Endocrine and metabolic emergencies: hypocalcaemia

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Abstract: Hypocalcaemia is a common electrolyte disturbance, especially in the inpatient setting. There are a wide variety of causes of hypocalcaemia and correct management depends on the underlying diagnosis. However, acute hypocalcaemia is associated with significant morbidity and mortality and should be managed as a medical emergency. Chronic care of the hypocalcaemic patient is also briefly described, as this is an important opportunity to reduce further admissions related to both hypocalcaemic and hypercalcaemic presentations.

Keywords: hypocalcaemia, parathyroid hormone, vitamin D

Introduction

Hypocalcaemia is a common electrolyte disturbance complicating approximately 26% of hospital admissions, and is found in as many as 88% of patients admitted to an intensive care unit (ICU) [Zivin *et al.* 2001]. There are a large number of recognized causes (see Table 1) and correct management depends on appropriate diagnosis [Matfin, 2009; Murphy and Williams, 2009]. Chronic hypocalcaemia may be asymptomatic even at low levels of serum calcium, but severe or acute hypocalcaemia is associated with predictable signs. Hypocalcaemia with neurological, muscular or cardiac dysfunction is associated with significant morbidity and mortality and should be managed as a medical emergency [Hästback and Pettilä, 2003].

Pathophysiology

Calcium, phosphate and magnesium are the major divalent cations in the body [Matfin, 2009; Murphy and Williams, 2009; Selby, 2002]. They are ingested in the diet, absorbed from the intestine, filtered in the glomerulus of the kidney, reabsorbed in the renal tubules and eliminated in the urine. Only a small amount of these three ions is present in extracellular fluid (ECF). This small, but vital, amount of ECF calcium, phosphate and magnesium is directly or indirectly regulated by vitamin D and parathyroid hormone (PTH) [Matfin, 2009; Murphy and Williams, 2009; Selby, 2002].

Although classified as a vitamin, vitamin D functions as a hormone [Pearce and Cheetham, 2010; Matfin, 2009; Murphy and Williams, 2009; Whyte and Thakker, 2009; Selby, 2002]. It acts to sustain normal plasma levels of calcium and phosphate by increasing their absorption from the intestine, and is also necessary for normal bone formation. Vitamin D₃ is synthesized by ultraviolet irradiation of 7-dehydrocholesterol, which is present in the skin or obtained from foods in the diet, many of which are fortified with vitamin D. Once vitamin D enters the circulation from the skin or intestine, it is concentrated in the liver. There it is hydroxylated to form 25-hydroxyvitamin D₃ (25-(OH)D₃). It is then transported to the kidney, where it is transformed into active 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃). The major action of the activated form of vitamin D, also called *calcitriol*, is to increase the absorption of calcium from the intestine. Calcitriol also sensitizes bone to the resorptive actions of PTH. There is also recent evidence that vitamin D controls parathyroid gland growth and suppresses the synthesis and secretion of PTH. The formation of 1,25-(OH)₂D₃ in the kidneys is regulated in feedback fashion by plasma calcium and phosphate levels.

PTH, a major regulator of plasma calcium and phosphate, is secreted by the parathyroid glands. There are four parathyroid glands located on the dorsal surface of the thyroid gland. The dominant regulator of PTH is the plasma calcium

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Table 1. Aetiology of hypocalcaemia.

Reduced entry of calcium into circulation	Increased movement of calcium out of circulation
Parathyroid dysfunction: Hypoparathyroidism Autoimmune Autoimmune polyglandular syndrome Postoperative Infiltrative Hypomagnesaemia Hypermagnesaemia Congenital disorders of the parathyroid glands Di George syndrome Defects in calcium-sensing receptor Pseudohypoparathyroidism secondary to G-protein defects Vitamin D deficiency: Dietary or malabsorption Lack of sunlight exposure Renal impairment	Movement into bone stores: 'Hungry bone' syndrome Osteoblastic metastases (e.g. prostate, breast) Chelation of ionized calcium: Acute pancreatitis Hyperphosphataemia Renal impairment Tumour lysis syndrome Rhabdomyolysis Citrate or EDTA in context of transfusions and phlebotomy Miscellaneous: Sepsis Drugs including chemotherapeutic agents and Foscarnet

concentration. A unique calcium receptor on the parathyroid cell membrane (extracellular calcium-sensing receptor) responds rapidly to changes in plasma calcium levels [Matfin, 2009; Murphy and Williams, 2009; Selby, 2002]. When the plasma calcium level is high, PTH is inhibited and the calcium is deposited in the bones. When the level is low, PTH secretion is increased and calcium is mobilized from the bones. The response to a decrease in plasma calcium is prompt, occurring within seconds.

The main function of PTH is to maintain the calcium concentration of the ECF. It performs this function by promoting the release of calcium from bone, increasing the activation of vitamin D as a means of enhancing intestinal absorption of calcium, and stimulating calcium conservation by the kidney while increasing phosphate excretion.

Aetiology

Calcium homeostasis is maintained through interactions involving the parathyroid glands, kidneys, bones and vitamin D metabolism [Matfin, 2009; Murphy and Williams, 2009; Whyte and Thakker, 2009; Cooper and Gittoes, 2008; Selby, 2002]. Hypocalcaemia occurs with either decreased entry of calcium into the blood supply, or through sequestration and effective removal of calcium (see Table 1). The most common cause of hypocalcaemia in the general population is vitamin D deficiency. However, the most commonly encountered cause of acute hypocalcaemia is postoperative hypoparathyroidism in the context of neck

surgery. Hypoparathyroidism can also less commonly be due to autoimmune or infiltrative conditions [Shoback, 2008]. Congenital disorders and pseudohypoparathyroidism cause hypocalcaemia through defects in the calcium-sensing receptor or parathyroid receptor. Hypomagnesaemia and hypermagnesaemia both cause abnormal PTH production and secretion. Vitamin D deficiency, which may be primary in the context of dietary or environmental causes or secondary due to hepatic or renal impairment, can cause hypocalcaemia or may exacerbate hypocalcaemia caused by other processes [Pearce and Cheetham, 2010].

Excessive movement of calcium into bone occurs with 'hungry bone' syndrome and osteoblastic bone disease including metastatic cancer (e.g. breast or prostate cancer). Hyperphosphataemia, most commonly seen in renal impairment but also a feature of tumour lysis syndrome and rhabdomyolysis, causes hypocalcaemia through sequestration and complexing of ionized calcium. Acute pancreatitis is associated with the formation of calcium complexes within the abdominal cavity. Calcium chelation can occur with ethylenediaminetetraacetic acid (EDTA), or citrate but is rare with normal renal and hepatic function. Sepsis-related hypocalcaemia is multifactorial but significant factors include renal impairment, magnesium abnormalities, release of inflammatory cytokines and frequent transfusions. Finally, a number of medications are associated with hypocalcaemia and this has been reviewed elsewhere [Liamis *et al.* 2009].

Diagnostic considerations

Normally, ECF calcium is maintained within a narrow reference range (2.1–2.6 mmol/L; 8.5–10.5 mg/dl). Hypocalcaemia is defined as a serum calcium level of less than 2.0 mmol/L (<8 mg/dl) or an ionized calcium level of less than 1.0 mmol/L (<4 mg/dl) [Matfin, 2009]. Forty per cent of total serum calcium is protein bound with the majority bound to albumin, whilst 50% is ionized and active. Albumin levels should therefore be considered when assessing possible hypocalcaemia, although most laboratories now provide a corrected calcium level. However, in states of acute albumin fluctuations such as sepsis, measurement of ionized calcium is a more reliable assessment of calcium status.

The finding of acute hypocalcaemia, whilst not delaying the emergent treatment outlined below, should prompt biochemical testing to elicit a cause [Cooper and Gittoes, 2008]. PTH, phosphate and magnesium levels, and vitamin D status should be evaluated in every patient with hypocalcaemia, and other tests that suggest a cause, such as renal function and markers of bone activity (e.g. alkaline phosphatase), should be considered. In addition, assessment of acid–base status is also warranted (i.e. alkalosis tends to decrease ionized calcium levels due to increased binding to albumin).

Clinical signs and features

The clinical manifestations of hypocalcaemia depend on the degree of hypocalcaemia (ionized calcium level) and the rate of its development. The majority of symptoms associated with hypocalcaemia relate to neuromuscular dysfunction. Perioral tingling and acral paraesthesia are the earliest symptoms and are almost always present, whilst other frequently reported features include muscle stiffness and myalgia, and confusion. Tetany is typically seen when the ionized calcium drops below 1.0 mmol/L (<4 mg/dl).

Chvostek's sign describes ipsilateral twitching of the facial muscle groups including the perioral, nasal and ocular regions, when the facial nerve is tapped 2 cm anterior to the earlobe beneath the zygomatic bone. However, perioral twitching is also seen in up to 25% of normal individuals, and conversely Chvostek's sign is negative in approximately 30% of those with hypocalcaemia [Hoffman, 1958].

Trousseau's sign is more sensitive (94%) and specific for hypocalcaemia and describes flexion of the wrist and metacarpophalangeal joints,

hyperextension of the fingers and flexion of the thumb producing a characteristic deformity known as *main d'accoucheur*. It is elicited by occluding the brachial artery 20 mmHg above systolic pressure for 3 minutes and is positive in only 1% of normocalcaemic patients.

Neurological manifestations of hypocalcaemia include dementia, depression, calcification of the basal ganglia and extrapyramidal systems, and seizures. In known epilepsy, hypocalcaemia lowers the threshold for seizure activity.

Cardiac features of hypocalcaemia include electrocardiographic (ECG) changes and cardiac impairment. The ECG hallmark of hypocalcaemia is prolongation of the corrected QT interval, the duration of which is proportional to the degree of hypocalcaemia. Other recognized abnormalities include reduced voltage or negative T waves, although T waves are normal in more than half of those with hypocalcaemia, and changes that mimic acute anterior myocardial infarction. Low calcium levels may cause resistance to digoxin, hypotension and refractory heart failure.

Acute intervention

Symptomatic patients (e.g. tetany, seizures, laryngospasm or cardiac arrhythmias or dysfunction) or those with a corrected calcium below 2 mmol/L (<8 mg/dl) should prompt urgent intervention with intravenous calcium replacement (see Figure 1). This treatment should be given in hospital and calcium levels carefully monitored (usually 4–6 hourly). Ten to twenty ml (1–2 standard ampoules) 10% calcium gluconate should be infused slowly in 50–100 ml 0.9% saline (or 5% dextrose) over 10–20 minutes (with cardiac monitoring). Calcium gluconate is the preferred formulation for acute calcium replacement and should be repeated until the patient is symptom free. Ten ml of 10% calcium chloride can also be used, but is more irritating to the veins than calcium gluconate. This will increase the serum calcium levels for 2–3 hours, and should be followed by a slow infusion of 100 ml (10 standard ampoules) 10% calcium gluconate in 1 L 0.9% saline (or 5% dextrose). The infusion should be commenced at 50–100 ml/hour and titrated to maintain a serum calcium level in the low–normal range (~2.0–2.1 mmol/L [~8–8.5 mg/dl]).

A solution of 10% calcium gluconate contains 10 g of calcium gluconate in 100 ml, and 10 g of

Figure 1. An algorithm for the management of acute hypocalcaemia.

calcium gluconate contains about 900 mg of elemental calcium. Therefore, adding 100 ml of 10% calcium to 1 L of fluid gives a preparation close to 1 mg/ml of elemental calcium. Calcium infusion is usually given at 0.5–1.5 mg/kg per hour of elemental calcium.

Infusion of calcium compounds is occasionally associated with the induction of cardiac arrhythmias and infarction (hence, the need for cardiac monitoring), and may cause chelation with resultant end-organ deposition if hyperphosphataemia is present and not addressed. Care should be taken if the patient has a known history of coronary artery disease or arrhythmias but in most

situations correction of severe hypocalcaemia would take priority.

Hypomagnesaemia should always be corrected if detected. Empirical administration of magnesium is recommended if there is likely to be a delay in acquiring a magnesium level. The preferred infusion is magnesium sulphate 2 g (8 mmol) in 5% dextrose over 10–20 minutes. This can be followed by a further 4 g (16 mmol) in the next 4 hours if necessary.

Intravenous calcium should be continued until the patient is receiving an effective regimen of oral calcium and vitamin D.

Maintenance therapy

Oral calcium replacement therapy should be initiated as soon as possible along with vitamin D replacement. Calcitriol (1,25-(OH)₂D₃) is the preferred preparation of vitamin D for patients with severe acute hypocalcaemia because of its rapid onset of action. Calcitriol should be started immediately at a dose of 0.5–1 µg per day. The doses of calcitriol and oral calcium should be adjusted to maintain serum calcium levels in the low–normal range (~2.0–2.1 mmol/L [~8–8.5 mg/dl]). For most other patients, the choice of vitamin D preparation will depend on the cause of the hypocalcaemia and the desired pharmacological properties (i.e. rapid acting versus long acting, oral versus parenteral, etc).

Monitoring of effect of vitamin D replacement should account for the varying half-lives of the available preparations. Whilst 1,25-(OH)₂D₃ has a half-life of approximately 6 hours, 25-(OH)₂D₃ preparations have half-lives of weeks to months. Repeat assessment of vitamin D levels when using these longer-acting products should be delayed until 3 months have elapsed since commencement [Whyte and Thakker, 2009].

A second consideration in those deficient of PTH action at the renal tubule is the resultant unopposed calciuria. Repletion of calcium to levels within the normal range reported by most laboratories will lead to excessive urinary calcium excretion, therefore favouring nephrolithiasis and nephrocalcinosis. A serum calcium level just below the normal range that relieves the patient's symptoms should therefore be the therapeutic goal. Urinary calcium excretion should be measured once a satisfactory calcium level has been achieved, either with a 24-hour collection of urine or calculated on a spot urine with a

calcium : creatinine ratio. If excessive excretion is detected, a lower serum calcium target should be set. If use of a lower target is associated with hypocalcaemic symptoms, a thiazide diuretic can be beneficial due to the reduced tubular calcium excretion produced by this class of medicines.

Even in stable patients, serum and urinary calcium levels should be monitored every 6 months to check for hypercalcaemia and hypercalciuria.

Emerging therapies

Teriparatide, a synthetic injectable human PTH (1-34), is currently licensed only for the treatment of osteoporosis. However, several randomized controlled trials have shown that when compared with conventional therapies (i.e. calcium and vitamin D), administration of teriparatide achieves similar restoration of normal calcium levels and prevents bone demineralization in patients with hypoparathyroidism [Winer *et al.* 2003]. In addition, urinary calcium levels remain normal in the teriparatide group in contrast to the frequent hypercalciuria observed (with consequent increased risk of renal disease) in conventionally treated patients. Furthermore, case reports suggest there may be a role for teriparatide in patients who fail to become asymptomatic on conventional therapies [Hall and Gallacher, 2006]. Patients with negligible or non-existent endogenous PTH hormone secretion such as postparathyroidectomy patients may benefit from use of this agent although current high costs preclude routine use. Typically patients are treated with 20 µg teriparatide subcutaneously, twice a day, or up to 2 µg/kg/day.

Other PTH analogues are in development for the treatment of hypoparathyroidism. These include NPSP558, which is an injectable human PTH (1-84) currently undergoing phase 3 clinical trials in hypoparathyroid patients.

Drugs that antagonize the calcium-sensing receptor (termed calcilytics), thereby increasing PTH secretion, are in development and may also have a role in the management of hypoparathyroidism [Saidek *et al.* 2009].

Conclusions

Hypocalcaemia is a common electrolyte disturbance, especially in the inpatient setting. Acute hypocalcaemia is associated with significant morbidity and mortality and should be managed as a medical emergency. Management of chronic

hypocalcaemia is complex due to the varying underlying diagnoses and different calcium and vitamin D formulations available. Patients on long-term, potent vitamin D formulations should be closely monitored for complications of therapy.

Conflict of interest

None declared.

References

- Cooper, M.S. and Gittoes, N.J.L. (2008) Diagnosis and management of hypocalcaemia. *BMJ* 336: 1298–1302.
- Hall, L. and Gallacher, S.J. (2006) Primary Hypoparathyroidism Resistant to Conventional Therapy. *Scott Med J* 51: 54.
- Hästbacka, J. and Pettilä, V. (2003) Prevalence and predictive value of ionized hypocalcemia among critically ill patients. *Acta Anaesthesiol Scand* 47: 1264–1269.
- Hoffman, E. (1958) The Chvostek sign: a clinical study. *Am J Surg* 96: 33–37.
- Liamis, G., Milionis, H. and Elisaf, M. (2009) A review of drug induced hypocalcemia. *J Bone Miner Metab* 27: 635–642.
- Matfin, G. (2009) Disorders of fluid balance and electrolytes. In: Porth, C.M. and Matfin, G. (eds), *Pathophysiology: Concepts of Altered Health States* (8th Ed). Wolters Kluwer Health: Philadelphia, PA.
- Murphy, E. and Williams, G. (2009) Hypocalcaemia. *Medicine* 37: 465–468.
- Pearce, S.H.S. and Cheetham, T.D. (2010) Diagnosis and management of vitamin D deficiency. *BMJ* 340: 142–147.
- Saidek, Z., Brazier, M., Kamel, S. and Mentaverri, R. (2009) Agonists and allosteric modulators of the calcium-sensing receptor and their therapeutic applications. *Mol Pharmacol* 76: 1131–1144.
- Selby, P. (2002) Normal calcium homeostasis. *Clin Rev Bone Mineral Metab* 1: 3–9.
- Shoback, D. (2008) Hypoparathyroidism. *N Engl J Med* 359: 391–403.
- Whyte, M.P. and Thakker, R.J. (2009) Rickets and osteomalacia. *Medicine* 37: 483–488.
- Winer, K.K., Ko, C.W., Reynolds, J.C., Dowdy, K., Keil, M., Peterson, D. *et al.* (2003) Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *J Clin Endocrinol Metab* 88: 4214–4220.
- Zivin, J., Gooley, T., Zager, R. and Ryan, M. (2001) Hypocalcemia: a pervasive metabolic abnormality in the critically ill. *Am J Kidney Dis* 37: 689–698.

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