Factors affecting drug metabolism

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Many factors affect the rate and pathway of metabolism of drugs, and the major influences can be sub-divided into internal (physiological and pathological) and external (exogenous) factors as indicated below:

Internal factors: species, genetic (strain), sex, age, hormones, pregnancy, disease.

External factors: diet, environment.

1. **Age**: Drug metabolism is affected by the changes in body composition associated with age. The decreased muscle and tissue mass that accompanies ageing will also influence the distribution of certain drugs, as will the reduced blood flow to tissues and organs.

2. **Sex**: Sex differences in metabolism (phase I and II) are believed to be the major cause of differential pharmacokinetics between men and women. Many CYP450 enzymes (phase I metabolism) show a sex-dependent difference in activity. Most of the phase II enzymes have a higher activity in men than in women. Activities of these enzymes can also change during pregnancy and with the use of oral contraceptives.

3. **Species**: Animal studies are commonly used to predict metabolism and toxicity of potential new human drugs. However, it is important to realize that humans differ from animals in isoform composition, expression and catalytic activities of enzymes involved in drug metabolism. In fact, even small changes in the amino acid sequences of these enzymes can give rise to profound differences in substrate specificity and catalytic activity. Therefore, differences in expression between species of the most important family of drug metabolizing enzymes, the cytochrome P450s (CYPs) are a major cause of species differences in drug metabolism.

4. **Hormones**: Activities of drug metabolizing enzymes (DME) are known to change throughout the course of physical and sexual maturation with the greatest variability noted during infancy and adolescence. The mechanisms responsible for developmental regulation of DME are currently unknown. However, the hormonal changes of puberty/adolescence provide a theoretical framework for understanding biochemical regulation of DME activity during growth and maturation. Important information regarding potential influences of growth and sex hormones can also be extrapolated from studies evaluating changes in activities of DMEs occurring as a consequence of physiologic, pathologic and/or pharmacologic hormonal fluctuations.

5. **Pregnancy**: Pregnancy is known to affect hepatic drug metabolism, but the underlying mechanisms remain unknown. Physiological changes accompanying pregnancy are likely responsible for the reported alteration in drug metabolism during pregnancy. These include elevated concentrations of various hormones such as estrogen, progesterone, placental growth hormones and prolactin.

6. **Disease**: There are several disease states (inflammation/diabetes/morbid obesity/cancer)

that can profoundly alter key drug transport and/or drug metabolic pathways in liver and intestine.

7. **Genetics:** The effect of genetic polymorphisms (differences) on catalytic activity is most prominent for three isoforms: CYP2C9, CYP2C19, and CYP2D6, which collectively account for about 40 per cent of drug metabolism mediated by cytochrome P450.

8. **Environment:** Environmental factors such as stress, pregnancy and smoking also affect drug response

9. **Diet:** Foods can enhance, delay, or decrease drug absorption. Foods impair absorption of many antibiotics. They can alter metabolism of drugs; eg, high-protein diets can accelerate metabolism of certain drugs by stimulating cytochrome P-450. Eating grapefruit can inhibit cytochrome P-450 34A, slowing metabolism of some drugs (eg, amiodarone, carbamazepine, cyclosporine, certain Ca channel blockers). Diets that alter the bacterial flora may markedly affect the overall metabolism of certain drugs.