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Editorial

The use of potassium in the treatment of heart disease

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Potassium salts are currently used for the treatment of digitalis intoxication, and in heart failure, especially where hypokalemia has occurred after the aggressive use of diuretics. They are also used prophylactically to prevent losses of potassium during the long-term administration of thiazide diuretics. A few patients with myocardial infarction and coronary artery disease have received potassium along with glucose and insulin.[1] In order to help find the proper place for potassium in the treatment of heart disease, I have undertaken to review what is known in this field, in the hope that this might suggest where future research would be rewarding, and possibly to forestall unwarranted enthusiasm for any general application of potassium therapy.

Abnormal distribution of potassium in heart disease. Over the past three decades evidence has accumulated showing that cardiac and skeletal muscle of patients dying of congestive failure is abnormally poor in potassium, phosphorous, and magnesium, and that sodium tends to be increased.[2-7] Calhoun and associates[4] further noted that potassium deficiency could be present in one ventricle but not in the other. When myocardial insufficiency resulted in pulmonary congestion, the potassium content of the left ventricle was diminished; and when myocardial insufficiency resulted in hepatic congestion and systemic edema, the potassium content of the right ventricle was decreased. They attributed the loss of potassium to overwork of the involved ventricle, noting that overworked skeletal muscle becomes deficient in potassium. Factors which would contribute to the diffusion of potassium from heart muscle in these circumstances are the associated lack of oxygen and the increased concentration of hydrogen ion.

Brown, Tanner and Hecht[8] have observed that patients with heart disease have a delayed excretion and a positive balance of orally administered potassium. They thought that potassium should be used with care in patients with heart disease, since these patients do not excrete potassium as rapidly as do normal patients.

Digitalis and loss of potassium. Calhoun and Harrison[9] were first to recognize that

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toxic doses of digitalis lowered the potassium content of ventricular muscle. This fact has now been confirmed by many investigators. Until recently, there was controversy whether therapeutic doses of digitalis caused an ingress of potassium into the heart or egress of it from the heart. Most investigators now concede that therapeutic doses of digitalis produce a small net gain in potassium by cardiac muscle, and that large and toxic doses produce a larger net loss.[9-19] The amount of potassium lost from cardiac muscle increases with the dose of digitalis glycoside, and Conn[15] has suggested that one action of digitalis is inhibition of an influx mechanism of potassium. It has also been observed that the loss of potassium which occurs after the administration of large or toxic doses of digitalis could be inhibited by the administration of excess potassium.[13]

These ideas have important therapeutic implications. It is obviously desirable to reverse by the administration of potassium the losses of cardiac potassium produced by toxic doses of digitalis. However, the hazard of producing potassium intoxication in this circumstance may be great, since less of the circulating potassium is free to enter the cellular compartment. For instance, Fisch and associates[20] have shown in experimental animals that the tolerance for intravenously administered potassium is related to the quantity of digitoxin administered prior to the injection of potassium. When potassium was administered to animals which had received an intoxicating dose of digitoxin, relatively small amounts of potassium caused a rapid rise in the plasma level of such a magnitude as to result in early cardiac standstill; whereas animals receiving only therapeutic amounts of digitoxin tolerated higher doses of potassium, with resultant lower levels of plasma potassium and fewer side effects. These data confirm the concept that large doses of digitalis block the entry of potassium into cells, but also make it evident that the threat to the organism is elevation of the level of extracellular potassium and not the total dose of potassium administered. The data also make clear the potential danger of administering potassium to fully digitalized patients with normal serum potassium; for in this instance the serum potassium may rise to high levels, producing potassium intoxication.

Potassium therapy in digitalis intoxication. Interest in the prevention and treatment of digitalis intoxication was awakened with the report by Lown and associates[21] that the amount of digitalis required to produce digitalis intoxication was related to the level of serum potassium. It was found that smaller doses of digitalis were required to produce intoxication when the serum potassium was low; and high levels of serum potassium had a protective effect in this regard. Prior studies by Loewi[22] in 1918, and Sampson and associates[23] in 1943, had reported that potassium was antagonistic to the toxic effects of digitalis, and that potassium was useful in the treatment of digitalis intoxication in man. Enselberg[24] had observed that increased A-V block was a side effect of such potassium therapy. It soon became evident from other studies that potassium was not a specific antagonist of digitalis. For instance, it was found that potassium would abolish ectopic beats equally well in patients who were receiving digitalis and in those who were not.[25,26] It was also observed that, when A-V block was produced as the result of digitalis intoxication, administration of potassium did not release the block, but rather potentiated it.[27-30] It was argued that potassium antagonism of digitalis was based on the rather nonspecific depressing effect of potassium on ectopic rhythm. The conclusion to be reached from these studies is that the ability of potassium to suppress abnormal ectopic rhythm is nonspecific but transiently effective whether or not such abnormal rhythm is the result of digitalis intoxication. Potassium therapy is most useful when digitalis intoxication is the result of potassium depletion, for in this instance the therapeutic margin of safety of digitalis is raised by returning the serum potassium to normal. Caution is advised in the use of potassium therapy when A-V block is a manifestation of digitalis intoxication, since under these circumstances digitalis and potassium are synergistic.

Prophylactic use of potassium with thiazide diuretics. The aggressive use of diuretic agents, such as the thiazide and mercurial

types, initially increases the urinary excretion of potassium, as well as sodium, and may cause hypokalemia in some patients. Weller[31] has presented the argument that the renal tubules of most patients and experimental animals have the ability to counteract the loss of potassium which occurs in the initial phase of thiazide administration, and can correct any resulting negative balance of potassium in spite of the continued daily use of these drugs. Prolonged thiazide treatment may result in hypokalemia without significant depletion of the cellular stores of potassium.

No evidence is available that potassium therapy is beneficial in heart failure unless there is potassium depletion. As has been pointed out, a shift of potassium from the intracellular to the extracellular compartment in heart failure is caused by the use of large doses of digitalis, and possibly is an early effect of thiazide or other diuretic therapy. The data to date do not suggest that this shift is either beneficial or detrimental, unless it reaches extreme proportions, in which case it may lead to digitalis intoxication. It is common knowledge that, when severe potassium depletion occurs after excessive diuresis, supplemental potassium is beneficial. Cort and Mathews[32] observed improvement in heart failure when a severe depletion of potassium was corrected. In this circumstance the finding of a low serum potassium, a reflection of the level of extracellular potassium, is the best guide of the need for supplemental potassium. When the need for supplemental potassium arises, as indicated by an excessive diuresis, by low serum potassium, or by the electrocardiographic changes of hypokalemia, the dose of potassium chloride required will generally be higher (such as 5 to 10 Gm. orally in divided doses) than the supplemental and routine dose now commonly prescribed (0.5 to 1 Gm. three times a day). A normal diet generally contains 0.8 to 1.5 Gm. of potassium per 1,000[33] calories and is the logical source of supply of potassium at other times.

Potassium toxicity. The toxic effects of potassium are related to the concentration of potassium at the site of action, as well as to conditions such as oxygen deficit, increased concentration of hydrogen ion, and decreased concentration of sodium, which may alter the normal potassium equilibrium across cell membranes. When potassium is administered, the rate of administration becomes important, since this will reflect the peak concentration at the site of action. A slow intravenous infusion of potassium in experimental animals induces widespread block in all parts of the heart, associated with a reduction in pacemaker automaticity until death occurs by cardiac arrest.[34] Rapid infusions are attended by increased automaticity throughout the heart, leading to ventricular premature beats and ventricular fibrillation.[35] Wiggers[36] has demonstrated that ventricular fibrillation of the dog's heart can be promptly stopped by large doses of potassium. This paradoxical effect of the infusion of potassium may be explained if it is assumed that the raising of the concentration of potassium to a moderately high level produces a condition of localized block throughout the heart which is favorable for the production of ventricular fibrillation. If the infusion has been rapid enough so that pacemaker automaticity is temporarily enhanced at the same time that local blocks are produced, then ventricular fibrillation may be precipitated by a single ventricular beat, as suggested by Nahum and Hoff.[35] If, on the other hand, the infusion is slow, the phase of increased automaticity is bypassed, and only depressed cardiac conduction and decreased pacemaker automaticity are encountered. The terminal event in this case is cardiac standstill. Still larger doses may slow conduction sufficiently to arrest all cardiac activity, whether or not ventricular fibrillation is present. The end result here is profound cardiac depression.

Several reports of toxic effect in patients receiving potassium salts for digitalis intoxication are of interest in that they point out the dangers of treating digitalis intoxication with potassium when A-V block is one of the chief manifestations, and they also point out the fact that the oral use of potassium can be just as hazardous as the intravenous administration. According to two reports, potassium was used to treat digitalis intoxication manifest by complete heart block. In both instances, cardiac arrest resulted, leading to death

in one instance and resuscitation with molar sodium lactate in the other.[37] Lown[38] has commented on the dangers of treating digitalis intoxication in patients with heart failure, since hyperkalemia may result. He reports on one such patient who received 5 Gm. of potassium chloride daily, and who developed atrial standstill and intraventricular block with tall T waves. Saline infusions were effective in reversing this only while the infusion was running. The patient developed pulmonary edema and died with cardiac standstill. Fisch[39] reports one case of transient cardiac arrest after the use of potassium for the treatment of paroxysmal atrial tachycardia with block caused by digitalis. Fisch[40] has also reported that the administration of potassium to a fully digitalized patient with atrial fibrillation led to complete heart block. There have also been reports of serious shocklike symptoms after the oral administration of potassium salts to patients with kidney disease, and in patients receiving only 5 Gm. of potassium acetate orally who had no evidence of nitrogen retention.[23]

Conclusions

It is apparent from the toxicity studies available that there is a high risk involved in potassium therapy in patients with renal disease, in patients with heart failure and digitalis intoxication when the serum potassium is normal, and in patients with high-grade A-V block.

There is little evidence to suggest that potassium antagonizes any feature of digitalis intoxication, other than digitalis-induced arrhythmias. Potassium therapy is of value in the disturbances in cardiac rhythm due to digitalis intoxication in cases in which A-V block is not the chief manifestation, and in certain disturbances in rhythm which are refractory to quinidine but which are not due to digitalis. Specifically, potassium is useful in the treatment of ventricular premature beats and ventricular tachycardia, but should be withheld in cases of atrial fibrillation with high-grade A-V block and a regular ventricular rhythm. Its use in atrial tachycardia with block has proved to be of value but carries additional risks because of the presence of block. It is contraindicated in the treatment of complete heart block caused by digitalis.

The use of potassium in small daily supplementary doses to prevent the depletion of potassium in patients receiving digitalis and thiazides is unsound in most instances, and the routine use of potassium in this situation should be discontinued. Supplementary potassium may be helpful in the initial phase of diuresis in congestive heart failure and when the serum potassium is lower than normal. There should be no hesitancy about replacing potassium when there is hypokalemia, since most of the severe toxic effects associated with potassium therapy have occurred when it was used in the presence of a normal serum potassium.

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