

OCCASIONAL PIECE

Cobalt chloride administration in athletes: a new perspective in blood doping?

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Blood doping is an illegal and unfair way of enhancing athletic performance by increasing the oxygen carrying capacity of the blood. Currently used methods usually involve stimulation of erythropoiesis. Gene therapy targeting the hypoxia inducible factor pathway may be an attractive alternative to traditional blood doping techniques. Hypoxia activates a large number of genes with essential roles in cell and tissue adaptation to low oxygen. Cobalt chloride is a well established chemical inducer of hypoxia-like responses such as erythropoiesis. Cobalt supplementation is not banned and therefore would not be detected by current anti-doping testing. Although there is as yet no direct or anecdotal evidence of cobalt chloride administration to athletes, its use should be warned against as being not only unfair but potentially dangerous.

glycosylation analogue of rHuEpo, and the continuous erythropoiesis receptor activator (CERA), which induces enhanced and sustained erythropoietic effects through continuous modulated erythropoiesis stimulation. Most recently, artificial oxygen carriers and allosteric haemoglobin modulators, originally designed as blood substitutes, have appeared. Remarkable progress in basic and applied biochemistry has greatly increased the temptation of athletes to use artificial, unfair, and dangerous methods to enhance their performances, and, in the near future, blood doping may be replaced by genetic engineering. We have recently hypothesised that gene therapy targeting the hypoxia inducible factor (HIF) pathway may be an attractive alternative to traditional techniques of blood doping.² Hypoxia activates a large number of genes that have essential roles in cell and tissue adaptation to conditions of low oxygen. Such a complex response is mainly mediated through endogenous gene modulation at the HIF pathway. Under normoxic conditions, the main mediator HIF1 α is rapidly degraded by the proteasome. However, under conditions of lower oxygen, HIF1 α undergoes a stabilisation process and ultimately induces activation of genetic sequences, including those of the erythropoietin gene, that promote efficient adaptation to hypoxia.³ It has been recently reported that administration of cobalt chloride may promote

A large reserve of intracellular energy substrates, an efficient circulation, and adequate blood oxygenation are the most important requirements for effective energy production in muscles, especially during demanding physical exercise. Anything that interferes with one or more of these factors promotes premature muscle fatigue and compromises performance.¹ Oxygen is carried in the blood by two efficient delivery systems: about 3% is dissolved in the plasma, and the rest is bound to haemoglobin, the main protein in erythrocytes. Any increase in haemoglobin in blood improves oxygenation, allowing the muscles to become more fatigue resistant and to perform better. The term “blood doping” or “blood boosting”, earlier known as “induced erythrocythaemia”, is traditionally used to describe methods or substances administered for non-medical reasons to healthy athletes with the aim to increase their maximal aerobic power and thereby improve aerobic performance.¹ Blood doping has recently become an integral part of elite and recreational sports. Several potential methods of blood doping have developed over the past few decades. For a long time, blood transfusion was the most suitable technique. Since recombinant human erythropoietin (rHuEpo) became available in the early 1990s, a large series of erythropoiesis stimulating substances have emerged, including darbepoetin-alpha, commonly known as the novel erythropoiesis stimulating protein (NESP), a

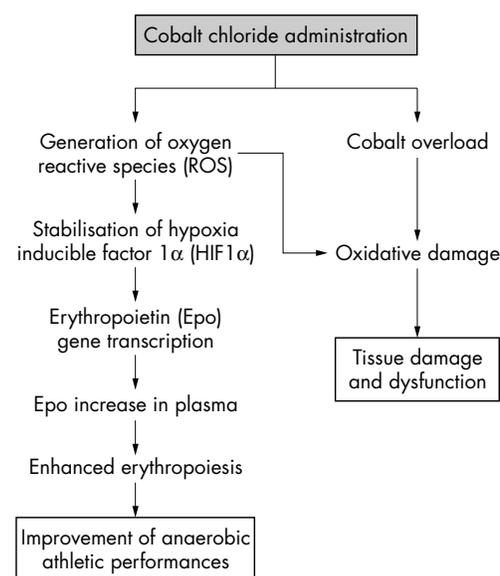


Figure 1 Potential ergogenic effects and complications of cobalt chloride administration in athletes.

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What is already known on this topic

Blood doping is an emerging health and social problem. There are several means of increasing the oxygen carrying capacity of the blood, most of which can be reliably detected by current anti-doping strategies.

the delaying of cardiac preconditioning through selective activation of the HIF1 signalling.⁴ Cobalt is a relatively rare transition metal with properties similar to those of iron, chromium, and nickel. Cobalt chloride, a water soluble compound traditionally used to treat anaemia in pregnant women, infants, and patients with chronic anaemia undergoing long term haemodialysis,⁵ is a well established chemical inducer of hypoxia-like responses, such as erythropoiesis and angiogenesis in vivo. The precise mechanism of this induction is not fully understood. However, the hypoxia-like response probably involves increased DNA binding activity of HIF1 α , as cobalt stabilizes HIF1 α through generation of reactive oxygen species by a non-enzymatic, non-mitochondrial mechanism. The final result of this induction is enhanced erythropoietin production and more efficient stimulation of the erythropoietic response, achievable at the moderate oral dose of 30 mg/kg.

Besides the relevant therapeutic benefits, especially in patients with acute myocardial ischaemia, cobalt chloride administration may have alternative and obscure potential applications. Given the athlete's innate inclination to experiment with novel doping strategies, irrespective of the biological and health risks, this low cost, water soluble compound may be an attractive, less challenging, and equally effective means of boosting endogenous erythropoietin production (fig 1). Cobalt supplementation is not banned, and thus virtually undetectable by current anti-doping testing for blood doping. Objective and definitive information on absorption, disposition, and health risks of inorganic cobalt salts after oral administration is not as yet available. Although several studies have reported no mortality and no appreciable toxic effects of cobalt chloride, even at the high oral dose of 40 mg/kg for up to four months,⁴ cobalt overload was earlier identified as a contributing factor to alcohol related cardiomyopathy.⁶ In addition, it has been reported that liver, kidney, and heart accumulates cobalt to a greater extent, causing hepatotoxicity, nephrotoxicity, organ damage and dysfunction, even at a dose of 33.3 mg/kg.⁷ Oxidative stress is often cited as a possible cause.⁸ Excessive administration of this trace element also produces goitre and reduced thyroid activity.⁹

There is as yet neither direct nor anecdotal evidence of cobalt chloride administration to athletes. However, we

What this study adds

Cobalt chloride administration is an alternative and dangerous blood doping technique, which is virtually undetectable by anti-doping testing.

cannot exclude the possibility that it may become an attractive alternative to traditional performance enhancing drugs. Owing to the severe and often unpredictable side effects, cobalt chloride administration may turn out to be a serious concern for the sporting community and athletes' health. Therefore we warn that the use of cobalt is an unfair and potentially harmful method of increasing endogenous erythropoietin production. We further raise the problem of whether testing for cobalt salts should be included by anti-doping panels. Unfortunately, testing for cobalt administration during competition may lead to much wasted effort, as its pharmacodynamic properties discourage misuse near or at the time of competition. In fact, after a single oral dose, the blood cobalt concentration-time curve appears triphasic. It peaks at 3.2 hours and displays an absorptive half life of 0.9 hours, an elimination phase half life of 3.9 hours, and a terminal elimination half life of 22.9 hours.⁷ Therefore the plasma kinetics of cobalt chloride mean that, at present, reliable in-competition anti-doping testing is not possible.

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