DRUG CLEARANCE IN OBESE PATIENTS: SHALL WE EXPECT VARIATIONS?

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Introduction

The maintenance dose of a drug is dependent on the clearance. Consequently any biochemical and physiological changes in obese patients that affect physiologic parameters (Fig. 1) may result in altered clearance thereby the maintenance dose, compared to those with normal weight[1]. With global increase in obesity[2], further knowledge to select appropriate maintenance dose in obese patient is essential. However, clinical data in obese subjects are sparse. But incorporating the relevant physiological and biochemical changes into predictive bottom-up pharmacokinetic models, known as 'systems approach'[3], may offer a logical alternative way forward in order to optimise dosage regimen, in this group of people.

Methods

- Step 1: Incorporation of population specific changes relevant to obesity (Fig.1) into Simcyp Simulator™.

- Step 2: Testing performance of the simulator by mimicking eight real clinical studies, available form the literature, where drug clearance in obese and lean groups where compared in alprazolam (APZ) (oral), caffeine (CAF) (oral), chlorzoxazone (CLHR) (oral), cyclosporine (CYC) (oral), midazolam (MDZ) (iv and oral), phenytoin (iv), theophylline (THEO) (oral) and triazolam (TRZ) (oral)[1]. The fold change in the clearance of the drugs in obese compare to lean subjects (CL_{Obese}/CL_{Lean}) ± 90% confidence interval (CI) were predicted and compared to the real values. The performance of the model were investigated by measuring Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV)[4,5].

- Step 3: The tested model was used to optimise the maintenance dose of a drug under development (Drug X), predominantly metabolically cleared by CYP2E1 liver enzyme.

Results

- The overall statistical measures of the performance of the Simulator were; Sensitivity (100%), Specificity (66%), PPV (60%) and NPV (100%); (Fig 2).

- Simulations of Drug X showed that clearance was greatly influenced by excess body weight in the obese group. The absolute clearance of Drug X (in L/hr) is 1.6 times faster in obese patients compare to that observed in lean subjects (Fig.3A). This demonstrated significantly lower exposure to the drug in this group (Fig.3C).

- The normalized clearance (in L/hr/kg) was remarkably similar in obese and lean subjects (only 1.1 fold); (Fig.3D). Administration of Drug X per kg of total body weight resulted same level of exposure as lean patients (Fig.3B).

Discussion and Conclusion

- These finding indicate that dosing of Drug X should be per kg of total weight basis to obtain the same level of exposure as lean patients.

- Reliable mechanistic pharmacokinetic models can utilize prior knowledge of physiological and biochemical changes associated with obesity to predict drug clearance and optimise the maintenance dose with reasonable accuracy. This can help to answer "what if" questions within a given confidence in the absence of any previously known clinical data.
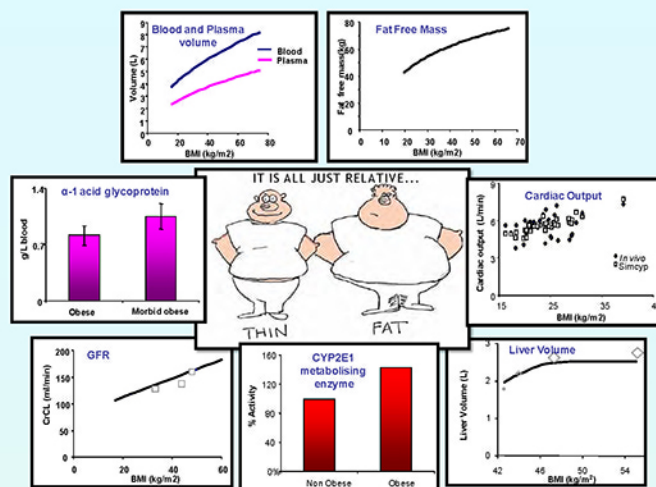

Fig.1 The main physiologic parameters that play the major role in disposition of drugs
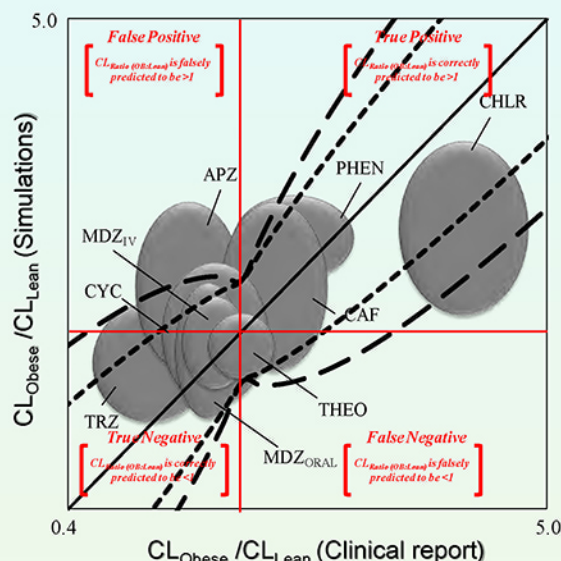

Fig. 2 The fold change in the clearance of eight drugs in obese groups compare to the lean control, as reported in clinical studies plotted against results from simulations. The ellipses delineate the 90% CI as degree of possible variability recovered in simulation and the from real clinical studies.
Key:
— — Two folds error
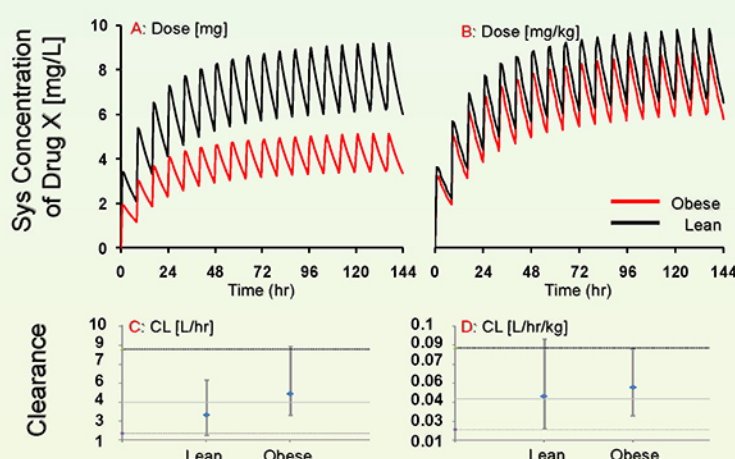– – – Three folds error
— No difference

Fig. 3 The systemic exposure of Drug X after taking absolute dose (in mg)(A) and dose per total body weight basis (in mg/kg)(B). The absolute clearance of Drug X (in L/hr)(A) and normalized for total body weight (in L/hr/kg)(D). Values expressed as median ± 5th and 95th percentile.

References

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