

Title: Understanding the influence of obesity on the time course of pharmacological response

Authors: Phey Yen Han (1), Stephen B Duffull* (1,2), Carl Kirkpatrick (1), Bruce Green (1)

Institutions: (1) School of Pharmacy, University of Queensland, Brisbane, Australia; (2) School of Pharmacy, University of Otago, Dunedin, New Zealand

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

Methods: We hypothesize that drug exposure is related to observable patient characteristics in the obese. The hypothesis states that (1) absolute clearance is greater in the obese individual, (2) clearance increases nonlinearly with total body weight (WT), and (3) clearance correlates linearly with lean body weight (LBW) [1]. LBW is defined as per [2]. This hypothesis was tested for renal processes using inulin [3] and for hepatic clearance pathways with fentanyl (identified from the literature [4]). A further 72 studies were identified that addressed the influence of obesity on drug exposure.

Results: Assessment of renal elimination using inulin as a marker of filtration was assessed. It was found that inulin clearance was 42% greater in the obese than non-obese ($P=0.003$), 36% lower when standardized by WT ($P=0.002$) and not significantly different when standardized by LBW ($P=0.27$). Assessment of hepatic clearance pathways showed that fentanyl clearance was greater in the obese, was lower when standardized to WT and not different when standardized to an empirically developed weight descriptor termed PK-mass. PK-mass was found to linearly correlated with LBW ($R^2=0.92$ males, $R^2=0.94$ females). Of the 80 studies identified only 4 studies considered LBW as a covariate, with the remainder choosing either ideal body weight or body mass index. Studies were generally of low power and risked confounding based on matching for measures of LBW between lean and obese groups. All except three studies indirectly supported at least 1 of our hypothesized tenets.

Conclusions: Obesity is a global epidemic. It is associated with significant morbidity and mortality including cancer, non-cardiovascular and cardiovascular disease [5]. Obese patients will receive pharmacological treatments. Understanding the time course of exposure is critical in this patient group in order to optimize therapeutic outcomes. We believe that a simple calculation of LBW [2] will provide a key step to better dosing, improved outcomes and greater understanding of physiological changes in the obese.

References:

- [1] Han et al. Clin Pharmacol Ther 2007;82:505-508
- [2] Janmahasatian et al. Clin Pharmacokinet 2005;44:1051-1065
- [3] Janmahasatian et al. BJCP 2007 (accepted)
- [4] Shibutani et al. Anesthesiology 2004 ; 101, 603–613
- [5] Flegal et al. JAMA 2007;298:2028-2037