Subcutaneous Bioavailability of Taspoglutide at 3 Different Injection Sites in Healthy Overweight/Obese Subjects

Carolina Sturm-Pellanda, PhD; Markus Abt, PhD; Patricia Sanwald-Ducray, PhD; and Christophe Schmitt, PharmD

F. Hoffmann-La Roche AG, Basel, Switzerland

ABSTRACT

Purpose: Taspoglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist that has >90% homology with the endogenous GLP-1 while retaining equivalent potency. Once-weekly subcutaneous injections with taspoglutide demonstrated meaningful antihyperglycemic and weight loss effects in patients with type 2 diabetes. The present study was performed to compare the relative bioavailability of taspoglutide injected subcutaneously in the abdomen, upper arm, and thigh.

Methods: Healthy overweight/obese subjects were randomized in an open-label, 3-way crossover study. A single 20-mg dose of taspoglutide was injected subcutaneously on 3 occasions in the abdomen, upper arm, or thigh. Each injection was separated by a 12-week washout period. Blood was sampled up to 12 weeks for the pharmacokinetic evaluation of taspoglutide.

Findings: Sixty subjects were randomized into the study (mean age, 45.5 years; body weight, 97.6 kg; and body mass index, 31.4 kg/m^2). AUC_{last} values (geometric mean) for subcutaneous injections in the abdomen, upper arm, and thigh were 44.2, 61.2, and 50.0 ng · h/mL, respectively. The geometric mean ratio (relative bioavailability) for the upper arm versus the abdomen was 1.41 (90% CI: 1.22–1.62) and for the thigh versus the abdomen was 1.13 (90% CI: 0.98–1.31). Corresponding C_{max} values for subcutaneous injections in the abdomen, upper arm, and thigh were 0.268, 0.382, and 0.341 ng/mL, respectively, and the geometric mean ratio for the upper arm versus the abdomen was 1.43 (90% CI: 1.24–1.64) and for the thigh versus the abdomen was 1.27 (90% CI: 1.10–1.46). Decreases in taspoglutide exposure were observed with each subsequent period. AUC_{last} values (geometric mean across injections sites) for periods 1, 2, and 3 were 97.2, 42.6, and 31.5 ng · h/mL, respectively. The geometric mean ratio for period 2 versus 1 was 0.44 (90% CI: 0.38–0.50) and for period 3 versus 1 was 0.32 (90% CI: 0.27–0.37). Analysis of pharmacokinetic data after first injection only (period 1) showed comparable AUC_{last} across the 3 injection sites and lower initial C_{max} after injection into the abdomen compared with the other 2 injection sites. Overall, taspoglutide was well tolerated by most subjects in all 3 injection sites, with a lower incidence of nausea and vomiting when injected in the abdomen.

Implications: Regardless of a pronounced period effect, relative bioavailability of taspoglutide was different across injection sites, with the lowest exposure and incidence of nausea and vomiting seen after administration in the abdomen. In the absence of comparable bioavailability, taspoglutide was recommended to be injected into the abdomen. (*Clin Ther.* 2015;37:2439–2448)

Key words: bioavailability, GLP-1 agonist, period effect, site of injection, taspoglutide.

INTRODUCTION

Taspoglutide is a 30-amino acid derivative of the native glucagon-like peptide-1 (GLP-1), which has >90% homology with the endogenous GLP-1. It has 2 α-aminoisobutyric acid substitutions that prevent degradation by dipeptidyl peptidase 4 and other plasma proteases.[1] Taspoglutide has comparable affinity to the natural ligand for the human GLP-1 (hGLP-1) receptor and exhibits comparable potency. It exerts an insulinotropic action in vitro and in vivo.[2] Stimulation of insulin secretion is concentration dependent and of greater magnitude compared with

Accepted for publication August 22, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.08.022
0149-2918/$ - see front matter

unmodified hGLP-1, attributed to an extended in vitro plasma half-life relative to hGLP-1.[2,3]

Taspoglutide was initially developed as an immediate-release formulation.[4,5] To enable a once-weekly dosing regimen, it was subsequently formulated in matrix-free sustained-release formulation (SRF), forming a precipitated depot after subcutaneous injection. Single subcutaneous injections of taspoglutide SRF showed initial peak plasma concentrations within 24 hours after injection followed by a second peak 10 to 14 days later.[6] Administration of 8- and 30-mg doses of taspoglutide SRF significantly improved glycemic parameters in type 2 diabetes patients for up to 14 days. The formulation was overall well tolerated. The 30-mg dose was associated with an increased incidence of transient nausea and vomiting, which usually occurred within 24 hours after injection and resolved within 1 day. These features rendered taspoglutide SRF suitable for weekly administration.[6] In later phase II and III clinical studies, once-weekly taspoglutide demonstrated good glycemic control with minimal hypoglycemic risk and favorable weight loss.[7–16]

In all phase II and III clinical studies, taspoglutide was injected in the abdomen. However, long-term treatment with subcutaneous injections can present challenges to patients who may appreciate flexibility regarding injection sites. Because the use of different anatomic sites for subcutaneous injection may affect the absorption of therapeutic peptides and possibly their safety or efficacy profiles, it was important to evaluate relative bioavailability at different injection sites to provide appropriate guidance to patients. This has been previously shown for human growth hormone, with faster absorption after subcutaneous injection in the abdomen compared with the thigh.[17] Similarly, injection of insulin in the abdomen produced a greater reduction of plasma glucose than injection in the thigh.[18] The present study investigated whether the site of subcutaneous injection affects the pharmacokinetics and safety of taspoglutide SRF in healthy overweight or obese subjects.

MATERIALS AND METHODS

Subjects

Healthy overweight/obese adult volunteers of either sex and 18 to 65 years of age were eligible for the study if they satisfied the following inclusion criteria: body mass index ≥ 28 and ≤ 35 kg/m^2; healthy as determined by medical history, physical examination, electrocardiographic and clinical laboratory measurements at the screening visit; and a stable body weight ($\pm 10\%$) for at least 3 months before screening. Female subjects had to be either surgically sterile or postmenopausal for at least 1 year. The main exclusion criteria were as follows: history of drug hypersensitivity; clinically relevant surgical history of the gastrointestinal tract and/or acute gastrointestinal symptoms; previous exposure to GLP-1 analogues; any clinically relevant abnormal laboratory test results, including positive test result for HIV, hepatitis B or C; smoking (>10 cigarettes a day) or excessive alcohol consumption or known history of drug or alcohol abuse; taking any drug (except paracetamol up to 2000 mg/d) within 2 weeks before first dosing or within 6 times the elimination half-life of the medication before first dosing (whichever was longer); blood or plasma donation ≥ 400 mL within 3 months of study start; and participation in another clinical trial <3 months before study. Subjects were screened for eligibility during a 4-week period before the start of the study (days -28 to -2).

All subjects gave written informed consent. The study was conducted at the Clinical Pharmacology Research Unit of Parexel International GmbH (Berlin, Germany), and the protocol was approved by the local independent ethics committee (Landesamt für Gesundheit und Soziales Berlin). The study was performed in accordance with the principles of the Declaration of Helsinki and with local laws and regulations.

Study Design

This was a Phase I, open-label, single-dose, 3-period crossover study in healthy overweight/obese volunteers. Each subject received 3 single 20-mg doses of taspoglutide, injected subcutaneously into the abdomen (A), upper arm (U), or thigh (T). Subjects were randomized to 1 of 6 treatment sequences (AUT, ATU, UAT, UTA, TAU, TUA). Each injection was separated by a 12-week washout period to avoid potential carryover effects. The selected dose corresponded to the highest dose tested in Phase III studies. For each treatment period, subjects were admitted to the clinical research unit in the morning of the day before dosing (Day -1) and stayed in the unit until 48 hours after subcutaneous injection (Day 3). Taspoglutide SRF was injected on Day 1 of each treatment period after an overnight fast of at least 10 hours. Subjects were required to return fasted to the unit for ambulatory visits for pharmacokinetic sampling and safety assessments at regular intervals during the study.