BIOEQUIVALENCE TRIALS SIMULATION: SELECTING THE MOST SENSITIVE ANALYTE FOR DRUGS WITH TWO PRESYSTEMIC METABOLIC PATHWAYS.

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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) (1, 2), especially in drugs with pre-systemic intestinal and hepatic metabolism, with two metabolic pathways in each one. Simulations about class I drugs undergoing saturable and non saturable metabolic clearance were performed.

METHODS:

A semi-physiological model was used, including systemic and peripheral compartments (C4 and C7), lumen (C1), gut (C2), liver (C3), principal (C5) and secondary (C6) metabolites. The dose is orally administered, as a solid form (C8), so different processes are considered in lumen: dissolution (E1) limited by the solubility: Kd·A8·(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 metabolized at gut (E3 and E4), liver (E5 and E6), get to systemic compartment and distributes to peripheral compartment (E7). 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 systemic compartment (C4) and slowly distributed in peripheral compartment (C7). The elimination of parent drug is by metabolism in gut (E3 and E4) and liver (E5 and E6), while the metabolites are eliminated renally (E8 and E9) (Figure 1).

Data were simulated using NONMEM VI (parameters are shown in Table 1). Three different scenarios were explored by combining saturable and non-saturable conditions in each metabolic pathway. Drugs were simulated for all four class types based on BCS with high or low solubility and high or low permeability.

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 scenario was explored for parent drug and metabolite after single dose (1000 mg). Afterward, AUC and Cmax were calculated to assess the ratios between reference and test.

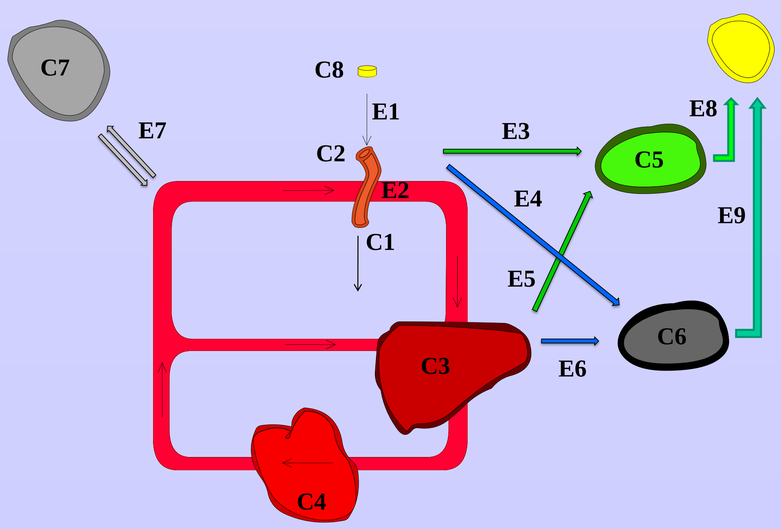

Figure 1: Scheme of semi-physiological model used in simulations, where 'C' represents the compartments and 'E' the equations present in the model.

Fixed Parameters	Values	Parameters defining scenario	Values
Absorption time (h)	7	Principal Intrinsic hepatic clearance (L/h)	300
Degradation rate in lumen (h^{-1})	0	Secondary intrinsic hepatic clearance (L/h)	30
Dissolution rate for reference form (h^{-1})	4	Km intrinsic hepatic clearance (mg/L)	1 10 000
Absorption rate (h^{-1})	2		
Maximum soluble amount (mg)	1000	Principal Intrinsic gut clearance (L/h)	60
Hepatic flow (L/h)	18	Secondary Intrinsic gut clearance (L/h)	6
Gut flow (L/h)	72	Km intrinsic gut clearance (mg/L)	1 10 000
Hepatic Volume (L)	1		
Gut Volume (L)	1	Dissolution rate for test form (h^{-1})	4 2 1 0.5 0.25 0.12
Central compartment volume (L)	40		
Peripheral compartment volume (L)	20		
Principal Metabolite compartment volume (L)	40		
Secondary Metabolite compartment volume (L)	40		
Distribution clearance (L/h)	1		
Renal clearance of metabolites (L/h)	20		

Table 1: Parameters used in simulations

RESULTS:

The relative absorbed fraction (Fabs rel), Cmax and AUC ratios for parent drug and metabolites between reference and test drug were obtained in each scenario, as shown in Figure 2. In each plot is represented the true AUC or Cmax ratios versus the Frel 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 all three analytes: parent drug (PD) , principal metabolite (PM) or secondary metabolite (SM).

When the metabolism is pre-systemic, the metabolites do not show higher sensitivity than the parent drug to detect changes in the pharmaceutical performance, even when pharmacokinetics of the parent drug is non-linear. In case of non-linear metabolism, higher parent drug sensitivity can be found, as compared with non-linear metabolites. Interestingly, in the specific scenario of class I drugs where the principal metabolic pathway saturated, the principal metabolite shows an increase in its AUC as dissolution rate constant decrease. This notable change in dissolution rate could occur in case of a prolonged release formulation developed as a line extension of an immediate release formulation.

CONCLUSIONS:

Despite FDA indication, when the pre-systemic metabolism occurs in gut and liver, neither principal or secondary metabolite show higher sensitivity than PD to changes in the pharmaceutical performance. This fact is more obvious when metabolism in liver and gut becomes saturated, so despite EMEA indication, metabolite data are not necessary when system is non-linear.

The substantial reduction in dissolution rate in the controlled release formulation for class I drugs could lead to a considerable increase of the AUC of the major metabolite thus compromising the bioequivalence in magnitude of both formulations at least for the metabolite. This fact supports the EMA recommendations regarding additional comparative clinical data are necessary for modified release products developed as line extension of an existing marketing authorization.

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

Figure 2: True AUC and Cmax ratios and % success BE studies (y axis) obtained for each drug type and scenario (x axis).

REFERENCES:

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