Should Hypertensives Take Potassium?

Some researchers question the common practice of prescribing potassium supplements to patients taking diuretics

For 25 years, doctors have been prescribing thiazide diuretics to reduce the blood pressure of hypertensive patients. And for 25 years, worried that these diuretics might dangerously deplete the body of potassium, doctors have been prescribing potassium supplements. But some medical researchers now question the wisdom of prescribing these supplements, saying they may be unnecessary and even dangerous.

The most recent occasion when the supposed link between diuretics and low body potassium concentrations came into play was in the analysis of a large clinical trial, the Multiple Risk Factor Intervention Trial (MRFIT). This study was expected to demonstrate that middle-aged men who reduce their smoking, serum cholesterol concentrations, and blood pressure—three major risk factors for heart disease—will live longer. The results, however, were inconclusive. The group of men in the trial who reduced their risk factors sufficiently to lower their mortality rate by a predicted 22 percent were found to have the same mortality rate as men who reduced their risk factors to a lesser degree (*Science*, 1 October, p. 31). It looked as if risk factor reduction might not be as effective as everyone thought it would be.

The MRFIT analysts proposed that the study's results were skewed by adverse effects in one subgroup. Men who had high blood pressure, electrocardiogram abnormalities, and who were treated with diuretics, seemed to have an unexpectedly high death rate. Although such subgroup analyses are difficult to justify statistically, the MRFIT investigators proposed that they may have uncovered a significant and unexpected drug toxicity. The reason the diuretics may be so toxic, the analysts speculated, is that they may cause fatal disturbances in heart rhythms as a result of their potassium-depleting effects.

Such reasoning is unwarranted, say John Harrington, Jeffrey Isner, and Jerome Kassirer of the New England Medical Center and Tufts University School of Medicine. They believe that this country's obsession with potassium is not founded on good scientific evidence and may, in fact, be causing unnecessary deaths in patients who are getting too much potassium as they attempt to correct the supposed loss of potassium that occurs with diuretic treatment. They point out, however, that potassium supplements do seem necessary for patients taking digitalis. In these patients, even mild potassium deficiencies can cause serious arrhythmias. Edward D. Freis of the Veterans Administration Hospital in Washington, D.C., also questions the potassium theory. "I agree with Harrington, Isner, and Kassirer 100 percent," he says. "I think potassium supplements are absolutely useless in most patients."

Potassium supplements, however, are wildly popular. When diuretics first came on the market, doctors advised their patients to eat bananas and drink orange juice to get extra potassium. (According to Kassirer and Harrington, one would need to eat four to six bananas a day or drink a liter of orange juice to get as much potassium as physicians think necessary.) Drug companies soon began marketing potassium supplements in ever-improved forms. First on the market were solutions of potassium salts which tasted so bitter that many patients simply refused to take them. Next came potassium tablets which caused intestinal ulcers. Finally, the drug companies came out with tablets that are formulated and coated so as to be safe.

Citing survey data from 1981, the New England Medical Center group notes that doctors wrote 7.5 million prescriptions for potassium supplements last year and 19 million prescriptions for special diuretics that avoid potassium depletion but that have other undesirable side effects. The cost of the potassium supplements and potassium-sparing diuretics in 1981 was more than $250 million.

Kassirer and Harrington first began to question the practice of prescribing potassium supplements in 1977 when they were asked to write a review article on diuretics and potassium metabolism. "We went in with the prejudice that patients taking diuretics need potassium supplements," says Kassirer. "But we came with the opposite finding." When they looked at data on how diuretics affect total body potassium they saw very little depletion.

People normally have 3500 to 4000 milliequivalents (meq) of potassium in their bodies, most of it within cells. Of this total body potassium, 100 to 200 meq are lost during diuretic therapy. "When you look at serum potassium, the numbers are slightly low in patients being treated with diuretics. They may have 3 or sometimes 2.8 meq per liter. But there is little evidence that serum potassium concentrations down to 3 meq per liter do anything bad to you," Kassirer says. Normal serum potassium concentrations are 4 or 5 meq per liter.

On the other hand, there is evidence that too much potassium in the body can cause cardiac arrest. The incidence of this complication is unknown, in part because doctors might easily mistake it for a heart attack. But one study of hospitalized patients, conducted by David H. Lawson of the Royal Infirmary in Scotland indicates the risk of serious harm or death might be as high as 1 in 200.

What about the threat of fatal arrhythmias from potassium deficiencies? Here the data are unclear. Some investigators saw abnormal rhythms on patients' electrocardiograms and related them to serum potassium values taken at any time within 24 hours of the recording. Others, studying patients who had heart attacks, related the heart attacks to serum potassium concentrations measured 12 to 24 hours after the attack, even though it is nearly impossible to interpret such readings. Some of the substances given to heart attack patients to resuscitate them can lower the serum potassium levels and the heart attack's consequences can raise them. These two groups of studies failed to provide evidence that low serum potassium preceded rather than followed arrhythmias or heart attacks.

In two other studies, researchers showed that patients' electrocardiograms are normal after their serum potassium concentrations are restored to normal, but in neither study were multiple 24-hour electrocardiograms recorded before and after potassium supplementation. Thus, says Kassirer, the investiga-

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tors failed to demonstrate that what they saw was not just a spontaneous variation in heart rhythms.

Freis and his associates recently did obtain such 24-hour electrocardiograms in patients who had arrhythmias and who were taking diuretics. These researchers then gave the patients potassium supplements and again took 24-hour continuous electrocardiograms. They saw no significant effect of the potassium on the arrhythmias.

Since the evidence that dangerous potassium deficiencies result from diuretic therapy is so inconclusive and since it is quite possible that potassium supplements themselves may be hazardous to some patients, Kassirer says, "I think the treatment with potassium supplements may be just as bad as or even worse than potassium deficiency."

Although the MRFIT analysts say they have no proof of potassium deficiencies in the trial participants, they suspect drug toxicity in the hypertensive men taking diuretics because those men did not reduce their death rate from heart disease as expected. Potassium deficiency, they believe, is a starting place to look for toxicities. But Freis points out that blood pressure lowering has not been shown to lower the risk of death from heart disease in patients with mild hypertension—like the MRFIT men. Those studies purporting to show a lower heart disease death rate were, he says, of "questionable design."

Another explanation of the MRFIT results, and one that has not yet been rejected by the study analysts, is that the high death rate among the subgroup of hypertensives is a statistical quirk. The trials are designed to be analyzed as a whole, not to be carved up into small subpopulations. Frequently, when analysts look at such subgroups, they find that some, by chance, do worse than expected and others, by chance, do better.

What concerns Freis and the New England Medical Center researchers is that with the publicity over the MRFIT results, the dogmas that potassium supplements are necessary and that treatment of even mild hypertension prevents heart attacks will become more firmly entrenched. As a result, patients may needlessly take potassium supplements and patients whose hypertension is too mild to justify the risks of treatment may start on a lifetime of taking antihypertension drugs.—GINA KOLATA

Additional Reading

1. "Our national obsession with potassium," J. T. Harrington, J. M. Isner, J. P. Kassirer, *Am. J. Med.* **73**, 155 (1982).
2. "Should mild hypertension be treated?," E. D. Freis, *N. Engl. J. Med.* **307** (No. 5), 306 (1982).

Predicting Susceptibility to Epileptic Seizures

An increased concentration of the enzyme β-glucuronidase in the blood is associated with susceptibility to grand mal epileptic seizures, according to a report by Ranbir Varma and Rajendra Varma of Warren State Hospital in Warren, Pennsylvania, at the recent American Chemical Society (ACS) meeting.* It is not clear whether high concentrations of the enzyme are a secondary effect or help cause the seizures, but the observation could provide a new way to monitor therapy of epileptics.

Using blood samples obtained for other purposes, the Varmas measured β-glucuronidase levels in 30 patients who had a history of epilepsy and in whom grand mal seizures were observed by the hospital staff. The samples were obtained as much as 5 weeks before a seizure and as long as 9 weeks after. The samples showed enzyme concentrations of 182 to 400 units per 10 milliliters of serum, compared to 56 to 146 units in healthy individuals. Enzyme levels were not increased in medicated epileptics who had not had a seizure within the prior year or in patients with other types of mental disorders. Enzyme concentrations were also elevated in patients with retinal degradation associated with diabetes, with liver injuries, and with cancer, but those conditions were readily distinguishable. The observations were independent of age or sex.

β-Glucuronidase degrades glycosaminoglycans, which are polyanionic mucopolysaccharides that form part of the structure of neurons (nerve cells). They bind positively charged biogenic amines and cationic electrolytes that are important in the electrical discharge or firing of neurons. Previous studies by several investigators have shown that an abnormal excretion of glycosaminoglycans in urine from epileptic patients and that application of β-glucuronidase directly to the surface of the brain induces an excess firing of neurons that mimics an epileptic seizure. The concentration of glycosaminoglycans in the blood of the Varmas's subjects was, however, found to be normal.

*184th National Meeting, 12 to 17 September, Kansas City, Missouri.

Potential New Drugs for Duodenal Ulcers

A potential new approach to the therapy of duodenal ulcers was described by Sandor Szabo of Harvard Medical School. Szabo and John L. Neumeyer of Northeastern University have found that dopamine agonists (chemicals that compete for the same binding sites as dopamine and thereby stimulate its activity) can both retard the formation of duodenal ulcers in rats and speed their healing. Duodenal ulcers are four to ten times more common than gastric ulcers; Szabo estimates that 8 to 10 percent of the population will develop ulcers at least once in their lives.

Szabo and Neumeyer's results stem from the search for chemicals that will induce duodenal ulcers in laboratory animals. In the early 1970's, Szabo and Hans Selye of the University of Montreal found that propionitrile and cysteamine specifically induce duodenal ulcers in rats. Further study showed that the ulcerogenic activity of these and subsequently discovered chemicals derives from a two-carbon (ethyl) group bearing methyl, cyano, sulfhydryl, or amino moieties on one or both ends of the carbon chain. Such groups are a common feature of histamine, gastrin, ibuprofen, aspirin, indomethacin, and phenylbutazone, all of which are known to stimulate excess acid secretion or to exert other undesired gastrointestinal effects. Such a group is also present in dopamine.

It has previously been observed that patients with untreated Parkinson's disease, which is associated with excess production of dopamine, have a high rate of ulcer disease, while schizophrenics (who may have an excess of L-dopa) are virtually immune to the disease. The Boston investigators thus studied several dopamine agonists, including bromocriptine, lergotrile, L-dopa, and apomorphine and its derivatives, and found that the best of these were about 10 to 20 times more potent than ergot alkaloids in preventing chemically induced duodenal ulcers in rats; these same compounds were about 200 times more potent than cimetidine, the most widely used therapeutic agent for ulcers.

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