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

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ABSTRACT

Recent research involving Ca sensing receptor (CaSR) antagonists (calcilytics) has focused on assimilating transient spikes in PTH observed with subcutaneous PTH (1-34, 1-84) administration. The goal has been to provide a "by mouth" osteoporosis treatment comparable to PTH without invasive dosing. Investigations have yet to achieve this target profile, with typical BMD elevations of no more than 2%–3% and often notably elevated serum calcium. A model-based approach to quantify the physiologic response to calcilytics was undertaken to support development of DS-9194b, an orally administered investigational calcilytic. An existing physiologically-based, multiscale systems pharmacology mathematical model (MSPM) [1] was expanded to include a capacity-limited PTH release pool. Pharmacokinetic (PK) and PTH data (ronacaleret [R], JTT-305 [J]) were used for this further MSPM model development. Results indicated a limit to the maximum achievable peak PTH response and described the characteristic persistent PTH elevation.

The MSPM results were coupled with a modeled relationship between peak PTH and BMD (fig 8); results suggested that mean PTHmax (~ 20 pM) from the investigated calcilytics equated to a mean BMD increase < 3%, as typically observed for these agents, whereas a PTHmax > 30 pM was considered necessary to provide appreciable BMD increase.

PK, PTH and Ca data were prospectively collected from a single-dose, first-in-human study including DS-9194b administration [0–100 mg]. PTHmax reached an apparent plateau (~ 30 pM) as doses increased above 15 mg (fig 6); this peak was well described by the MSPM, as were the prolonged elevations at higher doses. Urine Ca excretion decreased with increased DS-9194b dose (fig 7); this effect was included in the MSPM through PTH effects on urine Ca excretion. A maximal 12-month 4%–5% BMD increase was predicted for DS-9194b based on the prior modeling. Only the single-dose clinical data was required to support this prediction and suggests potential for DS-9194b as a future osteoporosis treatment option.

Overall, the modeling indicated that BMD elevation with calcilytic administration routines evaluated is possible but the magnitude of BMD elevation is unlikely to match that seen with exogenous PTH. The MSPM provided a physiologic explanation of maximal PTH response due to capacity-limited PT gland pool of PTH. Results can guide future considerations for calcilytic-related therapies for osteoporosis or other PTH-related disorders.

OBJECTIVES

Model-Based Decision Support

- Use model-based approach to quantify the physiologic response to calcilytics to support development of DS-9194b, an orally administered investigational calcilytic
- Develop target criteria for PTH response (extent and duration) for first-in-human clinical study of an investigational drug (DSI-9194b)
- Assess maximal PTH response and effects of urine Ca^{2+} excretion using DS-9194b first-in-human clinical data; support development criteria with expectations for maximal BMD changes achievable through CaSR antagonism

BACKGROUND – MULTISCALE SYSTEMS PHARMACOLOGY MODELS (MSPMs)

Multiscale Systems Biology / Pharmacology Models (Figure 1)

- Biologic systems expressed as mathematical expressions
- Quantify timecourses, magnitudes of changes (e.g., natural decays, interactions)
- Serve as in silico probes of biologic perturbation (e.g., disease, genetic variation)
- Multiscale systems pharmacology model (**MSPM**): include pharmacologic effects

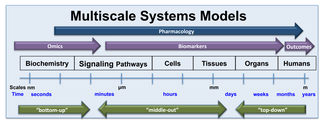

Figure 1: *Defining multiscale systems models and terminology; reproduced from Riggs 2011* [2]

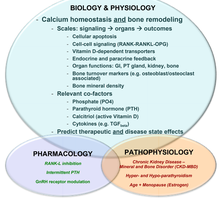

Figure 2: *MSPM conceptual framework and content overview.*

MSPM of Bone Mineral Homeostasis and Remodeling (Figures 2, 4)

- Mathematical (differential equations) construct from experimental and clinical data
- Scales: Cell signaling → organ functions → bone turnover markers (BTMs) → BMD
- Applications:
  - Denosumab: PTH, serum calcium, BTMs,[1] and lumbar spine BMD[3, 4]
  - Teriparatide: PTH, serum calcium, and BTMs[1]
  - Disease/Aging [CKD-MBD,[5] menopause and endometriosis[6]]: BTMs, BMD and fracture risk[7]
- Software: R (www.R-project.org/)[8] (Vienna, Austria)

BACKGROUND – CALCILYTICS

Calcilytics:

- Inhibit (pharmacologic antagonism) calcium-sensing receptor (CaSR) in PT gland
- Earlier calcilytic clinical trials: BMD elevations no more than 2%–3% and often notably elevated serum calcium[9, 10, 11, 12, 13]
- Where these effects due to compound specific (e.g., pharmacokinetic (PK)) effects or class-specific? ⇒ model related effects:
  - Drug concentration vs. time profiles (PK)
  - PTH release and kinetics associated with drug PK (exposure-response)
  - Include Ca^{2+} homeostatic effects in serum, kidney, gut, and bone using MSPM
  - Include osteoclast and osteoblast activity (BTMs) and BMD effects using MSPM

METHODS –PUBLIC DATA SOURCES

Pharmacokinetic (PK) and PTH data were used for this further MSPM model development:

- **Ronacaleret:** Fitzpatrick et al. ASMBR 2008, JCEM 2011[9]
- **JTT-305:** Fukumoto et al. ASBMR 2009,[11] ECTS/IBMS 2011[10]
- **PTH1-34:** NDA 21-318 Briefing Doc V1[17]
- **PTH1-84:** EPAR - Scientific Discussion 2007[18]

METHODS – DS-9194b CLINICAL DATA

- PK, PTH and urine Ca^{2+} data were prospectively collected from a single ascending dose, first-in-human study including DS-9194b administration [0–100 mg]
- Twenty-one healthy male subjects aged 18–45 randomized to receive single DS-9194b doses of 5 (N=3), 15 (N=6), 50 (N=5), and 100 mg (N=3) or placebo (N=5) under fasting conditions
- DS-9194b PK & PTH sampled predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, and 16 hours postdose
- Urine collections 2 hour window immediately before first dose and 0–8, 8–12, and 12–24 hours postdose

METHODS – MODELING

- Nonlinear mixed effects models for repeated serum PTH and urine Ca^{2+} measures, were fit using `nlme`, `mrgSim`, and `deSolve` packages in R
- BMD-PTHmax relationship was modeled using `nls` function in R
- Serum PTH and urine Ca^{2+} obversations were modeled simultaneously
- Urine Ca^{2+} modeled as cumulative amount of Ca^{2+} in urine as function of time

METHODS – MODEL EXPANSION OF PT GLAND POOL

An existing physiologically-based, MSPM mathematical model (fig 4) [1] was expanded to include a capacity-limited PTH release pool (fig 3).[14, 15, 16]

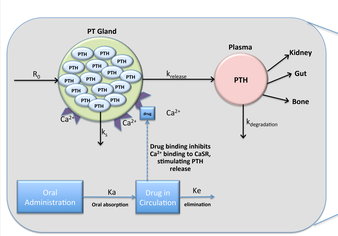

Figure 3: *Model of PTH pool within PT gland: PTH release stimulated by CaSR antagonist drug concentration.*

Equations related to PTH release

$$\frac{d}{dt}PREPTH = R_0 - k_t \cdot PREPTH - k_{release} \cdot PREPTH \cdot INH$$

$$\frac{d}{dt}PTH = k_{release} \cdot PREPTH \cdot INH - PTH \cdot k_{deg}$$

$$INH = 1 - (I_{CA} \cdot (1 - I_{DRUG}))$$

$$I_{CA} = \frac{CA^{\gamma_1}}{EC_{50,CA}^{\gamma_1} + CA^{\gamma_1}} \qquad I_{DRUG} = \frac{DRUG^{\gamma_2}}{EC_{50,DRUG}^{\gamma_2} + DRUG^{\gamma_2}}$$

$$R_0 = PREPTH_{ss} \cdot k_s + PTH_{ss} \cdot k_{deg}$$

Equations related to renal Ca2+ handling

$$REABS_{active} = \frac{Reabs_{max} \cdot CA}{Reabs_{50} + CA} \cdot PTH_{effect} \cdot RCA$$

$$\frac{d}{dt}RCA_1 = ktr \cdot \left[1 + \frac{SMAX \cdot DRUG}{EC_{50,rca} + DRUG}\right] - ktr \cdot RCA_1 \qquad ktr = \frac{n+1}{MTT} \qquad n = 8$$

$$\frac{d}{dt}RCA_m = ktr \cdot [RCA_{(m-1)} - RCA_m] \qquad m = 2, 3, 4, 5, 6, 7, 8$$

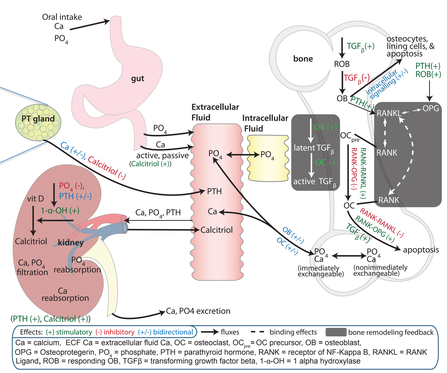

Figure 4: *Schematic of physiologically-based, multiscale systems pharmacology model; modified from figure 1 of Peterson and Riggs, 2010.* [1]

RCA1,ss = RCA2,ss = ... = RCAn,ss = 1

with : $kin = ktr \cdot \left[1 + \frac{SMAX \cdot DRUG}{EC_{50,rca} + DRUG}\right]$

Figure 5: *System of transit compartments allowing for delay in development of DS-9194b effect on renal Ca^{2+} reabsorption. In the final model, n=8.*

RESULTS – MSPM PREDICTION OF PTH RESPONSE

Quantitative, physiologically-based explanation of observed PTH response to CaSR antagonism:

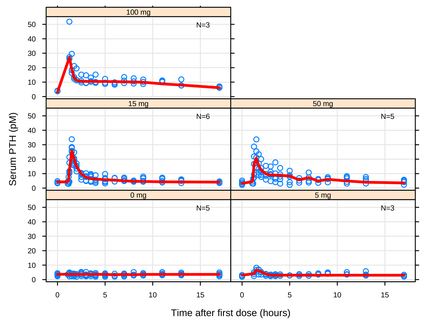

Figure 6: *Observed (circles) and median MSPM-predicted (red line) serum PTH after single oral DS-9194b dose. Parameter estimates [estimate (95% confidence interval)]: Baseline PTH: 34.7 pg/ml (31.2–38.5), k_{deg}: 6.60/hr (5.12–8.52), $k_{release}$: 6.87/hr (6.21–7.61), k_t: 0.922/hr (0.814–1.04), $EC_{50,DRUG}$: 0.5131 mg/L (0.400–0.658), γ_2: 1.98 (1.76–2.23). Subject-level variability [as standard deviation]: $\omega_{BaselinePTH}$: 0.224 (0.164–0.307), ω_{kdeg}: 0.368 (0.235–0.577), $\omega_{EC50,DRUG}$: 0.418 (0.289–0.603). Residual error, PTH [standard deviation σ_{PTH}]: 11.1 pg/ml (10.4–11.9).*

RESULTS – PTH EFFECT ON CALCIUM IN URINE (UCA)

MSPM also provides explanation of observed reduction in Ca^{2+} excretion due to hypothesized direct CaSR action in the kidney:

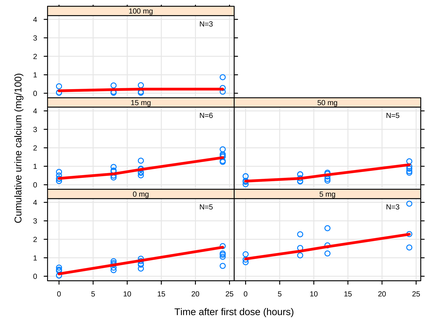

Figure 7: *Observed (circles) and median MSPM-predicted (red line) serum PTH after single oral DS-9194b dose. Parameter estimates [estimate (95% confidence interval)]: MTT: 21.9 hour (10.7–45.0), $EC_{50,rca}$: 0.501 mg/L (0.116–2.17), SMAX: 0.1 (fixed). Residual error, urine Ca^{2+} [standard deviation normalized to residual error for PTH $\sigma_{UCA}/\sigma_{PTH}$]: 2.03 (1.67–2.46).*

RESULTS – PTH vs. BMD: Maximal PTH predicted 3-, 6- and 12-month lumbar spine BMD

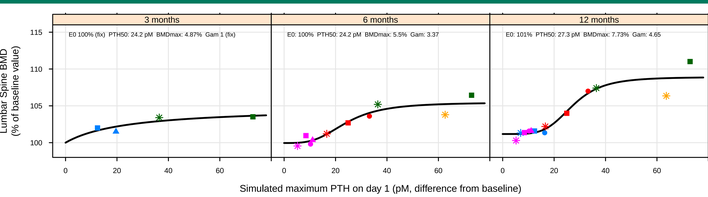

Figure 8: *Observed (symbols) and predicted (line) lumbar spine BMD relative to maximum PTH response (PTHmax). PTHmax was simulated for each agent based on pharmacokinetic (PK) and PK-PTH relationships. Notably, the BMD-PTHmax relationship held whether transient PTH elevation was affected through exogenously administered PTH (teriparatide or PTH1-84) or by CaSR antagonism. E0: placebo-corrected lumbar spine BMD when maximum day 1 PTH is zero; PTH50: maximum PTH concentration corresponding to 50% of maximum BMD increase; BMDmax: maximum placebo-corrected lumbar spine BMD increase; Gam: sigmoidicity factor for Emax equation.*

IMPLICATIONS

- MSPM can describe and explain: (1) PTH max "ceiling effect" (fig 6), (2) PTH "shoulder effect" (fig 6), and (3) urinary Ca excretion effects (fig 7)
- PTHmax predicted LS BMD changes (fig 8)
- MSPM with drug kinetics and dynamic effect on PTH can predict expected BMD response due to calcilytic antag candidates
- A maximal 12-month ~ 4 – 5% BMD increase was predicted for DS-9194b based on the prior modeling
- Only the single-dose clinical data was required to support this prediction and suggests potential for DS-9194b as a future osteoporosis treatment option

CONCLUSIONS

- Modeling indicated that BMD elevation with calcilytic administration routines evaluated is possible but magnitude of BMD elevation unlikely to match that seen with exogenous PTH
- The MSPM provided a physiologic explanation of maximal PTH response due to capacity-limited PT gland pool of PTH
- Results can guide future considerations for calcilytic-related therapies for osteoporosis or other PTH-related disorders

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