The management of hyperkalaemia in the emergency department

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Abstract

Life threatening hyperkalaemia (> 7.0 mmol/l) is commonly associated with acute renal failure. Moderate hyperkalaemia (6.1–6.9 mmol/l) is also common and well tolerated in patients with chronic renal failure. Renal failure is the most common cause of hyperkalaemia although other causes to consider include drugs (potassium sparing diuretics, angiotensin converting enzyme inhibitors), hyperglycaemia, rhabdomyolysis and adrenal insufficiency. Hyperkalaemia affects the cardiac conducting tissue and can cause serious arrhythmias including ventricular fibrillation and asystolic arrest. Therefore it is important to treat hyperkalaemia promptly in the emergency department. This paper evaluates the therapeutic options available for treatment of hyperkalaemia.

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Renal failure is the most common cause of hyperkalaemia seen in the emergency department.[1] Clinically significant hyperkalaemia occurs in 5–10% of patients requiring regular haemodialysis.[2] The medical management of hyperkalaemia in chronic renal failure (CRF) is similar to that in acute renal failure (ARF) except that the rate of rise in ARF is usually more rapid and treatment must be more aggressive.[3] Pseudohyperkalaemia (especially from extravascular haemolysis) is probably more common than true hyperkalaemia. Hence the plasma K should be rechecked before treatment is started unless there are electrocardiographic (ECG) changes.

Hyperkalaemia is classified as mild (K 5.5–6.0), moderate (K 6.1–6.9) or severe (K >7.0).[1] The definitive management of severe hyperkalaemia is haemodialysis. This is usually not immediately available in the emergency department (especially at weekends and nights) and other temporising measures have to be instituted. Ideally, these measures should be rapid, effective, predictable, sustained, and safe. Specific management should be tailored to the individual patient and aimed at the underlying cause while instituting treatment to reduce the raised K levels.

Insulin and glucose is the current standard acute treatment. Recently, salbutamol has been advocated as equivalent to insulin and glucose with the advantage of nebulisation as an option. This review seeks to establish the efficacy, mechanism of action, onset and duration of action and side effects of the currently used drugs in the management of moderate to severe hyperkalaemia in the emergency setting and to suggest a rationale for their effective use.

Methods

A literature search of Medline from 1993 to 1999 was performed linking the keywords "Hyperkalaemia", "Management", and "Treatment". Medline was also searched under the subject heading "Hyperkalaemia-Treatment" from 1966 to 1999. The Cochrane library was searched under similar headings and there were no systematic reviews of the subject. References from articles recovered were searched for relevant studies.

The ideal design of a study of a treatment for hyperkalaemia is one that is randomised, blinded, and controlled against a placebo or standard therapy. Table 1 illustrates a summary of studies of the treatment of hyperkalaemia. Two studies[9 15] were randomised (the method of randomisation was not stated). Two studies[2 7] were compared with placebo. The plasma K in these studies were relatively low as it would be unethical not to treat severely hyperkalaemic patients as insulin with glucose is an established treatment in an otherwise potentially fatal condition. One study[1]was double blinded. Six studies[2–15] had a crossover design to ensure uniformity in their comparisons.

Most studies examined patients with CRF; four studies[4 8 11 14] included patients with ARF. Except for the studies that included paediatric patients only,[4 14] the average age of the patients was more than 50 years. All studies excluded patients taking β blockers and most excluded patients taking digoxin. In seven trials[2 6 7 9 10 12 15] the K was only mildly increased (K<6.0 mmol/l). In four studies[2 10 12 15] between 10% and 20% of patients did not complete the treatment, mostly because of going on to dialysis. Two studies[6 9] excluded non-responders (defined as patients who had a maximal reduction in K^+ of <0.5 mmol/l after treatment) from their analysis.

Initial management

Treatment options include calcium (Ca) gluconate, insulin with glucose, salbutamol, sodium bicarbonate ($NaHCO_3$) and sodium (Na) polystyrene sulphonate.

CALCIUM GLUCONATE

There were no clinical studies looking solely at calcium in the management of hyperkalaemia. Ca gluconate antagonises cardiac membrane excitability and does not affect the plasma

Table 1 Comparison of methodology of clinical studies of drug treatments

Reference	*Sample size*	*Inclusion criteria*	*Exclusion criteria*	*Mean initial K (mmol/l)*	*Crossover design*
2	10	CRF		5.81	yes
3	8	CRF	ACE inhibitors	6.3	yes
4	13	Child <17 y; ARF and CRF		6.7	no
5	44	ARF and CRF	IHD, DM	7.0	no
6	15	CRF		5.53	yes
7	5	CRF	DM, IHD	4.29	yes
8	17	CRF (82%), ARF (18%)		7.02	no
9	34	CRF		5.8	no
10	12	CRF	DM	5.56	yes
11	44	CRF (50%), ARF (50%)	DM, IHD	7.0	no
12	10	CRF	ACE inhibitors	5.62	yes
13	10	CRF; Able to cooperate	DM	6.5	no
14	15	Children CRF (27%), ARF (73%)	Arrhythmias	6.6	no
15	11	CRF	Hypertension, IHD, DM β agonist, steroids, xanthine derivatives	5.9	yes
16	9	CRF	DM, β blockers, digoxin, ACE inhibitors	5.99	yes
17	45	CRF	DM, asthma, IHD	>6.0	no
18	9	CRF	DM	6.33	no

IHD = ischaemic heart disease, DM = diabetes mellitus, ACE = angiotensin converting enzyme.

K.[1 19] It is generally accepted that calcium should be given when there are ECG changes associated with hyperkalaemia.[7 20] The sensitivity of emergency physicians diagnosing moderate to severe hyperkalaemia (K >6.5) from the ECG is only 62%.[18] The ECG changes[1 21] include tall T waves >5mm (K 6–7), small broad P waves or absent P waves, wide QRS complex (K 7–8), sinusoidal QRST (K 8–9) and atrioventricular dissociation or ventricular tachycardia/fibrillation (K >9). Twenty ml 10% Ca gluconate[19] is given intravenously in adults (0.5 ml/kg in children[8]) over 5–10 minutes and may be repeated as necessary. Onset of action is immediate but its duration is only a few minutes.[1 19] Hyperkalaemic patients taking digoxin should be given calcium as a slow infusion over 20 to 30 minutes. This avoids hypercalcaemia that may potentiate the myocardial toxicity of digitalis.

INSULIN WITH GLUCOSE

Insulin binds to specific membrane receptors and via an unknown second messenger, stimulates the sodium-potassium (Na-K) adenosine triphosphatase (ATP) pump resulting in intracellular uptake of K.[5] This effect is independent of its hypoglycaemic action. Uraemia attenuates the hypoglycaemic response to insulin but does not affect its hypokalaemic action.[22 23] Insulin has been the traditional temporising treatment against which newer treatments are compared. It is indicated in every case of hyperkalaemia that needs emergency treatment. Ten units (in adults) soluble insulin is given with 40–60 g glucose intravenously as a bolus.

In children, a glucose load of 0.5 g/kg/h (2.5 ml/kg/h) should be given. This is because many of these patients increase their endogenous insulin production with the administration of a glucose load. If the blood glucose rises above 10 mml/l, insulin should be added at 0.05 u/kg/h.[24]

Seven studies[3 5 7 10 12 17 18] used insulin with glucose (table 2).

These studies show that the onset of hypokalaemic action is within 15 minutes and lasts for at least 60 minutes.[7 17] The reduction in K observed is 0.65–1.0 mmol/l.[5 10] Delayed (30–60 minutes post insulin) hypoglycaemia is common (up to 75% of patients[10]) if less than 30 g glucose is given.

SALBUTAMOL

Salbutamol binds to β_2 receptors in liver and muscle cells stimulating adenylate cyclase that converts ATP to 3'5'cyclic adenosine monophosphate. This stimulates the Na-K ATP pump resulting in intracellular K uptake.[4] The response in patients on β blockers and digoxin is attenuated. One author[22] has expressed reservation that there may be a hyperkalaemic response in the first three minutes of its administration that could be potentially deleterious. This fear was based on a baboon study[23] that used much higher doses intravenously (100 μg/kg) than have been used therapeutically in humans. Salbutamol 0.5 mg(4 μg/kg in children) is given intravenously or 10 mg of nebulised (Neb) salbutamol (in children: 2.5 mg if <25 kg or 5 mg if >25kg).

Thirteen studies[2 4–11 13–16] used salbutamol (table 3).

Table 2 Comparison of clinical studies of insulin with glucose

Reference	*Sample size*	*Dose of soluble insulin*	*Dose glucose*	*Mean initial K (mmol/l)*	*Peak reduction in K (mmol/l)*	*Time of maximal action (min)*	*Duration of effect (min)*	*Hypoglycaemia (%)*
3	8	5*	40 g	6.3	0.7	60	>60	0
5	10	10U	40 g	6.7	1.0	60	>360	20
7	5	5*	60 g	4.28	0.85	60	>60	0
10	12	10U	25 g	5.48	0.65	45	>60	75
12	10	5*	5†	5.62	0.92	60	>60	50
17	20	10U	30 g	>6.0	0.98	180	>360	0
18	9	10U	25 g	6.33	0.76	60	>60	11

*=mU/kg/min, †=mg/kg/min.

Table 3 Comparison of clinical studies of salbutamol

Route	Reference	Sample size	Dose	Mean initial K (mmol/l)	Peak reduction in K (mmol/l)	Time of maximal action (min)	Duration of effect (min)
IV	4	13	4 µg/kg	6.7	1.48	40	>120
IV	5	24	0.5 mg	7.0	1.4	30	>360
IV	6	15	0.5 mg	5.53	0.92*	30	>180
IV	8	17	4 µg/kg	7.02	1.32	40	>120
IV	9	17	0.5 mg	5.7	0.95*	30	>180
IV	11	24	0.5 mg	7.0	1.4	30	>360
IV	14	15	5 µg/kg	6.6	1.69	120	>180
IV	15	11	4 µg/kg	5.6	0.87	30	120
Neb	2	10	10 mg	5.93	0.62	90	>120
Neb	2	10	20 mg	5.81	0.98	90	>120
Neb	6	15	10 mg	5.66	0.85*	90	>180
Neb	7	5	10 mg	4.29	0.53	60	>60
Neb	9	17	10 mg	5.8	0.88*	90	>180
Neb	10	12	20 mg	5.56	0.66	60	>60
Neb	13	10	15 mg	6.5	0.9	30	>360
Neb	15	11	2.5/5 mg†	5.9	0.61	30	>300
Neb	16	9	15 mg	5.99	0.57	60	>60

*Excluded non-responders from analysis, †2.5 mg if <25 kg; 5 mg if >25 kg. IV = intravenous, Neb = nebulised.

Salbutamol produced a reduction in K of 0.87–1.4 mmol/l after intravenous administration[5 15] and 0.53–0.98 mmol/l after nebulisation.[2 7] Most studies used 10 mg nebulised salbutamol but 20 mg has been shown to be more effective at 120 minutes than 10 mg.[2] No difference was found when insulin with glucose was compared with intravenous salbutamol[5] or nebulised salbutamol.[10] Onset of action was within 30 minutes. There was no difference in maximum effect when intravenous salbutamol was compared with nebulised salbutamol.[6 9 15] However, the maximum effect was in 30 minutes for intravenous administration compared with 90 minutes for nebulisation. Tremor and tachycardia were more pronounced after intravenous treatment. Caution has been advised for use in patients with ischaemic heart disease. Some authors[6 9] suggest nebulised treatment only in these patients.

Some 12–40% patients[8 10] were unresponsive to salbutamol and it should always be used in conjunction with insulin. The cause of this unresponsiveness is unknown.[22]

Two studies[5 10] combined salbutamol and insulin with glucose (table 4). The combination of salbutamol and insulin was more effective than insulin alone in these studies. The hypoglycaemia associated with insulin was attenuated.

SODIUM BICARBONATE

$NaHCO_3$ has been recommended in textbooks for many years. It has no significant action on plasma K in the first 60 minutes after administration.[3 7 12 16] It may be indicated in severe metabolic acidosis (pH <7.2),[19 20] which may be an associated feature in ARF. Potential risks in giving $NaHCO_3$ include hypernatraemia, volume overload and tetany in patients with CRF and coexistent hypocalcaemia.

Table 5 Comparison of clinical studies of $NaHCO_3$

Reference	Sample size	Dose $NaHCO_3$ (mmol)	Concentration (%)	Mean initial K (mmol/l)
3	8	120	8.4	6.4
7	5	90	1.4	4.23
12	10	240	8.4	5.66
	10	120	1.4	5.83
16	9	2/kg	8.4	5.98

Four studies[3 7 12 16] examined the efficacy of $NaHCO_3$ (table 5) and all failed to show any reduction in K within 60 minutes.

These trials did not include patients with severe hyperkalaemia or severe metabolic acidosis. Allon and Shanklin[7] reported that $NaHCO_3$ had no additive effect on the action of insulin or salbutamol while Kim[3 16] reported that $NaHCO_3$ increased the effect of insulin and salbutamol. The patients in Kim's studies had a higher initial plasma K.

SODIUM POLYSTYRENE SULPHONATE (KAYEXALATE)

There were no clinical studies looking specifically at the efficacy of Na polystyrene sulphonate in the management of hyperkalaemia. This resin binds K in the intestinal lumen, especially large bowel and ileum.[19] It may be indicated if haemodialysis is delayed (>2–3 hours).[19] Fifty grams Na polystyrene sulphonate in 100–200 ml 30% sorbitol or 10% glucose at 37°C is given rectally and left for at least 60 minutes. Sorbitol is added as it increases faecal K excretion. The onset of action is slow, approximately one to two hours. One gram resin exchanges 1mEq Na for 1mEq K.[1] Rarely, ulceration of the bowel mucosa can occur, especially in constipated patients, and is probably attributable to to the action of sorbitol.[25] Concurrent use of a laxative helps prevent faecal impaction.

HAEMODIALYSIS

This is the definitive and most effective hypokalaemic measure.[1 22] It is indicated in severe hyperkalaemia. Mild to moderate hyperkalaemia in CRF may be managed without haemodialysis as an emergency depending on the cause. It has been reported to be of benefit in patients who have had a hyperkalaemic cardiac arrest when drug measures have failed.[26] During haemodialysis, plasma K falls rapidly in the first hour and very little thereafter.[12] If a potassium free dialysate is used, serum potassium may decrease as much as 1.2 to 1.5 mEq/h.[27] Potassium concentrations show a rebound after dialysis has finished and this rebound may require several hours to reach a

Table 4 Comparison of studies of combined salbutamol and insulin with glucose

Reference	Size	Dose soluble insulin	Dose Glu	Route Salb	Dose Salb	Mean initial K (mmol/l)	Peak reduction in K (mmol/l)	Time of maximal action (min)	Duration of effect (min)
5	10	10U	40 g	IV	0.5 mg	7.1	1.5	60	>360
10	12	10U	25 g	Neb	20 mg	5.89	1.21	60	>60

Glu = glucose, Salb = salbutamol.

plateau.[28] If the potassium is lowered with other agents such as salbutamol, this may reduce potassium removal during subsequent dialysis treatment, even though the achieved potassium concentration is lower.[29]

Conclusions

The emergency management of hyperkalaemia should be tailored to the individual patient. It involves (1) determining the cause and (2) instituting temporising measures to stabilise the myocardium and lower the plasma K by redistribution to the intracellular compartment while (3) arranging haemodialysis if necessary. Urgency of treatment is dependent on rate of rise of K in addition to the plasma concentration.

Using common sense interpretation of the available studies, moderate to severe hyperkalaemia in the emergency department should be treated (after confirmation) with (1) Ca gluconate if there are any ECG changes followed by (2) insulin with glucose and (3) intravenous salbutamol (nebulised if there is evidence of ischaemic heart disease). $NaHCO_3$ does not lower the K in the first 60 minutes but is given if there is severe metabolic acidosis (pH <7.20). Sodium polystyrene sulphonate can be given if there is an anticipated delay in haemodialysis, which is the definitive treatment in these patients.

Contributors
Ahee initiated, edited and coordinated the writing of the paper. Crowe provided core ideas from a nephrology perspective and edited the paper. Both authors are acting as guarantors.
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