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Severe hypophosphataemia associated with the management of hyperlipaemia in a miniature pony

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Summary

This report describes a case of severe hypophosphataemia associated with the management of hyperlipaemia in a miniature pony following colic surgery. Clinical signs attributed to hypophosphataemia included obtundation, anorexia, tachycardia, tachypnoea and generalised muscle fasciculations. Hyperlipaemia was managed with enteral and partial parenteral nutrition; insulin was also administered to control hyperglycaemia after the initiation of caloric support. Specific therapy for hypophosphataemia consisted of parenteral potassium phosphate at 0.03 mmol/kg bwt/h (i.v.). The pony made a full recovery without further complications. Hypophosphataemia may be an under-recognised clinical problem in certain populations of critically ill equids, such as those with hyperlipaemia and receiving

insulin as part of their management. The routine measurement of phosphate concentration in these cases is recommended.

Introduction

Hyperlipaemia is a well-described condition of miniature equine breeds that enter a negative energy balance, due to the high hepatic efficiency of this species in the synthesis and release of triglycerides (TG) into the circulation (Hughes *et al.* 2004; McKenzie 2011). Conditions that increase energy demand or limit energy intake, including recent colic surgery, are risk factors for hyperlipaemia (Jeffcott and Field 1985; Hughes *et al.* 2003). Differences in glucose, insulin and lipid dynamics, and the high incidence of obesity, may also explain the especially frequent occurrence of hyperlipaemia in miniature ponies and donkeys (Gay *et al.* 1978; Burden *et al.* 2011).

Various terminologies have been used to describe the degree of hypertriglyceridaemia in equids, including hyperlipidaemia, severe hypertriglyceridaemia and hyperlipaemia (McKenzie 2011). Hyperlipaemia is used when TG concentrations exceed 5.7 mmol/l (500 mg/dl), the plasma becomes grossly lipaemic and clinical signs of disease are present. Conversely, hyperlipidaemia is used when TG concentrations are between 1.0 and 5.7 mmol/l, the plasma remains clear and clinical signs of disease are absent. Severe hypertriglyceridaemia is usually reserved to describe TG concentrations greater than 5.7 mmol/l in large-breed horses that are typically asymptomatic (Dunkel and McKenzie 2003).

Early reports of equids with hyperlipaemia suggested that the prognosis was poor, with survival rates as low as 30% (Watson *et al.* 1992). The routine measurement of plasma TG concentrations in predisposed individuals is now standard practice at many hospitals. Early and aggressive caloric support has now improved the survival of individuals in which hypertriglyceridaemia is promptly identified (Durham 2006; Durham and Thiemann 2015).

Hypophosphataemia is a well-recognised comorbidity of critically ill humans that is associated with increased mortality when left untreated (Bugg and Jones 1998). Hypophosphataemia has also been mentioned as a potential sequela to hyperlipaemia, parenteral nutrition and insulin therapy in equids (Magdesian 2010; Toribio 2015), and it may therefore contribute to the morbidity or mortality of affected animals if not recognised and treated appropriately. To the authors' knowledge, there are no clinical case descriptions of acute hypophosphataemia in the equine literature. The purpose of this report was to describe the clinical progression of a miniature pony with severe hypophosphataemia associated with the management of hyperlipaemia, and to highlight the importance of routine phosphate measurement in these cases.

Case details

History and initial case management

A 10 year old miniature pony gelding (139 kg; BCS 7 out of 9 [Henneke *et al.* 1983]) presented to the University of Melbourne's Equine Centre with a 10 hour history of moderate colic that had been unresponsive to medical management. The referring veterinarian had administered flunixin meglumine (1.1 mg/kg bwt i.v.), xylazine hydrochloride (0.2 mg/kg bwt i.v.) and paraffin oil (200 ml via nasogastric tube); however, colic improved only temporarily. On admission the pony was moderately painful. Pertinent physical examination findings included tachycardia (80 beats/min), tachypnoea (30 breaths/min), absent borborygmi and abdominal distension. The oral mucous membranes were of normal colour but tacky to the touch with a prolonged capillary refill time. A limited rectal examination revealed marked gas distension of the large colon. Packed cell volume (33%; reference 25–45%), plasma total solids (56 g/l; reference 52–79 g/l), L-lactate (2.3 mmol/l; reference <1.5 mmol/l) and glucose (6.9 mmol/l; reference 4.2–6.7 mmol/l) concentrations were measured. Plasma electrolyte concentrations (sodium, potassium, chloride, ionised calcium) and venous blood gas analyses performed on admission were within normal ranges.

Based on the history, clinical findings and increasing level of pain, the pony was administered flunixin meglumine (1.1 mg/kg bwt i.v.), procaine penicillin (22 mg/kg bwt i.m.) and gentamicin (6.6 mg/kg bwt i.v.), and an exploratory laparotomy was performed. At surgery, marked gas distension of the large colon was relieved and a faecalith removed from the transverse colon via an enterotomy at the pelvic flexure. The pony received a buffered and balanced, polyionic crystalloid solution (Hartmann's[1]) whilst under anaesthesia (10 ml/kg bwt/h i.v.) and for 6 hours post-operatively (5 ml/kg bwt/h i.v.). Recovery from anaesthesia was uneventful.

Post-operative case management

Six hours after surgery the pony was bright and alert. Pertinent physical examination findings included tachycardia (60 beats/min) and reduced borborygmi. Hydration was considered adequate on the basis of physical examination findings, packed cell volume (32 %), plasma total solids (55 g/l) and L-lactate (1.2 mmol/l) concentration. Blood glucose concentration was 6.7 mmol/l, whilst plasma electrolyte concentrations (sodium, potassium, chloride, ionised calcium) and venous blood gas analyses were within normal ranges. Mild hyperlipidaemia was identified when plasma TG concentration (2.3 mmol/l; reference 0.1–1.0 mmol/l) was measured as part of the routine monitoring protocol for miniature equids. The pony had been inappetent for approximately 24 hours at this time.

A selection of fresh grass, pasture hay, lucerne chaff and pelleted feed was offered to encourage voluntary feed intake. Intravenous fluid therapy was discontinued, with a plan to closely monitor hydration status and water intake during the next 24 hours. Flunixin meglumine (1.1 mg/kg bwt i.v., q12h) was administered to provide pain relief. Post-operative antimicrobial prophylaxis consisted of procaine penicillin (22 mg/kg bwt i.m., q12h) and gentamicin (6.6 mg/kg bwt i.v., q24h) for 3 days. The pony maintained a moderate appetite during the first day, although due to the many feed options made available, actual intake was difficult to quantify. Hyperlipidaemia was found to have progressed 12 hours post-operatively (TG 4.3 mmol/l). Additional caloric support was instituted in an attempt to avert the potential development of clinical hyperlipaemia.

A pelleted feed (Gumnuts[2]; 14 MJ/kg digestible energy, 16% protein, 8% fibre, 7% fat) was blended with water to form a gruel and administered via nasogastric tube every 4 hours to meet estimated resting energy requirements of 100 kJ/kg bwt/d (Durham and Thiemann 2015). However, hyperlipidaemia continued to progress and TG concentrations were 5.7 mmol/l when measured 18 hours after surgery. Additional caloric support was subsequently provided with a balanced, polyionic (Hartmann's[1]) solution supplemented with dextrose to a concentration of approximately 2.5% and potassium chloride to a concentration of approximately 20 mmol/l. An initial maintenance fluid rate of 2 ml/kg bwt/h (i.v.) delivered dextrose at 1 mg/kg bwt/min, providing approximately 25 kJ/kg bwt/d. Enteral nutrition continued as outlined previously to provide the remainder of the estimated resting energy requirement. Blood glucose concentrations were measured regularly (q1h for the first 6 h and q2h for the next 12 h) after commencing the dextrose infusion (Fig 1). Significant hyperglycaemia (13.8 mmol/l; reference 4.6 – 7.9 mmol/l) was encountered after 3 hours of the dextrose infusion, for which a dose of regular insulin was administered (0.1 i.u./kg bwt s.c.). Blood glucose concentrations subsequently decreased and remained within acceptable ranges thereafter (Fig 1).

On the second day of hospitalisation and 30 hours after surgery, the pony was obtunded and minimally responsive to stimuli. Rectal temperature (38.0°C) was normal, but the pony was tachycardic (60 beats/min, regular rhythm) and tachypnoeic (40 breaths/min). Prominent generalised muscle fasciculations, most evident in the triceps and quadriceps muscle groups, were present. Triglyceride concentration was again higher (8.3 mmol/l) and the plasma now appeared lipaemic. Packed cell volume (35%), plasma total solids (58 g/l), and L-lactate concentration (1.3 mmol/l) were within normal ranges. A complete plasma biochemistry profile showed electrolyte concentrations (sodium, potassium, chloride, total

calcium, total magnesium) and markers of muscle, liver and renal function to be within normal ranges. However, plasma phosphate concentration was extremely low (0.1 mmol/l; reference 0.8–1.8 mmol/l).

Specific therapy to correct hypophosphatemia was initiated. Potassium phosphate[3] (1 mmol/ml phosphate ions; diluted in 0.9% saline solution) was provided at a rate of 0.03 mmol/kg bwt/h (i.v.). Enteral nutrition and the dextrose infusion continued as previously described. Phosphate concentration measured 8 hours after commencement of the infusion had only improved marginally (0.2 mmol/l) and clinical signs attributed to hypophosphataemia persisted. The infusion was continued overnight at 0.03 mmol/kg bwt/h.

On the third day of hospitalisation and 54 hours after surgery, the pony appeared bright and alert and muscle fasciculations had ceased. Physical examination findings were unremarkable. Phosphate concentration (24 hours after commencing the infusion) had improved to 0.6 mmol/l and hyperlipaemia had resolved (TG 1.4 mmol/l, transparent plasma). The phosphate and dextrose infusions were discontinued later that day, because phosphate and TG concentrations had returned to normal ranges (Fig 1) and the pony was eating well. The pony was walked to grass every 4 hours, small meals of chaff and pellets were provided every 6 hours, and hay was re-introduced using a graduated protocol for feeding post-operative colic patients. The pony was discharged on day 8 of hospitalisation and was reported to be clinically healthy 6 months later.

Discussion

Phosphate is an essential anion that must be readily available to cells for effective energy homeostasis (DiBartola and Willard 2012). Phosphate actively participates in glycolytic processes through the activation of key enzymes and the phosphorylation of many intermediate metabolites. The energy that is ultimately utilised by cells is stored within the phosphate bonds of adenosine triphosphate (ATP). Phosphate also plays important roles in cell membrane structure, acid-base equilibrium, oxygen transport and gene transcription (Toribio 2010). Most phosphorus (85%) is stored in the body as hydroxyapatite in bone, 14 to 15% is intracellular and less than 1% is extracellular (Schropp and Kovacic 2007). Approximately two-thirds of circulating phosphate is organic (as phospholipids and phosphoproteins) while the remaining one-third consists of the inorganic form that is measured by chemistry analysers.

Hypophosphataemia is likely to have the most profound effect on tissues with a high metabolic requirement such as erythrocytes, skeletal muscle and the central nervous system.

The clinical signs of hypophosphataemia in horses are not well characterised, but those described in human patients include muscular weakness, myalgia, obtundation, seizures, respiratory insufficiency and cardiac arrhythmias (Gaasbeek and Meinders 2005). More severe clinical signs include rhabdomyolysis and haemolytic anaemia. In agreement with these observations, the pony in this case report demonstrated obtundation, tachycardia, tachypnoea and generalised muscle fasciculations. Although these clinical signs are relatively non-specific, in the authors' opinion, the severity of obtundation and muscle fasciculations were more pronounced than expected with hyperlipaemia alone.

Hypophosphataemia can occur as the result of inadequate intake, excessive losses or intracellular redistribution. Chronic renal failure may be the most common cause of hypophosphataemia in horses, although clinical problems attributed to hypophosphataemia in these cases have not been recognised (Schott 2007). Other causes of hypophosphataemia include prolonged insufficient dietary intake or absorption, starvation and 'refeeding syndrome', parenteral nutrition, insulin therapy, respiratory alkalosis, hyperparathyroidism or the release of parathyroid hormone-related protein by certain tumours (Toribio 2011). Phosphatonins such as fibroblast growth factor-23 may play a role in the development of hypophosphataemia in critically ill humans through the induction of phosphaturia (Berndt and Kumar 2007). Spurious results should also be considered when evaluating phosphate concentrations; however, the presence of lipaemia usually causes a false increase in phosphate concentration (Hughes *et al.* 2004).

The development of hypophosphataemia in this pony was attributed to an intracellular redistribution of phosphate associated with the combination of probable insulin resistance, short-term inappetence, hyperlipaemia, the provision of enteral and partial parenteral nutrition, and the administration of exogenous insulin. The intracellular movement of phosphate accompanies insulin-mediated glucose uptake into cells in order to sustain glycolytic processes (Bugg and Jones 1998). Alkalaemia (respiratory alkalosis, bicarbonate administration) and catecholamine release also stimulate glycolysis and promote an intracellular redistribution of phosphate. Hypophosphataemia can be further exacerbated if intracellular phosphate stores become depleted during a period of anorexia before the initiation of caloric support.

Insulin therapy might be a precipitating cause in some cases of hypophosphataemia, although it is often difficult to separate this effect from coexisting risk factors. Although hypophosphataemia can occur without the administration of exogenous insulin, in previous cases managed by the authors the appearance of clinical signs attributed to

hypophosphataemia only occurred after exogenous insulin was given. Therefore, the routine monitoring of phosphate concentrations may be warranted in equids receiving insulin therapy.

Anecdotally, some clinicians have experience with the management of acute hypophosphataemia in equids that are being managed for hyperlipaemia (Toribio 2015). However, hypophosphataemia was not reported as a comorbidity in any of the major clinical case series of equine hyperlipaemia (Watson *et al*. 1992; Moore *et al*. 1994; Mogg and Palmer 1995; Dunkel and McKenzie 2003; Hughes *et al*. 2003; Durham 2006; Burden *et al*. 2011). It is not clear if this is because the animals studied were normophosphataemic or because phosphate concentrations were not measured. The absence of phosphate from some biochemistry panels could mean that hypophosphataemia is an under-recognised clinical problem in equids with hyperlipaemia.

Hypophosphataemia is a relatively frequently encountered condition in critically ill human patients (Taylor *et al.* 2004). The degree of hypophosphataemia can be defined as mild (0.66–0.80 mmol/l), moderate (0.32–0.65 mmol/l) and severe (<0.32 mmol/l) (Gaasbeek and Meinders 2005). Severe hypophosphataemia is associated with increased morbidity and mortality in hospitalised human patients and there is strong evidence that targeted phosphate replacement improves survival (Bugg and Jones 1998). However, there is conflicting evidence as to whether moderate hypophosphatemia requires specific treatment (Amanzadeh and Reilly 2006).

Recommendations for phosphate replacement therapy in horses have been extrapolated from human and small animal guidelines (Toribio 2015). Parenteral (i.v.) phosphorus replacement been suggested at rates of 0.01 to 0.08 mmol/kg bwt/h (Amanzadeh and Reilly 2006; DiBartola and Willard 2012). More aggressive rates, up to 0.3 mmol/kg bwt/h for 1 to 2 hours, have also been used (Geerse *et al.* 2010). One approach that has been suggested for horses is to replace the estimated deficit over a 1-hour period (yielding a rate of up to 0.3 mmol/kg bwt/h) with the treatment repeated every 8 hours as necessary (Toribio 2015). The extracellular phosphate deficit (mmol) can be calculated as: bwt (kg) x (desired phosphate concentration [mmol/l] – current phosphate concentration [mmol/l]) x 0.3 (the extracellular fluid coefficient). Care must be taken to avoid iatrogenic hyperphosphataemia, although the threshold rate at which this becomes a concern is not known for horses. In the present case, a cautious rate of parenteral phosphate supplementation was empirically selected (0.03 mmol/kg bwt/h), resulting in the resolution of clinical signs in 24 hours and a gradual return to normophosphataemia in 32 hours.

This case report highlights the importance of phosphate measurement in order to identify hypophosphataemia in critically ill equids, such as those with hyperlipaemia. Insulin resistance, enteral or parenteral nutrition, the administration of exogenous insulin and increased substrate phosphorylation may result in an acute intracellular shift of phosphate. Specific phosphate replacement therapy in cases of severe hypophosphataemia is warranted.

Authors' declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Institutional animal ethics approval was not required for this case report. Owner consent was obtained for all aspects of case management and prior to submission of the manuscript.

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Antimicrobial stewardship policy

The pony was not administered quinolones, extended spectrum beta-lactam antimicrobials or macrolides.

Authorship

All authors contributed to clinical case management. The manuscript was drafted by N. J. Bamford and revised by the other authors. All authors approved the final version of the manuscript.

Manufacturers' addresses

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[3]Hospira, Melbourne, Victoria, Australia.

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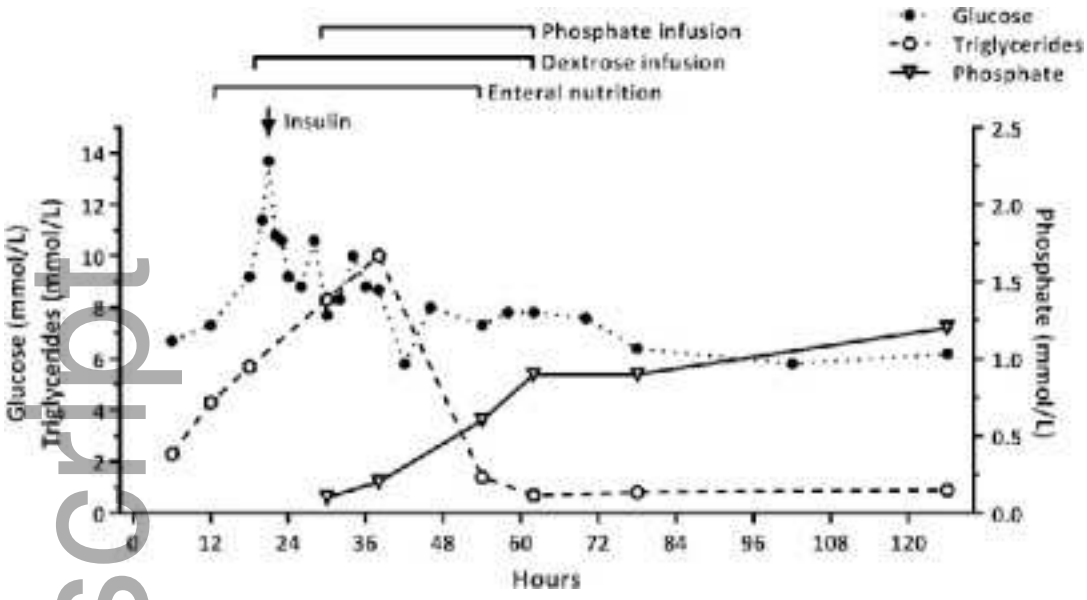
Figure legend

Fig 1: Sequential measurements of glucose, triglyceride and phosphate concentrations in this case. Time 0 indicates the end of surgery.



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