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A Rat Model for Hyperkalemia (42513)

ZEA BOROK, SANDRA M. SCHNEIDER, DONALD S. FRALEY, AND SHELDON ADLER

Department of Medicine, Montefiore Hospital, 3459 Fifth Avenue, Pittsburgh, Pennsylvania 15213

Abstract. It is often necessary to have a small animal model for hyperkalemia for use in electrolyte and acid base experiments. In reviewing the literature, we found a paucity of such animal models, especially for acute hyperkalemia. We have had difficulty in inducing acute hyperkalemia in rats using potassium chloride alone either intravenously or intraperitoneally and felt the need for an easily reproducible small animal model for hyperkalemia. We gave experimental animals a combination of intraperitoneal amiloride 3 mg/kg and potassium chloride 2 meq/kg in two divided doses while control animals received only the potassium chloride. Initial serum potassiums were similar but at 2 hr, the experimental group had significantly higher serum potassium levels which were sustained throughout the 8 hr of the experiment. Arterial blood gas revealed no significant difference in blood pH values at all time points during the experiment. We conclude that the combination of amiloride and potassium chloride is useful to produce acute hyperkalemia in rats and that this hyperkalemia is sustained beyond 6 hr. This model is convenient for use in metabolic experiments requiring the use of acutely hyperkalemic rats.

It is often necessary to have a small animal model for hyperkalemia for use in electrolyte and acid base experiments. In reviewing the literature, we found a paucity of such animal models, especially for acute hyperkalemia. Aynsley-Green *et al.* (1) have described a hyperkalemic rat model using amiloride chronically for a period of 10 days in a dose of 10 mg/kg. There was, however, no acute effect on the serum potassium concentration. Seneviratne *et al.* (2) in studying peripheral nerve excitability used a hyperkalemic cat model in which they gave intraperitoneal injections of 10% potassium chloride to produce hyperkalemia but they give no indication of the concentration of serum potassium obtained. We have had difficulty in inducing acute hyperkalemia in rats using potassium chloride alone either intravenously or intraperitoneally and felt the need for an easily reproducible small animal model for hyperkalemia. We describe a simple inexpensive rat model for hyperkalemia using intraperitoneal amiloride and potassium chloride and compare this with control animals receiving only potassium chloride.

Materials and Methods. Male Sprague–Dawley rats weighing 300–350 g were used. Eight animals were anesthetized with 0.3–0.5 mg of Nembutal (pentobarbital sodium USP, 50 mg/ml, Abbotts Laboratories, North Chicago, IL) intraperitoneally and placed on heated operating boards. A femoral arterial line was placed using heparinized PE-50 tubing (intramedic polyethylene tubing, Clay Adams, Becton–Dickinson, Parsippany, NJ) for blood sampling. After a 15-min postsurgical stabilization period, animals were divided into four control animals and four experimental animals. Control animals received 2 meq/kg of 0.3 *M* potassium chloride in divided doses 5 min apart, while experimental animals received 2 meq/kg potassium chloride in split doses and 3 mg/kg amiloride. Arterial blood

TABLE I. MEAN SERUM POTASSIUM CONCENTRATION

	Amiloride and potassium chloride	Potassium chloride	*P* value
Initial $[K^+]^a$	4.30 ± 0.07 (4)[b]	4.00 ± 0.18 (4)	NS[c]
2-h $[K^+]$	6.08 ± 0.19 (4)	4.40 ± 0.23 (4)	<0.01
4-h $[K^+]$	6.33 ± 0.39 (4)	4.67 ± 0.27 (3)	<0.05
6-h $[K^+]$	6.73 ± 0.35 (3)	4.25 ± 0.35	<0.05
8-h $[K^+]$	7.45 ± 1.18 (3)	—	—

Note. All data are means ± SEM, meq/liter. All hemolyzed samples and preterminal $[K^+]$ were excluded.

[a] $[K^+]$ = serum potassium concentration.

[b] Number of rats.

[c] No significant difference.

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TABLE II. MEAN ARTERIAL pH VALUES

	Amiloride and potassium chloride	Potassium chloride	*P* value
Initial pH	7.35 ± 0.12 (4)[a]	7.35 ± 0.01 (4)	NS[b]
4-h pH	7.41 ± 0.01 (4)	7.43 ± 0.01 (3)	NS
8-h pH	7.44 ± 0.01 (4)	7.44 ± 0.00 (2)	NS

Note. All data are means ± SEM.
[a] Number of rats.
[b] No significant difference.

samples were taken before injection for blood gas analysis and electrolyte measurement. Arterial blood gases were repeated at 4 and 8 hr and electrolyte measurements were repeated at 2, 4, 6, and 8 hr. Surviving animals were then sacrificed using lethal doses of Nembutal. Potassium was measured with a flame spectrophotometer (Instrument Laboratories, Inc., Lexington, MA). A blood gas analyzer (Radiometer America, c/o The London Company, West Lake, OH) was used for blood gas analysis. Statistical analysis was performed using the Student *t* test.

Results. Each group had four animals initially. In the potassium only group two rats survived until the 8-hr sample. Unfortunately both of the 8-hr samples were hemolyzed. One rat in the potassium only group died at 4 hr and one at 6 hr. All rats in the potassium plus amiloride group survived through 8 hr but one sample was hemolyzed. Table I summarizes mean initial, 2-, 4-, 6-, and 8-hr serum potassium concentrations in the potassium only and potassium and amiloride groups. Initial potassium concentrations of 4.30 ± 0.07 and 4.00 ± 0.18 meq/liter do not differ significantly. Table II summarizes the initial, 4-, and 8-hr blood pH values in the two groups. They are not significantly different. While there was little rise in serum potassium in the potassium only group, the group receiving potassium and amiloride showed a significant rise in serum potassium. There were insufficient data for statistical comparison at 8 hr but hyperkalemia was sustained in the potassium plus amiloride group.

Discussion. We have described a convenient reproducible small animal model for acute hyperkalemia in rats. The model is stable over a 6-hr period following the intraperitoneal injection of amiloride and potassium chloride. Amiloride is a potassium-sparing diuretic whose effects are most marked when given in conjunction with another diuretic, especially one that promotes potassium loss in the urine. Amiloride is thought to work by abolishing the sodium gradient in the distal renal tubule as well as by affecting sodium transport in other tissues (3). In all four rats given the combination of amiloride and potassium, significant hyperkalemia was evident by 2 hr and was sustained beyond 6 hr. Animals given only potassium had no demonstrable rise in serum potassium until they were preterminal. In the absence of amiloride it is probable that all excess potassium is excreted by the kidneys, and decreased distal sodium/potassium exchange with amiloride is necessary to produce significant hyperkalemia. The potassium only group appeared less stable than the potassium plus amiloride group, thus limiting statistical analysis at 8 hr. The potassium plus amiloride group was stable and showed marked elevations in serum potassium at all sampling periods. This model is convenient for use in renal metbolic experiments requiring the use of acutely hyperkalemic rats, but may not be as useful in studying metabolism of other tissues when the effect of amiloride on that tissue is unknown.

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