuresis. The rate of administration of intravenous fluid was the same in all cases (6L over 3 hours), although patients in the forced alkaline diuresis and forced cocktail diuresis groups were also administered bicarbonate 296 mmol and 222 mmol, respectively. The mean urine pH for the forced alkaline diuresis treated patients reached a peak of 7.4 during the fifth hour of treatment. The mean urine pH in those receiving the forced cocktail diuresis varied little from 7.0 during treatment. This study utilised the non-specific Trinder[15] method to measure both plasma and urine salicylate concentrations. Urine pH was measured by a pH meter.

Urine salicylate elimination averaged 600 mg/h in the two regimens containing bicarbonate compared with some 200 mg/h in the forced water diuresis group. Statistical differences between the specific treatment groups were not reported. The mean times for plasma salicylate concentrations to fall to two-thirds and one-third of their peak value are shown in table IV. The authors state that there was a significant ($p = 0.01$) correlation between increasing urinary pH and urinary excretion of salicylate, although no data are given in their paper. The authors also report that there was

Table II. Urine pH, urine flow rate, renal salicylate clearance, urine salicylate excretion and plasma half-life in patients receiving either oral fluids or urine alkalinization.[12] All values are shown as mean ± SD

Regimen	Mean urine pH	Urine flow rate (mL/min)	Renal salicylate clearance (mL/min)	Plasma half-life (h)		Urine salicylate excretion (g)	
				0–4h	4–16h	0–4h	0–16h
Control (oral fluids)	6.1 ± 0.4	1.4 ± 0.8	1.4 ± 1.4	19.4 ± 12.2	29.4 ± 7.6	0.16 ± 0.14	0.38 ± 0.32
Urine alkalinization	8.1 ± 0.5[a]	2.6 ± 0.7[a]	23.5 ± 13.7[a]	5.0 ± 1.6[a]	9.0 ± 6.1[a]	2.44 ± 1.59[a]	3.87 ± 1.28[a]

a Significantly different from control ($p < 0.05$).

SD = standard deviation.

Table III. Data reported by Dukes et al.[13] and Cumming et al.,[14] including discrepancies between data

Dukes et al.[13]		Cumming et al.[14]		Initial serum salicylate concentration (mg/L)	Serum salicylate concentration after 8h (mg/L)	Urine volume over 8h (L)	Salicylate excretion over 8h (g)
case	sex (age)	case	sex (age)				
1	M (41)	3	F (41)	670[13]/550[14]	350	1.4	4.9
2	F (16)	1	F (16)	760[13]/800[14]	450	4.3	9.1
3	M (43)	2	M (43)	880	310	4.3[13]/5.18[14]	8.2
4	M (58)	4	M (58)	840	350	3.4	6.7
5	M (18)	5	M (18)	630	250	1.8[13]/2.25[14]	6.1

F = female; **M** = male.

"rapid relief of salicylism" in the patients receiving bicarbonate therapy compared with those receiving oral fluids or forced water diuresis who were symptomatic for more than 34 hours. However, no clinical data were reported to substantiate this conclusion.

The effect of acetazolamide and sodium bicarbonate in the treatment of ten patients with moderate to severe salicylate poisoning (as defined by a serum salicylate concentration >500 mg/L or clinical salicylate intoxication) was reported by Morgan and Polak.[17] Each patient received acetazolamide 250mg intravenously. Additionally, 1L of intravenous fluid that contained bicarbonate 166.7 mmol was administered hourly. The identical intravenous fluid plus potassium 20 mmol was infused during the second hour. If clinical dehydration was still present, the patient received additional 1L hourly infusions of 0.9% sodium chloride, plus potassium 20 mmol, until rehydration was achieved. Thereafter, 1L containing bicarbonate 166.7 mmol and potassium 40 mmol was infused over a period of 2 hours for a total of 4 hours. If the serum salicylate concentration remained greater than 400 mg/L, acetazolamide 250mg was administered intravenously along with 1L of 0.9% sodium chloride plus potassium 40 mmol and 1L of 1.4% sodium bicarbonate plus potassium 40 mmol, infused in rotation every 2 hours for a total of 4 hours. The mean pre-treatment urine pH was 6.82 (range 6.30–7.30) compared with a mean treatment urine pH of 7.88 (range 7.78–7.95). Serum salicylate concentrations in this study were measured by the non-specific Trinder method[15] and those in urine by the method of Brodie et al.[9] Urine pH was measured by a pH meter. The mean amount of salicylic acid recovered in the urine was 4.91g.

Table IV. Mean times for plasma salicylate concentrations to fall to two-thirds ($C_{2/3}$) and one-third ($C_{1/3}$) of their peak value[16]

Group	Mean (±SD) peak salicylate concentration (mg/L)	Mean $C_{1/3}$ (h)	Mean (±SD) $C_{2/3}$ (h)
Forced water diuresis (n = 7)	673 ± 93	>24	8.00 ± 4.55
Forced cocktail diuresis (n = 13)	672 ± 118	18	5.15 ± 2.79
Forced alkaline diuresis (n = 11)	709 ± 110	9	2.55 ± 1.13

SD = standard deviation.

Although the authors imply that salicylate elimination was enhanced, no control group was presented for comparison and neither the contribution of acetazolamide nor sodium bicarbonate could be assessed. The data from only eight of the ten patients were utilised due to a treatment protocol deviation. Despite the use of continuous potassium supplements during acetazolamide and sodium bicarbonate therapy, the serum potassium concentrations dropped from an initial mean value of 4.4 to 3.0 mmol/L. Additional data from patients in this study[17] were reported subsequently.[18]

Morgan et al.[19] studied 11 patients who had a mean serum salicylate concentration of 591 mg/L (range 450–850 mg/L). Each patient received an intravenous infusion consisting of 1L of 10% mannitol administered over 1 hour with the objective of producing a urine flow of approximately 500 mL/h. When necessary, dehydrated patients were rehydrated prior to the initiation of mannitol therapy. Urine volume and pH were measured and cumulative fluid balance was calculated at the end of the infusion and every 2 hours thereafter. If the positive fluid balance was 1L or less and the urine pH was <7, the patient received 1L of lactate 1/6M solution over 2 hours. Patients with a urine pH >7 received 1L of 0.9% saline over 2 hours. A positive fluid balance of 1–2L dictated the administration of an additional litre of 10% mannitol over 2 hours. When the positive fluid balance exceeded 2L, 10% mannitol was administered at the slowest rate possible. The mean urine flow achieved was 447 mL/h (range 380–490 mL/h). This study used the non-specific Trinder method[15] to measure salicylate concentrations. Urine pH was measured by pH meter. No data were presented in the study to show the effect of urine pH on salicylate excretion. Therefore, no conclusions can be drawn about the impact of urine alkalinization on salicylate excretion or patient

outcome. Additional data from patients in this study were reported subsequently.[18]

Morgan and Polak[18] reviewed the impact of urine alkalinization on salicylate excretion in 23 patients with initial salicylate concentrations of 440–880 mg/L who were treated with either mannitol/sodium lactate (11 patients) or acetazolamide/sodium bicarbonate (12 patients) regimens. The eleven patients in the mannitol/sodium lactate group, all of whom had been reported previously,[19] were administered mannitol to initiate and, when necessary, to sustain diuresis. Sodium lactate (1.87%) was administered when the urine pH fell below 7.0. Of the 12 patients in the acetazolamide/sodium bicarbonate group, ten had also been reported previously.[17] All 12 patients were initially administered acetazolamide 250mg intravenously to achieve a urine pH of >7.5, which was maintained as required with an infusion of 1.4% sodium bicarbonate. Serum salicylate concentrations in this study were measured by the non-specific Trinder method[15] and those in urine by the method of Brodie et al.[9] Urine pH was measured by a pH meter. The mean urine pH for the mannitol/sodium lactate and acetazolamide/sodium bicarbonate regimens were 6.67 (range 5.20–7.30) and 7.84 (range 7.34–8.00), respectively. The corresponding urine flows were 5.80 (range 2.29–12.20) and 5.75 (range 1.95–12.00) mL/min.

Although a clinically significant direct correlation between urine flow and salicylate clearance was reported, the authors concluded that enhanced salicylate excretion was due predominantly to increased urine pH. A highly significant ($p < 0.001$) correlation was found in the pooled results between increasing urine pH and salicylate clearance. A significant inverse correlation ($p < 0.001$) was also observed between serum salicylate half-life and the mean urine pH for both treatment regimens.

Prowse et al.[20] studied 22 patients who received urine alkalinization for acute salicylate poisoning. The patients were divided into two groups through random allocation. Twelve patients with a mean initial serum salicylate concentration of 450 mg/L (range 210–760 mg/L) received a total of 10L of fluid containing 360 mmol bicarbonate and 365.5g glucose over 8 hours. The second group of ten patients had a mean initial serum salicylate concentration of 450 mg/L (range 300–620 mg/L) and received 10L of fluid containing bicarbonate 348 mmol and mannitol 475g over the same period. Patients who passed less than 200mL of urine in the first 90 minutes of treatment or who developed a positive fluid balance in excess of 2.5L were also given furosemide 40mg intravenously. Salicylate concentrations in this study were measured by a non-specific method.[21] Urine pH was measured by an Astrup microtechnique.[22]

Mean urine outputs were 14.6 and 18.7 mL/min for the bicarbonate and glucose group and the bicarbonate and mannitol group, respectively, with a corresponding salicylate excretion rate of 10.7 mg/min (total urine salicylate excretion over 8 hours 5.1g) and 11.3 mg/min (total urine salicylate excretion over 8 hours 5.4g), suggesting that increasing the volume of alkaline urine does not increase salicylate excretion. The mean urine pH over the 8 hours of treatment varied between approximately 7.25 and 7.5 for the bicarbonate and glucose group, and 7.2 and 7.3 for the bicarbonate and mannitol group. The mean serum salicylate half-life was 7.7 hours for the patients in the bicarbonate and glucose group and 5.8 hours for the bicarbonate and mannitol group. No conclusions can be drawn from this study regarding the impact of urine pH manipulation or urine alkalinization in salicylate poisoning.

Berg[23] described the use of urine alkalinization in 33 patients with a mean serum salicylate concentration of 588 mg/L (range 402–1650 mg/L). One patient, a 20-year-old male, died 5 hours after admission (peak serum salicylic acid concentration 1650 mg/L). All patients were given 0.9% sodium chloride, 5% glucose and 1.4% sodium bicarbonate in rotation. Potassium chloride 20 mmol/L, furosemide 20mg or bumetanide 0.5mg every 2 hours, and 10% calcium chloride 10–30mL every 24 hours were also administered. Twenty-four of 33 patients, with a serum salicylate concentration of 300–600 mg/L were infused at a rate of 250–300 mL/h; the remaining nine patients with a serum salicylate concentration of 600–900 mg/L were infused at a rate of 400–500 mL/h. Diuresis was maintained for 16–48 hours (mean 22.3 hours) with a mean 24-hour urine output ± standard error (SE) of 5976 ± 598mL and 9196 ± 708mL in the two groups, respectively. Mild tetanic symptoms developed in six patients who were then treated with calcium chloride. The urine pH increased to a maximum of 7.70 (range 7.29–8.10). This study utilised the non-specific Keller method[21] to measure salicylate concentrations. Urine pH was measured by a pH meter. There are some discrepancies between the numbers of patients in the two groups in the results and treatment sections, no controls were used and no salicylate excretion data were given. The impact of urine alkalinization on salicylate elimination cannot be assessed from the data presented.

4.2 Case Reports

Savege et al.[24] described the treatment of a 36-year-old man who was admitted in a coma 1.5 hours after ingesting aspirin 90g. Sodium bicarbonate 150 mmol was administered initially followed by the rapid infusion of sodium bicarbonate, normal saline and 5% dextrose in rotation. Fourteen litres of fluid were administered over the first 12 hours of treatment, during which time 10.3L of urine were collected. Mannitol 190g was also administered over this period. Intravenous fluids were administered at a much-reduced rate over the following 12 hours. The methods used to measure salicylate concentrations and urine pH were not stated. Urine pH increased steadily during treatment, approaching 8 after 7.5 hours of treatment and remaining at approximately that level for a further 7 hours. In the first 8 hours of treatment, 21.5g salicylate were eliminated with a further 12.5g eliminated over the

following 14 hours. The blood salicylate concentration fell from 1380 to 150 mg/L during the first 12 hours with a half-life of 5.6 hours. The authors found a significant correlation ($p < 0.05$) between the difference in urine and arterial pH and blood salicylate, with clearance increasing with increasing urinary pH. No relationship was found between salicylate clearance and urine volume. An impressive and clinically significant quantity of salicylate was excreted in the urine in this case and was the result of urine alkalinization rather than enhanced diuresis.

5. Rationale for Urine Alkalinization

The experimental studies of Williams and Leonards,[8] Reimold et al.[10] and Vree et al.[11] and the clinical studies of Prescott et al.,[12] Morgan and Polak[18] and Savege et al.[24] confirm that urine alkalinization increases salicylate elimination. However, close scrutiny of the generally accepted view as to why alkalinization is effective shows that it cannot be correct.

5.1 Conventional Rationale for Urine Alkalinization

Cell membranes are more permeable to substances that are lipid soluble and in the non-ionised, rather than the ionised form. It is widely held that urine alkalinization enhances the elimination of salicylate by ensuring that in renal tubular fluid as much salicylic acid as possible is in the ionised state and therefore incapable of being reabsorbed. This concept, which was first proposed in 1949,[25] is now known as ion trapping. According to this hypothesis, the rate of diffusion from the renal tubular lumen back into the blood is *decreased* when salicylic acid is maximally ionised and *increased* when it is non-ionised. As the ionisation of a weak acid, such as salicylic acid, is increased in an alkaline environment, manipulation of the urine pH potentially can enhance renal excretion. Since pKa is a logarithmic function, theoretically, a small change in urine pH could have a disproportionately larger effect on salicylate clearance.

5.2 Critique of Conventional Rationale

In 1942, evidence was first presented that indicated that salicylic acid was appreciably ionised within physiological pH limits.[26] The extent of ionisation (dissociation) of a weak acid, such as salicylic acid, in an aqueous solution is determined by the law of mass action as shown in equation 1 where Ka is the ionisation constant, $[H^+]$ the hydrogen ion concentration, $[A^-]$ the concentration of ionised acid and [HA] the concentration of non-ionised acid.

$$Ka = \frac{[H^+][A^-]}{[HA]} \quad \text{(Eq. 1)}$$

It is customary to express ionisation constants in the form of their negative logarithms (pKa). Hence, the stronger an acid, the lower its pKa; for example, salicylic acid (pKa 3.13[26]) has a lower ionisation constant than acetylsalicylic acid (pKa 3.5[27]) and is therefore a stronger acid. The relationship between pKa and the proportion of total drug in ionised form is determined by the Henderson-Hasselbalch equation (equation 2).

$$pH = pKa + \log_{10}\left(\frac{[A^-]}{[HA]}\right) \quad \text{(Eq. 2)}$$

When pH = pKa, the concentrations of ionised and non-ionised drug are equal. The percentage of ionised salicylic acid at any given pH can therefore be calculated according to equation 3 where the pKa is that of salicylic acid and the pH is that in question.

$$\% \text{ Ionised} = \frac{100}{1 + 10^{(pKa - pH)}} \quad \text{(Eq. 3)}$$

It can be seen from figure 4 that practically all salicylic acid would be ionised at urine pH 5. Alkalinization of the urine could not, therefore, significantly increase the extent of ionisation further and the conventional view of the mechanism by which alkalinization is effective is patently impossible. This view is supported by other authors.[28]

5.3 Alternative Hypotheses

Human studies have shown that alkali administration neither increases the glomerular filtration rate[6] nor the proportion of filterable salicylate at the glomeruli.[6,8] Similarly, it does not alter significantly the rates of elimination of salicyluric acid and salicyl phenolic glucuronide, the major metabolites of salicylic acid.[11] Also, although it is possible for salicyl acyl glucuronide to hydrolyse back to salicylic acid at high pH values, this did not contribute significantly to urine salicylate excretion.[11] Berliner[29] suggested that alkalinization acted by partitioning non-ionised salicylate from peritubular fluid to the luminal fluid. Macpherson et al.[28] considered that this hypothesis would explain their data

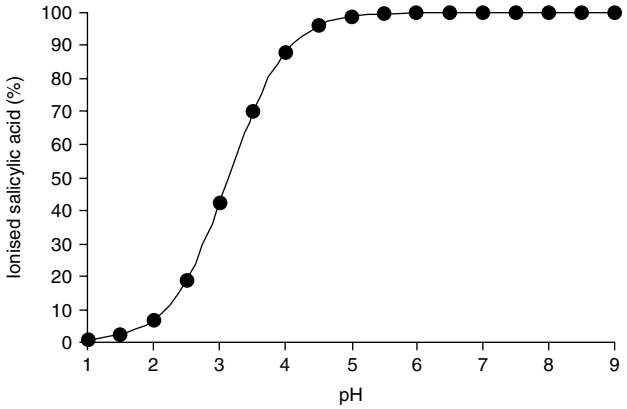

Fig. 4. Ionisation of salicylic acid at various pH values.

but since salicylic acid would be almost completely ionised at much lower pH values the proposition seems as unlikely as the conventional view. Moreover, it has been criticised on the grounds that net secretion (the balance between active tubular secretion and passive reabsorption) of salicylate can occur when urine pH is acid[3] and because drugs such as probenecid inhibit active secretion without altering urine pH.[3]

The studies reviewed above make it clear that alkalinization of the urine impairs tubular reabsorption of salicylic acid but how this is achieved remains unclear. Further experimental studies are required to elucidate the mechanisms of enhanced elimination.

6. Conclusion

Studies[8,10-12,18,24] confirm that urine alkalinization increases salicylate elimination. However, although urine alkalinization enhances the elimination of salicylates, the conventional view that this occurs by increasing the fraction of ionised drug in the renal tubular lumen cannot be correct. Adequate data to establish the mechanism of the pH dependency of renal salicylate clearance have proved elusive. Further investigation is required to elucidate the mechanism(s) of potential clinical benefit.

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