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Calcium and magnesium

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Calcium and magnesium homeostasis is often disordered in critically ill patients and an understanding of the role and management of these electrolytes is important for the ICU clinician. This article provides an overview of the causes, effects and treatment of abnormal serum calcium and magnesium levels.

Keywords: serum electrolyte concentration; intensive care; deficiency; excess

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MORTALITY AND ABNORMALITIES OF CALCIUM AND MAGNESIUM

Hypocalcaemia[1-4] and both hypo[5,6] and hypermagnesaemia[7] have been associated with increased mortality in some ICU patients. The rate of occurrence of abnormalities in magnesium and calcium in the ICU population is shown in TABLE 1.

Abnormality in Magnesium Reference		Number of patients	Type of ICU	% Hyper	% Hypo
Broner	1990	90	paediatric	18	26
Chernow	1989	193	postoperative	5	61
Reinhart	1985	102	medical	9	20
Rubeiz	1993	184	medical	6.6	20
Ryzen	1985	94	medical		65
Abnormality in Calcium					
Reference		**Number of patients**	**Type of ICU**	**% Hyper**	**% Hypo**
Broner	1990	88	paediatric	5	12
Chernow	1982	210	surgical/medical		64
Desai	1988	88	medical	3	70
Forster	1985	100	surgical-long stay	15	

TABLE 1. The incidence of abnormalities in magnesium and calcium in the ICU population.

CALCIUM (CA^{++})

Calcium is essential for:

- coupling of receptor-stimulated cellular events to cellular responses
- cardiac action potentials
- hormonal and neurotransmitter secretion
- cell division and repair
- enzyme activity
- membrane structure
- blood coagulation

It is an important mediator for myocardial contractility, the control of peripheral vascular tone, the action of many drugs and hormones, and in the function of skeletal muscle[7]. Calcium can be used to temporarily reduce the toxic effects of hyperkalaemia.

Measurement and normal concentrations

Normal ionised calcium is between 1.0 and 1.5 mmol/L. Heparin concentration should not exceed 10 IU/mL in blood samples used for calcium measurement as heparin forms complexes with calcium ions[8]. Ionised calcium may also vary depending on the blood sampling device used[9].

About 99% of the total body's calcium is found in bones and teeth.

Total serum calcium occurs in three forms:

- ionised, physiologically active
- protein-bound, primarily albumin
- chelated (non-ionised salts)

Alterations in serum albumin, common in the critically ill, can change total serum calcium concentration by as much as 30%. The percentage which is protein bound ranges from 30% to 50%. Calcium binding is affected by pH; acute acidosis decreases binding while acute alkalosis increases binding. Free fatty acids (FFA) are attached to albumin. Increased FFAs increase calcium binding and may form a portion of the calcium binding site. FFA concentrations are increased with heparin, catecholamines, intravenous lipids and alcohol and are often raised in the critically ill. Increased concentrations of chelating agents will decrease circulating ionised calcium concentrations. Chelating agents include phosphate, bicarbonate, albumin, citrate and radiocontrast dye. Citrate is used to preserve and anticoagulate stored blood and calcium may decrease during rapid transfusion of blood and blood products. Although there are formulae to correct total serum calcium for albumin concentration and pH they are poor predictors of ionised calcium. It is therefore essential that ionised calcium is measured[10-12].

Homeostatic mechanisms keep plasma calcium concentration within narrow limits. Control of calcium concentration is through parathyroid hormone and Vitamin D and their effects on bone, kidney and the gut.

Hypocalcaemia[13-16]

Causes of hypocalcaemia

Sepsis
Magnesium deficiency or excess
Hypoparathyroidism
Vitamin D deficiency
Chelation
Pancreatitis
Drugs: including aminoglycosides, heparin

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Hyperphosphataemia
Massive blood transfusion
Following cardiopulmonary bypass

Hypocalcaemia is common in the critically ill. Most hypocalcaemic patients have an impaired ability to mobilise calcium due to parathyroid-Vitamin D defects. Magnesium abnormalities may cause hypocalcaemia and both hyper and hypomagnesaemia inhibit parathyroid hormone (PTH) secretion and may affect PTH receptor action.

Effects of hypocalcaemia

Mild to moderate ionised hypocalcaemia (>0.8 mmol/L) is well tolerated.

Severe hypocalcaemia (<0.8 mmol/L) can induce:
- cardiac arrest
- hypotension
- arrhythmias
- paraesthesia
- tetany
- seizures
- weakness
- dementia and psychosis
- ECG changes: prolonged QT interval

At concentrations <1.0 mmol/L neurological and cardiovascular signs appear with arrhythmias and hypotension. Cardiac arrest occurs below about 0.6 mmol/L. A direct relationship has been described between ionised calcium and arterial pressure in ICU patients[17]. Correction of hypocalcaemia (ionised calcium <1.05 mmol/L) is followed by an increase in mean arterial pressure that is sustained for at least 60 minutes[16]. Low ionised calcium concentrations may be early predictors of mortality in critically ill surgical patients[1]. Recommendations are that calcium replacement should be given for an ionised calcium <0.7 mmol/L, or at 0.8-0.9 mmol/L in patients with hypotension, low cardiac output or both[11].

Treatment of hypocalcaemia

- Correct abnormal magnesium and phosphate concentrations
- Administer 10 mL of 10% calcium chloride (6.8 mmol) over 10 minutes, followed by infusion of about 10 mmol/day.
- Consider Vitamin D supplementation

Calcium is very irritant and is best given into a central vein. Tissue necrosis may occur with extravascular injection. Calcium chloride ($CaCl_2$) 10% contains 0.68 mmol/mL calcium whereas calcium gluconate 10% contains 0.225 mmol/mL calcium.

Hypercalcaemia[18]

Causes of hypercalcaemia

Malignancy
Hyperparathyroidism
Rebound hypercalcaemia following hypocalcaemia
Immobilisation
Renal failure
Granulomatous disease, e.g. sarcoidosis
Hyperthyroidism
Drugs: including lithium, theophylline, thiazides

Effects of hypercalcaemia

Cardiovascular
- hypertension
- arrhythmias
- sensitivity to digoxin
- resistance to catecholamines

Renal
- renal stones
- renal failure

Gastrointestinal
- anorexia
- nausea/vomiting
- pancreatitis
- constipation
- peptic ulcer

Neuromuscular
- weakness

Neurological
- seizures
- coma
- psychiatric disorders; e.g. depression, dementia, psychosis

Treatment of hypercalcaemia

- Treat the underlying disorder
- Correct dehydration and other electrolyte imbalance
- Enhance renal excretion: intravenous 0.9% saline and a loop diuretic (e.g. frusemide)

For severe symptomatic hypercalcaemia (>4.0 mmol/L) consider a biphosphonate (eg. disodium pamidronate) to inhibit mobilisation of skeletal calcium. Calcitonin, steroids, intravenous phosphate or haemodialysis may also be useful

Calcium and resuscitation

Uncontrolled intracellular release of calcium may be toxic to ischaemic cells. In this situation calcium accumulates in the cell and may worsen the cardiovascular and metabolic abnormalities. Calcium is rarely, if ever, indicated in resuscitation. European Resuscitation guidelines (1992) are to consider calcium as a second line drug in electromechanical dissociation.

MAGNESIUM (MG^{++})

Magnesium is essential for:
- regulation of most cellular functions
- many enzyme systems

Magnesium is required for the production and functioning of adenosine triphosphate (ATP), the energy source for the Na-K pump and almost all other energy-dependent cell functions. Magnesium is involved in approximately 300 enzyme systems, including most of the enzymes involved in energy metabolism. Oxidative phosphorylation is magnesium-dependent as are the production of DNA, RNA and protein synthesis. Magnesium regulates calcium access into the cell and the action of calcium within the cell. Magnesium acts in many ways as a physiological calcium antagonist[19].

Less than 1% of the total body magnesium is in extracellular fluids with over 99% of magnesium being intracellular or in the skeleton. The extracellular magnesium is 33% protein bound, 12% complexed to anions and 55% in free ionised form. Normal serum magnesium is 0.7-1.05 mmol/L. A normal serum magnesium concentration does not rule out deficiency[20]. Control of magnesium homeostasis is primarily by the kidney.

Hypomagnesaemia[3,21,22]

Causes of hypomagnesaemia

Gastrointestinal
- decreased intake: malnutrition
- decreased gut absorption
- excessive loss: diarrhoea, GI fistula, nasogastric suction, pancreatitis

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Renal
- impaired renal conservation

Other
- hypophosphataemia
- hyperaldosteronism
- drugs: diuretics, aminoglycosides, digoxin
- alcohol
- diabetes
- parenteral nutrition
- rapid massive transfusion: citrate chelation

Consider hypomagnesaemia when there is hypokalaemia, particularly associated with polyuria. Check magnesium concentrations at least once a week in patients on parenteral nutrition. As magnesium shares a common renal reabsorption pathway with sodium and calcium, increased renal sodium or calcium flow may result in magnesiuria. Thus patients being vigorously rehydrated, particularly with saline solutions, are at risk of developing magnesium deficiency. Gastrointestinal losses occur with diarrhoea, ileus or copious gastric drainage. Magnesium depletion may be associated with diabetes, alcoholism, sprue and renal disease. Trauma (physical, emotional, medical) releases catecholamines producing free fatty acids which may sequester or chelate magnesium.

Effects of hypomagnesaemia

Cardiac arrhythmias (ventricular and supraventricular)
Cardiac failure
Muscle weakness
ECG changes: prolonged PR interval, widened QRS, ST depression, low amplitude T wave

Hypomagnesaemia is associated with coronary vasospasm, acute infarction, arrhythmias and sudden death[12]. Magnesium should be considered as a factor in the cause of tachyarrhythmia even where there is a normal serum concentration. Hypomagnesaemia is common in critically ill patients postoperatively and will potentiate dysrhythmias from low calcium or digoxin toxicity. Magnesium affects vascular tone by modulating the vasoconstrictive effects of noradrenaline and angiotensin II so that as the magnesium/calcium ratio falls their vasoconstrictive effect is enhanced. Experimental evidence suggests that magnesium deficiency increases mortality associated with sepsis. There is a higher incidence of sudden death in soft water areas compared to hard water areas which may be due to smaller amounts of magnesium in drinking and cooking water.

Treatment of hypomagnesaemia

- Administer intravenous magnesium, 20 mmol in 100 mL of dextrose 5% over 30 minutes. Repeat as necessary; up to 160 mmol over 5 days may be required.
- Potassium supplements may also be required.
- Intramuscular magnesium is possible but painful.

The normal dose of magnesium (e.g. with parenteral nutrition) is 10-20 mmol/day. Oral supplements (e.g. magnesium glycerophosphate) may be given when appropriate. Gastrointestinal absorption is poor; thus the use of magnesium sulphate as an osmotic laxative.

Replacement is recommended for a serum magnesium concentration ≤ 0.7 mmol/L[12]. One gram of 50% magnesium sulphate ($MgSO_4$) provides approximately 4 mmol of magnesium.

Hypermagnesaemia[2]

Causes of hypermagnesaemia
Renal failure
Magnesium administration (e.g. treatment with magnesium for eclampsia, magnesium containing antacids)

Hypermagnesaemia is rare in ICU.

Effects of hypermagnesaemia

Bradycardia, heart block
Hypotension
Nausea/vomiting
Impaired neuromuscular activity (including respiratory muscle weakness)
Central nervous system depression
ECG changes: narrow QRS, tall peaked T wave

Hypermagnesaemia may convert existing AV block to a higher grade block and can cause extrasystoles. Hypermagnesaemia will enhance the activity of nondepolarizing neuromuscular blockers and may also prolong the effect of suxamethonium. Respiratory paralysis may be seen with a plasma concentration >5.0 mmol/L.

Treatment of hypermagnesaemia

- Calcium, 5 mmol intravenously
- Diuretics (e.g. frusemide)
- Consider haemodialysis

Therapeutic use of magnesium[23,24]

Magnesium is used for the prophylaxis and treatment of eclampsia/preeclampsia[25-30] and for the treatment of cardiac arrythmias[31-33]. It is a component of some cardioplegic solutions and may protect the ischaemic myocardium, particularly during reperfusion. It has been given to patients suspected of having a myocardial infarction[34]. Intravenous magnesium will ablate the hypertensive response to tracheal intubation[35]. Its use has been investigated during the anaesthetic management of patients undergoing phaemochromocytoma resection. Magnesium has also been investigated for use as a bronchodilator in the management of asthma.

Pre-eclampsia/eclampsia[25-30]

Magnesium is used for prophylaxis and treatment of pre-eclapsia/eclampsia. Conflicting results on its efficacy have been reported. Unless convulsions result from magnesium deficiency, magnesium probably does not have major anticonvulsant properties. Its effect in eclampsia may be secondary to its cerebral vasodilator action reversing cerebral vasospasm by blocking calcium influx through the NMDA (N-methyl-D-aspartate) subtype of glutamate channel. There is evidence that prostacyclin is a mediator of magnesium's effect.

Magnesium sulphate 4g (approximately 16 mmol magnesium) should be given over 20 minutes followed by an infusion at 1 g (approx 4 mmol) per hour. If seizures recur give an additional 2-4g magnesium sulphate. Monitor ECG, blood pressure and clinical signs of overdose. Monitor fetal heart rate. Consider monitoring plasma magnesium concentration.

Treatment of cardiac arrhythmias[31-33]

Magnesium is effective in treating a variety of serious arrhythmias, including ventricular arrhythmias resistant to other agents. It inhibits catecholamine-induced arrhythmias and may protect against bupivacaine-induced arrhythmias. It has been recommended for intractable ventricular tachycardia and fibrillation, torsades de pointes and multifocal atrial tachycardia. Magnesium may be useful in converting acute atrial tachyarrhythmias to sinus rhythm[35].

Administer as an i.v. bolus 8 mmol magnesium (approximately 2 g magnesium sulphate) over 10-15 minutes, repeated once if necessary.

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MULTIPLE CHOICE QUESTIONS

Which of the following statements are TRUE in the critically ill?

Question 1

Calcium Chloride

a. is recommended in European guidelines as a first line drug for the treatment of ventricular fibrillation.

b. can be safely administered in the same intravenous line as sodium bicarbonate.

c. should not be given down an endotracheal tube.

d. causes necrosis on extravasation.

e. contains 10 mmol of calcium in 10 mL of a 10% solution.

Question 2

Serum calcium

a. is mainly bound to free fatty acids.

b. is only active in the unionised form.

c. constitutes about 10% of the total body stores of calcium.

d. binding is increased by acute acidosis.

e. may fall following cardiopulmonary bypass.

Question 3

Magnesium

a. is important in the production of ATP.

b. must be measured daily in patients on total parenteral nutrition.

c. is contraindicated in pregnancy.

d. plasma concentration is normally about 0.9 mmol/L.

e. administered intravenously as 50% $MgSO_4$ contains approximately 4 mmol/mL.

Question 4

Causes of hypermagnesaemia include:

a. Acute and chronic renal failure.

b. Gastrointestinal disturbances.

c. Osmotic and other diuretic therapy.

d. Hyperaldosteronism.

e. Aminoglycoside antibiotics.

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(16)

Disorders of Calcium Homeostasis: Rationale for Treatment

David WR Macdonald
Peter H Baylis

Disorders of calcium homeostasis are associated with significant morbidity and mortality. Both hypercalcaemia and hypocalcaemia may present acutely and constitute medical emergencies, or more insidiously as chronic conditions. Diagnosis of the underlying pathology and an understanding of the mechanisms which have been disrupted can help to determine which treatment is most appropriate to restore normocalcaemia in the short term and in its long term maintenance. In this review a consideration of the various treatment options, their modes of action and the potential success in relation to the underlying pathology are presented.

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The average adult human body contains approximately 25 moles (1kg) of calcium of which 99% is present in bone. The small extraosseous fraction however has several important physiological roles, being concerned with neuromuscular function, coagulation and hormone action. Calcium acts in the control of nerve excitation, release of neurotransmitters and in the initiation of muscle contraction. It is to be expected therefore that the levels of this fraction of body calcium are maintained within narrow limits to sustain normal cellular function.

In plasma, calcium is present in three different forms. Approximately 45% (1.1mmol/l) is bound to plasma proteins (principally albumin), 8% (0.2mmol/l) is complexed with anions such as phospate, citrate and lactate while the remaining 47% (1.2mmol/l) is present as free cations. These freely diffusible ions constitute the biologically active form and levels are maintained within physiologically narrow limits by the actions of parathyroid hormone (PTH), calcitriol (1,25-dihydroxyvitamin D_3/1,25-dihydroxycholecalciferol) and calcitonin, which interact to regulate the fluxes of calcium between the gut, kidney, bone and extracellular fluid. The homeostatic mechanisms are regulated by a series of feedback loops which are either directly or indirectly dependent on the level of ionized calcium and as a result the net absorption of calcium from the gut is generally equivalent to the amount excreted in the urine[1]. Derangement of the homeostatic mechanisms may occur in a variety of pathological states, giving rise to either hypercalcaemia (Table 1) or hypocalcaemia (Table 4). Dependent upon the severity of the disorder, clinical features associated with hypercalcaemia (Table 2) or hypocalcaemia (Table 5) may or may not be present. The following article attempts to explain the investigation and management of patients with disordered calcium homeostasis and give some consideration to the factors involved.

Table 1

Causes of hypercalcaemia

Frequency	Cause
Common	Primary hyperparathyroidism
	Malignancy
Less common	Sarcoidosis
	Vitamin D overdose
	Milk-alkali syndrome
	Thiazide diuretics
	Thyrotoxicosis
	Renal failure
	Familial benign hypercalcaemia (familial hypocalciuric hypercalcaemia)
	Parenteral nutrition
Rare	Lithium
	Immobilization
	Tuberculosis
	Hypoadrenalism
	Vitamin A overdose
	Idiopathic hypercalcaemia of infancy
	Myxoedema
	Multiple endocrine neoplasia
	Beryllium poisoning

Measurement of calcium

Calcium may be estimated as either total calcium or ionized calcium. Total calcium estimation can be performed using any of a number of methods but levels are affected by variables unrelated to the homeostatic mechanisms and these need to be

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considered when interpreting results. Changing from a supine to an upright position will result in haemoconcentration and an apparent rise in the total calcium measurement. Prolonged venous stasis may produce artifactual hypercalcaemia due to an increase in the concentration of plasma proteins. Calcium levels do not appear to have a diurnal variation but do rise post prandially dependent on the content of the meal. Seasonal variation has been reported with higher levels in the summer. In disease states associated with hypoalbuminaemia, total calcium levels are low while the ionized fraction is normal. Attempts have been made to "correct" the calcium level for the protein/albumin level in the hope that this would improve the correlation with the ionized fraction. Some formulae include pH in the correction but at best these are only useful where a low albumin concentration is present and all other factors including anions and pH are constant. There is no substitute for estimation of the ionized calcium fraction[3]. This is done by means of an ion specific electrode and requires the blood to be kept from exposure to air after venepuncture. This is made possible by the use of a vacutainer for collection.

Hypercalcaemia

Pathological elevation of plasma calcium concentration occurs as a result of an imbalance in the flux of calcium through the extracellular compartment. This occurs through one or more of the following mechanisms:

- Increased absorption from the gut
- Increased net bone resorption
- Decreased renal excretion

Calcium absoption from the gut lumen occurs by both active transport and facilitated diffusion and the amount absorbed is dependent on the ingested load, the presence of dietary constituents such as phytate which may limit its availability and the circulating level of 1,25-dihydroxyvitamin D. Calcium transport is most efficient in the proximal small intestine but due to the length and relative surface area available the jejunem and ileum provide the major site of calcium absorption. The mechanism by which 1,25-dihydroxyvitamin D acts to increase absorption is not fully understood. Only in those conditions where increased levels of the active metabolite are present will dietary restriction and corticosteroids have any influence on calcium flux.

Bone constitutes the major component of body calcium but only small amounts are exchangeable with the extracellular fluid. Bone resorption and bone formation are relatively in balance with coupling between the activity of osteoclasts and osteoblasts which form the bone mineral units. PTH and 1,25-dihydroxyvitamin D both cause an increase in osteoclastic bone resorption whereas calcitonin inhibits. PTH enhances the rate of bone turnover but whether it has a direct effect on osteoblasts is uncertain. 1,25-dihydroxyvitamin D enhances the effect of PTH on bone and is important for bone mineralization. Other factors affecting the balance between bone resorption and formation include cytokines such as interleukin-1, tumour necrosis factor, lymphotoxin and interleukin-6, prostaglandins of the E series, the transforming growth factors TGFα and TGFβ , thyroxine, oestrogens, androgens and parathroid hormone related protein (PTH-rP).

A curvilinear relationship between urinary calcium excretion and serum calcium has been observed in normal individuals given calcium infusions[4] and on this basis increased renal reabsorption has been presumed to be present when the excretion rate in hypercalcaemic patients lies to the right of the curve. Only the ultrafilterable calcium crosses the glomerulus into the renal tubular lumen and of this 98% is reabsorbed (65% in the proximal tubule, 20-25% in the ascending limb of Henle and 10% in the distal convoluted tubule). Proximal tubule reabsorption is not under hormonal control but is closely linked with sodium reabsorption. A decreased plasma volume will promote sodium reabsorption and calcium will be similarly affected. This may be important in aggravating the hypercalcaemia in a dehydrated patient. The reabsorption at the distal convoluted tubule is under the control of PTH and 1,25-dihydroxyvitamin D and may also be the site of action of PTH-rP. The maintenance of plasma volume and establishment of a natriuresis form therefore the basis of treatment in overcoming renal mechanisms acting to promote hypercalcaemia.

The treatment of hypercalcaemia is best achieved by the identification of the underlying pathology and the appropriate therapy implemented to result in a cure. In a large study of hospital patients, hypercalcaemia was associated with either malignancy or hyperparathyroidism[5] in more thatn 90% of cases. However, in only 77% of patients with cancer who were hypercalcaemic could the hypercalcaemia be attributed to the malignancy[6]. It is therefore important that the presence of hypercalcaemia is not automatically dismissed as resulting from the known presence of a malignancy. As one of the commonest causes of hypercalcaemia is primary hyperparathyroidism it is important to exclude this diagnosis. as surgical excision of the adenoma or hyperplastic glands will result in cure. Measurement of the plasma level of parathyroid hormone (PTH) has been recently refined using an assay which measures the whole 1-84 peptide and which gives better discrimination between hyperparathyroidism and other causes. In primary hyperparathyroidism the level is elevated whereas in hypercalcaemia from other causes PTH secretion would be suppressed and the level should be undetectable. Although a relatively rare condition, it is important to exclude familial hypocalciuric hypercalcaemia as parathyroidectomy is inappropriate for this group of patients.

Table 2

Clinical features of hypercalcaemia

Symptoms	Signs
Asymptomatic	Corneal calcification
Lethargy Fatigue	EEG changes - slowing Decreased deep tendon reflexes
Depression Impaired concentration Confusion Hallucinations	ECG changes - shortened QT_c interval - bradyarrhythmias - bundle branch block
Anorexia Nausea Vomiting	Pancreatitis
Constipation Abdominal pain	Renal calculi Nephrolithiasis Nephrocalcinosis
Nocturia Polyuria Thirst/polydipsia	
Muscle weakness Bone pain	

In a study of cancer patients[6] the mean latency time from primary diagnosis to detection of hypercalcaemia was 26 months. The interval between detection and death was often less than a year although the prognosis varied with tumour type. Correction of hypercalcaemia may in itself not alter the survival time but achievement and maintenance of normocalcaemia has been shown to result in improvement in symptoms and patient well-being[7]. This allowed patients to return home from hospital even during what apparently was the terminal stage of their illness. In cases where severe and symptomatic hypercalcaemia exists, attempts to re-establish normocalcaemia may be clinically desirable either in the absence of any diagnosis or, where a diagnosis is known, to allow time for the appropriate therapy to be effective. Under these circumstances it is important that the relative contributions of each of the above mechanisms to the development of hypercalcaemia are assessed as these will determine the choice and subsequent efficacy of the therapeutic options available. The investigations and calculations which are helpful are listed in Table 3. A nomogram to simplify the calculation of the various components of the hypercalcaemia has been derived[8] and software for personal computers developed.

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Management

Patients who have any significant degree of hypercalcaemia will be salt and water depleted and the first line of treatment irrespective of the underlying cause is therefore rehydration with intravenous fluids. Restoration of the extracellular fluid volume is customarily done by administration of 2–4 litres of fluid daily, initially as 0.9% sodium chloride solution. This results in an improvement of glomerular filtration and promotes a sodium linked calcium diuresis. There appears to be no advantage in infusion of large volumes of fluid, often in association with high dose frusemide, which was a practice that had been previously advocated[9]. Indeed fluid overload was a common problem and these patients required intensive monitoring. Frequent estimation of plasma electrolytes should nevertheless be performed to anticipate the development of either hypokalaemia or hypernatraemia.

Table 3

Investigation of hypercalcaemia

(1) Assessment of hypercalcaemia

- Ionized calcium
- Total calcium
- Albumin & total protein

(2) Assessment of renal function/dehydration

- Urea
- Creatinine
- Electrolytes (Na^+, K^+, HCO_3^-, Cl^-)
- Phosphate
- Creatinine clearance

(3) Assessment of renal components of hypercalcaemia

- Calcium excretion $Ca_E = (Ca_U \times Creat_P) / Creat_U$ (mol/LGFR)

(4) Investigations for diagnosis

- Parathyroid hormone
- Protein electrophoresis
- Bence Jones proteinuria
- Serum immunoglobulins
- Alkaline phosphatase (including isoenzymes)
- 25-hydroxycholecalciferol
- 1,25-dihydroxycholecalciferol
- Angiotensin converting enzyme
- Thyroid function tests
- (Parathyroid hormone related protein)

(5) Monitoring response to treatment

- Ionized calcium
- Urine calcium
- Serum electrolytes
- Urea & creatinine
- Urine sodium
- Urine creatinine

The bisphosphonates are structural analogues of pyrophosphate and are, in contrast to pyrophosphate, resistant to chemical and enzymatic hydrolysis. Bisphosphonates bind strongly to hydroxyapatite and inhibit bone resorption. Three bisphosphonate preparations are currently licensed in the UK - pamidronate, etidronate and clodronate. Bisphosphonates are poorly absorbed from the gut and are, at least initially, given as intravenous infusions. The dose and whether single or repeat infusions are given is dependent on the particular bisphosphonate, but each has been shown to be effective where bone resorption is the major contribution to the hypercalcaemia. A comparative study of the use of these compounds showed that pamidronate, given as a single 30 mg infusion, had a more profound and sustained action than either etidronate, given as three infusions of 7.5mg/kg body weight on consecutive days, or 600mg clodronate given as a single infusion[10]. Following infusion of bisphosphonates a reduction in calcium levels is generally seen within 48 hours and the nadir seen at around five days. When achieved normocalcaemia lasts on average three weeks. The use of oral bisphosphonates has been suggested as being able to prolong the effect[11]. Only etidronate and clodronate are available as oral preparations.

Calcitonin is a 32 amino acid peptide hormone produced by the C-cells of the thyroid gland. Its use as a hypocalcaemic agent is due to its ability not only to decrease bone resorption by inhibition of osteoclast activity, but also to promote a renal calcium loss by inhibiting its reabsorption in the distal nephron[12]. Calcitonin is given either subcutaneously or intramuscularly in doses of 50-100 IU every 8-12 hours. The various calcitonins have different biological activities and this has resulted in the requirement for standardisation. The effect is generally seen within hours of administration but diminishes after approximately 72 hours. This may be partly overcome by the addition of corticosteriods[13]. The adminstration of calcitonin by rectal suppository or by the intranasal route has been developed but as yet these alternative routes of administration have not been evaluated as to their use in the treatment of hypercalcaemia.

Corticosteriods have only limited use in the management of hypercalcaemia. They are effective in treating hypercalcaemia associated with haematologic malignancies where the tumour is steroid responsive or where there is evidence that there is abnormal production of active vitamin D metabolities by the tumour, as found with the adult T cell lymphoma caused by the retrovirus HTLV-I[14]. Similarly high dose steroids should be used in Vitamin D overdose and in hypercalcaemia associated with granulomatous disease where there is extrarenal production of 1,25-dihydroxyvitamin D.

Plicamycin (mithramycin) is an RNA synthesis inhibitor with cytotoxic activity which inhibits osteoclastic bone resorption. The recommended dose is 25μg/kg body weight given by slow intravenous infusion. The drug is potentially nephrotoxic and is excreted by the kidney. Hepatotoxicity and myelosuppression are also a problem of repeated adminsitration.

Phosphate given as a slow intravenous infusion of 40mmol neutral phosphate is extremely effective at rapidly lowering the level of serum calcium. It does however result in extraskeletal precipitation of calcium and may cause hypotension, acute renal failure and death. Oral phosphate is effective as a hypocalcaemic agent but is associated with a high incidence of gastrointestinal disturbance particularly diarrhoea, and also can cause soft tissue calcification. Adminstration of phosphate is generally not recommended.

Gallium nitrate has been shown to be an effective hypocalcaemic agent due to its inhibition of osteoclastic bone resorption. When given as a continuous infusion of 200mg/ m^2 body surface area/day for 5 consecutive days it was shown to be more effective than maximal doses of calcitonin particularly with regard to its duration of effect[15].

Peritoneal dialysis can reduce serum calcium concentrations but calcium-free dialysis fluid must be used rather than the low calcium containing solutions in which all the calcium (1mmol/L) is present as ionized calcium. Recently the use of the somatostatin analogue **octreotide** has been reported as effective in treating the hypercalcaemia associated with neuroendocrine tumours[16] but as yet it is unclear if it may have a wider role as a hypocalcaemic agent.

In summary, the main aims of treatment are to enhance urinary excretion of calcium and inhibit bone resorption to achieve normocalcaemia. The restoration of extracellular fluid volume is an essential first step in any treatment regimen and the choice of agent may be determined by the relative contributions of bone resorption and renal reabsorption to hypercalcaemia. The bisphophonates have made a considerable impact in the management of patients with hypercalcaemia where bone resorption is the principal cause.

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Hypocalcaemia

Hypocalcaemia in practice may be a less common clinical problem than hypercalcaemia but it is associated with not insignificant morbidity and mortality[17,18]. The management of patients with hypocalcaemia, especially in the long term, can be particularly difficult. The aims of treatment are to increase the serum calcium into the range where symptoms are corrected and to maintain normocalcaemia in the long term to prevent the development of skeletal deformity associated with chronic hypocalcaemia.

Table 4

Causes of hypocalcaemia

Frequency	Cause
Common	Vitamin D deficiency
	Hypoparathyroidism
	Renal failure
	Pancreatitis
	Magnesium deficiency
	Septicaemia
	Alkalosis
Rare	Anticonvulsant therapy
	Pseudohypoparathyroidism
	Vitamin D dependent rickets
	Massive transfusion of citrated blood*
	Liver transplantation*

* Incidence of hypocalcaemia is high but is overall an uncommon cause of hypocalcaemia.

Acute hypocalcaemia is most commonly associated with surgery and resultant hypoparathyroidism which may be either temporary or permanent. Although most commonly related to parathyroidectomy and parathyroid biopsy[19] or thyroidectomy[20], it is seen with other forms of radical head and neck or upper gastrointestinal surgery[21]. It has been reported as a common feature of cadiopulmonary bypass[22] and profound reduction in ionized calcium levels may occur during the anhepatic phase of liver transplantation when citrate levels have been shown to rise in excess of twenty fold[23]. Infusion of fresh frozen plasma, which has the highest concentration of citrate per unit volume of any blood product, has been found to cause ionized hypocalcaemia particularly in children[24]. Other causes of acute hypocalcaemia include pancreatitis[18], septicaemia[17] and acute renal failure.

Management

Correction of acute symptomatic hypocalcaemia requires intravenous administration of calcium either as a solution of 10% calcium chloride or 10% calcium gluconate. This may then be followed by a continuous infusion of 40ml calcium gluconate solution which provides about 9mmol elemental calcium daily. In the case of refractory hypocalcaemia particularly in association with hypokalaemia, hypomagnesaemia should not be overlooked[25]. Infusion of up to 50mmol/day for 5 days of either magnesium chloride or sulphate may be required in some cases to restore the levels to normal.

Table 5

Clinical features of hypocalcaemia

Symptoms	Signs
Numbness and parasthesiae	Tetany
Muscle cramps/spasms	Latent tetany
Behavioural disturbances	- Trousseau's sign
Stupor	- Chvostek's sign
Bone/muscle pain	Laryngeal stridor
	Convulsions
	ECG changes
	- prolonged QT interval
	Cataracts
	Basal ganglia calcification

The treatment of chronic hypocalcaemia is designed to give sufficient calcium and vitamin D or a vitamin D metabolite to increase the uptake of calcium from the gut with a resultant increase in the level of serum calcium. Several preparations of oral calcium supplements are available which contain different amounts of elemental calcium and it is important that this should be considered when prescribing.

In summary, the rapid correction of acute hypocalcaemia is generally achieved following intravenous infusion of calcium salts. Where the hypocalcaemia is not a temporary phenomenon the long term maintenance will require treatment with vitamin D or a metabolite with or without calcium supplementation.

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Current concepts in the management of cardiac arrest

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SYNOPSIS

Improved understanding of the pathophysiology of cardiac arrest, together with a critical review of previously accepted treatment, has led to changes in management. However, conventional management algorithms tend to be complex and confusing. Rigid adherence to these can cause problems in the emergency situation.

Advanced cardiac life support can be divided into 'core' interventions required in almost all cases. These are 'blind' defibrillation, endotracheal intubation, hyperventilation, intravenous fluid loading and giving (high dose) adrenaline. Further interventions depend on which of asystole, ventricular fibrillation or electromechanical dissociation is present.

Index words: resuscitation, defibrillation, emergencies, life support.

Introduction

The prognosis for cardiac arrest remains very poor. However, there is proven benefit for early DC (direct current) countershock in ventricular fibrillation and for cardiopulmonary resuscitation by laypersons ('bystander CPR') if this is rapidly followed by advanced cardiac life support.

Treatment protocols for cardiac arrest, based on current concepts and research, are a *guide* to management (Fig.1). Doctors should be prepared to exercise their own clinical judgment.

Basic cardiac life support

Basic cardiac life support aims to restore a circulation of oxygenated blood before professional help arrives. It comprises the basic skills of cardiopulmonary resuscitation (CPR) and combines closed chest compression with artificial ventilation of the lungs.

Principles

1. Diagnose cardiac arrest by checking the patient's response to sound and touch, absent respirations and impalpable carotid or femoral pulses.
2. If the arrest is witnessed, consider giving one or two precordial thumps.
3. Assess and clear the airway with the patient on their side. Then position the patient on their back. To prevent obstruction of the upper airway by the tongue, lift the jaw forwards and tilt the head backwards.
4. Occlude the patient's nose and give two breaths into the mouth, or, in small children, into the mouth and nose together. Each breath should last about 1.5 seconds. Do not exhale too vigorously to avoid inflating the stomach. Observe the chest wall rising and falling with each expired air ventilation.
5. Perform external chest compressions:
   i. Locate the middle of the sternum by finding the point half-way between the suprasternal notch and the xiphisternum. Compress the chest at or just below this position.
   ii. Perform chest compressions at a rate of *80-100 per minute* in adults and *at least 100 per minute* in children and babies.
   iii. With each compression, depress the chest wall to a depth of approximately 4-5 cm in adults, 3-4 cm in children and 2-3 cm in babies.
6. The single resuscitator performs 15 chest compressions followed by two exhaled air ventilations. With two operators, cycles comprise 5 chest compressions followed by a pause, during which the lungs are inflated once. These sequences are continued until help arrives.

Simultaneous chest compression and ventilation is no longer advocated.

Devices such as resuscitation bags and masks and oropharyngeal airways may improve the efficiency, hygiene and aesthetics of CPR.

Advanced cardiac life support

Basic life support maintains viability for only a few minutes. For successful resuscitation, additional advanced cardiac life support is usually required and comprises electrical defibrillation, endotracheal intubation and intravenous drugs and fluids. The principles of management are similar in adults and children. Guidelines on paediatric advanced life support were published in 1996.[1]

Unless there is immediate return of spontaneous cardiac output, certain 'core' interventions are necessary in all cardiac arrests. Additional interventions depend on the specific circumstances of each arrest.

Core management

The 'core' interventions in the advanced management of all cardiac arrests are:

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- continued CPR
- early 'blind' defibrillation
- endotracheal intubation and ventilation of the lungs
- intravenous fluid loading
- adrenaline

Early 'blind' electrical defibrillation

Direct current (DC) cardioversion improves outcomes when cardiac arrest is due to ventricular fibrillation (VF). It should be performed as soon as the diagnosis of VF is confirmed. In cardiac arrest where the rhythm is in doubt, two or three DC shocks (200, 200 then 360 joules) should be tried 'blind'. The interval between each shock should be less than one minute with a check of rhythm being made after each shock.

Endotracheal intubation and ventilation of the lungs

Although not mandatory, endotracheal intubation is the most efficient means of providing artificial ventilation and a cuffed tube may protect the airway from aspiration of gastric contents. It may also be used as a conduit for giving certain drugs, in particular, adrenaline and lignocaine.

In order to correct respiratory acidosis, the lungs should be moderately hyperventilated at a rate of 12-15 ventilations per minute.

Intravenous fluids

An intravenous line should be established at the antecubital fossa (not at the hand or wrist) and 1000 mL of *normal saline* infused rapidly. Central venous cannulation is not mandatory, but may be required if other venous access cannot be gained. Volume loading is necessary to maintain an adequate venous return to the heart because, during cardiac arrest, there is pooling of blood in venous capacitance vessels and 'third space' fluid losses from the vascular compartment. Colloid solutions such as polygeline (Haemaccel) are not usually required. Dextrose solutions are contraindicated as they do not adequately expand the circulation and glucose may be toxic to hypoxic brain cells.

Adrenaline

In adults, current recommendations are for intravenous adrenaline 1 mg (10-15 microgram/kg) to be given immediately and repeated every 3-5 minutes. However, both the American Heart Association and the European Resuscitation Council recognise the theoretical advantages of adrenaline in higher doses (i.e. 100 microgram/kg) if the initial lower dose fails. In adults, this represents 5-10 mg every 5 minutes.

It does not matter whether 1:1000 or 1:10 000 strengths of adrenaline are used if it is injected into an intravenous fluid infusion. The currently available ampoules of either concentration contain 1 mg of adrenaline.

Rationale for high dose adrenaline

CPR produces only 10-15% of normal cardiac output and during cardiac arrest there is also loss of vasomotor tone and venous pooling of blood. As there is no hope of restoring a spontaneous cardiac output unless the myocardium itself is oxygenated, the highest priority in cardiac arrest is to maximise the available blood flow through the coronary arteries. The alpha adrenergic activity of high-dose adrenaline produces peripheral vasoconstriction and thereby redistributes the available circulatory output centrally, increases coronary artery perfusion pressure and promotes coronary blood flow. Adrenaline does not convert asystole to VF, nor does it 'coarsen' so-called 'fine' VF.

Note: Adrenaline should be withheld if VF becomes intractable despite treatment. It must also be ceased as soon as spontaneous cardiac output is achieved as adrenergically-induced vasoconstriction now represents a high afterload which is detrimental to a sick heart. Fortunately, the half-life of adrenaline is very short and its residual effects quickly wear off.

Although high-dose adrenaline contributes to improved initial survival from cardiac arrest, there is as yet no evidence that increased numbers of cardiac arrest victims actually leave hospital or that hypoxic neurological damage is reduced.

Routes of drug administration

All drugs should be given via the intravenous line with normal saline running. There is *no* role for intracardiac administration. If there is delay in gaining intravenous access, some drugs, including adrenaline, lignocaine and atropine, may be administered via the endotracheal tube at twice the intravenous dose (however, this is empiric and the bioavailability of drugs given endotracheally is unknown). In young children, the intraosseous route can be used for both fluid and drug delivery and is comparable to intravenous administration.

Management of specific dysrhythmias

The core procedures are continued throughout the management of the arrest. According to circumstances, additional specific interventions are also utilised.

Ventricular fibrillation

This is the commonest rhythm in cardiac arrest. VF can be triggered by acute ischaemia, electrolyte disturbance, hypothermia, hypoxia or electric shock. The ECG shows irregular electrical activity with no discrete P waves or QRS complexes.

DC countershock in ventricular fibrillation

Defibrillation is the *only* acceptable first-line specific therapy in VF and is the cornerstone of treatment.

Current flow through the heart is optimised by correctly positioning the paddles and reducing transdermal electrical resistance. Usually one paddle is located at the cardiac apex and the other to the right of the upper sternum. However, the operator should visualise a mental picture of the passage of current flow *through* the heart and should modify the paddle positions accordingly. Firm pressure should be applied to the paddles which should be in good electrical contact with the skin using either conducting gel or special conducting pads. Shocks should initially be at 200 joules, but if the first two or three have been unsuccessful, all subsequent shocks should be

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at 360–400 joules. For children, use 3-4 joules per kilogram.

Defibrillation is not benign, but as it is the most important therapeutic modality in VF, it should be used repeatedly according to the doctor's judgement.

Drugs in ventricular fibrillation

Drugs are secondary to electrical defibrillation and have limited efficacy. All drugs should be given as boluses, with lignocaine being tried first. Other drugs may be considered subsequently. There should be cycles of at least a further 3 DC shocks and continued CPR for one minute (approximately 10 sequences of 5:1 compression-ventilation) before each new drug is given.

Lignocaine. There is little (if any) evidence that lignocaine terminates VF and theoretically it may adversely raise the threshold for successful electrical defibrillation. The major effective use for lignocaine is to suppress ectopic ventricular activity once spontaneous circulation has returned. The initial dose is 1.5 mg/kg followed by an infusion of 2-8 mg/minute.

Other antiarrhythmic agents. In refractory VF which is not responding, other antiarrhythmic drugs may be tried, usually amiodarone (5 mg/kg) or sotalol (1.5 mg/kg). Both these drugs have beta blocking and class III antiarrhythmic activity, but their efficacy in intractable VF remains speculative. Procainamide (class Ia) is occasionally tried (50 mg increments at 5 minute intervals up to 20 mg/kg).

Electrolytes

Magnesium sulphate (5-20 mmol intravenously) may be useful in polymorphic ventricular tachycardia (torsades de pointes), especially when this is secondary to drug toxicity such as tricyclic antidepressants. It may be tried in VF, but there is no evidence of efficacy.

Potassium chloride (5-20 mmol intravenously) raises the threshold for membrane depolarisation. Many cardiac patients are chronically potassium-depleted due to diuretic therapy and this may predispose them to fibrillation. Potassium chloride probably has little effect in intractable VF.

Asystole or agonal bradycardia

Asystole carries a very grim prognosis. If the ECG shows a flat line, quickly check the connections and settings of the ECG monitor to exclude the possibility of instrument malfunction. It is worthwhile switching through the various leads on the monitor as a low amplitude VF in one lead may be misinterpreted as asystole.

Treatment of asystole is maintenance of CPR and repeated adrenaline. There are few specific therapies.

Atropine (1-2 mg) is often given, but probably has little or no effect in cardiac arrest. The dose is not repeated.

Transvenous cardiac pacing may be tried if a temporary pacing wire is immediately available. External transcutaneous pacing is ineffective in asystole.

Adenosine antagonism is a theoretical pharmacological approach. Myocardial accumulation of adenosine has been postulated as contributing to persistent asystole. Aminophylline (250 mg intravenous bolus) is an adenosine antagonist and has been reported to result in spontaneous cardiac output in some patients in asystole not responding to standard therapy. Such claims remain unproven.

Electro-mechanical dissociation (pulseless electrical activity)

Electro-mechanical dissociation is the presence of an electrical rhythm without mechanical cardiac output and may imply that there is little viable or functional myocardium. It may also be associated with profound hypovolaemia, drug toxicity, electrolyte imbalance or mechanical obstruction to cardiac output such as pulmonary embolism, cardiac tamponade or tension pneumothorax.

Along with ongoing CPR and repeated high-dose adrenaline, treatment is obviously directed at correcting any reversible underlying cause. Calcium is *not* used except in specific circumstances.

Other interventions in cardiac arrest

Bicarbonate

Bicarbonate is inappropriate in at least the first 20 minutes of cardiac arrest except in situations such as septicaemia where a profound metabolic acidosis may already exist. The acid-base disturbance during the early stages of cardiac arrest is respiratory in type due to a combination of ventilatory arrest and decreased pulmonary blood flow. Metabolic acidosis takes about 20 minutes to develop and may even be advantageous as myocardial high-energy phosphate stores are conserved in an acidotic environment.

The treatment of the respiratory acidosis of early cardiac arrest is CPR with hyperventilation. Giving bicarbonate theoretically makes the situation worse as it is buffered to carbonic acid which dissociates into carbon dioxide and water, increasing the already elevated $PaCO_2$. Carbon dioxide freely enters cells and induces a paradoxical intracellular acidosis. If bicarbonate *is* subsequently given, a small dose should be used (0.5-1.0 mmol/kg).

Arterial blood gases

Arterial blood gas analysis provides no useful information during cardiac arrest. Blood sampled from a peripheral artery during circulatory stasis does not reflect the acid-base status of myocardial cells. Additionally, in the rapidly changing circumstances of cardiac arrest, the results when received no longer reflect the *current* situation.

Isoprenaline

Isoprenaline is absolutely *contraindicated* in all cardiac arrests irrespective of cause (other than torsades de pointes). Its unopposed beta adrenergic activity not only increases myocardial oxygen demand but also reduces peripheral vascular resistance, lowers coronary perfusion pressure and reduces coronary arterial blood flow. Isoprenaline may be used to accelerate a bradyarrhythmia, but only in the presence of a cardiac output.

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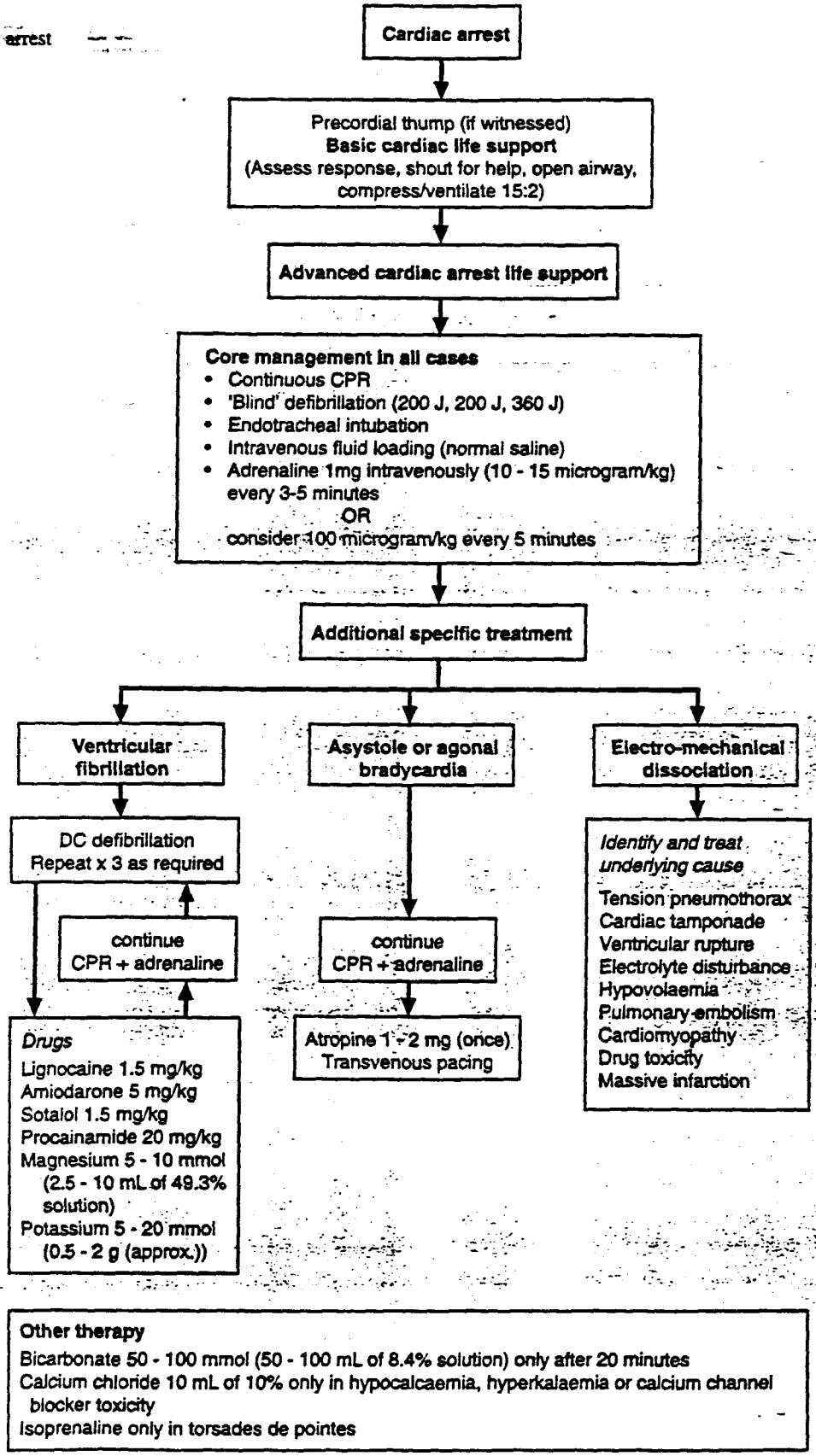
Fig. 1

Cardiac arrest



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Calcium gluconate and calcium chloride

Although calcium is essential physiologically for electro-mechanical coupling, it is erroneous to believe that pharmacological doses can promote myocardial activity in asystole or electro-mechanical dissociation. During cardiac arrest, hypoxic membrane dysfunction allows a net flux of calcium ions into cells, disrupting cellular architecture and accelerating cell death.

Calcium is only indicated in cardiac arrest in the presence of hypocalcaemia, calcium channel blocker toxicity or hyperkalaemia.

The decision to stop treatment

After 10 minutes without a spontaneous output, the chances of a patient surviving long term are very slim. Even in survivors, the probability of profound hypoxic neurological deficit is very high. Cardiac arrest with no return of spontaneous circulation for greater than 20 minutes is usually hopeless and, at this stage, withdrawal of treatment should be considered. Even if cardiac output is eventually restored, virtually none of these patients ever leave hospital. An exception to this general principle is made in the case of a profoundly hypothermic patient - especially in an immersion incident involving a child. In such cases, there have been reports of successful outcomes after protracted resuscitation lasting over an hour. Thus the aphorism: 'never dead until warm and dead'. Some clinicians also claim that patients in cardiac arrest secondary to overdose with some drugs such as tricyclic antidepressants should undergo prolonged resuscitative attempts as the occasional successful outcome has been reported.

Conclusion

Cardiac arrest still has a very poor prognosis, although recent advances based on scientific rather than anecdotal principles have increased the possibility of at least short-term survival. The issues of long-term survival and quality of life are unresolved.

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Self-test questions

The following statements are either true or false (answers on page 51)

3. Adrenaline is not a specific treatment for asystole or ventricular fibrillation, but it does increase the effectiveness of life support.
4. If you are trying to resuscitate a patient on your own, the correct compression/ventilation ratio is 15:2.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Board believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Board is prepared to do this. Before new drugs are prescribed, the Board believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Adapalene

Differin (Galderma Australia)

0.1% gel in 30 g tubes

Indication: acne

Adapalene is similar to the retinoids. It binds to a retinoic acid receptor and modulates keratinisation and the differentiation of cells.

The gel can be used by patients with comedonal, papular or pustular acne. It is applied once daily, at bedtime, after the skin is washed. Clinical improvement is evident in one to two months.

Adapalene 0.1% gel is reported to be as effective as 0.025% tretinoin gel.[1] As this strength of tretinoin gel is not marketed in Australia, it is not clear how adapalene compares with the available 0.05% tretinoin creams.

The gel can irritate the skin causing the patients to complain of pruritis, stinging and scaling. No systemic reactions have occurred, but phototoxicity is a potential problem. Adapalene should not be used by patients with eczema. As the drug could

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Annals of Emergency Medicine

Volume 31(6) June 1998 pp 777-781

Electromechanical Dissociation 48 Hours After Atenolol Overdose: Usefulness of Calcium Chloride

[Case Report]

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Received for publication November 11, 1996. Revisions received May 21, August 18, and December 17, 1997. Accepted for publication January 6, 1998.
Reprints not available from the authors.

Outline

Graphics

Abstract

Electromechanical dissociation (EMD) occurred in a 20-year-old woman 48 hours after an overdose of atenolol, despite intensive treatment of the[beta]-blocker poisoning (gastric lavage, charcoal, glucagon, epinephrine, atropine, correction of electrolyte abnormalities, administration of fluids, cardiac pacing, and mechanical ventilation). Administration of calcium chloride during EMD repeatedly restored blood pressure. Therefore it may have a role to play in management of atenolol overdose.

INTRODUCTION

Atenolol is a non-lipid-soluble [beta]-adrenergic blocker with greater selectivity for $[beta]_1$-adrenergic receptors. It is widely used in the treatment of hypertension and angina. Fewer than 10 cases of severe atenolol poisoning have been reported in the English-language literature; the clinical manifestations are described as bradycardia, hypotension, low cardiac output, cardiogenic shock, bronchospasm, respiratory depression, impaired level of consciousness, and asystole. Therapy in these cases is similar to that described for other [beta]-blocker overdoses including gastric lavage,

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charcoal, glucagon, [beta]-agonist agents, atropine, aminophylline or other phosphodiesterase inhibitors, cardiac pacing, and hemodialysis. 1-12 To our knowledge, this is the first report of electromechanical dissociation (EMD) induced by atenolol in which administration of calcium chloride repeatedly resulted in a dramatic restoration of blood pressure.

CASE REPORT

A 20-year-old previously well, 54 kg woman presented approximately 4 hours after reportedly ingesting 18 to 25 of her grandmother's 100-mg atenolol(1800 to 2500 mg) plus 18 to 25, 25-mg hydrochlorothiazide (450 to 625 mg) tablets, 12 fluoxetine tablets (240 mg), and 40 mL chlordesmetildiazepam (80 mL) drops in a suicide attempt. Her past medical history was unremarkable. Results of the initial physical examination were normal except for somnolence, blood pressure 70/60 mm Hg, and a pulse rate of 58 beats/minute. The patient's 12-lead ECG was within normal limits (sinus rhythm, PR interval 160 ms) (Figure. A). Initial laboratory data were as follows: sodium 142 mmol/L; potassium 2.8 mmol/L. and creatinine 1.2 mg/dL. After receiving intravenous fluids, her blood pressure rose to 100/70 mm Hg. The treatment started in the emergency department included gastric emptying, activated charcoal administration, cathartic, flumazenil (.2 mg by intravenous push, repeated at 1-minute intervals up to a 1-mg total dose), potassium chloride (10 mEq/hour), and intravenous fluids (crystalloids 120 ml/hour). After this treatment the patient was alert.

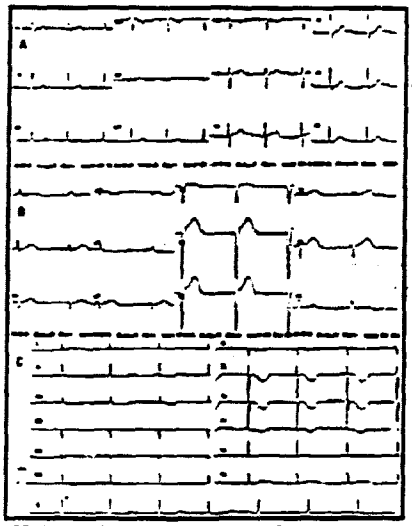

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Figure. **A.** Normal ECG on admission.**B,** 24 hours later, ECG shows junctional rhythm at 41 beats/minute, with left bundle branch block and prolonged QTc interval. **C.** 48 hours later, junctional rhythm at 38 beats/minute with prolonged QTc interval. ECG for C was recorded 4 hours before EMD.

In the following hours the patient's systolic blood pressure was stable at 80 to 90 mm Hg, the pulse rate at 50 to 55 beats/minute, diuresis at 30 mL/hour, and the ECG was normal except for a sinus bradycardia. She had no other symptoms. After 16 hours the systolic blood pressure dropped to 40 mm Hg, and the pulse rate to 38 beats/minute. The ECG showed junctional rhythm, left bundle branch block, and abnormal QTc interval (Figure. B). The patient was transferred to the ICU. At that time, serum drug concentrations were 32,000 ng/mL of atenolol (plasma concentration for usual therapeutic doses range from 200 to 500 ng/mL), 15 ng/mL of fluoxetine, and traces of benzodiazepines. Infusions of epinephrine (from .04 to .5µg/kg per minute titrated to blood pressure), magnesium sulfate (250 mg/hour), potassium chloride (10 mEq/hour), and glucagon (5 mg intravenous bolus followed by an infusion of 4 mg/hour) were started. A temporary transvenous pacemaker was inserted. The patient's systolic blood pressure rose to 90 mm Hg, the lungs were clear, and arterial oxygen tension was 91 mm Hg (room air, normal pH). An echocardiogram measured an

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ejection fraction of the left ventricle of 61%.

During the 4 hours after admission to the ICU, the patient's mental status progressively deteriorated followed by apnea that required tracheal intubation, sedation, and mechanical ventilation. An arterial line and a central venous line were inserted (central venous pressure 20.5 cm H_2O). Laboratory data demonstrated sodium 141 mmol/L; potassium 3.6 mmol/L; calcium 9.9 mg/dL; chloride 102 mmol/L; creatinine 2.1 mg/dL. The next morning, 44 hours after atenolol overdose, the ECG demonstrated a junctional rhythm at 41 beats/minute with a prolonged QTc interval but without the left bundle branch block seen on the previous day (Figure, C). Systolic blood pressure was 100 mm Hg, and diuresis was 40 ml/hour. The patient remained sedated with mechanical ventilation and normal blood gas values. The ejection fraction of the left ventricle was 56%. Laboratory data demonstrated sodium 135 mmol/L; potassium 3.0 mmol/L; calcium 8.6 mg/dL; phosphate 1.3 mg/dL; creatinine 1.2 mg/dL. Treatment with the same drugs at the same infusion rate of the previous day (epinephrine .5 (µg/kg per minute) was continued.

In this setting the patient experienced a sudden drop of blood pressure with pacemaker-induced QRS at the rate of 85 beats/minute (while spontaneous heart rate was 45 beats/minute with junctional rhythm). No carotid pulse was palpable bilaterally. CPR was immediately started with cardiac compression and ventilation (FiO_2 100%). Epinephrine, 1 mg, and calcium chloride, 1 g, were administered through the central venous line and within 30 seconds the patient had palpable pulses. Over the next 2 minutes the pulses became impalpable, and the patient gradually slipped into EMD. An additional gram of calcium chloride was given, and the patient's response was similarly impressive: her pulses returned. Another gram of calcium chloride as a bolus was administered through the central venous line followed by an infusion at the rate of 125 mg/hour. The CPR lasted 18 minutes and the patient recovered palpable radial pulses bilaterally without evident neurologic deficit. At this time, serum drug concentration included only traces of atenolol, fluoxetine, and benzodiazepines. Other laboratory data were as follows: sodium 131 mmol/L; potassium 4.1 mmol/L; calcium 12.5 mg/dL; phosphate 1 mg/dL. The epinephrine infusion was increased to a rate of .7 µu/kg per minute to maintain the patient's systolic blood pressure at 90 mm Hg. During the next 24 hours glucagon and magnesium sulfate were withdrawn. An attempt to reduce the epinephrine dose by using enoximone, a phosphodiesterase inhibitor (infusion rate from .3 mg/kg per hour to 1.5 mg/kg per hour) was unsuccessful. Acute nonoliguric renal failure (creatinine clearance 11.9 mL/minute) developed. Five days after admission the patient had a normal sinus rhythm at 70 beats/minute (normal 12-lead ECG) and a blood pressure at 110/70 mm Hg. The next day the patient was extubated after having fully recovered, and was discharged from the ICU without neurologic, cardiac, or renal sequelae the 12th day after admission.

DISCUSSION

Atenolol is a [beta]$_1$-selective adrenergic blocker. Approximately 50% of the drug is absorbed and 50% is excreted in feces. Accumulation of atenolol in human milk has been reported. 8 Peak plasma concentrations occur 2 to 4 hours after administration Once absorbed, only 5% to 15% of the drug is bound to plasma proteins. There is no first-pass effect. The half-life of atenolol is 6 to 7 hours, and its distribution volume is .7 L/kg of body weight. Major differences between atenolol and other [beta]-blockers include a longer half-life and minimal protein binding. 5 Atenolol has been intentionally administered(by increments) in doses of up to 1,200 mg without ill effects. 10 In other cases a prolonged hemodynamic toxicity after a single 500-mg dose has been described, 7 and sinus pauses on monitor persisted for about 34 hours after ingestion of 1,000 mg of atenolol. 4 By contrast, Love 13 reported a case in which a patient remained symptom-free despite a toxic (7,140 ng/mL) [beta]-

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blocker (metoprolol) blood level (therapeutic range 30 to 280 ng/mL). 13

Several authors have emphasized that blood levels correlate poorly with activity, 1,14,15 especially in poisoning with atenolol. 11 In our patient the ECG abnormalities(Figure, C), documented a few hours before the EMD, supported the hypothesis of a toxic effect of atenolol on the myocardium even though the plasma concentration of the drug was low. It has been reported previously that cardiotoxicity may persist even after this drug has become undetectable in the blood, 6,16 probably because of active metabolites that are not detected in the plasma assay. 17

The mechanism of [beta]-blocker-induced cardiotoxicity is poorly understood. One possible explanation is that [beta]-blockers induce ion dyshomeostasis, which produces cardiac hyperpolarization. In an animal model of atenolol toxicity, Kerns et al 18 treated the animals with low extracellular K^+ and high extracellular Na^+. The result was an increase of the heart rate and the restoration of the ability to pace. In other animal experiments, a toxic overdose of [beta]-blockers led to a partial or total loss of myocardial contractility. 19 This negative effect is not related to the effect of the [beta]-blocker on the[beta] receptor or to its additional properties, but it can probably be explained by a combination of effects: a direct negative inotropic effect of the [beta]-blocker, caused by a calcium-dependent mechanism; a decrease of serum calcium related to parathormone; and a centrally determined hypotensive effect. 9,18,20 In addition to a decrease in contractility, experiments on dogs have shown a decrease in serum calcium concentration and an increase in serum phosphate concentration with unaltered serum magnesium concentration. 19

Although this electrolyte combination occurs in disorders associated with hypoparathyroidism, it is not a plausible mechanism in our patient because we found normal calcium concentration and low serum phosphate levels in her blood.

Hemodynamic effects of calcium chloride have been evaluated in rats 21 and recently in a canine model 22 of acute [beta]-blocker toxicity. The authors demonstrated that calcium chloride produces a moderate elevation of blood pressure and significant improvements in [beta]-blocker-induced decrease in cardiac index and stroke volume. They concluded that calcium chloride therapy improved depressed hemodynamic status, mainly by a positive inotropic action. In our patient, during CPR, calcium chloride repeatedly produced restoration of blood pressure. We have evidence from a drug screen that a calcium channel antagonist could not have been ingested. Laboratory investigations showed normal levels of calcium and potassium in her blood. Serum calcium has a direct effect on myocardial contractility because influx of extracellular calcium, as well as calcium from the sarcoplasmic reticulum, contributes to contraction of the myofibrils.

We have a more clear explanation for the extracardiac signs of intoxication that are sometimes seen in severe toxicity. Apnea is caused by the effect of these drugs on the central nervous system and can, itself, be the cause of death in animals. 19 Neurologic signs may reflect a low cerebral blood flow, but changes in mental status and even coma have been seen without evidence of cardiovascular compromise in patients with[beta]-adrenergic- blocker drug overdose. 11,19 Severe bronchospasm is a surprisingly uncommon feature of [beta]-blocker poisoning, 23 although in our patient, epinephrine may have counteracted this symptom.

The guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care have only recommended the use of calcium in EMD associated with hyperkalemia, hypocalcemia, and calcium antagonist overdose. 24 On the basis of this and other case reports, 25 calcium may have a therapeutic role in[beta]-blocker overdose.

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Advanced pediatric life support: state of the art

ARNO ZARITSKY, M.D.

ABSTRACT Cardiopulmonary resuscitation in children is not well studied; many of the current recommendations for advanced pediatric life support (APLS) are based on anecdotal experience rather than scientific study. The following are unique issues in APLS requiring a consensus decision: What are the best methods of vascular access and of drug delivery and dosages? What constitutes minimal paramedic training and equipment? There are also many shared controversies between APLS and ACLS, including the use of calcium, epinephrine vs isoproterenol, methoxamine, and bicarbonate. This article presents the scientific basis for these controversial issues and highlights areas where information is lacking. A discussion of these questions generated a consensus on some issues and hopefully will stimulate further study to answer the questions that were raised.
Circulation 74(suppl IV), IV-124, 1986.

PEDIATRIC cardiopulmonary resuscitation has not been well studied. Compared with that in adults, the etiology of cardiac arrest in infants and children is diverse, making studies difficult to compare. The outcome from cardiac arrest is poor in children; mortality is 97% in out-of-hospital arrests[1] and 85% for in-hospital arrests.[2,3] Throughout this manuscript, "children" refers to the entire age range of pediatric patients, recognizing that most pediatric cardiac arrests occur in infants and that they present special problems because of age-related differences in pharmacology and physiology that may alter their response to therapy.

Respiratory conditions such as near drowning and idiopathic causes such as sudden infant death syndrome are the most common etiologies of pediatric cardiac arrest.[2,4,5] Asystole (77% to 79% of total) and bradyarrhythmias (11% to 12% of total) are most frequently seen in association with cardiac arrest in children[1,4,6]; only 10% of the arrhythmias are ventricular.

Outcome in children is related to initial rhythm, being poorest with asystole and best with ventricular arrhythmias.[1,4] This relationship probably reflects myocardial response to hypoxia; as the duration of hypoxia increases, heart rate slows and eventually ceases. Ventricular arrhythmias are more likely to result in sudden cardiovascular collapse, bringing the victim to immediate attention.

This article presents current scientific knowledge in the following topics, highlighting both controversies and deficiencies in scientific information: (1) methods of vascular access and drug delivery, (2) the role of calcium in advanced pediatric life support (APLS), (3) the use of isoproterenol and methoxamine, (4) APLS delivery in the field and triage of critically ill children, (5) treatment of metabolic acidosis, and (6) antiarrhythmics in pediatric patients.

A summary of the consensus recommendations reached by the American Heart Association panel session on APLS is included at the end of this article.

Methods of vascular access and drug delivery. Establishing vascular access is an early goal in APLS. This is traditionally by peripheral or central venous cannulation, although both may be difficult to achieve in children.[7] Central venous drug administration is theoretically preferable because it produces higher and more rapid peak drug concentrations than peripheral injections.[8] Inferior vena caval injections, however, produce lower peak drug concentrations than superior vena caval injections,[9] suggesting that drug delivery above the diaphragm would be more effective. Despite these studies done in adult animals and patients, it is not clear that the site of drug administration influences outcome,[10] and pediatric studies on the influence of the site of drug injection are lacking.

If infradiaphragmatic delivery (e.g., femoral vein) is not optimal, other routes may have to be considered. An effective alternative route is via the endotracheal tube.[11] Epinephrine, atropine, lidocaine, and naloxone are all well absorbed across the bronchial mucosa,[12] although the optimum dose and pharmacokinetics of absorption have not been studied in children. Endotracheal epinephrine in anesthetized baboons produces sustained elevations of plasma epinephrine concentration for 30 min[13]; however, 10 times the intravenous dose may be required to produce the same hemodynamic effect.[14] Since drugs such as epinephrine are effective in CPR by improving coronary perfusion pressure[15] (an action dependent on arterial drug concentration), optimal endotracheal doses should be

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identified. Based on current information, it is difficult to recommend a specific endotracheal dose of epinephrine; the endotracheal route, however, has been effective and is a reasonable alternative for drug delivery when vascular access is delayed.

Fluid and drug delivery by the intraosseous route has been described for more than four decades.[16, 17] A rigid needle is inserted into the proximal tibial bone marrow, which acts as a noncollapsible venous plexus. The intraosseous route has been successfully used for blood, plasma, crystalloid, and medication administration, including dopamine and dobutamine.[18] The technique is relatively simple, has few complications,[16, 17] and should be most useful in the infant or young child (with a relatively thin boney cortex) requiring volume resuscitation, but may not be optimal in cardiac arrest in view of the potential inadequacy of infradiaphragmatic drug administration (see above). The safety of administering hypertonic bicarbonate and calcium by this route must also be established.

Use of calcium. Although calcium has positive inotropic effects and has been successfully used in the resuscitation of pediatric patients after cardiac surgery,[19] recent data implicate calcium in organ dysfunction after ischemia.[20] Calcium is essential in excitation-contraction coupling in the heart,[21] but the need for or beneficial effect from calcium in resuscitation is not established in adults[22, 23] and no information is available in pediatric CPR.

Calcium chloride has been recommended in the treatment of electromechanical dissociation (EMD) and asystole.[24] but little clinical information supports its use, and data suggest that mortality is increased in patients receiving calcium[25]; other studies, however, have found a beneficial effect in a minority of patients with EMD.[26] No data are available on either the value of calcium in pediatric CPR or on the safety of currently recommended doses, which may achieve markedly elevated plasma calcium concentrations in adults.[27]

Since calcium entry into cells mediates an important pathway leading to eventual cell death[28] and the intracellular accumulation of calcium is implicated in myocardial[29] and cerebral[30] injury, recent studies suggest that calcium-channel antagonists may be beneficial after global ischemic insults.[30] Further study is needed to define which, if any, of the calcium-channel blockers may be beneficial.

Bolus administration of calcium in APLS is clearly indicated in the treatment of documented hypocalcemia and the antagonism of the adverse cardiac effects of hyperkalemia and hypermagnesemia.[31]

Use of isoproterenol and methoxamine. During CPR the beneficial action of catecholamines is mediated by peripheral vasoconstriction and increased coronary perfusion pressure rather than by a direct stimulatory effect on the heart.[15] Methoxamine, a pure α-adrenergic agonist, has been studied for more than 20 years and has been effective in restoring a stable rhythm.[32] No clinical studies, however, have verified its effectiveness, making recommendations difficult. Concern has also been raised that potent α-adrenergic vasoconstriction may have adverse effects on organ blood flow once a stable rhythm is established.

Isoproterenol is recommended in the treatment of hemodynamically significant bradycardia.[24] Although it may be effective in this setting, isoproterenol is a potent vasodilator that can redirect blood flow away from the viscera[33] and may compromise coronary perfusion by decreasing diastolic pressure. Epinephrine infusions generally increase heart rate but do not produce significant vasodilation; therefore infusion of epinephrine may be indicated in lieu of isoproterenol in the treatment of hemodynamically significant bradycardia.

APLS delivery and triage of critically ill children. Available emergency medical services for children are not equivalent to those for adults; most paramedical services are neither equipped nor well trained to handle pediatric patients.[34] Properly sized masks, bags, MAST trousers, and other supportive equipment are often lacking, and pediatric training of paramedics often consists of only a few hours of lectures.

Pediatric arrest is characterized by a wide variety of causes and underlying diseases, but pediatric arrests occur less frequently than arrests in adults. There is currently no organized educational process to educate health providers in the special needs of the pediatric patient. In view of the high mortality in pediatric cardiac arrest, better training is needed, proper equipment must be available, and additional research in pediatric CPR is required. Communities should also identify specialized centers to care for these high-risk, complicated patients.

Treatment of acidosis. Administration of sodium bicarbonate is standard therapy for the metabolic acidosis that frequently accompanies a cardiac arrest.[24] Bicarbonate therapy was relatively deemphasized in the most recent guidelines, and appropriate emphasis was placed on airway management[35]; this is particularly important in the pediatric victim in whom respiratory diseases are a major etiology leading to cardiac arrest.[2-4, 5]

Data demonstrating adverse effects after administration of sodium bicarbonate in both nonhypoxic[36] and

hypoxic[37] lactic acidosis bring new controversy to the use of bicarbonate. These adverse effects result from the buffering action of bicarbonate, which transiently increases Pco_2; the CO_2 can cross both cell membranes and the blood brain barrier more readily than bicarbonate, resulting in intracellular and intracerebral acidosis. It is the intracellular pH rather than the blood pH that exerts a greater adverse effect on cell function. The importance of transient increases in Pco_2 after bicarbonate administration in CPR remains to be established.

If bicarbonate is potentially harmful, what else can be used? Tris-hydroxy-methyl amino methane (THAM) has been used to treat metabolic acidosis, and its buffering action occurs without an increase in Pco_2.[38] On the other hand, THAM may produce alkalosis, hypoglycemia, respiratory depression (not an issue in CPR), and hyperkalemia. THAM has not been carefully evaluated in pediatric CPR but deserves reconsideration because it may be a useful alternative agent in the treatment of metabolic acidosis.

Antiarrhythmics. Bretylium has become the first- or second-line drug in the treatment of ventricular fibrillation.[39] Bretylium has not been evaluated in children, but in view of its effectiveness, relative safety, and standard dosage recommendations in adults, it appears to be indicated in pediatric patients with ventricular arrhythmias.

I would like to acknowledge the effective leadership of Leon Chameides, M.D., in organizing the pediatric life support panels and to thank him for his helpful suggestions in the preparation of this and other manuscripts related to the APLS guidelines and course.

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Panel recommendations

The APLS panel was charged with reaching agreement on the issues presented. Since there are no current guidelines in APLS, the panel was also charged with developing reasonable guidelines. The panel operated under two guiding principles in this endeavor. First, every effort should be made to achieve consistency between the ACLS guidelines and APLS guidelines to maximize educational efficiency. Second, differences will be accepted or changes will be made from existing guidelines only when scientific data clearly support such a change.

The following specific recommendations were made by the APLS panel:

(1) A course teaching APLS skills and knowledge should be developed and sponsored by the AHA. This course would fill a void in the training of paramedics, emergency room physicians, pediatricians, critical care nurses, and others responsible for pediatric victims requiring emergency care and resuscitation. The course should emphasize early recognition and therapy as well as management of the victim suffering a cardiorespiratory arrest.

Combined with the development of an organized educational approach to advanced life support in children, the panel urges communities to develop protocols for the transfer of critically ill children to medical centers having appropriately trained personnel.

(2) Despite the evidence for better drug delivery through vascular lines in the upper extremity, the panel recognizes the frequent difficulty of obtaining any vascular access in children. There are also no data in an appropriate pediatric model demonstrating the superiority of superior vena caval system injection. Therefore, femoral venous access and saphenous vein cutdown are still recommended sites. Additionally, tibial intraosseous infusions of colloid, crystalloid, and drugs appears useful, particularly in the treatment of shock, until intravenous access is obtained. Although there are currently no data evaluating the effectiveness of intraosseous drugs during a cardiac arrest, the panel recommends use of the intraosseous route as an alternative vascular access if intravenous access cannot be quickly obtained. The panel also recommends flushing an intravenous line with 2 to 5 ml of normal saline after drug administration to aid drug delivery into the central circulation and avoid adverse drug interactions in the intravenous tubing.

Endotracheal drug administration remains a rapid and useful alternative route for the delivery of epinephrine, lidocaine, and atropine. Although experimental data suggest that a larger dose is needed, the panel believes that further studies are needed before a change in recommended doses (same as intravenous) can be made. The panel agrees that deep endotracheal injection is important to ensure drug delivery into the lower airways.

(3) There is now a sufficient body of evidence showing no beneficial effect of calcium chloride in either asystole or electromechanical dissociation. Therefore calcium chloride is no longer indicated during CPR. Calcium is indicated, however, when hypocalcemia is documented and can be helpful to reverse myocardial depression from hyperkalemia, hypermagnesemia, and overdose of a calcium-channel blocker.

(4) There are insufficient clinical data to support the use of methoxamine, a pure α-adrenergic agonist, during CPR despite extensive animal data. Additionally, although isoproterenol has been recommended in the treatment of hemodynamically significant bradycardia, there is clear evidence that isoproterenol decreases coronary perfusion pressure through its β-adrenergic-mediated vasodilating effects. Therefore, epinephrine infusion is recommended as an alternative therapy for hemodynamically significant bradycardia.

(5) Ventricular arrhythmias are unusual in children and are usually controlled with lidocaine. The panel recommends the inclusion of bretylium, however, as a second-line drug after an inadequate response to lidocaine. This recommendation is based on adult clinical studies because data in children are lacking; the adult data are felt to be sufficiently convincing to apply the drug to the pediatric victim.

(6) In keeping with the recommendations of the pharmacology panel, sodium bicarbonate is not recommended as a first-line drug in the cardiac arrest victim. Securing the airway and providing adequate ventilation and circulation for the patient are believed to be more effective in normalizing acid-base balance than the administration of bicarbonate. Concern was raised by several panel members regarding this recommendation, but experimental data shows that bicarbonate may have deleterious effects and is ineffective in normalizing pH unless ventilation is adequate. Therefore if the patient fails to respond to adequate ventilation, chest compressions, and intravenous epineph-

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rine, the panel agreed that administration of bicarbonate may be considered in the hope that some correction of acidosis and improved cardiovascular responsiveness to epinephrine will result.

In this article several issues have been outlined and the consensus recommendations of the panel have been presented. It is easier to define deficiencies in scientific knowledge than to present what is known about pediatric CPR. In many ways, APLS is a microcosm of ACLS; the use of calcium, epinephrine vs isoproterenol infusions, methoxamine, and bicarbonate are issues in ACLS as well. Specific problems in APLS consist of the special needs of vascular access, drug delivery, drug dosages, and the provision of appropriate training, education, and equipment in the management of the critically ill pediatric patient.

A need for further research exists, and the information gained needs to be applied to the field, emergency department, and in-hospital management of the critically ill infant and child. Standardization of care can best be provided by developing a curriculum in APLS that will widely disseminate the current state of the art and will stimulate further refinement based on research on the issues raised at this forum.

Memorandum to File

To File: **NDA 21 117**
Calcium Chloride 10% Injection, USP, in Plastic Syringe
Approved 1/28/00, for "treatment of hypocalcemia in those conditions requiring a prompt increase in plasma calcium levels"

From: Joanna K. Zawadzki, M.D., F.A.C.P. /S/
Medical Reviewer
Division of Metabolic and Endocrine Drug Products
ODE II, CDER, FDA

Subject: **Post-Marketing Safety Data Regarding Calcium Chloride**

Date: 2/3/00

In response to a request to the post-marketing division during the review process, Lanh Green provided a listing of over 300 adverse events regarding calcium chloride reported to the FDA Adverse Event Reporting System (AERS) between 1971 and 1999. Most of these adverse events related to the parenteral products Ringer's solution and Dianeal, which comprise lower concentrations of calcium chloride. There were a total of 29 adverse events in which calcium chloride was used. In 15 reports, calcium chloride was used concomitantly with one or more other drugs. Thus, attribution of adverse event is more difficult. In 9 reports, calcium chloride was the only listed drug. Most of the adverse events related to irritation at the injection site, and are listed by the sponsor and in textbooks. One adverse event, however, raises concern regarding drug maladministration. Apparently, the calcium chloride vial and the sterile water for injection vial are very similar in color and graphics design, and a nurse almost inadvertently withdrew 10 ml of calcium chloride to reconstitute an antibiotic vial.

Recommendation:

1) Contact sponsor regarding this drug maladministration report to review the color and graphics design of the calcium chloride and sterile water vials.
2) If there is a strong similarity in the appearance of these products, recommend an alteration in the packaging and/or labeling.

Enclosure:
FDA Adverse Event Reporting System (AERS) Report of Drug Maladministration

Distribution:
Archival:HFD580/NDA21-117
HFD510/Jenkins/Colman/McCort/Lewis/Shore/Malozowski/Zawadzki

1 page

REDACTED

Confidential

Commercial

TEAM LEADER MEMO

NDA: 21-117

SPONSOR: Abbott

DRUG: Calcium Chloride 10% Injection

PROPOSED INDICATIONS: Treatment of hypocalcemia

DATE OF SUBMISSION: 4/9/99

DATE MO REVIEW COMPLETED: 1/18/00

BACKGROUND

Abbott's calcium chloride 10% injection (CaCl) in a glass syringe predates the 1938 Food, Drug and Cosmetic Act. As such, this product was grandfathered and the indications for its use are not based on data from "adequate and well-controlled studies."

Current regulations require a full NDA submission (with clinical data) for any drug product that is proposed for marketing in a new container – in this case, plastic. Given CaCl's unique regulatory history and its accepted and long-standing use in acute clinical conditions, Dr. Murray Lumpkin, Deputy Center Director (Review Management), issued a November 6, 1998 letter to Abbott Laboratories in which he stated, " Based on your description of the products, including the apparent substantial marketing history, you should consider whether an application under section 505(b)(2), which may sometimes consist ~~of simple~~ literature/medical textbook information to support safety and efficacy, may be feasible for each of these drug products."

Thus, an NDA was filed for CaCl in plastic syringe in which reference to medical literature was made in support of four indications: Treatment of 1) hypocalcemia

Following a review of the references submitted by the sponsor and her own literature review, Dr. Zawadski determined that there were "adequate" data to only support the indication for the treatment of hypocalcemia.

During a teleconference with the sponsor on Tuesday, January 18, 1999, it was agreed that the indications section of the proposed label would include the treatment of hypocalcemia

COMMENT

Pending receipt of the agreed upon changes to the labeling, CaCl injection in plastic syringe should be approved.

/S/ 1/19/00
Eric Colman, MD
Acting Team Leader

CC: NDA arch
McCort/Zav

/S/ 1/28/00

APPEARS THIS WAY
ON ORIGINAL