Drug Metabolism and Pharmacokinetics 30 (2015) 160–167

Contents lists available at ScienceDirect

Drug Metabolism and Pharmacokinetics

journal homepage: http://www.journals.elsevier.com/drug-metabolism-and-pharmacokinetics

Regular article

Population pharmacokinetic analysis for 10-monohydroxy derivative of oxcarbazepine in pediatric epileptic patients shows no difference between Japanese and other ethnicities

Ikuo Sugiyama [a, c, *], Thomas Bouillon [b], Masayuki Yamaguchi [a], Hikoe Suzuki [a], Takashi Hirota [c], Martin Fink [b]

[a] Drug Metabolism and Pharmacokinetics, Novartis Pharma K.K., Tokyo, Japan
[b] Integrated Quantitative Sciences, Novartis Pharma AG, Basel, Switzerland
[c] Department of Biopharmaceutics, Faculty of Pharmaceutical Sciences, Tokyo University of Science, Chiba, Japan

ARTICLE INFO

Article history:
Received 4 September 2014
Received in revised form
29 November 2014
Accepted 2 December 2014
Available online 10 December 2014

Keywords:
Population PK
Oxcarbazepine
Japanese population
Pediatrics
Epilepsy
Ethnic sensitivity assessment

ABSTRACT

Oxcarbazepine is an anti-epileptic drug, which is almost completely metabolized by cytosolic enzymes in the liver to the active 10-monohyroxy metabolite (MHD) following oral administration. The pharmacokinetic (PK) profiles of MHD were evaluated in pediatric epileptic patients and a possible ethnic difference in PK of MHD between Japanese and non-Japanese pediatric patients was assessed. A non-linear mixed effect modeling approach was used to determine the PK of MHD. A one-compartment population model with first-order absorption appropriately described the PK of MHD. No clinically relevant differences were found for using body surface area or weight to explain between-patient variability, therefore the final model included the effects of body weight on apparent clearance (CL/F) and apparent volume of distribution (V/F) of MHD, and in addition, the effect of 3 concomitant anti-epileptic drugs (carbamazepine, phenobarbital and phenytoin) on CL/F of MHD. Inclusion of ethnicity as a covariate in the final model, concluded no ethnic difference with respect to CL/F of MHD between Japanese and non-Japanese patients. Hence, oxcarbazepine can be generally applied using the same dosage and administration for the treatment of partial onset seizures in pediatric patients, regardless of ethnicity.

1. Introduction

Oxcarbazepine (10,11-dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide) is an anti-epileptic drug approved as monotherapy or adjunctive therapy in the treatment of partial onset seizures, in adults and in children [1]. Oxcarbazepine is structurally related to carbamazepine but displays improved tolerability and safety profiles in patients with epilepsy and a lower potential for drug–drug interactions [2–4].

The mechanism of action of oxcarbazepine and its pharmacologically active 10-monohydroxy derivative (MHD, 10,11-dihydro-10-hydroxy-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide) is mainly thought to be based on blockade of voltage-sensitive sodium channels, thus resulting in stabilization of hyper excited neural membranes, inhibition of repetitive neuronal firing, and diminishing the propagation of synaptic impulses [5–7]. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects [8].

Oxcarbazepine is rapidly and almost completely absorbed (>95%) following oral administration and is extensively metabolized to MHD by cytosolic enzymes in the liver [1]. In a mass balance study in man, following a single oral administration of ^{14}C-oxcarbazepine (400 mg), only 2% of total radioactivity in plasma consisted of unchanged oxcarbazepine, approximately 70% consisted of MHD, and the remainder attributable to minor secondary metabolites which were rapidly eliminated [1].

In Japan, oxcarbazepine has been developed clinically for the treatment of children with epilepsy since 2009, based on the recommendations of the expert committee established by the Ministry of Health, Labour and Welfare. A clinical trial was conducted to

* Corresponding author.
E-mail address: ikuo.sugiyama@novartis.com (I. Sugiyama).

http://dx.doi.org/10.1016/j.dmpk.2014.12.002

demonstrate the efficacy and safety of oxcarbazepine as adjunctive therapy in comparison to placebo in Japanese pediatric epileptic patients aged between 4 and 14 years with partial onset seizures refractory to other anti-epileptics (ClinicalTrials.gov Identifier: NCT00975715). In this study MHD concentrations in plasma at steady state were measured. The aim of this analysis was to evaluate the pharmacokinetic (PK) profiles of MHD in pediatric patients and to assess a possible ethnic difference in the PK parameters of MHD using pooled data from a study in Japanese pediatric patients and a preceding study in non-Japanese pediatric patients [9,10].

2. Methods

2.1. Clinical studies

The PK profiles of MHD for oxcarbazepine adjunctive therapy in pediatric epileptic patients with inadequately controlled partial onset seizures were evaluated by using data from two clinical studies, comprising a Japanese pediatric study and a preceding non-Japanese pediatric study [9,10]. These clinical studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group trials designed to investigate the efficacy and safety of oxcarbazepine compared with placebo as adjunctive therapy in pediatric patients with inadequately controlled partial onset seizures. These clinical studies were approved by Institutional Review Boards at each study center and conducted in accordance with the Declaration of Helsinki and the principle of Good Clinical Practice. Written informed consent was obtained from parents/legal guardians (and patients if appropriate) prior to their enrollment in the study.

2.1.1. Study in Japanese pediatric epileptic patients

Following an 8 week screening phase, patients were randomized to receive either oxcarbazepine or placebo for 8 weeks. On the basis of body weight, the study drug administration was started at an initial dose (8–10 mg/kg/day), which was up-titrated over the first 2 weeks of double-blind phase to a maximum total daily oral dose of 600–1800 mg/day given twice daily for 6 weeks. The stable regimen of 1 or 2 concomitant anti-epileptic drugs (AEDs) was maintained at least until the end of the double-blind phase. All patients were followed up for 3–5 weeks.

For determination of MHD in plasma, blood samples (sample 1–4) were collected at visits during the maintenance phase (the last 6 weeks of double-blind phase) from each patient at the following time points: Sample 1: trough (about 12 h after the last dose), Sample 2: approximately Tmax (about 4–6 h after administration), Sample 3: initial (around 30 min to 2 h after administration), Sample 4: trough (at another visit than that for the trough sample 1). The PK sample collection was optional and was performed only after the prior written consent was obtained from the parents/legal guardians (and patients if appropriate). Details on the study design and results in the study in non-Japanese pediatric epileptic patients were published previously [9,10].

2.2. Determination of MHD in plasma

In the study in Japanese patients, MHD concentrations in plasma were determined with a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The samples were processed by solid phase extraction followed by LC-MS/MS analysis with atmospheric pressure chemical ionization as an interface. Chromatography was performed on a C18 reversed-phase column using 20 mmol/L aqueous ammonium acetate, methanol and acetonitrile as the mobile phase. The lower limit of quantification of MHD was 0.1 μmol/L.

Details on the bioanalytical method to determine MHD concentration in plasma which was used in the study in non-Japanese patients were published previously [9].

2.3. Study population and data collection

This analysis used a total of 464 plasma concentrations from a total of 136 patients. Among the 464 plasma concentrations, 88 plasma concentrations from 27 patients and 376 plasma concentrations from 109 patients were obtained from the study in Japanese patients and the study in non-Japanese patients, respectively.

Baseline and patient characteristics in the population PK analysis are shown in Table 1. There was no difference in mean age between the study in Japanese patients and the study in non-Japanese patients. The mean body weight of Japanese patients was approximately 9 kg lower than that of non-Japanese patients across age range. Regarding frequency of ethnicity in the study in non-Japanese patients, majority was Caucasian (85%). The mean values for physiologic parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT) and serum creatinine] and frequency of concomitant AEDs (carbamazepine, diazepam, gabapentin, lamotrigine, phenobarbital, phenytoin and valproic acid) did not show notable differences between studies.

2.4. Data analysis and model evaluation

Non-linear mixed effects modeling of the data was performed using the NONMEM software system, version 7.2 (Icon Development Solutions, Ellicott City, MD, USA). Model building was

Table 1
Characteristics of patients in the population PK analysis.

Parameter	Study in non-Japanese	Study in Japanese
No. of patients	109	27
No. of plasma concentrations	376	88
Age (years)	11.0 ± 3.9 [3–17]	10.33 ± 2.631 [5–14]
Body weight (kg)	43.3 ± 20.7 [15.9–134.5]	34.46 ± 12.44 [15.3–67.5]
Height (cm)	143 ± 21 [98–186][a]	137.4 ± 16.15 [103.5–162.5]
BSA (m^2)	1.31 ± 0.39 [0.68–2.59][a]	1.151 ± 0.2596 [0.6782–1.74]
Gender		
Male	58 (53%)	16 (59%)
Female	51 (47%)	11 (41%)
Ethnicity		
Caucasian	93 (85%)	–
Black	7 (6%)	–
Asian excluded Japanese	1 (1%)	–
Other	8 (7%)	–
Japanese	–	27 (100%)
AST (U/L)	23.6 ± 15.1 [9–160]	23.52 ± 8.437 [12–50]
ALT (U/L)	16.4 ± 9.5 [0–58]	20.26 ± 15.16 [6–63]
Serum creatinine (mg/dL)	0.63 ± 0.16 [0.3–1.0]	0.4144 ± 0.06796 [0.28–0.54]
Concomitant anti-epileptic drugs		
Carbamazepine	58 (53%)	15 (56%)
Diazepam	4 (4%)	0 (0%)
Gabapentin	14 (13%)	1 (4%)
Lamotrigine	17 (16%)	3 (11%)
Phenobarbital	14 (13%)	3 (11%)
Phenytoin	15 (14%)	6 (22%)
Valproic acid	33 (30%)	10 (37%)
Dose range of oxcarbazepine (mg/day)	[300–2100]	[312–1800]

Values are expressed as mean ± standard deviation [range], n (%), n or [range].
BSA: body surface area, AST: aspartate aminotransferase, ALT: alanine aminotransferase.
[a] $N = 108$.