INTRODUCTION:

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

- FDA: measurement of metabolite(s) is 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 addition 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 guidelines 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), luminal (C1), gut (C2), liver (C3), principal (C5) and secondary (C6) metabolites. The dose is orally administered, as a solid form (C8), with different processes considered in luminal: 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 metabolized at gut (E3 and E4), liver (E5 and E6), and gastric clearance (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 classes 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 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.

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 assess 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 selectivity 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 is 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 selectivity 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.

REFERENCES:


ACKNOWLEDGES: This work is supported by Biosim EU grant: LSHB-CT-2004-005137 and Plan Nacional de I+D+i del Ministerio de Ciencia e Innovación de España (SAF2009-12768).