Using Models to Explore Whole-Body Metabolism and Accessing Models Through a Model Library

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A model is a mathematical representation of a system that can be used to explore the system in a number of ways: to determine the system's internal connections, to calculate properties of the system such as flow rates and pool sizes, and to make predictions about the system's behavior under different conditions. The use of modeling to explore whole-body metabolism is demonstrated using a compartmental model of zinc kinetics as an example. Because models are useful tools for exploring systems, a facility called a "model library" is being established on the Internet to provide access to working versions of published models.

A MODEL is a mathematical representation of a system that can be used to explore the structure and behavior of the system. According to Epstein,[1] "Mathematical modeling provides a systematic way of organizing data and observations of the behavior of a system at the cell, tissue, organ or whole animal (human) levels and affords the opportunity to better understand and predict physiological phenomena." Compartmental models have been widely applied to study biological systems, and the utility of compartmental models will be demonstrated here by showing how a model for zinc in humans has been used to analyze data from different physiological states (zinc loading, aging, and the perinatal period), to study zinc kinetics in other species, and to make predictions. Because of the general utility of published models for exploring systems, we will then describe how published models can be accessed using a new facility being established on the Internet, called a "model library."

A MODEL FOR ZINC KINETICS IN HUMANS

A multicompartmental model has been developed for whole-body zinc metabolism in humans based on data from radioactive and stable-isotope tracer studies.[2,3] This approach was used since it has the advantage over simpler algebraic or one- or two-compartmental models, in that it allows parameters related to specific physiological processes such as absorption and endogenous excretion to be calculated separately.[4] The model was initially developed in patients with taste and smell dysfunction,[5,6] but was subsequently expanded using data from healthy volunteers.

Normal volunteers were studied for 270 days following oral or intravenous administration of ^{65}Zn, a radioisotope of zinc ($t_{1/2}$ = 245 days).[2] Plasma, red blood cells, urine, and feces were collected while external counting was performed over the whole body and, using probes, over the liver and thigh areas. Data from all tissues were analyzed simultaneously using the modeling software SAAM/CONSAM.[7,8]

The model consists of compartments for zinc in plasma, red blood cells, liver, muscle, bone, and three tissue compartments (Fig 1). Release of zinc from bone was too slow to be determined from these studies of only 270 days, and was therefore based initially on calcium data.[2] Using this value, the model was tested and found to adequately fit data from a published study with sampling over an extended period of 600 days.[9] The model includes the main route for loss of zinc by endogenous excretion into the intestine and loss by excretion into urine. This was the simplest model (ie, with the smallest number of compartments and interconnections)[10] that was required to fit the data from all seven tissues simultaneously.

USING A PUBLISHED MODEL

To Analyze Data From Different Physiological States

Zinc loading. In the studies described above, subjects were studied for 270 days while on their normal zinc intake of approximately 10 mg/d. At the completion of this baseline period, they were administered an additional 100 mg Zn per day and were studied for a further 270 days (zinc loading period). By comparing zinc kinetics during the loading phase with kinetics during the baseline phase, it was possible to identify parameters that changed during zinc loading.[2] The parameters were identified by introducing a change in one parameter at a time until all the data were fitted using the "minimal change postulate."[10] Parameters that changed between the baseline and loading states represent sites of regulation. Five sites were identified: absorption, urinary excretion, endogenous excretion, exchange with red blood cells, and release from muscle. The model was therefore used to interpret changes in complex data curves between two conditions and to identify the sites of change.

Aging. The normal subjects in the study described above ranged in age from 20 to 80 years. By comparing parameter values across age, it was possible to determine which parameters were susceptible to change with age. Few parameters changed when subjects were on their regular diet. However, significant age-related changes occurred when subjects were challenged by a high zinc intake. Changes occurred at four sites of regulation: urinary excretion, red blood cell exchange, absorption, and endogenous excretion.[11] Again, the model

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Submitted September 19, 1996; accepted September 23, 1996.

Support by National Science Foundation Grant No. BIR-9503872.

Presented at the National Institutes of Health Symposium, "In Vivo Tracer Kinetics and Modeling," May 3, 1996, National Institutes of Health, Bethesda, MD.

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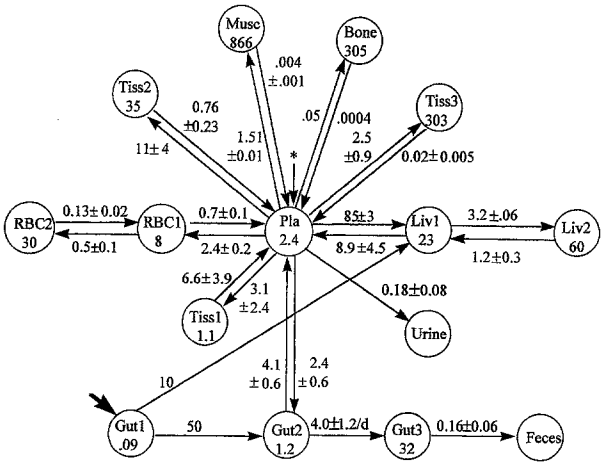

Fig 1. Model for zinc kinetics in humans. Circles represent compartments; arrows represent pathways between compartments. Compartments are shown for plasma (Pla), red blood cells (RBC1 and RBC2), liver (Liv1 and Liv2), muscle (Musc), bone, tissues with different rates of turnover (Tiss1, Tiss2, and Tiss3), gastrointestinal tract (Gut1, Gut2, and Gut3), urine, and feces. Numbers in compartments refer to compartment size (mg) and numbers by arrows are transfer coefficients (fraction per day, mean ± SD) for a population of healthy adults. *Site of tracer entry. Thick arrow into compartment Gut1 represents entry of zinc in the diet. (Reprinted with permission.[2])

facilitated identification of the sites of change in zinc metabolism, this time in association with age.

Perinatal period. Preterm infants (<38 weeks' gestation) have a high nutrient demand, but their organs are immature and hence they may be less efficient at absorbing and retaining nutrients than term infants. The ability of healthy preterm infants to absorb and retain zinc was studied following oral or intravenous administration of a stable zinc isotope. Data from plasma, red blood cells, urine, and feces were analyzed using the model developed for adults (Fig 1), suitably modified on the basis of literature information about zinc distribution in infants.[12] Both tracer and tracee (total zinc) data were fitted using similar but separate models, because the infants had an increase in weight of greater than 50% during the study period of up to 4 weeks, and zinc metabolism therefore was not in steady state.

The studies provided values for zinc kinetics in healthy preterm infants. These values are now available to determine whether zinc metabolism is abnormal in sick infants, for example, and whether different nutritional protocols are indicated. Here, the model developed for adults has been used as a basis for interpreting data in subjects, from whom less data are available.

To Analyze Kinetics in Other Species

The model developed for humans has been used as the basis to analyze data from other species, namely piglets and rats. For piglets, use of the model allowed calculation of changes in metabolism and tissue pool sizes in animals on normal and marginal zinc intake.[13] In rats, tissue data were obtained that were not available in humans, and these data may assist in identifying the three generic tissue compartments in the human model (Fig 1: Tiss1, Tiss2, and Tiss3; W.A. House, personal communication, March 1996). By using the same model to analyze data from other species, comparisons could be made for zinc distribution and pool turnover times, and the additional tissue data from the animals could be used to help identify parts of the human model.

To Make Predictions

The model was developed for humans on a normal zinc intake, but it can be used to explore other research issues. It can be used to simulate the answers to "What if?" questions and to make predictions, such as the effects of different dietary intakes or perturbations of certain pathways. For example, it has been used to predict how long it would take for plasma zinc to decline below normal levels on varying zinc intakes (Fig 2). On an intake of 5 mg/d (half the normal intake of 10 mg/d) plasma zinc remains in the normal range (>60 μg/dL) for 6 months. On 2 mg/d, plasma zinc decreases below normal after 130 days, or 4 months, whereas on very low intake (0.2 mg/d) it is predicted to decrease below normal within 50 days. These predictions agree with published observations.[14-17] The model could be used in a

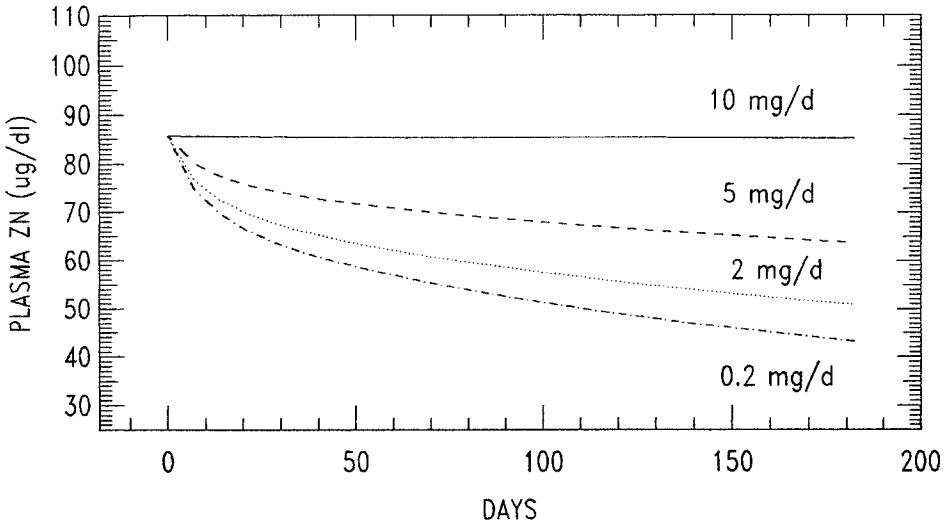

Fig 2. Simulation using the model (Fig 1) of changes in plasma zinc in subjects on different daily intakes of zinc ranging from a normal of 10 mg/d to 0.2 mg/d.

similar manner to predict changes in other tissues, for example, the liver, muscle, or bone, under varying dietary intakes or with increased endogenous or urinary loss such as occurs in some diseases.

A FACILITY FOR ACCESSING PUBLISHED MODELS

Models contain a large amount of information about a system. It is costly to obtain the developmental data and time-consuming to develop the model. Once developed, models encapsulate considerable knowledge regarding the current understanding of a system, but to take advantage of this information, models need to be readily accessible. Currently, they are published in journals, and the only way to convert them to computer-manageable working versions is by reconstructing them in a modeling language format. Without help from the original authors of the model, this process can be time-consuming and error-prone. Therefore, to address this need, a new facility called a "model library" is under development at Georgetown University in collaboration with the University of Pennsylvania.[18] The purpose of the library is to provide access to working versions of published models. It is being developed by a group with expertise in a number of disciplines including information management, computing, biological sciences, modeling software development, and modeling. An advisory panel with representatives from academic institutions, government, and industry oversees the project. The library can be accessed at the WorldWide Web site, http://gopher.dml.georgetown.edu/model/model.html.

Within the library, users can locate a model based on a subject of interest, by author, year, journal, or class of model, or by software used for model development. Once a model of interest is located, it can be investigated using model description, model graphics, and plots of various solutions. Limited simulations can be performed in the library, but users may download the models for use on their own system and with their own software package. Published models can be submitted to the library electronically using a menu within the library.

In summary, models are useful tools for exploring systems. Once developed, they can be used to analyze data and make predictions about the behavior of the system under different conditions. By making published models accessible online, they can be used for their intended purpose—to explore systems through simulation.

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