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ARTICLE

Position Paper on Urine Alkalinization

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ABSTRACT

This Position Paper was prepared using the methodology agreed by the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT). All relevant scientific literature was identified and reviewed critically by acknowledged experts using set criteria. Well-conducted clinical and experimental studies were given precedence over anecdotal case reports and abstracts were not considered. A draft Position Paper was then produced and presented at the North American Congress of Clinical Toxicology in October 2001 and at the EAPCCT Congress in May 2002 to allow participants to comment on the draft after which a revised draft was produced. The Position Paper was subjected to detailed peer review by an international group of clinical toxicologists chosen by the AACT and the EAPCCT, and a final draft was approved by the boards of the two societies. The Position Paper includes a summary statement (Position Statement) for ease of use, which will also be published separately, as well as the detailed scientific evidence on which the conclusions of the Position Paper are based. Urine alkalinization is a treatment regimen that increases poison elimination by the administration of intravenous sodium bicarbonate to produce urine with a pH $\geq$7.5. The term *urine alkalinization* emphasizes that urine pH manipulation rather than a diuresis is the prime objective of treatment; the terms *forced alkaline diuresis* and *alkaline diuresis* should therefore be discontinued. Urine alkalinization increases the urine elimination of chlorpropamide, 2,4-dichlorophenoxyacetic acid, diflunisal, fluoride, mecoprop, methotrexate, phenobarbital, and salicylate. Based on volunteer and clinical studies, urine alkalinization should be considered as first line treatment for patients with moderately severe salicylate poisoning who do not meet the criteria

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for hemodialysis. Urine alkalinization cannot be recommended as first line treatment in cases of phenobarbital poisoning as multiple-dose activated charcoal is superior. Supportive care, including the infusion of dextrose, is invariably adequate in chlorpropamide poisoning. A substantial diuresis is required in addition to urine alkalinization in the chlorophenoxy herbicides, 2,4-dichlorophenoxyacetic acid, and mecoprop, if clinically important herbicide elimination is to be achieved. Volunteer studies strongly suggest that urine alkalinization increases fluoride elimination, but this is yet to be confirmed in clinical studies. Although urine alkalinization is employed clinically in methotrexate toxicity, currently there is only one study that supports its use. Urine alkalinization enhances diflunisal excretion, but this technique is unlikely to be of value in diflunisal poisoning. In conclusion, urine alkalinization should be considered first line treatment in patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis. Urine alkalinization and high urine flow (approximately 600 mL/h) should also be considered in patients with severe 2,4-dichlorophenoxyacetic acid and mecoprop poisoning. Administration of bicarbonate to alkalinize the urine results in alkalemia (an increase in blood pH or reduction in its hydrogen ion concentration); pH values approaching 7.70 have been recorded. Hypokalemia is the most common complication but can be corrected by giving potassium supplements. Alkalotic tetany occurs occasionally, but hypocalcemia is rare. There is no evidence to suggest that relatively short-duration alkalemia (more than a few hours) poses a risk to life in normal individuals or in those with coronary and cerebral arterial disease.

Key Words: Urine alkalinization; Chlorpropamide; 2,4 dichlorophenoxyacetic acid; Diflunisal; Phenobarbital; Flouride; Methotrexate; Salicylate.

POSITION STATEMENT ON URINE ALKALINIZATION

Definition

Urine alkalinization is a treatment regimen that increases poison elimination by the administration of intravenous sodium bicarbonate to produce urine with a pH $\geq$ 7.5. The term *urine alkalinization* emphasizes that urine pH manipulation rather than a diuresis is the prime objective of treatment; the terms *forced alkaline diuresis* and *alkaline diuresis* should therefore be discontinued.

Rationale

Most drugs at physiological pH exist partly as undissociated molecules. The extent of dissociation is a function of the ionization (acid dissociation) constant (Ka) of the drug and the pH of the medium in which it is dissolved. Ionization (dissociation) constants are expressed in the form of their negative logarithms (pKa). Hence, the stronger an acid, the lower its pKa; conversely, the stronger a base, the higher the pKa. The relationship between pKa and the proportion of total drug in ionized form is represented by the Henderson-Hasselbalch equation. When pH=pKa, the concentrations of ionized and non-ionized drug are equal. Cell membranes are more permeable to substances that are lipid soluble and in the non-ionized, rather than the ionized form. The rate of diffusion from the renal tubular lumen back into the blood is *decreased* when a drug is maximally ionized and *increased* if the drug is non-ionized. As the ionization of a weak acid is increased in an alkaline environment, manipulation of the urine pH potentially can enhance renal excretion. For an acidic drug, there is a greater degree of ionization at pH 8 than pH 7.4. Thus, elimination of a weak acid by the kidneys is increased in alkaline urine. Since pKa is a logarithmic function then, theoretically, a small change in urine pH could have a disproportionately larger effect on clearance, especially for those drugs that have pKa values close to blood pH. For each change in urine pH of one unit there is theoretically a 10-fold change in renal clearance whereas at best the renal clearance of a reabsorbed drug varies directly with the urine flow rate. The effectiveness of urine alkalinization depends on the relative contribution of renal clearance to the total body clearance of active drug. If only 1% of an ingested dose is excreted unchanged in the urine, even a 20-fold increase in renal clearance will have no clinically significant effect on the total clearance.

Review of the Literature

This review cites only those studies which support the recommendations of the Position Paper. A critical

and comprehensive analysis of the literature is to be found in the Position Paper.

Chlorpropamide

Neuvonen and Kärkkäinen (1) investigated the effect of urine alkalinization and urine acidification on chlorpropamide kinetics in a randomized cross-over study in which each treatment modality was applied to six volunteers at two- to three-week intervals. Before each regimen, chlorpropamide 250 mg was administered orally. In the urine alkalinization phase sodium bicarbonate was administered orally between 1 and 64h after chlorpropamide dosing, to achieve and maintain a urine pH of 7.1–8.2. Urine alkalinization reduced significantly ($p < 0.001$) the chlorpropamide AUC_{0-72}, $AUC_{0-\infty}$ and the chlorpropamide elimination half-life (12.8 ± 1.1h) compared to control (49.7 ± (SEM) 7.4h), and increased significantly ($p < 0.001$) the total chlorpropamide clearance from 104 ± (SEM) 13 mL/h (control) to 363 ± 22 mL/h. The mean chlorpropamide ex-cretion over 72h was significantly greater ($p < 0.001$) in those volunteers undergoing urine alkalinization (213 ± (SEM) 11 mg) than in the control group (50.9 ± 7.3 mg) and in those subjected to urine acidification (3.5±0.52 mg).

In conclusion, the data suggest that urine alkalinization increases chlorpropamide elimination substantially and might therefore shorten the time-course of acute chlorpropamide poisoning. However, as the administration of dextrose alone is effective treatment in the majority of patients with chlorpropamide poisoning, which is now rare, urine alkalinization is only likely to be employed very occasionally.

2,4-D and Mecoprop

In a 39-year-old male poisoned severely with 2, 4-D and mecoprop (2,3), the renal 2,4-D clearance corrected for urine flow (adjusted to 1 mL/min) was directly proportional to urine pH (r=0.99). A mean corrected renal clearance of 0.28 mL/min over the urine pH range 5.1–6.5 and 9.6 mL/min over the pH range 7.55–8.8 was found. At pH 5.1 and pH 8.3 the uncorrected renal clearances were 0.14 mL/min and 63 mL/min, respectively. The plasma half-life of 2,4-D was approximately 219h before urine alkalinization and 3.7h over the period 96–112h post-ingestion when the urine pH exceeded 8.0. A substantially increased 2,4-D clearance was achieved only when the urine pH exceeded 7.5 and was accompanied by a urine flow rate of the order of 200 mL/h. The maximal uncorrected 2,4-D renal clearance of 63 mL/min at pH 8.3 would have required a urine flow rate of approximately 600 mL/h. In these circumstances 2,4-D clearance compared favorably with that achieved with hemodialysis (56.3–72.9 mL/min (4)), whereas the effect of urine alkalinization alone without high urine flow was markedly less efficient than hemodialysis as a means of removing 2,4-D.

The renal mecoprop clearance corrected for urine flow (adjusted to 1 mL/min) was directly proportional to urine pH (r = 0.94). A mean corrected renal clearance of 0.38 mL/min over the urine pH range 5.1–6.5 and 2.08 mL/min over the pH range 7.55–8.8 was found. The plasma half-life of mecoprop was shortened from 39 to 14h with urine alkalinization.

In conclusion, the data from the patient reported by Park et al. (2) and Prescott et al. (3) demonstrate enhanced chlorophenoxy herbicide elimination with urine alkalinization. If urine alkalinization is to be employed, however, both a high urine pH (> 8) and a high urine flow (of the order of 600 mL/h) are required to achieve a substantially increased renal clearance of 2,4-D (comparable to that achieved by hemodialysis) and mecoprop.

Fluoride

The effects of urine pH on fluoride ion excretion were investigated in 10 patients undergoing abdominal hysterectomy under enflurane anesthesia (5). To acidify the urine, patients in Group 1 (n=5) received ammonium chloride 1 g × 4 during the pre-operative day and 1 g on the morning of operation. Patients in Group 2 (n=5) received acetazolamide 500 mg intravenously 60min before the clearance determinations were started to alkalinize the urine. The mean maximum fluoride concentration was 0.502 ± (SD) 0.150 mg/L in Group 1 patients (urine pH 5.08 ± 0.25) and in Group 2 patients (urine pH 8.16 ± 0.26) was 0.256 ± 0.046 mg/L. Mean total urine excretion of fluoride during anesthesia was 0.06 ± 0.04 mg in Group 1 patients and 0.87 ± 0.29 mg in Group 2 patients ($p < 0.001$). Although the urine flow rate was greater in Group 2 patients (1.54 ± 1.10 mL/min) than in Group 1 patients (0.53 ± 0.18 mL/min), the difference was not of sufficient magnitude to account for the difference in fluoride excretion.

In conclusion, this volunteer study is suggestive that urine alkalinization increases fluoride excretion and is therefore likely to be of value in acute fluoride poisoning, though this must be confirmed in clinical studies.

Methotrexate

Sand and Jacobsen (6) studied the effects of increased urine flow rate and urine alkalinization on

methotrexate clearance in 11 patients (7 males, 4 females) undergoing chemotherapy for various malignant diseases. Methotrexate 1–2 g/m^2 was infused in 1 L saline over 4h. Urine was collected during the last 2h of the infusion, at the end of the infusion, twice daily (morning and afternoon) on the following two days and on the morning of day four. Blood was taken at the mid-point or at the beginning and end of each urine collection period. The eight patients with normal renal function (creatinine clearance 98–121 mL/min) were given up to 400 mL/h oral fluid for 7h on days two and three, with oral sodium bicarbonate 10 g over 3h before the afternoon collection period on day three. Three patients with impaired renal function (creatinine clearance 47–67 mL/min) were asked to drink as much as possible and received oral sodium bicarbonate up to 20 g/day.

The authors used the ratio of renal methotrexate clearance (C_{MTX}) to creatinine clearance (C_{creat}) to enable comparison of methotrexate clearance values between patients with different renal function. The results demonstrated a linear relationship ($r=0.596$) between urine pH and C_{MTX}/C_{creat} for the whole group (11 patients, 80 measurements), C_{MTX}/C_{creat} increasing from 0.88 at pH 5.5 to 2.62 at pH 8.4 ($p < 0.001$). A similar dependence of methotrexate clearance on urine pH was observed when data for patients with normal and impaired renal function were considered separately ($p < 0.01$). There was no correlation between C_{MTX}/C_{creat} and urine flow for each measurement period in the patients with impaired renal function, though this relationship approached significance ($r=0.299$, $p=0.05$) in patients with normal renal function.

In conclusion, this study showed that a combination of urine alkalinization and fluid load increased the rate of elimination of methotrexate. The effect of alkalinization was greater than that induced by increased urine flow. Limited data suggest that hemoperfusion (7) is more efficient than urine alkalinization.

Phenobarbital

Using a randomized cross-over design, Frenia et al. (8) compared urine alkalinization with multiple-dose activated charcoal in enhancing phenobarbital elimination in 12 volunteers who were administered phenobarbital 5 mg/kg intravenously. In the urine alkalinization phase, the urine pH was maintained between 7.5–8.0. Urine alkalinization reduced significantly ($p=0.013$) the phenobarbital elimination half-life (47.24 ± (SD) 42.04h) compared to the control group (148.1 ± 332.1h) and increased significantly ($p=0.001$) the mean total body phenobarbital clearance (8.29 ± (SD) 8.62 mL/kg/h) when compared to controls (2.79 ± (SD) 9.69 mL/kg/h); multiple-dose activated charcoal was superior (19.95 ± 11.55 mL/kg/h), however, to urine alkalinization ($p < 0.0005$) in increasing phenobarbital elimination.

Ebid and Abdel-Rahman (9) also described the impact of urine alkalinization (the urine pH was maintained between 7.5–8.0 and the urine volume was not less than 3–6 mL/kg/h) and multiple-dose activated charcoal on phenobarbital elimination. In each group there were 10 male patients poisoned with phenobarbital (the mean plasma phenobarbital concentration in the two groups was 100.6 ± 12.6 mg/L and 103.2 ± 12.2 mg/L, respectively). Compared to urine alkalinization (81.1 ± (SD) 14.6h), multiple-dose activated charcoal reduced significantly ($p<0.05$) the mean phenobarbital elimination half-life (38.6 ± 6.6h) and increased significantly ($p<0.05$) the mean total body clearance of phenobarbital (10.8 ± (SD) 1.8 mL/kg/h) compared to urine alkalinization (5.1 ± 0.9 mL/kg/h). With multiple-dose activated charcoal, the mean durations of assisted ventilation (40.2 ± (SD) 12.5h), intubation (29.7 ± (SD) 10.3h), and coma (24.4 ± (SD) 9.6h) were significantly shorter ($p<0.05$) than in the group treated with urine alkalinization (79.4 ± 20.9h; 54.2 ± 12.8h; 50.6 ± 12.5h, respectively). Although this study did not include a control group, urine alkalinization did not appear to increase phenobarbital clearance (mean 0.085 mL/kg/min) significantly compared to reported endogenous clearances (0.062 mL/kg/min (10)) but was less effective than multiple-dose activated charcoal.

In conclusion, urine alkalinization is less efficient than multiple-dose activated charcoal, which is the treatment of choice.

Salicylates

Vree et al. (11) conducted a randomized cross-over study in six volunteers who were administered sodium salicylate 1.5 g orally before initiation of urine alkalinization (mean urine pH 7.67 ± (SD) 0.65) or urine acidification (mean urine pH 5.54 ± 0.57). The mean peak salicylate concentrations were 93.3 ± (SD) 18.6 mg/L and 109.8 ± 17.8 mg/L (NS), respectively. The mean elimination half-life during urine alkalinization (2.50 ± (SD) 0.41h) was significantly less ($p=0.0156$) than that during urine acidification (3.29 ± 0.52). The mean total body clearance was increased significantly ($p=0.041$) during urine alkalinization (2.27 ± (SD) 0.83 L/hr) compared to urine acidification (1.38 ± 0.43 L/h).

Prescott et al. (12) studied six patients with a mean admission plasma salicylate concentration of 439 ± (SD)

86 mg/L who were given sodium bicarbonate 225 mmol and potassium 60 mmol in 1.5 L fluid (mean urine pH 8.1 ± (SD) 0.5) and 16 patients with a mean admission plasma salicylate concentration of 328 ± (SD) 57 mg/L who received only oral fluids and acted as control (mean urine pH 6.1 ± 0.4). There was a highly significant correlation ($r = +0.82$; $p < 0.001$) between urine pH and log salicylate clearance. Patients receiving urine alkalinization had a significantly greater ($p < 0.05$) mean renal salicylate clearance (23.5 ± 13.7 mL/min) than the control group (1.4 ± (SD) 1.4 mL/min). In addition, in those patients undergoing urine alkalinization, a significant ($p < 0.05$) decrease in the mean plasma elimination half-life $_{4-16hr}$ (9.0 ± (SD) 6.1h) compared to the control group (29.4 ± 7.6h) was reported. These data show that urine alkalinization enhances salicylate clearance. However, as the conclusions of the study were based on only six patients, there were insufficient data to determine if urine alkalinization had an impact on patient morbidity.

In conclusion, the volunteer study of Vree et al. (11) and the clinical study of Prescott et al. (12) indicate that urinary alkalinization is of value in the treatment of salicylate poisoning.

Indications for Urine Alkalinization

Urine alkalinization increases the urine elimination of chlorpropamide, 2,4-dichlorophenoxyacetic acid, diflunisal, fluoride, mecoprop, methotrexate, phenobarbital, and salicylate. Based on human volunteer and clinical studies urine alkalinization is appropriate first line treatment for patients with moderately severe salicylate poisoning that does not require hemodialysis. Urine alkalinization cannot be recommended as first line treatment in cases of phenobarbital poisoning as multiple-dose activated charcoal is superior. Supportive care, including the infusion of dextrose, is invariably adequate in the case of chlorpropamide poisoning. A substantial diuresis is required in addition to urine alkalinization in the case of the chlorophenoxy herbicides, 2,4-dichlorophenoxyacetic acid, and mecoprop, if clinically important herbicide elimination is to be achieved. Volunteer studies strongly suggest that urine alkalinization increases fluoride elimination but this is yet to be confirmed in clinical studies. Although urine alkalinization is employed clinically in methotrexate toxicity, currently there is only one study that supports its use. Urine alkalinization enhances diflunisal excretion, but this technique is unlikely to be of value in diflunisal poisoning.

In conclusion, urine alkalinization should be considered as first line treatment in patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis. Urine alkalinization and high urine flow (approximately 600 mL/h) should also be considered in patients with severe 2,4-dichlorophenoxyacetic acid and mecoprop poisoning.

Contraindications

Established or incipient renal failure is a contraindication to urine alkalinization. Significant preexisting heart disease is a relative contraindication.

Complications of Use

Administration of bicarbonate to induce alkaline diuresis results in alkalemia (an increase in blood pH or reduction in its hydrogen ion concentration); pH values approaching 7.70 have been recorded. Hypokalemia is the most common complication but can be corrected by giving potassium supplements. Alkalotic tetany occurs occasionally, but hypocalcemia is rare. There is no evidence to suggest that relatively short-duration alkalemia (more than a few hours) poses a risk to life in normal individuals or in those with coronary and cerebral arterial disease.

POSITION PAPER

Introduction

Forced diuresis and forced alkaline diuresis (alkaline diuresis) were introduced into clinical practice at a time when toxicokinetic principles were unknown or in their infancy; hemodialysis facilities were much less available than they are now, charcoal hemoperfusion was yet to become available and the benefits of multiple doses of oral activated charcoal were not appreciated. At that time, the major toxicological challenges facing clinicians were poisoning from barbiturates and salicylates. Forced alkaline diuresis offered a technique which appeared logical and required neither special equipment nor expertise. It was applied not only in barbiturate and salicylate poisoning but also in the treatment of intoxication with a variety of substances, present-day knowledge of the physicochemical properties of which makes it unlikely that the procedure achieved its clinical objective. Survival of the patient was all too often taken to mean that the treatment was a success (13). In addition, the methods of drug analysis available at the time were non-specific and commonly measured inactive metabolites in addition to parent compound. As a consequence, many

of the published attempts to assess critically the value of forced alkaline diuresis do not satisfy current scientific standards. Moreover, it must also be recognized that high renal clearances are not necessarily associated with excretion of toxicologically significant amounts of poison. For example, if only 1% of a poison is excreted unchanged in the urine, even a 20-fold increase in renal excretion would produce only a modest increase in overall elimination.

Although the objectives of forced alkaline diuresis (alkaline diuresis) are to increase the rate of urine flow and increase its pH, few authors have detailed precisely their objectives or how they achieved them. The approach has varied from poison to poison, the rate of fluid administration generally being lower the longer acting the substance. Forced alkaline diuresis has usually been attempted by infusing lactate or bicarbonate. Less commonly, acetazolamide, an inhibitor of carbonic anhydrase, was used but soon abandoned when it was appreciated that it increased intracellular acidosis. In barbiturate poisoning, osmotic diuretics such as mannitol or urea were used in addition to an intravenous fluid load to increase urine flow. Less commonly loop diuretics were employed.

Lawson et al. (14) lamented the variety of composition of infusion fluids and infusion rates used during forced alkaline diuresis for treatment of salicylate poisoning. Only Dukes et al. (15) defined their regimen as intended to produce a urine flow rate of about 0.5 L/h and a pH of no more than 8. To achieve this objective, they infused dextrose (0.5 L 5%), normal saline (0.5 L), and sodium bicarbonate (0.5 L 2%) in rotation at a rate of 2 L/h, omitting alkali when the urine pH exceeded 8.

This Position Paper adopts the term *urine alkalinization* to emphasize that urine pH manipulation rather than a diuresis is the prime objective of treatment. It is recommended therefore that the terms *forced alkaline diuresis* and *alkaline diuresis* should be abandoned.

Definition

Urine alkalinization is a treatment regimen that increases poison elimination by the administration of intravenous sodium bicarbonate to produce urine with a $pH \geq 7.5$.

Methodology

Using the methodology agreed by the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT), all relevant scientific literature was identified and reviewed critically using set criteria. Medline (1966–August 2003), Toxline Special (pre-1981–August 2003), and EMBASE (1974–August 2003) were searched using the terms urine alkalinization, alkaline diuresis, and forced diuresis. In all, 858 references were identified from Medline, 593 from EMBASE, and 309 from Toxline. The abstracts of all these papers were obtained and checked by a Senior Information Scientist (Sarah Cage). The majority did not deal with the treatment of poisoned patients; there was a high proportion of references on the use of forced diuresis as an adjunct to chemotherapy, for the treatment of renal calculi, cystinuria, and hemorrhagic cystitis after chemotherapy. The search strategy also retrieved papers in which urine alkalinization was mentioned as the treatment of choice for various types of poisoning.

In addition, after relevant literature had been identified, additional searches were carried out on particular poisons (barbiturates, chlorophenoxy herbicides, chlorpropamide, diuresis and diflunisal, fluoride, methotrexate, mushrooms, pentachlorophenol, and salicylates), which the first search strategy had suggested were possible indications for urine alkalinization. This search identified 412 additional references from Medline, 613 from Embase, and 132 from Toxline. The principal authors of the Position Paper then reviewed all the scientific papers identified by the Senior Information Scientist, which contained original data on urine alkalinization. Papers on forced diuresis alone were excluded.

A draft Position Paper was then produced and, to allow participants to comment on the draft, a summary was presented at the North American Congress of Clinical Toxicology in October 2001 and at the EAPCCT Congress in May 2002. In addition, the draft Position Paper was also subjected to detailed peer review by an international group of clinical toxicologists chosen by the AACT and EAPCCT.

RATIONALE FOR URINE ALKALINIZATION

The concentrations of poisons filtered at the renal glomerulus increase as water is reabsorbed during the passage of the filtrate down the nephron, increasing the tubule/plasma concentration gradient in favor of reabsorption of the poison. Forcing a diuresis enhances poison elimination by reducing its concentration in renal tubular fluid and therefore the gradient for reabsorption. The same end result may be achieved by increasing the rate of flow of filtrate in the nephron

and reducing the time spent in the tubule. Reabsorption can be further reduced and elimination enhanced by trapping the poison in the urine (ion trapping) by manipulating urine pH in such a way as to keep it in an ionized state.

Most drugs at physiological pH exist partly as undissociated molecules. The extent of dissociation is a function of the ionization (acid dissociation) constant (Ka) of the drug and the pH of the medium in which it is dissolved. Ionization (dissociation) constants are expressed in the form of their negative logarithms (pKa). Hence, the stronger an acid, the lower its pKa; conversely, the stronger a base, the higher the pKa. The relationship between pKa and the proportion of total drug in ionized form is represented by the Henderson-Hasselbalch equation. When pH=pKa, the concentrations of ionized and non-ionized drug are equal. Cell membranes are more permeable to substances that are lipid soluble and in the non-ionized, rather than the ionized form. The rate of diffusion from the renal tubular lumen back into the blood is *decreased* when a drug is maximally ionized and *increased* if the drug is non-ionized. As the ionization of a weak acid is increased in an alkaline environment, manipulation of the urine pH potentially can enhance renal excretion. For an acidic drug, there is a greater degree of ionization at pH 8 than pH 7.4. Thus, elimination of a weak acid by the kidneys is increased in alkaline urine. Since pKa is a logarithmic function then, theoretically, a small change in urine pH could have a disproportionately larger effect on clearance, especially for those drugs that have pKa values close to blood pH. For each change in urine pH of one unit, there is theoretically a 10-fold change in renal clearance, whereas at best the renal clearance of a reabsorbed drug varies directly with the urine flow rate.

The impact of urine alkalinization depends upon the extent and persistence of the pH change. A urine pH of at least 7.5 must not only be achieved but also maintained if renal excretion of poison is to be enhanced substantially. In addition, the effectiveness of urine alkalinization depends on the relative contribution of renal clearance to the total body clearance of active drug. If only 1% of an ingested dose is excreted unchanged in the urine, even a 20-fold increase in renal clearance will have no clinically significant effect on the total clearance.

ANIMAL STUDIES

Sodium Salicylate

Reimold et al. (16) studied the effects of urine alkalinization on salicylate elimination in dogs anesthetized with pentobarbital. Twenty-seven dogs age 3–6 months and weighing 5–8 kg were administered sodium salicylate 700 mg/kg intravenously over 1h. The serum salicylate concentration was greater than 1000 mg/L in all the animals, with a maximum of 1220 mg/L. The animals were divided in a non-randomized way into three groups of nine animals:

Group 1. *Water diuresis treatment group*. Following the intravenous administration of sodium salicylate, a solution of saline 0.225% with glucose 2.5% and potassium chloride 20 mmol/L was 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.

Group 2. *Bicarbonate treatment group*. The treatment regimen was the same as for 'water diuresis' except that sodium bicarbonate 1 mmol/min was

Table 1. The impact of urine pH on salicylate elimination (after Reimold et al. (16)).

Group	Urine pH 9h post-dosing	Mean serum salicylate concentration 9h post-dosing (mg/L)	Mean serum salicylate half-life (hr)	Mean±SD salicylate excretion over 9 hr (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[†]	192	5.2	2512±164[‡]	3/9 (33)
+Bicarbonate + acetazolamide (n=9)	7.8[†,*]	274	4.8**	2886±180[§]	1/9 (11)

[†]Significantly different from water diuresis group ($p<0.001$).
[‡]Significantly different from water diuresis group ($p<0.005$).
*Significantly different from water diuresis group ($p<0.05$).
**Figure in paper (16) suggests the value was 7.7.
[§]Significantly different from water diuresis group ($p<0.0005$).

administered 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 and continued until the end of the study. 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.

Group 3. *Acetazolamide treatment group*. The treatment regimen was the same as for the bicarbonate group except that, in addition, acetazolamide 10 mg/kg was administered when the blood pH fell below 7.45.

The urine pH, serum salicylate concentration, serum salicylate half-life, total salicylate excretion and survival rate for the three groups 9h after intravenous administration of sodium salicylate are shown in Table 1.

Comment. This study was designed to ensure that the two groups of animals treated with sodium bicarbonate achieved a urine pH $\geq$7.5. The method by which urine pH was measured is not stated. In fact, a pH of 7.5 was not reached in the dogs in Groups 2 and 3 for mean times of 305 and 275 minutes, respectively. Furthermore, as seven out of the nine dogs in Group 1, three of the nine in Group 2 and one in Group 3 died during the study, the data shown in Table 1 may be subject to bias due to small sample size. In addition, although original data are not given in the published paper (16), Fig. 2 in the paper suggests that the mean half-life was similar before and after the urine pH of 7.5 was reached in Groups 2 and 3. However, the mean total salicylate excretion over 9h of treatment was significantly greater and survival increased in the Groups treated by urine alkalinization.

VOLUNTEER STUDIES

Chlorpropamide

Neuvonen and Kärkkäinen (1) and Kärkkäinen et al. (17) investigated the effect of activated charcoal, urine alkalinization and urine acidification on chlorpropamide kinetics in a cross-over randomized study in which each treatment modality was applied to six volunteers at two- to three-week intervals. Before each regimen, oral chlorpropamide 250 mg was administered 1h after a light breakfast. In the urine alkalinization phase oral sodium bicarbonate was administered between 1 and 64h (frequency not stated) after chlorpropamide dosing to achieve and maintain a urine pH of 7.1–8.2. The mean sodium bicarbonate dose was 41.5±SEM 3.2 g. Serum was sampled before chlorpropamide dosing and at 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72h thereafter. Cumulative urine collections were undertaken for 72h in the following fractions 0–2, 2–4, 4–6, 6–8, 8–12, 24–36, 36–48, 48–60, and 60–72h (Note: The period 12–24h was not listed but the authors imply the collection was continuous) with urine pH determined immediately after each collection period.

Sodium bicarbonate administration significantly ($p<0.05$) shortened the time to peak serum chlorpropamide concentration from a mean of 4.7±SEM 1.0h to 2.7±0.4h though the peak concentration and volume of distribution were not changed significantly. Urine alkalinization (pH 7.1–8.2) also significantly ($p<0.001$) reduced the chlorpropamide AUC_{0-72}, $AUC_{0-\infty}$ and the chlorpropamide elimination half-life (from 49.7±SEM 7.4h to 12.8±SEM 1.1h), while total chlorpropamide clearance increased from 104±SEM 13 mL/h to 363±22 mL/h ($p<0.001$). Chlorpropamide excretion over 72h was 85±SEM 4.5% of the administered dose in alkaline urine compared to 20.4±SEM 0.03% in the control phase ($p<0.001$).

Comment. The marked dependence of chlorpropamide renal clearance on urine pH was emphasized by the observation that at urine pH 5 renal chlorpropamide clearance was of the order of 0.5–3 mL/h compared to 500–1000 mL/h at pH 8. The ratio of renal to non-renal chlorpropamide clearance (where total clearance=Dose /$AUC_{0-\infty}$ and non-renal clearance=total clearance- renal clearance) was also highly urine pH-dependent with predominantly non-renal clearance at pH 5–6, superseded at pH 8 by renal clearance more than 10-fold greater than non-renal elimination.

Role of Urine Alkalinization in Chlorpropamide Poisoning

The data suggest that urine alkalinization increases chlorpropamide elimination substantially and might therefore shorten the time-course of acute chlorpropamide poisoning. However, as the administration of dextrose alone is effective treatment in the majority of patients with chlorpropamide poisoning, which is now rare, urine alkalinization is only likely to be employed very occasionally.

Diflunisal

Balali-Mood and Prescott (18) investigated the effect of urine alkalinization on the elimination of diflunisal (pKa 3.3). In a control study six healthy adult volunteers ingested diflunisal 750 mg. Twelve plasma diflunisal concentrations were measured over the following 72h and urine pH and volume were monitored 2 hourly for 12h and then 12 hourly for the next 60h (mean urine output 1.3 L/day). The study was repeated

at least two weeks later with administration of oral sodium bicarbonate 3 g four times daily the day before and for 48h following ingestion of diflunisal 750 mg. Fluid intake was increased to maintain a urine output of some 4 L/day.

The authors stated that the mean renal clearance was significantly greater (no p value given) with alkalinization (0.46±SD 0.22 mL/min, mean pH=7.5± SD 0.4) than in the control study (0.27±SD 0.25 mL/min, mean pH=6.3±SD 0.3). However, there was no statistically significant correlation between renal clearance of diflunisal and urine pH or flow. Although the 72h excretion of unchanged diflunisal was more than doubled with urine alkalinization (from 22.4±SD 6.8 mg to 49.3±SD 13.2 mg), only 5–7% of the total dose was excreted unchanged in alkalinized urine. There was no significant reduction in the plasma half-life of diflunisal with alkalinization (control 12.9±SD 1.5h; 12.5±SD 1.5h with alkalinization) nor in plasma diflunisal concentrations.

Comment. Given that only 5–7% of diflunisal is excreted unchanged in the urine, a two-fold increase in diflunisal elimination in alkaline urine is not of clinical significance.

Role of Urine Alkalinization in Diflunisal Poisoning

Urine alkalinization is unlikely to be of value in the management of diflunisal poisoning.

Fluoride

Five healthy adult volunteers were administered sodium bicarbonate 1 g every 4h during the day preceding ingestion of sodium fluoride 3 mg, then sodium bicarbonate 10 g over the following 11h (19). Urine pH was monitored hourly for 12h. The study was repeated after an unspecified time with acidification of the urine using ammonium chloride.

The mean renal clearance was significantly greater ($p<0.01$) in the alkalinization phase (97.8±SD 10.4 mL/min, mean pH=7.43±0.18) than in the acidification phase (61.5±SD 8.1 mL/min, mean pH=5.25± 0.25). There was no significant difference between urine flow rates in the two phases of this study. The authors calculated that the extra-renal clearance of fluoride was also increased significantly ($p<0.001$) under the influence of alkalinization and attributed this to increased fluoride uptake into bone.

Comment. This study did not include a phase without urine pH manipulation, and its value in assessing the clinical effectiveness of urine alkalinization is therefore limited. However, the percentage increase in mean renal clearance of fluoride was approximately double that of extra-renal clearance (59% compared with 26.5%) at mean urine pH 7.43 compared with mean urine pH 5.43, indicating the greater importance of renal elimination at higher pH values.

The effects of urine pH on fluoride ion excretion were investigated in 10 patients undergoing abdominal hysterectomy under enflurane anesthesia (5). The patients were randomized into two groups of five each. To acidify the urine, patients in Group 1 received ammonium chloride 1 g×4 during the preoperative day and 1g on the morning of operation. Patients in Group 2 received acetazolamide 500 mg intravenously 60 min before the clearance determinations were started to alkalinize the urine. After induction of anesthesia plasma fluoride concentrations (measured by a fluoride ion-sensitive electrode) increased rapidly in both groups. The mean maximum fluoride concentrations were 0.502±(SD) 0.150 mg/L in Group 1 patients (urine pH 5.08±0.25) and in Group 2 patients (urine pH 8.16±0.26) were 0.256±0.046 mg/L. Mean total urine excretion of fluoride during anesthesia was 0.06±0.04 mg in Group 1 patients and 0.87±0.29 mg in Group 2 patients ($p<0.001$). Although the urine flow rate was greater in Group 2 patients (1.54±1.10 mL/min) than in Group 1 patients (0.53±0.18), the difference was not of sufficient magnitude to account for the difference in fluoride excretion.

Comment. Urine alkalinization increased fluoride excretion and decreased fluoride concentrations during and after fluoride administration.

Role of Urine Alkalinization in Fluoride Poisoning

These two volunteer studies (5,19) are suggestive that urine alkalinization increases fluoride excretion in the urine and is therefore likely to be of value in acute fluoride poisoning though this must be confirmed in clinical studies.

Pentachlorophenol

Uhl et al. (20) studied the toxicokinetics of pentachlorophenol in three healthy male volunteers, two of whom were later given ^{13}C-labeled pentachlorophenol orally together with small repetitive doses of sodium bicarbonate to increase urine pH in the range 6–7.5. The method used to measure urine pH was not stated. Fig. 4 in the published paper shows that the urinary excretion of pentachlorophenol more than doubled as pH increased from 5.4 to approximately 7.8.

Comment. The data are very limited. The study showed that plasma pentachlorophenol was very strongly protein-bound (96%). The renal clearance of free pentachlorophenol was only 1.25 mL/min, suggesting that some 99% of that filtered at the glomerulus was reabsorbed in the proximal tubule.

Role of Urine Alkalinization in Pentachlorophenol Poisoning

It is highly unlikely that urine alkalinization would be of value in pentachlorophenol poisoning.

Phenobarbital

Using a non-randomized cross-over design Frenia et al. (8) compared urine alkalinization with multiple-dose activated charcoal (MDAC) in the enhancement of phenobarbital elimination. Twelve volunteers (six females, six males) received phenobarbital 5 mg/kg intravenously. In the initial phase, phenobarbital only was administered. In the urine alkalinization phase, an intravenous bolus of sodium bicarbonate 1 mmol/kg was administered 30 min after the phenobarbital infusion. This was followed by an infusion of 1 L dextrose 5% containing sodium bicarbonate 100 mmol at a rate of 2.5 mL/min and then titrated to maintain a urine pH of 7.5–8.0. During the multiple-dose activated charcoal phase, activated charcoal 50 g (with sorbitol) was administered orally, 30 min after the conclusion of the phenobarbital infusion; activated charcoal 25 g was then administered every 4h, and activated charcoal 25 g with sorbitol was given every 12h.

Phenobarbital concentrations were measured using fluorescence polarization immunoassay. As illustrated in Table 2, the half-life of phenobarbital was reduced significantly with urine alkalinization and multiple-dose activated charcoal when compared to control. Furthermore, phenobarbital clearance was enhanced significantly for both interventions when compared to control.

Comment. Urine alkalinization reduced both phenobarbital half-life and total body clearance but multiple-dose activated charcoal was considerably superior in both regards.

Salicylates

Vree et al. (11) conducted a randomized cross-over study in six volunteers who were administered sodium salicylate 1.5 g orally and were then subjected to urine alkalinization (mean urine pH 7.67 ± (SD) 0.65) or urine acidification (mean urine pH 5.54 ± 0.57). The mean peak salicylate concentrations were 93.3 ± (SD) 18.6 mg/L and 109.8 ± 17.8 mg/L (NS), respectively. The mean elimination half-life during urine alkalinization (2.50 ± (SD) 0.41 hr) was significantly less ($p = 0.0156$) than the mean elimination half-life during urine acidification (3.29 ± 0.52 h). Mean total body clearance increased significantly ($p = 0.041$) during urine alkalinization (2.27 ± (SD) 0.83 L/hr) compared to urine acidification (1.38 ± 0.43 L/h).

Comment. This is a very well conducted study that employed HPLC to measure salicylic acid and its metabolites. Urine alkalinization increased elimination of salicylic acid significantly.

CLINICAL STUDIES

Barbiturate Poisoning

Case Series

Unfortunately, many of the early reports cannot be accepted without serious reservations either because the analytical methods used to measure barbiturate concentrations were not specified or were such as to include many of the metabolites (21). This was particularly important in assessing urinary excretion where the presence of polar metabolites of more lipid-soluble barbiturates gave a falsely inflated impression of the value of the procedure. In addition, blood concentrations were commonly expressed in terms of a different barbiturate from that ingested. These papers are included here for completeness and because they are

Table 2. Half-life and total body clearance of phenobarbital after urine alkalinization and multiple-dose activated charcoal (MDAC) (Adapted from 8).

	Control (n = 10)	Phenobarbital + $NaHCO_3$ (n = 10)	Phenobarbital + MDAC (n = 10)
Half-life (hr ± SD)	148.1 ± 332.1	47.24 ± 42.04	18.87 ± 14.70
Total body clearance (mL/kg/hr ± SD)	2.79 ± 9.69	8.29 ± 8.62	19.95 ± 11.55

often cited in the literature as providing support for the use of urine alkalinization.

Allobarbital

Allobarbital is a medium-to long-acting barbiturate. Myschetzky and Lassen (22) treated one patient (maximum serum allobarbital concentration 134 mg/L) with urea-induced osmotic diuresis and urine alkalinization. In the first 4h of treatment the patient was given 300 mL of an electrolyte solution (containing sodium lactate 40 mEq/L; sodium chloride 12 mEq/L; potassium chloride 12 mEq/L) per hour and urea 40 g/h. After 4h the infusion rate of electrolyte fluid was increased to 600 mL/h and the amount of urea given reduced to 15 g/h. Further adjustments were then made to maintain the diuresis and alkalinization and to ensure the blood urea concentration did not increase above 4 g/L. A total diuresis of 24.1 L was achieved with a clearance of 19.7 mL/min and a total of 3.2 g allobarbital excreted. The plasma allobarbital concentration fell by 72% in the first 24h period.

Comment. The analytical method used was not stated and its specificity for allobarbital is uncertain. Therefore, the conclusions of this study may be unreliable.

Aprobarbital

Aprobarbital is a long-acting barbiturate. Myschetzky and Lassen (22) treated 25 patients who were unconscious (average maximum serum aprobarbital concentration 117 mg/L) with urea-induced osmotic diuresis and urine alkalinization. In the first 4h of treatment, the patients were given 300 mL of an electrolyte solution (containing sodium lactate 40 mEq/L, sodium chloride 12 mEq/L, potassium chloride 12 mEq/L) per hour and urea 40 g/h. After 4h the infusion rate of electrolyte fluid was increased to 600 mL/h and the amount of urea given reduced to 15 g/h. Further adjustments were then made to maintain the diuresis and alkalinization and to ensure the blood urea concentration did not increase above 4 g/L. A mean diuresis of 22.6 L was achieved during treatment. The plasma aprobarbital concentration fell by 55% in the first 24h period. The mean serum total barbiturate excretion was 2.1 g and the mean barbiturate clearance was 15.1 mL/min during treatment with urea-induced osmotic diuresis and urine alkalinization. Treatment appeared to reduce the duration of coma by almost half.

Comment. The analytical method used was not stated and its specificity for aprobarbital is uncertain. Therefore, the conclusions of this study may be unreliable.

Aprobarbital/Barbital

Ten patients with mixed aprobarbital/barbital overdoses (average maximum barbital concentration 19.8 mg/L) were also treated with urea-induced osmotic diuresis and urine alkalinization (22). In the 4h of treatment, the patients were given 300 mL of an electrolyte solution (containing sodium lactate 40 mEq/L; sodium chloride 12 mEq/L; potassium chloride 12 mEq/L) per hour and urea 40 g/h. After 4h the infusion rate of electrolyte fluid was increased to 600 mL/h and the amount of urea given reduced to 15 g/h. Further adjustments were then made to maintain the diuresis and alkalinization and to ensure the blood urea concentration did not increase above 4 g/L. For this group a mean diuresis of 17.9 L was achieved with a mean barbiturate clearance of 17.5 mL/min and a mean total barbiturate excretion of 3.7 g. In the first 24h period the plasma barbiturate concentration fell by 60% (22).

Comment. The analytical method used was not stated but serum concentrations of the two barbiturates were expressed in terms of barbital.

Barbital

Four patients who were unconscious due to barbital poisoning (average maximum serum barbital concentration 273 mg/L) were treated with urea-induced osmotic diuresis and urine alkalinization (22). In the first 4h of treatment, the patients were given 300 mL of an electrolyte solution (containing sodium lactate 40 mEq/L; sodium chloride 12 mEq/L; potassium chloride 12 mEq/L) per hour and urea 40 g/h. After 4h the infusion rate of electrolyte fluid was increased to 600 mL/h and the amount of urea given reduced to 15 g/h. Further adjustments were then made to maintain the diuresis and alkalinization and to ensure the blood urea concentration did not increase above 4 g/L. A mean diuresis of 24.4 L was achieved with a clearance of 14.5 mL/min and a total of 6.9 g of barbital excreted. The plasma barbital concentration fell by 51% in the first 24h period.

Comment. The analytical method used was not stated and its specificity for barbital is uncertain. Therefore, the conclusions of this study may be unreliable.

Pentobarbital

Bloomer (23) studied the effect of urine pH on the excretion of pentobarbital in two patients. Urine alkalinization and mannitol-induced forced diuresis were employed. Initially the urine pH was increased

progressively at low rates of flow by the administration of intravenous isotonic sodium bicarbonate to values in excess of 7.5. After an observation period urinary flow was increased by infusing mannitol 5% while maintaining an alkaline urine. The total concentration of barbiturate in plasma and in an ultrafiltrate of plasma was measured by gas chromatography, the latter concentration taken to be the likely concentration of the drug in renal tubular fluid. There was little, if any, increase in elimination as urine pH increased, though clearance did increase with increasing urine flow rates.

Comment. Limited data show that urine alkalinization is of no value in pentobarbital poisoning.

Phenobarbital

Bloomer (23) reported the value of urine alkalinization and mannitol-induced forced diuresis in the treatment of three patients poisoned with phenobarbital. Initially the urine pH was increased progressively at low rates of flow by the administration of intravenous isotonic sodium bicarbonate to values in excess of 7.5. After an observation period urinary flow was increased by infusing mannitol 5% while maintaining an alkaline urine. The total concentration of barbiturate in plasma and in an ultrafiltrate of plasma was measured by ultraviolet spectrophotometry, the latter concentrations being taken to be the likely concentration of the drug in renal tubular fluid. Urine flow rates of up to 26 mL/min were induced. The ratio of urinary barbiturate to plasma filtrate concentration increased steeply to four-fold when the pH of the urine was greater than 7.5. At a high urine pH and a urine flow of 7 mL/min, the clearance of filterable phenobarbital rose to 15 mL/min, with phenobarbital excretion of 51 mg/h. When the urine pH was less than 7.5 and the urine flow was 1 mL/min, the clearance of filterable phenobarbital was 2 mL/min.

Comment. No control group was included in the study and, moreover, phenobarbital concentrations were measured by ultraviolet spectrophotometry and were therefore unreliable.

Mawer and Lee (24) used urine alkalinization and mannitol-induced diuresis to treat two patients poisoned with phenobarbital (plasma concentrations 145 and 114 mg/L) who required mechanical ventilation. Each hour 500 mL of fluid was administered in rotation using 500 mL of 1.25% sodium bicarbonate, 500 mL of 5% glucose, 500 mL of 0.87% sodium chloride, and 500 mL of 5% glucose. The aim was to increase the urine pH above 7.5. In addition, each patient was subjected to mannitol-induced diuresis and furosemide-induced diuresis to obtain a 500 mL/h urine flow. One patient received a 3h mannitol-induced diuresis and a 6h furosemide-induced diuresis; the second patient received a 6h mannitol-induced diuresis and a 3h furosemide-induced diuresis. Over a 9h period (mean urine flows respectively 310 and 410 mL/h) the mean urine pH was 7.8 (7.7–7.9) during mannitol-induced diuresis and 7.2 (6.5–7.9) during furosemide-induced diuresis. The urine excretion of phenobarbital over 9h was 207 mg and 153 mg, respectively (23 and 17 mg/h).

Comment. This study was well conducted though no control group was included. Drug concentrations were measured by gas chromatography and pH by pH meter. Urine alkalinization enhanced the urine elimination of phenobarbital.

Ebid and Abdel-Rahman (9) also described the impact of urine alkalinization and multiple-dose activated charcoal on phenobarbital elimination. In each group there were 10 male patients poisoned with phenobarbital (the mean plasma phenobarbital concentration in the two groups was 100.6±12.6 mg/L and 103.2±12.2 mg/L, respectively). Phenobarbital concentrations were measured by EMIT on admission (zero time), at 6, 12, 18, 24, 30, 36, 42, and 48 h. Compared to urine alkalinization (81.1±(SD) 14.6 h), multiple-dose activated charcoal reduced significantly ($p<0.05$) the mean phenobarbital elimination half-life (38.6±6.6 h) and increased significantly ($p<0.05$) the mean total body clearance of phenobarbital (10.8±(SD) 1.8 mL/kg/h) compared to urine alkalinization (5.1±0.9 mL/kg/h). With multiple-dose activated charcoal, the mean durations of assisted ventilation (40.2±(SD) 12.5 h), intubation (29.7±(SD) 10.3 h) and coma (24.4±(SD) 9.6 h) were significantly shorter ($p<0.05$) than in the group treated with urine alkalinization (79.4±20.9 h; 54.2±12.8 h; 50.6±12.5 h respectively). Although this study did not include a control group, urine alkalinization did not appear to increase phenobarbital clearance (mean 0.085 mL/kg/min) significantly compared to reported endogenous clearances (0.062 mL/kg/min (10)) and was less effective than multiple-dose activated charcoal. The impact of each treatment on the plasma half-life and total body clearance of phenobarbital is shown in Table 3.

Comment. This study did not include a control group and the value of urine alkalinization therefore cannot be assessed, though it was less effective than the administration of multiple-dose activated charcoal.

Myschetzky and Lassen (22) employed urea-induced osmotic diuresis and urine alkalinization in 16 patients who were unconscious due to phenobarbital poisoning (average maximum serum phenobarbital concentration 203 mg/L). In the 4h of treatment, the

Table 3. Half-life and clearance in patients poisoned with phenobarbital (after Ebid and Abdel-Rhaman (9)).

	Urine alkalinization (n=10)	Multiple-dose charcoal (n=10)
$T_{½}$ (hr)	81.1±14.6	38.6±6.6
CL (mL/kg/h)	5.1±0.9	10.8±1.8

patients were given 300 mL of an electrolyte solution (containing sodium lactate 40 mEq/L, sodium chloride 12 mEq/L, potassium chloride 12 mEq/L) per hour and urea 40 g/h. After 4h the infusion rate of electrolyte fluid was increased to 600 mL/h and the amount of urea given reduced to 15 g/h. Further adjustments were then made to maintain the diuresis and alkalinization and to ensure the blood urea concentration did not increase above 4 g/L. Thus, patients were administered a maximum of 13.2 L of fluid in the first 24h resulting in a corresponding mean diuresis of 12.9 L. The mean total diuresis during treatment was 23.5 L. The plasma phenobarbital concentration fell by 36% in the first 24h. The mean total excretion of phenobarbital during treatment was 4.3 g with a clearance of 9.7 mL/min. The duration of coma in those treated with diuresis/urine alkalinization was less than half of that in controls.

Comment. Although the treatment maintained the urine pH slightly alkaline, no urine pH values were reported, nor was the method by which barbiturate concentrations were measured stated. Moreover, the impact of the massive diuresis cannot be separated from attempts to alkalinize the urine, rendering the study of little value.

Data on six patients poisoned with phenobarbital were reported by Linton et al. (25) Each patient received in rotation per hour, 500 mL 5% dextrose and 50 mEq sodium bicarbonate, 500 mL 5% dextrose and 25 mEq potassium chloride and 500 mL 0.87% sodium chloride solution and a diuretic. The mean (±SD) amount of barbiturate removed during an 8h diuresis was 462.5±191.4 mg. Over an 8h period of forced alkaline diuresis two of these patients eliminated 30 and 40 mg barbiturate, respectively. Barbiturate clearance was determined in four of these patients and reached a maximum of 7 mL/min (urine flow rate 14 mL/min) without alkalinization and 14 mL/min (urine flow rate 10 mL/min) with alkalinization (pH > 7.8).

Comment. Because of the analytical method used, Mawer and Lee (24) suggested that as much as half the phenobarbital recovered in the urine in this study was metabolite.

Secobarbital

Bloomer (23) studied the effect of urine alkalinization and mannitol-induced forced diuresis on the excretion of secobarbital in two patients. Initially the urine pH was increased progressively at low rates of flow by the administration of intravenous isotonic sodium bicarbonate to values in excess of 7.5. After an observation period urinary flow was increased by infusing mannitol 5% while maintaining an alkaline urine. The total concentration of barbiturate in plasma and in an ultrafiltrate of plasma was measured using gas chromatography, the latter concentration being taken to be the likely concentration of the drug in renal tubular fluid. There was little, if any, increase in elimination as urine pH increased, though clearance did increase with increasing urine flow rates.

Comment. Limited data show that urine alkalinization is of no value in secobarbitol poisoning.

Role of Urine Alkalinization in Barbiturate Poisoning

There are no data to support the use of urine alkalinization in poisoning with short-and medium-acting barbiturates (which are more lipid-soluble), such as allobarbital, aprobarbital, pentobarbital, and secobarbital. Although urine alkalinization is undoubtedly effective in phenobarbital poisoning, it is less efficient than multiple-dose activated charcoal which is the treatment of choice. Since barbital has a longer half-life than phenobarbital and is at least as polar, it would be expected that urine alkalinization would enhance its elimination, though studies have not confirmed this.

Chlorophenoxy Herbicide Poisoning

The chlorophenoxy herbicides include a number of compounds that have pKa values between 1.9 and 4.8 (26). Serious acute poisoning is uncommon and usually involves 2,4-dichlorophenoxyacetic acid (2,4-D), 2-(4-chloro-2-methylphenoxy)propionic acid (MCPP, mecoprop) or 2-(2,4-dichlorophenoxy)propionic acid (DCPP, 2,4-DP or dichlorprop) (27).

Flanagan et al. (26). reported a case series of 30 patients poisoned with chlorophenoxy herbicides alone and 11 who had ingested a mixture of a chlorophenoxy herbicide and ioxynil. Seven of these patients died prior to or on hospital admission and 15 of the remaining 34 received supportive care only, while the other 19 patients (16 in the chlorophenoxy-only group and three in the ioxynil group) underwent alkaline diuresis (details not given). The authors stated that

plasma chlorophenoxy half-lives after alkalinization were below 30h but detailed results were described for only four patients, three of whom ingested 2,4-D in combination with another chlorophenoxy herbicide (or dicamba). These cases are discussed in the case reports below.

Case Reports

2,4-Dichlorophenoxyacetic Acid (2,4-D)

Friesen et al. (28) described a 61-year-old female found comatose an undetermined time after ingesting 2,4-D 38–50 g (as the amino salt). Alkaline diuresis (details not given) was instituted 12h after admission to maintain a urine pH >7.5 and urine output above 300 mL/h and continued for at least 30h. The hourly urine output was documented five times (values between 290 and 820 mL/h) and urine pH on four occasions (values between 7.5 and 8.5) during urine alkalinization. The authors cited a plasma 2,4-D half-life of 39.5 h prior to urine alkalinization and 2.7h after 30h of alkaline diuresis. The patient was extubated 22h after admission and made a full recovery.

Comment. In this single case report (28) no renal clearance data were presented correlating with urine pH, hence it is impossible to define the impact of urine alkalinization on 2,4-D elimination. Nonetheless, use of urine alkalinization with high urine flow produced an impressive reduction in the plasma half-life of 2,4-D from 39.5 to 2.7h.

A man aged 34 years who ingested 2,4-D (and dicamba) had a plasma 2,4-D concentration 8h post-ingestion of 670 mg/L (26). The authors stated that he recovered after being given alkaline diuresis cautiously over three days. In fact, a urine pH above 7.0 was not achieved until some 50h after ingestion and was seemingly maintained for some 24h. The elimination half-life of 2,4-D was calculated as 12.3h prior to urine alkalinization (pH $\geq$7.5) and 3.0h towards the end of urine alkalinization.

Comment. There were insufficient renal clearance data with respect to urine pH to define clearly the effect of urine alkalinization on 2,4-D elimination in this case (26). An alkaline urine was not present throughout the duration of alkaline diuresis.

A female aged 40 years who had ingested some 200 mL of a mixture of 2,4-D (and dichlorprop—see below) underwent alkaline diuresis 26h post-exposure (26). The first alkaline urine pH (7.5) was not recorded until approximately 60h post-exposure. Three further urine pH measurements were recorded between 60 and 132h post-ingestion (values 7.5 or 7.8) and the authors calculated an elimination half-life of 7.8h for 2,4-D between approximately 80 and 110h.

Comment. There were insufficient renal clearance data with respect to urine pH to define clearly the effect of urine alkalinization on 2,4-D elimination in this case (26). An alkaline urine was not present throughout the duration of alkaline diuresis.

A female aged 53 years was found collapsed after ingesting an unknown quantity of 2,4-D (and 2,4,5,-T—see below) (26). Alkaline diuresis was started 28.5h post-ingestion and was associated with increases in plasma 2,4-D and 2,4,5-T concentrations. Thereafter urinary excretion of these compounds was enhanced. However, the urine pH did not exceed 7.0 until approximately 38h post ingestion. Between 38 and approximately 42h post-ingestion, when the urine pH was seemingly maintained between 7.0 and approximately 7.4, the plasma 2,4-D concentration fell sharply, although the plasma 2,4-D half-life during this time was not stated and the graph too small for it to be determined accurately. Moreover, in this patient there was no evidence that a urine pH of 7.5 or greater was achieved at any time.

Comment. There were insufficient renal clearance data with respect to urine pH to define clearly the effect of urine alkalinization on 2,4-D elimination in this case (26). An alkaline urine was not present throughout the duration of alkaline diuresis.

A 39-year-old male was poisoned severely after the ingestion of a preparation containing 2,4-D 10% as the amino salt (and mecoprop 20%—see below) (2,3). The authors calculated from the plasma concentration and the volume of distribution that the patient had ingested 2,4-D 6.8 g. The admission urine pH was 6.4 with a plasma 2,4-D concentration of 400 mg/L. An alkaline diuresis was commenced some 42–51 hours post-ingestion by the administration of 14 L of fluid containing sodium bicarbonate 69.3 g (825 mmol) over the ensuing 48h (3). However, a urine pH greater than 7.5 was not achieved until approximately 75h post-ingestion. The renal 2,4-D clearance corrected for urine flow (adjusted to 1 mL/min) was directly proportional to urine pH (r=0.99) and clearance was estimated to increase almost five-fold for each unit increase in urine pH. The authors cited a mean corrected renal clearance of 0.28 mL/min over the urine pH range 5.1–6.5 and 9.6 mL/min over the pH range 7.55–8.8 (2). At pH 5.1 and 8.3 the uncorrected renal clearances were 0.14 mL/min and 63 mL/min, respectively (3). The plasma half-life of 2,4-D was approximately 219h before urine alkalinization and 3.7h over the period 96–112h post-ingestion when the urine pH exceeded 8.0 (2,3). The amount of 2,4-D

recovered in the urine was 6.66 g. In this patient clinical improvement paralleled the fall in chlorophenoxy herbicide concentrations and consciousness was regained on the fourth day post-ingestion when the plasma 2,4-D concentration was approximately 100 mg/L.

Comment. In this case (3), the unaided renal 2,4-D clearance (0.14 mL/min at urine pH 5.1) (3) correlates with that found by Wells et al. (0.17–1.4 mL/min) (29). 2,4-D renal clearance was increased with increasing urine pH although substantially increased clearance was achieved only when the urine pH exceeded 7.5 and was then accompanied by a urine flow rate of the order of 200 mL/h. Based on the author's graphical representation of corrected renal clearance-v-urine pH (Fig. 2 of the paper) the maximal uncorrected 2,4-D renal clearance of 63 mL/min at pH 8.3 (3) would have required a urine flow rate of approximately 10 mL/min (600 mL/h). In these circumstances 2,4-D clearance compared favorably with that achieved with hemodialysis (56.3–72.9 mL/min) (4). However, the corrected renal clearance data of Prescott et al. (3) (Fig. 2 in the published paper) show that the effect of urine alkalinization without high urine flow is markedly less efficient than hemodialysis as a means of removing 2,4-D.

2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T)

A female aged 53 years who was found collapsed after ingesting a mixture of 2,4-D and 2,4,5-T (see 2,4-D above (26)) was treated with alkaline diuresis commenced 28.5h post-ingestion. As for 2,4-D, there was a steep decline in the plasma 2,4,5-T concentration (half-life not known) between approximately 38 and 42h post-ingestion, when the urine pH was seemingly maintained between 7.0 and 7.4. Prior to this, when the urine pH was less than 7 the plasma 2,4,5-T concentration had increased.

Comment. The problems with 2,4,5-T data interpretation of this case are identical to those for 2,4-D (see above).

Dichlorprop

A 40-year-old female was admitted in deep coma after ingesting some 200 mL of a mixture of dichlorprop (and 2,4-D—see above) (26). Alkaline diuresis was instituted 26h post-exposure but the first alkaline urine pH of 7.5 was recorded approximately 60h post-exposure. Three further urine pH measurements were recorded between 60 and 132h post-ingestion (values 7.5 or 7.8), and the authors calculated an elimination half-life for dichlorprop between approximately 80h and 125h, of 14.2h.

Comment. There were insufficient renal clearance data with respect to urine pH to clearly define the effect of urine alkalinization on dichlorprop elimination in this case. Moreover, an alkaline urine was not present throughout the duration of alkaline diuresis.

Mecoprop

A 39-year-old male was poisoned severely after the ingestion of a preparation containing mecoprop 20% as the amine salt (and 2,4-D 10%—see above) (2,3) The admission urine pH was 6.4 with a plasma mecoprop concentration of 751 mg/L. An alkaline diuresis was instituted 42–51h post-ingestion by the administration of 14 L of fluid containing sodium bicarbonate 69.3 g (825 mmol) administered over the ensuing 48h (3). However, a urine pH greater than 7.5 was not achieved until approximately 75h post-ingestion. The renal mecoprop clearance corrected for urine flow (adjusted to 1 mL/min) was directly proportional to urine pH ($r=0.94$) and clearance was estimated to double for each unit increase in urine pH. The authors cited a mean corrected renal clearance of 0.38 mL/min over the urine pH range 5.1–6.5 and 2.08 mL/min over the pH range 7.55–8.8 (2). The plasma half-life of mecoprop was shortened from 39 to 14h with urine alkalinization (2,3). The amount of mecoprop recovered in the urine was 7.64 g. In this patient, clinical improvement paralleled the fall in chlorophenoxy herbicide concentrations and consciousness was regained on the fourth day post-ingestion when the plasma mecoprop concentration was approximately 100 mg/L.

Comment. In this case (2,3) mecoprop clearance was increased with increasing urine pH although to a lesser extent than 2,4-D. As discussed above, diuresis must have contributed to the recovery of poison in this case. The less beneficial effect of alkaline diuresis on mecoprop clearance compared to 2,4-D clearance may be explained by the different pKa values of the herbicides; pKa of 2,4-D=2.73, pKa of mecoprop=3.78 (30). In addition mecoprop may be metabolized more extensively than 2,4-D (3), although this has been disputed (26).

Flanagan et al. (26) described a 62-year-old male who had ingested 250 mL of a mixture of ioxynil and mecoprop plus ethylene glycol. On admission (less than 2h post-ingestion) the plasma mecoprop concentration was just over 400 mg/L (precise value not stated) with a blood ethylene glycol concentration of

800 mg/L. Alkaline diuresis (in addition to intravenous ethanol) was commenced 1.5h post-ingestion. The first urine pH greater than 7.0 was recorded approximately 15h post-ingestion, and the urine pH was then maintained between 7.0 and 8.0 for the next 40h. The plasma mecoprop half-life was calculated as 18.7h over approximately the first 28h of treatment and was 6.8h between approximately 30 and 50h post-ingestion.

Comment. This case is complicated by the fact that the patient was also poisoned severely with ethylene glycol. Again, there were insufficient renal clearance data with respect to urine pH to define clearly the effect of urine alkalinization on mecoprop elimination.

4-Chloro-2-Methylphenoxyacetic Acid (MCPA)

Schmoldt et al. (31) described a patient who presented within two hours of ingesting 50–100g MCPA (as the dimethylammonium salt). A forced diuresis was instituted within the first few hours of admission (day 1) when the plasma MCPA concentration was 546 mg/L, but by day 4 the plasma MCPA concentration had fallen only to 379 mg/L. At this stage forced alkaline diuresis was commenced and on day 5 the plasma MCPA concentration was 78 mg/L. The authors calculated a fall in the MCPA plasma half-life from approximately 133h prior to urine alkalinization to 12.6h after alkali was added. The patient recovered fully.

Comment. In this case (31) details of the forced diuresis and forced alkaline diuresis including urine pH were not documented, neither were renal clearance data given, making the findings uninterpretable.

Role of Urine Alkalinization in Poisoning Due to Chlorophenoxy Herbicides

No controlled trials of urine alkalinization have been carried out for chlorophenoxy herbicides and, of the available case reports, only for the patient reported by Park et al. (2) and Prescott et al. (3) were there sufficient renal clearance data to infer enhanced chlorophenoxy elimination with urine alkalinization and a high urine flow. The use of renal clearance values, corrected and uncorrected for urine flow, allows clarification of the relative contributions of urinary alkalinization and urine flow. Prescott's data (3) demonstrate that both urine alkalinization (urine pH >8) and a high urine flow (of the order of 600 mL/hour) are required to achieve a renal 2,4-D clearance comparable to that achieved with hemodialysis.

METHOTREXATE TOXICITY

Concern over the potential for methotrexate to precipitate in the renal tubules when given in high doses in the treatment of malignant disease prompted several studies that examined the effect of increasing urine flow and urine alkalinization on the clearance of methotrexate.

Case Series

Sand and Jacobsen (6) studied the effects of increased urine flow rate and urine alkalinization on methotrexate clearance in 11 patients (7 males, 4 females) undergoing chemotherapy for various malignant diseases. Methotrexate 1–2 g/m^2 was infused in 1 L saline over 4h with a minimum interval of two weeks between doses. Urine was collected during the last 2h of the infusion, at the end of the infusion, twice daily (morning and afternoon) on the following two days and on the morning of day 4. Blood was taken at the mid-point or at the beginning and end of each urine collection period. The eight patients with normal renal function (creatinine clearance 98–121 mL/min) were given up to 400 mL/hour oral fluid for 7h on days 2 and 3 with oral sodium bicarbonate 10 g over 3h before the afternoon collection period on day 3. Three patients with impaired renal function (creatinine clearance 47–67 mL/min) were asked to drink as much as possible and received oral sodium bicarbonate up to 20 g/day.

The average number of collection periods per methotrexate infusion was 4.2 and 3.8 for patients with normal and impaired renal function, respectively. The authors used the ratio of renal methotrexate clearance (C_{MTX}) to creatinine clearance (C_{creat}) to enable comparison of methotrexate clearance values between patients with different renal function. The results demonstrated a linear relationship ($r=0.596$) between urine pH and C_{MTX}/C_{creat} for the whole group (11 patients, 80 measurements), C_{MTX}/C_{creat} increasing from 0.88 at pH 5.5 to 2.62 at pH 8.4 ($p<0.001$). A similar (though $p<0.01$) dependency of methotrexate clearance on urine pH was observed when data for patients with normal and impaired renal function were considered separately. There was no correlation between C_{MTX}/C_{creat} and urine flow for each measurement period in the patients with impaired renal function, though this relationship approached significance ($r=0.299$, $p=0.05$) in patients with normal renal function.

Comment. This study is difficult to assess critically due to the complexity of the protocol, but it

shows that renal methotrexate elimination is increased by urine alkalinization and that the effect of urine alkalinization is greater than any effect of increased urine flow.

Christensen et al. (32) compared the effect of two hydration/alkalinization regimens on plasma methotrexate concentrations in children (<18 years of age) receiving high-dose methotrexate infusions in the treatment of acute lymphocytic leukemia. Intravenous methotrexate 500 mg/m^2 as a bolus was followed by methotrexate 1500 mg/m^2 as an infusion over 2h. This course of treatment was given twice to each patient. Twenty-nine patients received intravenous fluids 75–165 mL/m^2/ for 5h with sodium bicarbonate 2.5 g/m^2 in total added, beginning 2h before each course of methotrexate therapy (Regimen A). Sixty-three patients received intravenous fluids 200 mL/m^2/h for 8h, with 5.4 g/m^2 sodium bicarbonate added, commencing 1h before each course of methotrexate therapy (Regimen B). Plasma methotrexate concentrations were measured 21 and 44h after commencement of each methotrexate course. Mean methotrexate concentrations were significantly lower ($p=0.01$) in patients receiving Regimen B than in those receiving Regimen A at 21h (mean ± (SD) 0.36 – 0.41 mg/L and 0.63 ± 0.9 mg/L, respectively) and at 44h (0.08 ± 0.17 mg/L and 0.11 ± 0.23 mg/L, respectively). No urine pH measurements or volumes were cited.

Comment. This study did not enable differentiation between the effects of hydration and urine alkalinization on plasma methotrexate concentrations but demonstrated lower plasma methotrexate concentrations with more intensive hydration and alkali administration.

In another study (33), four pediatric and one adult patient with osteosarcoma were given four courses of intravenous methotrexate 7.5 g/m^2 over 6h, each course separated by one week. For two courses patients received hydration and urine alkalinization as intravenous 5% dextrose with 40–60 mmoL sodium bicarbonate per liter (3 L/m^2/day), to achieve a urine pH >7. On alternate courses sodium bicarbonate was replaced with a molar equivalent of sodium chloride, resulting in a urine pH generally between 6.0 and 6.5. Each patient therefore served as their own control. Hydration was commenced 12h before methotrexate administration and maintained for 48h following methotrexate dosing. Serum methotrexate concentrations were measured by radioimmunoassay at intervals during and after methotrexate infusion. Details of urine volumes or pH measurements were not given.

Under these conditions, urine alkalinization neither reduced the peak serum methotrexate concentration significantly nor increased the decay rate of serum methotrexate over the first 30h following completion of the infusion.

Comment. Urine alkalinization was not achieved in this study.

Tsavaris et al. (34) administered intravenous water 3L/24h with added sodium bicarbonate 24 mmol/L, potassium chloride 75 mmol/L and mannitol 20% 20 mL/L starting 16h prior to methotrexate administration, to 12 patients receiving methotrexate 500 mg/m^2/day and 4 patients receiving methotrexate 7500–8000 mg/m^2/day. Urine volume and pH were measured every 6h with urine output maintained at 160–220 mL/h and urine pH in the range 8–8.5. Using this regimen, plasma methotrexate concentrations fell dramatically within 24h of commencement of the lower, and within 48h of commencement of the higher, methotrexate dose.

Comment. No regimen without urine alkalinization was included in this study and conclusions regarding the efficacy of urine alkalinization are not possible.

Case Reports

Grimes et al. (7) described a young woman who developed methotrexate poisoning after the eighth dose (administered during week 33 of treatment) as part of a chemotherapy protocol for osteogenic sarcoma. During the methotrexate infusion (14.4 g in 1 l 5% dextrose over 4h) the patient developed a rash, then nausea, vomiting, and diarrhea. By 24h post-dose she was drowsy and oliguric despite hydration/alkalinization with 4 L intravenous fluids plus 12 g sodium bicarbonate to maintain a urine pH $\geq$7. At this time the serum methotrexate concentration was 574 μmol/L (261 mg/L). Forced alkaline diuresis using 8 L intravenous saline daily with 45 mmol/l sodium bicarbonate and furosemide 2.5 mg/h was commenced and continued for 14 days. With this regimen the patient maintained a urine output of at least 150 mL/h and urine pH $\geq$7.5. At 48h, multiple-dose charcoal 20 g every 2h was added to the regimen and continued for 6.5 days. At 53 hours, 8h hemoperfusion was commenced due to a persistently elevated serum methotrexate concentration, followed by six hours hemodialysis then a further 6h hemoperfusion. The patient was discharged well on day 17.

Between 24–28h when forced alkaline diuresis was in progress without other modalities to enhance methotrexate elimination, the methotrexate serum half-life was 24h. This compares to an estimated serum half-life during hemoperfusion/hemodialysis (between 53–77.5h) of 7.6h. Between 114 and 209h (from the peak rebound serum methotrexate concentration after

hemoperfusion until charcoal was stopped) the methotrexate serum half-life was 25h, and between 257 and 377h, when forced alkaline diuresis continued but charcoal was no longer being administered it was 45 hours.

Comment. This case is exceptional in that the serum methotrexate concentration was almost 400 times higher than any other previously reported. The authors attributed the relatively low morbidity and favorable outcome predominantly to the prompt initiation and maintenance of a high urine flow with urine alkalinization, with possibly a contribution to enhanced methotrexate elimination by multiple-dose activated charcoal therapy. The half-life during forced alkaline diuresis was substantially longer than during hemodialysis/hemoperfusion. However, despite the seemingly impressive reduction in serum half-life during the latter, the overall contribution of hemodialysis/hemoperfusion to methotrexate removal was only 9% of the administered dose (1.3 of 14.4 g).

A 52-year-old female (35) developed renal failure in association with methotrexate toxicity with a plasma methotrexate concentration of 2.4×10^{-6} mol/L (1.10 mg/L) 7h after intravenous methotrexate administration (10,580 mg over 23h) the recommended concentration for chemotherapy regime used being $<5 \times 10^{-8}$ mol/L). The patient was treated with forced alkaline diuresis, achieving a urine output of 8–9 L/day and urine ph above 7. The plasma methotrexate concentration had fallen to 7×10^{-8} mol/L seven days later with normalization of renal function after two weeks. The patient developed mild stomatitis but no other features of methotrexate toxicity.

Comment. Although the authors attributed the favorable outcome to the prompt initiation of forced alkaline diuresis and the use of intravenous folinic acid rescue, this was an observational case report which does not allow conclusions to be drawn regarding the effect of urine alkalinization in methotrexate toxicity.

Role of Urine Alkalinization in Methotrexate Toxicity

Two studies (6,32) showed that a combination of fluid load and urine alkalinization increased the rate of elimination of methotrexate. The earlier of them (6) also showed that the effect of alkalinization was greater than caused by increased urine flow. However, no controlled study has been undertaken and the limited data available suggest that hemodialysis hemoperfusion is more efficient (7) though the amount of drug removed by this technique was no more than 10% of that given.

Salicylate Poisoning

Salicylate poisoning has been a problem for many years and remains a common medical emergency in many countries. A number of studies have attempted to determine the value of induced diuresis with or without alkalinization of the urine in its treatment. Most of these are several decades old and, like similar studies in barbiturate overdose, have their value diminished by the use of analytical methods that measured the metabolites of salicylic acid as well as the parent drug. Moreover, Prescott et al. (12) noted a dependence on the elimination half-life of salicylate as the measure of drug removal. They considered it inappropriate and misleading on the grounds that the volume of distribution of salicylate was small and mainly extracellular and consequently could be increased considerably by the fluid retention that frequently complicates salicylate poisoning managed by forced diuresis.

Case Series

Five patients (four men, one woman; age range 16–58 years) with severe salicylate poisoning were treated with urine alkalinization and diuresis (15). All patients received an infusion of 500 mL 0.9% sodium chloride, 500 mL 5% glucose, and 500 mL 2% sodium bicarbonate (1/6 M 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 initial mean (± SD) salicylate concentration was 764 ± 109 mg/L. After 8h of treatment the mean (± SD) salicylate concentration had decreased to 342 ± 73 mg. Mean (± SD) urine output over this time was 3.04 ± 1.37 L. Mean (± SD) total salicylate excretion was 7.0 ± 1.7 g. Salicylate excretion was related directly to urine output.

Comment. It was reported that clinical improvement occurred as plasma salicylate concentrations declined, but no data were presented to confirm this. This was an observational study without a control group and conclusions regarding the efficacy of pH manipulation are not possible.

Further data, seemingly relating to the subjects reported previously (15), have been published (36), though there are a number of discrepancies in the sex, plasma salicylate concentrations, and urine outputs of the patients (Table 4). As described above, the patients received in rotation an infusion of 500 mL 0.9% sodium chloride, 500 mL 5% glucose, and 500 mL 2%

Table 4. Discrepancies between data apparently based on the same case series.

Dukes et al. (15)		Cumming et al. (36)		Initial serum salicylate (mg/L)	Urine volume over 8h (L)
Case 1	(M 41)	Case 3	(F 41)	670/550	1.4/1.4
Case 2	(F 16)	Case 1	(F 16)	760/800	4.3/4.27
Case 3	(M 43)	Case 2	(M 43)	880	4.3/5.18
Case 4	(M 58)	Case 4	(M 58)	840	3.4/3.36
Case 5	(M 18)	Case 5	(M 18)	630	1.8/2.25

sodium bicarbonate at an initial rate of 2 L/h to initiate diuresis; thereafter the infusion was adjusted to produce a urine output of 500 mL/h (15).

The initial mean (± SD) salicylate concentration was 732 ± 140 mg/L. The mean total urine output over 8h was 3.31 L with a peak of 5.18 L in one patient; between 3 and 8h after commencement of treatment the mean urine pH was approximately 8. During the 8h period of treatment the mean total salicylate excretion was 6.43 g. The mean serum salicylate half-life was 7.5 hours.

Comment. Salicylate concentrations in this study were measured by the nonspecific Trinder method (38). Urine pH was measured by pH meter. Although the urinary salicylate excretion was clinically significant, this study lacks a control group and the value of urine alkalinization cannot be assessed.

Lawson et al. (14) compared the decline in plasma salicylate concentrations in 40 patients with moderate or severe salicylate poisoning. A selection of patients whose mean (± SD) peak plasma salicylate concentration was 518 ± 71 mg/L (4 men, 5 women; age range 14–46 years) were treated with oral fluids only. The remaining patients (peak plasma salicylate concentrations 480–880 mg/L) were allocated randomly to one of three treatment groups:

(i) Group 1. *Forced water diuresis*. Four men and three women (age range 18–67) whose mean (± SD) peak plasma salicylate concentration was 675 ± 93 were administered in rotation 500 mL 0.9% sodium chloride, 500 mL 5% fructose, and 500 mL fructose at a rate of 2 L/h. Potassium chloride 13.4 mmol/L was added to each 500 mL fluid after the first hour. In all 107 mmol was administered over 6h.

(ii) Group 2. *Forced alkaline diuresis*. Four men and seven women (age range 16–63) whose mean (± SD) peak plasma salicylate concentration was 709 ± 110 received in rotation 500 mL 0.9% sodium chloride, 500 mL 5% fructose and 500 mL 1.26% sodium bicarbonate at a rate of 2 L/h. Potassium chloride 13.4 mmol/L was added to each 500 mL fluid after the first hour. In all 296 mmol bicarbonate and 197 mmol potassium were administered over 6h.

(iii) Group 3. *Forced cocktail diuresis*. Seven men and six women (age range 15–59) whose mean (± SD) peak salicylate concentration was 672 ± 118 were administered 500 mL 0.9% sodium chloride, 1 L 5% fructose, 500 mL 1.26% sodium bicarbonate and potassium chloride 40 mmol/L as a mixture. In all 222 mmol bicarbonate and 120 mmol potassium were administered over 6h.

The rate of administration of intravenous fluid was the same in all cases (6 L over 3h). The mean urine pH for the forced alkaline diuresis-treated patients (Group 2) 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. The mean arterial pH before treatment in the three randomized groups was 7.46 (Group 1), 7.42 (Group 2), and 7.45 (Group 3). While it did not go above 7.45 in groups 1 and 3, it reached 7.55 in Group 2.

Urine salicylate elimination averaged 600 mg/h in the two regimens containing bicarbonate compared to some 200 mg/h in the oral fluid and forced water diuresis groups. Statistical differences between the specific treatment groups were not reported. The mean times for plasma salicylate concentrations to fall to two-thirds ($C_{2/3}$) and one-third ($C_{1/3}$) of their peak values are shown in Table 5. The mean (± SD) admission plasma potassium concentration in groups 1, 2, and 3 was 4.06 ± 0.42, 3.81 ± 0.53, and 4.00 ± 0.26, respectively. The lowest plasma potassium concentrations were usually found 20–30 hours after the start of treatment and the mean lowest plasma potassium concentrations were 3.13 ± 0.34, 2.61 ± 02.5, and 3.34 ± 0.26, respectively. The mean potassium excretion per hour was of the order of 10–15 mmol/h irrespective of the treatment modality, confirming that the observed hypokalemia in the forced alkaline diuresis group

Table 5. Mean times for plasma salicylate concentrations to fall to two-thirds ($C_{2/3}$) and one-third ($C_{1/3}$) of their peak value (after Lawson et al. (14)).

Group	Mean (± SD) $C_{2/3}$ (h)	Mean $C_{1/3}$ (h)
Oral fluids	13.00 ± 4.56	>24
Forced water diuresis	8.00 ± 4.55	>24
Forced cocktail diuresis	5.15 ± 2.79	18
Forced alkaline diuresis	2.55 ± 1.13	9

was due to a bicarbonate-induced shift of potassium into cells.

Comment. This study utilized the nonspecific Trinder method (38) to measure both plasma and urine salicylate concentrations. Any benefit from therapeutic interventions was magnified to an uncertain degree. Urine pH was measured by pH meter. The authors state in the discussion that there was a significant ($p=0.01$) correlation between increasing urinary pH and urinary excretion of salicylate, though no data are given in the text. The authors also report that there was rapid relief of salicylism in the patients receiving bicarbonate therapy compared to those receiving oral fluids or forced water diuresis. However, no clinical data were reported to substantiate this conclusion.

Prescott et al. (12) studied 44 patients with salicylate intoxication. Plasma and urine salicylate concentrations were measured by high-performance liquid chromatography. The method of urine pH measurement is not stated. Patients with plasma salicylate concentrations above 700 mg/L were excluded from the study. Sixteen patients [mean (± SD) age 29±12 years] who were mildly intoxicated [mean (± SD) plasma serum salicylate concentrations 328 ±57 mg/L] served as controls, receiving oral fluids only. Sixteen others [mean (± SD) age 29±11 years] with a mean (± SD) plasma salicylate concentration of 467±102 mg/L received a forced alkaline diuresis similar to the forced cocktail diuresis as described by Lawson et al. (14) (not forced alkaline diuresis as the authors stated) consisting of 6 L of fluid containing 225 mL bicarbonate, 450 mmol sodium, and 120 mmol potassium. A further six patients [mean (± SD) age 29±15 years] with a mean (± SD) plasma salicylate concentration of 463±84 mg/L were administered 6 L of intravenous fluid over 6h which contained 120 mmol potassium but no bicarbonate. The remaining six patients [mean (± SD) age 27±8 years] with a mean (± SD) plasma salicylate concentration of 439±86 mg/L were given 225 mmol bicarbonate and 60 mmol potassium in 1.5 L fluid. All three treatment groups contained equal numbers of men and women. In all groups the infusions were given over 3 to 4h.

The renal salicylate clearances were calculated over 16h for each of the interventions (Table 6). Urine pH correlated significantly ($p<0.05$) with urinary salicylate clearances. Patients receiving forced alkaline diuresis (pH 7.3±0.4) and alkali alone (pH 8.1±0.5) had significantly greater ($p<0.05$) renal salicylate clearances than controls (pH 6.1±0.3) and from each other ($p<0.05$). Analysis of the combined data from all groups also showed a highly significant ($p<0.001$) correlation between renal salicylate clearance and urine pH. In addition, a significant ($p<0.05$) decrease in mean (± SD) plasma half-lives compared to the control group was reported (Table 7).

Comment. These data show that urine alkalinization without diuresis enhances salicylate clearance. However, the conclusions of the study are based on only six patients who received urine alkalinization and there were insufficient data to determine if urine alkalinization had an impact on patient morbidity.

The effect of acetazolamide and sodium bicarbonate in the treatment of 10 patients with moderate to severe salicylate poisoning (as defined by a serum

Table 6. Urine pH, flow rate and renal clearance of salicylic acid over the time period 0–16h (after Prescott et al. (12)).

Regimen	Urine pH	Urine flow rate (mL/min)	Renal salicylate clearance (mL/min)
Control	6.1 ± 0.4	1.4 ± 0.8	1.4 ± 1.4
Forced diuresis	6.5 ± 0.3	5.8 ± 1.9*	4.4 ± 1.8*,†
Forced alkaline diuresis	7.3 ± 0.4*	5.1 ± 1.2*	17.5 ± 10.1*
Sodium bicarbonate alone	8.1 ± 0.5*,†	2.6 ± 0.7*,†	23.5 ± 13.7*,†

All values are shown as mean ± SD.
*Significantly different from control ($p < 0.05$).
†Significantly different from forced alkaline diuresis ($p < 0.05$).

Table 7. Urine pH plasma half life and urine salicylate recovery (after Prescott et al. (12)).

		Plasma half-life		Urine salicylate (g)	
Treatment	Urine pH	0–4 h	4–16 h	0–4 h	0–16 h
Control	6.1±0.4	19.4±12.2	29.4±7.6	0.16±0.14	0.38±0.32
Forced diuresis	6.5±0.3	8.0±3.4*	38.6±14.5*	0.44±0.49*,†	1.53±1.27*,†
Forced alkaline diuresis	7.3±0.4*	5.9±3.4*	12.3±9.1*	1.55±1.87*	3.60±0.94*
Alkali alone	8.1±0.5*,†	5.0±1.6*	9.0±6.1*	2.44±1.59*	3.87±1.28*

All values are shown as mean±SD.
*Significantly different from control ($p<0.05$).
†Significantly different from forced alkaline diuresis ($p<0.05$).

salicylate concentration >500 mg/L or clinical salicylate intoxication) were reported by Morgan and Polak (37). Each patient received acetazolamide 250 mg intravenously. Additionally, 1 L 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 1 L hourly infusions of sodium chloride 0.9% plus potassium 20 mmol until rehydration was achieved. Thereafter, 1 L that contained bicarbonate 166.7 mmol and potassium 40 mmol was infused over a period of 2h for a total of 4h. If the serum salicylate concentration persisted at >400 mg/L, acetazolamide 250 mg was administered intravenously along with 1 L of sodium chloride 0.9% plus potassium 40 mmol and 1 L of sodium bicarbonate 1.4% plus potassium 40 mmol, infused in rotation every 2h for a total of 4h. The mean pretreatment urine pH was 6.82 (range 6.30–7.30) compared to a mean treatment urine pH of 7.88 (range 7.78–7.95).

The authors demonstrated that the combination of acetazolamide and sodium bicarbonate increased urine pH approximately one pH unit above pretreatment urinary pH. The mean amount of salicylic acid recovered in the urine was 4.91 g.

Comment. Serum salicylate concentrations in this study were measured by the non-specific Trinder method (38) and those in urine by the method of Brodie et al. (39). Urine pH was measured by pH meter. 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 8 of the 10 patients were utilized 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 mmol/L to 3.0 mmol/L. Additional data from patients in this study (37) were reported subsequently (40).

Morgan et al. (41) studied 11 salicylate-poisoned adult 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 1 L of mannitol 10% administered over 1h with the objective of producing a urine flow of approximately 500 mL/hour. 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 2h thereafter. If the positive fluid balance was 1 L or less and the urine pH was <7, the patient received 1 L of lactate 1/6M solution over 2h. Patients with a urine pH >7 received 1 L of saline 0.9% over 2h. A positive fluid balance of 1 to 2 L dictated the administration of an additional liter of mannitol 10% over 2h. When the positive fluid balance exceeded 2 L, mannitol 10% was administered at the slowest rate possible. The mean urine flow achieved was 447 mL/h (range 380–490 mL/h).

Comment. This study used the non-specific Trinder method (38) to measure salicylate concentrations. Urine pH was measured by pH meter. While the study illustrated the ability of mannitol to produce a diuresis, no data were presented with regard to 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 (40).

Morgan and Polak (40) reviewed the impact of urine pH and urine flow on salicylate excretion in 23 patients with salicylate poisoning (initial total salicylate concentration 440–880 mg/L) who were treated with either mannitol/sodium lactate (11 patients) or acetazolamide/sodium bicarbonate (12 patients) regimens. The 11 patients in the mannitol/sodium lactate group, all of whom had been reported previously (41), 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 and sodium chloride (0.9%) when it was above 7.0. Of the 12 patients in the second group, 10 had also been reported previously; (37) all 12 patients were initially administered acetazolamide 250 mg iv to achieve a urine pH of >7.5 which was maintained as required with an infusion of sodium bicarbonate 1.4%. 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. 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.

Comment. Serum salicylate concentrations in this study were measured by the non-specific Trinder method (38) and those in urine by the method of Brodie et al. (39). Urine pH was measured by pH meter. 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.

Prowse et al. (42) studied 22 patients who received forced alkaline diuresis for acute salicylate poisoning. Through random allocation the patients were divided into two groups. Twelve patients (5 men, 7 women; average age 31.6 years) with a mean initial serum salicylate concentration of 450 mg/L (range 210–760 mg/L) received a total of 10 L of fluid containing 360 mmol bicarbonate and 365.5 g glucose over 8h. The second group of 10 patients (5 men, 5 women; average age 27 years) had a mean initial serum salicylate concentration of 450 mg/L (range 300–620 mg/L) and received 10 L of fluid containing bicarbonate 348 mmol and mannitol 475 g over the same period. Patients who passed less than 200 mL of urine in the first 90 min of treatment or who developed a positive fluid balance in excess of 2.5 L were also given furosemide 40 mg intravenously.

Mean urine outputs were 14.6 and 18.7 mL/min for the glucose and mannitol groups, respectively, with a corresponding salicylate excretion rate of 10.7 (total urine salicylate excretion over 8h 5.1 g) and 11.3 mg/min (total urine salicylate excretion over 8h 5.4 g), suggesting that increasing the volume of alkaline urine does not increase salicylate excretion. The mean urine pH over the 8h of treatment varied between approximately 7.25 and 7.5 for the glucose group and 7.2 and 7.3 for the mannitol group. The mean serum salicylate half-life was 7.7h for the glucose patients and 5.8h for the mannitol patients.

Comment. Salicylate concentrations in this study were measured by a non-specific method (Keller). Urine pH was measured by an Astrup microtechnique. As this study was a comparison between mannitol and glucose diuresis, no conclusions can be drawn regarding the overall efficacy of urine pH manipulation.

Berg (43) described the use of diuretic-induced forced alkaline diuresis in 33 patients above 12 years of age admitted 1–14h (mean 6.2h) after salicylate ingestion. The mean serum salicylate concentration was 588 mg/L (range 402–1650 mg/L). One patient, a 20-year-old male, died 5h after admission having ingested aspirin 100 g (peak serum salicylic acid concentration 1650 mg/L). All patients were given sodium chloride 0.9%, glucose 5%, and sodium bicarbonate 1.4% in rotation. Potassium chloride 20 mmol/L, furosemide 20 mg, or bumetamide 0.5 mg every 2h, and calcium chloride 10% 10–30 mL every 24h were also administered. Of the 33 patients, 24 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 16–48h (mean 22.3h) with a mean 24h urine output (±SE) of 5976 (±598) mL and 9196 (±708) mL 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). Diuresis was achieved through the use of diuretics.

Comment. This study utilized the non-specific Keller method to measure salicylate concentrations. Urine pH was measured by 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. The mean salicylate half-life of 9.6h was compared to published half-lives of 18–22h in untreated adults.

Case Reports

Savege et al. (44) described the treatment of a 36-year-old man who was admitted in coma 1.5h after ingesting aspirin 90 g. Sodium bicarbonate 150 mmol was administered initially followed by the rapid

infusion of sodium bicarbonate, normal saline, and 5% dextrose in rotation. Fourteen liters of fluid were administered over the first 12h of treatment, during which time 10.3 L of urine were collected. Mannitol 190 g was also administered over this period. Intravenous fluids were administered at a much-reduced rate over the following 12h. Urine pH increased steadily during treatment, approaching 8 after 7.5h of treatment and remaining at approximately that level for a further 7h. In the first 8h of treatment, 21.5 g salicylate were eliminated with a further 12.5 g eliminated over the following 14h. The blood salicylate concentration fell from 1380 to 150 mg/L during the first 12h with a half-life of 5.6h. 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.

Comment. 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. However, the methods used to measure salicylate concentrations and urine pH were not stated.

Higgins et al. (45) reported the clinical course of a 43-year-old man who was thought to have ingested 105 g aspirin and alcohol. On admission 5h post-overdose, the plasma salicylate concentration was 952 mg/L. Although sodium bicarbonate was administered, the urine pH did not exceed 7 at any stage.

Comment. This study did not detail the methods used to measure salicylate concentrations or urine pH. The authors' claim that ''with effective alkalinization the salicylate level had fallen by 45% five hours after admission'' is not justified.

Role of Urine Alkalinization in Salicylate Poisoning

Theoretically, there is no doubt that urinary alkalinization should enhance the urinary elimination of salicylates, but generating adequate data to establish its role in the management of salicylate poisoning has proved elusive. Some studies simply failed to achieve alkalinization while most of the older ones are compromised by the analytical methods of the time which overestimated salicylate concentrations and recoveries of the drug. For the same reasons, studies that do not state the analytical method cannot be accepted without reservation. The outcomes of the studies that used shortening of the plasma salicylate decay curve may be equally suspect if measures to alkalinize the urine were combined with administration of a large fluid load. Ultimately, therefore, only the volunteer study of Vree et al. (11) and the clinical study of Prescott et al. (12) indicate that urinary alkalinization is of value in the treatment of salicylate poisoning.

COMPLICATIONS OF URINE ALKALINIZATION

Severe Alkalemia

A shift of blood pH toward alkalinity (reduction in its hydrogen ion concentration) is an inevitable consequence of any regimen which involves the administration of bicarbonate. When given to salicylate-intoxicated patients whose arterial hydrogen ion concentration is already normal or high (as is common, particularly in adults), bicarbonate may increase pH (reduce hydrogen ion concentrations) to an extreme degree. Lawson et al. (14) found that arterial pH rose to 7.63 (H^+ concentration 24 nmol/L) in 1 of 11 patients treated with forced alkaline diuresis and to 7.53 (H^+ concentration 30 nmol/L) in 1 out of 13 given the forced cocktail diuresis. Although they considered alkalotic tetany a potential complication, it did not occur and there was no evidence for adverse effects from the high blood pH. Nor did Cumming et al. (36) observe adverse effects with a mean blood pH of 7.51 (H^+ concentration 31 nmol/L) and a maximum of 7.69 (H^+ concentration 20 nmol/L). However, Berg (43) reported mild tetanic symptoms in 6 out of 33 patients treated with forced alkaline diuresis. Their blood pH values were not stated. Literature search (1965–2003) has failed to reveal any publication attributing serious adverse effects to an imposed, short-lived, alkali load.

Illnesses associated with alkalemia are common in hospitalized patients (46) and carry a high mortality in both medical and surgical conditions, but especially the former. A mortality rate of 32% was found in medical patients who had an arterial pH in the range 7.48–7.54 (H^+ concentration 33–29 nmol/L) and 46% when pH exceeded these values. Neither the diagnoses nor the role of alkali administration in the etiology of the metabolic disturbance were given and it is doubtful if these observations are relevant to poisoned patients subjected to urine alkalinization. It is reassuring, however, that while the authors admitted the possibility that alkalemia exerted independent untoward effects in some cases, they found no proof that this was the case.

Hypokalemia

The administration of sodium bicarbonate shifts potassium into cells and is thus hypokalemia potentially may be observed during urine alkalinization, particularly if this treatment is introduced before preexisting hypokalemia has been corrected.

Hypokalemia has been observed in untreated salicylate poisoning and when forced alkaline diuresis was used as a treatment measure. Several studies (14,44,47,48) have demonstrated that the infusion of 120 mmol potassium chloride over the 3h of forced alkaline diuresis maintained normokalemia.

Hypocalcemia

Hypocalcemia also complicated treatment with forced alkaline diuresis but, despite concomitant alkalemia, it did not appear to cause symptoms (49). Tetany is more likely to result from shifts in bound and unbound calcium concentrations secondary to alkalemia.

Coronary Vasoconstriction

Alkalemia shifts the oxyhemoglobin dissociation curve to the left and reduces oxygen delivery to tissues. It could therefore pose a risk to patients with ischemic heart disease. Several studies have shown that voluntary hyperventilation in patients with ischemic heart disease can produce mean arterial pH values of as high as 7.58 (H^+concentration 26 nmol/L) and ischemic changes in the electrocardiogram (50,51). However, coronary artery constriction does not occur (51) and the ECG changes may be due to potassium fluxes and autonomic nervous system activity rather than alkalemia (52).

Cerebral Vasoconstriction

Cerebral vasoconstriction is probably a desirable rather than an unwanted effect of alkalemia.

APPENDIX: PROCEDURE FOR PERFORMING URINE ALKALINIZATION IN SALICYLATE POISONING

Baseline biochemical assessment

- Measure plasma creatinine and electrolytes
- Measure plasma glucose
- Measure arterial acid-base status

Clinical preliminaries

- Establish an intravenous line
- Insert a central venous line, if appropriate
- Insert a bladder catheter
- Correct any fluid deficit
- Correct hypokalemia, if indicated
- Measure urine pH using narrow-range indicator paper (use fresh urine as pH will change as carbon dioxide blows off on standing) or pH meter

Achieving alkalinization

- In an adult, give sodium bicarbonate 225 mmol (225 mL of an 8.4% solution) intravenously over 1h
- In a child, give sodium bicarbonate 25–50 mmol (25 mL of an 8.4 % solution) intravenously over 1h
- The period of administration of the loading dose of sodium bicarbonate may be shortened and/or the dose increased if there is preexisting acidemia

Maintaining urine alkalinization

- Give additional boluses of intravenous sodium bicarbonate to maintain urine pH in the range 7.5–8.5

Monitor

- Urine pH every 15–30 min until urine pH is in the range 7.5–8.5, then hourly
- Plasma potassium hourly
- Central venous pressure hourly
- Acid-base status hourly. (Note: Arterial pH should not exceed 7.50)
- Plasma salicylate concentrations hourly
- Urine output—should not exceed 100–200 mL/h

Discontinue urine alkalinization

- When plasma salicylate concentrations fall below 350 mg/L in an adult or 250 mg/L in a child

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