Novel Oral PTH (1-34) formulation with reduced pharmacokinetic variability

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BACKGROUND

The oral absorption of polypeptides is characterized by high dose-to-dose variability due to their low bioavailability. As a result, maintaining the blood drug levels within the therapeutic window is very challenging.

An orally administered PTH may have prodigious advantages in the treatment of bone related disorders due to improved patient compliance and adherence. However, in order for PTH, a drug whose specific PK profile is critical for its physiological activity, to be effective and safe, a consistent and reproducible absorption profile is essential.

Enterabio previously developed and presented an oral formulation of PTH(1-34) that achieved biologically relevant plasma concentrations of the drug similar to those of the commercial SC injection. In anticipation of entering more advanced clinical studies, further development of oral PTH(1-34) formulation was performed focusing on the control of the drug absorption while minimizing its variability. The main source of high variability was revealed through numerous *in vitro* and preclinical studies resulting in the development of a novel and improved oral PTH (1-34) formulation.

We now present results from a clinical study utilizing the novel formulation technology in our oral PTH (1-34) tablets with decreased inter-subject variability and an absorption profile close to that of the commercially available injectable PTH (1-34).

STUDY DESIGN

A Phase I, open label, crossover pharmacokinetic study was conducted at the Hadassah Clinical Research Center at the Hebrew University – Hadassah Medical Center.

Ten healthy male volunteers were included in the study receiving a commercial PTH (1-34) SC formulation and Enterabio's original and modified oral PTH (1-34) formulations. Blood samples were analyzed externally at the Bioanalytical Facility at the University of East Anglia by validated chemiluminescence based assay on the IDS-ISYS automated analyzer.

RESULTS

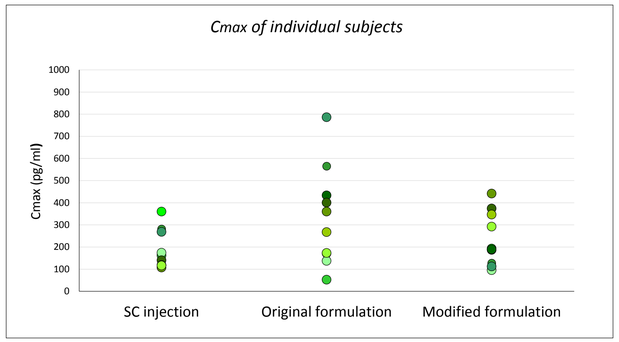

Figure 1. *Scatter plot of PTH (1-34) showing individual maximal plasma concentrations (Cmax) following SC injection, oral administration of original and modified formulations in a group of ten volunteers.*

The pharmacokinetic profile of oral PTH (1-34) is characterized by rapid absorption and elimination rates of the drug. The maximal plasma concentration (C_{max}) of the modified oral formulation was slightly greater than the Cmax of the injectable formulation (236 ± 114 vs 184 ± 83 pg/ml, mean ± SD) (Table 1).

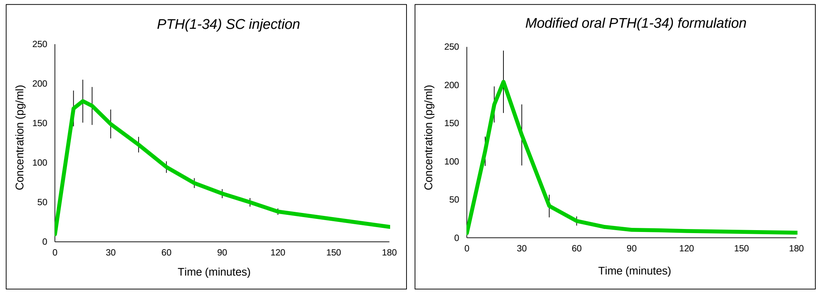

Figure 2. *Pharmacokinetic profiles of PTH (1-34) plasma concentrations following subcutaneous injection and the modified oral PTH (1-34) formulation in a group of ten healthy volunteers. Data is presented as the mean ± SE.*

The minimal C_{max} among the same group of volunteers was 95 pg/ml for the oral formulation and 107 pg/ml for the SC injection (Figure 1). Intersubject absorption variability of the modified oral PTH (1-34) delivery system was comparable with the variability in absorption of the injectable drug (CV% 48 vs 45% respectively).

RESULTS

PTH (1-34) formulation	n	Cmax (pg/ml)	Tmax (min)	Cmax CV (%)
SC injection	10	184.2 ± 26.3	16.0 ± 1.8	45.2
Modified oral formulation	10	235.6 ± 36.1	16.5 ± 1.2	48.4

Table 1. *Summary of the main pharmacokinetic parameters found. C_{max} – the maximal PTH (1-34) plasma concentration. T_{max} - average time to reach maximal plasma concentration; C_{max} CV% - coefficient of variation among the C_{max} levels of different volunteers. Data presented as a mean ± SE.*

SAFETY

The safety profile of Enterabio's modified formulation was consistent with previous studies. The study drug was very safe and well tolerated with no drug related adverse events reported.

CONCLUSIONS

Modification of the original Enterabio oral delivery system of PTH (1-34) resulted in significantly reduced variability in both the Cmax values and the total drug exposure, AUC. Presented results focused on C_{max} which is the most relevant factor for determining biological activation of anabolic pathways and calcium regulation. In the specific case of Enterabio's oral PTH (1-34) delivery system, this essential 'sharp and short' exposure to the drug is achieved due to the fast absorption of the molecule and its rapid elimination from the body.

Reduced inter-subject C_{max} variability achieved by the modified dosage form, which is close to the levels of variability achieved by subcutaneous injection and comparable to the variability of commercially available small molecule drugs, ensures an improved safety profile of oral PTH (1-34) on the one hand and biologically effective blood concentrations of the drug on the other hand. These together with the expected improvement in compliance significantly enhance the potential of Enterabio's oral PTH (1-34) becoming a clinical success.

