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CLINICAL INVESTIGATION

Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients

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Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. We evaluated in maintenance hemodialysis patients the potassium lowering effects of intravenous insulin with glucose, nebulized albuterol, and a regimen combining both modalities. There was a similar decrease in plasma potassium following either insulin with glucose (0.65 ± 0.09 mmol/liter) or albuterol (0.66 ± 0.12 mmol/liter), and a substantially greater fall with the combined regimen (1.21 ± 0.19 mmol/liter, $P < 0.02$ vs. either drug alone). Baseline plasma glucose concentrations were similar (about 4.8 mmol/liter) prior to all three treatments. Following insulin with glucose, plasma glucose increased transiently, but then fell to 2.8 ± 0.3 mmol/liter at one hour, with concentrations below 3 mmol/liter in 9 of 12 patients. None of the patients had symptoms of hypoglycemia. Plasma glucose increased to 6.8 ± 0.5 mmol/liter with albuterol. After the combined drug regimen plasma glucose rose transiently and was back to baseline (4.7 ± 0.7 mmol/liter) at one hour. Treatment with insulin or albuterol produced trivial increases in heart rate, whereas the combined drug regimen was associated with a significant rise (15.1 ± 6.0 min^{-1}). These observations suggest that albuterol and insulin with glucose are equally efficacious in lowering plasma potassium in uremic patients, and that the hypokalemic effects of the two drugs is additive. The hypoglycemic effect of insulin is attenuated by coadministration albuterol. Combined therapy with insulin, glucose and albuterol is efficacious and safe for the acute treatment of hyperkalemia in hemodialysis patients.

Severe hyperkalemia in the anephric patient requires urgent hemodialysis treatment, to remove excess potassium from the body. As a temporizing measure until the initiation of dialysis, various maneuvers may be employed that result in transient shifts of potassium from the extracellular to the intracellular fluid compartments. Treatment with bicarbonate and insulin with glucose is the standard recommendation for promoting transcellular potassium shifts [1–3]. The efficacy of bicarbonate therapy in lowering plasma potassium has not been consistently observed [4, 5]. Insulin treatment, while unequivocally efficacious in lowering potassium in uremic patients [5–7], may be associated with significant hypoglycemia [5].

Beta-2 agonists, such as albuterol, have also been shown to have a hypokalemic effect in hemodialysis patients [6, 8–10]. Since the mechanism of transcellular potassium shift with β_2-stimulation is distinct from that produced by insulin [11–14], it is possible that the hypokalemic effect of the two drugs may be additive. Moreover, since beta-agonists promote gluconeogenesis [11], they may prevent the hypoglycemia associated with insulin therapy.

There is little published information comparing the hypokalemic effects of albuterol and insulin. The purpose of the present study was to evaluate the potassium lowering effects of intravenous insulin with glucose, nebulized albuterol, and the combined drug regimen in a group of hemodialysis patients. In addition, the changes in plasma glucose associated with the three treatments were evaluated.

Methods

Subjects

We screened all maintenance hemodialysis patients at our medical center for hyperkalemia, defined as a predialysis plasma potassium higher than 5 mmol/liter on at least three separate measurements during a one month period. Twelve hyperkalemic patients were recruited into the study after obtaining their informed consent for participation. The protocol was approved by the University of Oklahoma Institutional Review Board. Each patient had been on a stable hemodialysis regimen for at least three months, and had been receiving three- to 4-hour dialysis sessions three times weekly. No patient was a diabetic or receiving a beta-blocker. The patients were between 34 and 72 years of age (mean, 56.5 ± 3.6 years).

Each patient was studied on three different days, that were separated from each other by at least one week. Each experiment was performed 72 hours following the previous hemodialysis session and immediately before the next scheduled hemodialysis treatment. The patients fasted the night before each study. An indwelling catheter was placed in the dialysis venous access for repeated blood samplings. After obtaining a baseline blood sample, the patients received one of three treatments: (a) regular insulin, 10 units, given as an intravenous bolus, followed by glucose, 50 ml of a 50% solution, given intravenously over five minutes; (b) a nebulized treatment of albuterol, 20 mg in 4 ml normal saline, inhaled over a 10 minute period; or (c) a combined regimen consisting of intravenous insulin and dextrose, as well as a nebulized albuterol treatment.

Follow-up blood samples were collected through the venous catheter at 15 minute intervals for one hour. Hemodialysis was initiated after the last blood sampling. Blood pressure and pulse were measured at baseline (prior to the medical treatment) and immediately before each blood sampling. The patients were also questioned about any symptoms, such as tremor, palpita-

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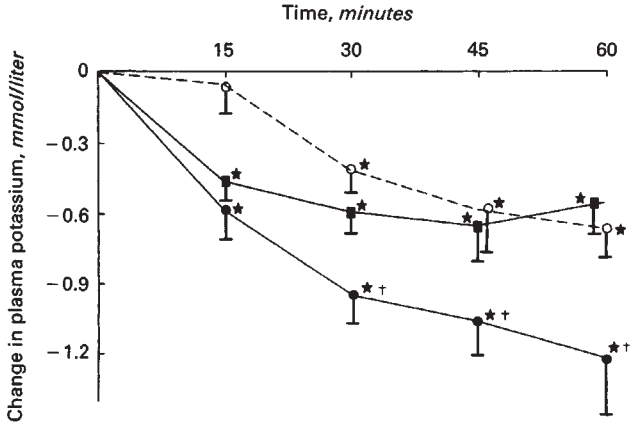

Fig. 1. *Changes in plasma potassium (mmol/liter) following treatment with insulin + glucose (■), albuterol (○), and insulin + glucose + albuterol (●).* $*P < 0.001$ vs. baseline value; + $P < 0.05$ vs. the other two treatments regimens.

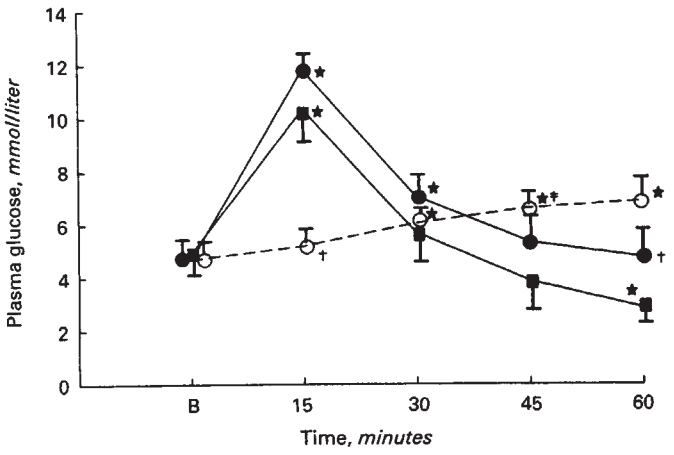

Fig. 2. *Changes in plasma glucose (mmol/L) following treatment with insulin + glucose (■), albuterol (○), and insulin + glucose + albuterol (●).* $*P < 0.005$ vs. baseline value; ≠ $P < 0.001$ vs. insulin treatment; $+P < 0.01$ vs. the other two treatment regimens.

tions, or sweating. All twelve patients received the treatment with insulin and dextrose. Due to the withdrawal of one patient from the study, and the transfer of another to peritoneal dialysis, only ten patients received the other two treatment regimens.

Analytic methods

Blood samples were collected in heparinized tubes and centrifuged promptly. Plasma potassium was assayed by flame photometry and glucose by a Beckman Analyzer (Beckman Instruments, Fullerton, California, USA). Plasma insulin concentrations were measured by radioimmunoassay. Mean blood pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure.

Statistical procedures

All values were expressed as mean ± SE. The changes in plasma potassium, glucose, mean blood pressure and heart rate were compared using analysis of variance, followed by Student *t*-tests with a Bonferroni correction for repeated comparisons. Since the insulin concentrations were not normally distributed they were compared by nonparameteric tests, the Kruskall-Wallis test, and the Mann-Whitney two-sample test. Differences within groups were analyzed by the Wilcoxon signed ranks test. A *P* value less than 0.05 was considered statistically significant.

Results

The plasma potassium concentration at baseline was similar in all patients before the administration of insulin with glucose (5.48 ± 0.21 mmol/liter), albuterol (5.56 ± 0.22 mmol/liter), and combined drug therapy (5.89 ± 0.25 mmol/liter). Intravenous insulin with glucose produced a significant fall in plasma potassium concentration that was apparent within 15 minutes of drug administration and persisted for at least one hour (Fig. 1). Nebulized albuterol resulted in a significant decrease in plasma potassium within 30 minutes of initiating treatment, that persisted thereafter. The mean decrease in plasma potassium was not different at 30, 45, or 60 minutes following the two respective treatments. The maximal decrease was 0.65 ± 0.09 and 0.66 ± 0.12 mmol/liter after insulin with glucose and albuterol, respectively. The magnitude of fall in plasma potassium was significantly greater following combined drug therapy than after either drug alone. The maximal decrease in mean plasma potassium concentration after insulin with glucose plus albuterol was 1.21 ± 0.19 mmol/liter.

The decrease in plasma potassium concentration in 4 of the 10 patients following treatment with albuterol was less than 0.5 mmol/liter (mean, 0.23 ± 0.08), suggesting a relative resistance to the effect of the beta-agonist. In contrast, the mean change in potassium for the other six patients was 0.89 ± 0.12 mmol/liter.

The plasma glucose concentration at baseline was similar in all patients prior to the administration of insulin (4.9 ± 0.2 mmol/liter), albuterol (4.7 ± 0.3 mmol/liter), and combined drug therapy (4.7 ± 0.1 mmol/liter). As expected, the dextrose given with the insulin resulted in a transient hyperglycemia (10.3 ± 0.6 mmol/liter) at 15 minutes, which virtually resolved by 30 minutes (Fig. 2). Subsequently, there was a progressive decline in plasma glucose concentration to frankly hypoglycemic levels at 60 minutes (2.8 ± 0.3 mmol/liter). The administration of nebulized albuterol resulted in a progressive rise in plasma glucose to a mean concentration of 6.8 ± 0.5 mmol/liter at 60 minutes. Following combined drug treatment, there was a transient hyperglycemia similar to that observed after insulin with dextrose (Fig. 2). However, hypoglycemia did not occur with the combined treatment; at 60 minutes the plasma glucose concentration was not different from baseline (4.7 ± 0.7 mmol/liter). The plasma glucose concentration dropped below 3 mmol/liter in 9 of 12 patients receiving insulin alone, but in only 2 of 10 receiving insulin and albuterol ($P = 0.01$, Chi square test).

Plasma insulin concentration was normal at baseline prior to the three drug regimens (Table 1). As expected, it rose acutely to supraphysiologic levels following insulin alone or insulin plus albuterol, with a subsequent rapid decline. At 60 minutes the concentrations were still significantly elevated above baseline values. Following treatment with nebulized albuterol, there was a moderate rise of plasma insulin concentration, to approxi-

Table 1. Plasma insulin concentrations during various treatments

Time *min*	Albuterol	Insulin	Albuterol + insulin
0	4.9 ± 1.2	8.8 ± 2.2	4.8 ± 0.8
15	13.4 ± 3.6[b]	319 ± 39[a]	408 ± 151[a]
30	22.4 ± 6.1[a,b]	185 ± 33[a]	132 ± 37[a]
45	27.2 ± 7.4[a,b]	98.8 ± 26.3[a]	102 ± 35[a]
60	25.3 ± 6.9[a]	61.9 ± 21.6[a]	43.2 ± 13.2[a]

[a] $P < 0.01$ vs. baseline value
[b] $P < 0.05$ vs. the other two treatment regimens

mately fivefold higher than baseline at 60 minutes. The insulin concentrations were not different among the three treatment groups at the end of the hour.

The baseline mean blood pressures were not different prior to the administration of each of the three drug regimens (101.4 ± 8.3, 99.4 ± 7.1, and 102.7 ± 7.0 mm Hg before albuterol, insulin, and the combined drug regimen, respectively). There were no significant changes in blood pressure following any of the treatments. The baseline mean heart rates were similar in all three treatment groups (85.2 ± 2.5, 73.7 ± 3.3, and 83.2 ± 3.3 before albuterol, insulin, and the combined drug regimen, respectively). The heart rate rose slightly following treatment with insulin and albuterol (+ 6.6 ± 2.3 and 6.9 ± 3.0 min^{-1}, respectively), although these changes failed to achieve statistical significance. Combined drug therapy was associated with a greater rise in heart rate +15.1 ± 6.0 min^{-1} at 60 minutes, $P < 0.02$).

Discussion

Intravenous insulin with glucose and nebulized albuterol in the doses used had a similar potassium-lowering effect. The magnitude of decrease in plasma potassium following nebulized albuterol was similar to that previously reported in hemodialysis patients receiving such treatment [8]. The onset of hypokalemic effect of albuterol was delayed by about 15 minutes, as compared to the time course following insulin. This difference was most probably a consequence of the modes of administration, with the nebulized albuterol being administered over 10 minutes, as compared to the insulin, which was given as a rapid intravenous bolus. A similar delay in the increase in plasma glucose concentration was observed following nebulized albuterol in the present study (Fig. 2). In contrast, in a previous study utilizing intravenous beta-agonists, the hypokalemic effect was apparent within a few minutes [15].

Four of the hemodialysis patients manifested a relatively small change in plasma potassium following the administration of albuterol. A relative resistance to the hypokalemic effect of beta-agonists has been previously noted in a minority of hemodialysis patients [8, 16]. The mechanism responsible for this resistance is not known.

Combined treatment with albuterol and insulin resulted in a substantially greater decrease in plasma potassium than that observed following each drug administered separately. Such an additive effect is consistent with several previous observations. In the isolated rat skeletal muscle, both insulin and the beta-agonist, epinephrine, stimulate potassium uptake; this uptake is greater following concomitant exposure to both drugs [12]. Both beta-agonists and insulin stimulate the activity of the Na^+, K^+-pump; the effect of the former is mediated via stimulation of cyclic AMP, whereas the precise mechanism by which the latter promotes potassium uptake is not known [11]. Two human studies observed a blunting of the hypokalemic effect of insulin during simultaneous beta-adrenergic blockade [13, 14]. In the latter study the decrease in plasma potassium during insulin administration was in part due to hypoglycemia-induced release of epinephrine. During the acute treatment of hyperkalemia in hemodialysis patients, dextrose is routinely administered with insulin. While this helps to prevent severe hypoglycemia, it may also limit the magnitude of reduction in plasma potassium, either by preventing the release of epinephrine or due to an osmolar effect of glucose [17]. Exogenous administration of beta-agonists restores the adrenergic-mediated shift of potassium into cells, thereby potentiating the hypokalemic effect of insulin, while reducing the risk of hypoglycemia.

Albuterol therapy was associated with an increase in plasma insulin concentrations, as has been previously reported [8, 9]. It is not likely, however, that the hypokalemic effect of albuterol is mediated by insulin. Similar hypokalemic effects have been observed following albuterol therapy in diabetic and nondiabetic hemodialysis patients [8, 9]. Moreover, Montoliu, Lens and Revert [9] found a potassium-lowering effect of albuterol in diabetic patients even in the absence of endogenous insulin release as deduced from free C-peptide levels. Albuterol stimulates gluconeogenesis, thus promoting hyperglycemia [11]. It is likely, therefore, that the observed rise in plasma insulin concentrations was in response to the hyperglycemia.

The most recent editions of three major nephrology textbooks recommend the administration of bicarbonate and insulin with glucose for the acute treatment of severe hyperkalemia [1–3]. Despite reports of a hypokalemic effect of bicarbonate in a small number of patients [18], this has not been a consistent finding in other studies [4, 5]. Plasma potassium decreased with bicarbonate in only 5 of 14 hyperkalemic patients studied by Fraley and Adler [4]. Likewise, bicarbonate therapy did not have a hypokalemic effect in ten hemodialysis patients reported by Blumberg et al [5].

Beta-agonists are not offered as a therapeutic option for severe hyperkalemia in three major nephrology textbooks [1–3]. In a recent poll of 63 directors of nephrology training programs, beta-agonists were never included in the prescription for either initial or two subsequent treatments of patients with severe hyperkalemia, while the administration of insulin was recommended frequently [19]. Both the present study and that by Lens et al [6] show albuterol to be at least as efficacious as insulin in lowering plasma potassium.

Hypoglycemia occurred in 75% of our patients following insulin with glucose. Blumberg et al [5] reported the development of hypoglycemia in 5 of 10 hemodialysis patients receiving intravenous insulin (approximately 20 units) with glucose (approximately 20 g). To avoid hypoglycemia, they recommended halving the insulin dose. Even though we followed their suggested dose regimen, hypoglycemia still occurred commonly. In contrast, by providing 40 g of glucose with 10 units of insulin, Lens et al [6] prevented this complication. Simultaneous administration of albuterol in the present study also appeared to prevent the insulin-induced hypoglycemia. This last finding is at variance with previous reports in normal subjects, in whom beta-receptor blockade during insulin-induced hypoglycemia did not affect the magnitude of hypoglycemia [14, 20]. The

reason for this discrepancy between dialysis patients and normal subjects is not readily apparent.

Based on the results of the current investigation, we propose that in hemodialysis patients with severe hyperkalemia a combined regimen of albuterol and insulin with glucose should be employed as a temporizing measure to acutely shift potassium into the cell. Such a therapeutic approach will maximize the hypokalemic effect, while preventing hypoglycemia.

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