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Refined biokinetic model for humans exposed to cobalt dietary supplements and other sources of systemic cobalt exposure

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ABSTRACT

An updated biokinetic model for human exposures to cobalt (Co) was developed based on a comprehensive set of human pharmacokinetics data collected from five male and five female volunteers who ingested ~1 mg Co/day of a Co supplement for 3 months. Three key experimental observations from the human dosing studies were incorporated into the model: (1) an increase in the measured fraction of large molecular serum protein bound Co from 95% during dosing to 99% after dosing; (2) a linear decrease in Co red blood cell concentration after dosing; and (3) Co renal clearance consistent with estimated glomerular filtration rates and free Co^{2+} concentration. The model was refined by adding compartments accounting for (1) albumin bound Co in intravascular fluid (serum); (2) albumin bound Co in extravascular fluid with physiologic exchange rates of albumin bound Co between extravascular and intravascular fluid; and (3) a novel sequential cascade of compartments representing red blood cell ages between 1 and 120 days. Reasonable agreement between the modeled and measured urine, serum, and whole blood concentrations were observed ($r > 0.84$, slope = 0.79–1.0) with gastrointestinal absorption rates between 9% and 66%. In addition, model predictions agreed well with data from several external studies representing healthy human volunteers, dialysis patients, anephric patients, a Co-poisoning incident and whole body retention studies. Our revised model considerably improves the state of knowledge on human Co kinetics, and should be helpful for evaluating elevated blood Co concentrations in currently exposed populations, such as metal-on-metal (MoM) hip implant patients.

1. Introduction

Biokinetic models provide important insight into the biological processes that affect dose–response relationships. These models have been successfully used to improve the characterization of human risk from multi-pathway exposure to various stable and radioactive metal isotopes. Two of the best known biokinetic models that incorporate physiological compartments and processes are the International Commission for Radiation Protection (ICRP) Age-Specific Biokinetic Model for Lead prepared by the ICRP [41] and the Integrated Exposure Uptake Biokinetic (IEUBK) model prepared by the U.S. EPA [82]. These models estimate likely blood lead (Pb) concentrations, which can be used to assess potential neurological health effects based on relationships between blood Pb concentrations and intelligence quotients (IQ). Biokinetic models with physiologic compartments are typically developed for chemicals with some data available on tissue distribution and whole body retention, but they lack a sufficient dataset to calibrate a physiologically-based pharmacokinetic model [42].

Recently, the human kinetics and health hazards of cobalt (Co) have received increased attention based on the availability of over-the-counter Co dietary supplements, the use of Co-containing alloys in medical devices, and the concern that Co-containing salts could potentially be misused by amateur or professional athletes as a erythropoietin (Epo) transcription inducer [76,60,33]. To provide a tool to characterize potential human health risk associated with various exposure scenarios leading to elevated blood Co concentrations, Unice et al. [76] linked an alimentary tract model with the Leggett [42] human Co biokinetic model originally prepared to update the ICRP [41] radiological worker assessment model. The Unice et al. [76] model indicated that over-the-counter Co dietary supplements were likely to result in whole blood

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concentrations of at least 1 to 12 μg Co /L with extended dosing (>30 days). Subsequent reviews of Co health hazards based primarily on oral dosing studies with modeled or measured blood concentrations indicated that adverse health effects, including cardiomyopathy and vision or hearing impairment, are generally associated with peak blood concentrations exceeding 700 μg Co/L following 8–40 weeks of dosing [23,60]. In addition, reversible health effects including hypothyroidism and polycythemia have been associated with blood concentrations exceeding 300 μg Co/L following at least 2 weeks of dosing.

While the Unice et al. [76] model was found to have good agreement with published whole blood Co concentrations and urinary excretion data [23,60], several biological processes, potentially important for predicting Co distribution and elimination, were not considered explicitly in this model because of lack of available data for model calibration and validation. Recently, several *in vivo* and *in vitro* studies addressing key toxicokinetic processes have been completed that make significant refinements in the Co biokinetic model possible. These data allow for the development of an integrated conceptual model linking Co albumin binding kinetics, Co red blood cell uptake and kinetics, and Co renal filtration and reabsorption. To date, the relationship between these processes and Co^{2+} ion transport, distribution, and elimination has been underappreciated because of the lack of kinetic data necessary to quantify these relationships. An integrated conceptual model allows a more thorough understanding of the toxicokinetics of free (unbound) ionic Co^{2+}, and other more readily measured quantities, such as serum or plasma Co concentration, red blood cell (RBC) Co concentration, whole Co blood concentration, urinary Co excretion, and percent of Co protein bound in serum [60].

In this study, multiple lines of evidence were used to develop an updated conceptual model describing Co kinetics. The revised Co biokinetic model incorporates data on serum Co protein binding [35,36]; whole blood, serum and urinary Co concentrations measured in humans following Co-supplementation [24,75]; renal reabsorption of Co [17]; and Co RBC uptake kinetics [68,69]. The primary goal of the refined biokinetic model presented here is to provide an improved characterization of Co-RBC kinetics and serum protein binding, and to provide additional metrics (such as the total and protein-bound concentration of Co in plasma and the Co concentration in RBCs) that should be useful for characterizing exposed populations. In addition, a major aim of this research was to improve the characterization of dose-dependent renal excretion of Co. Most historical studies of Co-kinetics have relied on low-dose, Co radiotracer isotope (<0.01 μg Co) studies in which renal conservation likely contributed to an appreciable reduction in the measured net renal excretion fraction of Co as compared to a higher net renal excretion fraction that is expected following exposure to relatively large doses of Co [44,70,17,75,13]. This improved characterization of urinary excretion should increase the reliability of the systemic Co body burden predicted by the model at low and high doses. A final purpose was to quantitatively relate changes in a clinical measure of kidney function (i.e., estimated glomerular filtration rate (GFR)) to changes in anticipated blood Co concentrations, tissue concentrations, and systemic body burden.

2. Materials and methods

The Leggett [42] human systemic Co biokinetic model and subsequent [76] model incorporating GI absorption were refined using data available from several recent studies regarding: (1) human oral Co supplementation up to 90 days; (2) RBC uptake and recycling; (3) Co-plasma protein binding; and (4) Co urinary excretion. Based on a review of the available literature, additional compartments were added to the model, and a revised code was written to account for the key transfer processes identified in the conceptual model. Where possible, model parameter values for compartments added to the model were assigned based on physiologic rates, such as the lifetime of a RBC, albumin intravascular and extravascular exchange rates, and the GFR. Model parameters were selected based on: (1) the key data and revised conceptual model described in Section 3 below; (2) a sensitivity analysis of selected model parameters to achieve measureable clinical characteristics such as GFR and hematocrit (HCT); (2) human experimental data; (3) animal experimental data; and (4) *in vitro* experimental data. A guiding principle of the model refinement was the addition of the minimum number of physiologically meaningful compartments necessary to describe the available data with a minimal number of parameters requiring calibration.

The refined systemic model was coded in Berkeley Madonna Version 8.3.9 linked to the standard human alimentary tract model described in Unice et al. [76] to account for GI absorption [32,42]. The alimentary tract model was unchanged during model refinement, and the transfer coefficients for this model are presented in the Supplementary data (Supp. Fig. 1). Blood and urinary data obtained during and after dosing from 10 human volunteers ingesting ~1 mg Co/day for up to 3 months were used to evaluate the hypothesis that the revised conceptual model was consistent with simultaneously recorded whole blood concentrations, serum concentrations, urinary excretion rates, and the fraction of Co bound to large molecular proteins. The primary objective of the model calibration was to identify a single set of parameters (with the exception of gastrointestinal (GI) absorption and measured individual characteristics such as HCT or GFR) that adequately described the data collected from the 10 human volunteers, followed by successful validation using available external data. Initial values for the parameters added to the model were estimated from the literature. The values revised in the calibration were limited RBC uptake rate, the transfer rate from the albumin-bound phase to the unbound plasma phase, and the total rate of transfer from the unbound plasma phase to tissues. The percentages of Co systemically transferred from blood to individual tissue compartments derived from the available animal studies by Leggett [42] were retained, and were used to calculate updated transfer coefficients taking into account the refined total rate of transfer from unbound plasma to tissues.

An adequate fit during model calibration was defined by the set of parameters that resulted in a (1) R^2 of at least 0.75; (2) a slope of 0.8–1.2; and (3) an intercept of approximately 0 for pooled modeled versus measured whole blood, serum, and estimated RBC concentrations, and urinary excretion rate on both linear and log-transformed scales. Model fit was also evaluated by visual examination of modeled versus measured plots on linear and log scales relative to the 1:1 line, as well as plots of several modeled and measured quantities versus time for the 10 individual human volunteers, including blood concentration, urinary excretion, and the percent of Co bound to albumin during and after dosing. In total, the number of pooled modeled and measured results included 137 whole blood pairs, 137 serum pairs, 133 RBC pairs and 58 urinary excretion pairs. In four instances, the calculated RBC concentration estimated from the HCT and measured whole blood and serum concentration was less than 0, and was excluded from the analysis.

Volunteer specific body weight, HCT, and GFR used during model development are summarized in Table 1. GFR rates presented in the text are not normalized for surface area unless noted. Volunteer kidney function and potential Co filtration of free or low molecular weight (<0.5 kDa) protein bound Co was assessed using the estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [45]. The CKD-EPI equation was developed using data with a GFR range between 2 and 190 mL/min/1.73 m^2 and accounts