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Personal View

Cobalt chloride doping in racehorses: Concerns over a potentially lethal practice ☆

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Introduction

Blood doping is an illegal and unacceptable way of enhancing athletic performance by increasing the oxygen carrying capacity of blood (Lippi et al., 2005). Currently used blood doping methods usually involve stimulation of erythropoiesis using erythropoietin (EPO) or its recombinant form (Debeljak and Sytkowski, 2012). EPO is the hormone responsible for controlling erythropoiesis in bone marrow, therefore erythropoiesis-stimulating agents (ESAs) and metal salts that can substitute for and simulate the erythropoietic actions of EPO have been used as potential performance-enhancing agents (Lippi et al., 2006; Duh et al., 2008). Although these agents may possibly have some physiological effects, there are significant risks associated with the illicit use of these substances in athletes (Franz, 2009).

The popular press frequently publishes revelations about the possible use of anabolic steroids and other banned substances in racehorses. The most recent report comes from Australia and involves the detection of cobalt chloride in racehorses competing in New South Wales and Victoria.[1] Although these convictions were the first in that country, it is suspected that cobalt chloride doping may have been practiced for some time.

Cobalt chloride is a well-established hypoxia mimetic and inducer of hypoxia-like responses, which can cause gene modulation at the hypoxia inducible factor pathway to stimulate EPO transcription and increase its levels in blood (Ho et al., 2015). Cobalt (symbol Co, atomic number 27) is a transition metal in the periodic table. In biological systems cobalt is at the active centre of coenzymes such as cobalamins, the most common example of which is vitamin B_{12}. Therefore, cobalt is an essential trace micronutrient that is important for the formation of the vitamin B_{12} complex. As an activator of enzymes it is involved in the oxygen-carrying function of red blood cells and can replace the co-factor zinc in some enzymes. There are no published reports of cobalt dietary deficiency. A variety of foods including nuts, green leafy vegetables, fish and cereals contain cobalt and it is unlikely for humans to develop dietary deficiencies.

Currently there is no evidence to suggest that cobalt chloride can enhance human or equine performance. A recent study examined the pharmacokinetics and pharmacodynamics of cobalt following intravenous (IV) administration to 18 horses (Knych et al., 2014). The authors showed that a single IV dose of cobalt chloride or cobalt gluconate had no effect on EPO concentrations, red blood cell parameters or heart rate in any of the horses studied. The rationale for its use in racehorses is likely to be based on preclinical research done in cell lines and some anecdotal evidence from in vivo studies in laboratory animals, suggesting that cobalt chloride *may* have the same effect as EPO on erythropoiesis in bone marrow.

Cobalt chloride is not a prescription medication and various cobalt salts are available for purchase from a variety of commercial sources. The salts are inexpensive, easily accessible, not subject to medicine regulation and orally active. Therefore, ill-informed and unscrupulous trainers can easily obtain cobalt chloride and administer it to horses. However, regulatory bodies have recently implemented a urinary threshold of 2000 ng/mL and a plasma threshold of 10 ng/mL for the control of cobalt abuse in non-race day or out-of-competition samples (200 μg/L plasma in Australia and 100 μg/L in Hong Kong) (Ho et al., 2015).

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[1] See: http://www.theage.com.au/sport/horseracing/stewards-find-first-cobalt-chloride-irregularity-in-victoria-20141204-120dwm.html (accessed 8 March 2015).

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Aside from the lack of evidence for enhanced athletic performance in horses, one of the key concerns is the paucity of information about the long-term safety of cobalt chloride administration and toxicity, especially in vital organs. In the US there have been reports of unexplained deaths in horses that were found to have elevated blood levels of cobalt chloride. Although cobalt salts have medical applications for the treatment of anaemia (Bowie and Hurley, 1975; Duckham and Lee, 1976), cobalt can be highly toxic. It exerts well-known and well-documented neurotoxic effects (Catalani et al., 2012) in addition to its toxic actions on the thyroid, the heart and the haematopoietic system. High doses of cobalt in patients exposed to abnormal levels from damaged hip prostheses induce optic and auditory neuropathy (Apostoli et al., 2013). Furthermore, there are reports that cobalt exposure may lead to fatal cardiomyopathy and ischaemic heart disease in cobalt-exposed workers (Barborik and Dusek, 1972; Jarvis et al., 1992; Centeno et al., 1996) and occurred in regular beer drinkers who had consumed beer from breweries with cobalt contamination (Alexander, 1972). It is also worth commenting that cobalt–drug interactions are unknown, which could be significant as racehorses commonly receive non-steroidal anti-inflammatory drugs and, in some racing jurisdictions, can race on furosemide medication.

However, the lay public does not have access to detailed information about the potential risks and many trainers do not have the scientific knowledge to assess the risk:benefit ratio for the use of cobalt salts. Unfortunately, the Internet is a source of inaccurate, conflicting and misleading information about cobalt and its salts. This is the introductory text that describes uses of cobalt chloride in horses on one site[2]:

> '*Cobalt chloride, also nicknamed blue salt by the horse and cattle community, is often associated with the dietary needs of cows. Cobalt chloride isn't only for cattle, however. Horses can also benefit from supplements of this essential electrolyte, as non-traditional as their consumption of it may be. Horse owners should use caution in dispensing cobalt chloride to avoid overdoses and unnecessary iodine intake, but there are usually few risks involved.*'

The author of this non-refereed article is Kirsty Ambrose, a regular contributor to eHow. She holds a Bachelor of Arts in English literature from the University of Victoria and enjoys writing about pet care. Her article is a top hit on Google (fifth item in a Google search (article accessed 8 March 2015) using the keywords 'cobalt', 'chloride' and 'equine'). This style of writing clearly gives readers the impression that providing cobalt chloride to horses can improve their overall health. The paper has not had any kind of peer-review and the author does not cite any scientific or clinical papers to back up the claim that '*Horses can also benefit from supplements of this essential electrolyte*'. Clearly cobalt is not a conventional electrolyte. It is a micronutrient and research suggests that micronutrients can be toxic in high concentrations.

Medical uses of cobalt and cobalt chloride

It is important to highlight some of the medical uses of cobalt and cobalt chloride. Cobalt-60 (^{60}Co) is a radioactive form of cobalt used in radiotherapy for targeting inoperable tumours.[3] The concept of ^{60}Co radiotherapy was developed in the 1950s by scientists at the University of Saskatchewan in Canada (Johns et al., 1952; Morrison et al., 1952). Although cobalt therapy has partly been replaced by linear accelerator radiation therapy (the electron beam), which can generate higher energy radiation, cobalt treatment still has a useful role in radiotherapy. ^{60}Co is also one of the most commonly used radio-isotopes for food irradiation[4] (Deitch, 1982).

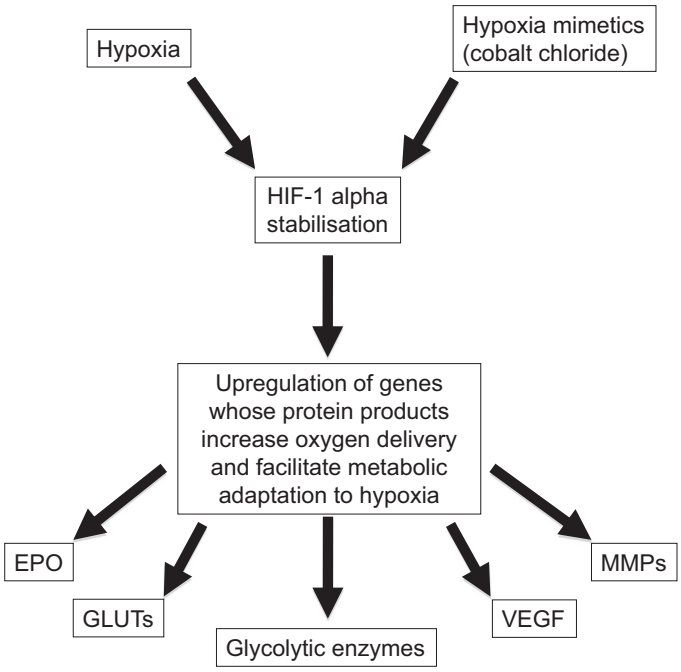

Fig. 1. Physiological and pathophysiological regulation of hypoxia-inducible factor (HIF)-1 α by hypoxia and cobalt chloride. HIF-1α is a basic-helix–loop–helix transcription factor that activates expression of genes encoding erythropoietin (EPO), glucose transporters (GLUTs), glycolytic enzymes, vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs) and other genes whose protein products increase oxygen delivery and facilitate metabolic adaptation to hypoxia (Semenza, 1999, 2000; Sethi et al., 2012). Cobalt chloride acts as a hypoxia mimetic by activating the expression of genes that contain a hypoxia response element. Proteosomal pathways degrade HIF-1α during normoxia but this transcription factor is stabilised under hypoxic conditions and in the presence of hypoxia mimetics such as cobalt chloride.

Cobalt salts have been proven to be effective therapies for stimulating erythropoiesis in both non-renal and renal anaemia. Cobalt chloride has been effective for the management of uraemic patients with refractory anaemia, especially in patients undergoing long-term haemodialysis (Bowie and Hurley, 1975; Duckham and Lee, 1976). Cobalt chloride stabilises the transcriptional activator hypoxia-inducible factor (HIF)-1α and thus mimics hypoxia so stimulating EPO production (Fig. 1).

However, as with any type of drug, there are also serious medical adverse effects associated with long-term use, especially in high concentrations. Safe and effective use in the human medical field has been dependent upon accurate prescribing and diligent monitoring by clinicians for adverse reactions. The same mechanisms involved in HIF-1α activation may potentially have genotoxic (De Boeck et al., 2003) and carcinogenic (Simonsen et al., 2012) effects, through cobalt mediated inhibition of DNA repair (Lison et al., 2001). Oral intake of inorganic cobalt salts can cause severe organ damage, especially by inducing toxicity in the gastrointestinal tract, the thyroid, the heart and the sensory systems (Ebert and Jelkmann, 2014). These undesirable side effects should deter professional equine trainers (and

[2] See: http://www.ehow.com/info_8740774_use-cobalt-chloride-equines.html (accessed 8 March 2015).

[3] See: http://www.epa.gov/radiation/radionuclides/cobalt.html (accessed 8 March 2015).

[4] See: http://www.epa.gov/radiation/sources/food_irrad.html (accessed 8 March 2015).

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