Diuretics and potassium in the elderly

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The perceived clinical wisdom has it that diuretics (thiazide and loop) prescribed for chronic cardiac failure often lead to potassium depletion [1] and, further, that in the elderly this complication is both more frequent and more profound [2,3]. Consequences of significant potassium depletion (increased cardiac irritability and muscle weakness) are such that seemingly appropriate preventive action by the use of potassium supplements or potassium-sparing agents is mandatory when treating elderly patients with cardiac failure. This approach is emphasised and reinforced by the endless deluge of advertising literature from pharmaceutical firms, especially those promoting potassium-sparing diuretics. Whilst the pros and cons of ‘potassium therapy’ in the treatment of hypertension have been debated [4–7], this is not so for cardiac failure. Confusion often exists over the relationship between total body potassium and blood levels; the effects of normal ageing on potassium status (most patients with cardiac failure are elderly); the effect of cardiac failure itself; different diuretics used in treatment; and finally the relevance of hypokalaemia to cardiac arrhythmias. The prevalence and significance of hyperkalaemia are rarely discussed.

The increasing tendency to indiscreet and unnecessary prescription of diuretics is widely apparent—the almost routine use of added potassium supplement or potassium-retaining diuretic combinations commonly go hand in hand with this trend. The known facts and, perhaps more importantly the unknown facts, warrant review.

Body and blood potassium

Potassium is distributed throughout the body water with 90 per cent being intracellular and only 2.5 per cent in the extracellular fluid [8]. Homeostatic mechanisms actively maintain this gradient across cell membranes. Extracellular fluid potassium concentration is measured in plasma which contains only 0.4 per cent of total body potassium. It is not surprising therefore that changes in plasma potassium reflect poorly on changes in total body stores [9].

Age and body potassium

It is true that the healthy elderly have a lower whole-body potassium than younger subjects of the same body weight [10]. They are not however ‘depleted of potassium’. With increasing age, in healthy humans lean body mass (muscles/ organs) decreases while fat stays the same or even increases. Body fat contains very little potassium (less than 8 mmol/kg) whereas lean body mass is rich in potassium (more than 100 mmol/kg) [11,12]. Thus, with increasing age, the body potassium capacity decreases so that a lower total body potassium content is entirely appropriate in the elderly even though overall body weight may have changed little [13].

Cardiac failure and potassium

It is difficult to know the relationship of cardiac failure to the plasma potassium because of the confounding effects of treatment. In the days prior to the introduction of effective diuretic agents, many patients with cardiac failure died of hyperkalaemia. In a review of the literature Morgan and Davidson [14] found that the plasma potassium of patients with cardiac failure before treatment was much higher than in hypertensive patients before treatment. It is likely therefore that cardiac failure itself does not lead to hypokalaemia, but rather the opposite.

Methodological considerations

The assessment of body potassium in cardiac failure has been beset by problems of method and selection. Measurement of plasma or red cell potassium are poor reflections of the total body content [15,16]. Isotopic dilution measurements of body potassium content are satisfactory in both young and old healthy subjects [17,18]. There have been many reports over the last 30 years of exchangeable potassium measurements in cardiac failure [19–23]. Most of these studies have recorded a 20–30 per cent reduction in cardiac failure patients, on a
variety of treatments compared with predicted values. There are two isolated reports showing no reduction in exchangeable potassium in treated cardiac failure [24,25]. A few studies have ascribed this apparent reduction in exchangeable potassium to a reduction in potassium capacity—muscle wasting or cardiac cachexia [26–29]. However, it is now appreciated that total exchangeable measurements of potassium variously underestimate the total body content in states of past or present fluid retention [30,31], including patients with oedema-free cardiac failure [32]. The most accurate assessment of total body potassium is provided by the measurement of naturally occurring $^{40}$K, using a total body counter [33]. Unfortunately, this method of measurement is expensive and not readily available.

One final methodological problem is related to the particular difficulty in determining what is the normal or expected value of an individual total body potassium, especially if the subject or patient is elderly [34]. The bulk of patients with chronic cardiac failure are elderly. An independent measure of potassium capacity is probably best arrived at by some estimate of the lean body or fat-free mass [35].

Treatment of heart failure and potassium status

Body potassium and diuretics

Diuretic agents used for the treatment of cardiac failure have been blamed for a reduction in total exchangeable potassium [36–38]. In an extensive review of the literature, Morgan and colleagues concluded that there was no evidence that there was any depletion in exchangeable potassium which could be attributed to the use of diuretics [39]. This seems to be confirmed by a few reports of body potassium measurements, using the more accurate method of whole body counting, which have demonstrated little or no reduction in body stores and no evidence that diuretics are implicated in any way [40–43]. A similar conclusion based on studies of total body potassium in elderly cardiac failure patients has been reported by ourselves [35,44].

Plasma potassium and diuretics

Numerous surveys attest to the fact that diuretic agents (thiazides and loop agents) seem to lower the plasma potassium, supposedly via their kaliuretic action [6,42,45–48]. The results of these studies and others were well summarised by Morgan and Davidson [14] who concluded that thiazide diuretics reduce plasma potassium by, on average, 0.6 mmol/l and loop diuretics by, on average, 0.3 mmol/l. In other large surveys the proportion of patients found to be variably hypokalaemic ranged from 3.6 per cent [49,50] to 4.9 per cent [51].

At what level is hypokalaemia clinically relevant and dangerous? It has been suggested that levels above 3.0 mmol/l do not indicate the need for potassium, and that added potassium is sometimes ‘cosmetic’ [7,47,52,53]. On the other hand, others claim that even a modest hypokalaemia of less than 3.5 mmol/l, could predispose patients to cardiac arrhythmias. It is said that the electrical stability of the myocardial cell is more dependent on the extracellular potassium concentration than the intracellular level [54–56].

The MRC working party on mild to moderate hypertension [57] studied the relationship between ventricular extrasystoles and thiazide treatment. Their findings can be summed up as follows:

1. With short-term thiazide treatment, in spite of the expected plasma changes, there was no significant increase in the number of ventricular extrasystoles.

2. In long-term thiazide treatment, counts of ventricular ectopics were significantly higher, but no significant association of ventricular ectopics and plasma potassium levels could be shown. However, the correlation between the number of extrasystoles and the plasma urate concentrations was significant.

3. Pooled data from both groups did show a significant correlation between the numbers of extrasystoles and the plasma potassium, but the association with plasma urate levels was similarly strong. These workers point out that the biochemical changes may only be markers of thiazide intake, and do not prove that in the chronic situation hypokalaemia has a causal relationship to ectopic activity.

Do potassium supplements prescribed with diuretics prevent the modest reduction in plasma potassium? The answer is probably that they have very little practical effect in the doses usually prescribed [41,50,53,58]. Davidsen and colleagues [59] demonstrated that potassium supplements in a dose of 48 mmol/day did slightly raise the average plasma potassium by 0.1–0.2 mmol/l in a group of patients with chronic diuretic treated cardiac failure, but this effect was not sustained. In a group of elderly out-patients taking long-term diuretics, Krakauer and Lautritten [60] found that women were somewhat more likely to be hypokalaemic than men but potassium supplements did not influence the plasma potassium in either sex. It is possible that in some of these studies, the dose of potassium was too low and that higher doses might have had more effect. Fixed combination diuretic/potassium tablets containing 7 mmol of potassium are useless [61].

There is however a paradox. Potassium supplements given with diuretics are associated in a number of patients with the development of significant hyperkalaemia [51,62]. Most surveys of electrolyte abnormalities associated with diuretic usage have concentrated on hypokalaemia and so the incidence of hyperkalaemia is less well defined. However, Lawson [51] found hyperkalaemia in 179 out of 4,921 (3.6 per cent) patients taking potassium supplements; 21 patients in whom the hyperkalaemia was life threatening and a further seven patients in whom it was a contributory cause of death. In all, adverse reactions occurred in 283 patients (3.8 per cent). Gastrointestinal disturbances developed in 1.6 per cent. The frequency of hyperkalaemia was significantly related to increasing age, and was more common when supplements were given for presumed body potassium depletion or administered by the oral and intravenous routes simultaneously. The presence of deteriorating renal function
was powerfully associated with the development of hyperkalaemia and may explain the relationship with age. Elderly patients with cardiac failure are especially at risk because of the age-related decline in glomerular filtration rate, potentiated by the cardiac failure.

There are other case reports and supporting reviews of the dangers of hyperkalaemia [63-66]. Again, most reports have implicated, to a greater or lesser extent, the association with impaired renal function [67]. In contrast to the incidence of hyperkalaemia, Lawson [51] found that out of 1,294 patients receiving diuretic agents without potassium supplementation, only 63 (4.9 per cent) became hypokalaemic and in no case was this life threatening.

Studying the clinical toxicity of frusemide, Greenblatt et al. [49] reviewed 2,367 hospitalised patients, of whom 320 had chronic cardiac failure and 52 were hypertensive. Hypokalaemia developed in 4.6 per cent of patients without potassium supplement or potassium-sparing diuretic, and even in 3 per cent taking supplements or potassium-sparing agents. Lowe et al. [50] reported a similar finding of hypokalaemia in 3.6 per cent of patients. None had overt symptoms. It was suggested that potassium supplements only be used in circumstances of maximum risk (grossly oedematous patients with a brisk diuresis). Unfortunately, many practitioners, believing that potassium supplementation is essential, when prescribing diuretics for the elderly, see the various diuretic combinations with a built-in potassium retaining facility as a convenient option, obviating the need for additional medication (potassium). One forgets that the ‘placebo’ has a role not only for patients but for doctors themselves. It is very tempting, when faced with the anxiety of creating possible potassium depletion, to give routine potassium supplements. Even more potentially dangerous, is the attraction of the various potassium-retaining diuretics. In fact, from time to time, one finds patients on a potassium-retaining diuretic and added potassium—obviously a very dangerous combination. It is clear that many colleagues are unaware of the insidious, potentially lethal effects of potassium-retaining drugs in the elderly [62,68,69].

Potassium supplements are still amongst the most widely prescribed drugs to patients of all ages but especially to the elderly [42,70]. Although the plasma potassium may fall with the use of diuretics, it rarely falls to dangerous levels, and is not directly associated with a reduction in exchangeable or total body potassium. As we have seen, hyperkalaemia is in fact more likely to threaten life than hypokalaemia.

Non-steroidal anti-inflammatory drugs

There is a high incidence of musculo-skeletal and articular disorders among the aged. It is not surprising that non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to elderly patients already taking diuretics for the treatment of chronic cardiac failure. The danger of using the NSAIDs in combination with diuretics (especially potassium retaining diuretics) is frequently overlooked. The NSAIDs, by inhibiting the renal syn-

thesis of prostaglandin E, can impair the renin-angiotensin system. In this way renal blood flow and glomerular filtration rate can be further reduced and so too can potassium excretion. A potentially lethal rise of the plasma potassium can occur in these circumstances. An iatrogenic state of hyporeninaemic hypoaldosteronism can thus be induced. The striking finding is often a grossly elevated plasma potassium level with a relatively modest rise in the blood urea. Predisposing clinical conditions include underlying chronic renal insufficiency, advanced age, arteriosclerosis and diabetes [71-76].

A practical approach

The dietary intake of potassium regarded as normal is in the range 50-150 mmol/day [77]. Judge et al. [78] estimated the dietary intake of potassium in 46 men and 88 women randomly selected from persons 65 years and over living in their Glasgow homes. The mean intake was 71 mmol/day in men and 54 mmol/day in women. The sex and age differences were largely eliminated when lean body mass was taken into account. Daily urinary excretion of potassium averaged 51 mmol and 44 mmol in men and women respectively, similarly related to lean body mass. About 5-8 mmol/day are lost in the faeces. A negative balance could be expected if the dietary potassium was less than 27 mmol/day in men and 35 mmol/day in women. Thus, it may be assumed that the elderly are potentially more at risk of developing potassium depletion when there is increased potassium loss. However, this is unlikely to be a major problem in elderly patients with cardiac failure and other factors leading to hypokalaemia (Table 1) should not be forgotten.

We would suggest that the following approach is

| Table 1. Some common causes of hypokalaemia in the elderly. |
|-------------------------------------------------------------|
| **Metabolic** | **Excessive loss:** |
| Glycosuria | Gastrointestinal |
| Alkalosis | Diarrhoea |
| Respiratory | Laxatives |
| Metabolic | Vomiting |
| | Ileostomy |
| | Renal |
| | Tubular Acidosis |
| | Hyperaldosteronism |
| **Acute (myeloid) leukaemia** | |
| **Drugs** | Mineralocorticoids |
| | Carbenoxolone |
| | Gentamicin |
| | Penicillin |
| | Carbenicillin |
Table 2. Important dietary sources of potassium.

| Substance          | Potassium Content (mmol K/100g) |
|--------------------|----------------------------------|
| Bananas (peeled)   | 9.0                              |
| Oranges (peeled)   | 5.1                              |
| Rhubarb, with sugar| 10.2                             |
| Chocolate (milk)   | 10.8                             |
| Marmite            | 66.6                             |
| Grapefruit juice   | 84.0                             |
| Tomato juice       | 20.1                             |
| Avocados           | 30.8                             |
| Beans (baked)      | 23.0                             |
| Milk               | 10.8                             |
| Raisins            | 22.0                             |

Figures from McCance and Widdowson [79].

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Practical and safe:
1. Use diuretics with discretion and only when indicated and essential. Try to avoid being pressurised into using them for cosmetic reasons, e.g. postural oedema secondary to immobility and local factors.
2. Choose the gentlest effective diuretic. Opt initially for a thiazide type of diuretic if adequate. In any case, thiazides are more convenient than loop diuretics for elderly patients with borderline continence and problems with mobility.
3. Routinely counsel patients to include appropriate sources of potassium in their diets (Table 2).
4. The serum electrolytes and urea should be checked before prescribing the diuretic, and repeated at two and four weeks after commencing the drug. If the plasma potassium is reproducibly below 3.0 mmol/l, and only after a search for ‘non-diuretic’-induced causes of hypokalaemia (Table 1), should a potassium supplement be prescribed.
5. Consider potassium supplementation under the following conditions:
   (a) Pre-existing hypokalaemia discovered before initiating diuretic therapy having excluded other causes. This situation is perhaps more likely to arise in elderly women.
   (b) Likelihood of excessive potassium loss from the gastrointestinal tract or from the kidney due to intrinsic renal disease.
   (c) The coincident use of certain drugs, such as steroids or glycyrrhizic acid derivatives (carbenoxolone).
   (d) The presence of secondary hyperaldosteronism, as is likely with cirrhotic ascites, nephrotic syndrome or severe prolonged congestive heart failure.

If added potassium is deemed necessary, use an effervescent form of potassium chloride in adequate dosage. Traditional, small doses need to be questioned [60,61].
6. If, for some reason, even the addition of adequate potassium chloride is not effective, only then add a potassium-retaining diuretic. However, if this proves necessary, it is wise to monitor the urea and electrolyte levels from time to time, particularly when a change in the clinical circumstances (any superimposed acute illness with dehydration) causes a further fall in renal function.
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