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Towards the elimination of excessive cobalt supplementation in racing horses: A pharmacological review

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ABSTRACT

Cobalt is an essential trace element for many vital physiological functions. Cobalt is also known to stabilise hypoxia-inducible transcription factors leading to increased expression of erythropoietin which activates production of red blood cells. This implies that cobalt can be used to enhance aerobic performance in racing horses. If this becomes a pervasive practice, the welfare of racing animals would be at risk because cobalt is associated with cardiovascular, haematological, thyroid gland and reproductive toxicity as observed in laboratory animals and humans. It is expected that similar effects may manifest in horses but direct evidence on equine specific effects of cobalt and the corresponding exposure conditions leading to such effects is lacking. Available pharmacokinetic data demonstrates that intravenously administered cobalt has a long elimination half-life (42–156 h) and a large volume of distribution (0.94 L/kg) in a horse implying that repeated administration of cobalt would accumulate in tissues over time attaining equilibrium after ~9–33 days. Based on these pharmacokinetic data and surveys of horses post racing, threshold cobalt concentrations of 2–10 μg/L in plasma and 75–200 μg/L in urine have been recommended. However, there is no clearly defined, presumably normal cobalt supplementation regimen for horses and characterisation of potential adverse effects of any established threshold cobalt concentrations has not been done. This review outlines the strengths and limitations of the existing literature on the pharmacological effects of cobalt in horses with some recommendations on what gaps to bridge to enable the determination of optimal threshold cobalt concentrations in racing horses.

Contents

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1. Introduction

Cobalt is a trace element that serves many beneficial roles in physiology and cellular biochemical processes. Most notable is the fact that cobalt is an important component of vitamin B_{12}, an essential factor for DNA synthesis, fatty acid and amino acid metabolism, neural function and the formation of components of blood (Battersby, 1993; Kobayashi and Shimizu, 1999). In horses, cobalt deficiency is very rare but the presumed legitimate use of cobalt containing supplements for blood restoration or in disease processes that may interfere with the absorption and assimilation of vitamins and minerals is occasionally done. Cobalt containing injectable formulations such as Hemoplex® and Hemo-15® are approved for clinical use by veterinary drug regulating authorities in many countries including Australia, Canada and Hong Kong, and several cobalt containing oral supplements such as Avalia-4®, Boost Paste® and Horsepower® are commercially available. The acknowledged use of cobalt containing compounds in medicine or simply as a necessary nutritional supplement is bound to be abused as a doping strategy in sports given the ability of cobalt to induce erythropoiesis, enhance aerobic performance and alter lipid and glucose metabolism (Shrivastava et al., 2008; Saxena et al., 2012; Ebert and Wolfgang, 2014). In humans and laboratory animals, high doses of cobalt have been associated with direct cardiovascular, haematological, neurological, endocrine and reproductive toxicity (Simonsen et al., 2012). This raises the prospect of animal cruelty and a serious breach of animal welfare guidelines. To reconcile these two extremes in the utilisation of cobalt in veterinary medicine, a thorough evaluation of pharmacokinetic and pharmacodynamic features of cobalt should be undertaken. This review summarises the evidence relating to pharmacodynamic and pharmacokinetic features of cobalt in horses with the aim of outlining strengths and weaknesses of the existing literature. Some recommendations are made with respect to what gaps in knowledge should be bridged to enable the determination of optimal threshold plasma or urine cobalt concentrations in racing horses. Interpretation of laws that relate to the use of cobalt in racing horses or other animals is beyond the scope of this review.

2. Pharmacodynamic features of cobalt

2.1. Physiological functions of cobalt

Cobalt is a vital cofactor in vitamin-B_{12}-dependent enzymes where it exists as a substituted macrocycle in a porphyrin-like structure but other cobalt containing proteins with varied physiological functions have been identified. The most prominent example for mammals is methionine aminopeptidase-2, an enzyme that does not use the corrin ring but binds cobalt directly and serves a critical role in the hydrolytic removal of methionine residues from proteins, contributing to protein degradation, tissue repair and angiogenesis (Kobayashi and Shimizu, 1999). Perhaps, the most important physiological role for cobalt as a trace element is in its being an integral component of the structure and function of vitamin B_{12} (cobalamine). Cobalamine is not synthesised by mammalian, fungal or plant cells but it is critical for normal metabolic activities including the regulation of nucleotide synthesis, fatty acid and amino acid metabolism, neural function and the formation of cellular components of blood. A detailed review of the physiological, biochemical and nutritional aspects of cobalamine and related compounds in animals was presented by McDowell (1989). In ruminants, cobalt is a dietary essential requirement for rumen microorganisms to synthesise vitamin B_{12} and, cobalt deficiency is associated with unthriftiness and wasting, and decreased disease resistance in cattle and sheep (Suttle and Jones, 1989). By contrast, vitamin B_{12} deficiency that is attributable to a deficit in cobalt has not been described in horses. This indicates that there may be marked interspecies variability in the metabolism and processing of cobalt for physiological functions. Specific cobalt requirements for horses have not been fully determined and there are no studies on effects of cobalt supplementation in this species. By extrapolation from other species, the National Research Council (NRC, 1989) recommended a minimum daily cobalt intake of 0.05 mg/kg of dietary dry matter equating to approximately 0.5 mg of cobalt per day for a 500 kg horse. This would suggest that under normal circumstances, adult horses can obtain sufficient cobalt from dietary sources as they are able to synthesise and absorb vitamin B_{12} in the caecum and colon (NRC, 1989). Indeed, horses may remain in good health while grazing pastures so low in cobalt where cattle and sheep have died (Filmer, 1933). This however, has not entirely precluded the potential for a beneficial use of cobalt or vitamin B_{12} containing supplements in horses. For example, the Australian Pesticides and Veterinary Medicines Authority (APVMA) approved the use of Hemoplex® injection (APVMA no. 50442) for blood restoration after worm infestation, stress associated with racing and heavy work, and convalescence after disease processes that may interfere with the absorption and assimilation of vitamins that are essential for formation of blood elements. Hemoplex® contains 0.7 g/L of cobalt gluconate and 150 mg/L of cyanocobalamin and other over-the-counter, cobalt containing supplements as injectable or oral formulations are commercially available (Table 1).

2.2. Evidence for pharmacological effects of cobalt in humans and laboratory animals

The prolonged complimentary use of cobalt and especially at higher doses is known to cause many pharmacological effects. In a recent systematic review of several experimental studies as well as clinical trials, Ebert and Jelkmann (2014) outlined that in humans and laboratory animals, cobalt ions will stabilise hypoxia-inducible transcription factors (HIF) leading to increased expression of the erythropoietin gene which activates production of erythrocytes and haemoglobin (Shrivastava et al., 2008; Befani et al., 2013). In humans, the daily intake of 150 mg of cobalt chloride under experimental conditions increased erythrocyte numbers by one million per microliter within 7 to 22 days with values returning to normal within 9 to 15 days (Davis and Fields, 1958). In addition, the stabilised alpha isoforms of HIF forms heterodimers that then regulate the transcription of up to 70 different effector genes via the hypoxia responsive element (Wenger et al., 2005). More specifically, cobalt-induced stabilisation of HIF enhances the expression of cellular pathways that protect against oxidative stress, promote glucose uptake, and enhance energy and oxygen utilisation (Saxena et al., 2010, 2012). Exposure of rat clone-9 liver cells and, mouse 3T3-L1 fibroblasts and C2C12 myoblasts to cobalt chloride resulted in an increase in glucose uptake and glucose phosphorylation (Hwang and Ismail-Beigi, 2002). Direct evidence for hypoxic preconditioning with cobalt leading to up-regulation of glutathione, heme oxygenase-1 and metallothionein as essential components of the anti-oxidative capacity for protecting muscle from exercise-induced damage has been demonstrated in rats (Saxena et al., 2010). Cobalt may also cause direct toxicity and most notable effects include the inhibition of tyrosine iodinase resulting in thyroid malfunction, goitre and myxedema. Other observed effects include cardiomyopathy, aberrant immune function and, direct genotoxicity caused by oxidative DNA damage and inhibition of DNA repair leading to carcinogenesis. Detailed reviews on the organ specific effects of cobalt and the underlying putative mechanisms have been published previously (Lauwerys and Lison, 1994; Paustenbach et al., 2013). To date, the systematic evaluation of threshold plasma cobalt concentrations or the frequency and duration over which cobalt-induced toxicity may manifest are limited to a few studies in humans and laboratory animals. A review of the available dose–response data concluded that biological responses and adverse effects in humans were not observed below measured blood cobalt concentration equivalent to 300 μg/L (Finley et al., 2012). Reversible hypothyroidism and polycythemia may be observed at 300 μg/L with at least 2 weeks of exposure while cardiomyopathy and vision or hearing impairment are reported at peak cobalt concentrations over 700 μg/L following 8–40 weeks of exposure