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Pharmacokinetics of an Oral Human Growth Hormone (hGH) Formulation in Rats and Mice

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BACKGROUND

Many drugs being developed today are biologics; peptides, proteins and other large molecules, which are currently administered by injection or intravenously. Oral delivery of biologics is challenging, as it leads to negligible systemic exposure due to enzymatic degradation within the gastrointestinal tract and poor permeability though the intestinal wall. Entera Bio's technology is designed to address both of these issues by enhancing the transcellular permeability of the molecule and by preventing its degradation by enzymes within the gastrointestinal tract. Entera Bio's novel formulation for the oral delivery of human parathyroid hormone [hPTH(1-34)] for the treatment of Hypoparathyroidism and Osteoporosis is in Phase 2 clinical studies and oral formulations of other molecules are being developed for treatment of various indications. Human growth hormone (hGH) is a widely used therapeutic molecule, currently only administered via subcutaneous injection for the treatment of Growth Hormone Deficiency as well as other indications. This study therefore tests the feasibility of Entera Bio's technology to orally deliver hGH in mice and rats. Moreover, hGH serves as a model molecule for numerous therapeutic drugs of similar molecular weight (~22 kDa), currently only administered as injections. An oral formulation devoid of injection-related complexities can have numerous advantages, including greater patient compliance, reduced pain, longer shelf life, no toxicity at injection site, and lower immunogenicity.

STUDY METHODS AND DESIGN

Mice Study Recombinant hGH, purchased from PeproTech LTD., was formulated utilizing Entera Bio's oral delivery platform. 10 mg/kg of the oral hGH formulation was administered to fasting Balb/C male mice (n=34). Blood samples from 4 animals were withdrawn at each of the study time points (a single blood sample was taken from each animal). Samples were analyzed by Bio-Gems ELISA immunoassay according to the manufacturer's instructions. Rat Study Commercially available hGH (Genotropin®), purchased from Pfizer LTD., was reformulated utilizing Entera Bio's oral delivery platform. Injectable formulation of hGH (Genotropin®) dissolved in water was used as a control. Both hGH formulations were administered by oral gavage to fasted female Wistar rats at 10 mg/kg (n=8, formulated; n=3, control). Blood samples from 4-8 rats were taken at each time point for the formulated hGH group and from 3 rats at each time point for the control group. Samples were analyzed with the Bio-Gems ELISA immunoassay according to the manufacturer's instructions.

RESULTS: MICE STUDY

Clinical observations No abnormal clinical signs were noted, and no animals were found in moribund condition during this study. Pharmacokinetic Results Substantial gastrointestinal absorption of the oral hGH formulation was observed, providing significant systemic exposure to the drug. Analysis of the variability in plasma concentration at each of the time points indicated consistent absorption between animals during the first 30 minutes following the drug administration. At later time points, significantly higher variability in absorption was observed. The biphasic absorption profile is most likely an artifact of the study design according to which a single timepoint was taken from each animal. It can be assumed that the animals with high levels of hGH at 60 and 90 minutes post-dose also had significantly higher blood levels of hGH at earlier timepoints.

RESULTS: RAT STUDY

Clinical observations No abnormal clinical signs were noted, and no animal was found in moribund condition during this study. Pharmacokinetic Results While no hGH was detected in the plasma when animals received the unformulated drug, substantial levels of hGH were detected in the plasma when animals were administered the oral formulation of hGH. Formulated hGH reached a maximal plasma concentration level (235 ng/ml) approximately 30 min post administration (Tmax) and returned to baseline within 2 hours post administration.

CONCLUSIONS

Entera Bio's oral drug delivery platform allowed for the gastrointestinal absorption of hGH in mice and rats. Plasma concentration levels observed in rats were notably higher than those reported for commercial SC hGH injections in humans. Therefore, this preliminary screening study indicates the feasibility of Entera Bio's technology to orally deliver hGH and other drugs of similar molecular size. In order to better analyze the specific absorption profile of hGH, and in order to further evaluate the feasibility of Entera Bio's technology to orally deliver molecules of similar size for therapeutic use, additional preclinical studies in larger animals should be performed