Journal of Pharmacological and Toxicological Methods 63 (2011) 123–133

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Original article

A pharmacokinetic–pharmacodynamic model for cardiovascular safety assessment of R1551

Angèle Fleury [a], Thierry Lavé [a], Fredrik Jonsson [b], Monique Schmitt [a], Gerard Hirkaler [c], Liudmila Polonchuk [c], Alexander Breidenbach [c,*]

[a] Drug Metabolism and Pharmacokinetics Department, F. Hoffmann-La Roche Ltd., Basel, Switzerland
[b] Pharsight, A Certara Company, St. Louis, MO, USA
[c] Global Safety Pharmacology, Non-Clinical Safety Department, F. Hoffmann-La Roche Ltd, Basel, Switzerland, and Hoffmann-La Roche, Inc. Nutley, USA

ARTICLE INFO

Article history:
Received 2 October 2009
Accepted 17 August 2010

Keywords:
Preclinical cardiac safety
Population PK–PD modelling
PR interval
QRS complex
Telemetry

ABSTRACT

Introduction: Pharmacokinetic–pharmacodynamic relationships are crucial in understanding a drug's arrhythmogenic potential. Models assist to quantitatively relate parent and metabolite concentrations to adverse electrocardiographic effects, including an apparent delay between effect and circulating parent species concentration. Here, we used an effect compartment model to investigate PR and QRS prolongation previously observed in preclinical studies with the NK1–NK3 antagonist R1551. **Method:** Using a cross-over design, beagle dogs received a single oral dose of R1551 (0–100 mg/kg), and cynomolgus monkeys received oral doses of 0–30 mg/kg once daily for 5 days. PR and QRS intervals and heart rate were measured by telemetry, for ≥24 h after each dose in dogs, and on treatment days 1, 3, and 5 in monkeys. Pharmacokinetic parameters were estimated by fitting a two-compartment model to the data. For each species, a linear effect compartment model was used to relate PR and QRS intervals to effect compartment concentrations. **Results:** The effect compartment model provided a good fit to the observed data for both ECG parameters in dogs, and for QRS interval in monkeys ($PR_0 = 95.1$ ms ± 2.74 and 64.9 ms ± 1.46, $QRS_0 = 42.5$ ms ± 1.24 and 46.5 ms ± 1.11 in dog and monkey, respectively). For PR interval in monkeys, the fit was improved by adding a placebo effect compartment to the linear model. R1551 effects on intervals in dogs suggested the presence of responder and non-responder sub-populations. In monkeys, only the highest R1551 dose prolonged PR intervals. Effect slope factors were similar between dog and monkey for both intervals ($S_{PR} = 0.00930$ ms $mg^{-1} kg^{-1} l^{-1} \pm 0.00133$ in dog and 0.00934 ms $mg^{-1} kg^{-1} l^{-1} \pm 0.00141$ in monkey; $S_{QRS} = 0.00274$ ms $mg^{-1} kg^{-1} l^{-1} \pm 0.00101$ in dog and 0.00200 ms $mg^{-1} kg^{-1} l^{-1} \pm 0.000552$ in monkey). **Discussion:** Our results indicate a non-linear relationship between R1551 plasma kinetics and electrophysiological effects and suggest that the parent was not responsible for the observed ECG effects. In addition, the population based approach allows exploitation of sparse PK data in dog and monkey, analysis throughout the complete effect time course, and assessment of inter-individual variability, all in a single comprehensive model.

1. Introduction

The arrhythmogenic potential of investigational drugs not intended for cardiovascular indications is one of the major reasons for drug withdrawal (Fung, Thornton, Mybeck, Wu, Hornbuckle and Muniz, 2001). One particular adverse effect (prolongation of the cardiac repolarization phase of the cardiac action potential, which can lead to fatal *torsades de pointes* arrhythmia) even resulted in the formulation of regulatory guidelines (EMEA, 2005).

The most commonly used methods to assess cardiac toxicity are *in vitro* cardiac electrophysiology studies (mainly on the hERG [human ether-a-go-go-related gene] channel, assessing delayed cardiac repolarization), and *in vivo* electrocardiographic (ECG) evaluation (Hammond et al., 2001) focusing as per ICH S7B guideline on repolarization delays. However, investigation of ECG effects in relevant non-rodent species also provides information on a drug's potential to interact with depolarizing cardiac ion channels. *In vivo*, inhibition of ionic currents during depolarization can disrupt atrioventricular (AV) conductivity (seen as PR-interval prolongation), or intra-ventricular conductivity (seen as widening of the QRS complex). PR-interval prolongation can cause second-degree AV blocks (Barold, 2002), while QRS widening can cause life-threatening ventricular arrhythmias (Boukens, Christoffels, Coronel, & Moorman, 2009). In the past, simple concentration/effect analysis has yielded a better understanding of the relationship of ionic currents in the heart

* Corresponding author. F. Hoffmann-La Roche Ltd, Pharmaceuticals Division, CH-4070 Basel, Switzerland. Tel.: +41 61 688 2568; fax: +41 61 688 3050.
E-mail address: alexander.breidenbach@roche.com (A. Breidenbach).

1056-8719/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.vascn.2010.08.003

and their effects on PR and QRS intervals (Hanafy, Dagenais, Dryden, & Jamali, 2008; Jamali & Mayo, 1999; Sattari, Dryden, Eliot, & Jamali, 2003). To fully comprehend these safety concerns, the potential of a substance to cause such conduction delays needs to be related to the concentration of this substance and if present, of its metabolites *in vivo* by pharmacokinetic–pharmacodynamic (PK–PD) modelling (EMEA, 2005). In literature, drug-induced QT interval prolongation has been reported for numerous compounds (Cavero, Mestre, Guillon, & Crumb, 2000; Fermini & Fossa, 2003; Hanada et al., 1999; Jonker et al., 2005; Le Coz, Funck-Brentano, Morell, Ghadanfar, & Jaillon, 1995; Minematsu, Ohtani, Sato, & Iga, 1999; Ohtani et al., 2000; Ollerstam et al., 2006). Recently, Ollerstam et al. (2006) used dofetilide, a pure, potent hERG blocker (and Vaughan Williams class III antiarrhythmic drug) to demonstrate the benefits of complete characterization of the concentration–effect time course in dogs for cardiac safety assessment. In humans, the relationship between plasma exposure and QT interval prolongation has been shown to display anti-clockwise hysteresis (Le Coz et al., 1995; Minematsu et al., 1999; Rasmussen et al., 1992); this phenomenon was described in dog for dofetilide concentration–time data related to QT interval prolongation (Ollerstam et al., 2006). Similarity between dog and human ERG channels has been observed by Wang et al. (2003). The dog is a widely used model to assess cardiovascular safety and results are considered to be relevant for human. Wang et al. (2003) still suggest comparing and relating ECGs obtained in dogs to parameters from hERG assays and in human ECG so as to enable prediction of the risk of QT prolongation in human.

When a shift between plasma concentration and effect occurs, such effect is still developing at the time when the concentration of the drug is measured. If a delay in time is not taken into account applying appropriate modelling (for example if assessment of effect is based at Cmax), it potentially underestimates any cardiac liability and might result in a false prediction of safety margin (Ollerstam et al., 2006). Therefore, it is of utmost importance to employ appropriate PK/PD modelling for safety assessment of an investigational compound.

R1551 is a dual NK1–NK3 antagonist previously under development for the treatment of schizophrenia. The hypothesized pharmacology of this class of compounds has a generally beneficial effect on positive and negative symptoms of schizophrenia by modulating the dopaminergic, serotoninergic and noradrenergic systems (Spooren, Riemer, & Meltzer, 2005). During *in vivo* safety assessments of R1551, delays in AV conduction and ventricular depolarization were observed in two non-rodent species (dog and monkey). Telemetry studies were conducted in dogs, and subsequently also in monkeys to assess cardiac safety. In dogs, statistically significant PR-interval prolongation and QRS-complex widening were observed, starting at an oral dose of 30 mg/kg. Isolated sporadic second-degree Wenckebach AV blocks were seen in dogs at higher doses. In monkeys, R1551 also prolonged PR and QRS at the same dose, but no second-degree or higher AV block was observed. Neither assays of receptor or ion channel binding (>100 targets) nor functional ion channel tests (assessing hERG current in transfected CHO cells, and fast sodium and L-type calcium currents in isolated human cardiomyocytes) with the parent compound could explain the *in vivo* findings. Furthermore, a high inter-individual variability but no obvious direct relationship between plasma concentration and ECG effect was observed. As any delay between plasma exposure and unwanted side effects is a particular concern in clinical trial design due to uncertainties in calculating safety margins and hence in defining a safe starting dose, we decided to assess the relationship between R1551 exposure and ECG changes (prolongation of PR and QRS intervals) in monkeys and dogs using a pharmacokinetic–pharmacodynamic approach. The objective was to get insights into possible causes for such changes in order to contribute to the preclinical safety assessment and enable informed decision making whether to move the compound into clinical development.

2. Methods

2.1. Animals

Animal investigations conducted in the United States conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). The monkey telemetry study conducted at the Centre de Recherche Biologique (CERB), Baugy, France, was approved by the CERB Internal Ethics Committee. All beagle dog and cynomolgus monkey pharmacokinetic studies were conducted in Switzerland in accordance with the local animal welfare regulations.

2.1.1. PK studies

We conducted intravenous (i.v.) and oral dosing PK studies both in beagle dogs (Marshall Bio Resource, North Rose, USA) and in cynomolgus monkeys (Bioprim, Baziège, France [1 monkey]; Centre de Primatologie ULP, Niederhausbergen, France [6 monkeys]; Novartis International AG, Basel, Switzerland [2 monkeys]). Two fasted beagles (9.9 and 10.9 kg) were used in the i.v. single-dose PK study, administered R1551 by gavage. Two fasted male cynomolgus monkeys (5.8 and 11.6 kg) were used in the i.v. single-dose PK study and eight fed male cynomolgus monkeys (7.2–10.8 kg) were treated orally by gavage in the oral single-dose PK study.

2.1.2. Telemetry studies

We conducted ECG telemetry with sparse PK sampling in beagles (Marshall Bio Resource, North Rose, USA) and cynomolgus monkeys (Noveprim Ltd, Port-Louis, Mauritius, and Siconbrec Inc., Makati, Philippines). Four female and four male conscious radiotelemetry-implanted beagle dogs (6.7–11.1 kg) were treated orally by gavage under fed conditions. In the monkey telemetry study, three female and four male fed cynomolgus monkeys (3.4–6.1 kg) were treated orally by gavage. Except for the high dose (3 females and 2 males) 3 female and 3 male monkeys were included.

2.2. Doses and formulations

2.2.1. PK studies

For i.v. dosing in dogs, R1551 was administered as a solution in mixed micelles consisting of glycocholate:lecithin (ratio 1:1) at a volume of 0.5 ml/kg, corresponding to a R1551 dose of 1 mg/kg. For oral dosing in dogs, the compound was administered as an emulsion in Capryol®:octenyl succinic anhydride (OSA) (26%:9%:65%) at a volume of 2 ml/kg, corresponding to a dose of 30 mg/kg.

For i.v. dosing in monkeys, R1551 was administered as an aqueous solution in mixed micelles of glycocholate (50%:50%) at a volume of 0.5 ml/kg, corresponding to a dose of 0.75 mg/kg. For oral dosing, all monkeys received a volume of 3 ml/kg, corresponding to a dose of 10 mg/kg. As the main purpose of the monkey study was formulation screening, four formulations were administered (two monkeys per formulation, data on file). Drug exposure from the four formulations was found to be similar, so data from all eight animals were pooled for the population model.

2.2.2. Telemetry studies

For the telemetry studies in the dog and monkey, R1551 was administered in a Gelucire (44%:14%): Capryol (60%:40%) formulation, at four doses, using a cross-over design. All dogs received a single dose of R1551 given as 0, 2, 6 and 20 mg/ml (0, 10, 30 and 100 mg/kg), each separated by a wash-out period of ≥3 days. In monkeys, a similar cross-over design was used, all animals receiving R1551 once daily for 5 days (5 mg/ml). Volumes given equated to R1551 doses of 0, 3, 10 and 30 mg/kg, each separated by a wash-out period of 9 days.