European Journal of Pharmaceutical Sciences 74 (2015) 86–94

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Semi-physiologic model validation and bioequivalence trials simulation to select the best analyte for acetylsalicylic acid

Ana Cuesta-Gragera [a], Carmen Navarro-Fontestad [a], Victor Mangas-Sanjuan [b], Isabel González-Álvarez [b], Alfredo García-Arieta [c,1], Iñaki F. Trocóniz [d], Vicente G. Casabó [a,2], Marival Bermejo [b,*]

[a] Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Valencia, Av. Vicente Andrés Estellés s/n, 46100 Burjassot, Valencia, Spain
[b] Department of Engineering, Pharmacy Section, Miguel Hernández University, Carretera Alicante Valencia km 87, 03550 San Juan de Alicante, Alicante, Spain
[c] Pharmacokinetics Service, Division of Pharmacology and Clinical Evaluation, Department of Human Use Medicines, Spanish Agency for Medicines and Health Care Products (AEMPS), Campezo 1, 28022 Madrid, Spain
[d] Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Irunlarrea 1, 31008 Pamplona, Navarra, Spain

ARTICLE INFO

Article history:
Received 21 February 2015
Accepted 5 April 2015
Available online 11 April 2015

Keywords:
Acetylsalicylic acid
Bioequivalence
Simulation
First-pass metabolism
Analyte

ABSTRACT

The objective of this paper is to apply a previously developed semi-physiologic pharmacokinetic model implemented in NONMEM to simulate bioequivalence trials (BE) of acetyl salicylic acid (ASA) in order to validate the model performance against ASA human experimental data. ASA is a drug with first-pass hepatic and intestinal metabolism following Michaelis–Menten kinetics that leads to the formation of two main metabolites in two generations (first and second generation metabolites). The first aim was to adapt the semi-physiological model for ASA in NOMMEN using ASA pharmacokinetic parameters from literature, showing its sequential metabolism. The second aim was to validate this model by comparing the results obtained in NONMEM simulations with published experimental data at a dose of 1000 mg. The validated model was used to simulate bioequivalence trials at 3 dose schemes (100, 1000 and 3000 mg) and with 6 test formulations with decreasing *in vivo* dissolution rate constants versus the reference formulation (k_D 8–0.25 h^{-1}). Finally, the third aim was to determine which analyte (parent drug, first generation or second generation metabolite) was more sensitive to changes in formulation performance.

The validation results showed that the concentration–time curves obtained with the simulations reproduced closely the published experimental data, confirming model performance. The parent drug (ASA) was the analyte that showed to be more sensitive to the decrease in pharmaceutical quality, with the highest decrease in Cmax and AUC ratio between test and reference formulations.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

According with EMA and FDA guidelines (EMA, 2010; FDA, 2001, 2003), the evaluation of bioequivalence should be based on the parent drug concentrations, because concentration–time profile of the parent drug is more sensitive to changes in formulation performance than that of a metabolite (EMA, 2010; FDA, 2003). However, EMA and FDA have different recommendations related to the situations in which measurement of a metabolite can be accepted. In case of inactive pro-drugs with low plasma concentrations and quickly eliminated, EMA considers acceptable to demonstrate bioequivalence for the main active metabolite without measurement of parent compound. The use of a metabolite as a surrogate for an active parent compound can only be considered in exceptional cases, due to the sensitivity of the analytical method (EMA, 2010). FDA may prefer the measurement of a metabolite when parent drug levels are too low to allow reliable analytical measurement. When a metabolite is formed as a result of a presystemic metabolism and it contributes meaningfully to safety and/or efficacy, FDA recommends both the metabolite and the parent compound to be measured (FDA, 2003).

Due to these differences in regulatory recommendations it is interesting to know the situations in which measuring the metabolite would give additional or better information than the parent compound concentrations. This question was studied using different pharmacokinetic models (Chen and Jackson, 1991, 1995, 1987, 1989, 2000; el-Tahtawy et al., 1995, 1998; Rosenbaum, 1998). Our

* Corresponding author at: Facultad de Farmacia, UMH, Carretera Alicante-Valencia, km 87, 03550 San Juan de Alicante, Alicante, Spain. Tel.: +34 965919217; fax: +34 963544911.

E-mail address: mbermejo@goumh.umh.es (M. Bermejo).

[1] This article reflects the author's personal opinion and not necessarily the policy or recommendations of the AEMPS.

[2] Deceased, July 7, 2013.

http://dx.doi.org/10.1016/j.ejps.2015.04.002
0928-0987/© 2015 Elsevier B.V. All rights reserved.

investigation group developed some semiphysiological models (Fernandez-Teruel et al., 2009a,b; Navarro-Fontestad et al., 2010) to study this issue, concluding that the parent drug was the most sensitive analyte to the differences in pharmaceutical performance.

Following the previous works, the present study shows a semiphysiological model for a sequential metabolism, with two main metabolites created in two generations. This model was used to represent the acetylsalicylic acid (ASA) metabolism. The aims of this study were (1) to present a semiphysiological model showing a sequential metabolism, (2) to validate the model comparing plasma concentrations and pharmacokinetic parameters with experimental ASA and salicylic acid (SA) data and (3) to determine which analyte (parent drug, first generation metabolite or second generation metabolite) was more sensitive to changes in the formulation performance when ASA bioequivalence trials were simulated.

2. Material and methods

2.1. Description of the New Proposed Model

ASA is rapidly absorbed in the intestinal tract by passive diffusion and suffers hepatic and intestinal first-pass metabolism. Once ASA reaches the systemic compartment, it is rapidly distributed in one compartment and it is eliminated mainly by metabolism in gut and liver, although a small fraction is eliminated unchanged by renal excretion. Its main and first generation metabolite is SA. Both ASA and SA are bound to serum proteins, primarily albumin, being the normal protein binding value of SA at therapeutic concentrations 80–90%. The first generation metabolite SA is eliminated by five ways: unchanged renal excretion and four metabolic pathways. SA is conjugated with glycine to form salicyluric acid (SU), it is conjugated with glucuronide to form salicylphenolicglucuronide (SPG) and salicylacylglucuronide (SAG), and it is oxydated to gentisic acid (GA). The elimination pathways of SA to SU and SPG follow Michaelis–Menten kinetics, being the formation of SU the most important one. The other metabolic pathways follow linear kinetics (Bayer Hispania, 2013; Navarro et al., 2011; Needs and Brooks, 1985)

The semiphysiological model used (Fig. 1) represents ASA pharmacokinetics and it considers the following compartments: ASA (parent compound) in solid form in lumen, solved ASA in lumen, ASA in enterocytes, ASA in liver, ASA in central compartment, SA (first generation metabolite) in central compartment, SA in enterocyte, SA in liver and SU (second generation metabolite) in central compartment. SU and SPG have been grouped together as only one metabolite (SU), formed by Michaelis–Menten kinetics. The linear pathways of elimination of SA are the linear metabolism to form SAG and GA and the SA renal excretion, and they have been grouped together as only one linear elimination process.

The dose is orally administered as a solid form in a single dose scheme. The solid form is first solved in lumen. Once solved, the ASA in lumen is absorbed into enterocytes. It has been established a limited time to allow the absorption process: the operative absorption time (OAT), considering the intestinal transit time (Mudie et al., 2010). After drug absorption, ASA is partially metabolized in the enterocytes (intestinal first-pass metabolism) and the non metabolized fraction reaches the liver, where it is partially metabolized (hepatic first-pass metabolism). The non metabolized fraction of ASA reaches the systemic circulation, where it is rapidly distributed in one compartment. The ASA is eliminated by intestinal and hepatic metabolism and in a small fraction by renal excretion. The SA is formed as result of ASA metabolism, it is distributed in one compartment and it is eliminated by renal excretion and by intestinal and hepatic metabolism producing SU. Finally, the SU is distributed in one compartment and it is eliminated unchanged by renal excretion.

The equations representing the amount change of ASA, SA and SU over the time in each compartment are:

– ASA amount change rate in the solid form depends on ASA dissolution in lumen from the solid form:

$$\frac{dQ_{SF}}{dt} = -k_D \cdot Q_{SF} \cdot \left(1 - \frac{Q_L}{S}\right) \tag{1}$$

where k_D is the *in vivo* dissolution first order rate constant of ASA and Q_{SF} is the amount of ASA in the solid pharmaceutical formulation, Q_L is the amount of solved drug in lumen and S is the maximum amount of drug that can be solubilized.

Taking into account that the solubility of ASA at 37 °C is high (10 g/L) (Merck and Co., 2006) and that ASA is rapidly absorbed (Bayer Hispania, 2013), it is assumed that S is much higher than Q_L at any time (at standard doses of ASA), so the previous equation would be equivalent to the following one:

$$\frac{dQ_{SF}}{dt} = -k_D \cdot Q_{SF} \tag{2}$$

– ASA amount change rate in the lumen depends on the dissolution from the solid form and the absorption into the enterocytes:

$$\frac{dQ_L}{dt} = k_D \cdot Q_{SF} - k_{A_{ap}} \cdot Q_L \tag{3}$$

where k_{Aap} is the apparent first order absorption rate constant of ASA.

The ASA absorption is only possible during a fixed period of time, the operative absorption time (OAT). The apparent absorption first order rate constant is defined by the following equation:

$$k_{A_{ap}} = k_A \cdot \left(1 - \frac{t^h}{OAT^h + t^h}\right) \tag{4}$$

where k_A is the *true* absorption first order rate constant, t is the time from administration and h is the shape parameter (Hill coefficient) that makes the apparent absorption rate constant k_{Aap} being close to k_A when time is less than OAT, and being zero when time exceeds the OAT. As shown in Table 1, an OAT of 3.5 h was chosen considering the transit through the small intestine (Mudie et al., 2010).

– ASA amount change rate in the enterocytes (Q_E) depends on the absorption process, the ASA coming from the central compartment and the exit to the portal vein in two fractions: as SA once ASA is metabolized and as unchanged ASA. ASA is metabolized with an extraction rate to form SA, and the fraction escaping the enteric metabolism ($1-E_E$) goes to the liver as unchanged ASA:

$$\frac{dQ_E}{dt} = k_{A_{ap}} \cdot Q_L + \phi_E \cdot C_C - \phi_E \cdot E_E \cdot C_E - (1 - E_E) \cdot \phi_E \cdot C_E \tag{5}$$

where ϕ_E is the enteric blood flow, C_C is the ASA concentration in the central compartment, E_E is the enteric extraction rate and C_E is the ASA concentration in the enterocytes.

– ASA amount change rate in the liver depends on the ASA coming from the portal vein (it is the fraction of ASA escaping the enteric metabolism), the ASA coming from the central compartment, and the exit to the central compartment in two fractions: as SA once ASA is metabolized and as unchanged ASA. ASA is metabolized with a extraction rate to form SA and the fraction escaping the hepatic metabolism goes to the central compartment as unchanged ASA:

$$\frac{dQ_H}{dt} = (1 - E_E) \cdot \phi_E \cdot C_E + \phi_H \cdot C_C - (\phi_H + \phi_E) \cdot E_H \cdot C_H - (\phi_H + \phi_E) \cdot (1 - E_H) \cdot C_H \tag{6}$$

where ϕ_H is the hepatic blood flow, E_H is the hepatic extraction rate and C_H is the ASA concentration in the liver.

Download English Version:

https://daneshyari.com/en/article/5809771

Download Persian Version:

https://daneshyari.com/article/5809771

Daneshyari.com