Schmidt WFJ[1], Hoffmeister T[1], Wachsmuth N[1], Byrnes WC[2]

Cobalt Misuse in Sports

Kobaltmissbrauch im Sport

REVIEW

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1. UNIVERSITY OF BAYREUTH, *Dept. of Sports Medicine/Sports Physiology, Bayreuth, Germany*
2. UNIVERSITY OF COLORADO, *Dept. of Integrative Physiology, Boulder, Colorado, USA*

Summary

› **Cobalt is a heavy metal,** that was used between the 1940s and 1980s as a therapeutic agent to treat anemic diseases. Similar to hypoxia, cobalt stabilizes the HIFα subunits and stimulates the renal production of erythropoietin.

› **For several decades,** it has been suggested that cobalt is also used in sports to optimize oxygen transport via increased hemoglobin mass. In 2015, WADA put it in the list of banned substances. In various dietary supplements purporting to increase performance, cobalt was detected whilst incorrectly or not declared by the manufacturers. Our research suggests that an oral dose of 5mg/day exceeds the erythropoietic threshold. As a result, a 3-week supplementation period at this dose leads to an increase in Hb mass of 2% and to a tendency of higher performance, which corresponds to the effects of a training camp lasting 200h at 2000m. About 10% of the administered cobalt is absorbed by the body and excreted in urine with a half-life of 4-12 hours.

› **In order to detect doping with cobalt,** a reference limit of 14ng/ml in urine has been suggested, which is 4 standard deviations higher than the normal urine cobalt concentration. This value is clearly exceeded during and until one week after a 3-week supplementation period at 5 mg/day. Since it is possible that athletes use higher amounts of cobalt for doping purposes in hopes of achieving greater gains in performance, WADA must set appropriate reference limits and introduce regular test procedures to avoid serious health risks to these athletes.

KEY WORDS:
Hemoglobin Mass, Performance, Erythropoietin, Nutritional Supplement, Blood Manipulation

Zusammenfassung

› **Kobalt ist ein Schwermetall,** das in den 1940-iger bis 1980-iger Jahren als Therapeutikum bei Anämieerkrankungen eingesetzt wurde, wobei schwerwiegende Nebenwirkungen beobachtet wurden. Ähnlich wie Hypoxie stabilisiert Kobalt die HIFα-Untereinheiten und stimuliert somit u. a. die renale Bildung von Erythropoietin.

› **Seit mehreren Jahrzehnten** wird vermutet, dass Kobalt auch im Sport eingesetzt wird, um über eine erhöhte Hämoglobinmasse den Sauerstofftransport zu optimieren, sodass es 2015 von der WADA auf die Liste der verbotenen Substanzen gesetzt wurde. In Nahrungsergänzungsmitteln wird Kobalt als sogenannter Performance-Booster eingesetzt, wobei es zumeist nicht oder falsch deklariert wird. Bei einer oralen Dosis von 5mg/Tag wird eine erythropoietische Schwelle überschritten und verstärkt Erythropoietin gebildet, was bei 3-wöchiger Anwendung zu einem Anstieg der Hb-Masse von 2% führt und tendenziell die Leistungsfähigkeit steigert, was den Effekten eines 200h langen Trainingslagers auf ca. 2000m Höhe entspricht. Etwa 10% des verabreichten Kobalts wird vom Körper aufgenommen und mit einer Halbwertzeit von 4-12h Stunden über den Urin ausgeschieden.

› **Um Doping mit Kobalt nachweisen zu können,** wurde ein Grenzwert von 14ng/ml im Urin vorgeschlagen, was der 4-fachen Standardabweichung der normalen Kobaltkonzentration im Urin entspricht. Dieser Wert wird während und eine Woche nach einer 3-wöchigen Supplementation mit 5mg/Tag klar überschritten. Da zu erwarten ist, dass Sportler auch höhere Kobaltmengen zu Dopingzwecken missbrauchen und dadurch ihre Leistung deutlich steigern dürften, aber damit auch schwerwiegende Gesundheitsrisiken in Kauf nehmen, muss die WADA entsprechende Grenzwerte festlegen und regulär danach testen.

SCHLÜSSELWÖRTER:
Hämoglobinmasse, Leistung, Erythropoietin, Nahrungsergänzungsmittel, Blutmanipulation

Introduction

Maximum oxygen uptake as a measure of endurance performance is closely related to the absolute amount of circulating hemoglobin. After phlebotomy or after application of recombinant human erythropoietin (rhEPO), a change of 1 g of hemoglobin causes a change in VO_2max of approx. 4ml/min (29). Therefore, altitude training is used as an allowed method and blood manipulations, either by blood transfusions or by erythropoiesis stimulating agents (ESAs), are assumed to occur frequently as a malpractice among elite endurance athletes (30, 36). The following review provides an overview of oral cobalt ingestion as a possible doping measure to stimulate erythropoietic activity. Key data and opinions are mostly based on two original publications from Hoffmeister et al. (15, 16). ›

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CORRESPONDING ADDRESS:
Prof. Dr. Walter Schmidt
Head of Department, Dept. Sports Medicine/Sports Physiology, University of Bayreuth
Universitätsstrasse 30
95440 Bayreuth, Germany
✉: walter.schmidt@uni-bayreuth.de

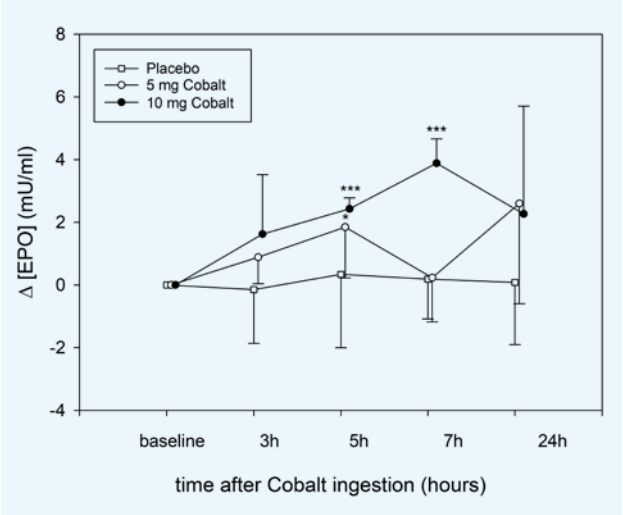

Figure 1

Changes in plasma erythropoietin concentration after a single oral Co^{2+} ingestion of 5 mg and 10 mg. Significant changes from baseline values: *, ***p<0.05, 0.001. Figure from (16).

Co^{2+} mimics the effects of hypoxic exposure by stabilizing the HIF 1α and 2α subunits. HIF 1 stimulates the synthesis of the vascular endothelial growth factor (VEGF), while HIF 2 augments the production of endogenous erythropoietin (18). Actual data indicate that Co^{2+} may bind to HIF 1α and 2α preventing the interaction with the von-Hippel-Landau tumor suppressor protein (pVHL) (18). The application of cobaltous ions is therefore one possibility to stimulate endogenous EPO production resulting in an increase in hemoglobin mass and improved endurance performance.

In equestrian sports, doping with cobalt has become an important issue. National and international equine organisations have discussed upper reference limits for cobalt in blood and urine and responsible persons have already been sanctioned (5, 14, 24).

Although there are no scientific data available, scientists have also warned of its abuse in human sports (22, 23) and in 2015 WADA has put cobalt on the list of prohibited substances and methods (35). In accordance to the anti-doping regulations, doping cases have already been reported (19).

Erythropoietic Effect of Co^{2+} Administration

From the mid-1940s until the 1980s, cobalt ions (Co^{2+}) were used for patients suffering from anemia from various causes (8, 18). Co^{2+} acts similarly as a hypoxic stimulus; it stabilizes HIF-1α and HIF-2α and thereby induces increased renal erythropoietin production (for a review see (18)). Before the development of recombinant erythropoietin, one unit of EPO was defined as the erythropoietic effect achieved by 5µmol of Co^{2+} (17). Because of the severe side effects of high-dose Co^{2+} treatment, it was replaced by anabolic steroids and later by recombinant erythropoietin (8). In clinical practice, daily doses between 11 to 135 mg Co^{2+} were administered for several months (for review, see (8, 18)). While higher doses consistently improved conditions of anemia, doses of 11-25 mg Co^{2+} (e.g. (3, 7)) also increased hemoglobin concentration ([Hb]), hematocrit (Hct), and reticulocytes. Unfortunately, high dosing in anemic patients (>25 mg Co^{2+}/day (4, 11)), was associated with a high risk for intolerability, i.e., acute poisoning and organ injury, gastro-intestinal sickness, thyroidal dysfunction, myocardial effects, and neural and sensory disturbances (8). Because of this high toxicity and the frequent side effects, cobalt therapy was abandoned in the late 1970s, and anabolic steroids were used until recombinant erythropoietin became available (8)

In healthy subjects, low dosages (0.45mg Co^{2+}/day for 31 days (12); 1mg Co^{2+}/day for 90 consecutive days (33)) did not have any effect on [Hb], Hct or red blood cell count (RBC), nor showed any side effects. Oral application of high dosages, i.e. 70mg Co^{2+}, however, increased [Hb] by 20% and the reticulocyte count from 1.1% to 2.7% within 7-22 days. After cessation, baseline values were reached within 15 days (6).

Cobaltous Supplements

Although there are no scientific data available, many manufacturers of nutritional supplements claim erythropoietic stimulatory effects of their cobalt-containing products and suggest a subsequent enhancement of endurance performance. To manipulate their blood, cheating athletes may therefore use cobalt salts offered for chemical purposes or veterinarian nutrition, or they may use dietary supplements that can be purchased over the counter without any restriction. The Co^{2+} concentrations in these mostly liquid supplements are between 0.03mg/ml and 0.5mg/ml, and the recommended daily dose is between 0.15 and 1.0mg/day (31). This is far below the therapeutic dosages formerly used for treatment of anemia but well above the amounts required as the central component of vitamin B12 (0.1µg/day (32)). These recommendations are within the range classified as harmless by two international health and nutritional organizations indicating upper limits as 0.009mg/kg/day (9) and 0.02mg/kg/day (10), corresponding to 0.6mg and 1.4mg for a 70kg subject. The oral reference dose (RfD), i.e., the maximum daily amount of cobalt ingestion considered not to cause adverse non-cancer health effects during a lifetime, has been indicated to 2.1mg/day for a 70kg subject (0.03mg/kg) (11).

Recently, Thevis et al. analyzed 19 commercially available dietary supplements advertised as endurance performance enhancers (31). Eleven of them contained up to 2.6mg Co^{2+}/ml, which was only declared in two of these supplements. The Co^{2+} concentration of the supplements we used in two recent studies (15, 16) was declared to be 0.2mg/ml. However, in almost half of the units used for supplementation, the real concentration was more than 3 times higher. This data suggests that 'performance enhancing' dietary supplements have to be used with caution to avoid any side effects caused by undeclared and/or falsely declared Co^{2+} content.

Erythropoietic Effect of Low Dose Co^{2+} Administration

To evaluate the effects of cobaltous supplements, we (16) determined the minimum doses of oral cobalt administration exerting any erythropoietic effect. While Co^{2+} dosages of 1mg/day or 2mg/day did not exert any hematological changes, a single dose of 10mg of Co^{2+} clearly increased plasma [EPO] and 5 mg showed a strong tendency for elevated [EPO] suggesting that this dosage might be a cobalt threshold for EPO stimulation (Fig. 1). Similar to hypoxic exposure, [EPO] increased after a delay of 3-5h (28) which was explained by similar effects of Co^{2+} and of hypoxia on HIF stabilization (18). A 5-day Co^{2+} administration of 10 mg/day clearly passed the erythropoietic threshold, as indicated by increased plasma [EPO], a higher percentage of the immature reticulocyte fraction (IRF), and decreased plasma ferritin concentration proving the effectiveness of this dosage (16). In a follow up study (15) we administered 5mg of Co^{2+}/day for three

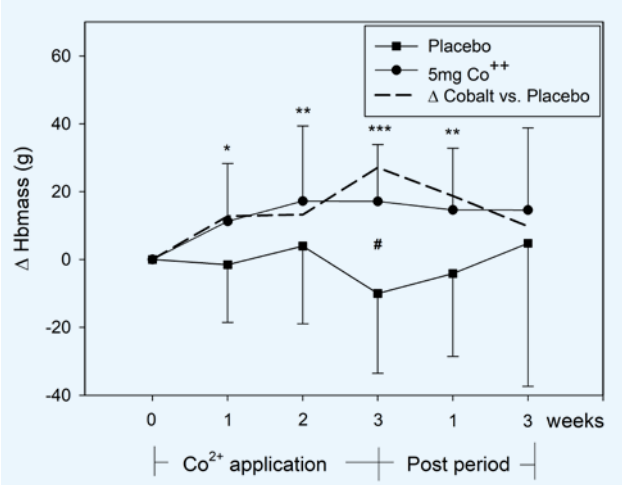

Figure 2

Changes in hemoglobin mass during and after a 3-week cobalt application period. Significant changes from baseline values: *, **, ***p<0.05, 0.01, 0.001; between groups: #p<0.05. The dashed line indicates the difference between cobalt and placebo groups. Figure from (15).

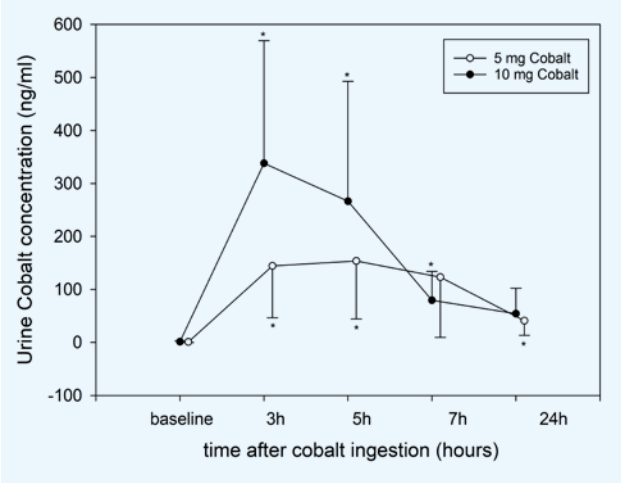

Figure 3

Urine Co^{2+} concentration after a single oral Co^{2+} ingestion of 5mg and 10mg. Significant changes from baseline values: *p<0.05. Figure from (16).

weeks which produced clear erythropoietic stimulation, resulting in a 2% increase in Hb_{mass} (Fig. 2), which is similar to what has been observed during hypoxic training camps lasting 200h at an altitude of ~2,000m (13).

Although suppliers of nutritional supplements claim enhanced endurance performance from Co^{2+} supplementation, this hypothesis has not yet been verified in the scientific literature. In a meta-analysis of 145 elite athletes, Saunders et al. (27) found a 3% increase in Hb_{mass} and VO_2max after hypoxic exposure ("live high – train high" and "live high – train low" protocols). The correlation between these changes was, however, weak, and it explained less than one-sixth of the variation, indicating that, apart from increased Hb_{mass}, other factors must also be important in causing the elevated VO_2max after altitude training (27). Like after altitude training measures, also after the 3-week Co^{2+} administration period described above VO_2max tended to increase and there was a strong tendency for a relationship (r=0.40, p=0.1) for changes in Hb_{mass} and changes in VO_2max (15). We, therefore, concluded the occurrence of stronger effects on VO_2max in case of higher Co^{2+} dosages.

Urinary Cobalt Concentration and Possible Reference Limits

The normal [Co^{2+}] in urine is relatively low and shows a small scattering (0.34ng/ml, 95% confidence limits (CL) 0.31-0.37ng/ml, (34)). A recently conducted study from the anti-doping laboratory in Cologne / Germany yielded slightly, but significantly higher values in endurance trained athletes than in untrained subjects (0.36ng/ml vs 0.28ng/ml, (20)), while acute exercise did not change urinary Co^{2+} concentration neither in trained nor in untrained subjects (25). Exposure to cobalt containing environments, however, massively increases urinary [Co^{2+}]. People living closer to mines than 3 km show in the mean approx. 50-fold increased [Co^{2+}] (2). Similarily, hard metal factory workers are characterized by extremely high values reaching up to 2000 ng/ml (26). Another source of cobalteous ions are endoprosthetics. Metal-on-metal hip implants deliver the highest systemic and urinary Co^{2+} concentrations which range normally between 0.2 and 10ng/ml, but may rise in state of malfunction up to 1085ng/ml (21).

When Co^{2+} is ingested most of it is excreted in the feces (1). Urinary excretion accounts for only 10-27% of ingested Co^{2+} (1, 16) and the elimination half-life after low-dose oral ingestion is between 4h and 12h (1, 32). The time course of urinary Co^{2+} excretion after a single oral application of 5 mg and 10mg Co^{2+} shows maximum values 3-7h (increase from 0.8ng/ml to 150 ng/ml and 340ng/ml, respectively; Fig. 3)) after ingestion and still 50-fold elevated values after 24h. There exists also a relatively high inter-individual variation of urine Co^{2+} which may be attributable to differences in gastrointestinal Co^{2+} absorption as well as an intra-individual variation due to different diuresis.

During a 3-week Co^{2+} application period (5 mg/day), we (15) found the highest urine Co^{2+} concentrations at the end of the administration period (310 ng/ml after one week; 460ng/ml after 3 weeks), which also exceeded those values measured after a single or 5-day application of the equal Co^{2+} dosage. We therefore assumed that Co^{2+} accumulates in body fluids, which may lead to a stronger erythropoietic response than expected from short-term administration. After cessation of the administration, urine Co^{2+} concentration dropped by approx. 80% within two days, which is consistent with the elimination half-life of Co^{2+} after low-dose oral ingestion (1, 32). Compared to baseline, urine [Co^{2+}] was still elevated until two weeks after cessation, which has implications for establishing threshold limits to combat its misuse. Krug et al. (20) calculated 14ng/ml as a tentative reference limit for urine Co^{2+} concentration, which was determined by multiplying the reference population (n=100 subjects) standard deviation by four. In our study (15), all participants except one individual exceeded this threshold one week after cessation (mean=43.1±47.1ng/ml), and some individuals exceeded it even after 2 or 3 weeks. Therefore, using the reference limit proposed by Krug et al. (20), it should be possible to detect cheating athletes during the Co^{2+} ingestion period and in most cases for at least one week after cessation.

Another way to establish reference limits may be the determination of Co^{2+} in erythrocytes. Co^{2+} is rapidly cleared from the plasma (33) but it is stored in the red cells until they are destroyed after a maximum lifespan of approximately 120 days. ›

Detection of cheating athletes, may therefore even easier by measuring Co^{2+} in red cells. Until now, however, a routine detection method has not yet been established.

Conclusions

Cobalt is a strong erythropoiesis stimulating agent which can easily be acquired by cheating athletes. In 2015, WADA put cobalt on the list of prohibited substances; but until today no detection procedure has been introduced. Cobalt can be used by athletes to mimic the effects of hypoxic training measures (live high – train high, or live high – train low) or to prolong the effects of a preceding altitude training camp. Because cobalt acts in a dose dependent manner and because many athletes may try to get the maximum "benefit" from a cobalt supplementation, there exists the reasonable assumption that some athletes will use very high dosages which are associated with severe side effects. WADA has, therefore, to implement reasonable reference limits which we suggest being 14ng/ml in urine to keep sports as clean as possible and to protect the cheating athletes. WADA should also conduct re-tests of stored urine samples and it will be interesting to know whether and in which prevalence cobalt has been used by cheating athletes in the past.

Conflict of Interest

The authors have no conflict of interest.

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