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Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure

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Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. In hemodialysis patients with hyperkalemia, i.v. sodium bicarbonate has recently been found to be ineffective in lowering plasma potassium within one hour. In the present study the effect of a prolonged bicarbonate infusion on plasma potassium was investigated. Twelve patients with terminal renal failure who were on hemodialysis were infused i.v. with 8.4% sodium bicarbonate (4 mmol/min) for one hour and with 1.4% (0.5 mmol/min) for five hours (total amount 390 mmol). Plasma bicarbonate rose from 17.5 at baseline to 28.4 and 29.6 mmol/liter, and blood pH from 7.32 to 7.46 and 7.48 at one and six hours, respectively. Plasma potassium did not change significantly after one and two hours (6.04 at baseline, 5.91 and 5.77 mmol/liter, respectively). Only at four and six hours did a moderate decline to 5.44 ($P < 0.05$) and to 5.30 ($P < 0.01$) occur, of which approximately half was calculated to be due to ECF volume expansion. However, no change or a very moderate decrease was observed in three patients even after six hours (+0.19, −0.32, −0.33 mmol/liter). Five patients with higher baseline plasma potassium (6.15 to 8.15 mmol/liter) behaved like seven with lower levels (5.25 to 5.87 mmol/liter). Tented T-waves in the ECG of seven patients disappeared after one hour only in one patient. Plasma aldosterone, norepinephrine and epinephrine were normal to elevated before and tended to fall during i.v. bicarbonate. Plasma dopamine and insulin were in the normal range. It is concluded that in patients with terminal renal failure maintained on hemodialysis and with sufficient levels of potassium regulating hormones, i.v. bicarbonate was ineffective as a treatment of hyperkalemia for up to two hours; after four and six hours it was accompanied by a modest fall in plasma potassium which, however, was not quite reliable and was obtained at the cost of a considerable sodium-volume load.

Patients with chronic terminal renal failure are at a high risk for life-threatening hyperkalemia. This is the result of diminished renal potassium excretion but also of an impaired extrarenal potassium tolerance [1–4]. The mechanisms underlying the impaired extrarenal potassium homeostasis are not entirely clear. Major regulating factors include acid-base changes and hormones such as insulin, epinephrine, and aldosterone [1, 2].

Based on these interactions, various therapeutic approaches have been recommended for the treatment of hyperkalemic emergencies [1, 5–10]. Among them intravenous bicarbonate still seems to be a favorite choice of many nephrologists, as indicated in a recent survey [10]. In hemodialysis patients, intravenous bicarbonate was previously shown to be ineffective in lowering plasma potassium within 60 minutes [11]. However, the effect of this treatment was not followed over several hours. Therefore, the present study was designed to investigate the effects of a prolonged intravenous infusion of bicarbonate in patients with terminal renal failure and hyperkalemia.

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Methods

Patients

Twelve patients with terminal renal failure receiving maintenance hemodialysis were studied. They were selected because they repeatedly had predialysis plasma potassium levels of ≥ 5.8 mmol/liter. There were six women and six men, aged 24 to 66 years [mean age 48.5 ± 3.5 (SEM) years]. The renal diagnosis was chronic glomerulonephritis in four, polycystic kidney disease in four, analgesic nephropathy in two, and nephrosclerosis or interstitial nephritis of unknown origin in one each. Hemodialysis with capillary dialyzers was performed thrice weekly using bicarbonate as a buffer in the dialysate. All patients continued to receive their usual medication, including phosphate binders (aluminum hydroxide or calcium salts) and, in some cases, benzodiazepines at bedtime; four patients received a small dose of the cardio-selective β-blocker, atenolol (4 times 25 mg/week), and one received nifedipine for treatment of hypertension, but none was taking angiotensin converting enzyme inhibitors.

Study design

The measurements were performed in the morning after an overnight fast during the hours preceding a regularly scheduled hemodialysis. Upon arrival of the patient, standard hemodialysis fistula needles were placed. The needle close to the arteriovenous anastomosis was used for blood sampling, the second was used for intravenous bicarbonate infusion given with a constant infusion pump (IVAC 531, IVAC Corporation, San Diego, California, USA). After one hour of recumbency, basal levels of blood gas parameters and plasma sodium, potassium, chloride, osmolality, renin, aldosterone, catecholamines and insulin were measured.

Thereafter, bicarbonate was infused intravenously over six hours. During the first hour, bicarbonate 8.4% in water (without glucose) was delivered at a rate of 4 mmol/min (except in 1 very small and light female patient who received only 2 mmol/min) and in a total volume of 240 ml. During the second to sixth hour, 1.4% bicarbonate in water (without glucose) was given at a rate of 0.5 mmol/min and in a total volume of 900 ml. Consequently,

the volume infused over the entire six-hour treatment period amounted to 1140 ml with a total of 390 mmol of sodium.

Plasma potassium, sodium, and blood gas parameters were measured at 30, 60, 120, 240 and 360 minutes, osmolality at 60 and 360 minutes, whereas the other determinations were repeated at 60, 120, 240 and 360 minutes (except in 3 patients in whom hormone measurements were obtained only after 60 and 360 min). At baseline and after 60 and 360 minutes a standard 12 lead electrocardiogram was recorded. The subjects remained in a supine position throughout the procedure. They were allowed up to 300 ml of water if thirsty, but no food. Urine was collected by spontaneous voiding over the entire period in four subjects with some residual diuresis for measurement of potassium excretion; eight patients were anuric.

Analytical procedures

Plasma potassium and sodium were measured by flame photometry, chloride was determined by mercury (II) thiocyanate method in a Greiner G 400 Analyzer (Langenthal, Switzerland). Blood pH and partial pressure of carbon dioxide were determined immediately after withdrawal with an Instrumentation Laboratory 213 blood gas analyzer (Milan, Italy). Bicarbonate concentration was calculated with the Henderson-Hasselbalch equation using a pK of 6.10 and a solubility coefficient for carbon dioxide of 0.0301. Plasma glucose and osmolality as well as insulin, renin activity, aldosterone and plasma catecholamines were determined as described previously [11].

Calculation of extracellular fluid (ECF) volume changes and of bicarbonate space

The ECF volume participating in rapid fluid volume changes was calculated as one third of whole body water, which was assumed to be 60 and 50% of body weight in men and in women, respectively [12]. Changes in ECF volume (ΔECF) were estimated using chloride space arithmetic as follows:

$$\Delta ECF = eECF - iECF$$

$$eECF = (iECF \times i[Cl]_e + b_{Cl})/e[Cl]_e$$

where eECF is the experimental ECF volume, iECF the initial ECF volume, $i[Cl]_e$ is the initial extracellular chloride concentration, b_{Cl} is the chloride balance (representing urinary chloride losses), and $e[Cl]_e$ is experimental extracellular chloride concentration. Chloride space arithmetic assumes that internal shifts of chloride do not occur.

Bicarbonate space was calculated using the formula: retained bicarbonate in mmol/kg body weight divided by final minus initial plasma bicarbonate. In order to correct for volume expansion, initial bicarbonate was multiplied by the ratio of final over initial plasma chloride concentration (= corrected bicarbonate space).

Statistical analysis

Statistics were performed with the help of the Statistical Analysis System software package (version OS 6.03, SAS Institute, Inc., Cary, North Carolina, USA). Comparison of variations over time was by analysis of variance with Scheffe's multiple comparison and also by paired *t*-test. Pearson correlation analysis was used for assessment of relationships between

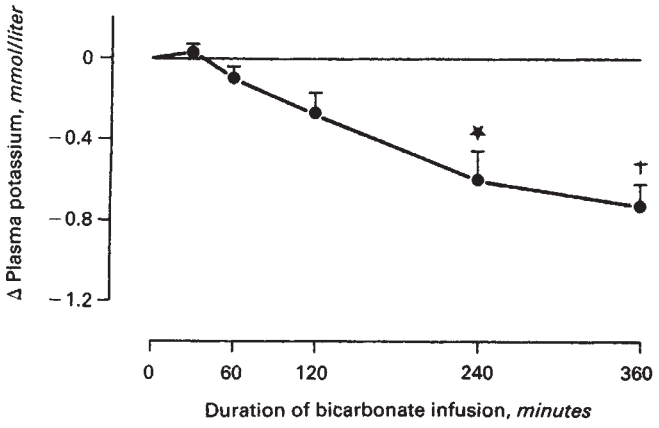

Fig. 1. *Changes in plasma potassium (mmol/liter) during intravenous infusion of bicarbonate.* Vertical bars denote SEM. $*P < 0.05$; $\dagger P < 0.01$.

variables. Values are given as mean ± SEM. Since natural logarithmic transformation rather than absolute values followed a Gaussian distribution, the transformed values of plasma renin activity, aldosterone, insulin, epinephrine, norepinephrine and dopamine levels were used for statistical analysis.

The study was approved by the ethical committee of Kantonsspital Aarau, Switzerland.

Results

Effect on plasma potassium, sodium, osmolality, glucose and blood gas parameters

Mean basal plasma potassium was 6.04 ± 0.23 mmol/liter (SEM). Five patients had severe hyperkalemia with plasma potassium levels ranging from 6.15 to 8.15 mmol/liter (mean 6.76 ± 0.36 mmol/liter); the other seven had moderate hyperkalemia of 5.25 to 5.87 mmol/liter (mean 5.53 ± 0.10 mmol/liter). During bicarbonate infusion, plasma potassium was unchanged at 30 minutes (6.06 ± 0.25 mmol/liter) and 60 minutes (5.90 ± 0.26 mmol/liter; Fig. 1). At 120 minutes, plasma potassium averaged 5.77 mmol/liter, a change that was still not significant by ANOVA. Only 240 and 360 minutes after the start of the intravenous bicarbonate infusion did a significant decline in plasma potassium become evident. The five patients with a plasma potassium above 6 mmol/liter had no greater decline at 60 and 360 minutes than the seven with a plasma potassium below 6.0 mmol/liter (−0.01 and −0.66 vs. −0.13 and −0.77 mmol/liter; Fig. 2).

Plasma sodium increased significantly from 136.9 ± 0.4 to 144.7 ± 0.5 mmol/liter ($P < 0.001$) at 60 minutes of bicarbonate infusion and remained in this range over the entire study period (143.9 ± 0.7 mmol/liter at 360 min). Osmolality rose from 303 ± 3 to 313 ± 3 at 60 minutes and to 309 ± 2 mOsm/liter at 360 minutes. This change was not significant by ANOVA but highly significant by paired *t*-test ($P < 0.001$). Mean plasma glucose remained in the normal range throughout the study period.

Plasma bicarbonate increased markedly from 17.5 ± 0.9 to 24.2 ± 1.0 mmol/liter ($P < 0.001$) at 30 minutes and to 28.4 ± 1.1 mmol/liter ($P < 0.0001$) at 60 minutes, and remained in the latter range thereafter. Blood pH rose in parallel from 7.31 ± 0.01 to 7.40 ± 0.01 ($P < 0.001$) at 30 minutes and to 7.45 ± 0.01 ($P <$

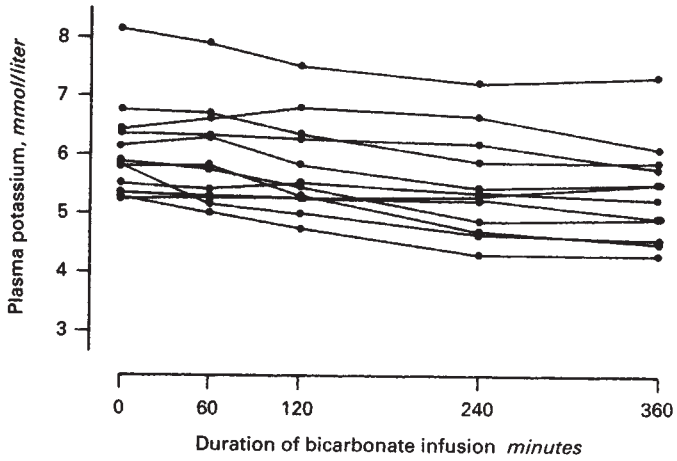

Fig. 2. *Changes of plasma potassium in individual patients during intravenous infusion of bicarbonate.*

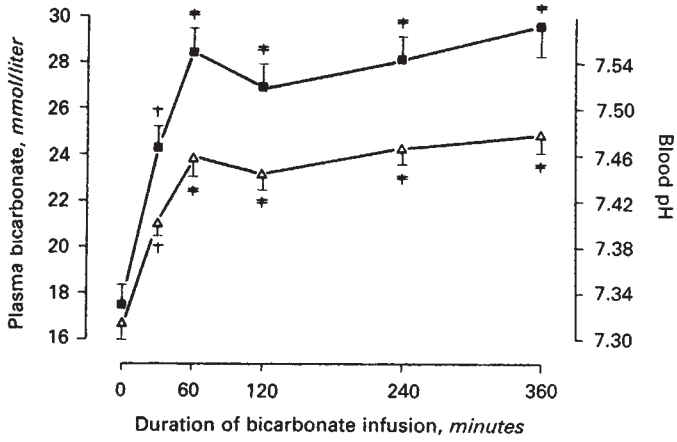

Fig. 3. *Changes in bicarbonate (mmol/liter) (■——■) and in pH (△——△) during intravenous infusion of bicarbonate.* Vertical bars denote SEM. †$P < 0.001$, ‡$P < 0.0001$.

0.0001) at 60 minutes (Fig. 3). Plasma chloride decreased from 101.9 ± 0.8 to 98.9 ± 1.2 mmol/liter ($P < 0.002$) at 60 minutes and to 96.2 ± 1.4 mmol/liter ($P < 0.001$) at 360 minutes.

The four patients with some residual diuresis excreted 2, 3, 9 and 10 mmol, respectively, of potassium over the entire study period.

Correlations

Changes in plasma potassium during bicarbonate infusion did not correlate with basal values or changes in plasma bicarbonate or blood pH. This held true when the 12 hemodialysis patients of the present study were analyzed alone or together with nine patients from our previous study, who underwent the same protocol for 60 minutes [11] and did not participate in the present investigation. Similarly, no significant correlation was found between plasma potassium or changes in plasma potassium on the one hand and plasma osmolality or plasma sodium on the other.

Based on changes in plasma chloride concentration it could be calculated that ECF volume expanded considerably during bicarbonate infusion. The contribution of expansion of ECF to the fall of plasma potassium was then calculated using the ECF figures of Table 1. It was found that the minute drop of plasma potassium at 60 minutes could be fully accounted for by dilution in all patients, except one who had an extraordinarily large fall of plasma potassium of 0.68 mmol/liter; at 360 minutes, 50.0 ± 6.7% of the decrease of plasma potassium was calculated to be due to ECF volume expansion (with similar figures at 120 and 240 min, that is, 50.2 ± 7.3 and 54.7 ± 7.0%, respectively). Bicarbonate spaces increased during the experiment; they were 4 to 5% smaller when corrected for ECF volume expansion (Table 1).

Table 1. Extracellular fluid volume changes (Δ ECF) and bicarbonate space during intravenous infusion of bicarbonate

		Bicarbonate space *ml/kg body wt*	
	ΔECF *ml*	Uncorrected for ΔECF	Corrected for ΔECF
At 60 minutes	389 ± 73	349 ± 20	335 ± 19
At 360 minutes	762 ± 94	531 ± 24	501 ± 24

Effect of bicarbonate infusion on ECG

Basal ECG tracings revealed tented T-waves in seven patients (plasma potassium 5.25 to 8.15 mmol/liter) and no signs of hyperkalemia in the other five (plasma potassium 5.28 to 6.15 mmol/liter). The patient with the highest value manifested a pronounced S-T-elevation in lead V_2 (resembling acute myocardial infarction). Loss of P-waves or widening of the QRS-complex were not observed. The T-wave tenting improved or disappeared after 60 minutes in one patient without a change in plasma potassium (5.62 vs. 5.60 mmol/liter) and after 360 minutes in two others whose plasma potassium had decreased from 6.35 to 5.76 and from 6.40 to 6.08 mmol/liter, respectively. In the patient with the initial plasma potassium of 8.15 mmol/liter, S-T elevation in lead V_2 improved after 360 minutes when plasma potassium had decreased to 7.30 mmol/liter.

Effects on hormones

Mean supine plasma renin activity was elevated in comparison with the age related normal range under basal conditions and was not significantly modified during bicarbonate infusion (Table 2).

Mean supine plasma aldosterone was increased under basal conditions and tended to decrease during the study procedure (statistically not significant). Aldosterone correlated significantly with corresponding plasma potassium concentrations under basal conditions or throughout the study, ($r = 0.59$, $P < 0.05$ and $r = 0.60$, $P < 0.001$, respectively).

Plasma epinephrine and norepinephrine also were on average increased under basal conditions and tended to decrease (statistically not significantly) during the study procedure. Plasma dopamine and insulin were normal and unaltered during bicarbonate infusion.

Discussion

It is widely held that intravenous bicarbonate acutely restores elevated plasma potassium levels in patients with renal failure. Bicarbonate infusion is advocated in standard textbooks of nephrology and electrolyte metabolism and in reviews [5–7].

Table 2. Plasma renin, aldosterone, insulin and catecholamines during intravenous infusion of bicarbonate

	Time *min*				
	0	60	120	240	360
Plasma renin activity *ng/ml/h* (normal 0.4–3.4)	5.8 ± 1.4	5.7 ± 1.5	6.0 ± 1.7	4.7 ± 1.2	4.5 ± 1.1
Plasma aldosterone *ng/dl* (normal 2–10)	35.3 ± 9.6	17.7 ± 6.0	14.7 ± 6.5	13.8 ± 5.6	13.0 ± 4.3
Plasma insulin *mU/liter* (normal 5–20)	13.7 ± 2.7	10.9 ± 1.1	10.3 ± 0.5	9.0 ± 0.6	8.7 ± 0.6
Plasma epinephrine *ng/dl* (normal 2–11)	21.5 ± 7.5	10.9 ± 2.9	13.8 ± 4.8	14.0 ± 5.3	13.4 ± 3.7
Plasma norepinephrine *ng/dl* (normal 10–50)	147 ± 78	59 ± 19	65 ± 23	58 ± 17	56 ± 19
Plasma dopamine *ng/dl* (normal 2–15)	5.0 ± 1.7	4.0 ± 1.5	6.2 ± 2.8	5.0 ± 1.9	4.3 ± 1.6

Moreover, in a recent survey intravenous bicarbonate still ranked second (after intravenous calcium gluconate) as the initial treatment for hyperkalemia in a majority of 65 directors of nephrology training programs [10]. This recommendation is based on uncontrolled clinical studies performed in the surprisingly small number of a total of 17 patients with renal failure [13–16]. However, in a recent study intravenous infusion of bicarbonate in 13 patients with terminal renal failure undergoing hemodialysis failed to lower plasma potassium within sixty minutes [11]. The results of the present investigation extend this observation and corroborate that intravenous bicarbonate is ineffective as an emergency treatment of hyperkalemia in patients with terminal renal failure who are on maintenance hemodialysis.

In such patients the plasma potassium-lowering effect of intravenous bicarbonate seems to have a very slow onset, requiring several hours to develop. This time interval was 3.5 hours in the often cited study by Fraley and Adler [16], as pointed out recently by us and others [11, 17]. For this reason, the bicarbonate infusion was prolonged to six hours in the present study. The absence of a significant improvement of hyperkalemia after two hours and appearance of a reduction after four hours is in agreement with an earlier study [16] and a recent abstract describing a modest lowering of plasma potassium by isotonic bicarbonate infusion after three hours [18]. However, it must be pointed out that even prolonged bicarbonate application may be unreliable since in three of our 12 hemodialysis patients no or a minor fall of plasma potassium was found even after six hours (+0.19, −0.32 and −0.33 mmol/liter, respectively; Fig. 2).

Since infusions of hypertonic mannitol or saline (but not of hypertonic bicarbonate) have been shown to elevate plasma potassium [19, 20], the possibility that hypertonicity might *per se* antagonize a plasma potassium-lowering action of bicarbonate had been investigated in our previous study [11]. It was found that isotonic bicarbonate which did not elevate plasma osmolality and sodium similarly failed to decrease plasma potassium. In the present study, the lack of a correlation between plasma potassium or change in plasma potassium on the one hand and plasma osmolality or sodium on the other are an additional argument against the role of hypertonicity in this respect.

It seemed to be important to assess the contribution of expansion of ECF volume in the fall of plasma potassium. A recent report suggested that hemodilution is negligible, because hematocrit and osmolality did not change [18]. However, the volume of isotonic sodium bicarbonate infused over two hours was so small (roughly 400 ml) that no significant change was to be expected even if the whole volume had remained in the extracellular volume space. In our study, the amount of sodium (390 mmol) and of total volume (1,140 ml) infused was much larger. We examined this issue using chloride space arithmetic and found that roughly half of the fall of plasma potassium could be accounted for by dilution arising from expansion of ECF space after two to six hours of bicarbonate infusion.

The situation concerning bicarbonate distribution is quite complex [21, 22]. The bicarbonate space increased during infusion in our study, indicating that a considerable part of the administered bicarbonate entered the intracellular space. Assuming that mean whole body water amounts to 55% of body weight, the value of 501 ml/kg body weight for bicarbonate space indicates that the buffer was almost evenly distributed in body water from 120 minutes onward. It must be pointed out that the usefulness of intravenous bicarbonate in acidosis of various etiology has been seriously questioned, since physiological studies indicate that this may entail dangerous paradoxical intracellular acidosis [23–26]. Moreover, the considerable expansion of ECF volume induced by our protocol is of concern especially in patients without excretory renal function. During the infusion of 8.4% sodium bicarbonate at a high rate ECF was expanded by about 400 ml at 60 minutes, considerably more than the 240 ml infused. This was undoubtedly due to a shift of water out of the cells in consequence of the induced hypertonicity. The further rise of the ECF volume to a total of roughly 800 ml at 360 minutes was promptly relieved in our patients, because hemodialysis was initiated immediately after the end of the study. However, in a clinical situation without rapid availability of a dialysis procedure, the protocol used may impose a substantial risk of pulmonary edema to the patient with end-stage renal failure. Since these patients usually have fluid overload when they develop hyperkalemia, the substantial obligatory fluid expansion of alkali therapy in general may be life-threatening.

The present results obviously apply only to patients with terminal renal failure maintained on regular hemodialysis. Although the mean basal plasma potassium was somewhat higher in the patients of the present study than in our earlier study (6.04 vs. 5.66 mmol/liter), it was generally not as high as it can be in emergencies. In the group of patients studied, those with higher plasma potassium (6.15 to 8.15 mmol/liter) responded no better than those with hyperkalemia of a more modest degree (Fig. 2). Moreover, there was no correlation between the basal plasma potassium and its change during bicarbonate infusion. This demonstrates the lack of acute therapeutic efficacy regardless of the severity of hyperkalemia in patients with terminal renal failure on maintenance hemodialysis.

The general influence of the degree of acidosis is difficult to

evaluate from the present study. Although less cooperative hemodialysis patients with a tendency to poor dietary compliance were included, and plasma bicarbonate was lower than in the earlier investigation (17 to 18 vs. 21 to 22 mmol/liter), extreme degrees of metabolic acidosis as seen in uremic emergencies were not present. In our patients no correlation between basal blood pH or plasma bicarbonate and changes in plasma potassium after 60 minutes were found. This held true when the patients of our previous study were added in order to increase sample size. Moreover, another study evaluating the increase of plasma potassium after intravenous potassium also failed to find a relationship with the degree of acidosis [27]. Nevertheless, it is still possible that alkali therapy for hyperkalemia is most effective when severe acidosis is also present [28] as in advanced uremia.

The ECG tracings revealed tenting of T-waves in seven patients and additionally a pseudoinfarction pattern described previously as a rare sign of hyperkalemia [29] in one of them. After one hour of bicarbonate infusion, a single patient only manifested improvement in tenting without a change in plasma potassium, whereas hyperkalemic ECG changes improved or disappeared in three more patients after six hours only. The unchanged ECG in the majority of patients with alterations induced by hyperkalemia after 60 minutes of therapy is an additional argument for the inefficacy of bicarbonate as an emergency treatment of hyperkalemia in patients with terminal renal failure.

Considering hormonal factors involved in the homeostasis of extracellular potassium, basal plasma aldosterone was elevated, and aldosterone values correlated positively with potassium levels in the present and in previously studied hemodialysis patients [11, 30]. Basal plasma norepinephrine and epinephrine also ranged from normal to elevated, as noted in previous studies [11, 31, 32], while dopamine levels were normal. The tendency of plasma aldosterone, norepinephrine and epinephrine to decrease during the course of bicarbonate infusion probably reflects in part the physiological diurnal variation, and in part the increase in ECF volume. The decrease in aldosterone is likely to have been promoted by the concomitant mild reduction in plasma potassium.

Plasma insulin levels were in the normal range over the entire study period, which is in agreement with earlier studies by us and by others [11, 31]. This is of some importance considering the marked potassium lowering effect of intravenous insulin in glucose [11]. Since alkalemia increases while acidemia diminishes the action of insulin, it seems possible that this effect might have played a role in the observed mild decrease of plasma potassium [33]. It is of note that one of the patients had a borderline low blood glucose level and another was frankly hypoglycemic, both without any clinical symptoms.

We conclude that in patients with terminal renal failure who are maintained on hemodialysis and who have sufficient levels of potassium regulating hormones, intravenous bicarbonate was ineffective as a treatment of hyperkalemia for up to two hours; after four and six hours it was accompanied by a modest fall in plasma potassium which, however, was not quite reliable and was obtained at the cost of a considerable sodium-volume load.

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