DEVELOPMENT OF HEPATIC FUNCTION

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Question

Which of the following hepatic enzymes involved in drug metabolism is **MOST** mature in a term newborn?

A. Cytochrome P450
B. Glucuronosyltransferase
C. Sulfotransferase
D. N-acetyltransferase

Key Points

- Hepatic metabolism transforms lipid-soluble drugs into water-soluble compounds that can be excreted in bile and urine.
- Most liver enzymes involved in drug metabolism are immature at birth. The cytochrome P450 (CYP450) system functions at 50% adult levels at birth.
- Among the enzymes involved in phase II reactions, the sulfotransferase enzyme system is mature at birth.

Hepatic Metabolism

- The liver serves as the primary organ for drug metabolism. It biologically transforms drugs into hydrophilic compounds amenable to excretion in the urine or bile. Hepatic metabolism of drugs can be categorized into phase I, II, and III reactions.[1] (Table 1)

Phase I reactions	Cytochrome P450 enzymes convert lipophilic molecules to hydrophilic molecules through oxidation, reduction, or hydrolysis.
Phase II reactions	Conjugation of products of phase I reactions with hydrophilic moieties to make them more water soluble. For example, glucuronidation (or conjugation of drugs with glucuronic acid) by uridine 5'-diphosphoglucuronlysyltransferases.
Phase III reactions	Excretion of compounds into bile by molecular transporters such as multidrug resistance protein, cystic fibrosis transmembrane conductance regulator, and multidrug-resistance-related protein.

Table 1: Phase I, II, and III reactions in the hepatic metabolism of drugs.

Developmental Changes in Hepatic Metabolism

- The enzyme activities responsible for hepatic metabolism are reduced in neonates. In general, the half-lives of medications that eliminated by the liver are prolonged in neonates, decreased in children 4-10 years of age, and reach adult levels in adolescents.[1]

Cytochrome P450 Enzymes

- The CYP450 enzyme levels increase with gestational age and reach about 50% of adult levels at term.[1] Some CYP450 systems rapidly develop while others can take several months or years to reach adult levels (Table 2).

Enzymes	Drugs metabolized	Age when adult levels are reached
CYP1A2	acetaminophen, caffeine, theophylline, warfarin	4 months
CYP2C19	phenytoin, diazepam, omeprazole, propranolol	6 months
CYP2D6	codeine, hydrocodone, amitriptyline, ondansetron, propranolol	3-5 years
CYP3A4	acetaminophen, alfentanil, midazolam, diazepam, lidocaine, theophylline	6-12 months

Table 2: Developmental changes with CYP450 enzymes. Adapted from reference 1.

Phase II Reactions

- Enzymes involved in phase II reactions are also immature at birth. The major phase II enzymes include glucuronosyltranferase, sulfotransferase, and N-acetyltransferase.
- Glucuronidation reaches adult levels by about 6-18 months of age.
    - Morphine, acetaminophen, and dexmedetomidine all undergo glucuronidation, explaining their decreased clearance in neonates.
    - Morphine undergoes glucuronidation to morphine-3-glucuronide and morphine-6-glucuronide, which is the active metabolite[2] (Figure 1). Morphine clearance reaches adult levels by about 5-6 months of age.[1]

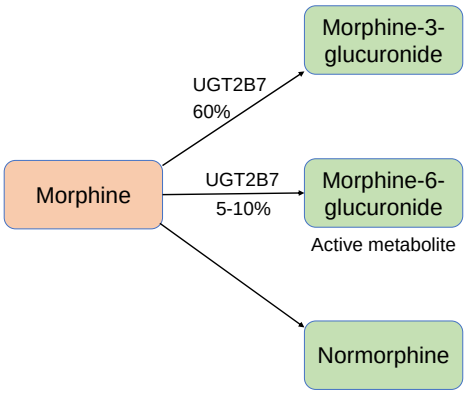


Figure 1: Morphine metabolism via glucuronidation

- The sulfotransferase enzyme system is well developed in neonates, which might compensate for the limited glucuronidation of certain drugs. For example, the limited glucuronidation of acetaminophen is compensated by the mature sulfotransferase system. A greater percentage of the acetaminophen dose is excreted as the acetaminophen-sulfate conjugate.[1]
- The N-acetyltransferase system is immature at birth and reaches adult levels by 1-3 years of age.

References

1. Anderson BJ, Lerman J, Cote CJ. Pharmacokinetics and pharmacology of drugs used in children. In: Cote and Lerman's A Practice of Anesthesia for Infants and Children. 6th edition. Philadelphia, PA. Elsevier. 2019: 111-3.
2. Chidambaran V, Sadhasivam S. Pharmacogenomics. In: Cote and Lerman's A Practice of Anesthesia for Infants and Children. 6th edition. Philadelphia, PA. Elsevier. 2019: 83-99.

Answer C. Most liver enzyme systems involved in drug metabolism are immature at birth, except the sulfotransferase system, which is fully mature at birth.

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