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Cobalt whole blood concentrations in healthy adult male volunteers following two-weeks of ingesting a cobalt supplement

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ABSTRACT

Recently, there has been an increase in the marketing and sales of dietary supplements, energy drinks, and other consumer products that may contain relatively high concentrations of essential elements. Cobalt-containing supplements are readily available in the U.S. and have been marketed to consumers as energy enhancers. However, little information is available regarding cobalt (Co) body burden and steady-state blood concentrations following the intake of Co dietary supplements. We assessed Co whole blood concentrations in four healthy adult male volunteers who ingested a commercially available Co supplement (0.4 mg Co/day) for 15 or 16 days. Pre-supplementation blood Co concentrations were less than the reporting limit of 0.5 μg/L, consistent with background concentrations reported to range between 0.1 and 0.4 μg/L. The mean whole blood Co concentration in the volunteers after 15 or 16 days of dosing was 3.6 μg Co/L and ranged from 1.8 to 5.1 μg Co/L. The mean observed concentration in the study group was approximately 9–36 times greater than background concentrations. Further studies of Co whole blood concentrations following supplementation over longer time periods with additional monitoring of physiological parameters may provide useful information for evaluating the health of persons who take various doses of Co.

1. Introduction

In recent years, the consumption of dietary supplements has become increasingly popular. The manufacturers of these products attract users with various claims, such as the ability to improve physical health, increase energy, extend endurance, prevent chronic disease, and improve overall well-being (Briefel and Johnson, 2004; Marik and Flemmer, 2012; GAO, 2009). It has been estimated that about 75,000 different dietary supplements are available for purchase by consumers, and sales of dietary supplements in the United States (U.S.) reached approximately $25 billion in 2008 (Hoback, 2011; Lindquist, 2009; GAO, 2009). The most commonly used over-the-counter supplements include multivitamins, mineral supplements, sports nutrition blends, and weight loss formulas (Bailey et al., 2011; Hoback, 2011; Marik and Flemmer, 2012).

Results from the 2005–2008 National Health and Nutritional Examination Survey (NHANES), conducted by the U.S. Centers for Disease Control and Prevention (CDC), have indicated that approximately 51% of adults (people 20 years and older) use some form of dietary supplement (CDC, 2011) and results from the 2003–2006 NHANES survey have shown that as many as 65% of adults between 51 and 70 years of age use dietary supplements (Bailey et al., 2011). Furthermore, use of dietary supplements is not limited to adults. Results from the 2003–2006 NHANES survey have also indicated that 46% of boys and 40% of girls aged four to eight years of age use some form of dietary supplements (Bailey et al., 2011). No prescription is required to obtain these supplements, and, in many cases, there is no clear body of scientific evidence to support their claimed health benefits, nor are the possible risks to health frequently mentioned.

In the U.S., dietary supplements are regulated by the U.S. Food and Drug Administration (FDA) under the Dietary Supplement Health and Education Act (DSHEA) (NIH, 1994). Under the DSHEA, the dietary supplement manufacturer is "*responsible for determining that the dietary supplements it manufactures or distributes are safe*." Supplement manufacturers are not required to submit proof of safety or efficacy to the FDA before marketing their product because dietary supplements marketed before 1994 are broadly

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presumed to be safe (FDA, 2012; GAO, 2009). However, in the case of a new dietary ingredient, pre-market review of safety data, provided by the manufacturer, is required to establish that a new dietary ingredient is reasonably expected to be safe under the conditions of use recommended in the supplement labeling (NIH, 2011). For the most part, the FDA relies primarily on post-market surveillance efforts to identify potential safety concerns related to dietary supplements (GAO, 2009). Currently, for a product to be removed from market, the FDA has to offer evidence that the product is unsafe, that it contains a controlled substance, or that it does not contain the ingredients claimed on the manufacturers' label (GAO, 2009). The FDA has recently proposed several changes to dietary supplement regulation, including new regulations pertaining to the manufacturing and labeling of products, as well as the requirement for companies to report adverse events reported in people taking these products (GAO, 2009). In July, 2011, the FDA published a draft guidance that would increase the burden of dietary supplement manufacturers to prove a product's safety by requiring all supplements introduced into the marketplace after 1994 to undergo drug-like safety testing prior to product marketing (DHHS, 2011). The FDA recently announced its decision to revise this draft guidance, but has not yet done so (Ryan, 2012).

Numerous cobalt (Co)-containing dietary supplements are available for sale in the U.S., and several manufacturers have recommended daily doses up to 1 mg Co/day to help with fat and carbohydrate metabolism, protein synthesis, and red blood cell production (DRN, 2012; Mineralife, 2012; MEMI, 2011). A 2002 health and diet survey conducted by the FDA indicated that 0.07% of 888 people surveyed had taken a Co dietary supplement in the past 12 months (Lin, 2007). In addition, some energy drink products contain vitamin B_{12} in amounts as high as 41,677% of the U.S. FDA Daily Value of 6 μg (Zipfizz Corp, 2011; U.S. Food and Drug Administration, 2012b), which corresponds to an intake of about 100 μg of Co per serving. Further, because of the known erythropoetic effects of Co following the ingestion of certain doses, concerns have also been raised recently about the potential misuse of Co by athletes as a blood doping agent (Jelkmann and Lundby, 2011; Lippi et al., 2006). Treatment with $CoCl_2$ (10 mg Co/kg) has been reported to enhance physical performance in rats when compared to non treated animals (Saxena et al., 2010). In addition to dietary supplementation, daily doses of Co ranging from 0.5 mg Co/day up to 1.12 mg Co/day have been recommended to correct excessive excretion of estrogen that sometimes occurs during female hormone replacement therapy (Wright, 2005). Further, Co has been proposed to be used as a drug or "nutraceutical" for enhancing oxygen-carrying capacity at high altitudes where lower atmospheric pressures lead to lower partial pressures for oxygen (Shrivastava et al., 2010). However, the FDA has not established an allowable daily intake (ADI) value for Co. The only Co known to be required by the human body is in the form of Vitamin B_{12}, and only trace amounts of Co (~0.1 μg/day) are required for Vitamin B_{12}-mediated enzymatic reactions (ATSDR, 2004; Taylor and Marks, 1978). The use of vitamins B_6 and B_{12} dietary supplements is most common among adults over 50 years of age and children over eight years of age (Bailey et al., 2011).

While the FDA has not established an ADI for Co, the United Kingdom Expert Group on Vitamins and Minerals concluded that supplementing a 60 kg adult with 1400 μg Co/day was unlikely to cause adverse health effects (EGVM, 2003). This value was based on a lowest-observed-adverse-effect level (LOAEL) of 23 mg Co/kg-day that was associated with decreased testicular weight and seminal sperm concentrations in mice (Pedigo et al., 1988). Uncertainty factors of 10 for LOAEL to NOAEL extrapolation, 10 for inter-species variation and 10 for inter-individual variation were applied to the LOAEL of 23 mg Co/kg identified by Pedigo et al. (1988) to derive an aggregate uncertainty factor of 1000 and a guidance dose of 0.023 mg Co/kg day (EGVM, 2003; Pedigo et al., 1988). The European Food Safety Authority (EFSA) has suggested a lower guidance value for non-carcinogenic effects of 600 μg Co/day (EFSA, 2009). In 2008, the U.S. EPA's Office of Research and Development's National Center for Environmental Assessment (NCEA) published a provisional peer reviewed toxicity value (PPRTV) for Co which is functionally a proposed chronic oral reference dose (RfD) of 0.3 μg Co/kg-day (EPA, 2008). This dose would represent a maximum lifetime daily Co dose that would be considered "safe" for all age groups and most potentially sensitive subpopulations (EPA, 2008). The EPA provisional RfD was based on a LOAEL of 1 mg/kg-day (Roche and Layrisse, 1956), associated with decreased iodine uptake in humans and an uncertainty factor of 3,000 was applied to this value (EPA, 2008; Roche and Layrisse, 1956). It is important to note that the EPA proposed RfD is within the range of current background dietary Co intake by Americans (5–40 μg/day). Thus, the EPA's proposed value suggests that nearly any Co dose above dietary background is a potential health concern. This topic was recently discussed in a paper by Finley et al. (2012a) in which the authors derived an alternative RfD value of 0.03 mg Co/kg-day which is 100-fold higher than the EPA's provisional RfD (see below for further discussion).

Historically, Co has been used to treat anemia in adults and children. Typical adult doses have ranged from 25 to 150 mg $CoCl_2$/day, but doses as high as 300 mg $CoCl_2$/day have been reported (approximately 11.25–135 mg Co/day) (Gardner, 1953; Licht et al., 1972; Taylor et al., 1977; Wolf and Levy, 1954). The most common side effects associated with Co therapy were endocrine effects, such as goiters and decreased iodine uptake (Gross et al., 1955; Kriss et al., 1955). In a small number of patients undergoing Co therapy, hearing loss, optic atrophy, cardiomyopathy, and peripheral neuropathy have been reported (Bowie and Hurley, 1975; Curtis et al., 1976; Duckham and Lee, 1976; Gardner, 1953; Kriss et al., 1955; Manifold et al., 1978; Schirrmacher, 1967; Schleisner, 1956). However, most observed effects were transient and reversible upon cessation of Co therapy (Bowie and Hurley, 1975; Gardner, 1953; Schirrmacher, 1967). Further, the serum Co concentrations at which these effects were reported were extremely high. For instance, hearing loss was reported in three hemodialysis patients with peak Co serum concentrations of 2100, 600, and 560 μg/L during eight weeks of treatment with liquid $CoCl_2$ (four weeks at 25 mg $CoCl_2$ followed by four weeks at 50 mg $CoCl_2$) (Bowie and Hurley, 1975). In the two patients that were available for follow-up, it was noted that their hearing loss resolved upon discontinuing Co therapy. Since these patients suffered from renal disease, it is possible that the Co serum concentrations associated with these Co exposure levels were higher than what would be expected in a normal individual receiving the same dose, as it has been shown that Co blood concentrations in anephric patients can be four to eight times higher than those observed in a normal individual receiving the same dose (Curtis et al., 1976).

While Co supplement manufacturers generally recommend daily doses far less than what has historically been used to treat anemia, there is little information in the published literature regarding Co body burden and steady-state levels that can occur following Co dietary supplementation. Thus, we evaluated Co whole blood concentrations following 15 or 16 days of oral exposure to a liquid Co dietary supplement in four healthy male volunteers. This data set was then used to evaluate a Co biokinetic model developed by Unice et al. (2012), proposed to be useful for estimating Co whole blood concentrations as a function of oral Co dose (Unice et al., 2012). We also assessed the Co content in four different Co liquid dietary supplements to determine if the actual Co content matched what was claimed on the manufacturers' labels.