Comprehensive Pharmacy Review

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Drug Metabolism, Prodrugs, and Pharmacogenetics

Marc W. Harrold

I. INTRODUCTION TO DRUG METABOLISM. Drug metabolism (also called **biotransformation**) refers to the biochemical changes that drugs and other foreign chemicals **(xenobiotics)** undergo in the body, leading to the formation of different metabolites with different effects. Xenobiotics can undergo a variety of biotransformation pathways, resulting in the production of a mixture of intermediate metabolites and excreted products, including unchanged parent drug. Rarely is only one metabolite produced from a single drug.

A. **Inactive metabolites.** Some metabolites are inactive (i.e., their pharmacologically active parent compounds become inactivated or detoxified).

1. The hydrolysis of **procaine** to *p*-aminobenzoic acid and diethylethanolamine results in a loss of anesthetic activity.
2. The oxidation of **6-mercaptopurine** to 6-mercapturic acid results in a loss of anticancer activity.

B. **Metabolites that retain similar activity.** Certain metabolites retain the pharmacological activity of their parent compounds to a greater or lesser degree.

1. **Imipramine** is demethylated to the essentially equiactive antidepressant, **desipramine.**
2. **Acetohexamide** is reduced to the more active hypoglycemic, **l-hydroxyhexamide.**
3. **Codeine** is demethylated to the more active analgesic, **morphine.**

C. **Metabolites with altered activity.** Some metabolites develop activity different from that of their parent drugs.

1. The antidepressant **iproniazid** is dealkylated to the antitubercular, **isoniazid.**
2. The vitamin **retinoic acid** (vitamin A) is isomerized to the anti-acne agent, **isoretinoic acid.**

D. **Bioactivated metabolites.** Some pharmacologically inactive parent compounds are converted to active species within the body. These parent compounds are known as **prodrugs.**

1. The prodrug **enalapril** is hydrolyzed to **enalaprilat,** a potent antihypertensive.
2. The prodrug **sulindac,** a sulfoxide, is reduced to the active sulfide.
3. The antiparkinsonian **levodopa (L-dopa)** is decarboxylated in the neuron to active **dopamine.**

II. BIOTRANSFORMATION PATHWAYS

A. **Phase I reactions** are those in which polar functional groups are introduced into the molecule or unmasked by oxidation, reduction, or hydrolysis.

1. **Oxidation** is the most common phase I biotransformation.
   a. The majority of oxidations occur in the **liver;** however, extrahepatic tissues, such as the **intestinal mucosa, lungs,** and **kidney,** can also serve as metabolic sites.
   b. The vast majority of oxidations are catalyzed by a group of mixed-function oxidases known as **cytochrome P_{450} (CYP450).** These oxidases are bound to the smooth endoplastic reticulum of the liver and require both NADPH and a porphyrin prosthetic group. Unlike most enzymes, CYP450 uses a variety of oxidative biotransformations to metabolize a diverse group of substrates.

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