EDITORIALS

A New Era for the Treatment of Hyperkalemia?

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The potassium concentration within human cells is approximately 140 mmol per liter, yet extracellular potassium concentration is normally 3.5 to 5.0 mmol per liter.[1,2] Hyperkalemia is defined as a plasma potassium level of greater than 5.0 mmol per liter. Mild hyperkalemia (>5.0 to 5.9 mmol per liter) requires monitoring and the avoidance of a high intake of potassium and, often, changing therapies that may be increasing potassium levels. Greater degrees of hyperkalemia — potassium levels of 6.0 to 7.0 mmol per liter (moderate hyperkalemia) and more than 7.0 mmol per liter (marked hyperkalemia) — may lead to cardiac arrhythmias and cardiac arrest, with fatal outcomes.

Hyperkalemia is particularly common in patients with chronic kidney disease and those with heart failure.[2] Ironically, protective therapy for these conditions often includes medications that interrupt the renin–angiotensin–aldosterone system (RAAS) and by doing so may lead to increases in plasma potassium.[3]

Reasons for elevated potassium levels in patients with chronic kidney disease[4] include increased potassium intake, altered potassium handling by the kidneys, aldosterone resistance (leading to decreased potassium excretion in the distal tubule), acidosis, and lack of insulin. Medications such as RAAS inhibitors, spironolactone or eplerenone, and potassium supplements, all of which may increase potassium levels, compound the problem.

Control of hyperkalemia in patients with chronic kidney disease and in those with heart failure has proved to be difficult. Dietary limitation, vigorous use of diuretic therapy, provision of bicarbonate, and limiting the use or lowering the dose of drugs that increase potassium levels may control potassium so that specific potassium-binding therapy is not needed. However, such strategies are often unsuccessful. Medications that lower potassium levels, as opposed to shifting potassium into cells, have been limited to sodium polystyrene sulfonate (Kayexalate),[2] which exchanges potassium for sodium, or the similar drug, calcium polystyrene sulfonate,[4] which exchanges potassium for calcium. Neither is an appealing option. Kayexalate, which was developed in the mid-20th century, requires administration with water, most often with sorbitol added. The preparation, which is taken by mouth, has a noxious taste and may cause diarrhea. When administered as an enema, it is also unpleasant. On rare occasions, necrosis of the colon may occur with its administration, a complication that has resulted in a black-box warning. Loop diuretics, such as furosemide, may not work well in patients with chronic kidney disease. Therefore, new medications would be welcome.

Weir et al.[5] and Packham et al.[6] now report in the *Journal* the results of clinical trials of two different oral medications that lower plasma potassium levels. One trial[5] assessed patiromer (formerly called RLY5016) in patients with chronic kidney disease and hyperkalemia who were receiving RAAS inhibitors, and the other[6] studied sodium zirconium cyclosilicate (ZS-9) in patients with a variety of diagnoses associated with hyperkalemia.

The two new agents, neither of which has been approved by the Food and Drug Administration, have different mechanisms of action. According to the manufacturer, patiromer FOS (for oral suspension) is a dry powder, primarily a spherical bead that is not absorbed and that binds potassium when mixed in small amounts

of water. However, it does so mainly in the colon; it does not appear to bind potassium in the small intestine. It exchanges potassium for calcium, which would be of considerable concern if the drug were absorbed. It appears, however, that the drug is not absorbed and that the amount of calcium absorbed is small. ZS-9 is a compound with a crystalline lattice structure that traps potassium preferentially; in vitro, it traps about 10 times as much potassium as Kayexalate does. It is insoluble and remains in the intestine during transit.

In the study of patiromer, Weir and colleagues studied patients with chronic kidney disease who were taking RAAS inhibitors and whose serum potassium levels were 5.1 to less than 6.5 mmol per liter. All entered a single-blind treatment phase and received patiromer (initially 4.2 g or 8.4 g twice a week) for 4 weeks. A total of 76% of the patients had normal potassium levels at the end of this phase; 107 of these patients entered an 8-week placebo-controlled, randomized, withdrawal phase, in which the primary outcome was the median change in potassium level after 4 weeks. Hyperkalemia recurred in 60% of the patients who were switched to placebo, as compared with 15% of those who continued patiromer. The most common adverse event was constipation (in 11% of the patients), and hypokalemia occurred in 3% of the patients. Whether constipation would be more troublesome with longer-term treatment is unclear. Although the adverse effects appear to have been mild, even the patients who received the drug during the withdrawal phase received it for no longer than 12 weeks. Thus, caution is required, since many patients are likely to take this agent for a much longer time. In addition, the decrease in potassium with patiromer therapy appears to be gradual, so how well this agent would perform in the acute situation is unclear.

In the two-phase, double-blind, phase 3 trial of ZS-9 by Packham et al., 753 participants with hyperkalemia were randomly assigned to receive the drug (at a dose of 1.25 g, 2.5 g, 5 g, or 10 g) or placebo three times daily for 48 hours. Patients whose potassium levels normalized (3.5 to 4.9 mmol per liter) at 48 hours were randomly assigned to receive the drug or placebo once daily on days 3 to 14. The primary outcome was the exponential rate of change in mean serum potassium levels at 48 hours. A total of 75% of the participants had reduced renal function (estimated glomerular filtration rate <60 ml per minute per 1.73 m^2 of body-surface area), 60% had diabetes, and 40% had heart failure; in addition, 65% were receiving RAAS-inhibitor therapy, which was continued unchanged during the study. Baseline characteristics at the start of the acute phase of the study were well matched, except for potassium levels, with more patients in the placebo group and in the group receiving 10 g of ZS-9 having mild baseline elevations. As in the study by Weir et al., the potassium levels decreased in patients receiving the active drug. The mean serum potassium decreased from 5.3 mmol per liter at baseline to 4.9 mmol per liter, 4.8 mmol per liter, and 4.6 mmol per liter at 48 hours in the groups that received 2.5 g, 5 g, and 10 g of the drug, respectively ($P<0.001$ for all comparisons), as compared with a rate of 5.1 mmol per liter at 48 hours in the group that received placebo and in the group that received 1.25 g of the drug. In the second phase of the study, the patients who received 5 g and 10 g maintained serum potassium at levels at 4.7 mmol per liter and 4.5 mmol per liter, respectively, during days 3 to 15, as compared with a level of more than 5.0 mmol per liter in the placebo group ($P<0.01$ for all comparisons). The patients in the study of ZS-9 had few adverse events, but the study was short. A 28-day study with zirconium silicate has shown similar results but is also not truly a long-term study.[7]

The two relatively short-term studies by Weir et al. and Packham et al. excluded patients with serum potassium levels greater than 6.5 mmol per liter or electrocardiographic changes, hospitalized patients, and patients undergoing dialysis. Thus, the durability and side-effect profile of these agents over time remain unclear. Certainly, whether either or both of these agents will permit long-term administration of renoprotective and cardioprotective agents that block the RAAS will require more investigation. In addition, neither study included cases of markedly elevated levels of potassium (>6.5 mmol per liter). However, both agents appear to offer some promise for the treatment of hyperkalemia in patients with chronic kidney and cardiac disease.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Making (Anti)Sense of Factor XI in Thrombosis

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Inhibiting thrombosis without inducing bleeding is the holy grail of anticoagulant therapy. Currently, there are no commercially available anticoagulants that achieve this goal. Although many antithrombotic agents improve survival by interfering with vessel thrombosis, this protection always comes at the cost of an increased risk of bleeding.

The observation that inhibitors of thrombosis increase bleeding is no surprise. Current dogma holds that the same blood constituents and mechanisms that are responsible for generating thrombin and fibrin to prevent excessive blood loss (hemostasis) can cause vessel stenosis or occlusion under pathologic conditions (thrombosis).

But what if this were not the case? Perhaps hemostasis and thrombosis are closely related but distinct processes, and perhaps factors can be identified that are essential for thrombosis but dispensable for hemostasis. As the study of clotting has moved from the test tube to animal models, increasing evidence has transformed this idea from fantasy to practicable hypothesis. Studies in factor XI knockdown mice have shown that these animals are protected from experimentally induced thrombosis without increased bleeding.[1] In a primate model, antibodies directed at factor XI inhibited thrombus formation without affecting template bleeding times.[2] Investigators have also used antisense oligonucleotides to target factor XI and have shown that reduction of factor XI levels provides protection from thrombosis in rabbits and primates, again with no increase in bleeding.[3,4]

Büller et al. now report in the *Journal* the results of a study of an antisense oligonucleotide in humans.[5] They conducted a phase 2 study involving 300 patients to evaluate the safety and efficacy of a factor XI antisense oligonucleotide for the prevention of deep-vein thrombosis after knee arthroplasty. Two regimens of the factor XI antisense oligonucleotide (200 mg and 300 mg) were compared with 40 mg of enoxaparin administered once daily, and venography to detect thrombosis was performed 8 to 12 days after surgery. The incidence of thrombosis did not differ significantly between the patients receiving enoxaparin and those receiving the 200-mg regimen of the antisense oligonucleotide (30% and 27%, respectively), with the 200-mg dose reducing factor XI levels by 68% of the baseline levels. Yet thrombosis was detected in only 4% of the patients receiving the 300-mg regimen, with that regimen reducing factor XI levels by 83%. Differences in the incidence of major bleeding among patients receiving the 200-mg dose of the factor XI antisense oligonucleotide (3%), those receiving the 300-mg dose of the factor XI antisense oligonucleotide (3%), and those receiving enoxaparin (8%) were not significant.

Do these findings prove that reduction of factor XI levels inhibits thrombosis without affecting bleeding? The conservative answer is no. The incidence of clinically relevant bleeding is relatively low after knee arthroplasty, even when patients are receiving anticoagulants.[6,7] Although the incidence of bleeding was increased in the enoxaparin group as compared with the group receiving the 300-mg dose of the factor XI antisense oligonucleotide, the difference was not