What Can Pharmacokinetic Models Tell Us about the Disposition of Lycopene and the Potential Role of Lycopene in Cancer Prevention?¹

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EXPANDED ABSTRACT

Mathematical modeling refers to a variety of techniques that involve representing a system with mathematical equations for the purpose of investigating and understanding its functioning. Types of modeling include compartmental, empirical, deterministic, stochastic, and physiologically based pharmacokinetic. While the specific approaches differ for different types of modeling, the purpose remains similar: to use the tools of mathematics as a system of bookkeeping to elucidate order in complex systems.

Generally, tools of modeling reveal kinetic information, allowing determination of rates of biological processes involved in uptake, metabolism, and disposition of compounds by the body. This includes information about nutrient bioavailability, irreversible elimination, and storage pool sizes, all of which are important for making reliable recommendations for nutrient intake.

Compartmental modeling, which is especially well suited to nutrition research, involves setting up a system of compartments and connecting those compartments with mathematical equations to describe the transfer of material from one compartment to another. A mathematical “simulation” is then performed to test the model behavior against experimental data. The results from the model-simulated experiment are compared with the results of a human or an animal experiment, and the model structure and/or parameters are adjusted until the model results are in good accord with actual experimental observation.

Understanding dose–response and nutrient disposition is a key use of modeling, and a compartmental model of lycopene disposition was recently published by Diwadkar-Navsariwala et al. (1) to assess dose–response for a single ingestion of lycopene. A clinical study was conducted in which 25 men ingested a single dose of a tomato beverage that was composed of tomato paste, olive oil, and water. The men were divided into 5 groups (5 per group) and received 1 of 5 treatment levels: 10 mg, 30 mg, 60 mg, 90 mg, or 120 mg lycopene. Serial plasma samples were drawn for 1 mo after the dose, and plasma samples were analyzed for lycopene by HPLC. A compartmental model was developed based on an earlier model of β-carotene metabolism (2), because carotenoids have similarities in metabolic pathways (3), and the plasma lycopene response curves were analyzed using the model. The model revealed that saturation of lycopene absorption occurs with increasing dose. The absorption efficiency at the 10-mg dose was on average 34%, whereas the absorption efficiency of the 120-mg dose was about 5.5%. When considering the mass absorbed, a 12-fold increase in dose produced less than a doubling of the mass absorbed.

Further simulations (unpublished data) showed the model to be in agreement with results of several published studies involving multiple dosing regimens of lycopene contained in foods. The longer term studies used for these simulations included lower doses of 20–35 mg/d (4,5) and a higher dose of 70 mg/d (6). The daily dosing studies also involved different lengths of treatment: 15 d for Hadley et al. (5), 21 d for Edwards et al. (4), and 28 d for Paetau et al. (6). In all cases, the model produced predictions for plasma lycopene concentration within or nearly within 1 SD from the mean outcome of the experimental study. In other words, the single-dose model presented in Diwadkar-Navsariwala et al. (1) is in good accord with longer-term feeding studies of lycopene. Thus, this model offers a worthwhile opportunity to investigate the outcome of chronic ingestion of lycopene, and such information would be very useful for evaluating the efficacy of different dosing regimens on circulating plasma lycopene and lycopene tissue pools.

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Another very powerful use of modeling is to identify metabolic pathways that differ among populations. This type of modeling has not been conducted with lycopene or any other carotenoid to date, so the power of this approach will be explained through an example of calcium modeling. A key problem related to calcium nutrition is that of bone mass. Bone mass peaks in early adulthood, then decreases throughout the remainder of life. Low bone mass is associated with increased risk of fracture, so understanding the mechanisms behind bone deposition and investigation of how to improve bone density would be potentially very useful.

Wanstey et al. (7) performed a study to identify processes that differed during rapid vs. slow bone accretion. In this study, two population groups (teen girls aged 13 ± 1 y and young women aged 22 ± 4 y) received 2 tracers: an oral tracer of 44Ca and an intravenous tracer of 45Ca. A compartmental model of calcium metabolism was developed to include gastrointestinal absorption, serum exchange, bone deposition, and urinary loss. Tracer appearance in blood, urine, and feces was used to determine rates of transfer among compartments, and the model highlighted the specific pathways that differed between these two population groups. The young women had a lower calcium absorption efficiency in the gut and a more efficient clearance of calcium into urine, both of which decreased calcium availability for bone deposition. Exchange among serum calcium pools was also affected by age. The model not only highlighted the differing paths but also specifically quantified the differences. Teenage girls absorbed 74% more calcium than young women. In addition, for young women, calcium in blood was twice as likely to be excreted into urine than for teenage girls. This experiment was followed by another experiment to determine the processes by which high calcium intake promotes bone retention. The kinetics of calcium in girls was studied while the girls consumed different calcium intakes. The girls on the high calcium intake absorbed twice as much calcium, excreted 35% more calcium into urine, but ultimately retained 4-fold more calcium. This type of approach could be used for comparing lycopene disposition in different population groups. Groups to be compared might differ in a key polymorphism or in risk for prostate cancer. As modeling highlights pathways whose transfer rates differ among population groups, follow-up studies focusing on these pathways can uncover the biochemical mechanisms behind the changes. In this way, modeling may prove useful for understanding the potential role of lycopene in prevention of disease.

Another very important use of pharmacokinetic modeling is for the extrapolation of animal data to humans. Mathematical extrapolation across species is useful when metabolic pathways are common among the species. For these experiments, blood and tissue concentrations of the parent compound and its metabolites are measured in animals across time after known doses. These types of models contain detailed information about body sizes, organ sizes, blood volume, blood-flow rate, and tissue composition to accurately account for factors that would influence the pharmacokinetics of the compound. These models are frequently developed in more than one species to lend to the validity. As an example, the disposition of an antifungal agent, voriconazole, was modeled in mouse, rat, rabbit, guinea pig, dog, and human (8). Trans-species physiologically based pharmacokinetic modeling might be useful for understanding the prostate’s handling of lycopene. Recent studies involving administration of 14C-lycopene to F344 rats have begun to produce tissue specific kinetic and metabolic data for lycopene (9). Individual tissues were analyzed for 14C-lycopene and polar products for 168 h after the dose to reveal clear differences among tissues in the accumulation and metabolism of lycopene.

CONCLUSIONS

Mathematical modeling is a very useful tool for understanding the disposition of nutrients. Absorption efficiencies, elimination rates, and tissue metabolism of compounds are key pieces of information for developing sound recommendations for nutrient intakes. As the potential role of lycopene in prevention of prostate cancer unfolds, mathematical modeling could certainly play an important role in improving intake recommendations and clarifying modes of action in lycopene disease prevention.

LITERATURE CITED