

## About Potassium, and Relaxing about Its Lowness – The APRIL Study

IRB Protocol

Chris Winterbottom

March 8, 2010

### A. Study Purpose and Rationale:

Hypokalemia is a commonly encountered clinical problem, particularly among inpatients on medical housestaff services. Because of the easy accessibility of blood chemistry monitoring, patients often have their potassium levels checked daily as part of routine medical care. Given this plethora of information, there has been a trend towards aggressive repletion of potassium in recent years, and the standard of care has become repletion of K<sup>+</sup> to values > 4.0 mEq/L at many academic medical centers.

This practice is not without harm. Patients often complain about oral potassium repletion, as potassium pills are quite large and uncomfortable to swallow, and potassium liquid supplements are not widely considered to be tasty. Furthermore, IV potassium supplementation is known to cause an uncomfortable burning sensation on administration, and is also thought to cause direct toxicity to the vascular membrane, which can compromise patient's IV access on subsequent hospitalizations, leading to more invasive procedures, including central venous catheter placement.

From a hospital/systems perspective, the adverse effects of aggressive potassium repletion include the cost of the drug (as much as \$1/pill for oral tablets, significantly more for IV formulation), the deleterious effect on provider's time in writing several such orders each day, and the deleterious effect on nursing staff's time and priorities, as patients on potassium supplementation frequently complain and refuse treatment, leading to long conversations with these patients when the nurses' time might be better spent on such things as checking O<sub>2</sub> saturations on patients admitted with COPD exacerbations, or temperatures of patients admitted with septic shock.

The causes of hypokalemia include decreased dietary intake,<sup>i</sup> transcellular shifts in the setting of metabolic alkalosis,<sup>ii</sup> excess insulin production or administration,<sup>iii</sup> elevated B-adrenergic activity,<sup>iv</sup> and other less-common disorders, such as hypokalemic periodic paralysis, chloroquine administration, hypothermia, and other drug effects.<sup>v</sup> Other common causes of hypokalemia include GI losses in the setting of diarrhea, vomiting, or laxative use, and renal losses, as in diuretic use,<sup>vi</sup> mineralocorticoid excess, or metabolic acidosis in settings such as diabetic ketoacidosis, or type I or II renal tubular acidosis.<sup>vii</sup>

The effects of hypokalemia are well known, and include muscle weakness/paralysis, which is usually only seen when K<sup>+</sup> values fall to less than 2.5 mEq/L,<sup>viii</sup> and cardiac abnormalities. Cardiac abnormalities include ST segment depressions, T wave flattening, and the appearance of U waves (ibid). Furthermore, hypokalemia can induce a variety of arrhythmias, most notable ventricular arrhythmias such as ventricular tachycardia and ventricular fibrillation. A 1992 study in the Journal of the American Medical Association

studied the effect of thiazide diuretic usage in patients with hypertension, and found a two-fold increase in ventricular arrhythmias on 24 hour holter monitoring in patients whose K<sup>+</sup> had fallen to less than 3.0 after 2 months of treatment.<sup>ix</sup> However, this study was not sufficiently powered to address the effect of K<sup>+</sup> levels between 3-4 mEq/L. Indeed, only 12 patients of the 233 enrolled developed K<sup>+</sup> values < 3.

Given the paucity of literature on the subject, and the small size of the only previously published trial, we propose to conduct a randomized controlled trial on the effect of tight potassium control on the incidence of ventricular arrhythmias in an inpatient population. The underlying hypothesis of the study is that relaxing the threshold for potassium repletion from 4.0 mEq/L to 3.0 mEq/L will not significantly increase the incidence of ventricular arrhythmias in these patients.

#### B. Study Design and Statistical Analysis:

Patients will be randomly assigned to either the tight control or relaxed control arm, in an 1:1 fashion. On admission, informed consent will be obtained, and randomization will be achieved via a coin flip, with heads indicating relaxed control, and tails indicating tight control.

The primary outcome measure will be the incidence of ventricular arrhythmias during the patients' stay in the hospital, as measured by telemetry monitoring. These arrhythmias will be defined as non-sustained ventricular tachycardia of greater than 5 beats, as well as sustained ventricular tachycardia, ventricular fibrillation, or any other new arrhythmia requiring cardioversion. Other primary end points will include the appearance of new ST depressions and U waves on EKG, and death.

In order to achieve 80% power with a P value of 0.05, a sample size of 8,514 patients in each group was calculated using the Chi-square test, assuming a minimal clinically-significant effect size of an absolute risk increase of 1% in the relaxed group from a baseline incidence of 5% in the standard therapy group.

#### C. Study procedure:

Patients will be enrolled on admission to the hospital in 20 prestigious academic medical centers throughout the country, and will be monitored on telemetry throughout their stay. In addition, daily K<sup>+</sup> levels will be checked, as will EKGs on admission, and daily throughout the patient's hospital stay. Potassium will be repleted through both oral and intravenous routes, as per the provider's discretion and usual standard of practice. Thresholds for repletion in the two groups will be 4.0 mEq/L and 3.0 mEq/L for the standard and relaxed treatment arms, as mentioned above. Providers will be instructed to replete patients with 10 mEq for every 0.1 mEq/L difference between the target and actual potassium level. The study will be non-blinded.

#### D. Study drugs:

Potassium Chloride tablets

Potassium Chloride oral liquid  
Potassium Chloride IV formulation

E. Medical device:

Patients will be monitored on standard telemetry devices, and standard EKG machines

F. Study Questionnaires:

None

G. Study Subjects:

Inclusion criteria:

Admission to an inpatient medical service or intensive care unit

Exclusion criteria:

Patients with known structural heart disease, defined as a known diagnosis of congestive heart failure or obstructive coronary artery disease, as well as end-stage renal disease requiring hemodialysis will be excluded.

H. Recruitment of subjects:

Patients will be recruited by dedicated medical personnel on their admission to the hospital.

I. Confidentiality of Study data:

All study data will be stored in a confidential manner.

J. Potential conflict of interest:

None

K. Location of the study:

The study will be conducted on the inpatient medical services and intensive care units of Columbia University Medical Center, as well as 19 other leading medical centers throughout the country.

L. Potential Risks:

Potential risks include an increased incidence of ventricular arrhythmias, including those requiring cardioversion, as well as death, paralysis, rhabdomyolysis, and renal dysfunction in the relaxed arm of the study.

M. Potential Benefits:

The benefits of treatment include decreased patient discomfort, decreased vascular damage, and improved quality of care to these and other patients, as well as improved allocation of hospital resources, as detailed in the study rationale above.

N. Alternative therapies:

N/A

O. Compensation of Subjects:

Patients will not be compensated. Billing will be conducted as per hospital routine.

P. Costs to subjects:

There will be no costs to subjects

Q: Minors as research subjects:

Patients under 18 will not be included in the study.

R. Radiation or Radioactive Substances:

N/A

S: References:

---

<sup>i</sup> Squires, RD, Huth, EJ. Experimental potassium depletion in normal human subjects. I. Relation of ionic intakes to the renal conservation of potassium. J Clin Invest 1959; 38:1134.

<sup>ii</sup> Adrogué, HJ, Madias, NE. Changes in plasma potassium concentration during acute acid-base disturbances. Am J Med 1981; 71:456.

<sup>iii</sup> Clausen T; Flatman JA. Effects of insulin and epinephrine on Na<sup>+</sup>-K<sup>+</sup> and glucose transport in soleus muscle. Am J Physiol 1987 Apr;252(4 Pt 1):E492-9

<sup>iv</sup> Brown MJ; Brown DC; Murphy MB Hypokalemia from beta2-receptor stimulation by circulating epinephrine. N Engl J Med 1983 Dec 8;309(23):1414-9.

<sup>v</sup>

[http://www.uptodate.com/online/content/topic.do?topicKey=flldlytes/26875&selectedTitle=2~150&source=search\\_result](http://www.uptodate.com/online/content/topic.do?topicKey=flldlytes/26875&selectedTitle=2~150&source=search_result)

<sup>vi</sup>

[http://www.uptodate.com/online/content/topic.do?topicKey=flldlytes/31152&source=see\\_link](http://www.uptodate.com/online/content/topic.do?topicKey=flldlytes/31152&source=see_link)

<sup>vii</sup>

[http://www.uptodate.com/online/content/topic.do?topicKey=flldlytes/26875&selectedTitle=2~150&source=search\\_result](http://www.uptodate.com/online/content/topic.do?topicKey=flldlytes/26875&selectedTitle=2~150&source=search_result)

---

<sup>viii</sup> Rose, BD, Post, TW, Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed, McGraw-Hill, New York, 2001, pp. 857-863.

<sup>ix</sup> Siegel D; Hulley SB; Black DM; Cheitlin MD; Sebastian A; Seeley DG; Hearst N; Fine R Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. JAMA 1992 Feb 26;267(8):1083-9.