Letter to the Editors

Birthweight and cytochrome P4503A4/5 activity in obese women

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Large interindividual variability in drug pharmacokinetics is a challenge in the delivery of optimal pharmacotherapy. Obesity is a confirmed source of interindividual variability in the activity of cytochrome P4503A4/5 (CYP3A4/5) [1], an important determinant of drug pharmacokinetics. In a recently published study [2], we observed a large interindividual variability in CYP3A4/5 activity within obese women. However, the magnitude of change did not correlate linearly with the magnitude of obesity or the percentage of body fat, leading to speculation that sources other than sex and body mass index are at play. The need for understanding and predicting interindividual variability within these patients is critical given the current obesity epidemic.

In utero growth restriction is strongly correlated to a higher incidence of obesity during adulthood [3]. *In utero* growth restriction is accompanied by morphological and physiological alterations in various organs [4]. These changes, especially to the liver, may affect drug metabolism during postnatal life, resulting in interindividual variability. We hypothesize that CYP3A4/5 is functionally altered by *in utero* growth restriction. The objective of this study is to determine whether birthweight, a surrogate marker of *in utero* growth restriction, is predictive of CYP3A4/5 enzyme activity in obese women.

A randomized, prospective study was conducted at the Oregon Health & Science University. The Institutional Review Board approved the study protocol, and all subjects provided written informed consent. Thirty-two obese women (18–35 years old; body mass index ≥ 30 kg m⁻²) were divided into quartiles based on their self-reported birthweight (in kilograms): (1) <2.72; (2) 2.72–3.17; (3) 3.18–3.63; and (4) >3.63. There were no statistical differences in age or body mass index in the four quartiles of women. Venous blood samples were collected via an indwelling catheter at 0 (baseline), 0.25, 0.5, 1, 2, 4, 5, 6, 12 and 24 h following a single 2 mg oral dose of midazolam. Plasma was separated, and aliquots were stored at –80°C prior to analysis. Both bioanalysis and

Figure 1

Effect of birthweight on midazolam clearance. Each box represents 25–75 percentile data, with a line representing the median and whiskers depicting 5–95 percentile data; $n = 5–11$. The 95% confidence intervals (whiskers) were not computed for quartiles 1 and 4 as a result of small sample size

pharmacokinetics analysis were described previously [2]. A one-way ANOVA was used to examine the effect of birthweight on midazolam oral clearance. The relationship between birthweight and oral clearance was also tested using regression analysis.

The CYP3A4/5 activity, measured as midazolam oral clearance, was similar among the four quartiles of birthweight (Figure 1). However, an interesting, inverted U-shaped trend was observed; clearance trended to increase as quartiles of birthweight increased until

quartile 3 (normal birthweight; 3.18–3.63 kilograms), then the trend reversed as birthweight continued to increase further. In order to confirm the U-shaped trend, clearance was fitted using polynomial regression, which demonstrated a statistically significant third-order polynomial fit to birthweight ($P = 0.044$).

The change in clearance that is related to growth in the womb suggests that the complex determinants of drug disposition are permanently changed by the intrauterine environment. It is striking that the nature of this observed relationship between birthweight and clearance in the present study is similar to those linking birthweight to the incidence of diseases during adulthood [5, 6]. This similarity is suggestive of the critical role played by an adverse *in utero* environment in drug pharmacokinetics. Clearance is of critical importance in the therapeutic use of a drug, and our data suggest that part of the biological variation in the clearance is related to historical prenatal growth patterns.

Birthweight is a relatively accessible, no-cost, patient-specific parameter that could be utilized in the optimization of pharmacotherapies. Along with other patient-specific parameters, such as body mass index, age, ethnicity, race, etc, birthweight could serve as useful information to personalize medicine. Although our observation was novel, the small sample size limits our ability to reach definitive conclusions. Further studies with a larger sample size, both sexes and a wider body mass index range are required, along with recorded birthweight, to establish conclusively the relevance of birthweight information in clinical practice.

Competing Interests

There are no competing interests to declare.

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