First in Man Studies of Pharmacokinetic Profiles of a Novel Oral Parathyroid Hormone PTH (1-34) delivery system

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Introduction

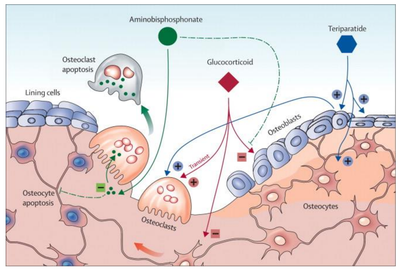
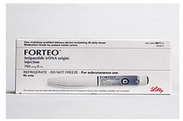
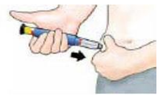


Figure 1: Effects of teriparatide, glucocorticoids and bisphospohates on bone cells[1]

- PTH(1-34) (Teriparatide) is an anabolic agent used in treatment of osteoporosis. It promotes bone formation and reduces the risk of vertebral and some non-vertebral fractures.
- The route of administration by daily subcutaneous (sc) injection can cause problems in certain patients. A new oral delivery system for human PTH(1-34) has been developed as a possible treatment option.
- Galitzer *et al.* first presented pre-clinical data (ASBMR 2012, MO0402) and first-in-human results (ASBMR 2013, FR0378) on safety, tolerability and absorption dynamics of oral PTH(1-34) in various dosages.





Aims and Objectives

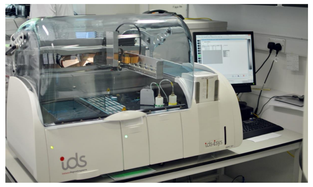
- A single-center, double blinded, triple crossover study was designed to compare the 1.8 mg optimal dose of oral PTH(1-34) against standard dosage of teriparatide injection and oral placebo.

Methods

- The study was conducted following and in accordance with the Hadassah Medical Center ethical approval committee.
- 12 healthy volunteers (6m/6f), 18-50y, received three treatments: single subcutaneous injection of 20µg FORTEO®, 1.8 mg oral PTH(1-34), or placebo.
- Blood samples were collected at time 0, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180, 240, 300 minute post dose.
- Plasma concentration of PTH(1-34) (IDS, Tyne and Wear, UK) and cyclic adenosine 3',5'monophosphate (cAMP) were measured on all samples.

Sample analysis

IDS iSYS automated immunoassay



PTH(1-34)

- Linear 4-1000 pg/mL
- Interassay imprecision: mean 11.7 pg/mL SD ±0.82, CV 5.4%, 46.7 pg/mL SD ±2.52, CV= 5.4%.
- Interassay imprecision: mean 18.5 pg/mL SD ±0.78, CV 4.2%, 46.7 pg/mL, SD ±3.2, CV= 7.0%.

Ab Sciex API 4000 LC-MS/MS system

Cyclic Adenosine 3' 5' Monophosphoric acid (cAMP)

- Negative Ion mode
- 13C5-cAMP as internal standard.
- cAMP m/z transition 328 > 134

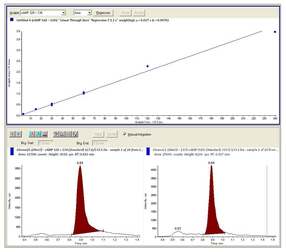


Figure 2: Typical calibration curve and chromatogram showing of plasma cAMP.

Results

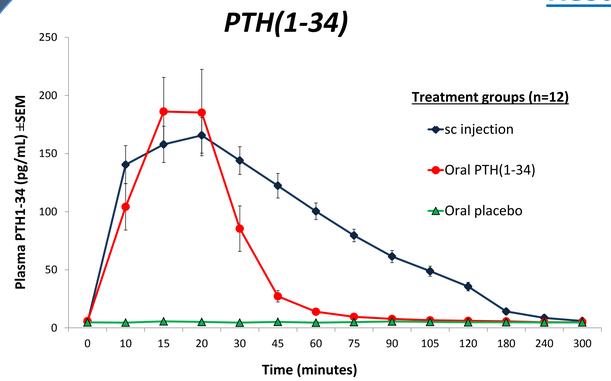


Figure 3: Pharmacokinetic profile showing changes in plasma PTH(1-34) levels in response to treatments.
One-way ANOVA analysis showed no significant difference in Cmax value achieved between oral PTH(1-34) and sc treatment. Plasma PTH (1-34) concentration declined more rapidly after oral treatment. Significant difference ($p<0.05$) in plasma PTH(1-34) was observed 20 minutes post treatment.

- All 12 subjects completed the study, no serious adverse events (SAE) were reported. Frequency of AEs were moderate.
- Serum adjusted calcium in all subjects remained within normal limits throughout the studies.
- All 12 subjects on oral PTH(1-34) showed rapid, post dose increase then decrease of PTH(1-34), from baseline mean (±SD) of 5.9 (1.8) pg/mL to peak mean of 185.3 (±128.8) pg/mL.
- PK profiles of oral PTH(1-34) showed Cmax (pg/mL), Tmax (mins), $AUC_{0\text{-last}}$ of 238.3 (110.8), 17.5 (5.4) and 6161.7 (2726.7), respectively; whereas sc group showed mean Cmax (pg/mL), Tmax (mins), $AUC_{0\text{-last}}$ of 172.3 (55.7), 20.8 (8.7) and 13965.9 (2984.8), respectively.

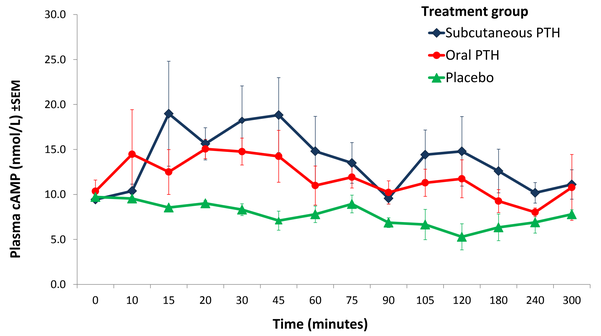


Figure 4: Pharmacokinetic profile showing changes in plasma cyclic AMP levels in response to treatments.

- A transient increase in plasma cAMP were seen in all subjects in response to PTH(1-34) treatments. Although the increase is less apparent in oral than sc both showed a similar PK profile and a significant difference in plasma concentration ($p<0.05$) compared to placebo group 20 minutes post treatment.
- Increase in cAMP is indicative of PTH bio-activity, suggesting that the administered peptide is pharmacologically active and not degraded during GI transport.

Conclusions

- PK profiles showed that a single oral dose of 1.8 mg PTH(1-34) is rapidly absorbed, and there is no significant difference in Cmax and Tmax when compared with 20µg of Forteo injection.
- A significant difference in the rate of plasma clearance and $AUC_{0\text{-last}}$ value was observed between oral and sc groups. These differing profiles and modality of administration of PTH(1-34) could offer unique advantages in the treatment of calcium and metabolic bone disorders.

References:
[1] Gennari *L et al*. *The Lancet* - 11 April 2009 (Vol. 373, Issue 9671, Pages 1225-1226) Glucocorticoid-induced osteoporosis: hope on the horizon
[2] *Ziller V et al.* Adherence and persistence in patients with severe osteoporosis treated with teriparatide. Curr Med Res Opin 2010;26(3):675–81.
[3] *Hämmerle SP et al.* The single dose pharmacokinetic profile of a novel oral human parathyroid hormone formulation in healthy postmenopausal women. Bone. 2011:50,(4): 965-973