THE CARDIOVASCULAR AND METABOLIC EFFECTS OF MIXTURES OF ACETATE AND SUCCINATE: A POTENTIAL IMPROVEMENT IN DIALYSATE SOLUTIONS

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Summary

Various mixtures of acetate (AC) and succinate (SUC) were studied for their metabolic and cardiovascular (CV) effects in 10 dogs. The CV effects seen with all mixtures were similar to those reported for SUC alone with the only changes being increased cardiac output and decreased total peripheral resistance. The 50:50 per cent AC/SUC offered the advantage of a rapid but less marked and more sustained HCO₃⁻ production. The pH changes in all mixtures followed HCO₃⁻ values. Since the addition of SUC seems to reduce the untoward CV changes seen with AC alone, the ratio of AC/SUC should be based on metabolic considerations. The present data suggest that a 50:50 per cent AC/SUC mixture is optimal for metabolic and CV effects.

Introduction

Sodium acetate has been used as a substitute for sodium bicarbonate in dialysis solutions since 1964 [1]. Since bicarbonate has a low solubility and tends to precipitate in the presence of calcium and magnesium, the preparation of concentrated solutions presented major difficulties. Thus, the use of bicarbonate required proportioning pumps and/or delicate pH adjustment. The shift to acetate as a source of fixed base circumvented the physical problems associated with bicarbonate. Since acetate is rapidly metabolised and generates bicarbonate in the process [2], it can restore bicarbonate in patients undergoing haemodialysis.

Sodium acetate, however, is not a pharmacologically inert substance. It has been shown to have significant cardiovascular effects like hypotension and myocardial depression when given intravenously either as a bolus [3] or by continuous infusion [4]. There is, therefore, a need for a compound that displays fewer cardiovascular effects than acetate but will generate bicarbonate.

Kirkendol et al [5,6] previously reported that bolus injections and infused succinate produced less pronounced cardiovascular changes than acetate. This
study relates to the cardiovascular and metabolic effects of sodium acetate: sodium succinate mixtures as a source of fixed base in dialysate solutions.

Materials and methods

In three mongrel dogs of either sex weighing from 18 to 24kg each were anaesthetised intravenously with 30mg/kg of pentobarbital sodium. A polyethylene cannula was inserted in the right femoral vein for infusion of the sodium salts. The mean arterial blood pressure was measured using a Statham P23DC transducer via a polyethylene cannula inserted into the right femoral artery. Heart rate was continuously recorded using a Grass cardiac tachograph. Cardiac output was determined by the right heart thermal washout technique. A Swan-Ganz thermistor-tipped catheter was placed in the pulmonary artery via the jugular vein, with the saline indicator injected at the level of the right atrium through a port in the same catheter. The cardiac output was calculated by an Instrumentation Laboratory Cardiac Output Computer Model 601. The cardiac output values used in this study were the average of three determinations per observation period. A catheter was placed in the left ventricle via the left carotid artery for the measurement of left ventricular pressure. The maximum rate of rise of the left ventricular pressure (dp/dt), an index of myocardial contractility, was obtained using a Grass Polygraph differentiator (7P20). Total peripheral resistance was calculated as mean blood pressure (mmHg) divided by cardiac output (L/min), and femoral vascular resistance was calculated as mean blood pressure divided by femoral blood flow (ml/min). After preparation of the animal and recording of the control parameters, mixtures of sodium acetate, sodium succinate, 25:75 acetate/succinate, 50:50 acetate/succinate or 75:25 acetate/succinate were infused at doses of 0.125, 0.25, 0.5, and 1.0mEq/kg/min for 10 minutes at each dose level. At the end of each 10 minute infusion period, cardiac output was determined. All other parameters were continuously recorded, but the values reported are those obtained at the end of each infusion period.

In another series of experiments, the mixtures of sodium acetate:succinate were infused at the rate of 0.25mEq/L/min in a volume of 0.25ml/kg for one hour in seven acutely nephrectomised dogs. Blood samples were taken every 20 minutes for the first two hours and every hour for the next two hours. Blood pH on each sample was determined using a Beckman Micro Sensor assembly and a Corning digital 110 pH meter. Plasma bicarbonate levels were determined by the titration method using standard acid and base.

Results

The cardiovascular effects of the solutions were determined. Figure 1 shows the effects of these solutions on total peripheral resistance. All three mixtures produced similar decreases in TPR with the maximum being about a 50 per cent reduction. Along with the decreases in TPR there were dose-related increases in cardiac output with the 25:75 AC/SUCC mixture increasing the CO from 4 to 8.5L/min. The infusion of these solutions resulted in no changes either in blood pressure, heart rate or dp/dt.
Figure 1. The effects of mixtures of acetate and succinate on total peripheral resistance.

Figure 2 shows the effects of the various mixtures on plasma bicarbonate. Succinate, alone, produced bicarbonate at the slowest rate and lowest amounts. As the amounts of acetate were increased, the rate of generation of bicarbonate increased with the highest rate seen with acetate alone. The changes in blood pH in these animals, in general, followed the bicarbonate. All the solutions produced similar increases in plasma sodium with the concentrations increasing by about 40mEq/L. The solutions of acetate:succinate at various concentrations did not produce changes in plasma potassium or in the haematocrit.

Discussion

Metabolic acidosis is a feature of end-stage renal disease which must be corrected during dialysis. Sodium bicarbonate was first used as a replacement buffer system in dialysis but later was replaced in most of the cases by sodium acetate to avoid its low solubility and relative low stability [1]. Sodium acetate has been shown in animal and human studies [3,7] to be associated with a reduction in peripheral resistance due to vasodilation and myocardial depression. As a consequence hypotension frequently develops as a complication of the use of acetate in the uraemic patient undergoing haemodialysis. A number of sodium salts of organic substances which should generate bicarbonate were evaluated for their effects on the cardiovascular system using doses equivalent to those used
with acetate. Several compounds previously tested in animal studies have included lactate, pyruvate, alpha-keto-butyrate, succinate, glutamate, gluconate, fumarate, malate, oxaloacetate and glyoxylate. All these compounds were compared with equivalent doses of bicarbonate [5,8,9]. The cardiovascular effects produced by fumarate, malate, oxaloacetate and glyoxylate were much more marked than those seen with acetate and some even proved to be lethal to the experimental animals [5]. Lactate and pyruvate produced myocardial depression and decreases in blood pressure similar to those seen with acetate and appeared to offer no advantage over the currently used acetate [5]. Glutamate, aspartate, gluconate and succinate all produced fewer cardiovascular complications than acetate and therefore merited additional evaluations as possible sources of fixed bases.

The effect of succinate on the various cardiovascular parameters show that it more closely resembles bicarbonate than acetate. Succinate has no effect on cardiac output, dp/dt, heart rate or stroke volume and the blood pressure was not significantly affected with dose-related decreases in total peripheral resistance.

From the metabolic point of view, succinate generates bicarbonate at a slower rate than acetate, producing less marked changes. However, this slower rate of bicarbonate production with succinate results in an initially increased anion gap acidosis. This observation led to the evaluation of mixtures of acetate and succinate in an attempt to find a solution with less cardiovascular effects but taking advantage of the bicarbonate generating characteristics of both acetate and succinate.
Of the various mixtures of acetate and succinate studied in the present investigation, the 50:50 AC/SUCC offered the advantage of a rapid but less marked production of bicarbonate due to reduced levels of acetate but a sustained and steadier production of the base due to the succinate. This solution produced dose-related increases in cardiac output and decreases in TPR with no changes in blood pressure, heart rate or dp/dt. The cardiovascular effects seen with this solution were less than those seen with acetate alone and more closely resemble those seen with succinate alone. The addition of succinate to the dialysate solution probably will be beneficial because it has less cardiovascular effects than acetate. Further, the addition of succinate allows one to reduce the concentration of acetate in the dialysate. Therefore, the best acetate/succinate combination should be based on metabolic considerations.

In summary, our data would suggest that a 50:50 acetate/succinate mixture may be a better combination for optimal metabolic and cardiovascular effects during dialysis.

References

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