Pharmacokinetics and pharmacodynamics of tecarfarin, a novel vitamin K antagonist oral anticoagulant

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Summary

Tecarfarin is a vitamin K antagonist (VKA) with reduced propensity for drug interactions. To evaluate the pharmacokinetic (PK), pharmacodynamic (PD), and safety of tecarfarin, we performed single ascending dose (SAD) (n=66), multiple ascending dose (MAD) (n=43), and tecarfarin versus warfarin (n=28) studies in human volunteers. In the SAD, tecarfarin was administered to 5 of 6 subjects (1 received placebo) in each of 11 cohorts. $AUC_{0-\infty}$ exhibited linearity and dose proportionality. Elimination $T_{1/2}$ ranged from 87–136 hours (h) across all doses. In the MAD, tecarfarin was administered to 5 of 6 volunteers in each of 7 cohorts. The starting dose was continued until the subject's INR reached the target range (TR) of 1.7 to 2.0. Dosing was down-titrated if the TR was achieved. Elimination $T_{1/2}$ ranged from 107–140 h. Doses <10 mg had insignificant effect on INR. Higher doses raised INRs and required down-titration to maintain the TR. Steady state INR dosing was 10–20 mg. INR declined promptly after discontinuation. In the comparative study, subjects received tecarfarin or warfarin and dose titrated to a TR of 1.5–2.0. Mean dose after TR was achieved was 13.9 mg (range 10.0–25.5 mg) for tecarfarin and 5.3 mg (range 2.5–9.0 mg) for warfarin. At similar INR levels, the concentration of coagulation factors II, VII, IX, and X were similar for tecarfarin and warfarin. Tecarfarin was tolerated well without serious adverse events in all three studies.

Keywords

Tecarfarin, warfarin, VKA, pharmacokinetics, pharmacodynamics

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Introduction

Vitamin K antagonists (VKA) such as warfarin, acenocoumarol or phenprocoumin are effective anticoagulants for the prevention and treatment of arterial and venous thrombosis (1–3). However, they have narrow therapeutic windows affected by age, concomitant medications, concomitant diseases, renal function and genetic polymorphism, which make it difficult to establish stable anticoagulation in many patients (4, 5). Warfarin metabolism involves seven isoenzymes of the Cytochrome P450 enzyme system in the liver. This metabolism is prone to many drug-drug interactions (6, 7), and genetic polymorphism is associated with haemorrhagic complications (8). A recent review of warfarin drug interactions found well over 120 drugs interfering with warfarin metabolism (6). Unstable anticoagulation with warfarin was reported to be the leading cause among 99,628 emergency hospitalisations for adverse drug events in older adults in the United States from 2007–2009 (7). Given the continuing need for VKA based anticoagulation in many indications (9), the development of new options is desirable (10–12).

Tecarfarin, a structural analog of warfarin, is a synthetic, small organic molecule being developed as a novel VKA anticoagulant. Tecarfarin is an orally active vitamin K epoxide reductase (VKOR) inhibitor with no measurable activity against a broad variety of unrelated receptors and ion channels. Tecarfarin metabolism occurs through human carboxylesterase 2 (h-CE2) to a single inactive metabolite ATI-5900 (►Figure 1) and is not dependent on the cytochrome P450 (CYP450) system. Like warfarin, tecarfarin is highly bound to plasma protein in humans (>99%). In a drug-drug interaction study with fluconazole, a broad CYP450 inhibitor, tecarfarin metabolism and clearance were unaffected, whereas warfarin clearance decreased and half-life doubled in the presence of fluconazole (13). Previously reported clinical studies have demonstrated tecarfarin's ability to achieve stable anticoagulation, specifically in difficult to manage patients with genetic variants for CYP2C9 and taking CYP2C9 interacting drugs (14, 15).

In order to fully characterise the pharmacokinetic (PK) and pharmacodynamic (PD) profile of tecarfarin, we performed three Phase 1 studies in healthy volunteers: a single ascending dose study, a multiple ascending dose study and a study evaluating the pharmacodynamic effects of tecarfarin in comparison to warfarin.

Methods

Three separate studies are presented here, all three were performed in a single centre, PPD Development, LP (Austin, TX, USA). Tecarfarin, warfarin, and metabolite concentrations were performed and analysed using HPLC tandem mass spectrometry based on the re-

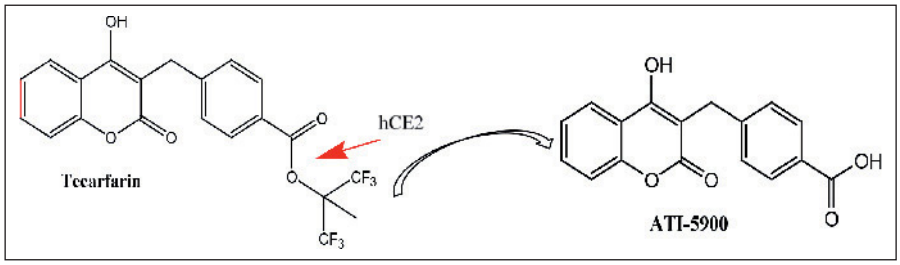

Figure 1: Tecarfarin is a non-chiral molecule metabolised by hCE2 to a single inactive metabolite ATI-5900.

sults of a full validation study in human plasma by Alta Analytical Laboratory (El Dorado Hill, CA, USA) and by Combs Consulting Service (Mountain View, CA, USA). The assay was performed on samples extracted from 300 µl of 0.4% ethanolic paraoxon-treated human plasma (K_3EDTA) by liquid-liquid extraction using 50:50 ethyl acetate:hexane. Run times were approximately 6 minutes (min). The lower limit of quantitation (LLOQ) was 1.0 ng/ml, and the range of reliable response was 1 .0–400 ng/ml. (R)-warfarin and (S)-warfarin concentrations in plasma samples were determined using liquid-liquid extraction with subsequent analysis by Alta's LC-API/MS/MS. The lower limit of quantitation was 2.0 ng/ml for both enantiomers. A full description of the bioanalytical methods appears in the Supplementary Material (available online at www.thrombosis-online.com). Coagulation factor and PD monitoring was performed by Hemostasis Reference Laboratory (Burlington, NC, USA). Data Management and Statistical Reporting was performed by Synteract (Carlsbad, CA, USA), using SAS version 8.2 software and WinNonlin Professional 5.1.1 (Pharsight Corp.). The first study was a double-blind, placebo-controlled, single ascending dose study of tecarfarin. The second study was a randomised, double-blind placebo-controlled, multiple ascending dose study of tecarfarin. The third study was an open-label, parallel-group comparison of tecarfarin with warfarin. All three studies were performed in healthy human volunteers. The studies were conducted in accordance with the U.S. Food and Drug Administration (FDA) Code of Federal Regulations (CFR), 21 CFR Part 312.20, as well as the Declaration of Helsinki (2000) and the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP, 1996). All protocols were reviewed and approved by institutional review boards (Research Consultants Review Committee, 706B Ben White Blvd, West, Austin, TX 78704, USA for the single and multiple ascending dose studies and Integreview Ethical Review Board 3001 S Lamar Blvd., Suite 210, Austin, TX 78704, USA for the tecarfarin and warfarin comparison study). All subjects provided written informed consent.

Tecarfarin single ascending dose study (CLN-501)

The primary objective of this double-blind, placebo controlled, randomised, parallel-group study was to evaluate the safety and tolerability of a single oral dose of tecarfarin compared to placebo when given to healthy volunteers. The secondary objectives were to determine the pharmacokinetic (PK) profile and anticoagulant activity of a single dose of tecarfarin. Cohorts of 6 subjects received a single dose of tecarfarin (5 per cohort) or placebo (1 per cohort) in sequential ascending doses: 0.2, 0.6, 1.5, 3.0, 4.5, 6.0, 8.0, 10, 20, 30, and 40 mg. PK parameters were calculated from plasma concentrations of tecarfarin and its metabolite ATI-5900 obtained from serial blood draws at 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 168, and 360 hours (h) post-dose. PK parameters calculated included area under the concentration-time curve (AUC), maximum observed serum concentration (C_{max}), time point for maximum concentration (T_{max}), half-life ($T_{1/2}$), elimination rate constant, clearance (CL/F), and volume (V/F) of distribution. PD variables included international normalised ratio (INR), PT, aPTT, and coagulation factors II, VII, and X levels. Serial blood draws for assessment of these variables were obtained on Day 1 at 1, 4, 8, 12 hours post dose and Days 2, 3, 4 (INR, PT, and a PTT only), 8, and 15 (INR, PT, and a PTT only). Tolerability and safety were assessed by adverse event collection, clinical laboratory evaluations, vital sign assessment, 12-lead ECG recordings and physical examinations at screening and on Days 2, 3 and 8.

Tecarfarin multiple ascending dose study (CLN-502)

The primary objectives of this double-blind, placebo controlled, randomised, parallel-group study were to determine the pharmacokinetic (PK) profile and anticoagulant activity of multiple doses of tecarfarin. The secondary objective was to evaluate the safety and tolerability of a multiple oral doses of tecarfarin compared to placebo when given to healthy volunteers. Cohorts of six subjects received multiple doses of tecarfarin (5 per cohort) or placebo (1 per cohort) in ascending starting doses: 1, 3, 6, 10, 20, 30, and 40 mg. The starting dose was continued for 7–14 days or until the subject's INR reached the target range of 1.7–2.0. If the target range was achieved prior to Day 14, the dose was down-titrated to achieve a steady-state INR within the target range. PK parameters calculated were C_{max}, T_{max}, T_{lag}, AUC, $T_{½}$, CL/F and V/F. PD variables included INR, PT, aPTT, and coagulation factors II, VII, and X levels. Serial blood draws for assessment of these variables were obtained on Day 1 through 15, 22, 29 and 36. Tolerability and safety were assessed by adverse event collection, clinical laboratory evaluations, vital sign assessment, 12-lead ECG recordings and physical examinations at screening and on Days 2, 8 and 15.

Tecarfarin and warfarin comparison study (CLN-503)

The primary objectives of this open-label, randomised, parallel-group study were to compare the rate and extent of reductions in vitamin K–dependent coagulation factor activity (factors II, VII,

