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Characterizing the time-course of antihypertensive activity and optimal dose range of fimasartan *via* mechanism-based population modeling

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ABSTRACT

Fimasartan is a novel angiotensin II receptor blocker. Our aims were to characterize the time-course of the antihypertensive activity of fimasartan *via* a new population pharmacokinetic/pharmacodynamic model and to define its optimal dose range. We simultaneously modelled all fimasartan plasma concentrations and 24-h ambulatory blood pressure monitoring (ABPM) data from 39 patients with essential hypertension and 56 healthy volunteers. Patients received placebo, 20, 60, or 180 mg fimasartan every 24 h for 28 days and healthy volunteers received placebo or 20 to 480 mg as a single oral dose or as seven doses every 24 h. External validation was performed using data on 560 patients from four phase II or III studies. One turnover model each was used to describe diastolic and systolic blood pressure. The input rates into these compartments followed a circadian rhythm and were inhibited by fimasartan. The average predicted (observed) diastolic blood pressure over 24-h in patients decreased by 10.1 ± 7.5 (12.6 ± 9.2; mean ± SD) mmHg for 20 mg, 14.2 ± 7.0 (15.1 ± 9.3) mmHg for 60 mg, and 15.9 ± 6.8 (11.5 ± 9.9) mmHg for 180 mg daily relative to placebo. The model explained the saturation of antihypertensive activity by counter-regulation at high fimasartan concentrations. Drug effect was maximal at approximately 23 ng/mL fimasartan for diastolic and 12 ng/mL for systolic blood pressure. The proposed mechanism-based population model characterized the circadian rhythm of ABPM data and the antihypertensive effect of fimasartan. After internal and external model validation, 30 to 60 mg oral fimasartan given once daily was predicted as optimal dose range.

1. Introduction

Fimasartan is a novel angiotensin II receptor blocker (ARB) that selectively targets the angiotensin II type 1 receptor (AT1). Radioligand binding data showed an improved affinity of fimasartan for the AT1 receptor compared to that of losartan (Chi et al., 2011; Kim et al., 2012). Fimasartan did not show a partial agonistic effect of the angiotensin II receptor in animal models of hypertension that was observed for other ARB drugs (Kim et al., 2012; Lee et al., 2013a). Fimasartan (Kanarb®, Boryung Pharm. Co., Ltd) has been approved in Korea in 2010 and in twelve Latin American countries in 2014 for the treatment of mild-to-moderate hypertension (Lee et al., 2012a; Lee et al., 2012b).

Most human pharmacokinetic/pharmacodynamic (PK/PD) data on fimasartan have been obtained in Korean patients (Chi et al., 2011; Lee et al., 2013a; Lee et al., 2012a; Lee et al., 2013d; Lee et al., 2012b). Potential PK differences between various patient groups may affect optimal dosing. Food slightly decreases the extent of absorption (Chi et al., 2011; Lee et al., 2013d). Fimasartan has a 69.4% higher clearance in young (age: 19–45 y) compared to elderly (≥ 65 y) healthy volunteers (Lee et al., 2011) and showed PK interactions with ketoconazole and rifampicin (Kim et al., 2013). Moreover, fimasartan undergoes extensive enterohepatic recirculation (EHC) in rats and humans (Chi et al., 2011; Kim et al., 2014; Kim et al., 2015) which considerably

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enhances its apparent terminal half-life and drug exposure (Kim et al., 2015).

Ambulatory blood pressure monitoring (ABPM) provides frequent observations which can be used to calculate the average blood pressure during the day, at night and over the 24-h period. These blood pressure data follow a circadian rhythm and provide in-depth information on the time-course of the antihypertensive drug effect. In patients, baseline blood pressure and its fluctuation over time often show considerable between subject variability (BSV) even without exposure to a drug (Sheng et al., 2013). A previous PK/PD model for fimasartan in healthy volunteers (Lee et al., 2013d) fitted blood pressure data at five time-points over 24 h, but lacked a placebo group and borrowed the time-course of average blood pressure after placebo from another study (Hempel et al., 1998).

Current PK/PD models for the circadian rhythm of blood pressure use the sum of multiple harmonics (usually two cosine functions) to describe the time-course of blood pressure in the absence of drug (Hempel et al., 1998; Lee et al., 2013c; Sheng et al., 2013; Snelder et al., 2014; Snelder et al., 2013; van Rijn-Bikker et al., 2013). The drug effect is then modelled as the difference of the observed blood pressure profile with and without drug. These models provide an empirical fit of the circadian rhythm for the average patient, but most often lack BSV for the parameters of the cosine functions (*i.e.* the amplitude[*s*] and phase shift[*s*]). Furthermore, these parameters do not reflect the physiological processes which contribute to the circadian rhythm of blood pressure. Based on these empirical models, it is difficult to predict the antihypertensive drug effect for patients with altered physical activity (*e.g.* due to sports) and for patients with an altered day/night rhythm. We are not aware of models for antihypertensive drugs that describe the circadian rhythm of blood pressure (*e.g.* using ABPM data) and estimate the BSV of all parameters.

Population PK/PD modeling can characterize the antihypertensive drug effect and a placebo effect based on ABPM data and estimate the BSV. Such models can describe the circadian rhythm of blood pressure. Moreover, mechanism-based models can compare drug effects in 'normal' and special patient populations with potentially altered PK and predict the impact of different physical activity levels and altered day/night rhythms.

Our first aim was to describe the time-course of diastolic and systolic blood pressure based on 24-h ABPM data and characterize the antihypertensive activity of fimasartan by a new population PK/PD model. We estimated the subjects' physical activity over time to describe the circadian rhythm of blood pressure. Secondly, we externally validated the population model based on four published phase II and III studies. Our third aim was to propose the optimal fimasartan dose range *via* Monte Carlo simulations.

2. Materials and methods

2.1. Datasets

The clinical data sets (Table S1) which were utilized for parameter estimation were provided by Boryung Pharm. Co., Ltd. The experimental blood pressure data (without a modeling analysis) (Chi et al., 2011; Lee et al., 2012a), the LC-MS/MS assay (Lee et al., 2013a), and a population PK model with EHC (Kim et al., 2015) have been previously published. We simultaneously fit all fimasartan plasma concentrations, diastolic and systolic blood pressure profiles in healthy volunteers (n = 56) and patients (n = 39; Table S1) (Chi et al., 2011; Kim et al., 2015; Lee et al., 2012a). Studies were conducted following the recommendations of the revised version of the Declaration of Helsinki. External validation was conducted based on four published clinical phase II and III studies (Lee et al., 2013b; Lee et al., 2012a; Lee et al., 2012b; Youn et al., 2014).

2.2. Clinical studies

The clinical details of a single and a multiple dose study in Korean healthy volunteers have been described previously (Chi et al., 2011). The single dose study ('study A' in (Chi et al., 2011)) included 40 healthy volunteers who received placebo, 20, 60, 120, 240, and 480 mg (Table S1). After a 7-day washout period, five subjects in the 240 mg group received fimasartan with food and two subjects received placebo with food. The multiple dose study ('study B' in (Chi et al., 2011)) included 16 healthy volunteers who received placebo (n = 4), 120 (n = 6) or 360 mg (n = 6) fimasartan every 24 h for 7 days.

Diastolic and systolic blood pressure were measured after subjects had been in supine position for at least 5 min (Chi et al., 2011). Observation times were 0 (pre-dose; in triplicate), 0.5, 1, 2, 4, 6, 8, 12, and 24 h for the single dose and additionally 48, 72, 96, 120, 144, 144.5, 145, 146, 148, 152, 156, 168, and 192 h for the multiple dose study.

Our population PK/PD modeling additionally included the PK, systolic and diastolic ABPM data of a phase II study in Korean patients with mild-to-moderate essential hypertension. The clinical details of this phase II study ('study 1' in Lee et al.) have been described previously (Lee et al., 2012a). Essential hypertension was defined as a sitting diastolic blood pressure of 95 to ≤ 115 mmHg. A washout period of at least 1 week was used to minimize a potential carryover effect of other antihypertensive drugs. After the washout period, patients were assessed in a 2-week placebo run-in period and subsequently received placebo, 20, 60, or 180 mg fimasartan every 24 h for 4 weeks. Our PK/PD modeling analysis was based on the 39 per-protocol patients for whom detailed PK data were obtained after the first and last (*i.e.* 28th) dose. The ABPM data (Tonoport V, GE Healthcare) were obtained during the 24 h before the first dose (pre-treatment baseline) and after 4 weeks of treatment (Lee et al., 2012a). Blood pressure was measured every 30 min during daytime (from 6 AM to 10 PM) and every 1 h at night (from 10 PM to 6 AM).

2.3. Population pharmacokinetic/pharmacodynamic modeling

2.3.1. Pharmacokinetic model

We adapted with minor modification our population model (Kim et al., 2015) that simultaneously described the PK and EHC of fimasartan in rats, dogs, and humans. In the present clinical studies, fimasartan was dosed as an oral tablet and data on an oral solution were not available. Thus, the present absorption model was simplified to only contain a stomach and a gut compartment (Fig. S1). To describe the PK after oral dosing, a model with two disposition compartments was sufficient for humans. Relative bioavailability ($F_{food,Rel}$) with food was described by a partial loss of drug between the stomach and the gut compartment. With exception of the two changes described above, all equations for the present PK model in humans (Fig. S1) were identical to those described in our previous PK model (Kim et al., 2015).

2.3.2. Pharmacodynamic model

To describe the time-course of blood pressure data it is necessary to account for a circadian rhythm and for a potential placebo effect. The proposed PK/PD model explained the circadian rhythm by estimating the times when subjects were active during the day or rested at night. Blood pressure was assumed to follow these differences in activity with a small delay. The proposed PK/PD model quantified the antihypertensive drug effect in the presence of this circadian rhythm and accounted for BSV of all model parameters. We also estimated a placebo effect between the first and the last day of the studies informed by the data from the placebo group.

In the present study, the time-course of blood pressure in the absence of drug was described by one turnover model each for systolic and diastolic blood pressure (Fig. 1). The input rates (R_{Sys} and R_{Dia}) into these compartments followed a circadian rhythm to reflect different activity levels during day and night (Fig. 1). We estimated the baseline