Bighead in Horses - Not an Ancient Disease

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Summary

In 1974 nutritional secondary hyperparathyroidism (NSH), *osteodystrophia fibrosa* (OF) or 'bighead' was first diagnosed in Australian horses grazing subtropical pastures. Since then it has been widely recognized in horses grazing buffel, pangola, setaria, kikuyu, green panic, guinea, signal and purple pigeon grasses. These tropical grasses, planted along the seaboards of Australia, contain oxalate – a chemical which significantly interferes with mineral utilization by horses. This article reviews the literature on NSH and presents evidence that the condition continues to occur 36 years after it was originally described in Australian horses grazing tropical and subtropical pastures.

Introduction

First described in 400AD, nutritional secondary hyperparathyroidism (NSH), is considered a rare disease. Also referred to as "bran disease", "bighead" and "Miller's disease", NSH has been reported in horses in Australia (Jones et al 1970; Groenendyk and Seawright 1974; McKenzie 1982; Caple et al 1982), Canada (Menard et al 1979), Ethiopia (Clarke et al 1996), Hawaii (Gusman 2004), Hong Kong (Mason and Watkins 1988), Japan (Chiba et al 2000; Sasaki et al 2005), Netherlands (Benders et al 2001), New Zealand (Hoskin and Gee 2004), Panama (Williams et al 1991); the Philippines (Gonzalez and Villegas 1928), South Africa (Ronen et al 1992), Spain (Estepa et al 2006) and the United States (Joyce et al 1971; David et al 1997). The disease is caused by hypocalcaemia induced by a diet with a persistent imbalance of calcium and phosphorous (Krook and Lowe 1964; Krook 1968; Joyce et al 1971; Schryver et al 1971; Argenzio et al 1974; Walthall and Mckenzie 1976; Capen 1989). NSH has been described in unweaned foals (Estepa et al 2006), stabled horses (Caple et al 1982; Mason and Watkins 1988) and grazing horses (Groenendyk and Seawright 1974; Hoskin and Gee 2004). Several tropical grasses contain oxalic acid at levels that significantly interfere with calcium and other cation utilization by horses (Franceschi and Horner 1980; Blayney et al 1981a; Gartner et al 1981; McKenzie et al 1981, 1982, 1984, 1985, 1988, 1994; McKenzie and Schultz 1983; Hintz et al 1984; Cheeke 1995; Marais 2001; Allan et al 2007; NSW DPI 2008). This review focuses on NSH occurring in horses in Australia grazing pasture, with particular emphasis on oxalate-containing pastures.

Aetiology

Secondary hyperparathyroidism is an excessive production of parathyroid hormone (PTH) due to decreased serum ionized calcium or magnesium. Regardless of its genesis, persistent hypocalcemia stimulates hyperactivity of the parathyroid glands and a secondary hyperparathyroidism is induced (Krook 1968). The most common cause of secondary hyperparathyroidism is a dietary calcium:phosphorus imbalance and is referred to as NSH. A diet high in phosphorus, low in calcium or with a calcium:phosphorus ratio of less than 1:1, will cause NSH regardless of whether dietary calcium is supplied at optimal or even excessive levels (Krook 1968). In addition, high phosphorus diets depress calcium and magnesium digestibility (Schryver et al 1971; van Doorn et al 2004).

Certain grasses contain a high content of oxalates that bind calcium to form calcium-oxalate ($Ca[COO]_2$), which is insoluble at the alkaline pH most common in the horses intestinal tract. In the horse, most ingested oxalate is utilized as a carbon source by bacteria in the caecum. The bulk of dietary calcium is absorbed in the upper small intestine of the horse (Schryver at al 1970), therefore, calcium freed by bacterial action in the lower alimentary tract would be unavailable for absorption (McKenzie et al 1981). Grasses with more than 0.5% oxalate or calcium:oxalate ratios of less than 0.5 result in a negative calcium balance and are capable of inducing hypocalcaemia in horses (Walthall and McKenzie 1976; Blayney et al 1981a,b; McKenzie 1985, 1988; McKenzie et al 1981; McKenzie and Schultz 1983).

Oxalates

An equine diet with a 1% oxalate content reduces calcium absorption by 66% and increases faecal calcium excretion (Schwartzman et al 1978). Oxalate content of grasses under conditions of rapid growth may exceed 6% which is enough to bind the entire calcium content of the grass (Marais 1990). Calcium crystals associate with poorly digestible tissue such as the xylem and phloem which further reduces the availability of calcium (Franceschi and Horner 1980). In addition, oxalic acid may also bind magnesium and zinc (Hintz et al 1984).

There are species differences in the ability to utilise the calcium bound in calcium oxalate. Horses have unique features with regard to calcium metabolism including: high serum total and ionized calcium concentrations compared with other species; poorly regulated intestinal absorption of calcium; high urinary fractional clearance of calcium; low serum concentrations of vitamin D; a high calcium set-point (Toribio et al 2003) and complete inability to utilise calcium bound to oxalic acid in grasses (Blayney et al 1981; McKenzie and Schultz 1983).

Calcium and phosphorus homeostasis – the role of parathyroid hormone

PTH is responsible for the minute-to-minute regulation of extracellular calcium (Ca^{2+}) concentrations. The relationship between serum Ca^{2+} concentrations and PTH is inverse and sigmoidal in the horse (Aguilera-Tejero et al 1998; Toribio et al 2001). This enables the parathyroid gland to respond rapidly to minimal changes in Ca^{2+} concentrations (figure 1).

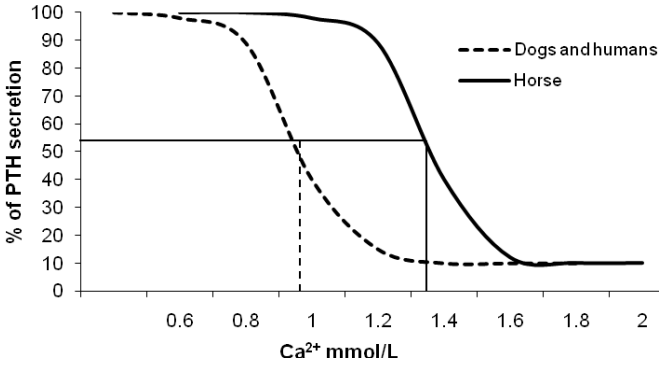

Figure 1*. Sigmoidal relationship between Ca^{2+} and parathyroid hormone, and Ca^{2+} set-point in healthy horses, humans and dogs. The Ca^{2+} set-point is the serum Ca^{2+} concentration at which serum parathyroid hormone concentrations are 50% of maximal during induction of hypocalcaemia. Horses have a sigmoidal relationship between serum Ca^{2+} and parathryroid concentrations and a Ca^{2+} set-point (1.37 mmol/L) that is higher than the set-point reported for humans and dogs (1.0-1.2 mmol/L). *(adapted from Toribio 2004)

High phosphorus and low calcium diets induce parathyroid cell hyperplasia (Krook and Lowe 1964) and increased serum PTH concentrations in the horse (Benders et al 2001). PTH stimulates calcitriol synthesis in the kidney; Ca^{2+} reabsorption in the kidney and uptake in the intestine; osteoclastic resorption in bone and inhibits phosphate (P_i) absorption in the renal tubules.

Interaction of PTH with PTH receptors in the osteoblasts increases the synthesis and release of receptor activators and macrophage colony-stimulating factor (M-CSF) - both of which are essential regulators of osteoclast function. The increased synthesis and release of receptor activators and M-CSF stimulates osteoclasts, resulting in PTH-induced bone resorption (Toribio 2004).

In the kidney, PTH acts in the proximal renal tubules and induces natriuresis and diuresis, and inhibits HCO_3 reabsorption. There are no PTH receptors in the intestine, however PTH indirectly increases Ca^{2+} and decreases P_i absorption in the intestinal tract by increasing synthesis of calcitriol. PTH induced bone resorption and elevated serum calcitriol causes increased plasma phosphate (P_i) concentrations which may interact with Ca^{2+} to form insoluble precipitates and thereby decrease plasma Ca^{2+} concentrations. To avoid dangerous insoluble Ca- P precipitates, PTH decreases P_i reabsorption in the kidney and increases P_i elimination. The end result is decreased P_i reabsorption and increased fractional urinary clearance of P_i (Toribio 2004) (figure 2).

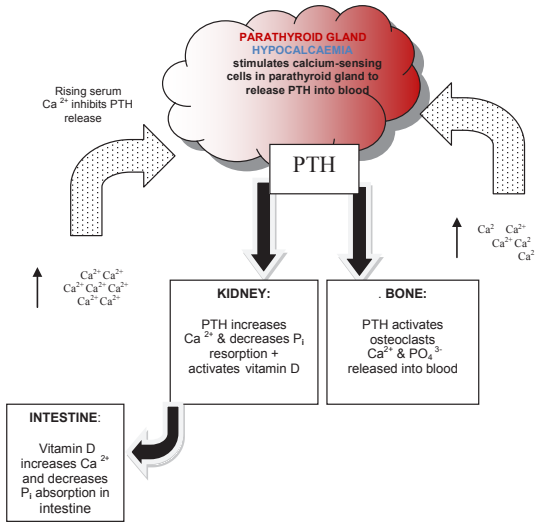

Figure 2. Parathyroid-mediated calcium regulation in response to hypocalcaemia

Clinical signs

Most cases of NSH in Australia occur in spring, summer and autumn, with prevalence ranging from 1-100%. The onset of clinical signs after first grazing high oxalate pasture is 2-8 months, with young, pregnant and lactating horses more susceptible (Walthall and McKenzie 1976). There are three classical clinical manifestations: ill-thrift, lameness, and swelling of the maxilla and mandible. However the clinical signs may present solely as a watery nasal discharge, mild swelling of the distal pasterns, facial distortion, sinusitis or upper respiratory tract noise (Freestone and Seahorn, 1993). Difficulty passing a stomach tube may also be noted, which also could be due to dental eruption cysts

in 2, 3 and 4 year olds, maxillary sinus disease or tooth root infection.

The first clinical sign is usually intermittent shifting lameness due to focal periosteal avulsion, torn or detached ligaments and tendons, or subepiphyseal microfractures. Joint pain may result from articular cartilage erosions due to loss of underlying trabeculae (Joyce et al 1971; Brewer 1987). Lameness is usually insidious with general tenderness of the joints or a stiff stilted gait, and varies from mild shortening of stride, especially at faster paces, to a reluctance to move, recumbency and difficulty in rising. These changes are thought to result from separation of tendon and ligament attachments, and from pain due to defective mineralization and osteoporosis – which results in weakening and bending of the bones McKenzie 1984). Some horses prefer to canter rather than trot, others are reluctant to move. The appetite is often normal but affected horses are often seen eating dirt.

The most severe changes occur in the skull bones, notably the jaws, maxilla, mandible and nasal bones - giving the disease the expressive name of 'bighead' (figure 3). The mineral content of the facial bones and mandible is replaced with increased amounts of osteoid and fibrous tissue, a process termed *osteodytrophia fibrosa*. Changes to the maxillary and mandibular bones are bilateral but not necessarily symmetrical.

Figure 3. Classical 'bighead' in a 3 year old stockhorse

Swelling, secondary to the osteodystrophic changes in the maxillae and ramus of the mandibles, is usually bilateral and first seen as a ridge over the nasal bones above the facial crest, or as swellings of the maxillae over the roots of the anterior cheek teeth (figure 4).

Figure 4. Swelling over the nasal bones

These changes, in combination with resorption of the *laminae dura*, may result in problems with mastication late in the course of the disease, however difficulty chewing and dental pain may be the first sign. Reduced feed intake can result in weight loss and poor body condition. In advanced cases, marked distortion of the mandible can lead to gradual separation of the upper and lower incisors (figure 5) so that they become completely unopposed, and the horse may be less able to masticate short grass.

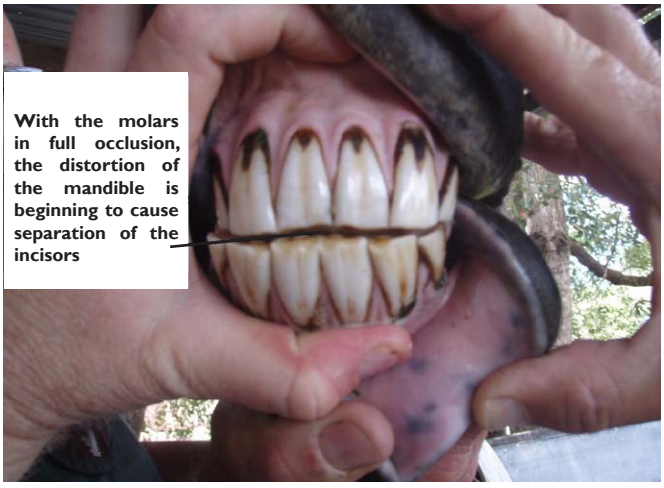

Figure 5. Separation of the upper and lower incisors secondary to distortion of the mandible.

The condition typically develops slowly, therefore horses adapt and learn to cope remarkably well. This contrasts with the situation when incisors are rapidly taken out of occlusion, as occurs with over aggressive filing of the incisors. Mouths of NSH affected horses often have very "clean" periodontal structures (less gingivitis than the average horse) in the mandibular and maxillary dental arcades, possibly due to a reduced risk of feed trapping and gingivitis because the cheek mucosa is no longer apposed with the teeth. However, bone loss in NSH peridontal disease is a forerunner to more severe manifestations such as vertebral and long bone fractures (Whalen and Krook 1996).

In young growing horses, the skeletal calcium cannot be mobilized in the skeleton rapidly enough to maintain a normal serum calcium level and the result is rapid development of clinically recognisable NSH. In the adult animal however, the dietary deficiency can be compensated for by the parathyroids, and *osteitis fibrosa* occurs only in severe deficiency. Therefore, NSH in the adult horse is frequently characterised by osteoporosis due to increased bone apposition and even more accelerated bone resorption. Low-grade secondary hyperparathyroidism is associated with osteoporosis and elevated serum PTH levels in adult animals (Jowsey et al 1974). In adult horses there is slight parathyroid hyperplasia, but the degree of parathyroid overactivity is too low to result in the classical clinical findings (Krook 1968; Mason and Watkins 1988). A high incidence of vertebral compression fractures may be the only manifestation of NSH in the adult horse and Caple et al (1982) speculated that much of the lameness, tendonitis and spontaneous fractures in racehorses may be due to undetected NSH.

Pathological anatomy

Detailed descriptions of the pathology of NSH are readily available (Kintner and Holt 1932; Krook and Lowe 1964). The most important pathological change is osteolytic resorption of the outer circumferential lamellae of long bones (Gries 1966). There is no definite site of predilection for the resorption of the outer circumferential lamellae. The periosteum becomes attached by the Sharpey's fibres to the fibrous tissue which replaces the resorbed lamellae. It now yields to tension from tendons and ligaments and this is the most important cause of lameness. Any bone may be affected and temporary healing may explain the shifting lameness (Krook 1968).

Between four and 18 weeks after beginning a low calcium-high phosphorus diet (ratio 1:3.7), osteolysis alone is able to compensate and maintain normocalcaemia. However, after 18 weeks, a specialised response to the presence of abnormal skeletal material, osteoclasia, also occurs (Gries 1966).

Nephrosis with renal congestion, interstitial fibrosis, white granular deposits in the cortices, necrosis of the tubular epithelium and oxalate crystals in the lumen has been reported in horses grazing setaria (Walthall and McKenzie 1976; McKenzie 1984).

Radiography

The earliest radiographic changes in an experimental model of NSH were progressive radiolucency, miliary mottling and progressive loss of the *laminae durae dentes* (Krook and Lowe 1964). In addition, subperiosteal resorption appeared in ventrodorsal radiograms of the mandible and in the cortical bone lateral to the roots of the corner incisor teeth. The radiographic changes in the metacarpi during the experimental model were endosteal roughening, radiolucent linear striations in the cortex, and coarse trabeculation of the spongy bone at the metaphyseal ends of the medullary cavity (figure 6).

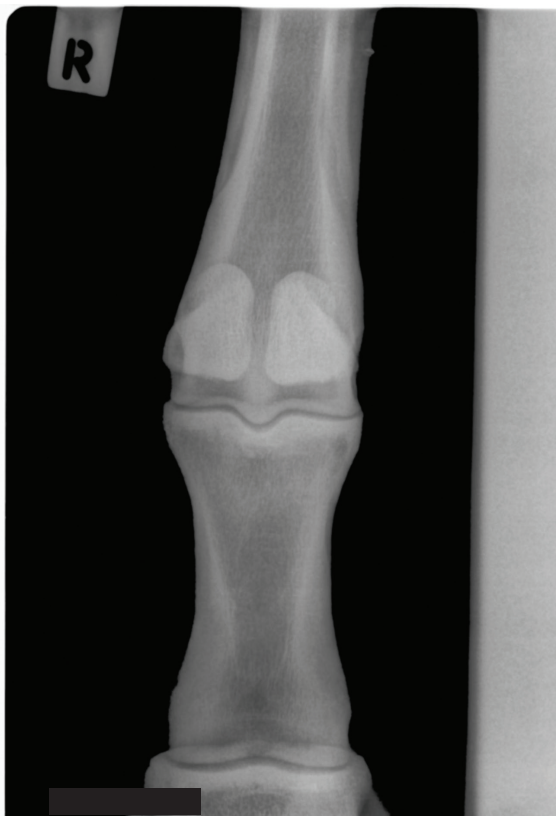

Figure 6. Fetlock radiograph of 16 year old horse grazing setaria pasture and with swelling over the nasal bones and facial crests

Clinical signs preceded radiographic changes by up to 14 weeks. The radiographic changes are insidious and progressive, appearing sooner and progressing faster in the maxilla and mandible than in the canon bones, but there is extreme porosity of the entire skeleton (Krook and Lowe 1964). The *laminae dura dentes* is less radiodense due to lack of calcium mineralisation (figure 7).

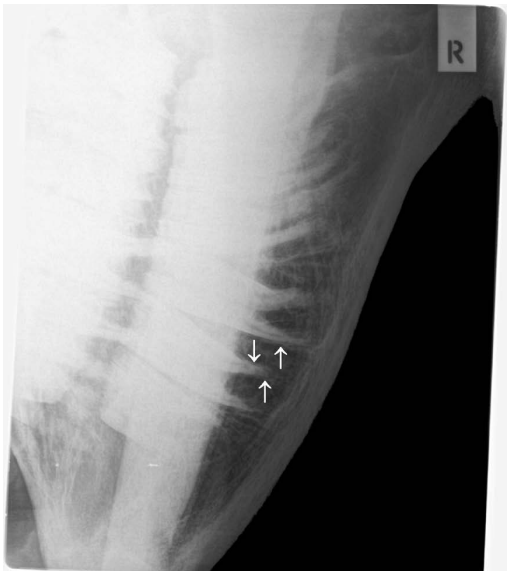

Figure 7. Laminae durae in a 16 year old with chronic nutritional secondary hyperparathyroidism showing lack of contrast, and the more fibrous appearance to the mandibular trabecular bone. (Note: The exposure factors for the cases were not as high as normal due to the reduced mineralisation of the bone).

There can be reduced dentine production and thus reduced tooth root development (figure 8). Root development depends on production of dentine followed by cementum produced over the top of the dentine. All 3 structural components of teeth are highly mineralised, and if insufficient calcium is available, long term structural deficits may result – especially in the enamel which does not undergo continual production as with dentine and cementum.

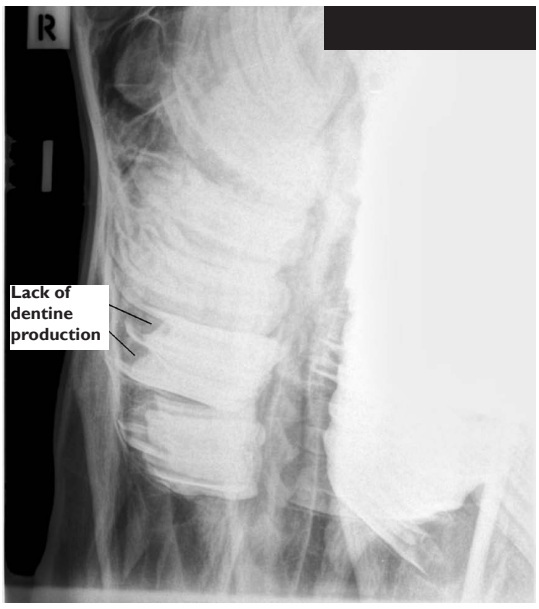

Figure 8. Reduced dentine production and thus reduced tooth root development in a three year old with clinical signs of nutritional secondary hyperparathyroidism.

Clinical pathology

Dietary oxalate produces a net loss of calcium and phosphorus primarily through the faecal route in horses (Swartzmann et al 1978). There are no consistent abnormalities in serum calcium, phosphorus, magnesium or alkaline phosphatase, but faecal calcium and faecal calcium:phosphorus ratios may be elevated (Krook and Lowe 1964). The plasma calcium concentration is often normal even though the calcium:phosphorus ratio is disturbed because the parathyroid gland functions to maintain ionized calcium concentration. Serum alkaline phosphatase may be increased in some horses. Common laboratory findings are normocalcaemia, normophosphataemia to hyperphosphataemia and increased fractional excretion of phosphorus. Fractional excretion of calcium does not reflect calcium balance because $CaCO_3$ crystals are formed in the bladder. The urinary fractional clearance of calcium and phosphorus have been proposed as methods to estimate calcium and phosphorus intake, but interpretation can be difficult because horses eliminate large amounts of calcium in the urine (Brewer 1987).

Diagnosis

Clinical pathologic data, physical examination and diet analysis can be used to support a diagnosis for NSH, which should be based on history, clinical signs and diet analysis (Mason and Watkins 1988; Freestone and Seahorn 1993).

Treatment

Affected animals can only be treated by correcting the dietary imbalance and even severe lesions may resolve with correct treatment. A dietary supplement to prevent or treat cases must have high a calcium concentration, be able to correct the phosphorus deficiency due to increased faecal and urinary P_i loss, be consumed in sufficient quantity to promote storage when supplied regularly, and be inexpensive, easy to use, palatable and safe for prolonged use.

Sources of calcium for inclusion in drinking water do not fulfil these criteria. Once weekly supplementation with 1kg of lime mixed with 1.5kg of molasses restored a positive calcium balance but exacerbated the negative phosphorus balance in horses on kikuyu. This effect was not observed when daily supplementation was used (Gartner et al 1981). Several feeding trials have shown that horses do not consume enough calcium in the form of lime or DCP (dicalcium phosphate), either alone or mixed with salt, to overcome a dietary calcium deficiency and correct the negative phosphorus balance (Schryver et al 1978, Gartner et al 1981).

Table 1 lists the mineral composition of some equine mineral supplements used to meet the requirements of horses on pasture. Dolomite is around 21% calcium (table 1) but does not address the phosphorus deficiency.

Table 1: Comparison of equine mineral supplements

Mineral/100g	$CaCO_3$	DCP	Dolomite	QWHB	OEB	OF007	HPMPB	HPMB	BHB	PHB	CS	RDI
Calcium (g)	36.5	17	21	2	7	10.5	13.5	4.6	5	17.5	15	16
Phosphorus (g)	0.04	21.5	-	1	3.3	4.8	8	4	2	15	4.4	11
Ca:P ratio	912.5	0.790698	21	2	2.12	2.19	1.69	1.15	2.50	1.17	3.41	1.45
Salt (g)	0.1	-	-	4	3.9	62	18	30	15	65	20	40
Magnesium (g)	0.05	-	-	4	4	0.002	2.5	4.8	-	30	3	6
Cobalt (mg)	-	-	-	0.006	-	40	1	1.5	1.2	2.5	0.6	0.4
Copper (mg)	-	-	-	6	-	-	110	150	12	15	40	80
Iodine (mg)	-	-	-	-	-	16.7	1	10	1.2	3.9	1	2.8
Iron (mg)	30	-	-	24	-	97.5	-	-	-	20	32	350
Manganese (mg)	26.9	-	-	24	-	10	200	280	-	20	160	320
Selenium (mg)	-	-	-	-	-	-	1.5	0.5	0.1	0.08	0.2	0.8
Zinc (mg)	-	-	-	24	-	18	220	400	20	55	160	320

CaCO3 - Lime, DCP - Dicalcium phosphate, QWHB - Quest working horse block, OEB - Olssons equine block, OF007 - Olssons formula 007, HPMPB - Horsepower mineral plus block, HPMB - Horsepower mineral block, BHB - Barastoc horse block, PHB - Prominavite horse block, CS - Calsorb, RDI - Recommended daily intake 400kg maintenance

There is a limit of 20mg for calcium and 10mg/kg body weight/day for phosphorus, and a mineral retention of only 35% with a once weekly supplement (Gartner et al 1981). Increasing the frequency of supplementation or extending the time of consumption is more efficient than increasing the dose. The practical implications are that in horses grazing grasses of low calcium:oxalate ratios and losing 20mg calcium and 10mg phosphorus/kg bodyweight per day, NSH can be prevented by 1kg of rock phosphorus or 1kg of a mixture of rock phophorus and lime with 1.5kg of molasses given once a week. Unfortunately, the negative calcium balances with buffel, kikuyu and setaria are often double the losses examined experimentally. In addition, free oxalate in the grass can bind calcium in the small intestine.

Mineral retention is improved significantly by daily supplementation and inclusion of chelated calcium which is unavailable to free oxalate in the intestine. In addition, calcium absorption is improved by increased magnesium concentration (Hintz and Schryver 1972) and calcium digestibility improved by increased NaCl concentration in the diet (Schryver et al 1987).

To manage the clinical cases occurring in Australia several formulations have been trialled. Unfortunately, some horses receiving recommended daily mineral supplementation to protect against oxalate-induced mineral deficiencies, still developed clinical 'bighead'. A mineral block* for use in pastured horses has been formulated. The calcium:phosphorus ratio is 3.5:1 and chelated calcium, magnesium and salt were added. The block has been trialled over 2 years, daily intake under a range of management and feeding systems has been adequate and it has been consistently effective in alleviating clinical signs and preventing new cases. Further trials are being run on several properties to monitor faecal calcium and PTH levels in horses with access to the block.

Many theories have been proposed as to the aetiology of bighead – including poor ventilation (Berns 1890) and infectious disease (Jasme 1891). Severe treatments such as applying a hot iron to the affected area and puncturing the enlarged area with an awl and pouring arsenic into the opening were used without success (Stowell 1858). Although nutrition is an inexact science and results can be variable, treatment and prevention of NSH is possible.

*Calsorb

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