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Validation of a semi-physiological model for caffeine in healthy subjects and cirrhotic patients

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ABSTRACT

The objective of this paper was to validate a previously developed semi physiological model to simulate bioequivalence trials of drug products. The aim of the model was to ascertain whether the measurement of the metabolite concentration–time profiles would provide any additional information in bioequivalence studies (Fernandez-Teruel et al., 2009a,b; Navarro-Fontestad et al., 2010).

The semi-physiological model implemented in NONMEM VI was used to simulate caffeine and its main metabolite plasma levels using caffeine parameters from bibliography. Data from 3 bioequivalence studies in healthy subjects at 3 different doses (100, 175 and 400 mg of caffeine) and one study in cirrhotic patients (200 or 250 mg) were used. The first aim was to adapt the previous semi-physiological model for caffeine, showing the hepatic metabolism with one main metabolite, paraxanthine. The second aim was to validate the model by comparison of the simulated plasma levels of parent drug and metabolite to the experimental data.

The simulations have shown that the proposed semi-physiological model was able to reproduce adequately the pharmacokinetic behavior of caffeine and paraxanthine in both healthy subjects and cirrhotic patients at all the assayed doses. Therefore, the model could be used to simulate plasma concentrations *vs.* time of drugs with the same pharmacokinetic scheme as caffeine, as long as their population parameters are known, and it could be useful for bioequivalence trial simulation of drugs that undergo hepatic metabolism with a single main metabolite.

1. Introduction

Different population semi-physiological models have been employed in previous studies (Fernandez-Teruel et al., 2009a,b; Navarro-Fontestad et al., 2010) to determine whether the measurement of the concentration–time profiles of metabolites would provide any relevant information on the biopharmaceutical performance of the products under comparison in bioequivalence studies, since FDA and EMA bioequivalence guidelines differed with regard to metabolite requirements (EMA, 2010; FDA, 2003). In principle, the evaluation of bioequivalence should be based on parent drug concentrations because the concentration–time profile of the parent drug is more sensitive to changes in the biopharmaceutical performance than that of a metabolite. However in certain cases the measurement of the metabolites is also necessary (e.g. for the FDA when the metabolite is active and it is formed pre-systemically, and for the EMA it was necessary when the pharmacokinetics is non-linear). In other cases, where the parent drug concentrations are difficult to measure due to its rapid elimination or instability, the metabolite is used as a substitute of the

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parent drug. Therefore in these cases, it is necessary to verify that the metabolite is sensitive to changes in the biopharmaceutical performance and able to discriminate between bioequivalence and non-bioequivalent products based on the parent drug exposure, especially if activity resides in the parent drug.

In order to explore parent drug and metabolite suitability for bioequivalence comparisons several semi-physiological models were designed and implemented in NONMEM to perform bioequivalence trials simulations and to establish the more sensitive analyte to detect drug product differences (Fernandez-Teruel et al., 2009a,b; Navarro-Fontestad et al., 2010).

The next step was to validate the proposed semi-physiological model, comparing the results of NONMEM simulations with published *in vivo* results in humans. The present paper shows the application of the previously designed models to caffeine, a well-known substance with hepatic metabolism and one main metabolite. The aims of this study were (1) to adapt the semi-physiological model (with hepatic metabolism and one main metabolite) implemented in NONMEM to caffeine and (2) to validate the model by comparing the simulated plasma concentrations of caffeine and its main metabolite with experimental caffeine data in healthy subjects and cirrhotic patients.

2. Material and methods

2.1. Caffeine pharmacokinetics

Caffeine gastrointestinal absorption is rapid and complete. In man, 99% of the administered dose was absorbed in 45 min, mainly from the small intestine but also 20% from the stomach (Fredholm, 2010). It is widely distributed in the total body water and it is eliminated by apparent first-order kinetics. There is minimal or no first-pass metabolism (Fredholm, 2010; McLean and Graham, 2002).

In vivo and *in vitro* studies have demonstrated that caffeine is metabolized mainly via N-3 demethylation to paraxanthine (Begas et al., 2007). Caffeine is metabolized in the liver by the cytochrome P-450 enzyme system. In human adults, more than 80% of caffeine is biotransformed to paraxanthine (Fredholm, 2010; McLean and Graham, 2002). Theobromine, theophylline and 1,3,7-trimethyluric acid are other metabolites (Kot and Daniel, 2008), being the kidney the main organ responsible for their elimination (Fredholm, 2010; McLean and Graham, 2002).

2.2. Description of the proposed model

A semi-physiological model (Fig. 1) was used to represent caffeine pharmacokinetics, with the following compartments: caffeine dissolved in lumen, caffeine in enterocytes, caffeine in liver, caffeine in the central compartment and paraxanthine (main caffeine metabolite) in the central compartment. Other metabolites were not included in the model, but 80% paraxanthine formation was considered.

The dose was administered as an oral solution of caffeine in a single dose scheme. Caffeine in the lumen is absorbed into enterocytes within a fixed operative absorption time (OAT) (Mudie et al., 2010). Once absorbed, caffeine reaches the systemic circulation after passing through the liver. Caffeine is rapidly distributed in one compartment and it is eliminated by hepatic metabolism. Paraxanthine is formed in the liver and it is distributed in one compartment and eliminated by renal excretion.

The equations that represent the amount change of caffeine and paraxanthine over time in each compartment are:

- The rate of change of caffeine amount in lumen depends on the absorption into the enterocytes:

$$\frac{dQ}{dt} = -k_{Aap} \cdot Q_L \tag{1}$$

where k_{Aap} is the apparent first order absorption rate constant of caffeine and Q_L is the drug amount dissolved in lumen.
Caffeine absorption takes place only during a fixed time (Mudie et al., 2010), called operative absorption time (OAT). The apparent absorption rate constant is defined by the following equation:

$$k_{Aap} = k_A \cdot \left(1 - \frac{t^h}{OAT^h + t^h}\right) \tag{2}$$

where k_A is the *true* absorption rate constant, t is the time after administration and h is the Hill constant, the shape parameter that makes the apparent absorption rat constant, k_{Aap} being close to k_A when time is less than OAT, and being zero when time exceeds the OAT.

- The rate of change of the amount of caffeine in the enterocytes (QE) depends on the absorption process, the caffeine coming from the central compartment, and the caffeine exit to the portal vein:

$$\frac{dQ}{dt} = k_{Aap} \cdot Q_L + \phi_E \cdot C_C - \phi_E \cdot C_E \tag{3}$$

where ϕ_E is the enteric blood flow, C_C is the caffeine concentration in the central compartment and C_E is the caffeine concentration in the enterocytes.

- The time course of the amount of caffeine in the liver (Q_H) depends on the input of caffeine coming from the portal vein and central compartment, and the exit to the central compartment in two fractions: as paraxanthine after caffeine metabolism and as unchanged caffeine. Caffeine is metabolized to form paraxanthine and the caffeine fraction escaping the hepatic metabolism returns to the central compartment as unchanged caffeine:

$$\frac{dQ}{dt} = \phi_E \cdot C_E + \phi_H \cdot C_C - (\phi_H + \phi_E) \cdot E_H \cdot C_H - (\phi_H + \phi_E) \cdot (1 - E_H) \cdot C_H \tag{4}$$

where ϕ_H is the hepatic blood flow, E_H is the hepatic extraction ratio and C_H corresponds to the caffeine concentration in the liver.

- Similarly, the rate of change of the caffeine amount in the central compartment (Q_C) is governed by the fraction of caffeine escaping metabolism in liver (which reaches the systemic circulation with a blood flow that sums gut and liver blood flows) and the exit of caffeine to enterocytes and liver:

$$\frac{dQ_C}{dt} = (1 - E_H) \cdot (\phi_H + \phi_E) \cdot C_H - \phi_E \cdot C_C - \phi_H \cdot C_C \tag{5}$$

- The rate of change of the amount of the metabolite paraxanthine in the central compartment (Q_{CPx}) depends on the rate of paraxanthine formation as a result of the caffeine metabolism in liver (considering that the 80% of the caffeine metabolism results in paraxanthine (Fredholm, 2010; McLean and Graham, 2002)) and the paraxanthine elimination rate in urine:

$$\frac{dQ_{CPx}}{dt} = 0.8 \cdot E_H \cdot (\phi_H + \phi_E) \cdot C_H - k_{elPx} \cdot Q_{cPx} \tag{6}$$

where C_{CPx} is the paraxanthine concentration in the central compartment, k_{elPx} is the paraxanthine first order elimination rate constant of elimination.