MEDICAL PRACTICE

Occasional Review

Hyperkalaemia in patients in hospital

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Abstract

Significant hyperkalaemia occurred in 406 out of 29 063 patients admitted to a major Scottish teaching hospital in one year (1·4%). Mortality was higher in these patients than in control patients and was strongly correlated with the severity of the hyperkalaemia. Overall seven deaths were directly due to hyperkalaemia (out of 58 deaths among patients with hyperkalaemia). Factors contributing to a poor prognosis were severity and speed of onset of hyperkalaemia and the presence of appreciable renal impairment. Patients with hyperkalaemia were older and more likely to be male; this trend was present in all diagnostic subcategories. Genitourinary disease, gastrointestinal disease, and cancer were significantly more common among the patients with hyperkalaemia than the controls. Hyperkalaemia due to drug treatment was invariably mild and non-fatal, whereas genitourinary disease was often associated with moderate to severe hyperkalaemia, which in two cases proved fatal. Use of electrocardiographic monitoring was rare, and although the treatment of hyperkalaemia was effective, it was often used when not required. Hyperkalaemia is a potential hazard in diabetic ketoacidosis, and use of potassium supplements should be carefully monitored during correction of the acidosis.

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Introduction

Hyperkalaemia is generally considered to constitute a major life threatening event if severe.[1] Little information has been published, however, on the overall incidence with which it occurs in large inpatient populations. Several workers have highlighted its occurrence in patients given potassium supplements and potassium sparing diuretics.[2 3] Lawson *et al* reported that the incidence of life threatening hyperkalaemia in patients in hospital with heart failure who received potassium supplements was 1·3/1000.[4]

We describe a study in which we assessed the incidence of hyperkalaemia over one year in a busy Glasgow teaching hospital. We aimed to identify the conditions most often associated with hyperkalaemia, to determine which group of patients were at greatest risk within a given diagnostic category, and to evaluate the efficacy of treatment.

Patients and methods

From September 1980 details of all patients whose serum electrolyte concentrations had been measured at least once in this hospital were reviewed using the computerised record system of the biochemistry department. There were 29 063 such patients. The normal reference range for serum potassium concentration in this laboratory is 3·5-4·5 mmol(mEq)/l. Subjects were regarded as having significant hyperkalaemia if the serum potassium concentration was 6·0 or more mmol/l on one occasion and 5·5 or more mmol/l subsequently. This two stage procedure was adopted to exclude spurious results arising from in vitro haemolysis and to avoid excluding patients whose hyperkalaemia had been treated promptly by appropriate treatment. The details of these patients obtained from the computer included name, ward, age, sex, hospital number, and serum electrolyte concentrations.

A total of 429 patients fulfilled the criteria for significant hyperkalaemia during the year of the study. All were visited by one of us (BP) within 48 hours of identification and followed up thereafter for 12 days unless death or discharge intervened. Of the original 429 patients, 23 were excluded, 18 because the persistent hyperkalaemia was shown to be due to regular incorrect sampling from an intra-

venous infusion line containing potassium supplements and five because of pseudohyperkalaemia arising from in vitro leakage of potassium from abnormal blood cells, three of these five patients having leukaemia and two thrombocytosis.[5 6] In all five patients the diagnosis of pseudohyperkalaemia was verified by the finding of normal potassium concentrations when heparinised blood was transported and assayed immediately after withdrawal. Thus 406 patients (1·4%) had significant hyperkalaemia as defined above in the year of study.

Patients with hyperkalaemia were evaluated to determine the suspected aetiology of the abnormality and the effect of treatment thereon. To facilitate detailed analysis the patients were classified into three mutually exclusive groups according to the severity of the abnormality: group 1, serum potassium concentration 6·0-6·4 mmol/l; group 2, serum potassium concentration 6·5-6·9 mmol/l; and group 3, serum potassium concentration $\geqslant$7·0 mmol/l.

For comparison a control group of 1218 subjects was obtained from the original data source of 28 657 patients without hyperkalaemia to provide a ratio of three controls to one patient with hyperkalaemia. Data were obtained as before, and in both groups of patients the hospital number was used to obtain details of condition on discharge, duration of hospital stay, and diagnosis at discharge from records collected centrally by the Scottish Home and Health Department.[7] Details of the method of obtaining this information have been reported previously.[8]

Results

The average age of the 406 patients found to have significant hyperkalaemia was 58$\pm$1·6; this was significantly older than the age of the 1218 randomly selected controls (55$\pm$1·2 years, $p<0·01$). Similarly, there was a significantly greater proportion of men among the patients with hyperkalaemia (232 (57%)) compared with the controls (626 (51·4%); $\chi^2_1=4·0$, $p<0·05$). Fifty eight patients with hyperkalaemia died (14·3%) compared with only 71 controls (5·8%) ($p<0·01$).

Of the 406 patients with hyperkalaemia, 244 (60%) had a mild increase in serum potassium concentrations (group 1), 93 (23%) had a moderate increase (group 2), and the remaining 69 (17%) had severe hyperkalaemia (group 3). There was a positive correlation between the severity of hyperkalaemia and serum creatinine concentration on admission, serum bicarbonate concentration, and mortality (table I). By contrast, there was no relation between sex and the severity of the hyperkalaemia (table I).

TABLE I—*Severity of hyperkalaemia related to sex, serum creatinine concentration on admission, and mortality*

	Controls	Patients with hyperkalaemia		
		Group 1	Group 2	Group 3
Potassium (mmol/l)	3·5-4·5	6-6·4	6·5-6·9	$\geqslant$7·0
No of subjects	1218	244	93	69
No (%) of men	626 (51)	143 (59)	50 (54)	39 (57)
No (%) dying	71 (6)	22 (9)	17 (18)	19 (28)
Mean ($\pm$SD) serum creatinine (μmol/l):				
Men	125$\pm$10	257$\pm$25	352$\pm$47	535$\pm$78
Women	110$\pm$10	245$\pm$23	336$\pm$45	489$\pm$74
Mean serum bicarbonate (mmol/l)	28$\pm$2	24$\pm$1·3	20$\pm$1·3	17$\pm$1·3

Conversion: SI to traditional units—Potassium: 1 mmol/l = 1 mEq/l. Creatinine: 1 μmol/l = 11·3 μg/100 ml. Bicarbonate: 1 mmol/l = 1 mEq/l.

Hyperkalaemia was first noted on admission in 73 patients (18%), during the first five hospital days in 110 (27%), and after the fifth day of admission in 223 (55%).

PRIMARY DIAGNOSIS

The primary discharge diagnoses of genitourinary disease ($\chi^2_1=43$, $p<0·001$), gastrointestinal disease ($\chi^2_1=11·4$, $p<0·01$), and cancer ($\chi^2_1=4·1$, $p<0·05$) occurred more commonly in the patients with hyperkalaemia than the controls (table II). The observed overall excess of men among the patients with hyperkalaemia was present in each of these diagnostic subcategories of patients. The relation between genitourinary disease and hyperkalaemia was clearly related to potassium retention consequent on acute or chronic renal failure. By contrast, the relation between gastrointestinal disease and hyperkalaemia appeared to be a consequence of overenthusiastic replacement of potassium intravenously in patients who had undergone abdominal surgery and had mild (often transient) renal impairment postoperatively. The relation between cancer and hyperkalaemia is more complex. In the study group there was no significant excess of any one organ specific cancer that might explain the association. Rather, the hyperkalaemia, which was rarely severe, arose as a result either of tumour blocking the ureters (four cases of bladder carcinoma, two of ovarian carcinoma) or of the drugs or surgical methods used to treat the malignancy.

TABLE II—*Primary discharge diagnosis in patients with hyperkalaemia and controls (figures are numbers (%) of subjects)*

Primary discharge diagnosis*	Patients with hyperkalaemia (n = 406)	Controls (n = 1218)
Genitourinary	97 (23·9)	131 (10·8)
Cardiovascular	68 (16·7)	199 (16·3)
Accident or trauma	67 (16·5)	255 (20·9)
Gastrointestinal	62 (15·3)	113 (9·3)
Cancer	44 (10·8)	94 (7·7)
Respiratory	26 (6·4)	69 (5·7)
Other	42 (10·3)	357 (29·3)

* Based on ninth revision of International Classification of Diseases, 1977.

AETIOLOGY

The apparent aetiology of the hyperkalaemia was impaired renal function in 175 (43%), drug treatment in 151 (37%), and redistribution of potassium in 61 (15%); in 19 (5%) the aetiology was unknown. Table III shows the relation between the severity of the hyperkalaemia and the aetiology of the condition.

Renal disease—Renal elimination of potassium was impaired in 175 patients (43%). In 124 this arose during an episode of acute renal failure and in a further 47 it developed in patients with known endstage chronic renal disease. Four patients had adrenal insufficiency. Overall, these patients showed a tendency towards having moderate to severe hyperkalaemia (table III).

TABLE III—*Severity of hyperkalaemia related to apparent aetiology (figures are numbers (%) of patients)*

Apparent aetiology	Group 1 (n = 244)	Group 2 (n = 93)	Group 3 (n = 69)
Impaired renal excretion of potassium	74 (30)	58 (62)	42 (62)
Drug treatment	112 (46)	25 (27)	14 (20)
Other or unknown	58 (24)	10 (11)	12 (17)

Drug treatment was the primary aetiological factor in 151 patients (37%). In most cases (71 patients) the hyperkalaemia was attributed to oral potassium supplements, although intravenous potassium (33 patients) and potassium sparing diuretics alone (33 patients) or in combination with oral potassium supplements (14 patients) were also implicated. Moderate to severe hyperkalaemia occurred in 39 patients as a result of drug treatment, almost exclusively in those treated with both oral potassium and potassium sparing drugs and in those receiving intravenous potassium supplements in the presence of renal impairment.

Redistribution of potassium was the apparent aetiology in 61 patients (15%); catabolic states were present in 49 and severe acidosis in 12.

Twelve patients with acute diabetic ketoacidosis were found to have appreciable hyperkalaemia. This was moderate to severe in eight cases: in four it was present on admission, but in the other four it resulted from a combination of renal impairment and excessive intravenous potassium replacement during early phases of treatment (table IV).

DEATH IN PATIENTS WITH HYPERKALAEMIA

Although 58 patients with hyperkalaemia died during admission, death was directly attributable to hyperkalaemia in only seven, in whom cardiac arrhythmias occurred when the serum potassium

concentration was grossly raised. In all seven renal impairment was considerable; it was accompanied by acute pancreatitis in three and acute hepatic failure in two. None of these seven patients had received potassium supplements during their admission, and none received calcium gluconate before the terminal arrhythmia. Electrocardiographic monitoring was infrequent during the period of hyperkalaemia, and in only one patient were the classical electrocardiographic changes of hyperkalaemia recorded.

TABLE IV—*Serum electrolyte concentrations in patients with hyperkalaemia and diabetic ketoacidosis (expressed as means ± SD)*

	Potassium (mmol/l)		Creatinine on admission (μmol/l)	Total intravenous supplements over 24 hours
	On admission	At 12 hours		
Mild hyperkalaemia on admission (n = 4)	6·2 ± 0·08	4·9 ± 0·2	123 ± 28	102 ± 18
Moderate to severe hyperkalaemia on admission (n = 4)	6·7 ± 0·15	5·2 ± 0·15	138 ± 18	92 ± 28
Hyperkalaemia due to treatment (n = 4)	5·9 ± 0·2	6·7 ± 0·05	230 ± 28	108 ± 18

All seven patients who developed fatal arrhythmias had had normal serum potassium concentrations within the 36 hours before the onset of arrhythmia. Such rapid increases in potassium concentrations were noted only in those seven patients. By contrast, patients in group 3, who had potassium concentrations persistently above 7·0 mmol/l (usually associated with chronic renal failure), did not develop fatal cardiac arrhythmias, and the classical changes of hyperkalaemia were not recorded on the electrocardiograph in any of these subjects, raising the possibility that the deaths associated with hyperkalaemia were due to the rate of change of potassium concentrations or that the potassium ion interacts with another ion, such as magnesium, before exerting its full toxic potential.

TREATMENT

The treatment of hyperkalaemia varied widely. In virtually all the 150 cases in whom hyperkalaemia was attributed to drug treatment stopping the drug implicated was sufficient to correct the abnormality. Cation exchange resins were given to 102 patients (25%) and in 22 of the 69 patients in group C (20%) were the only treatment prescribed. Hypokalaemia after successful treatment with exchange resins occurred mainly in patients after gastrointestinal surgery, or with subacute obstruction or ileus in whom hyperkalaemia was relatively mild or retention of the ion exchange enema was prolonged. Glucose insulin treatment was used in 63 patients and appeared highly effective. Nevertheless, 14 of these patients had pretreatment potassium concentrations below 6·5 mmol/l and so the need for this treatment was not clearly shown. Peritoneal dialysis and haemodialysis were used in 80 patients and were highly effective in treating hyperkalaemia of all degrees accompanying renal impairment. Calcium gluconate was used in 22 patients with moderate to severe hyperkalaemia to reduce the risk of them developing potassium induced arrhythmias. Forty one patients did not receive any treatment.

Electrocardiography was used infrequently as an aid to diagnosis or to monitor the effect of treatment. In only 42 of the 162 patients (26%) in groups 2 and 3 was continuous electrocardiographic monitoring used to assess progress.

Discussion

Hyperkalaemia is a common life threatening medical emergency[1] and is most important when the potassium concentration is greater than 6·0 mmol/l.[9] In this study 406 out of 29 063 consecutive patients admitted to hospital developed significant hyperkalaemia, of whom seven patients died as a direct result of potassium cardiotoxicity. Pseudohyperkalaemia was recognised in five patients and constitutes an important entity since attempts to correct this artefact might give rise to profound life threatening hypokalaemia.

A highly significant excess of men was present in all diagnostic categories of patients with hyperkalaemia. No satisfactory explanation of this was apparent, but it contrasts with a significant excess of women reported in patients with hypokalaemia.[8] These observations suggest that there are differences in potassium handling between the sexes, which require further evaluation.

An excess of genitourinary and gastrointestinal diseases was found in the patients with hyperkalaemia, which could readily be explained on physiological grounds. An association between cancer and hyperkalaemia, however, was less readily explained. No specific malignancy predominated, but gross muscle wasting, tumour necrosis, and the catabolic effect of steroids and cytotoxic drugs may all result in increased release of potassium from the intracellular compartment, and this together with impaired renal function from dehydration, operative procedures, or obstructive lesions in the urinary tract probably accounted for the observed association.

Renal failure and drug treatment were the commonest causes of hyperkalaemia. The severity of hyperkalaemia correlated well with creatinine concentration on admission, and, as expected, severe hyperkalaemia occurred most often in association with renal failure. Combination potassium treatment and excessive intravenous potassium supplementation accounted for most cases of severe hyperkalaemia due to drug treatment, confirming previous reports.[2 3 10]

Current treatment of active diabetic ketoacidosis includes early administration of intravenous potassium supplements.[11] Four diabetics with renal impairment in this study received potassium supplements routinely, and all developed prolonged moderate to severe hyperkalaemia during the early stages of treatment. This suggests that in diabetics with renal impairment potassium replacement should be undertaken cautiously and under full biochemical and electrocardiographic control. Although rare, severe hyperkalaemia due to potassium replacement treatment may account for some previously unexplained deaths during the early phases of treatment of acute diabetic ketoacidosis.

Seven patients with severe hyperkalaemia developed fatal cardiac arrhythmias. All seven had normal serum potassium concentrations 36 hours before the arrhythmia and all had considerable renal impairment. Patients with chronic renal failure develop severe hyperkalaemia over a longer period of time and do not appear to be at risk of potassium induced cardiotoxicity or show the classical changes of hyperkalaemia on the electrocardiogram, possibly because slowly developing hyperkalaemia allows the neuromuscular and cardiac conducting systems time to compensate for the altering potassium gradient across the membrane.[12]

The treatment of hyperkalaemia was found to be effective in most cases but in some seemed inappropriate. The most important consideration is the rapid reversal of potassium induced cardiac arrhythmias. This may be achieved by using 20 ml 10% calcium gluconate over 10 minutes and repeating this if arrhythmias recur. For less severe electrocardiographic abnormalities an infusion of 500 ml 10% dextrose with 12 units of soluble insulin will facilitate transport of extracellular potassium back into the intracellular compartment. As with calcium gluconate the effect of glucose and insulin is only temporary. Once the infusion is stopped the potassium concentrations rise rapidly again. These methods, however, allow time for other treatments specifically aimed at lowering the serum potassium concentration to be instituted. Cation exchange resins and dialysis both effectively lower whole body potassium concentrations. When the hyperkalaemia is severe or associated with gross electrolyte disturbance as in severe renal failure or in association with extensive tissue destruction such as is seen after crush injuries peritoneal dialysis or haemodialysis is necessary. Cation exchange resins either by mouth or by enema are effective in mild hyperkalaemia or when it is due to exogenous potassium loading, but their action is slow and unpredictable. Their use should be confined mainly to patients

whose potassium concentrations are moderately raised and in whom there is no electrocardiographic upset.

We conclude that although hyperkalaemia is common in patients in hospital, it is rarely life threatening. Those with rapidly increasing potassium concentrations, in the presence of renal failure, are most at risk of developing potassium cardiotoxicity. Patients in this high risk group should undergo continuous biochemical and electrocardiographic monitoring. Acute cardiac toxicity induced by hyperkalaemia should be reversed promptly with calcium gluconate, while severe abnormalities will respond readily to glucose and insulin treatment. Cation exchange resins should be used to correct moderate hyperkalaemia due to excess potassium loading and dialysis when hyperkalaemia is severe or due to diminished potassium excretion.

References

[1] Stephen ST, Dluhy RG. Hyperkalaemia and hypokalaemia. *JAMA* 1975;**6**:631-3.

[2] Lawson DH. Adverse reactions to potassium chloride. *Q J Med* 1974; **171**:433-40.

[3] Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone. *JAMA* 1973;**1**:40-3.

[4] Lawson DH, O'Connor PC, Jick H. Drug attributed alterations in potassium handling in congestive heart failure. *Eur J Clin Pharmacol* 1982;**23**:21-5.

[5] Bronson WR, DeVita VT, Carbonne PP, Cotlove E. Pseudohyperkalaemia due to release of potassium from white blood cells during clotting. *N Engl J Med* 1966;**274**:369-75.

[6] Hartmann RC, Melinkoff SM. The relationship of platelets to the serum potassium concentration. *J Clin Invest* 1955;**4**:938-40.

[7] Heasman MA. Scottish hospital inpatient statistics—sources and uses. *Health Bull* 1968;**26**:10-3.

[8] Lawson DH, Henry DA, Lowe JM, Gray JMB, Morgan HG. Severe hypokalaemia in hospitalised patients. *Arch Intern Med* 1979;**139**: 978-80.

[9] Levinsky NG. Management of emergencies: VI hyperkalaemia. *N Engl J Med* 1966;**274**:1076-7.

[10] Shapiro S, Slone D, Lewis GP, Jick H. Fatal drug reactions among medical inpatients. *JAMA* 1971;**3**:467-72.

[11] Alberti KGMM. Low dose insulin in the treatment of diabetic ketoacidosis. *Arch Intern Med* 1977;**137**:1367-76.

[12] Surawicz B, Chlebus H, Mazzoleni A. Haemodynamic and electrocardiographic effects of hyperpotassaemia. Differences in response to slow and rapid increases in concentration of plasma K. *Am Heart J* 1967;**73**:647-51.

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New Drugs

Alpha-blockers and converting enzyme inhibitors

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Alpha-blockers and converting enzyme inhibitors have been introduced for the treatment of hypertension and more recently in refractory congestive cardiac failure. These drugs cause dilatation of both the arterial and venous side of the circulation by specific mechanisms: antagonism of catecholamines at alpha receptors and prevention of angiotensin II generation respectively.

The principal role of these drugs at present is in the more severe or resistant grades of hypertension. Several new treatment strategies have emerged, however, for the management of congestive cardiac failure. Traditional therapeutic approaches have included the use of diuretics and cardiac glycosides. In addition, drug treatment is now used also to produce vasodilatation. On the arterial side of the circulation this will reduce the load against which the heart must pump (afterload), while on the venous side there will be a reduction in blood volume load delivered to the failing heart (preload). Alpha-blockers and converting enzyme inhibitors not only have beneficial acute haemodynamic effects but may lead to longer term improvement in patients who are refractory to more conventional management.

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Alpha-blockers

Prazosin, labetalol, and indoramin are alpha-adrenoceptor antagonists, but only prazosin shows this as its sole effect at doses used and concentrations achieved therapeutically. Labetalol is primarily a beta-adrenoceptor antagonist with modest alpha-blocking activity. Indoramin is an alpha-adrenoceptor antagonist but also has a range of additional pharmacological effects.

Alpha-adrenoceptors exist in at least two forms. $Alpha_1$-receptors are found on postsynaptic membranes such as the smooth muscle of arteries and veins. Stimulation of these receptors by catecholamines leads to vasoconstriction. $Alpha_2$-receptors are found both peripherally and in the central nervous system. In the periphery they have been identified on presynaptic nerve terminals and here their stimulation by catecholamines or other agonists results in a diminished release of noradrenaline. Recent reports suggest that these receptors may also be located postsynaptically and respond particularly to circulating catecholamines. In the central nervous system $alpha_2$-receptors are found primarily on postsynaptic nerve cell membranes, and their stimulation results in diminished sympathetic outflow. $Alpha_2$-receptors in the brain are also intimately concerned in the mechanisms controlling sleep, and thus a consequence of central $alpha_2$-receptor stimulation is sedation.