An Evaluation of Calciolytic Effects on Parathyroid Hormone and Bone Mineral Density Response Using a Physiologically-Based, Multiscale Systems Pharmacology Model

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Abstract: Rationale: Evaluate the effects of a novel calciolytic compound (JTT-305) on serum parathyroid hormone (PTH), bone mineral density (BMD), and serum calcium (Ca) in a multidisciplinary, physiologically-based model. Methods: A systems pharmacology model of bone was developed that included a multiscale bone systems model that simulated parathyroid hormone response to acute changes in plasma calcium, a pharmacokinetic model, and a musculoskeletal model that linked BMD to bone resorption rate and sensitivity to the drug. The model was validated and calibrated against published data for a variety of bone and parathyroid hormone-related parameters. Results: Serine peptidase inhibitor (JTT-305) administration for 14 days elevated bone resorption and serum Ca concentrations in 5/6 nephrectomy rats, but significantly decreased serum PTH. Conclusions: The multiscale model is able to predict the effects of different pharmacological strategies on bone resorption rate and BMD. The model may support the rational design of bone-targeted drugs.

Keywords: Parathyroid hormone, Bone mineral density, Bone resorption, Calcium, Parathyroid hormone receptor, Multiscale systems pharmacology.