Multiscale physiology-based modeling of mineral bone disorder in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis: application to etelcalcetide treatment effects on calcium homeostasis

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Abstract

Objectives: To evaluate contributions of physiologic disease (chronic kidney disease (CKD)) progression and feedback mechanisms, as well as the pharmacokinetic (PK) and pharmacologic effects of the calcimimetic etelcalcetide on the time- courses of changes in serum corrected calcium (Ca) and parathyroid hormone (PTH). **Methods**: Clinical data from 5 studies (2 Phase 1, 1 Phase 2, 2 Phase 3) provided single and repeated intravenous dosing information on etelcalcetide PK and responses to placebo and individually titrated etelcalcetide in patients with CKD and secondary hyperparathyroidism on hemodialysis. Individual exposure estimates were obtained from a 3-compartmental population PK model. An expanded multi-scale systems pharmacology model [1] was first calibrated to describe Ca and PTH balance in CKD patients, using the R package *mrgsolve*.[2]. Drug effects were then considered as effects on calcium sensing receptor (CaSR) in PT gland and bone. Parameters were estimated using *newuoa* in the *minqa* R package [3]. Goodness-of-fit diagnostics guided model development. One Phase 3 study was withheld for external evaluation. **Results**: Model calibrations included removal of exchangeable intracellular phosphate, suspension of calcitriol effect on renal calcium excretion and its adjustment as a function of kidney filtration, adjustment in PT Ca-sensitivity with CKD progression, and reversibility of PTH secretion capacity with treatment. Drug effects included maximal inhibition of PT sensing (89%) and relative osteoclast function (39%). The model described PTH and Ca changes following single and repeated dosing. Notably, the model captured the time-courses and magnitudes of the near 10% and 60% maximal mean decreases in calcium and PTH, respectively, from both Phase 3 studies. **Conclusions**: Long-term changes in Ca and PTH were predicted with a modified systems pharmacology model after adjusting for CKD. This provided estimates of expected contributions of physiologic disease progression, feedback mechanisms and pharmacologic effects of etelcalcetide on Ca homeostasis.

DISCLOSURES: KTB and MMR are employees of Metrum Research Group LLC, and served as paid consultants to Amgen Inc during the conduct of these analyses. MM was an employee of Amgen Inc at the time of this work.

Goals

Objective:

- What is the expected contribution of physiologic disease (CKD) progression and feedback, as well as pharmacologic effects of etelcalcetide, on long-term changes in calcium and PTH?

Intended Outcomes:

- Model provides insight and plausible mechanistic explanations into observed calcium and PTH changes in CKD patients under different treatment conditions.
- Explore explanations for relatively slow Ca rebound and absence of PTH rebound in some patients including inherent compensatory mechanisms and potential effects of supplements (Ca, Vitamin D, etc.)

Methods

Existing models

- Multi-scale physiologic model (Figure 1)
- Etelcalcetide population PK model
  - 3 compartment, IV dosing
  - Included hemodialysis (3 days/wk MWF) through additional effect on CL

Data

- 5 clinical studies:
  - Development and estimation: 2 Phase I, 1 Phase II (4169005), 1 Phase III (20120230)
  - External validation: 1 Phase III (20120229)
- PK, Ca and PTH clinical data following etelcalcetide administration

Software

- Mathematical expressions coded using R package `mrgsolve` [2]
- Optimization: *newoua* function in the `minqa` R package [3]

Model Extension

- Compare disease state predictions with clinical (CKD) data (in absence of drug)
- Integrate PK and pharmacology-related effects for etelcalcetide
- Investigate inherent feedback (Figure 2) & effects of possible concomitant interventions or adynamic bone disease (Figure 3)

Model and Modifications

Model Schematic

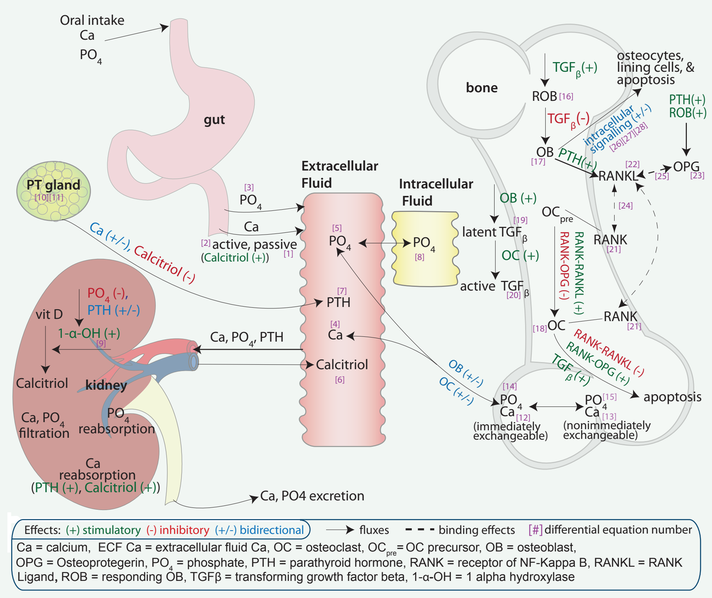


Figure 1: *Multiscale physiologic model; reproduced from Peterson and Riggs[1]*

Disease and Pharmacology

Disease Effects:

1. CKD-related hyperphosphatemia, phosphate binds with Ca[4, 5] : Include new fluxes
2. CKD affected over 10-year progression period to end stage status GFR$\leq$ 15 mL/min[6]
3. Change sensitivity of PTH release to Ca sensing to match with those clinical data[7]
4. Adjust the urine Ca reabsorption maximum: maximal value decreased as GFR decreased

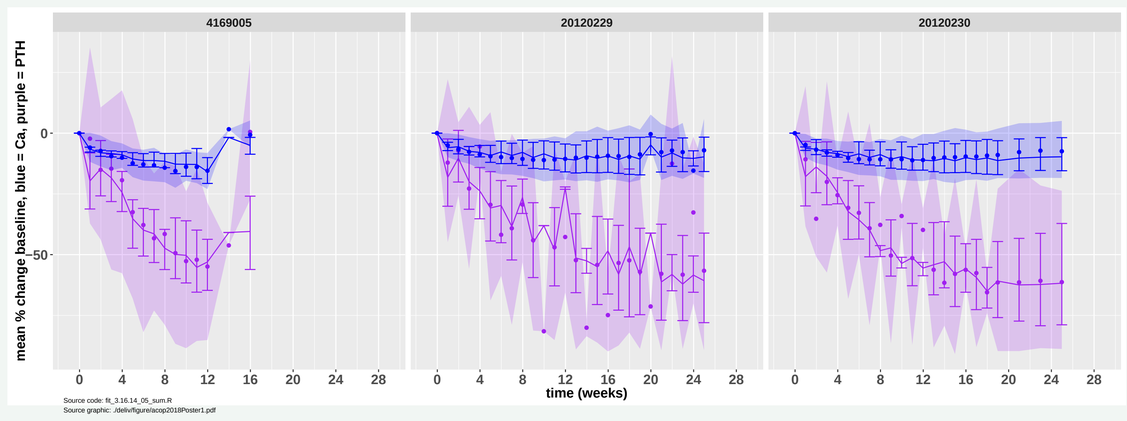
Drug Effects:

1. Sigmoidal effect on responsiveness, and
2. Hyperbolic effect on sensitivity for Ca-related endogenous PTH release [8]
3. Reduced PT gland hyperplasia to reduce PTH available for release
4. Ca-sensing effect in bone

Note: all terms and estimates, except those noted above, retained as in original model.[1]

Results

Long-Term Predictive Checks

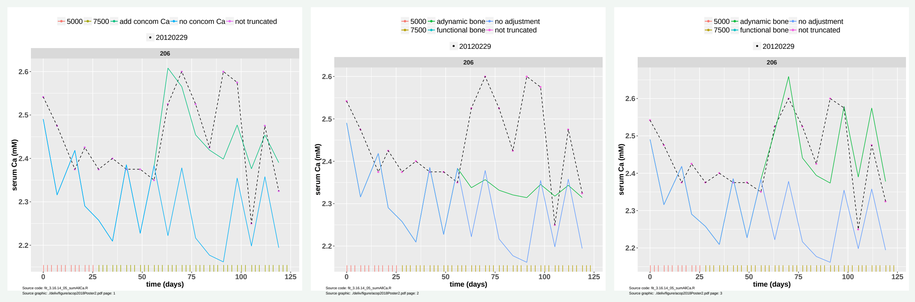


Despite continued decline in PTH (e.g., beyond weeks 4-6), feedback controls lead to leveling and partial rebound in Ca.

Figure 2: *Predictive check: change from baseline (percentage) for serum calcium (blue) and PTH (purple)*

Phase 3 Study 20120229 was included as external validation. Observed data: solid circle (mean) and 10th - 90th percentile range (shaded region); Simulated data: mean (solid line) and 10th - 90th percentile range (error bars).

Model exploration



Either an arbitrary calcium supplementation and/or a decrease in flux of Ca from bone (e.g., due to adynamic bone) provided plausible means for individual patient Ca rebound. Complete turn off of Ca flux to/from bone did not match with clinical observations.

Figure 3: *Serum Ca time-course from one individual (ID 206) assuming Ca supplementation (left), Ca bone flux off from adynamic bone (center), Ca flux from bone slowed by 27.5% from adynamic bone (right).*

Conclusions

- Long-term changes in Ca and PTH were predicted with a modified systems pharmacology model after adjusting for CKD.
- Provided quantitative descriptions of physiologic disease progression, feedback mechanisms and pharmacologic effects of etelcalcetide on Ca homeostasis.

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