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Pharmacokinetics of Novel Oral PTH 1-34 Dosage Form (Tablet) in Rodents

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Introduction

Current therapies for osteoporosis are based on antiresorptive agents, such as bisphosphonates, estrogen, selective estrogen receptor modulators (SERMs), calcitonins and a monoclonal antibody against receptor activator of Nf kappa B ligand (RANKL).[1]

The only currently available anabolic treatment option for osteoporosis is parathyroid hormone (PTH), which has consistently demonstrated a significant increase in bone formation leading to increased bone mass and substantial reduction in vertebral and non-vertebral fracture risk. PTH is only available as a daily parenteral dosage form. Compliance and adherence with a daily injectable regimen is often wanting due to the discomfort and local irritation associated with such a course of therapy. An oral form of PTH would very likely improve patient acceptance, and long-term compliance and adherence.[2]

A new oral formulation of human PTH1-34 is being developed as a more convenient option for the treatment of osteoporosis.

We report herein the first pharmacokinetic results of PTH1-34 in a rodent model

Technology

The technology is a novel drug delivery technology that enables the absorption of intact bioactive polypeptides and proteins through the gastrointestinal tract (GIT). It is based on known pharmacopeial agents recognized as GRAS with no new chemical entities (NCEs).

Objectives

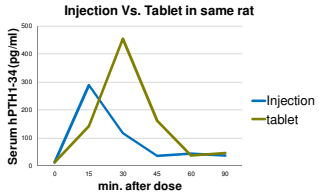
The primary objective was to investigate the absorption characteristics of a single oral dose of PTH1-34 in a rodent model and compare it with the pharmacokinetics(PK) of the human PTH1-34 drug that is in clinical use and administered by s.c. injection.

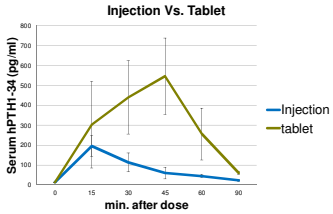
Methods

Experiments were conducted in S.D. rats with an average weight of 250 gr. Animals were administered either a s.c. injection of the commercially available human PTH1-34 (2.5µg per rat) or a synthetic human PTH1-34 mini tablet (200 µg per rat) administered orally. Blood samples were withdrawn at regular intervals for PK analysis using the immutopics High Sensitivity Human PTH1-34 ELISA Kit.

Results

Following an injection of Human PTH1-34 a typical absorption profile was achieved, consisting of a sharp increase in serum PTH levels followed by a somewhat slower decrease back to base line levels. When the same rat was dosed with an oral formulation of human PTH1-34 using EnteraBio's novel drug delivery technology a similar profile was obtained with a slight delay.

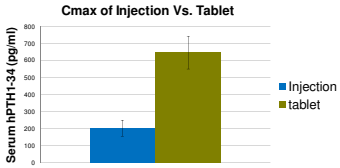




The study was repeated in a group of rats. However due to Tmax variability the average results do not present the desirable sharp increase and subsequent decrease in PTH levels. Additionally, the variability in Tmax also led to inconsistent bioavailability.

Results (continued)

Analysis of the group PK with regard to the individual Cmax results, which were obtained at varying time points (30 - 45 min. post dose) reveal significantly less variance between individual rats, SE= 95 vs. SE of 130-215 for the four time points between 15 and 60 post dosing.



Conclusions

PTH1-34 administered orally in rodents demonstrates consistent enteral absorption with a PK profile characterized by a rapid Tmax and rapid elimination to optimally simulate the desired PTH profile required for its anabolic effect.[3,4]

Our first non- optimized formulation of oral PTH1-34 shows that with 200 µg per rat we can achieve exposure levels exceeding those of injectable PTH1-34 at 2.5 µg per rat, albeit with some variability in overall bioavailability.

Oral drug absorption in general, has inherent greater variability in absorption as compared to parenteral administration. The main causes of such variability is the different feeding patterns, food effect , stomach emptying and transit time in the GIT. An optimal formulation and the mitigation of food effect on absorption variability could likely result in a potential therapeutically relevant oral PTH1-34 dosage form.

References

1. *Reid IR.* Anti-resorptive therapies for osteoporosis. Semin Cell Dev Biol 2008;19(5):473–8 Epub 2008 Aug after first paragraph of currently available therapies

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. - insert at the importance of benefit of adherence to PTH in treatment of OP.

3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021318s015lbl.pdf. reference to the optimal kinetics of oral PTH (Forteo)

4. *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 Opyimal kentics by Novartis

