Tolerability and Dose Proportional Pharmacokinetics of Pasireotide Administered as a Single Dose or Two Divided Doses in Healthy Male Volunteers: A Single-Center, Open-Label, Ascending-Dose Study

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ABSTRACT

Background: Pasireotide is a multireceptor-targeted somatostatin analogue with high binding affinity for somatostatin receptor subtypes SST 1, 2, 3, and 5.

Objective: To evaluate the safety profile, tolerability, and pharmacokinetic profile of pasireotide in single- and divided-dose regimens in healthy volunteers.

Methods: A single-center, open-label, ascending-dose study was performed in healthy volunteers. Pasireotide, 900, 1200, and 1500 μg SC, was administered as either a single dose or as two divided doses given 12 hours apart, with a 7-day washout period between treatments.

Results: Seventeen men (median age, 26 years) were enrolled. Their median weight was 81 kg, and 65% were white. One participant dropped out because of a grade 2 adverse event; most other adverse events were mild and affected the gastrointestinal tract. Blood glucose concentration increased after pasireotide administration, but returned to normal within 10 hours. After single-dose administration, pasireotide plasma concentration peaked rapidly at 15 minutes to 1 hour after dosing, followed by a tri-exponential (α, β, and γ phases) decline over time. Mean $t_{½}$ values during the α, β, and γ phases were approximately 2 to 3, 12 to 17, and 54 to 97 hours, respectively. In the single-dose cohort, the mean (SD) AUC_{∞} was 110 (29), 149 (42), and 188 (52) h · ng/mL in the 900-, 1200-, and 1500-μg groups, respectively. Time to reach C_{max} was 0.69 (0.41), 0.59 (0.38), and 0.56 (0.18) hours in the 900-, 1200-, and 1500-μg groups, respectively. AUC_{∞} values were similar in the single-dose and divided-dose cohorts. Mean total body clearance was 8 to 9 L/h across the dosage groups and dosing regimens, indicating a linear pharmacokinetic profile between doses.

Conclusions: When administered as a single- or divided-dose regimen, pasireotide had a favorable tolerability profile in this selected group of healthy male volunteers. Its pharmacokinetic profile indicated rapid absorption, low clearance, high volume of distribution, and a long terminal half-life. (*Clin Ther*. 2012;34: 677–688)

Key words: pasireotide, SOM230, tolerability, pharmacokinetics, healthy volunteer.

INTRODUCTION

Pasireotide is a multireceptor-targeted somatostatin analogue with high-affinity binding for somatostatin receptor subtypes SST 1, 2, 3, and 5.[1] As an agent with greater binding affinity for SST 1, 3, and 5 than octreotide,[2] pasireotide is a potential medical therapy for pituitary adenomas (eg, Cushing disease[3] and acromegaly[4]) and tumors arising from the diffuse neuroendocrine system throughout the body.[5–7]

Previous studies in healthy volunteers have reported that pasireotide is well tolerated as a 7-day continuous SC infusion of up to 2025 μg/d.[8] It has also been reported that pasireotide SC has a lower clearance and longer half-life than does octreotide, and is rapidly absorbed with an approximately linear dose-exposure relationship.[9] Based on the estimated effective half-life of pasireotide SC (approximately 12 hours), a twice-daily

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dosing interval may be the optimal regimen in patient populations.

As part of the clinical trial program for pasireotide, the present Phase I study was designed to evaluate the safety profile, tolerability, and pharmacokinetic (PK) profile of pasireotide at higher doses (up to 1500 μg), administered as either a single dose or two divided doses in healthy volunteers. This is the first study to examine the effects of twice-daily administration of pasireotide SC.

PATIENTS AND METHODS

Subjects

Seventeen healthy male volunteers aged 18 to 40 years were enrolled. The protocol called for 16 volunteers to be enrolled (eight per cohort), with certain dropouts to be replaced with new recruits. One subject was replaced in this study. Subjects had normal blood pressure (systolic, 90–140 mm Hg; diastolic, 50–90 mm Hg), pulse rate (40–90 beats/min), body weight (≥50 kg and within −15% to +15% of normal for height and frame size[10]), and oral temperature (35.0°C–37.5°C). Inclusion criteria were alanine aminotransferase concentration within the normal range, γ-glutamyl transpeptidase and alkaline phosphatase concentrations not exceeding twice the upper limit of the normal range, and serum bilirubin concentration not exceeding 27 μmol/L. Before administration of the drug, participants were to abstain from donating blood for 8 weeks, strenuous physical exercise for 7 days, alcohol for 72 hours, and caffeine for 48 hours. Exclusion criteria were a history of gallbladder disease, major gastrointestinal tract surgery, pancreatic injury, or pancreatitis.

The study was performed at Universitätsklinikum Essen (Essen, Germany). The study protocol and informed consent forms were approved by the institutional review board (Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg–Essen). All subjects provided written informed consent before screening. The study was performed in accordance with the Declaration of Helsinki.[11]

Study Design

In this single-center, open-label, ascending-dose study, healthy volunteers received three increasing doses of pasireotide administered 7 days apart (days 1, 8, and 15). Pasireotide was given as either a single dose or as two divided doses administered 12 hours apart.

Subjects in the single-dose cohort received a single injection of pasireotide, 900, 1200, or 1500 μg, and those in the divided-dose cohort received two injections of pasireotide, 450, 600, or 750 μg, delivered 12 hours apart (ie, total daily doses of pasireotide were 900, 1200, and 1500 μg). Each dosage level was assessed for tolerability before the next higher dosage was administered.

All subjects received pasireotide between 8:00 and 9:00 AM after an overnight fast. They then fasted for another 4 to 5 hours, and were given a standardized midday meal between 12:00 noon and 1:00 PM, and an evening meal 4 to 5 hours later. In the divided-dose cohort, a second pasireotide injection was administered between 8:00 and 9:00 PM. Study medication was injected SC in the abdominal wall by study center personnel.

Assessments

The primary objective of the present study was to evaluate the tolerability of ascending doses of pasireotide SC administered as either a single dose or two divided doses in healthy volunteers. Adverse events were recorded throughout the study as mild, moderate, or severe. A dosage was considered intolerable if, in a single cohort at each dosage, two subjects or more experienced a common toxicity criteria (CTC) grade ≥3 event, four subjects or more experienced an event of CTC grade 2, or five subjects or more experienced an event of CTC grade 1 that led to refusal to continue the study, based on an intended enrollment of eight participants per cohort. Pasireotide dosing could also be terminated if it was thought to jeopardize subject safety.

The secondary objective was to assess the PK profile of pasireotide as a single or divided dose in healthy volunteers. Pharmacokinetic parameters included C_{max}, T_{max}, AUC_{0-last}, AUC_{∞}, CL/F, and $t_{½}$ of α, β, and γ phases ($t_{½,\alpha}$, $t_{½,\beta}$, and $t_{½,\gamma}$). In the divided-dose cohort, T_{max1} and C_{max1} referred to samples obtained after the morning pasireotide injection, and T_{max2} and C_{max2} to samples obtained after the evening injection. Blood samples were collected before dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, 10, 12, 24, 48, 72, 96, 120, and 144 hours after dosing. In the divided-dose cohort, additional blood samples were collected after the second pasireotide injection, at 12.25, 12.5, 13, 13.5, 14, 15, and 16 hours. Blood samples were obtained via either direct venipuncture or from an indwelling cannula inserted in a forearm vein. Samples (1.5 mL) were stored in EDTA and kept frozen at −18°C or lower.

Bioanalysis of pasireotide plasma concentrations was performed using a validated radioimmunoassay