Diuretic-induced hypokalemia

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Case presentations

A 52-year-old woman with a history of alcohol abuse (more than 6 beers daily for years) was admitted to the hospital because of acute precordial pleuritic pain that had begun abruptly 12 hours earlier. Three weeks prior to admission she sought medical attention, for the first time in 20 years, because of upper abdominal pain. An evaluation revealed gastritis; she was also found to have hypertension, diabetes mellitus, and chronic obstructive pulmonary disease. She discontinued ingesting alcohol and began receiving treatment with cimetidine (300 mg 4 times daily), theophylline (200 mg twice daily), and clonidine, 0.1 mg, plus chlorthalidone, 15 mg, in a combination preparation. One week prior to admission she developed increased fatigue and nausea, but she denied vomiting or diarrhea.

Physical examination at the time of admission revealed a disheveled, thin, white female in no acute distress. The blood pressure was 190/100 mm Hg with a pulsus paradoxus of 8 mm Hg; the pulse was 86 beats/min and regular. The skin was dry, no peripheral edema was present, and the jugular venous pressure was normal. Funduscopic examination revealed grade-I hypertensive retinopathy. Breath sounds were diminished bilaterally and a few scattered expiratory wheezes were heard. A two-component, scratchy pericardial friction rub was apparent at the left lower sternal border; an S4 was also heard. Cardiac examination revealed grade-I hypertensive retinopathy. Breath sounds were dimin-

Discussion

DR. RICHARD L. TANNEN (Director, Division of Nephrology, and Professor of Internal Medicine, The University of Michigan Medical Center, Ann Arbor, Michigan): This woman presented with severe hypokalemia 3 weeks after the initiation of diuretic therapy. In association with the profound hypokalemia, she manifested ventricular ectopy, which culminated in an episode of ventricular tachycardia and fibrillation. In the course of my discussion, I will address the role played by diuretics in the development of her hypokalemia, and I will also consider the relationship between hypokalemia and the development of the cardiac arrhythmias.

Although it is widely recognized that diuretic therapy commonly results in hypokalemia, considerable controversy exists regarding the clinical importance and appropriate management of this complication [1–8]. In this Forum I will (1) review the pathophysiology of diuretic-induced hypokalemia; (2) summarize the clinical characteristics of this condition; and (3) consider when potassium maintenance therapy might be indicated in patients receiving diuretic drugs. I will use the term “potassium maintenance therapy” to refer to the use of either potassium-chloride supplements or potassium-sparing drugs to maintain normal potassium levels during diuretic therapy.

Pathophysiology of diuretic-induced hypokalemia

Diuretics that either inhibit reabsorption in the thick ascending limb of Henle (drugs such as furosemide, ethacrynic acid, bumetanide) or in the early distal tubule (such as thiazides, chlorothalidone) are kaliuretic and induce hypokalemia when ingested on a chronic basis (Table I) [1]. The kaliuresis produced by these agents results from increased delivery of tubular...
fluid to the distal convoluted tubule and also possibly from increased sodium delivery to the distal nephron, especially the cortical collecting duct [9–12]. The effect of increased distal sodium delivery on potassium excretion may be enhanced by the high aldosterone levels that are frequently present under conditions of diuretic use.

In addition to the kaliuresis that results directly from the diuretic properties of these drugs, at least one other pathophysiologic process plays a critical role in the development and maintenance of hypokalemia. Hypokalemia is sustained in these patients in part as a result of the accompanying chloride depletion. The role of chloride depletion was elucidated elegantly by Schwartz and colleagues [13]. The major clinical causes of primary chloride depletion are diuretic therapy and the loss of gastric secretions from either vomiting or nasogastric drainage. Because a low-sodium diet is also a low-chloride diet, chloride depletion results from diuretic use because these agents are chloruretic as well as natriuretic. As clearly demonstrated in a sequence of studies by Schwartz and coworkers, a primary deficit of chloride results in potassium depletion with hypokalemia, metabolic alkalosis, and mild volume contraction [13]. The volume contraction, which persists despite the provision of adequate dietary sodium, is not necessarily clinically apparent. Similarly, so long as correction of the chloride deficit is prevented—that is, by ingestion of a low-chloride diet—the alkalosis is sustained because the daily production of endogenous acid, otherwise more than sufficient in quantity to accomplish correction, is balanced by renal acid excretion. More relevant to the present discussion is that the hypokalemia and potassium deficiency persist despite the provision of adequate potassium in the diet. All of the electrolyte abnormalities can be corrected upon provision of adequate chloride to restore the underlying deficit. These experimental observations provide the cornerstone for the clinical principle that diuretic-induced hypokalemia can only be managed successfully with the chloride salt of potassium, KCl. Other potassium salts such as those of citrate, gluconate, and phosphate are ineffective in correcting diuretic-induced hypokalemia secondary to chloride depletion. It should be appreciated that this dependency on the chloride salt of potassium applies only to potassium replacement therapy and would not necessarily be the case if potassium-sparing agents were used, because such agents interfere directly with the renal tubule’s capacity to secrete potassium.

The tubular mechanisms accounting for how chloride depletion induces renal potassium losses are still unresolved. It has been suggested that increased aldosterone secretion secondary to volume depletion may account for the kaliuresis [14]. Although elevated aldosterone levels may foster more intense kaliuresis under conditions of diuretic use, it appears that chloride depletion can result in potassium depletion even in the absence of increased aldosterone levels [15–17]. An elevated pH per se can increase renal potassium secretion and could play a role in the potassium loss, but the magnitude of this effect is unclear [18, 19]. Finally, recent evidence suggests that the concentration of chloride in distal tubule fluid can directly influence potassium secretion. Although the precise mechanism has not been elucidated, hypochloremia stimulates net potassium secretion [20].

Thus it is clear that diuretics with sites of action at either the ascending limb or the early distal tubule can produce kaliuresis and potassium depletion by at least two mechanisms. Recent experiments in our laboratory have raised the possibility that diuretics, especially furosemide, might stimulate potassium secretion in yet another way, namely by a direct tubular effect [19]. These experiments, which utilized isolated perfused kidneys from potassium-depleted rats, indicated that furosemide can induce a kaliuresis of a magnitude that cannot be accounted for entirely by an increase in either urine flow rate or sodium excretion. Furthermore, studies with amiloride indicated that this direct effect of furosemide on potassium excretion resulted from an increase in potassium secretion rather than from a decrease in potassium reabsorption. Whether hydrochlorothiazide can also stimulate potassium secretion directly was not definitively resolved by these experiments but, if hydrochlorothiazide has this property, its effect is much less prominent than that of furosemide. What, if any, role a direct effect of diuretics on potassium secretion might play in vivo has not been examined.

### Clinical characteristics of diuretic-induced hypokalemia

The clinical characteristics of the abnormality in potassium metabolism accompanying chronic diuretic use have been defined carefully in the past decade [1, 2] and are summarized in Table 2. We now know that the fall in serum potassium concentration occurs rapidly and reaches a plateau within about one week after diuretic therapy is initiated [21, 22]. As we will consider shortly, the degree of hypokalemia with standard doses of diuretics (hydrochlorothiazide, 50–100 mg/day or equivalent doses of other thiazide diuretics; chlorthalidone, 50–100 mg/day; furosemide, 40–80 mg/day) is modest [22–44]. Less than 7% of patients taking thiazides and less than 1% of patients taking furosemide exhibit a decrease in serum potassium below 3.0 mEq/liter [1, 21]. For this reason, it is appropriate to consider the possibility of other causes for hypokalemia in patients whose serum potassium falls to less than 3.0 mEq/liter during diuretic therapy. The patient today, whose serum potassium was 2.3 mEq/liter on admission, is a case in point. In most instances primary aldosteronism is high on the list of diagnostic possibilities when hypertensive patients manifest this degree of hypokalemia in response to treatment with diuretics. This patient’s hyponatremia and low urinary concentration of sodium (less than 10 mEq/liter) and chloride (less than 15 mEq/liter) at the time of presentation, and her ability to maintain normal potassium levels later in the hospital course, made this an unlikely possibility. Despite her denial, the impressive metabolic alkalosis (serum HCO₃ of 40 mEq/liter) along with the low urinary chloride concentration strongly suggest the possibility of vomiting. Alternatively, her intake of diuretic could have markedly exceeded the recommended dose. It is difficult to distinguish between these latter two possibilities after the fact.
since they both result in chloride depletion and therefore in a similar clinical picture.

Several other clinical features of chronic diuretic use are worth mentioning. Women seem to be more prone to hypokalemia than men seem to be [45], and some data suggest that whites are more susceptible than are blacks [44]. The degree of hypokalemia is minimized by moderate sodium restriction (~60–110 mEq/day). Both severe sodium restriction (<20 mEq/day) and a more liberal sodium intake (>200 mEq/day) appear to accentuate the magnitude of diuretic-induced hypokalemia [23, 24]. Finally, although one might surmise that patients treated with diuretics for congestive heart failure would be more prone to severe hypokalemia than would those treated for uncomplicated hypertension, this expectation is not supported by the available data [8, 21, 46].

The magnitude of the fall in serum potassium and in the degree of potassium depletion induced by chronic diuretic therapy has been reviewed by several authors; the data summarized in Table 3 were obtained in patients treated with standard doses of diuretics and without potassium maintenance therapy [1, 21]. The average decrement in plasma potassium with thiazides is 0.6 mEq/liter; this decrement appears to be significantly greater than the average decline of 0.3 mEq/liter with furosemide therapy [21]. With chlorthalidone the decline in plasma potassium is equivalent to that with thiazides [21].

Considerable variability has been found in the degree of actual total body potassium depletion measured either with total body counter or with exchangeable potassium techniques. The data available prior to 1977 were carefully assessed by Kassirer and Harrington, and the reports that have appeared since that time are consistent with their earlier analysis [1, 22–43]. As Table 3 shows, estimated deficits have ranged from as low as 0 to as high as 400 mEq (0% to 10% body potassium deficit) with all three classes of diuretics. Several studies have failed to detect a significant decrease in total body potassium and some investigators have concluded from these findings that diuretic-induced hypokalemia occurs independently of a decrease in intracellular potassium stores. An analysis of multiple studies, however, yields the mean values presented in Table 3. This analysis suggests that the average deficit is approximately 200 mEq, equivalent to a 5% decline in total body potassium stores. Given the limited sensitivity of the methods available, it is not surprising that estimated deficits ranging from 0% to 10% would be reported in the presence of a real deficit of this magnitude. Indeed, the recent analysis by Sterns et al of pure potassium depletion in humans described a strong correlation (r = 0.9) between the magnitude of the potassium deficit and the decrease in plasma potassium, with a decrease in plasma potassium of 0.3 mEq/liter being associated on average with a deficit of 100 mEq [47]. In line with this analysis, a decline of 0.3 mEq/liter would be expected with a deficit of 100 mEq and a decline of 0.6 mEq with a deficit of 200 mEq; these values agree reasonably well with the mean decrements measured with thiazides and furosemide. Direct measurements of muscle potassium concentrations also are consistent with this conclusion [1, 41–43].

Hence, it seems reasonable to conclude that diuretic-induced hypokalemia is associated with a decline in total body potassium stores, but that the total potassium deficit is quite modest. As with other potassium depletion states, the percent fall in plasma potassium of 15% (that is, 0.6/4.0 mEq/liter) is greater than the percent fall in intracellular potassium of 5%; thus, the ratio of extracellular to intracellular potassium (Ke/Ki) is reduced. Furthermore, in view of the ability of the myocardium to protect its cellular potassium content more effectively than other muscle tissue can, alterations in the potassium gradient may be even more pronounced in cardiac tissue [48, 49].

**Indication for potassium maintenance therapy**

Whether potassium maintenance therapy should be employed to correct mild diuretic-induced potassium deficiency obviously depends on the risks of mild potassium depletion as contrasted with the risks and costs of possible therapeutic interventions. First, I would like to consider the risks of potassium depletion in this setting.

**Risks of diuretic-induced hypokalemia and potassium depletion.** Mild degrees of experimentally induced potassium depletion (that is, 200–300 mEq) modify renal ammonia production and urinary acidification and also perturb the renal concentrating mechanism [50, 51]. The former effect may be a physiologic adaptation [50], but the concentrating defect is a pathophysiologic byproduct of potassium deficiency. Although impaired urine concentration is not of particular clinical importance, its occurrence does emphasize that even mild potassium depletion can induce organ dysfunction.

The potentially important clinical consequences of diuretic-induced hypokalemia are listed in Table 4. Recent interest has focused especially on the issue of hypokalemia-induced ventricular arrhythmias. To properly address this question, I will divide the issue into two subsets: (1) an increase in serious

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**Table 2. Clinical characteristics of diuretic-induced hypokalemia**

<table>
<thead>
<tr>
<th>Indication for potassium maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma K⁺ stabilizes in one week</td>
</tr>
<tr>
<td>1%–7% of patients exhibit decreased plasma K⁺ to less than 3.0 mEq/liter</td>
</tr>
<tr>
<td>Degree of hypokalemia related to Na⁺ intake</td>
</tr>
<tr>
<td>a. Very low or high Na⁺ accentuates hypokalemia</td>
</tr>
<tr>
<td>b. Modest Na⁺ restriction (100 mEq/day) minimizes the degree of hypokalemia</td>
</tr>
<tr>
<td>Females are more susceptible to hypokalemia than are males</td>
</tr>
<tr>
<td>Whites are more susceptible to hypokalemia than are blacks</td>
</tr>
<tr>
<td>No clear difference in the degree of hypokalemia exists whether treatment is for hypertension or for CHF</td>
</tr>
</tbody>
</table>

**Table 3. Altered potassium balance in hypertensive patients treated with diuretics**

<table>
<thead>
<tr>
<th>Indication for potassium maintenance therapy</th>
<th>ΔPlasma K⁺</th>
<th>ΔK Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td>(n)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>mEq/liter</td>
<td>mEq</td>
</tr>
<tr>
<td>Thiazides</td>
<td>510</td>
<td>−0.58</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>380</td>
<td>−0.67</td>
</tr>
<tr>
<td>Furosemide (40–80 mg/day)</td>
<td>181</td>
<td>−0.30</td>
</tr>
</tbody>
</table>

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*a Adapted from Ref. 21.  
*b Number of patients.  
*c Refers to the mean deficit recorded in each study.  
*d 50–100 mg/day of hydrochlorothiazide or equivalent dose of another thiazide.
ventricular arrhythmias in stable patients with or without underlying cardiac disease, and (2) an increased risk of ventricular tachycardia or fibrillation in the setting of acute myocardial infarction.

It is widely appreciated that hypokalemia can provoke arrhythmias in patients treated with digitalis. Several recent publications have suggested that hypokalemia per se increases the risk for development of ventricular arrhythmias [33, 52–77]. The ventricular ectopy varies from an increase in the frequency of unifocal ventricular premature beats to the development of complex ventricular arrhythmias, including multifocal ventricular premature beats, ventricular couplets, and/or ventricular tachycardia. In a recent critical review of this topic, Harrington, Isner, and Kassirer pointed out that a clear association between hypokalemia and ventricular arrhythmias could be established only if: (1) other causes of ventricular ectopic activity were rigorously excluded; (2) a firm temporal relationship between the development of hypokalemia and ventricular ectopy were demonstrated; and (3) correction of the underlying potassium deficit was associated with alteration of the ventricular ectopy [5]. Indeed, of the 17 reports they analyzed, only one fulfilled these three criteria [5, 52–67], and all but one were case reports or retrospective analyses of data.

Today’s patient illustrates the difficulty in delineating a clear association between hypokalemia and arrhythmias. Hypokalemia certainly could have been a significant factor in either directly producing or substantially increasing the susceptibility for the development of ventricular ectopy. However, in view of the underlying pericarditis and the severe hypoosmolality complicated by a seizure, it is impossible to delineate the precise role, if any, hypokalemia played in the abnormal rhythm.

Since publication of the review by Harrington et al, several prospective studies have appeared that specifically address this question in patients with diuretic-induced hypokalemia [33, 55, 68–77]. Table 5 summarizes these prospective studies. In three of them, in which a total of 50 patients were examined, and also in the chronic phase (3 to 50 month treatment) of the large Medical Research Council (MRC) study, in which an additional 74 patients were examined, an increase in the frequency of ventricular premature beats was noted to occur with the development of diuretic-induced hypokalemia [33, 55, 70–74, 77]. Approximatey 25% to 50% of patients exhibited a susceptibility to more frequent ventricular premature beats and, furthermore, the development of complex ventricular ectopy was also noted in 15% to 30% of patients in these four positive studies. In contrast to these findings is the absence of a significant change in ventricular ectopy in the short-term (9 to 10 week) MRC study of 16 patients as well as in three other studies encompassing 48 patients [68, 69, 71–73, 75, 76].

A similar lack of uniformity is apparent in the data collected during normalization of plasma potassium concentration. Three studies encompassing 35 patients reported an improvement in ventricular premature beats [55, 71–74]; one study reported improvement only with simultaneous potassium and magnesium therapy [70]; and one study of 16 patients found no improvement with an increase in plasma potassium concentration to 3.7 mEq/liter [68].

It is of note that Caralis and coworkers found evidence of hypokalemia-induced arrhythmias only in a subset of patients who had preexisting, significant cardiac disease as documented by abnormal results on EKGs, chest films, and 24-hour Holter monitor [74]. In all the other studies, criteria specifically excluded patients with angina, previous myocardial infarctions, abnormal exercise tests, or high-grade ventricular ectopy. Only patients without any evidence of heart disease or with mild cardiomegaly documented by a chest film, left ventricular hypertrophy by voltage criteria, or nonspecific EKG changes were included in these other studies. Thus, the possibility exists that a specific subset of patients, perhaps those with underlying cardiac disease, is at particular risk; but if so, we certainly lack the capacity to identify them uniformly.

Nevertheless, when this recent group of prospective studies is considered in conjunction with the other reports in the literature, the evidence seems to indicate that diuretic-induced hypokalemia can result in ventricular ectopy and that the type of ectopy can fall into the complex category, which has ominous implications. The data suggest that the risk of complex ventricular ectopy may be higher when the serum potassium is 3.0 mEq/liter or less; however, it seems clear that this complication can also arise with milder degrees of hypokalemia.

Even given these conclusions, to truly assess adverse consequences it is necessary that we know the actual risk of morbidity and mortality associated with the development of ventricular ectopy. One recent study that followed patients for up to 10 years suggests that asymptomatic, healthy individuals without underlying cardiac disease experience no increased risk of death from frequent and complex ventricular ectopy that occurs spontaneously [78]. Whether this prognosis would apply to patients with hypokalemia-induced arrhythmias is unknown. Furthermore it is widely accepted that ventricular ectopy predisposes to sudden death in patients with underlying ischemic heart disease [78–80]. Because the patient population receiving diuretics for hypertension is at increased risk for ischemic heart disease, and those undergoing therapy for congestive heart failure have established cardiac disease, one might speculate that diuretic-induced ventricular ectopy is likely to be more ominous than is spontaneously occurring ectopy in an otherwise healthy individual.

Several recent publications have addressed the role of hypokalemia in the occurrence of arrhythmias at the time of acute myocardial infarction [56, 57, 64, 81–86, 87]; this topic was reviewed recently by Solomon [81]. An analysis of the data from six studies, including a total of 8327 patients, is provided in Table 6 and reveals a number of salient and reasonably consistent observations. First, and most important, the incidence of serious ventricular arrhythmias (that is, ventricular tachycardia and/or fibrillation) was increased significantly in every study in the presence of hypokalemia (defined as a serum potassium less than either 3.6 or 3.5 mEq/liter). In most studies, the incidence of combined ventricular tachycardia and fibrilla-

<table>
<thead>
<tr>
<th>Table 4. Adverse consequences of diuretic-induced hypokalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ventricular arrhythmias</td>
</tr>
<tr>
<td>a. Increased ventricular premature beats</td>
</tr>
<tr>
<td>b. Increased risk of ventricular tachycardia and ventricular</td>
</tr>
<tr>
<td>fibrillation with acute MI</td>
</tr>
<tr>
<td>2. Impaired hypertensive control</td>
</tr>
<tr>
<td>3. Glucose intolerance</td>
</tr>
<tr>
<td>4. Lipid abnormalities (?)</td>
</tr>
<tr>
<td>5. Glucose intolerance</td>
</tr>
<tr>
<td>6. Lipid abnormalities (?)</td>
</tr>
<tr>
<td>7. Increased risk of ventricular tachycardia and ventricular</td>
</tr>
<tr>
<td>fibrillation with acute MI</td>
</tr>
<tr>
<td>8. Impaired hypertensive control</td>
</tr>
<tr>
<td>9. Glucose intolerance</td>
</tr>
<tr>
<td>10. Lipid abnormalities (?)</td>
</tr>
</tbody>
</table>

During normalization of plasma potassium concentration, three studies encompassing 35 patients reported an improvement in ventricular premature beats [55, 71–74]; one study reported improvement only with simultaneous potassium and magnesium therapy [70]; and one study of 16 patients found no improvement with an increase in plasma potassium concentration to 3.7 mEq/liter [68].
tion during the first 1 or 2 days of hospitalization was reported [56, 57, 83, 84]; however, in the two series with the lowest incidence of arrhythmias, the data are provided in a different fashion. Hulting only reported the incidence of ventricular fibrillation during the first 12 hours of hospitalization [64], and Johansson and Dziamski only provided data on the incidence of malignant arrhythmias resulting in circulatory arrest [85]. Although these specific events occurred less frequently than did the combination of ventricular tachycardia and ventricular fibrillation, in general the increased frequency in the hypokalemic group followed a similar pattern and was from two- to fourfold greater.

Whereas the likelihood of malignant arrhythmias complicating an acute myocardial infarction appears to be higher in the presence of hypokalemia, the data suggest that the frequency of ventricular premature beats is not increased [56, 57, 81, 84]. Consistent with this view is one recent series (not included in Table 6) that analyzed the incidence of all arrhythmias in 103 patients with an acute myocardial infarction and found no significant difference between hypokalemic and normokalemic patients, although the frequency of arrhythmias was 72% with hypokalemia compared with 58% in its absence [86].

Several other important observations emerge from these studies. Although patients taking digitalis were not specifically excluded, the data in three studies were analyzed to address the possible role of digitalis. The increased frequency of malignant arrhythmias with hypokalemia appeared to be independent of this agent [56, 57, 81, 84].

Evaluation of the role of diuretics suggests that they are a potential significant risk factor because of their propensity to cause hypokalemia. Indeed, in every study the incidence of hypokalemia was approximately twofold greater or more in patients treated with diuretics than did those not receiving diuretics; this finding indicates that it is the increased likelihood of hypokalemia rather than the diuretics per se that results in an increased risk for this complication [56, 57, 83, 85].

Approximately 10% of the patients who have not received antecedent therapy with diuretics exhibit hypokalemia in association with an acute myocardial infarction [57, 83–85]. This raises the possibility that hypokalemia might reflect a shift in potassium into the intracellular compartment, which might be the result of the increased sympathetic adrenal activity that can accompany an acute myocardial infarction [88]. Indeed, the possibility arises that hypokalemia is a marker, rather than the primary cause of the arrhythmogenic potential, both of which result from an increase in catecholamines. Nonetheless, the degree of hypokalemia induced by epinephrine appears to be more profound in the presence of preexisting diuretic-induced potassium depletion; this additive effect on lowering serum potassium could increase the likelihood that a serious arrhythmia will develop [88]. Another criticism of a primary role for potassium depletion in the induction of ventricular arrhythmias is that in many studies the level of potassium used for analysis was not necessarily recorded prior to the development of the arrhythmia [57, 64, 85]. The pitfalls of measurement after an acute episode is emphasized by the observations by Thompson and Cobb, who found that 49% of patients resuscitated out of hospital for ventricular fibrillation were hypokalemic, as compared with 19% of patients admitted to the hospital with an acute myocardial infarction, and 9% of ambulatory patients with coronary heart disease [53]. However, the percentage of patients taking diuretics did not differ among these three groups and, in the resuscitated group, the serum potassium after resuscitation did not differ between those who had and those who had not received antecedent diuretic therapy. The authors concluded that the high incidence of hypokalemia in the resuscitated group resulted from the resuscitative effort itself, and they cautioned against inferring from these data that hypokalemia predisposes to ventricular fibrillation. Nevertheless, in defense of the suggestion that preexisting potassium depletion might predispose to arrhythmias, several of the reports in Table 6 contained data based solely on the serum potassium level at the time of admission to the hospital [56, 83, 84].

In none of the studies cited in Table 6 was a significant increase in malignant arrhythmias reported in the diuretic-treated compared with nondiuretic-treated patients. However there is also no information provided regarding which diuretic-treated patients received potassium maintenance therapy [56, 57, 64, 83–85]. Thus, although these observations raise significant

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### Table 5. Diuretic-induced ventricular arrhythmias in hypertensive patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Mean serum K⁺ mEq/liter</th>
<th>VPBs</th>
<th>Complex VPBs</th>
<th>Mean serum K⁺ mEq/liter</th>
<th>VPBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holland et al [55, 77]a</td>
<td>21</td>
<td>3.0</td>
<td>↑</td>
<td>↑</td>
<td>4.0</td>
<td>↓</td>
</tr>
<tr>
<td>Hollifield &amp; Slaton [33, 70]</td>
<td>13</td>
<td>3.4</td>
<td>↑</td>
<td>↑</td>
<td>4.2</td>
<td>↓</td>
</tr>
<tr>
<td>Caralis et al [74]</td>
<td>16</td>
<td>3.5</td>
<td>↑</td>
<td>↑</td>
<td>4.1</td>
<td>↓</td>
</tr>
<tr>
<td>MRC [71–73]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute (9–10 weeks)</td>
<td>16</td>
<td>3.6</td>
<td>NC</td>
<td>NC</td>
<td>3.5</td>
<td>↓</td>
</tr>
<tr>
<td>Chronic (3–50 months)</td>
<td>74</td>
<td>3.6</td>
<td>↑</td>
<td>↑</td>
<td>3.7</td>
<td>NC</td>
</tr>
<tr>
<td>Papademetriou et al [68]</td>
<td>16</td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papademetriou et al [69]</td>
<td>15</td>
<td>3.0</td>
<td>NC</td>
<td>NC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Madias et al [75]</td>
<td>20</td>
<td>3.0</td>
<td>NC</td>
<td>NC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leif et al [76]</td>
<td>13</td>
<td>3.0</td>
<td>NC</td>
<td>NC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Symbols: VPB, ventricular premature beat; ↑, increase; ↓, decrease; NC, no change.

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*a Numerals in brackets are reference numbers.

*b Symbols: VPB, ventricular premature beat; ↑, increase; ↓, decrease; NC, no change.
Table 6. Relationship of serum potassium to ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients with acute myocardial infarction

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Hypokalemia</th>
<th>Normokalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solomon &amp; Cole [57]</td>
<td>151</td>
<td>48</td>
<td>21</td>
</tr>
<tr>
<td>Nordrehaug [56]</td>
<td>1035</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Hulting [65]</td>
<td>537</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Dyckner et al [83]</td>
<td>676</td>
<td>50</td>
<td>37</td>
</tr>
<tr>
<td>Reuben [84]</td>
<td>586</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Johansson &amp; Dziamski [85]</td>
<td>5342</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

* Serum potassium < 3.5 or 3.6 mM.  

The magnitude of potassium deficiency required for the development of glucose intolerance is modest and consistent with the degree of depletion that develops in many diuretic-treated patients. Rowe observed glucose intolerance following experimentally produced potassium deficits of 1.0% to 8.4% that were documented by total body potassium counting [96]. Other authors using balance techniques have observed abnormalities in glucose metabolism with mild to moderate potassium depletion (that is, deficits ranging from 200 to 569 mEq) [97, 105].

These observations support both the primacy and likelihood of potassium depletion in the development of disordered glucose homeostasis. It has been estimated that 30% of hypertensive patients receiving thiazide diuretics exhibit abnormal glucose tolerance, and population studies with adequate controls clearly indicate that development of glucose intolerance is causally related to diuretic therapy [100, 101, 103]. In most instances, only mild glucose intolerance develops and does not require hypoglycemic therapy; but rarely overt diabetes becomes manifest [4]. The potential risk, therefore, relates mainly to whether the subtle abnormalities in glucose metabolism predispose toward accelerated cardiovascular disease. This issue is unresolved in the selected population of patients with diuretic-induced glucose intolerance.

A potential relationship between diuretic use and lipid abnormalities is less clear than for glucose intolerance [93]. Most but not all studies suggest that therapy with thiazide or chlorothalidone results in an increase in cholesterol and triglyceride concentrations and in the ratio of low- to high-density lipoprotein cholesterol [93, 101, 106–113]. Two large, well-controlled investigations both uncovered a significant lipid alteration in patients treated with diuretics [106, 107]. The mechanism underlying the abnormality in lipid metabolism and its relationship to hypokalemia are unknown [93]. The latter issue requires careful study, and the cardiovascular risk of the lipid abnormality also needs to be delineated.

Potassium maintenance therapy. A decision regarding the appropriateness of potassium maintenance therapy must balance the adverse consequences of such a treatment program against the litany of potential hypokalemia-induced side effects. Potassium maintenance therapy can be accomplished successfully either with the use of potassium chloride supplements or with the use of potassium-sparing diuretics (such as aldactone, triamterene, or amiloride). Each of these approaches can correct diuretic-induced hypokalemia, but it should be recognized that KCl in doses of 40 to 60 mEq/day is needed for adequate...
therapy [114]. The data also suggest that potassium-sparing agents may be somewhat more effective in normalizing potassium than are potassium supplements [21].

Regardless of which approach to potassium maintenance therapy is used, the most serious risk is the development of hyperkalemia, a life-threatening complication. Whereas the risk of this complication has not been well-defined for the non-hospitalized patient, 3.9% of 1910 hospitalized patients who received oral potassium chloride developed significant hyperkalemia (potassium greater than 5.5 mEq/liter) [115]. Of hospitalized patients treated with spironolactone without potassium supplements, hyperkalemia occurred in 5.7% [116]. Comparably large studies have not been reported with the potassium-sparing drugs triamterene and amiloride, but the risks of hyperkalemia with these drugs are well documented. Regardless of whether potassium supplements or potassium-sparing diuretics were used, renal impairment was an important factor predisposing to hyperkalemia. The elderly and patients who received potassium in addition to potassium-sparing drugs are also at increased risk for the development of hyperkalemia [6, 115, 116]. Although these data indicate that hyperkalemia is a risk of potassium maintenance therapy, they do not establish the incidence of clinically significant hyperkalemia in ambulatory patients with acceptable levels of renal function treated selectively with either potassium supplements or potassium-sparing agents.

In addition to hyperkalemia, other adverse consequences of potassium maintenance therapy can occur that are drug-specific. All forms of KCl (liquid, wax matrix, and polymer-coated microencapsulated products) entail a risk of gastrointestinal ulceration, although the incidence of clinically significant ulceration appears to be low. Spironolactone can cause estrogen-like side effects, and triamterene can produce renal stones as well as folate-deficiency anemia [117]. In addition, both these agents as well as amiloride are associated with gastrointestinal side effects, and there also exists the risk of drug-induced allergic manifestations.

Finally, a substantial economic cost is associated with potassium maintenance therapy, regardless of whether potassium supplements or potassium-sparing diuretics are employed. Harrington and Kassirer estimated a few years ago that $250 million per year is spent for potassium treatment in the U.S. [5].

**Therapeutic recommendations**

Given this body of information, the physician is confronted with the need to make a decision regarding the use of potassium maintenance therapy. All would welcome a well-designed trial to assess the risk-benefit ratio of potassium maintenance treatment in order to arrive at a therapeutic strategy, but it seems unlikely that a study of appropriate scope and design will be carried out in the near future. Hence, a treatment plan must be formulated based on the incomplete data currently available.

My personal biases are listed in Table 7. There is general agreement that potassium maintenance treatment is indicated in patients receiving digitalis, in those predisposed to hepatic coma, or in those in whom serum potassium falls to less than 3.0 mEq/liter [1, 2, 6]. In view of the well-defined risks of hypokalemia-induced arrhythmias in patients treated with digitalis, and in view of the capacity for hypokalemia to induce hepatic encephalopathy by stimulating renal ammonia production, there is a broad consensus that the risks of hypokalemia in these settings outweigh those of therapy. Similarly, when serum potassium falls below 3.0 mEq/liter, the likelihood of hypokalemia-induced cardiac, muscular, and gastrointestinal symptoms are increased and, despite the absence of rigorous proof, there appears to be no argument that the risk of therapy is justified under this circumstance.

The last three indications listed in Table 7 are more controversial. In my view, treatment is indicated in any patient who develops overt glucose intolerance, because this disorder may represent a pathologic sequela of hypokalemia. Whereas the long-term risk of mild glucose intolerance is undefined, the risks of potassium maintenance therapy are small and seem appropriate to forestall the potential sequelae of accelerated cardiovascular disease.

The fifth indication, that is, to treat any patient with underlying cardiac disease, evokes the most heated debate. It is based on a judgment regarding the potential risk for hypokalemia-induced ventricular arrhythmias both under stable conditions and in the setting of an acute myocardial infarction. My rationale is as follows: Although some studies do not reveal an increased risk of ventricular arrhythmias in patients with diuretic-induced hypokalemia, several carefully performed evaluations have uncovered a statistically significant alteration. Furthermore, complex as well as unifocal ventricular arrhythmias have been delineated. Because the failure to detect an effect does not prove its absence, the disparate findings can be interpreted as suggesting that the groups selected for study differed, perhaps in ways we are not yet sophisticated enough to identify. In this regard, the study by Caralis and colleagues points strongly to the presence of underlying cardiac disease as an important risk factor for hypokalemia-induced ventricular arrhythmia [74]. In view of the documented increased risk of sudden death in patients with ventricular arrhythmias superimposed on underlying cardiac disease, I believe that potassium maintenance therapy, judiciously monitored, is a preferable alternative to hypokalemia. My convictions are strengthened by the data regarding the risk of hypokalemia in the setting of acute myocardial infarction. Granted that each of these studies is subject to criticism, the evidence as it currently exists suggests that there is, rather than is not, a real risk of sudden death in patients with preexisting potassium depletion.

These two lines of reasoning lead to my conclusion that potassium maintenance therapy should be used if cardiac disease is evident. The corollary is that I would not routinely advise potassium maintenance therapy for patients receiving diuretics who do not have evidence of underlying cardiac disease. This subgroup would seem to be less prone to arrhythmias, to be at less risk if arrhythmias develop, and is probably at less risk for development of an acute myocardial infarction.

My final recommendation is to initiate a trial of potassium

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<th>Table 7. Indications for potassium maintenance therapy</th>
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<tr>
<td>1. Digitalis therapy</td>
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<td>2. Predisposition to hepatic coma</td>
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<td>3. Serum potassium &lt; 3.0 mEq/liter</td>
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<td>4. Development of glucose intolerance</td>
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<td>5. Underlying cardiac disease</td>
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<td>6. Symptoms attributable to hypokalemia</td>
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maintenance therapy in any patient with symptoms that can be ascribed to hypokalemia. This includes a variety of vague complaints including malaise, fatigue, muscular weakness, and muscle cramps. Granted that all these symptoms are nonspecific, but they nevertheless can be manifestations of potassium depletion. If therapy relieves the symptoms, the response could be due either to specific correction or to a placebo effect. In either case, long-term potassium maintenance treatment would seem indicated, as the patient experiences a benefit and the risks are minimal.

Questions and answers

DR. DAVID BUSHINSKY (Renal Section, Mitchell Hospital, Chicago): Many authorities recommend that antihypertensive therapy begin with the use of diuretic agents. In view of the risks of hypokalemia, would you recommend the use of agents other than diuretics as first-line therapy in the treatment of hypertension?

DR. TANNEN: This issue is certainly pertinent in view of the finding in the MRFIT study that the special intervention group (which was treated with diuretics) had an increased incidence of unexplained sudden death [89, 90], and the report by Ruberman et al. of a twofold increase in the rate of sudden death in patients treated with diuretics following an acute myocardial infarction [80]. Neither of these studies definitively incriminates diuretics as the culprit however. Furthermore, the long-term risks of the other antihypertensive therapies are not well delineated. Diuretics are relatively safe and have few unpleasant side effects, so I still recommend them as first-line antihypertensive drugs. However, if the patient has underlying cardiac disease, I concurrently recommend potassium maintenance.

DR. GARY TOBACK (Renal Section, Mitchell Hospital): What drug do you use for the management of diuretic-induced hypokalemia?

DR. TANNEN: I formerly favored potassium chloride supplementation. However, you have to use enough KCl—40 to 60 mEq/day and in some instances more—to maintain normal serum potassium levels, and recent data in the literature suggest that potassium-sparing agents are more effective in sustaining normal serum potassium levels than is potassium chloride. In addition, both triamterene and amiloride are well tolerated by most patients. My current bias leans towards amiloride, which I think is a little bit more predictable and perhaps better tolerated in terms of side effects. But that is a personal bias and I think one can make arguments for using the other forms of potassium maintenance therapy as well.

DR. TOBACK: I would like to hear your comments about the relationship between hypokalemia and cardiac injury. It is not talked about much anymore, but the older pathology literature suggested that the ingestion of a potassium-deficient diet could result in myocardial necrosis, which could become striking when potassium deficiency was marked [118]. In addition to death of myocardial cells, there appears to be a proliferation of fibroblasts [118]. So if there is underlying heart disease, one could argue that there might be cells suffering from borderline ischemia and that hypokalemia might cause enough further damage to make sublethally injured cells become necrotic. I wonder if you would comment on that.

DR. TANNEN: In the 40-year-old literature that you are quoting, Dr. Toback, the patients and the animal models studied were severely potassium deficient, and the clinical studies often had other complicating features [117]. Whether milder degrees of potassium depletion can in some way sensitize the cell to ischemic injury, for example, has not been addressed to my knowledge, but I think it is a reasonable issue to consider. Furthermore, potassium has direct effects on the vasculature: a high potassium concentration is vasodilatory and a low potassium concentration is vasoconstrictive. The Sodi-Pallares solution, which contains potassium, insulin, and glucose, might confer benefit by delivering more potassium to ischemic sites and thus produce vasodilation and improved perfusion of ischemic areas. I am unaware, however, of any convincing studies utilizing this approach [81].

DR. JOHN T. HARRINGTON: In contrast to the early report of Rubini in 1961 [51], Healy and colleagues demonstrated no effect of diuretic-induced potassium depletion on urine concentrating ability in 7 hypertensive patients [38]. How do you reconcile these conflicting reports?

DR. TANNEN: The absence of a significant change in either concentrating ability or urine acidification in the study by Healy is difficult to reconcile with the two carefully performed studies of dietary induced potassium depletion, which have demonstrated significant effects. It should be noted, however, that the trends in Healy's study were in a similar direction, although they failed to achieve statistical significance.

DR. SUSAN FELLNER (Renal Section, Mitchell Hospital): I agree with your recommendations regarding potassium maintenance. But I think that we as physicians could do a better job in helping to prevent potassium depletion, particularly with regard to the issue of dietary salt restriction. A real commitment to the education of our patients about dietary sodium might prevent at least some of the diuretic-induced hypokalemia that we see.

DR. TANNEN: I agree. If we could get patients to ingest approximately 100 mEq/day of sodium, we would tend to minimize the degree of hypokalemia and would probably in many instances improve their antihypertensive control as well. However, even if we do, some patients will, for example, develop serum potassium levels of 3.5 mEq/liter, which in my view are not normal. If these people have underlying cardiac disease, I think a normal serum potassium should be maintained, and this probably will require some form of potassium maintenance therapy.

DR. JORDAN J. COHEN: We all agree that there is a large group of individuals who have no heart disease and who do not become very potassium-depleted when given diuretics. If such individuals are truly at risk from the modest hypokalemia they manifest, then nature has endowed us with an extremely narrow margin for error in maintaining potassium homeostasis. There being no evidence to the contrary, I prefer to believe that the mammalian organism is more resilient than that. Only if one believes otherwise would it be justifiable to expose patients treated with diuretics routinely—and I emphasize routinely—to the admittedly small but definite risk of hyperkalemia from potassium maintenance therapy. Do you agree?

DR. TANNEN: I should have mentioned whom I would not treat. In view of our current knowledge of the risks associated with hypokalemia and of the costs and risks of potassium maintenance therapy, at present I don't think the weight of evidence is sufficient to subject the group of patients who don't have underlying, detectable cardiac disease to potassium-main-
tenance therapy. I am not sure what fraction of the hypertensive population that encompasses, but certainly more patients receiving antihypertensive therapy don’t have detectable cardiac disease than do.

**DR. COHEN:** There are several bothersome issues about the reported relationship between hypokalemia and malignant ventricular arrhythmias in the setting of an acute myocardial infarction. First, as you noted, no firm evidence exists for a cause-and-effect relationship; hypokalemia in this setting might be merely a marker, especially in view of the known effects of catecholamines in shifting potassium intracellularly. Second, because in many of the reported cases hypokalemia was documented only after successful resuscitation from the arrhythmias, we must consider, as you did, the question of whether hypokalemia was the consequence of the treatment (for example, alkali infusion) or of the stress (such as catecholamines) or of something else. Finally, as you also noted, a substantial subset of patients who are admitted with an acute MI and hypokalemia and who develop ventricular tachycardia or fibrillation have never been exposed to diuretics. And in those who had been receiving diuretics, we don’t know how many also had been treated with potassium supplements or potassium-sparing agents and developed hypokalemia anyway. But the dilemma here is the following: If one is convinced that hypokalemia in the aftermath of a myocardial infarction promotes malignant arrhythmias, and one wants to do something to prevent this complication, one would have to give potassium supplements to everybody in the country who is at potential risk of developing an MI, whether they were receiving diuretics or not. Of course, such a strategy is absurd.

**DR. TANNEN:** Let’s again consider the individuals who have an acute myocardial infarction and have not been preexposed to diuretics. Presumably their hypokalemia is not the result of antecedent potassium depletion but instead reflects an intracellular shift of potassium. There really wouldn’t be any way to pretreat people with potassium to prevent that from happening unless we were going to propose making everybody walk around substantially hyperkalemic. Alternatively, some have suggested that the antiarrhythmic effects of therapy with beta blockers might be mediated through inhibition of epinephrine-mediated cellular potassium uptake, but there is no firm evidence in this regard [81]. Thus, with the possible exception of therapy with beta blockers, there is no prophylactic therapy for the group with normal potassium homeostasis that is potentially at risk for a myocardial infarction. But we can diminish the likelihood for hypokalemia in the diuretic-treated patients at risk for myocardial infarction by providing them with potassium maintenance therapy.

**DR. MARSHALL LINDHEIMER (Renal Section, Mitchell Hospital):** Let’s change the discussion from the pros and cons of potassium maintenance therapy to another aspect of the patient’s problems. This patient’s serum sodium level of 116 mEq/liter reminds me of a series of patients described by Dr. Fichman and coworkers more than a decade ago [119]. In these patients, severe hyponatremia was associated with diuretic-induced hypokalemia, and one of the causes considered was the “inappropriate” secretion of vasopressin. Would you care to speculate on the cause of the hyponatremia in this patient?

**DR. TANNEN:** In this particular patient, the low urinary sodium and chloride suggested that volume depletion at least partially accounted for the hyponatremia. Although her hyponatremia ultimately resolved in response to concurrent treatment with NaCl and KCl, it didn’t correct as rapidly as I would have anticipated with uncomplicated sodium depletion. No other reason for the development of hyponatremia was detected. Prior to discharge from the hospital, she was able to sustain a normal serum sodium concentration in the absence of specific therapy. Thus she might fit into the group of diuretic-treated hypokalemic patients who appear to manifest “inappropriate” ADH secretion. The patients reported by Fichman et al developed hyponatremia in the absence of detectable volume depletion, and these authors speculated that hypokalemia might have modified either the osmoreceptors or the releasing mechanism for vasopressin. Perhaps supporting their hypothesis, recent data indicate that vasopressin levels are increased in potassium-depleted rats, and that the elevated levels appear to be a defense mechanism for protecting systemic hemodynamics [120]. On the other hand, this phenomenon has been described mainly in the elderly population, so I always have wondered whether mechanisms other than hypokalemia might be at play. For example, might a subset of the elderly population have baroreceptor mechanisms that can be activated with lesser degrees of volume contraction than in younger individuals, so that we don’t recognize the degree of volume contraction as being a stimulus? I think it would be quite interesting to study this phenomenon more carefully in terms of what we now understand about the nonosmotic release of vasopressin.

**DR. BRIAN DUFFY (Attending Nephrologist, Michael Reese Hospital):** What is your approach to the unusual patient who becomes severely hypokalemic during administration of small doses of diuretics?

**DR. TANNEN:** If a hypertensive patient develops diuretic-induced hypokalemia to a level less than 3.0 mEq/liter, I believe it is appropriate to evaluate for primary aldosteronism. Another consideration would be renal artery stenosis; patients with this disorder can have significant degrees of secondary hyperaldosteronism and develop hypokalemia on that basis, as can those with other forms of mineralocorticoid or glucocorticoid excess. Of course, other causes of potassium depletion also should be kept in mind, including vomiting and laxative abuse. In effect, the patient with severe hypokalemia needs to be completely worked up. Of course this is not the case with the average patient taking diuretics, who is mildly hypokalemic; in this situation, there is a very clear explanation.

**DR. COHEN:** If you proceed with that algorithm, you will work up a lot of people to obtain a very low yield of patients with primary aldosteronism. By definition, you are talking about patients who were normokalemic prior to the introduction of diuretics, because presumably you would have already pursued the possibility of primary aldosteronism had they been spontaneously hypokalemic. Thus we are considering maybe as many as 5% of patients treated with diuretics who will become hypokalemic to this degree. I believe the number of patients in that subset who have primary aldosteronism will be extremely small.

**DR. TANNEN:** I agree that the yield might be quite low. But the workup for primary aldosteronism is not difficult. Screening by the measurement of plasma renin is easy, and the finding of normal renin levels should eliminate the vast majority of patients from requiring further evaluation.
DR. Serafino Garella (Renal Division, Michael Reese Hospital): You mentioned that the level of dietary sodium intake least likely to be associated with major potassium deficits in patients on diuretic therapy is approximately 100 mEq/day. Would you speculate on the mechanisms responsible for the linkage between a higher level of salt intake and the increased likelihood of potassium wasting?

DR. TANNEN: In the study by Ram and coworkers, potassium depletion was significantly greater when diuretics were taken for 4 weeks with a dietary sodium content of approximately 200 mEq/day as compared with 70 mEq/day [23]. Aldosterone levels were higher in the group on the lower sodium intake. Thus, one could speculate that the higher sodium intake resulted in greater fluid and sodium delivery to the distal nephron, and thereby resulted in heightened urinary losses of potassium; but the actual underlying mechanism was not subjected to rigorous investigation. It is of interest that Wilcox and colleagues recently reported no evidence of negative potassium balance in normal volunteers ingesting a sodium intake of 270 mEq/day during 3 days of furosemide treatment [121]. Obviously the two sets of studies were carried out in different fashions, but the possibility does exist that the kaliuretic response might differ between normotensive and hypertensive individuals.

DR. KAI LAU (Renal Division, Michael Reese Hospital): There are at least two reasons why potassium balance studies in humans might underestimate the true magnitude of the potassium deficits induced by diuretics. (1) Many hypertensive patients ingesting a low-salt diet are also taking salt substitutes, which are generally potassium-rich and which we often don’t know about because of the absence of a careful history. (2) We are beginning to uncover increasing numbers of patients who take variable amounts of prostaglandin inhibitors without a prescription. If this piece of history is not specifically sought, one can miss intervals of variable lengths over which renal potassium retention can have occurred. Wouldn’t these two factors obscure the true magnitude as well as the incidence of potassium deficits?

DR. TANNEN: I would agree with you that either of these phenomena could influence the degree of potassium depletion and of hypokalemia in patients taking diuretics. I suspect, however, that these two possibilities have not had a meaningful impact on the incidence and magnitude of potassium depletion reported in the literature. First, the data on the incidence and degree of hypokalemia include an enormous number of patients, the studies have been reported over several decades, and the data are all reasonably consistent. Second, in the studies that determined actual potassium deficits using either exchangeable or total body potassium measurements, the degree of hypokalemia was comparable to that reported in the voluminous data that measured only blood levels. Thus the potassium deficit appears to have been measured on a representative sample.

DR. COHEN: Dr. Lau’s question brings up another point. You commented that Lawson’s data published in the ‘70s and collected retrospectively from several hospitals [115] might have overestimated the current risk of hyperkalemia, even in the hospitalized patient, because we now use potassium supplements and potassium-sparing agents more cautiously and with more understanding of the hazards. But it’s also true that patients are now being exposed to several new antikaliuretic drugs that potentially compound the risk of hyperkalemia; I’m referring to the nonsteroidal antiinflammatory agents, the beta blockers, captopril, and no doubt others.

DR. TANNEN: That’s a good point. Clearly if one is going to use potassium-sparing drugs or potassium supplementation, all the drugs that can predispose towards development of significant hyperkalemia must be kept in mind. Also, great care should be exercised in treating insulin-dependent diabetics with any potassium maintenance regimen. Finally, the elderly and individuals with decreased GFRs who are also at increased risk for hyperkalemia need to be individualized so that we can assess the need for and the risks versus benefits of potassium therapy.

DR. James Bourdeau (Renal Division, Michael Reese Hospital): In experimental animals not given diuretics, chronic administration of potassium chloride results in a phenomenon of potassium adaptation, whereby acute potassium loads are excretory by the kidneys more rapidly than normal. Do patients who are taking diuretics and who are being given supplements of potassium chloride also develop potassium adaptation? That is, are they able to excrete an acute potassium load more rapidly than do normal individuals? If so, and if their potassium chloride supplementation was stopped, would they be at increased risk for developing hypokalemia?

DR. TANNEN: I would assume not. I suspect that the induction of adaptation requires at least transitory hyperkalemia. However, I am unaware of any studies that have directly tested the question you raise.

DR. Bushinsky: As you noted, a reasonable correlation exists between the serum potassium concentration and potassium balance over a wide range of potassium depletion. Yet you also noted that the fall in serum potassium observed with three different diuretic agents correlated poorly with the change in potassium balance. Could you comment on this apparent contradiction?

DR. TANNEN: I don’t have a good answer to your question, but I would caution that the data summarized in Table 3 represent a composite of multiple studies using different measurement techniques, and with some variation in sodium intake. In the furosemide group, which has the lowest patient number, elimination of the 12 patients who were ingesting a sodium intake of 196 mEq/day [23] reduces the mean potassium deficit to 132 mEq. This would square better with the lower decrement in plasma potassium, but I think there are insufficient total body potassium data to make a firm comparison of the furosemide and thiazide data.

DR. Jerome P. Kassirer: Dr. Tannen, whether or not one believes that it is appropriate to prevent hypokalemia in diuretic-treated patients depends in part on one’s strength of conviction about the correlation between hypokalemia and life-threatening rhythm disturbances. John Harrington and I have a somewhat different view from yours about the validity of this correlation. A recent study by Nordrehaug, which you did not mention, is a case in point. Nordrehaug concluded, in a study of patients with acute myocardial infarction complicated by serious rhythm disturbances, that hypokalemia increased the chance of a serious arrhythmia [122]. Careful review of his study, however, discloses that other factors, including digitalis administration and preexisting coronary artery disease, could have explained the higher frequency of rhythm disturbances in
the hypokalemic group. This comment raises questions about the validity of the experimental design, a problem we have addressed before [5]. Even if one accepts the Nordrehaug report as valid, however, we are concerned that the fraction of patients developing ventricular fibrillation was the same or higher in patients with hyperkalemia as in two groups of his patients with hypokalemia. This finding speaks to our concern that the risks of hyperkalemia need to be balanced against the risks of hypokalemia. Can you address these issues?

DR. TANNEN: There is one very recent report by Nordrehaug and coworkers that I did not mention [123]. In this study, 60 patients with an acute myocardial infarction and no treatment with cardioactive drugs were evaluated prospectively. This study also delineated a significant negative correlation between serum potassium level and ventricular tachycardia, supporting other retrospective analyses suggesting that digitalis does not explain this relationship [56, 57, 81, 84].

You are correct in pointing out that in the study by Nordrehaug, as well as in several other studies, the incidence of ventricular tachycardia/fibrillation was increased by hyperkalemia as well as by hypokalemia [56, 57, 83, 84]. Dyckner and coworkers suggest that the hyperkalemia is secondary to hypoxia and acidosis and that the increase in ventricular arrhythmias may be related to the more serious condition of these patients, but the authors do not provide any data on this point [83]. Certainly the cardiac risks of severe hyperkalemia are undisputable. In my view, the goal should be maintenance of normal potassium balance in patients at risk for myocardial infarction in order to reduce the risk of sudden death before they arrive at the hospital.

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