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Pharmacokinetics and safety of recombinant human parathyroid hormone (1-34) (teriparatide) after single ascending doses in Chinese healthy volunteers

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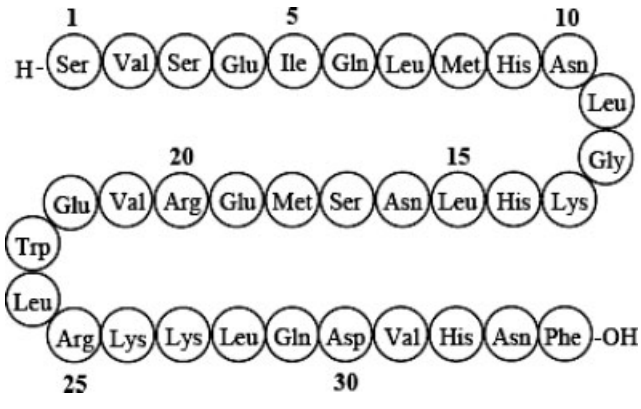
The pharmacokinetics and safety of recombinant human parathyroid hormone (1-34) [rhPTH (1-34)] after single ascending doses were evaluated in Chinese healthy volunteers. Nine healthy volunteers (five male and four female) were recruited for an open label, randomized, three multiply three crossover, single ascending dose (10, 20, and 40 μg) study. Using a validated radioimmunoassay, we determined the plasma concentrations of rhPTH (1-34). The mean peak plasma concentration (C_{max}) were 123.6, 195.6, and 318.2 pg · mL^{-1} respectively, and were reached from 25.6 to 36.1 min after subcutaneous administration. After C_{max} was reached, the plasma drug level decreased quickly, with elimination half-life ($t_{1/2}$) of 53.9 to 64.1 min. The mean $AUC_{0-\infty}$ (the area under the plasma concentration versus time curve from time zero to infinite) of rhPTH (1-34) were 11794.2 ± 974.8, 21606.7 ± 4753.9, 33877.0 ± 8374.4 pg · min · mL^{-1}, respectively. The mean AUC_{0-t} (the area under the plasma concentration versus time curve from time zero to the last quantifiable concentration) of rhPTH (1-34) were 9034.4 ± 1073.9, 17883.3 ± 4597.1, 31693.5 ± 6574.8 pg · min · mL^{-1}, respectively. Dose-related linear trend were observed for AUC_{0-t} and C_{max} of rhPTH (1-34). $t_{1/2}$ and T_{max} (time to C_{max}) of rhPTH (1-34) were independent of administered dose. rhPTH (1-34) was safe and well tolerated by all volunteers.

1. Introduction

Recombinant human parathyroid hormone (1-34) [rhPTH (1-34)] is a synthetic polypeptide obtained by the the recombinant DNA technique and containing the amino acids 1-34 from the amino-terminal region of human parathyroid hormone (PTH). The first 34 amino acids of the complete 84-amino acid molecule of the endogenous PTH (PTH 1-84) are responsible for its biological action. Therefore, rhPTH (1-34) is identical with the biologically active fraction of PTH (1-84) and, when administered intermittently, stimulates the formation of bone tissue, improves bone microarchitecture which, in turn, will increase bone strength and lead to a reduction of fracture risk (Oliveira et al. 2003). Teriparatide, also referred to as rhPTH (1-34), was first approved in the United States in November 2002 for the treatment of osteoporosis in men and women. Teriparatide became available in other countries, such as the United Kingdom and several other countries in the European Union, in April 2003 (Quattrocchi and Kourlas 2004). rhPTH (1-34) has a molecular weight of 4117.8 daltons.

The bioavailability of rhPTH (1-34) is approximately 95% after subcutaneous administration (sc). The rates of absorption and elimination are rapid. rhPTH (1-34) reaches peak serum concentrations about 30 min after subcutaneous injection of a 20 μg dose and declines to non-quantifiable concentrations within 3 h (EliLilly and Co 2002). The systemic clearance of rhPTH (1-34) (~62 L/h in women and ~94 L/h in men) exceeds the rate of normal hepatic plasma flow, consistent with both hepatic and extrahepatic clearance (Quattrocchi and Kourlas 2004; EliLilly and Co 2002). The aim of the study was to evaluate the single-dose pharmacokinetics and safety of rhPTH (1-34) following subcutaneous administration of single ascending doses of rhPTH (1-34) (10 to 40 μg) in healthy Chinese volunteers.



rhPTH (1-34) (teriparatide)

Table: Pharmacokinetic parameters of rhPTH (1-34) after subcutaneous administration of a single dose of rhPTH (1-34) to 9 healthy volunteers (mean ± SD)

Parameters	10 μg	20 μg	40 μg
AUC_{0-t}/pg · min · mL^{-1}	9034.4 ± 1073.9	17883.3 ± 4597.1	31693.5 ± 6574.8
$AUC_{0-\infty}$/pg · min · mL^{-1}	11794.2 ± 974.8	21606.7 ± 4753.9	33877.0 ± 8374.4
c_{max}/pg · mL^{-1}	123.6 ± 12.0	195.6 ± 49.3	318.2 ± 99.9
T_{max}/min	25.6 ± 5.3	36.1 ± 13.4	35.6 ± 12.1
$t_{1/2}$/min	53.9 ± 6.7	64.1 ± 36.3	57.1 ± 19.0
MRT/min	55.7 ± 2.0	74.4 ± 12.2	79.0 ± 14.3
CL/F/mL · min^{-1}	853.0 ± 69.6	967.7 ± 222.3	1271.1 ± 436.4
V/F/L	66.5 ± 11.1	86.4 ± 42.6	101.3 ± 39.3
K_e/min^{-1}	0.013 ± 0.002	0.013 ± 0.0041	0.014 ± 0.0054

2. Investigations and results

2.1. Pharmacokinetic results

The mean concentrations of rhPTH (1-34) from the plasma-versus-time profiles obtained after subcutaneous administration of a single dose of rhPTH (1-34) (10, 20 and 40 μg) to fasted Chinese volunteers are shown in Fig. 1. The results of the noncompartmental pharmacokinetics analysis derived from the concentrations in plasma are summarized in the Table. The absorption of rhPTH (1-34) from the subcutaneous injection site to blood was rapid, and peak plasma concentration (C_{max}) values of 123.6, 195.6, and 318.2 pg · mL^{-1} appeared 25.6 to 36.1 min after subcutaneous administration. After C_{max} was reached, the plasma drug level decreased quickly, with elimination half-life ($t_{1/2}$) of 53.9 to 64.1 min. The mean $AUC_{0-\infty}$ (the area under the plasma concentration versus time curve from time zero to infinite) of rhPTH (1-34) were 11794.2 ± 974.8, 21606.7 ± 4753.9, 33877.0 ± 8374.4 pg · min · mL^{-1}, respectively. The mean AUC_{0-t} (the area under the plasma concentration versus time curve from time zero to the last quantifiable concentration) of rhPTH (1-34) were 9034.4 ± 1073.9, 17883.3 ± 4597.1, 31693.5 ± 6574.8 pg · min · mL^{-1}, respectively. The increase in exposure with increasing dose was less than would be expected under conditions of strict proportionality. The apparent total body clearance (CL/F) of rhPTH (1-34) were 853.0 ± 69.6, 967.7 ± 222.3, 1271.1 ± 436.4 mL · min^{-1}, respectively. The apparent volume of distribution of the central compartment (V/F) were 66.5 ± 11.1, 86.4 ± 42.6, 101.3 ± 39.3 L, respectively.

The results of dose proportionality analysis were as follows: dose proportionality coefficients were between 0.889 and 0.643 for AUC_{0-t} and C_{max}. 95% confidence interval

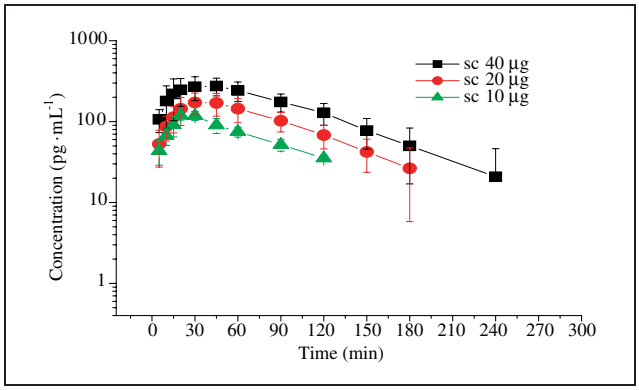


Fig. 1: Mean concentration in plasma-time profiles for rhPTH (1-34) in healthy Chinese volunteers following subcutaneous administration of single ascending doses of rhPTH (1-34) ranging from 10 μg to 40 μg. Error bars indicate SDs (n = 9)

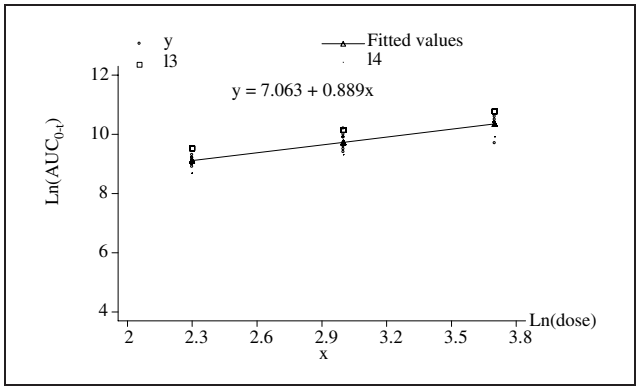


Fig. 2: Log transformed AUC_{0-t} of rhPTH (1-34) by log transformed dose (10, 20, and 40 μg)

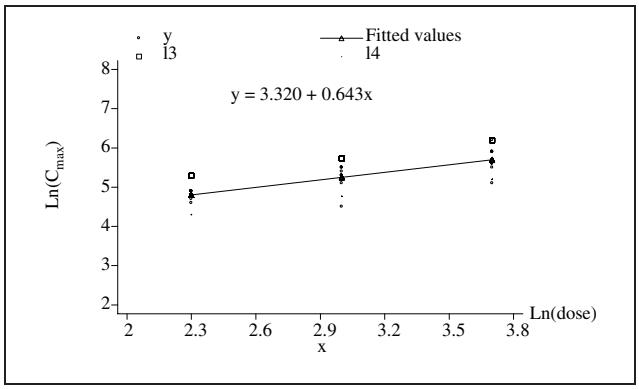


Fig. 3: Log transformed C_{max} of rhPTH (1-34) by log transformed dose (10, 20, and 40 μg)

(CI) for for AUC_{0-t} and C_{max} were 0.738 ~ 1.040, 0.466 ~ 0.820, respectively. Although there was a linear trend with dose, proportionality was not established in this study. Results of the dose proportional analysis are plotted for AUC_{0-t} in Fig. 2 and C_{max} in Fig. 3. There were no significant differences between 10, 20, and 40 μg dose with regard to $t_{1/2}$ (P was 0.670, > 0.05) and T_{max} (P was 0.135, > 0.05). That is to say, $t_{1/2}$ and T_{max} of rhPTH (1-34) were independent of the administered dose.

2.2. Safety results

rhPTH (1-34) was safe and well tolerated by all volunteers. During the course of the study, no adverse event was reported. No drop-out or death occurred. There were no clinically significant changes in hematological, biochemistry and urinalysis parameters. 12-lead electrocardiograms (ECGs)

were recorded at screening and post study assessment, and no clinically relevant morphological ECGs changes were seen.

3. Discussion

In the present study, the main pharmacokinetics parameters (C_{max}, $t_{1/2}$, T_{max}) are consistent with those of previous studies of rhPTH (1-34) (Quattrocchi and Kourlas 2004; EliLilly and Co 2002). The rates of absorption and elimination of rhPTH (1-34) in Chinese healthy volunteers are rapid. After subcutaneous injection of a single dose (10, 20 or 40 μg), the rhPTH (1-34) reaches peak concentrations within about 30 min which declined to non-quantifiable concentrations within 3 h. In this study, the half-time ($t_{1/2}$) of rhPTH (1-34) after subcutaneous injection was approximately 60 min. However in another published study, when administered by intravenous injection, $t_{1/2}$ of rhPTH (1-34) in serum was only 5 min. The longer $t_{1/2}$ after subcutaneous administration possibly reflects the time required from the injection site.

In the present study, rhPTH (1-34) was safe and well tolerated when it was administered in single ascending doses from 10 to 40 μg in Chinese healthy volunteers. In some foreign clinical trials, advent events associated with rhPTH (1-34) were reported such as headache, nausea, diarrhea, leg cramps, dizziness et al (Body et al. 2002; Neer et al. 2001). The advent events were mild and generally did not lead to discontinuation of therapy. But in an ongoing carcinogenicity study of rhPTH (1-34) in rats, osteosarcoma was found at all dose levels and in the lower dose ranges was first detected after approximately 20 months of therapy (Vahle et al. 2002). To date, these is no osteosarcoma to be found in humans, but the rarity of the cancer in humans makes assessment of the relative risk impossible at present (Kurland et al. 2000; Orwoll et al. 2003). The safety and efficacy of rhPTH (1-34) have not been evaluated beyond 2 years of treatment. Consequently, use of the rhPTH (1-34) for more than 2 years is not recommended (Tashjian and Chabner 2002). These would suggest that further multiple-dose pharmacokinetic and clinical trials of rhPTH (1-34) in Chinese subjects should be initiated.

4. Experimental

4.1. Study medication

rhPTH (1-34) was prepared by Shanghai Celgen Pharmaceutical co. Ltd. and supplied as formulated 20 μg sterile powder which were packaged in small glass bottles. The medication was stored at 4 °C. Before subcutaneous administration, the medication was dissolved by 1 mL 0.9% normal saline.

4.2. Study subjects and design

Five healthy male volunteers, aged 21–23 years with a body mass index between 20.68 and 23.48 $kg \cdot m^{-2}$, and four healthy female volunteers, aged 20–22 years with a body mass index between 18.37 and 24.97 $kg \cdot m^{-2}$, gave informed consent to enter the study. Prior to the study, all volunteers underwent physical examination, safety laboratory including blood chemistry, hematology and urine routine, ECG and vital signs. Neither prior (within two weeks before the start of the study with the exception of paracetamol up to 48 h before the start of the study) nor concomitant medication was allowed. During the course of the study, no other medications were allowed, except for treatment of adverse events. The study was performed at Clinical Pharmacology Center (Zhongshan Hospital, Shanghai, China) and was approved by the local Medical Ethics Committee.

This study was an open label, randomized, three multiply three crossover, single ascending dose pharmacokinetics study. Target enrollment was 9 volunteers, randomized into three groups of 3 volunteers each. On the first treatment period, each group subjects were randomized to receive a single dose of rhPTH (1-34) 10, 20 or 40 μg, respectively. After the first wash-out period, on the second treatment period, each group subjects received a single dose of rhPTH (1-34) 20, 40 or 10 μg, respectively. Finally after the second wash-out period, on the third treatment period, each group subject received a single dose of rhPTH (1-34) 40 , 10 or 20 μg, respectively. The wash-out period between the three treatments was seven days. All test doses were administered for subcutaneous injection (2 cm far from the left side of navel) after an 10-h overnight fast. Volunteers were allowed to lie supine for 4 h after administration except during performance of study procedures. Food was prohibited until 4 h, and water was prohibited until 2 h, after administration of the test preparations. Standardized lunch was to be served earliest 4 h after dosing.

4.3. Sample collection and analytical methods

Blood samples of 3 mL were collected in vacutainers containing anticoagulant (15% EDTA) at pre-dose and at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180 and 240 min after subcutaneous injection of rhPTH (1–34). The blood samples were immediately centrifuged at 1500 × g for 10 min at 4 °C to separate the plasma. The separated plasma (2.0 mL) was transferred to a polypropylene tube and was added with 96 μL mixed protease inhibitor to stabilize the rhPTH (1-34). After this, the plasma samples were stored at the study center at −20 °C until shipment to the laboratory where the analyses of rhPTH (1-34) concentrations were performed.

The radioimmunoassay for determination of rhPTH (1-34) in human plasma was validated in terms of specificity, sensitivity, linearity, intra-batch and inter-batch precision and accuracy test. In the study, the lower limit of quantification of rhPTH (1-34) was 31.25 $pg \cdot mL^{-1}$.

4.4. Determination of the plasma pharmacokinetics

Non-compartimental pharmacokinetic (PK) analysis was used to analyze plasma drug concentration-time data. The elimination rate constant ($K_e \approx \lambda_z$) was determined by linear regression of the logarithm of the concentration in plasma with time over the terminal phase. The elimination half-time ($t_{1/2}$) was calculated as $0.693/K_e$. The maximum concentration in plasma (C_{max}) and the time required to reach C_{max} (T_{max}) were read from the observed values. Area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) was determined by summing up the areas from time (0) to the time of last quantifiable concentration by trapezoidal and log-trapezoidal methods (AUC_{0-t}) and the extrapolated area. The extrapolated area was determined by dividing the last detectable concentration by the slope of terminal log-linear phase. The mean residence time (MRT) was calculated as the ration of the first moment curve from time zero to infinity ($AUMC_{0-\infty}$) to the AUC from time zero to infinity ($AUC_{0-\infty}$). The apparent total body clearance (CL/F) was calculated by using the equation $CL/F = dose/AUC_{0-\infty}$. The volume of distribution (Vd/F) was determined by using the equation $Vd/F = CL/F/K_e$.

4.5. Statistical analysis

Pharmacokinetic parameters were summarized over the set of evaluable subjects by means and SD. Dose proportionality was assessed using a power model (log-transformed AUC_{0-t} amd C_{max}), and was regressed on log-transformed dose. The slope and its 95% confidence interval (CI) was calculated from the regression model. Effects of ascending dose on $t_{1/2}$ and T_{max} were determined by using analysis of variance (ANOVA) and non-parametric test, respectively.

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