Obesity is a world wide epidemic (1)

Dosing guidelines for patients who are obese are not available for most pharmacological agents

No suitable size descriptor is available that helps to explain the influence of obesity on the pharmacological actions of drugs

Objective

To assess the influence of obesity on the time course of drug exposure

Lean Body Weight

The standard measure of lean body weight (LBW) was originally computed based on an analysis of three studies (2).

Less than 10% of patients enrolled in these studies were obese

The empiric formula although accurate for non-obese patients significantly under-predicts LBW for obese individuals (see Figure 1).

We have recently developed a semi-mechanistic model for LBW (3) which accurately predicts actual lean body weight for patients from BMI=17 to 70 kg/m²

The Lean Body Weight Hypothesis

LBW adequately predicts drug exposure by accounting for changes in body composition (4)

The LBW hypothesis includes three tenets that can be tested:

Absolute clearance is greater in obese individuals

Clearance increases non-linearly with WT

Clearance correlates linearly with LBW

80 studies were identified in the literature which addressed clearance and obesity. All but three agreed with at least one tenet

LBW to describe glomerular filtration rate (5)

GFR data from a previous study at Tel Aviv University Medical School, Israel was re-analysed

9 subjects: Lean (BMI 20.1 – 24.6 kg/m²)

8 subjects: Obese (BMI 38.1 – 61.3 kg/m²)

GFR was compared between lean and obese using repeated measures ANOVA (Figure 2)

LBW to describe High Hepatic Clearance (6)

Hepatic clearance data were assessed by investigators at New York Medical College, USA

16 subjects: Lean (BMI 20.8 - 28.1 kg/m²)

10 subjects: Obese (BMI 30.9 - 54.1 kg/m²)

Exclude liver or renal disease, and those requiring chronic analgesic medications

Hepatic clearance was measured using fentanyl as a probe (Figure 3)

Conclusions

We believe that LBW is sufficient to explain the influence of body composition on CL

Use of LBW as a covariate for CL in PK studies can enable quantitative predictions about the dose-exposure response relationship in the obese

References

1. World Health Organization. Global database on body mass index (BMI) www.who.int/bmi


Modelling and Simulation Lab