MEDICAL PRACTICE

Occasional Review

Hypokalaemia and diuretics: an analysis of publications

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Summary and conclusions

Published data have been used to define the characteristics of the fall in serum potassium concentration after taking diuretics and the efficacy of the various treatments given to prevent or correct it. The average fall is less after the usual doses of frusemide (about 0·3 mmol/l) than after the usual doses of thiazides (about 0·6 mmol/l) and is little influenced by the dose or duration of treatment. The fall with a given drug is the same in heart failure and hypertension, but the initial serum potassium concentration is higher in heart failure, so that the final value is lower in hypertension. In standard doses potassium supplements are less effective than potassium-retaining diuretics in correcting the hypokalaemia.

The relation between the average serum potassium value and the frequency of low values (hypokalaemia) is such that very low values after taking diuretics are unusual in patients with hypertension or heart failure. Hypokalaemia would almost disappear as an important complication of diuretic treatment if it was defined as a value less than 3·0 mmol/l rather than as a value less than 3·5 mmol/l.

Introduction

A fall in serum potassium concentration is a well-known effect of the thiazide diuretics and of some of the more recently introduced diuretics. There has been little interest, however, in the magnitude of the fall and its variation with the type or dose of diuretic, or between one disease and another, or indeed between one patient and another.

We have used the published data to define these characteristics of the fall in serum potassium concentration and to assess the efficacy of the several treatments used to prevent or correct the fall in serum potassium concentration.

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Methods

We collected those publications that included not only the serum potassium concentration before and after treatment with diuretics, but which also detailed the number and type of patients, the dose of diuretic, and the duration of the treatment with diuretics. The suitable reports were largely restricted to frusemide and the thiazides (chlorothiazide, hydrochlorothiazide, and chlorthalidone) and to their use in heart failure and hypertension. In all but a few studies serum rather than plasma potassium concentration was measured.

The overall mean and standard deviation of the serum potassium concentration or its change after treatment were calculated after weighting the values in each study for the number of patients studied.

Results

TIME COURSE OF HYPOKALAEMIA

A fall in serum potassium concentration has been reported within a few hours of taking frusemide[1] and chlorothiazide.[2] Table I, which

TABLE I—*Mean fall in serum potassium concentration (K; mmol/l) according to duration of treatment with either thiazides or chlorthalidone without potassium supplements*

	Weeks				
	-1	-2	-4	-8	-16
Mean fall in serum K concentration	0·7	0·65	0·56	0·69	0·56
No of patients	52	96	136	255	141
No of studies	5	7	7	10	6

is based on all the available cross-sectional data, shows that the maximum fall in the serum potassium value after the thiazides or chlorthalidone had happened by the end of the first week of treatment and that there was little further fall thereafter. A similar pattern was seen in most of the longitudinal studies,[3-8] even those that lasted two years.[9]

In contrast, when the diuretics are stopped the serum potassium value takes several weeks to return to normal.[10] If this delay is the time taken to replete the body potassium then it is surprisingly long, as the deficit of body potassium is small.[11]

DOSE OF DIURETICS

The relation between the dose of the diuretic and the fall in the serum potassium concentration can be examined in detail only for hydrochlorothiazide and chlorthalidone. Figure 1 shows that the fall in the serum potassium concentration was only slightly greater after the largest dose than after the smallest dose of these diuretics. This is in keeping with the flat dose-response curve for the diuretic and antihypertensive properties of the thiazides. Unfortunately, there were insufficient data to make a similar detailed assessment for frusemide, but in one study[12] the dose response in terms of the fall in plasma potassium value was almost flat whereas in terms of the diuresis there was a steep dose-response relation.

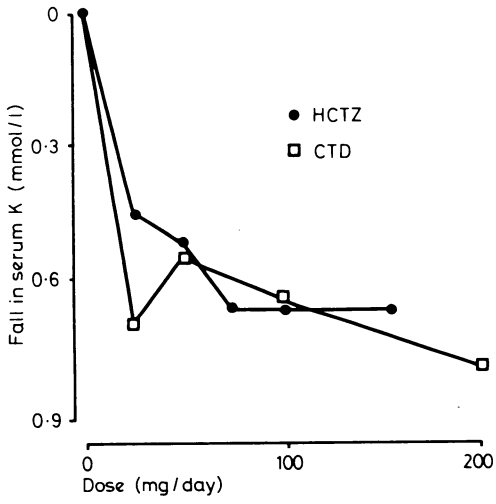

FIG 1—Mean fall in serum potassium concentration (mmol/l) according to dose (mg) after hydrochlorothiazide (HCTZ) or chlorthalidone (CTD).

DIFFERENT DIURETICS

As the duration and dose of treatment are not major determinants of the magnitude of the fall in serum potassium concentration, the data may be pooled to compare the fall in serum potassium concentration after different diuretics and in different diseases.

Table II shows that on average the different thiazides cause about the same fall in the serum potassium value, and that this fall (about 0·6 mmol/l) was greater ($p < 0·01$) than the fall after frusemide (0·3 mmol/l). In the few studies that have been made cyclopenthiazide caused a smaller fall in serum potassium (0·3 mmol/l) than the other thiazides ($p < 0·01$).

EFFECTS OF DIURETICS IN DIFFERENT DISEASES

The effect of thiazides and frusemide can be studied in detail only in heart failure and hypertension. Table III shows that the two diuretics caused the same average fall in the serum potassium concentration in heart failure and in hypertension. The serum potassium concentration before treatment, however, was higher in the patients with heart failure than in those with hypertension.

EFFECT OF VARIOUS TREATMENTS ON THE FALL IN SERUM POTASSIUM CONCENTRATION

Potassium supplements, or potassium-sparing diuretics, are given to prevent or correct the fall in serum potassium concentration after diuretics. The effects of these treatments have been studied either by comparing groups of patients taking diuretics with and without these treatments, or by comparing the effects of these treatments in

TABLE II—*Fall in serum potassium concentration (K; mmol/l) after different diuretics. Values of the mean, standard deviation (SD), and standard error of the mean (SEM) are weighted according to number of patients in each of the studies that have been combined to give these values. (Figures in parentheses indicate number of studies and patients where standard deviation was available)*

	Hydrochlorothiazide	Bendrofluazide	Chlorothiazide	Cyclopenthiazide	Chlorthalidone	Frusemide
Fall in serum K concentration						
Mean	0·62	0·56	0·51	0·31*	0·67	0·30*
SD	0·50	0·56	0·44	0·40	0·33	0·60
SEM	0·040	0·067	0·076	0·085	0·042	0·055
No of patients	284 (152)	116 (69)	110 (33)	75 (22)	380 (106)	181 (117)
No of studies	16 (8)	7 (4)	6 (2)	4 (1)	15 (4)	11 (7)
Dose (mg)						
Mean	90	12	1200	1·2	100	75
Range	25-150	10-15	1000-2000	1-2	50-250	20-120

TABLE III—*Serum potassium concentration (K; mmol/l) before (B) and after (A) thiazides or frusemide in patients with hypertension or chronic heart failure*

	Thiazides				Frusemide			
	Hypertension		Chronic heart failure		Hypertension		Chronic heart failure	
	B	A	B	A	B	A	B	A
All studies								
Fall in serum K concentration								
Mean	4·18	3·52	4·48	3·8	4·09	3·73	4·41	4·22
No of studies	36	36	13	13	5	5	8	8
No of patients	878	878	168	168	200	200	121	121
Studies with standard deviation								
Fall in serum K concentration								
Mean	4·22	3·55	4·61	3·78	4·10	3·73	4·41	4·22
SD	0·351	0·432	0·443	0·447	0·460	0·460	0·558	0·568
No of studies	24	24	6	6	2	2	8	8
No of patients	428	428	55	55	145	145	121	121
Difference B to A								
Mean	0·66		0·68		0·36		0·19	
Confidence limits	0·60-0·72		0·51-0·85		0·25-0·47		0·05-0·33	

patients who already have hypokalaemia caused by treatment with diuretics. Table IV summarises these studies. On average, the potassium-sparing diuretics were more effective than the potassium supplements, but neither fully corrected the fall in serum potassium concentration. In the case of potassium supplements the rise in serum potassium concentration was no greater in those groups with a relatively low initial concentration than in those whose initial value was near the normal range.

TABLE IV—*Effect of various treatments on the low serum potassium concentration (K; mmol/l) in patients with hypokalaemia taking diuretics*

	Potassium supplements	Amiloride	Trimaterene	Spironolactone
Serum K concentration				
Mean before	3·61	3·68	3·28	3·42
Mean rise	0·32	0·39	0·46	0·65
Daily dose				
Mean	36 mmol	15 mg	150 mg	75 mg*
Range	7-80	5-20	100-300	50-100
No of patients	353	142	104	126
No of studies	13	9	6	7

*For studies before 1963 100 mg has been taken as equivalent to 25 mg of the present-day preparation.

FREQUENCY OF HYPOKALAEMIA AFTER DIURETICS

In clinical practice the need for treatment in the individual patient is often based on whether the serum potassium value is below the lower limit of the normal range (usually less than 3·5 mmol/l). Clearly, an individual may have a fall in the serum potassium concentration but yet not have hypokalaemia. It is relevant therefore to consider the relation between a fall in the serum potassium value after diuretics and the frequency of hypokalaemia.

In a group of patients whose serum potassium concentration has fallen because of diuretics the frequency of hypokalaemia depends on the mean serum potassium concentration both before and after treatment, and the distribution of the individual values (expressed as the standard deviation) before and after treatment.

Figure 2 shows the predicted relation between the mean value of serum potassium and the frequency of hypokalaemia (less than 3·5 mmol/l) in patients with hypertension or heart failure. These relationships are calculated from the means and standard deviations before taking diuretics (table II), and are based on the assumption that the standard deviation of the values does not change after treatment. The relationship in hypertension agrees closely with that obtained when the data of Ramsey and his colleagues[13] are plotted (fig 2). This agreement suggests that the standard data (table 2) can be used to estimate the frequency of values less than 3·5 mmol/l and less than 3·0 mmol/l in the various groups of patients on the basis of the mean values in those groups.

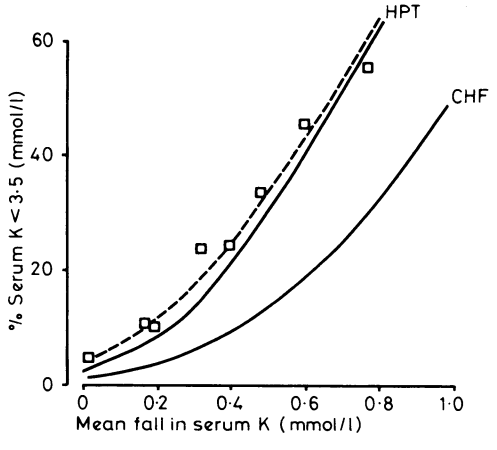

FIG 2—Relation between mean fall in serum potassium (K) concentration and frequency (%) of values of serum potassium less than 3·5 mmol/l. Continuous lines are relations in hypertension (HPT) and heart failure (CHF) calculated from pretreatment means and standard deviation shown in table III. Open squares and dotted line show results reported for patients with hypertension given thiazides.[12]

VARIABILITY BETWEEN PATIENTS

Table II shows that the standard deviation of values after treatment is not much greater than before treatment, which suggests that the fall does not vary much between individuals. The calculated standard deviation of the fall after thiazides is 0·22 mmol/l with a mean fall of 0·6 mmol/l.

Discussion

This survey of publications and analysis of published data supports long-held beliefs about the effect of diuretics on serum potassium concentrations and challenges others. Most of the studies we have included date from the early 1960s as after that potassium supplements were given routinely. The analysis also combines data from different countries with differing intakes of potassium, differing ethnic groups, and differences in the severity of disease. Nevertheless, the conclusions drawn from all these studies taken together support the findings from smaller, individual studies.

The characteristics of the fall in serum potassium concentration after taking diuretics, such as its time course, dose-response curve, and differences between drugs, have been noted previously but not studied in detail. The onset is rapid but not progressive, and the dose-response curve is flat. There are major differences among the various diuretics; in particular, frusemide causes a much smaller fall in serum potassium concentration than do the thiazides in the commonly used doses as reported in individual studies.[14] Bumetanide probably causes a similar fall in serum potassium value to frusemide,[15] although there are few, if any, studies with bumetanide or ethacrynic acid in which no potassium supplements were given. There is therefore no support for the belief that potassium supplements are much more important with the potent loop diuretics than with the thiazides.

The effect of diuretics on serum potassium values has not previously been compared in different diseases. The fall in serum potassium concentration after a given drug is similar in hypertension and heart failure. Unfortunately, there is insufficient data for renal disease and cirrhosis, where there might be a greater fall in the serum potassium value because of secondary hyperaldosteronism.

FREQUENCY OF HYPOKALAEMIA

The frequency of hypokalaemia after diuretics depends on the initial value as well as the fall in serum potassium concentration. The frequency of hypokalaemia is less in patients with heart failure than in patients with hypertension, because the patients with heart failure have a higher serum potassium concentration before treatment. In cirrhosis the serum potassium value tends to be low even before treatment,[16 17] and the frequency of hypokalaemia in patients with cirrhosis who are taking diuretics is therefore probably much greater than in patients with hypertension or heart failure. In renal failure the frequency of hypokalaemia would be less because of a relatively high serum potassium concentration before treatment.

Some treatment is regularly given to prevent or correct the hypokalaemia caused by diuretics. The most common treatment is potassium supplements, but our analysis of the published data suggests that conventional doses of potassium have a relatively small effect on the average serum potassium concentration (see also Schwartz and Swartz[18]). In practice, however, even a small effect on the average serum potassium concentration will have a surprisingly large effect on the frequency of hypokalaemia, because of the curved relationship between them (fig 2). If potassium supplements diminished the fall in serum potassium concentration after thiazides (from 0·66 to 0·34 mmol/l) the frequency of hypokalaemia would decrease from 48% to 17%. The potassium-sparing diuretics,

however, were, on average, more effective than potassium supplements in preventing or correcting the fall in serum potassium value and are the treatment of choice when this fall is likely to be harmful.

Perhaps the most important aspect of this study is that it has defined for the first time in detail the magnitude of the fall in serum potassium concentration and its relation to the frequency of hypokalaemia after diuretics. The average fall in serum potassium value was 0·6 mmol/l after thiazides and 0·3 mmol/l after frusemide. As a result about half the patients taking thiazides because of hypertension will have a serum potassium value of less than 3·5 mmol/l, but only 7% will have one of less than 3·0 mmol/l. In patients with heart failure taking frusemide (by far the most commonly prescribed diuretic in this condition) calculations suggest that the corresponding figures are 5% less than 3·5 mmol/l and 0·2% less than 3·0 mmol/l

CLINICAL CONSEQUENCES

What are the clinical consequences of a fall in serum potassium concentration of this magnitude? Most experimental potassium depletion has resulted in much lower values than those considered here. In a large clinical study Davidson and Surawicz[19] found little evidence to suggest that a serum potassium value between 3·0 and 3·5 mmol/l was harmful. Most other studies with diuretics have failed to find any clinical consequences from the fall in serum potassium concentration[20 21] and this bears out general clinical experience. Although in one recent study some patients whose serum potassium value dropped to the range 3·0-3·5 mmol/l had arrhythmias,[22] most evidence suggests that only values less than 3·0 mmol/l are potentially harmful to the patient. These results and our calculations, therefore, suggest that the dangers of hypokalaemia in hypertension and heart failure have been exaggerated simply because it has not been appreciated that the fall in serum potassium concentration is so small.

There has been increasing argument against the need to prescribe routine potassium supplements in hypertension.[11 13 21] This review suggests that we should now question the need to give potassium supplements routinely when patients with heart failure are given loop diuretics. Previous recommendations[23] have been based on the fear of digoxin toxicity with hypokalaemia and a large apparent deficit of body potassium in heart failure. That view, however, does not take account of the small fall in the serum potassium concentration after frusemide and recent studies, which suggest that the deficit in body potassium, if present at all, is small.[24 25]

Most patients who are given diuretics fall into one of two groups. The majority have heart failure or hypertension and are treated in general practice with little or no monitoring of serum potassium values. This review suggests that the risks of appreciable hypokalaemia (say, less than 3·0 mmol/l) are small in this group, and the need for routine potassium supplements is not clear. Indeed, some have argued[26] that the widespread routine use of potassium supplements do more harm than good, because of the risk of hyperkalaemia.

The second and much smaller group of patients have severe heart failure or renal or liver disease, and are under supervision in hospital, including monitoring of the plasma potassium concentration. When a patient in this group has a plasma potassium value low enough to justify treatment (say, less than 3·0 mmol/l) it could be argued that the treatment of choice is a potassium-sparing diuretic, which is more effective, more convenient, and not much more expensive than potassium supplements.

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The full list of references on which the review is based may be obtained from the authors on request.

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Are a pregnant woman's gums more likely to bleed than when she is not pregnant?

Yes. Hypertrophy of the gums is commonplace in pregnancy, ranging from being very slight to sometimes very gross. Bleeding is therefore not uncommon either. The hypertrophy is probably a response to oestrogens affecting the ground substance of the connective tissue, as they do throughout the body.[1]

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