

Hypokalaemia

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ABSTRACT

Objective: To review the metabolism and function of potassium and causes and management of hypokalaemia.

Data sources: A review of studies reported from 1966 to 1998 and identified through a MEDLINE search of the English-language literature of hypokalaemia.

Summary of review: Potassium is predominantly an intracellular ion that contributes to approximately 50% of the intracellular fluid osmolality and is largely responsible for the resting membrane potential. The latter accounts for its influence on the excitability of muscle and nervous tissue.

Hypokalaemia is defined as a serum potassium of less than 3.5 mmol/L or plasma potassium less than 3.0 mmol/L and may be asymptomatic. Clinical features associated with hypokalaemia include abnormalities of cardiovascular, neurological and metabolic function and may be treated with oral potassium salts, although tachycardia and muscle weakness are the two life threatening disorders which may require rapid intravenous correction. The potassium salts of chloride, phosphate and acetate are often used, although the choice is often guided by the presence of an associated hypochloraemic alkalosis, non-anion gap acidosis or hypophosphataemia, indicating treatment with potassium chloride, potassium acetate, or potassium phosphate, respectively. The infusion rates of intravenous therapy depends upon the salt used. Potassium chloride is usually infused at a rate up to 40 mmol/h, whereas potassium acetate and potassium monohydrogen or dihydrogen phosphate are usually infused up to 5 mmol/h and 2 mmol/h respectively.

Conclusions: Hypokalaemia can be asymptomatic or it may cause cardiovascular, neurological or skeletal muscle dysfunction. If intravenous potassium therapy is required, then correction with potassium chloride, acetate, or phosphate salts are usually guided by the presence of a metabolic acidosis, alkalosis or hypophosphataemia. (**Critical Care and Resuscitation 1999; 1: 239-251**)

Key Words: Potassium, hypokalaemia, potassium deficiency, potassium chloride, potassium acetate, potassium phosphate

Potassium is the principle intracellular cation and is responsible for approximately 50% of the intracellular fluid osmolality. As the cell membrane is approximately 20 times more permeable to potassium ions than sodium ions, potassium is also largely responsible for the resting membrane potential and therefore the function of excitable tissues.

Hypokalaemia is defined as a serum potassium of less than 3.5 mmol/L or plasma potassium less than 3.0 mmol/L (serum concentration is 0.7 mmol/l higher than plasma concentration due to in vitro contamination by intracellular red blood cell potassium). Hypokalaemia is

the most frequently seen electrolyte abnormality found in the hospitalised population, occurring in up to 21% of patients¹ and is associated with an increased mortality in this group.

NORMAL POTASSIUM DISTRIBUTION

Total body potassium is 45-50 mmol/kg in males and 35-40 mmol/kg in females, decreasing with increasing age and reduced muscle mass. Potassium, as well as being the most abundant intracellular cation, is predominantly distributed intracellularly, with the intracellular: extracellular ratio being 98%:2%. The

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intracellular potassium concentration $[K^+]_i$ ranges from 145 to 155 mmol/L and the extracellular potassium concentration $[K^+]_e$ ranges from 3.1 to 4.2 mmol/L. About 70% of total body potassium resides in skeletal muscle, 8.5% in erythrocytes and 6.5 % in hepatocytes (Table 1).^{2,3}

Extracellular potassium levels are determined by the balances between extracellular efflux, intracellular influx, gastrointestinal intake, and urinary, gastrointestinal and tegmental losses.

Table 1. Potassium compartments in a 70 kg male

	Total (mmol)	mmol/kg
Total body K	3500	50
Exchangeable K	3300	47
Intracellular K	3200	45
Extracellular K	65	1
Plasma K	12	0.2

POTASSIUM BALANCE

Gastrointestinal regulation

The daily intake in a standard Western society diet varies from 40-150 mmol. Faecal excretion varies from 5-20 mmol/day with only minor losses (<5 mmol/day) occurring through the saliva and skin,^{3,4} sweat normally has a potassium concentration of 9 mmol/L.

Gastrointestinal excretion of potassium becomes relatively more important when renal excretion is reduced; the normal 10-15% gastrointestinal loss of the daily ingested potassium load may increase up to 35% by an aldosterone effect enhancing sodium absorption and potassium excretion in the colon.⁵ While upper gastrointestinal tract secretions have low potassium concentrations (e.g. 5-10 mmol/L), during diarrhoea, potassium concentration in the stool may vary from 10 to 100 mmol/L.

Renal Regulation

The normal urinary excretion in a standard Western society diet varies from 30 to 150 mmol/day.³ Glomerular filtration filters 600-900 mmol of potassium daily, all of which is reabsorbed before the filtrate reaches the mineralocorticoid responsive distal segment, irrespective of the body's potassium status. The distal nephron is therefore responsible for renal potassium excretion, which can vary from 10 – 700 mmol/day.³ Distal nephron potassium excretion is normally influenced by aldosterone, distal delivery of sodium and non-reabsorbable anions.

Aldosterone. This is secreted by the zona glomerulosa of the adrenal cortex in response to angiotensin II, angiotensin III, ACTH and high plasma potassium concentrations.⁶ Atrial natriuretic peptide,⁷ heparin infusions,⁸ endogenous dopamine⁹ and hypokalaemia¹⁰ can inhibit aldosterone secretion.

The renal site of action of aldosterone is limited to the distal nephron,¹¹ where aldosterone increases the activity of the basolateral cell membrane Na^+/K^+ pump. This increases intracellular potassium concentration as well as selectively increasing potassium permeability of the luminal cell membrane and sodium permeability of the apical cell membrane.¹² This facilitates an intracellular potassium (or H^+) exchange with luminal sodium.¹¹

However, the effect of aldosterone on kaliuresis may only be only be significant when supraphysiological doses are administered¹³ or hyperkalaemia exists.¹⁴

The distal filtrate. The important components of this are:

1. *sodium delivery to the distal tubule:* conditions that increase sodium delivery to the distal tubule (e.g. diuretics, ECF volume expansion) enhance renal potassium excretion;¹⁵ conversely a reduction in sodium delivery to the distal nephron reduces renal potassium excretion.¹⁶
2. *presence of unreabsorbable anions:* the normal electrical potential in the distal nephron is lumen negative, and increases throughout the distal nephron from 9-12 mV to 45 mV due to the transport of Na^+ from the lumen into the peritubular capillary; as the lumen becomes progressively more electronegative, the movement of anions with sodium reabsorption is encouraged. If anions exist with sodium which cannot be reabsorbed (e.g. sulphate, carbenicillin), then sodium movement will increase the negative potential and increase potassium (or hydrogen ion) excretion.

Metabolic alkalosis enhances renal potassium loss, by encouraging distal nephron Na^+/K^+ , rather than Na^+/H^+ , exchange.

Plasma potassium concentration also plays a major regulatory role in potassium excretion.¹⁷ When potassium depletion exists, mechanisms to retain potassium are inefficient compared with mechanism for sodium conservation. Even with severe potassium depletion, urinary loss of potassium continues at a rate

of 10-20 mmol/day.

Intracellular fluid (ICF)/extracellular fluid (ECF) potassium balance

While plasma potassium concentration normally varies with total body potassium, because the quantity of extracellular potassium is small, minor shifts of potassium into, or out of, cells even in the absence of changes in total body potassium, can produce large and potentially lethal changes in plasma potassium concentrations. Conversely, large changes in total body potassium may occur without major alterations in plasma potassium levels if there is a concomitant intra- or extra-cellular shift in potassium.

The negative electrochemical potential difference across the cell membrane generated by membrane bound NaK-ATPase is the major force keeping potassium intracellularly. The two key hormone groups in regulating the transcellular distribution of potassium are the β_2 -adrenergic agonists and the insulins. Increased activity of cell membrane NaK-ATPase by either hormone increases intracellular potassium concentrations.¹⁸ Direct stimulation of the enzyme appears to be the mechanism for β_2 -adrenergic agonists.¹⁹ However, with insulin, the mechanism is complex as the sodium pumped extracellularly had previously entered the cell via the electroneutral Na^+/H^+ exchanger.²⁰

Potassium is the predominant ion affecting the transmembrane electrical potential, as defined by the Goldman-Hodgkin-Katz constant field equation:

$$E_M = -61.5 \log \frac{P_K[\text{K}^+]_i + P_{\text{Na}}[\text{Na}^+]_i + P_{\text{Cl}}[\text{Cl}^-]_i}{P_K[\text{K}^+]_e + P_{\text{Na}}[\text{Na}^+]_e + P_{\text{Cl}}[\text{Cl}^-]_e}$$

where P is the membrane permeability for each ion and $[\text{K}^+]_i$ and $[\text{K}^+]_e$, etc., are the intracellular and extracellular concentrations of potassium, and the various other ions, respectively. As the resting permeability for potassium is much greater than for sodium or chloride ions, the transmembrane potential approaches that calculated by the Nernst equation for K^+ :

$$E_M \text{ K} = -61.5 \log \frac{[\text{K}^+]_i}{[\text{K}^+]_e}$$

From this equation it can be seen that the ratio of intracellular to extracellular potassium concentrations is the major determinant of the resting membrane potential and that small changes in K_e can produce large changes in K_i / K_e (and thus, the resting membrane potential). An increase in ECF potassium reduces the resting membrane potential. In excitable tissues, this not only

reduces the ability to generate an impulse but will also slow its conduction velocity. A decrease in ECF potassium increases the resting membrane potential, increasing membrane excitability and conduction velocity, which may lead to supraventricular and ventricular tachycardias in patients with hypokalaemia.

Acid-base

Acidosis promotes a shift of potassium from the ICF to ECF, whereas alkalosis promotes the reverse shift. It has been reported that for every 0.1 pH unit change, the plasma potassium concentration changes by approximately 0.6 mmol/L,²¹ but this varies with the type, duration and circumstance of acid-base derangement.

For example, during an infusion of hydrochloric acid, for each 0.1 pH unit decrease, the plasma potassium increased by 0.7 mmol/L.²² During an acute metabolic alkalosis, induced by an infusion of sodium bicarbonate, for each 0.1 pH increase, the plasma potassium decreased by 0.5 mmol/L. During acute respiratory acidosis for each 0.1 change in pH, the serum potassium increases by 0.1 mmol/L.

Hypokalaemia accompanies acute respiratory alkalosis,²³ but an early hyperkalaemic response may be seen.²⁴ Chronic respiratory and metabolic acidosis and alkalosis may be associated with minimal or no change in plasma potassium. However, both chronic metabolic alkalosis and acidosis are often associated with marked total body potassium deficits.²⁵

Tonicity

Hypertonicity caused by glucose or mannitol increases plasma potassium by 0.1-0.6 mmol/L for each 10 mosmol/kg increase in osmolality,²⁵ although the increase in insulin release in response to glucose commonly counters the hypertonic hyperkalaemic effect of hyperglycaemia.

Insulin

Insulin has been shown to decrease the ICF/ECF potassium leak (i.e. hyperpolarising muscle tissue) and stimulate NaK-ATPase, increasing intracellular potassium retention and uptake. The mechanism by which insulin stimulates NaK-ATPase is not well characterised, but is not mediated by cAMP.²⁶

Two isoforms of the α -subunit of NaK-ATPase exist, α_1 and α_2 ²⁷ and insulin increases the affinity of the α_2 -subunit for sodium,²⁸ inducing translocation of the α_2 -subunit from the intracellular (inactive pool) to the membrane bound (active pool),²⁹ thereby providing a mechanism for increasing NaK-ATPase activity.³⁰

The decrease in plasma potassium begins 10-15 minutes after insulin administration; the peak effect

occurring at 60 minutes and persisting for up to 3 hours. This effect is independent of glucose uptake.³ Initially, the uptake of potassium occurs in the liver; later skeletal muscle plays a major role.³¹

Potassium also has an effect on insulin release. Hypokalaemia inhibits, and hyperkalaemia stimulates, insulin release, effects which operate to reduce severe alterations in plasma potassium rather than to modulate the normal moment-by-moment plasma potassium levels.¹⁰

Sympathomimetic effects

Beta₂-adrenergic agonists promote cellular uptake of potassium by a cAMP-dependent activation of the Na⁺/K⁺ pump,³ an action which can be inhibited by β-adrenergic blockers. Alpha-adrenergic agonists increase the plasma potassium level by increasing hepatic potassium release and decreasing skeletal muscle potassium uptake.

Adrenaline, therefore has a biphasic effect,³²⁻³⁴ increasing plasma potassium initially due to an α effect, followed by a decrease in the potassium level due to a β₂ effect. During β-blockade, adrenaline causes a dose-dependent increase in plasma potassium.³⁰

HYPOKALAEMIA

Causes of hypokalaemia due to inadequate intake, abnormal gastrointestinal and renal losses and transcellular shifts are listed in table 2. Hypokalaemia is a feature of all forms of primary aldosteronism except glucocorticoid-remediable aldosteronism. Spontaneous hypokalaemia with metabolic alkalosis and a serum sodium at the upper end of the normal range, or hypernatraemia, are often observed, and although hypertension is a strong indicator that aldosteronism is present, normokalaemia is present in at least 20% of patients.³⁵

Bartter's syndrome is not a single disease but a set of closely related renal tubular disorders characterised by hypokalaemia, hypochloaemic metabolic alkalosis, increased urinary excretion of potassium, calcium and prostaglandins, normal or low blood pressure despite increased plasma renin activity and high serum aldosterone concentrations. Other features include a relative vascular resistance to the pressor effects of exogenous angiotensin II, and hyperplasia of the juxtaglomerular apparatus.³⁶ Genetic defects result in defective transepithelial transport of sodium chloride in the thick ascending limb of Henle's loop. In Bartter's syndrome, hypomagnesaemia is uncommon and, when present, mild.

Gitelman's syndrome is a variant of Bartter's syndrome in which patients have hypomagnesaemia and

hypocalciuria.^{36,37} Mutations associated with a putative loss of function of the sodium-chloride transporter in the distal convoluted tubule have been identified in patients with Gitelman's syndrome.³⁸ Loss of function of this sodium-chloride transporter causes defective reabsorption of sodium chloride in this segment. This increases solute delivery to the collecting tubule, with consequent mild volume contraction and aldosterone-stimulated secretion of potassium and hydrogen ions, resulting in mild hypokalaemic metabolic alkalosis.

In Liddle's syndrome, mutations in the gene encoding the aldosterone-sensitive epithelial sodium channel in the collecting tubule result in persistent unregulated reabsorption of sodium and increased secretion of potassium. Unregulated reabsorption of sodium across the collecting tubule results in volume expansion, inhibition of renin and aldosterone secretion, and hypertension.³⁶

Amphotericin B increases urinary potassium loss by up to 50%. Proposed mechanisms include: a) increased membrane permeability secondary to the interaction of amphotericin and membrane sterols, leading to increased potassium permeability at the luminal membrane³⁹ and, b) concurrent type I renal tubular acidosis. The tubular toxicity of amphotericin is potentiated by concurrent hypokalaemia.⁴⁰

Concurrent hypomagnesaemia occurs in up to 40% of cases of hypokalaemia,⁴¹ particularly in association with loop diuretics, alcohol abuse,⁴² malabsorption, gentamicin⁴³ and cisplatin.⁴⁴ Evidence exists that magnesium is essential in the stabilization of the intracellular concentration of potassium and may play a role in the regulation of cellular and subcellular potassium distribution, being a cofactor in the NaK-ATPase pump responsible for active potassium transport into cells. In experimental magnesium depletion, there are increased losses of intracellular potassium, particularly from cardiac and skeletal myocytes.⁴⁵

Hypomagnesaemia may lead to hypokalaemia by increasing urinary and faecal losses. The mechanisms are unclear but may be associated with, a) increased aldosterone secretion or, b) increased leakage of potassium from luminal cell membranes in the thick ascending loop of Henle⁴⁶ caused by opening of potassium channels in the presence of hypomagnesaemia.

In these instances, correction of hypokalaemia requires initial restoration of serum magnesium; giving potassium alone is ineffective as exogenous potassium is excreted rather than taken up by cells. Hypokalaemia refractory to K⁺ repletion is highly suggestive of concurrent hypomagnesaemia.

Table 2. Causes of hypokalaemia

Decreased intake (urine K ⁺ < 20 mmol/day)	starvation clay ingestion
Abnormal body losses	
<i>Gastrointestinal</i> (urine K ⁺ < 20 mmol/day)	vomiting, nasogastric aspiration, diarrhoea, fistula formation villous adenoma of the colon, laxative abuse
<i>Renal</i> (urine K ⁺ > 20 mmol/day)	Primary aldosteronism Conn's syndrome idiopathic aldosteronism unilateral or primary adrenal hyperplasia adrenal carcinoma Secondary hyperaldosteronism renal artery stenosis reninoma malignant hypertension volume depletion Cushing's syndrome Bartter's syndrome Gitelman's syndrome Liddle's syndrome Congenital adrenal hyperplasia Ectopic ACTH syndrome oat cell carcinoma of the lung, bronchial carcinoid, pancreatic carcinoma, thymoma, medullary carcinoma of thyroid, phaeochromocytoma Diuretic phase of acute tubular necrosis Polycystic kidney disease, chronic pyelonephritis Magnesium deficiency Renal tubular acidosis Osmotic diuresis Diabetic ketoacidosis Drugs: diuretics corticosteroids, carbenicillin, ampicillin, amphotericin B, gentamicin cisplatin, licorice, carbenoxolone
Compartmental shift	hypothermia alkalosis insulin NaK-ATPase stimulation β_2 -adrenergic agonists, methylxanthines (theophylline, caffeine) barium poisoning toluene intoxication chloroquine overdosage verapamil overdosage refeeding syndrome treatment of severe megaloblastic anaemia hyperthyroidism familial hypokalaemic paralysis

Theophylline-induced hypokalaemia is well established.^{47,48} The severity of hypokalaemia has been shown to correlate with the peak serum theophylline concentration.⁴⁹ Chronic theophylline intoxication is less often associated with hypokalaemia than acute intoxication.⁵⁰ Mechanisms of hypokalaemia in theophylline overdose include, a) β_2 -receptor stimulation (as raised serum adrenaline levels correlate with the hypokalaemia),⁵¹ b) adenosine receptor antagonism⁵² which may facilitate NaK-ATPase activation by increasing intracellular ATP availability, and, c) phosphodiesterase inhibition which will increase intracellular cAMP. Vomiting induced by theophylline toxicity will also induce hypokalaemia. Caffeine has also been associated with hypokalaemia.⁵³

Muscular weakness, often accompanied by respiratory failure, is the main clinical feature of barium poisoning, although other features of hypokalaemia, including ventricular arrhythmias occur frequently.^{54,55} Barium reduces passive membrane permeability to potassium ions, with little effect on either sodium permeability or NaK-ATPase activity, resulting in net movement of potassium intracellularly. As extracellular potassium concentration falls, NaK-ATPase activity declines markedly;⁵⁶ consequently the resting membrane potential approaches the resting ionic diffusion potential. At this degree of depolarisation, muscle fibers are inexcitable. Reversible blockade of potassium channels also leads to hypokalaemia in chloroquine poisoning, the extent of hypokalaemia correlating with the severity of poisoning.⁵⁷

In pseudohypokalaemia, potassium ions are taken up by metabolically active cells after the blood has been drawn, e.g. acute myeloid leukaemia.⁵⁸ Therefore, blood should be separated and stored at 4°C, if there is to be a delay in measuring plasma potassium concentrations.

Hypokalaemia is also a feature of many anabolic states. Increased haematopoietic cell production, causing increased potassium uptake by new cells, may be seen within 48 hours of commencing treatment for megaloblastic anaemia,⁵⁹ and severe hypokalaemia has been reported with granulocyte-macrophage colony stimulating factor.⁶⁰

Activation of NaK-ATPase and hypokalaemia is recognised in a diverse variety of clinical situations including: following head injury,⁶¹ during therapy for asthma,⁶² following massive transfusion,⁶³ and during alcohol withdrawal.⁶⁴ Use of β_2 -adrenergic agonists in the management of preterm labour may lead to profound hypokalaemia (2.5mmol/L) and associated cardiac arrhythmias.⁶⁵

Thyrotoxic periodic paralysis has a marked male preponderance (20:1), and over 90% of cases have been

reported in Chinese populations. Overt findings of thyrotoxicosis are rarely present with the initial paralytic attack, which usually occurs the second to fourth decades. The mechanism of intracellular potassium shift is unknown, but there are an increased number of cell membrane Na⁺/K⁺ pumps present.⁶⁶

Familial hypokalaemic paralysis has an autosomal mode of inheritance with a male preponderance (3:1). Onset usually occurs during adolescence, with Caucasians most frequently affected. Recurrent episodes of muscle weakness and paralysis may be precipitated by rest following a period of exercise, stress, a carbohydrate meal, and the administration of insulin. Potassium moves intracellularly, the plasma potassium concentration typically falling to 1.5 - 2.5 mmol/L, and returns to normal after 6-48 hours. The membrane defect is not fully understood, but there appears to be a increased cell membrane sodium-potassium pump independent potassium influx.⁶⁶

Clinical manifestations

Clinical manifestations of hypokalaemia vary greatly between patients but features suggestive of hypokalaemia are listed in table 3.

Skeletal muscle is affected by hypokalaemia to a greater degree than cardiac muscle. Muscle weakness is usually not seen at plasma levels above 3.0 mmol/L. Below 2 mmol/L, increases in plasma creatine phosphokinase and aspartate transaminase may be seen and, rarely, rhabdomyolysis and myoglobinuria occur.^{67,68} Rhabdomyolysis occurs as hypokalaemia impairs the augmentation of skeletal blood flow that normally occurs during exercise, leading to ischaemia. This occurs more frequently in individuals with a history of heavy alcohol intake. The pattern of muscle weakness is relatively characteristic. Lower extremities are most commonly involved first, particularly the quadriceps but in more severe cases, muscles of the trunk, upper extremities and eventually of respiration become affected. Muscles innervated by cranial nerves are rarely affected.⁶⁹

Tetany is more frequently associated with hypocalcaemia but occasionally occurs with hypokalaemia;⁷⁰ however, correction of hypokalaemia in the presence of hypomagnesaemia may also precipitate tetany.⁷¹

Characteristic ECG changes are seen with hypokalaemia (Table 4), due to delayed repolarisation of myocardial cells, which is normally due to K⁺ efflux down its electrochemical gradient. With hypokalaemia, membrane potassium permeability is less, leading to reduced potassium efflux. ECG changes do not correlate well with the degree of hypokalaemia in individual

Table 3. Effects of hypokalaemia

<i>System</i>	<i>Effects</i>
<i>Neuromuscular</i>	Cramps Paraesthesia Tetany Muscle weakness Rhabdomyolysis
<i>Cardiac</i>	Predisposition to digoxin toxicity ECG changes and arrhythmias Atrial and ventricular tachycardias Hypertension
<i>Gastrointestinal</i>	Anorexia Constipation Ileus
<i>Endocrine</i>	Glucose intolerance
<i>Central nervous system</i>	Depression Coma Central pontine myelinolysis
<i>Renal</i>	Abnormal NaCl reabsorption Reduced concentrating ability Increased ammonia production Reduced bicarbonate reabsorption Nephropathy

Table 4. ECG changes in hypokalaemia

Increased U wave
Flattened or inverted T waves
ST depression
Prolonged QT interval
Prominent P wave (esp II, III, aVF)
Prolonged PR interval
Widening of the QRS complex

patients, but typical changes are present in 90% of cases when the plasma potassium is less than 2.5 mmol/L.⁷²

Prominence of the U-wave in leads V₂₋₄ is the earliest and most common ECG finding in hypokalaemia. Criteria used to determine prominence of the U wave include: amplitude > 1mm, height > 0.5 mm in lead II and > 1mm in lead V₃, height greater than the T wave in the same lead, and T:U ratio 0.5:1 in lead II or V₃.⁷³ Intraventricular conduction defects due to hypokalaemia are uncommon.

The electrophysiological changes associated with hypokalaemia include increased resting membrane and

threshold potentials, prolonged action potential duration and refractory period, and enhanced automaticity and conductivity.⁷⁴ Delayed ventricular repolarisation leads to an increased relative refractory period, increasing the risk of re-entrant tachycardias. Table 5 lists the arrhythmias associated with hypokalaemia.

Table 5. Arrhythmias occurring in hypokalaemia

Premature atrial complexes
Premature ventricular complexes
Sinus bradycardia
Multifocal atrial tachycardia
Junctional tachycardia
AV block
Paroxysmal atrial tachycardia
Torsades de pointes
Ventricular tachycardia
Ventricular fibrillation

The most frequent cardiac arrhythmias encountered are atrial premature contractions, atrial tachycardia with or without atrioventricular block, and supraventricular tachycardia. AV nodal tachycardia or escape rhythm, and reciprocal beats or rhythm are less common. AV block other than a prolonged P-R interval is rare.⁷³

The arrhythmogenic potential of hypokalaemia is enhanced in the presence of digoxin,⁷⁵ myocardial ischaemia,^{76,77} congestive cardiac failure⁷⁸ or left ventricular hypertrophy. Hypokalaemia is associated with an increased frequency of primary ventricular fibrillation and mortality complicating acute myocardial infarction⁷⁹ but correction of plasma potassium has little effect on the incidence of serious arrhythmias.⁸⁰ As well as being a major risk factor for arrhythmia and sudden death, experimental data suggest that severe or long-standing potassium depletion may exacerbate congestive heart failure by impairing the function and contractility of myocardial and skeletal muscle, by allowing greater vasoconstriction and retarding vasodilatory mechanisms, and by accelerating myocardial pathological processes.⁸¹ Diuretic-induced hypokalaemia has variably been associated with an increased incidence of arrhythmias and this has been postulated as to why diuretics are not associated with a reduction in mortality in heart failure unlike other pharmacological agents.⁸²

Epidemiological evidence suggests a link between hypokalaemia and development of hypertension, with dietary potassium intake related inversely to blood pressure.^{83,84} Recommendations on dietary intake of potassium in the management of hypertension have concluded that, a) potassium supplementation may be effective in reducing blood pressure in patients with

hypokalaemia during diuretic therapy, and b) the daily dietary intake of potassium should be 60 mmol or more (as this level of intake has been associated with a reduced risk of stroke-related mortality). Acute reductions in plasma potassium following haemodialysis have been shown to increase mean arterial pressure by up to 10mmHg.⁸⁵

The effects of hypokalaemia on cardiac haemodynamics are variable. Stroke volume and cardiac output have been found to be reduced, or unchanged, in dogs rendered hypokalaemic.^{86,87} However, recent evidence from randomized controlled trials indicates that increasing intake or supplementing the diet with potassium above the recommended daily dietary intake of 60 mmol is not beneficial as a treatment for hypertension.⁸⁸

Hypokalaemia impairs insulin secretion but not the peripheral utilisation of glucose which is reversible on correction of the hypokalaemia.⁸⁹ This mechanism has been proposed to explain thiazide-induced glucose intolerance.

Hypokalaemia has several effects on renal function (Table 3). Chronic hypokalaemia leads to vacuolar degeneration of renal tubular epithelial cells⁹⁰ which is reversible after several months of correction. It may also lead to interstitial fibrosis, tubular atrophy, cyst formation in the renal medulla.⁹¹ These tubulointerstitial changes are irreversible. Reduced concentrating ability caused by hypokalaemia has several mechanisms: 1) reduced collecting tube responsiveness to antidiuretic hormone, and 2) impaired countercurrent function due to interference with NaCl transport in the thick ascending loop of Henle. The concentrating defect is dose and time related, taking 2-3 weeks to develop. The degree of polyuria is usually mild, as the maximum urinary osmolality remains greater than 300 mosmol/kg. Hypokalaemia also increases tubular cell ammonia production, which may be clinically important in patients with severe liver disease when hypokalaemia may precipitate encephalopathy. Reduced bicarbonate reabsorption perpetuates the concurrent metabolic alkalosis by preventing excretion of excess bicarbonate in urine and hypokalaemia reduces the ability to excrete a sodium load, which may exacerbate hypertension.

Investigations

Investigations include,

Plasma

- Na⁺

Hyper-aldosteronism should be suspected if plasma Na⁺ is high or at the high end of the normal range. The most marked hypokalaemia is

seen with adrenocortical carcinoma or aldosteronoma.

- K⁺
- Renin activity
- Aldosterone
- Thyroid function tests
- Acid-base status

Blood gases will determine the presence or absence of a concomitant metabolic acidosis or alkalosis (Table 6).

Table 6. Hypokalaemic metabolic acidosis or alkalosis

Metabolic acidosis

loss of lower intestinal secretions
diabetic ketoacidosis
types 1 and 2 renal tubular acidosis
salt-wasting nephropathies

Metabolic alkalosis

diuretic therapy
vomiting or nasogastric suction
mineralocorticoid excess
penicillins

Urine

- Electrolytes
Urinary chloride concentrations less than 25 mmol/L are strongly suggestive of vomiting or diuretic therapy.
- Potassium excretion
With extra-renal losses, urinary chloride loss is usually less than 25 mmol/L, excretion greater than this suggests a contribution from urinary potassium wasting. However, volume depletion will raise the potassium concentration in a spot specimen of urine and a 24 hour specimen may be required. Hypovolaemia may diminish the degree of kaliuresis in primary mineralocorticoid excess.
- Anion gap
This is calculated by using the equation $[Na^+]_U + [K^+]_U - [Cl^-]_U$ and is approximately 40 mEq/L. Unmeasured sulphate, di- and mono-hydrogen phosphate anions account for 70 mEq/L, whereas unmeasured ammonium cations contribute 30mEq/L. Bicarbonate anions only become important when pH becomes less than 7.0. A negative urinary anion gap suggests the

presence of a large unmeasured cation e.g. large NH₄Cl excretion, indicating normal distal tubule acidification mechanisms. A positive anion gap indicates a low unmeasured cation, e.g. low NH₄Cl excretion, as seen in type I renal tubular acidosis.

- *pH.*
This will help differentiate between type I RTA [distal; classic](Table 7) and type II RTA [proximal](Table 8). The former should be suspected if an overnight urinary pH is greater than 5.4, whereas urinary pH below 5.4 are found in type II RTA, as normal distal tubule mechanisms exist.

Treatment

Several principles guide the management of hypokalaemia. The primary aim is to rapidly correct dangerously low potassium concentrations (e.g. < 2.5 mmol/L) to safe levels (e.g. 3.0 - 3.5 mmol/L), but not to correct the entire deficit immediately. However, the total body deficit can only be estimated, as there is no definite relationship between plasma potassium concentrations and total body potassium stores.

Table 7. Causes of Type I renal tubular acidosis

<i>Idiopathic</i>	
<i>Hereditary</i>	Marfan's disease Wilson's disease Ehlers-Danlos
<i>Immunological</i>	Sjögren's syndrome Rheumatoid arthritis Systemic lupus erythematosus Cirrhosis Chronic active hepatitis Thyroiditis Hyper-gammaglobulinaemia
<i>Diseases associated with nephrocalcinosis</i>	Medullary sponge kidney Chronic hydronephrosis Renal transplantation Analgesic nephropathy 1° hyperparathyroidism
<i>Drugs</i>	Amphotericin B Lithium Toluene

Table 8. Causes of type II renal tubular acidosis

<i>Idiopathic</i>	
<i>Inherited systemic disease</i>	Fanconi-like syndromes
<i>Disorders associated with hyperparathyroidism</i>	Primary hyperthyroidism
<i>Vitamin D deficiency</i>	
<i>Vitamin D resistance</i>	
<i>Drugs or toxins</i>	Cadmium, mercury, copper or lead poisoning Acetazolamide Streptozotocin
<i>Miscellaneous renal diseases</i>	Multiple myeloma Nephrotic syndrome Amyloidosis Renal transplant rejection

If the serum potassium level is greater than 3 mmol/L, 100 -200 mmol of potassium are required to raise it by 1 mmol/L; 200 - 400 mmol are required to raise the serum potassium level by 1 mmol/L when the potassium concentration is less than 3mmol/L, assuming a normal distribution between cells and the intracellular space,⁹² and a linear relationship between plasma potassium and body deficit (which has been described, i.e. 0.27 mmol/L/100 mmol deficit/70 kg⁹³), exists. The rate of administration of potassium will be influenced by the presence and seriousness of the pathophysiological changes caused by hypokalaemia. The underlying disorder should also be treated simultaneously.

General measures include ensuring adequate intake, the avoidance or minimal use of kaliuretic drugs, potassium supplements, and the use of potassium sparing drugs (e.g. spironolactone, amiloride).

The oral route may be adequate for supplementation in many cases, with average doses of 20 - 40 mmol 6 to 12-hourly. However, large doses can be difficult to deliver enterally, as potassium compounds are gastrointestinal mucosal irritants, with both tablet and liquid forms reported to cause ulceration. Potassium chloride is the preferred salt in the majority of cases, as hypochloraemic alkalosis is also a feature of diuretic therapy and gastrointestinal losses. Replacement of deficits with gluconate, phosphate, citrate or bicarbonate salts may not adequately correct potassium deficits as gluconate and citrate are metabolised to bicarbonate. Filtered bicarbonate and phosphate are not reabsorbed

in the distal tubule, obligating further potassium loss in the distal tubule.

Potassium bicarbonate can be used for maintenance therapy for the hypokalaemia associated with type I RTA. When phosphate depletion also exists, potassium phosphate may be used, although phosphate can be infused only slowly (e.g. maximum rate of 2 - 6 mmol/h/70kg).⁹⁴ Intravenous administration of potassium salts should be in a saline solution, as metabolism of dextrose (if a dextrose solution is used) may initially worsen the hypokalaemia due to stimulation of insulin release.⁹⁵

Replacement rates of up to 40 mmol/h have been safely administered to critically ill patients independent of renal function⁹⁶ and up to 100 mmol/h have been replaced in diabetic ketoacidosis when hypokalaemia is present at presentation. Some have advocated an antiarrhythmic dose of 2 mmol as a bolus⁹⁷ or 6 mmol over 1 minute (to increase the plasma potassium by 2 mmol/L)⁹⁸ to manage hypokalaemic tachyarrhythmias; however, even with such a low dose it is conceivable that in patients with low cardiac outputs, a dangerously high level of plasma potassium might occur transiently to cause sudden sinus arrest, AV block or asystole.⁹⁹ In the presence of acute myocardial infarction, hypokalaemia should be corrected rapidly; intravenous potassium at a rate of 10 mmol/30 min and repeated as necessary until the serum potassium is 4.0-4.5 mmol/L has been recommended.¹⁰⁰

When a transcellular shift has led to hypokalaemia, the plasma potassium concentration will normalise when the precipitating factor is alleviated,¹⁰¹ the vigorous administration of potassium supplements during the hypokalaemic period has later been associated with hyperkalaemia,⁶¹ which has occasionally been fatal.¹⁰² However, potassium administration may be required during the period of hypokalaemia, particularly if ECG changes and arrhythmias are present. Administration of an intravenous non-cardioselective β -adrenergic blocker e.g. propranolol may be of benefit in cases of hypokalaemia when NaK-ATPase activity has produced the transcellular shift, reversing the receptor-mediated activation of the membrane-bound enzyme. This has been successfully used in cases of theophylline and β_2 -agonist overdoses.⁵⁵

Acute episodes of weakness in familial hypokalaemic periodic paralysis and thyrotoxic periodic paralysis may be treated with oral potassium supplements, but paralysis requires intravenous supplementation at 20 mmol/h while monitoring the patient clinically. A low carbohydrate diet with potassium supplements and spironolactone have been used as prophylaxis against recurrence in familial hypokalaemic periodic paralysis, although

acetazolamide has been shown to be the most effective agent in this condition, with the induction of a metabolic acidosis blunting the intracellular translocation of serum potassium.⁶⁶

However, acetazolamide exacerbates thyrotoxic periodic paralysis. Beta-adrenergic blockers can block attacks of thyrotoxic paralysis but control of the hyperthyroid state is the most successful prophylaxis.

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