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Inorganic cobalt supplementation: Prediction of cobalt levels in whole blood and urine using a biokinetic model

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ABSTRACT

Soluble cobalt (Co) supplements with recommended daily doses up to 1000 μg Co/day are increasingly being marketed to consumers interested in healthy living practices. For example, some athletes may consider using Co supplements as blood doping agents, as Co is known to stimulate erythropoesis. However, the distribution and excretion kinetics of ingested Co are understood in a limited fashion. We used a Co-specific biokinetic model to estimate whole blood and urine Co levels resulting from oral exposure or ingestion of Co in amounts exceeding typical dietary intake rates. Following 10 days of Co supplementation at a rate of 400 to 1000 μg/day, predicted adult Co concentrations range from 1.7 to 10 μg/L in whole blood, and from 20 to 120 μg/L in urine. Chronic supplementation ($\geqslant$1 year) at a rate of 1000 μg Co/day is predicted to result in blood levels of 5.7 to 13 μg/L, and in urine levels from 65 to 150 μg/L. The model predictions are within those measured in humans following ingestion of known doses. The methodology presented in this paper can be used to predict urinary or blood Co levels following acute or chronic occupational incidental ingestion, medicinal therapy, supplemental intake, or other non-occupational exposures.

1. Introduction

Cobalt (Co) is a transition metal with physical and chemical properties similar to iron (Fe), and is found throughout the environment, as well as in foods such as fish, green leafy vegetables, and cereals (ATSDR, 2004; EGVM, 2003). Internationally, typical total dietary Co intake ranges from 11 to 45 μg/day (Hokin et al., 2004). Trace amounts of Co (~0.1 μg/day) are required by the human body in the form of vitamin B_{12}, which serves as a cofactor in the synthesis of methionine and metabolism of folates and purines (Barceloux, 1999; IOM, 1998; Varela-Moreiras et al., 2009). With the exception of vitamin B_{12}, there is no known essential nutritional requirement for Co in healthy human populations (ATSDR, 2004). Accordingly, governmental agencies have established dietary reference intakes (DRIs) for vitamin B_{12} but have not established DRIs for inorganic Co. For example, the Food and Nutrition Board of the Institute of Medicine has established a Recommended Daily Allowance of 2.4 μg/day vitamin B_{12} for adults, this corresponds to trace levels of Co (0.1 μg/day) (ATSDR, 2004; IOM, 1998).

Nonetheless, some purveyors of dietary supplements recommend daily intake of cobalt chloride ($CoCl_2$) formulations ranging from 200 to 1000 μg Co/day (Desert Rain Nutrition, 2012; Mineralife, 2012; Mother Earth Minerals, 2012). These recommended doses exceed the amount of Co associated with dietary and supplement vitamin B_{12} sources by many orders of magnitude. The bases for these specific recommended intakes are not identified, but the purported benefits of inorganic Co intake appear to be based on treatment of vitamin B_{12} deficiencies, such as central nervous system and hematopoietic effects (Desert Rain Nutrition, 2012; IOM, 1998; Mineralife, 2012; Mother Earth Minerals, 2012; Ott, 1999). The United Kingdom Expert Group on Vitamins and Minerals has concluded that supplementation of 1400 μg Co/day, while unnecessary, was unlikely to cause adverse health effects in adults (EGVM, 2003). The European Food Safety Authority has suggested a slightly lower non-cancer "acceptable safe amount for humans" of 600 μg Co/day (EFSA, 2009).

$CoCl_2$ intake at a sufficient oral dose has long been known to stimulate red blood cell (RBC) production, and is a potent erythropoietin (Epo) transcription inducer (Davis and Fields, 1958;

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Gardner, 1953; Jelkmann and Lundby, 2011). In the 1970s and earlier, 25–150 mg/day of $CoCl_2$ (11–68 mg Co/day) was often administered to anemic patients to increase RBC counts; however, this practice was discontinued when enlarged thyroids and goiters were observed at higher doses (Barceloux, 1999; Gardner, 1953; Jelkmann and Lundby, 2011; Taylor et al., 1977). In the 1960s, the use of Co-sulfate ($CoSO_4$) or $CoCl_2$ as anti-foaming agents in roughly 25% of the beer sold in the United States and Canada was associated with cardiomyopathy in some heavy beer drinkers (4–10 L/day), with anorexia and insufficient food intake observed at doses of approximately 3 mg Co/day (8 mg $CoSO_4$/day) to 10 mg Co/day (27 mg $CoSO_4$/day) (Alexander, 1969; Alexander, 1972; Morin and Daniel, 1967; Morin et al., 1971). Whether the cardiovascular effects would have occurred due to the alcohol intake alone is unclear. In addition, Co-containing alloys have been used in some medical implant devices from the 1940s to the present day (McKee, 1970) and these can result in a range of Co concentrations in blood (Daniel et al., 2010).

In the last decade, several weeks of oral $CoCl_2$ administration averaging 0.5–1.12 mg/day has been recommended to correct hyperexcretion of estrogen that sometimes occurs during female hormone replacement therapy (Wright, 2005). It has been hypothesized that Co use may be considered by some athletes as an alternative to Epo-related erythropoiesis-stimulating agents (Jelkmann and Lundby, 2011; Lippi et al., 2005, 2006). Fairly recently, sensitive analytical methods for determining metal ions in serum and whole blood have been developed, allowing for monitoring of sub part-per billion metal concentrations in these matrices (Case et al., 2001). Subsequently, studies have shown that some individuals with Co-containing hip implants have blood and urine Co levels elevated above general population background levels (Daniel et al., 2009; Daniel et al., 2010).

Understanding Co biokinetics is important to assessing the potential health implications for current Co-exposed populations. In the absence of a specific occupational, therapeutic, medical device or dietary supplement source, the general population concentrations of Co in whole blood and urine are <1 μg/L and 0.1–2 μg/L, respectively (ACGIH, 2010). In general, to understand the pharmacological or toxicological impact of a drug, it is helpful to understand the circulating blood levels rather than the administered dose, since blood concentrations account for both the amount of absorption and rates of elimination (which vary from person to person to some degree). Fortunately, whole blood and urinary reference values in a representative Italian sample including urban, suburban and rural subpopulations of 0.01–0.91 μg/L (n = 441, mean = 0.39 μg/L) and 0.18–0.96 μg/L (n = 468, mean = 0.57 μg/L), respectively, are available (Minoia et al., 1990). Blood or urine concentrations can vary appreciably by subpopulation, and in a second study of an Italian population restricted to healthy adults in an urban area, the average Co whole blood concentration was only 0.11 μg/L (n = 110), with 95% of individuals having concentrations less than 0.24 μg/L (Alimonti et al., 2005). There is a paucity of information concerning Co blood and urinary levels under various exposure conditions, including Co supplementation, historical, current, or future therapeutic use, and historical use of $CoSO_4$ or $CoCl_2$ in beer as an anti-foaming agent. As a result, predictive models describing the relationship between oral Co dose and tissue levels of Co have not been published to date.

The purpose of this paper is to describe the application and validation of a biokinetic model for Co to predict urinary or blood Co levels following acute or chronic oral occupational exposures, medicinal therapy, supplement intake, or other non-occupational exposures. In this analysis, we estimate blood and urinary Co levels expected to occur in individuals ingesting Co under currently relevant or historical exposure scenarios. The methodology described here should be useful for interpreting biomonitoring results in human exposure studies in which Co is the analyte of interest in a particular sub-population, as well as, in interpreting animal studies (Hays and Aylward, 2009; Paustenbach and Galbraith, 2006).

2. Materials and methods

The Leggett (2008) biokinetic model for Co was coded in Berkeley Madonna Version 8.3.9 and paired with a standard human alimentary tract model to assess oral absorption (ICRP, 2006; Leggett, 2008). The alimentary tract model represents the transport time through the mouth, esophagus, stomach, small intestine and large intestine. The biokinetic model accounts for Co excretion in bile, secretion to the ascending colon, filtration through the glomerulus, and transfer from the kidneys to bladder. This model consists of twenty-seven transfer coefficients proposed by Leggett based on calibration of model results to human data for total body retention and animal data for tissue distribution (Leggett, 2008). The Leggett (2008) model was selected because it takes into account a large database of literature on Co distribution in human and animals, and incorporates the physical realism necessary to reliably estimate the exchange of Co between key tissue compartments and blood. An alternative biokinetic model developed by the International Commission on Radiological Protection (ICRP) (1993) lacks the level of detail necessary to reliably estimate Co blood concentrations, including the rapid-turnover and slow exchanging blood pools incorporated into the Leggett (2008) model. Ingested Co was assumed to be in soluble form (i.e., $CoCl_2$ or $CoSO_4$), and alimentary tract transit times corresponding to total diet were used (ICRP, 2006). Absorbed Co was loaded to the rapid-turnover plasma pool of the model. A blood volume of 5.3 L and urinary excretion rate of 1.5 L/day approximately corresponding to a 70 kg adult were assumed (Leggett and Williams, 1991; McNally et al., 2011). The transfer coefficients used in the model are listed in Supplementary Tables S1 and S2. Renal efficiency of Co at steady state was calculated with the formula [renal efficiency (unitless)] = [urine concentration (μg Co/L)]/[plasma concentration (μg Co/L)], with an assumed Co whole blood/plasma ratio of 0.7–1.0 (Daniel et al., 2007; Smolders et al., 2011; Walter et al., 2008). Whole blood concentrations were tabulated as instantaneous values predicted by the kinetic model 12 h after oral administration, and urine concentrations were calculated as 24-h averages covering the period of time since the last oral administration.

The gastrointestinal absorption of Co is recognized as highly variable, and depends on form, dose, vehicle, solubility, amount of time since last meal and Fe status (Harp and Scoular, 1952; Leggett, 2008; Paley and Sussman, 1963; Smith et al., 1972; Sorbie et al., 1971; Valberg et al., 1969). Co appears to share a common absorptive transport mechanism with Fe (Valberg et al., 1969). At very low Co doses (<1 μg), evidence suggests that Co is not readily absorbed into systemic circulation (Smith et al., 1972). In two controlled human studies, the average fractional absorption of trace $CoCl_2$ (<1 μg Co) was less than 5% in contrast to much greater absorption with higher administered masses (1–12 mg Co) of 10%–30% (Paley and Sussman, 1963; Smith et al., 1972). However, these human studies consisted primarily of male subjects (~90%), and urinary excretion data from a more recent 10-day administration study of 0.5 mg Co/day as $CoCl_2$ with 12 males and 11 females suggest that Co absorption in women may be more efficient than in men by about a factor of three to four (Christensen et al., 1993). Taking into account the available data for men and women, a central tendency gastrointestinal absorption factor for greater than trace amounts of soluble inorganic Co ingestion of 25% with a minimum and maximum of 15% and 35% was assumed. This range for soluble Co is also consistent with inorganic Co absorption in mature rats, with gastrointestinal absorption ranges from 13% to 34% for $CoCl_2$ and only 1%–3% for insoluble Co oxide (ATSDR, 2004).

3. Results and discussion

Chronic ingestion of a soluble Co supplement in an amount equal to the UK guidance value of 1400 μg/day results in predicted whole blood Co concentrations of 7.9–18 μg/L, 12 h after last administration, or, on average, approximately an order of magnitude higher than the typical upper bound of 1 μg/L in unexposed individuals (Table 1). The corresponding predicted typical urinary 24-h time weighted average concentrations at this dose are approximately 46–105 times higher than upper bound background urine concentrations of 2 μg/L. The ingestion of soluble Co in amounts greater than 400–500 μg/day in supplements or with hormone replacement therapy is predicted to be detectable by laboratory blood analysis, with whole blood concentrations greater than 1 μg/L and urinary concentrations greater than 10 μg/L after at least 10 days of administration. At doses similar to those observed in historical cardiomyopathy cases associated with anorexic heavy beer drinkers, about 3–10 mg Co/day for one year, the predicted whole blood concentrations were 17–130 μg/L 12 h after last