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Clinical Consequences of Altered Drug Disposition in Obesity

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Obesity is a major health problem in the United States and world-wide. About 30% of the population in the US is obese (Body Mass Index [BMI]>30 kg/m^2), while ~5% of the population is morbidly obese (BMI >40 kg/m^2) [1,2]. Obesity and morbid obesity are associated with changes in metabolism and clearance of drugs. This can increase the risks of adverse drug reactions and drug-drug interactions in obese individuals.

Alterations in drug metabolism in obese individuals were reported in the early eighties. Drug metabolism is primarily regulated by the Drug Metabolizing Enzymes (DMEs), which are broadly classified into phases I and II. Phase I DMEs primarily comprise of the Cytochrome (CYP) 450 family of enzymes. CYP3A4 is the most common isoform expressed in human liver and metabolizes ~50% of known drugs [3,4]. Phase II metabolism consists of conjugation reactions such as glucuronidation, sulfation, glutathione conjugation or methylation forming polar metabolites leading to enhanced excretion [4].

Obesity was associated with significantly lower metabolism of the CYP3A4-substrates, N-methyl-erythromycin and triazolam, indicating reduced CYP3A4 metabolic activity [5-7]. Other CYP3A4-metabolized drugs such as carbamazepine, alfentanil and taranabant were also reduced in obese patients compared to their non-obese counterparts [8-10]. Obesity associated changes in drug metabolism by other CYP isoforms have also been reported. For e.g. increased metabolism of chlorzoxazone (CYP2E1 substrate) to 6-hydroxychlorzoxazone was observed in obese individuals. This was attributed to increased CYP2E1 activity associated with obesity [11]. CYP2D6-mediated metabolism of nebivolol was increased [12], while CYP1A2-mediated theophylline metabolism was decreased [13] in obese individuals compared to nonobese individuals. In obese patients, clearances of oxazepam and lorazepam, (widely used benzodiazepines and excreted as glucuronide conjugates) were significantly increased [14]. The authors attributed this to increased UGT activity in obese individuals. Thus, the effects of obesity on the metabolism of drugs may depend on the enzymatic pathway.

Several studies in animal models of obesity have shown that expression of DMEs is altered in obesity. For e.g. altered gene expression of DMEs in genetically obese zucker fatty rats (reduction in CYP2B1/2 and Mrp3) and leptin-resistant (*db/db*) mice (increase in CYP2B10) have been reported [15,16]. Cyp3a11 gene and protein expression were significantly reduced in both long-term (12 weeks) and short-term treatment (1 week) of high fat diet (HFD, 60% kcal from fat) [16]. On the other hand, gold thioglucose induced obese mice had significant elevations in Cyp2b1 and Cyp4a10 gene expression [16]. We recently showed that mRNA levels of the phase II DMEs (Ugt1a1, Sult1a1, Sultn) were reduced ~30-60% in mice fed HFD (60% kcal fat for 14 weeks) compared to low fat diet (LFD, 10% kcal fat) mice [17]. Cyp2e1 and Cyp1a2 expression were unaltered in HFD mice, while Cyp3a11 expression was reduced [17]. This caused disparities in the Pharmacodynamics (PD) of midazolam, CYP3A substrate, (increased sleep time) and zoxazolamine, CYP2E1 substrate (no change in sleep time) in HFD mice [17]. These findings indicate that regulation of CYPs is dependent on the model of obesity and is tissue-, isoform- and species-specific.

The mechanism underlying changes in drug metabolism/clearance in obesity is not known. Among other factors, obese patients have relatively more fat, and less lean tissue per kilogram of total body weight than lean individuals. Blood volume is also increased, particularly in morbidly obese individuals [18]. In addition, obese patients were shown to suffer from chronic, low-grade inflammation. Release or over-expression of TNF-α and C-reactive protein in adipose tissue of obese individuals have been reported [19,20]. However, the role of inflammation in regulation of DMEs and transporters in obesity remains unclear. All these and other factors can contribute to alterations in drug disposition in obese individuals.

The kidneys are the primary organs involved in the elimination of drugs. Elimination of drugs through the kidneys involves glomerular filtration, tubular secretion and tubular re-absorption. The exact effect of obesity on these functions is not fully understood. Clearance of renally eliminated drug was found to be higher in obese patients because of increased glomerular filtration and tubular secretion. However, the influence of obesity on the tubular re-absorption is not known.

Future clinical trials should put emphasis on assessing the impact of obesity on the pharmacokinetics of the particular drug, as well as the enzymes involved in the metabolism and clearance process. Furthermore, the molecular mechanism underlying the changes in the metabolism and elimination of the drug in obesity needs to be elucidated. This will enable the extrapolation of the results to other drugs which are eliminated by the same pathway. Future research should focus on individual metabolic and elimination pathways in adults and children that are altered in obese individuals compared to their non-obese counterparts. Most studies have been conducted in the adult population, with very limited information on the metabolism and clearance of drugs in obese children. Currently, findings from obese adults are extrapolated to obese children, as clinical studies in obese children are not available. Studies have shown differences in expression and activity of drug metabolizing enzymes, glomerular filtration and tubular processes, blood flow etc. among obese and non-obese patients. Impact of obesity on drug metabolism and elimination greatly differs per drug metabolic or elimination pathway.

Most of the studies so far have been conducted in over-weight or moderately obese individuals (~30 kg/m^2). Future studies need to include morbidly obese (BMI>40 kg/m^2) and super-obese (BMI>50 kg/m^2) patients in these studies.

Since prevalence of obesity is increasing world-wide, it is critical to

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assess the impact of obesity on drug safety and efficacy in obese children and adults. This will lead to the development of rational approaches to counteract undesirable effects of drugs in these individuals. Ultimately, this will increase the safety of drugs in individual patients.

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