BIOEQUIVALENCE TRIALS SIMULATION TO SELECT THE BEST ANALYTE FOR DRUGS WITH PRESYSTEMIC INTESTINAL AND HEPATIC METABOLISM.

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INTRODUCTION:

The analyte (parent drug or metabolite) to be evaluated in bioequivalence trials is still today a controversial issue, with different solutions in EMEA and FDA guidance:

- FDA: measurement of metabolite(s) is(are) required in addition to the parent drug when metabolite(s) is(are) formed as a result of *pre-systemic metabolism.*
- EMEA: bioequivalence determinations based on metabolites in addittion to the parent drugs are required when the *pharmacokinetic system is non-linear*

The objective of this work is to use computer simulation approach to solve gaps in regulatory guidances regarding bioavailability (BA) and bioequivalence assessment (BE), especially in drugs with pre-systemic intestinal metabolism with efflux transporter from enterocyte to lumen, in addition to the previous model (1, 2). Simulations about class I drugs undergoing saturable and non saturable metabolic clearance were performed.

METHODS:

A semi-physiological model was used, including systemic plasma compartment (C4), lumen (C1), gut (C2), liver (C3), and metabolite (C5). The dose is orally administered, as a solid form (C6), so different processes are considered in lumen: dissolution (E1) limited by the solubility: Kd·A6·(S-A1) where AX is the amount in the compartment X and Kd the dissolution rate. And a luminal degradation and absorption (E4), in this study the luminal degradation was fixed to zero. Moreover the intestinal transit is considered as an absorption time (AT) fixed to 7 h. After drug absorption, it is partially sent to lumen by the efflux transport (E2) and partially metabolized at gut (E3), liver (E5) and get to systemic compartment. This metabolism in gut and liver can be linear (Km=10000) or non-linear (Km=1). In the next step, the drug is rapidly distributed in one compartment (C4), so the elimination of parent drug is renal (E6), intestinal (E3) and hepatic (E5), while the metabolite is eliminated renally (E7) (Figure 1).

Data were simulated using NONMEM VI (parameters are shown in Table 1) under PSN 2.3.1 using a grid system with SunGrid 6.2 and gfortran 4.3.2 x64 running under OpenSuse 11.1 x64. Sixteen different drug types were explored by combining high and low intrinsic clearance in gut (Cl_{gut}=10 and 300 L/h), high and low intrinsic clearance in liver (Cl_{liver}=10 and 300 L/h) and saturable and non-saturable conditions. Drugs were simulated for Class I type based on BCS with high solubility and high permeability.

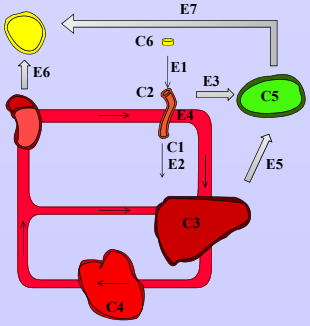

Figure 1: Scheme of semi-physiological model used in simulations, where 'C' represents the compartments and 'E' the equations present in the model.

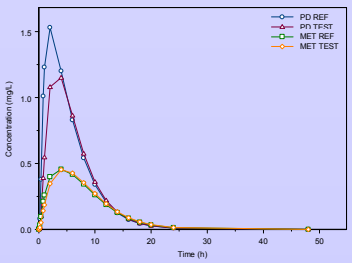

Figure 2: Plasma concentrations of reference and test in scenario Cl_{gut}=10 L/h, Cl_{liver}=10 L/h, Km=1 mg/L and kdr= 0.25.

Fixed Parameters	Values	Parameters defining scenario	Values
Absorption time (h)	7	Intrinsic hepatic clearance (L/h)	10 300
Degradation rate in lumen (h^{-1})	0		
Dissolution rate for reference form (h^{-1})	4	Km intrinsic hepatic clearance (mg/L)	1 10 000
Absorption rate (h^{-1})	2		
Vm efflux transport (mg/L·h)	20	Intrinsic gut clearance (L/h)	10 300
Km efflux transport (mg/L)	2		
Renal clearance of parent drug (L/h)	0.05	Km intrinsic gut clearance (mg/L)	1 10 000
Hepatic flow (L/h)	18		
Gut flow (L/h)	72	Dissolution rate for test form (h^{-1})	4 2 1 0.5 0.25 0.12
Hepatic clearance of metabolite (L/h)	20		
Hepatic Volume (L)	1		
Gut Volume (L)	1		
Central compartment volume (L)	40		
Metabolite compartment volume (L)	40		
Maximum soluble amount (mg)	1000		

Table 1: Parameters used in simulations

Moreover 6 different scenarios were studied changing the dissolution constant (Kd) for the test form ranged from 0.03 to 1 relative (Kd rel) to reference (Kd=4 h^{-1}). Each drug type/scenario was explored for parent drug and metabolite after single dose. Afterward, AUC and Cmax were calculated to assess the ratios between reference and test.

The procedures for control files building and data extraction were carried out by automated procedures based on Visual Basic for Excel and SPSS.

RESULTS:

Parent drug and metabolite simulated plasmatic concentrations in one scenario are shown as example in Figure 2. The relative absorbed fraction (Fabs rel), Cmax ratio, AUC ratio, percentage of success in BE studies using AUC ratio and Cmax ratio for parent drug and metabolite between reference and test drug were obtained in each scenario, as shown in Figure 3. In each plot is represented the true AUC or Cmax ratio and the rate of success in bioequivalence studies using AUC and Cmax ratios versus the Fabs rel and the relative Kd of the test formulation. Each figure allows to asses how the lack of pharmaceutical quality of the test product (due to the progressive reduction of its dissolution rate) is reflected in the average Cmax and AUC ratios for both analytes; parent drug (PD) or metabolite (MET).

CONCLUSIONS:

Despite FDA indication, when the pre-systemic metabolism occurs, metabolite does not show higher sensitivity than PD to changes in the pharmaceutical performance. This model has been evaluated for high solubility and high permeability drugs, and in this class I dugs, the PD presents the most sensitive moiety to detect changes in the dissolution constant in single dose studies when drug is metabolized in gut and liver, and moreover, an efflux transport in gut wall exists. This fact is more obvious when intrinsic clearance in liver and gut are high and metabolism becomes saturated, so despite EMEA indication, metabolite data are not necessary when system is non-linear.

Summarizing, when the present model is applicable, the PD is always the most sensitive moiety when there are efflux transport in the absorption compartment and intestinal and hepatic pre-systemic metabolism.

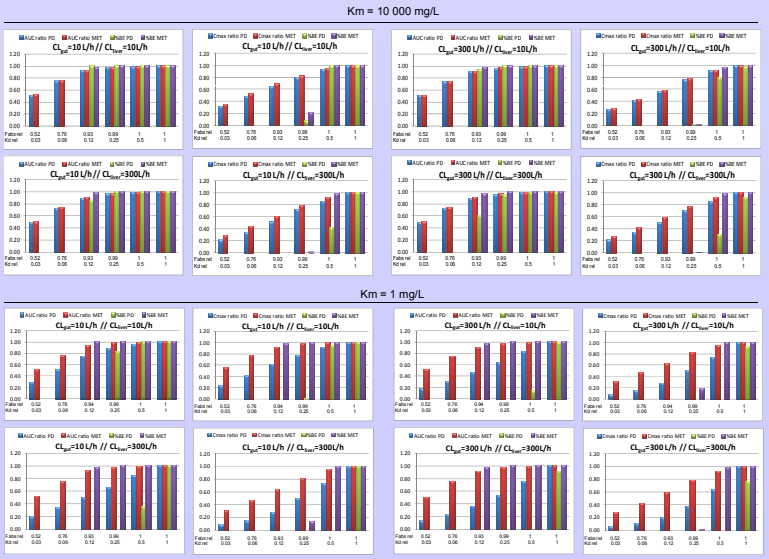

Figure 3: True AUC and Cmax ratios and % success BE studies (y axis) obtained for each drug type and scenario (x axis).

REFERENCES:

(1) Fernandez-Teruel, C., Nalda Molina, R., Gonzalez-Alvarez, I., Navarro-Fontestad, C., Garcia-Arieta, A., Casabo, V.G. and Bermejo, M. (2009) Computer simulations of bioequivalence trials: selection of design and analyte in BCS drugs with first-pass hepatic metabolism: linear kinetics (I), *Eur J Pharm Sci*, **36**, 137-146.

(2) Fernandez-Teruel, C., Gonzalez-Alvarez, I., Navarro-Fontestad, C., Garcia-Arieta, A., Bermejo, M. and Casabo, V.G. (2009) Computer simulations of bioequivalence trials: selection of design and analyte in BCS drugs with first-pass hepatic metabolism: Part II. Non-linear kinetics, *Eur J Pharm Sci*, **36**, 147-156.

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