

Lecture 6 – Drug metabolism (brief review)

Key objectives:

1. Be able to describe the general aspects of Phase 1 metabolism
2. Be able to describe cytochrome P-450 and its metabolic cycle
3. Be able to describe several types of P-450 metabolic transformations
4. Be able to describe the general aspects of Phase 2 metabolism

On a high level, drug metabolism can be divided into two broad categories; Phase 1 and Phase 2 metabolism. **Phase 1** metabolism tends to involve processes like carbon hydroxylation and N- or O-dealkylation. **Phase 2** metabolism tends to involve conjugation.

Phase 1 metabolism:

A. Mono-oxygenation

The importance of the mono-oxygenase enzyme called cytochrome P-450 cannot be overstated. It's actually a large family of enzymes that are in very high amounts in the liver. They likely evolved as protective enzymes in living systems that became optimized to remove toxins, pollutants, poisons that enter the body through the air, water, and food. And as a species that resides at the top of many food chains, humans are especially vulnerable to the concentrating effects of these contaminants.

Some special forms of cytochrome P-450 reside outside the liver in organs such as the adrenals, testes, and ovaries. More on these enzymes and their specific inhibitors later.

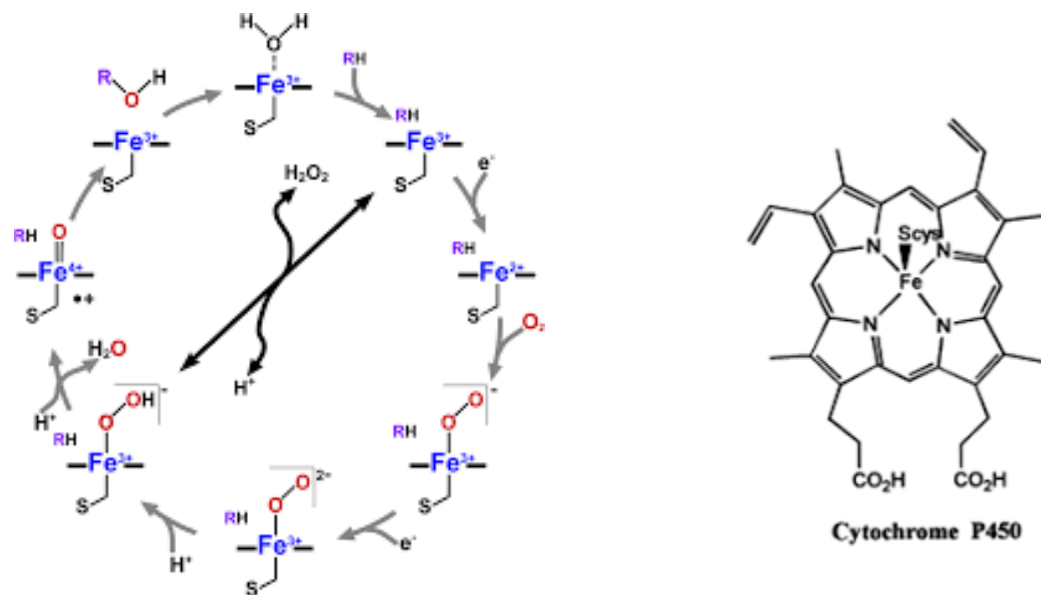
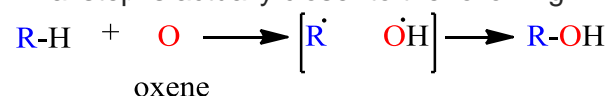


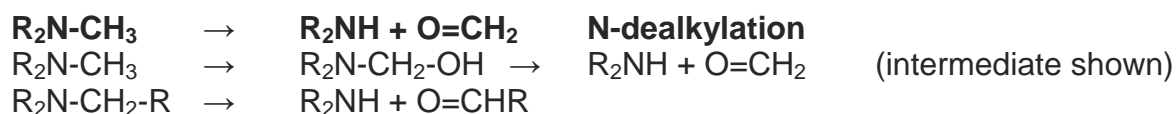
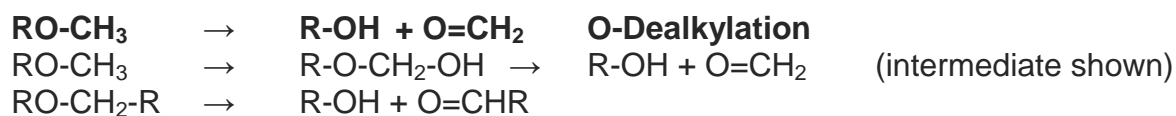
Figure 1. The catalytic cycle of cytochrome P-450 (left) and the structure of the heme unit that is in the cytochrome P-450 active site (right)

Final step is actually closer to the following:



Cytochrome P-450 gets its name from the simple fact that if carbon monoxide is bubbled through a solution that contains lots of the enzyme, one can do a spectral scan of the solution and observe an absorption peak at 450 nanometers. This is a very old test that was done by biologists decades ago to determine if an enzyme preparation contained cytochrome P-450 or not. Anyway, in the overall process, a substrate (R-H) can be converted to an oxidized form (R-OH). This simple step makes the substrate more polar (R-H converted to R-OH) and more easily excreted. Plus, the R-OH metabolite can be conjugated to enhance polarity and excretion even more.

An expanded list of oxidations by cytochrome P-450 is here:



Know the examples in bold above.

Some real drug examples:

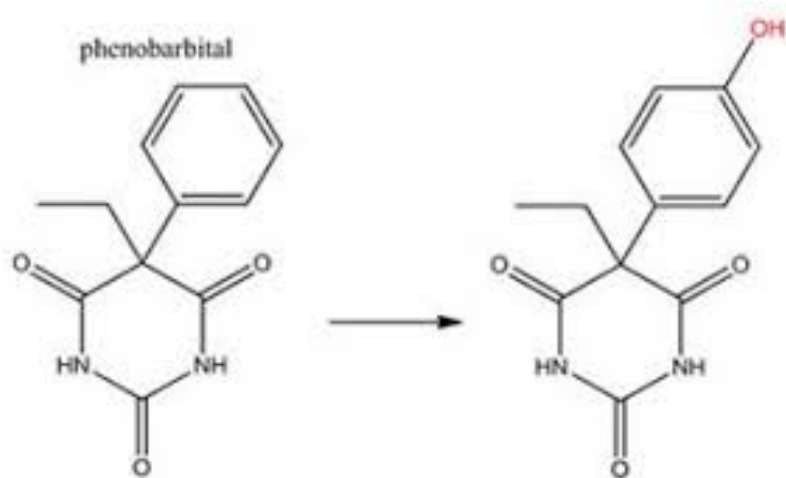
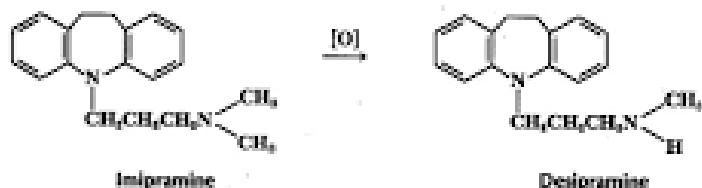


Figure 2. The structures of phenobarbital and a hydroxylated metabolite

N-Dealkylation



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Figure 3. The structures of imipramine and an N-dealkylated metabolite (desipramine)

B. Hydrolysis

Hydrolysis is another type of Phase 1 metabolism. It can occur with esters or amides (Figures 4a and 4b) and carbamates, which we will discuss later. In these cases, the process always gives rise to a more polar metabolite. An ester gives rise to a carboxylic acid and an alcohol, and an amide gives rise to a carboxylic acid and an amine.

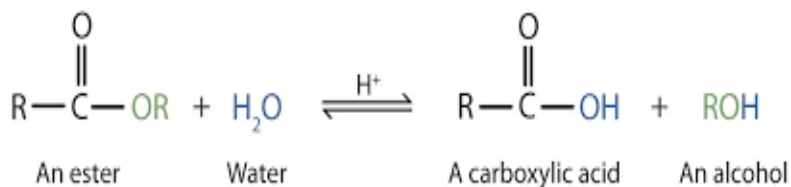


Figure 4a. The hydrolysis of an ester

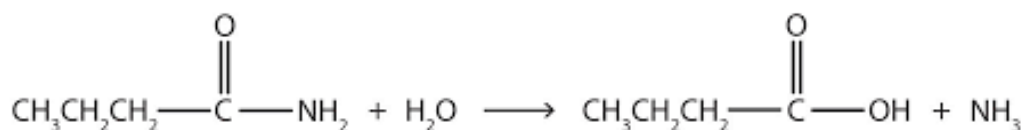


Figure 4b. The hydrolysis of an amide

Some real drug examples:

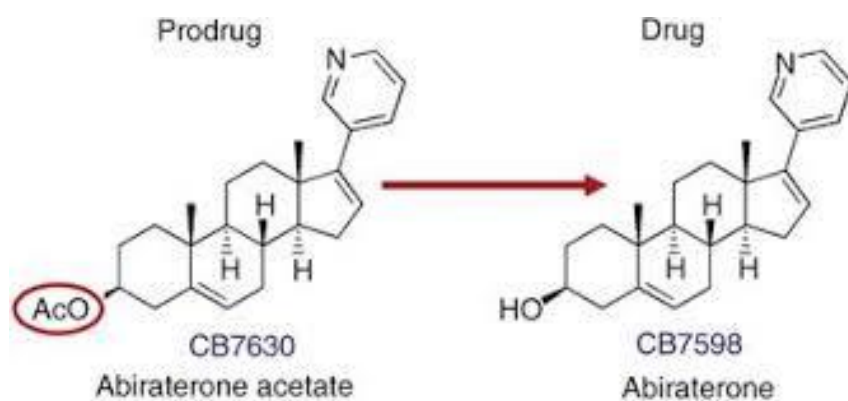


Figure 5. The hydrolysis of abiraterone acetate to abiraterone

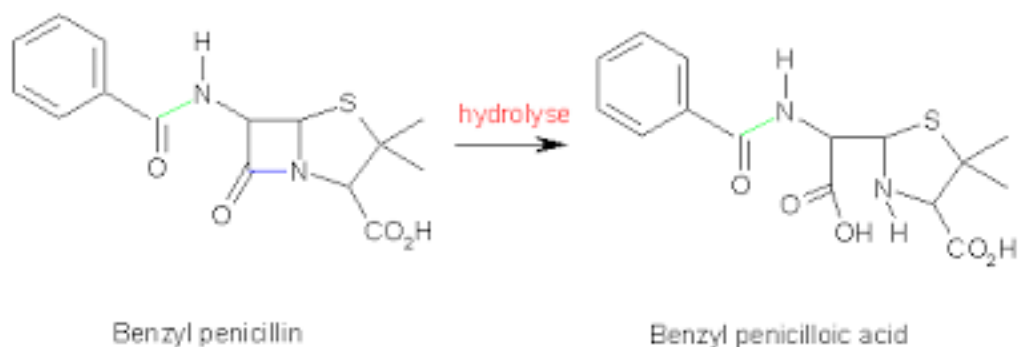


Figure 6. The hydrolysis of benzyl penicillin to the metabolite benzyl penicilloic acid. (Note in this case the amide is cyclic. A cyclic amide is called a lactam; the open ring metabolite is inactive)

Phase 2 metabolism:

Involves conjugation of substrates (e.g. drugs or drug metabolites) to groups that are more polar and/or charged, such as sulfate or glucuronic acid (Figure 7).

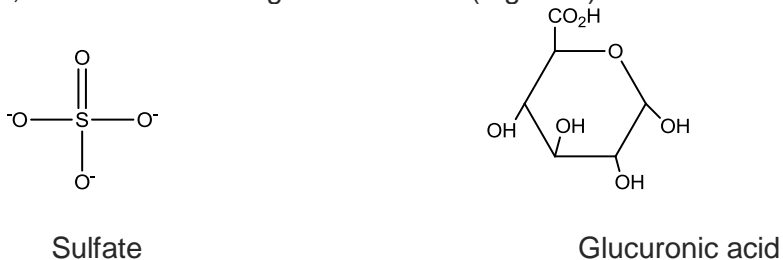


Figure 7. The structures of the sulfate group and the glucuronic acid (glucuronide) group

So in general, R-OH can be converted to R-OSO₃⁻² or R-O-G⁻¹ where OSO₃⁻² is a sulfate group and G⁻¹ is a glucuronide group. And both the sulfate and glucuronide groups add polarity and charge to the molecules. The bottom line is that the increased polarity in a molecule facilitates urinary excretion.

Some real drug examples:

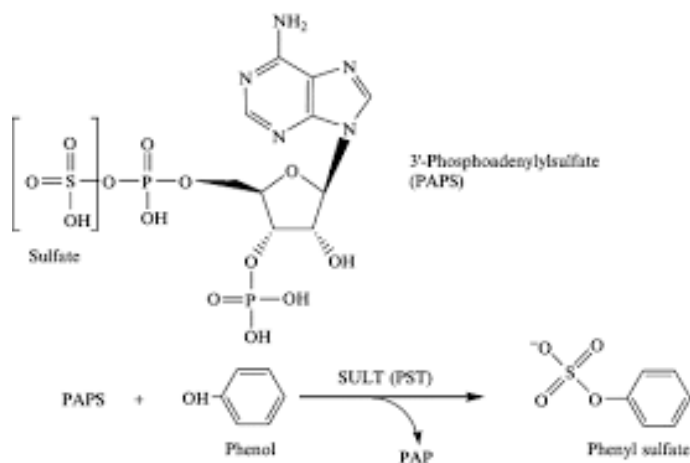


Figure 8. The structures of PAPS and the sulfation of phenol to phenyl sulfate

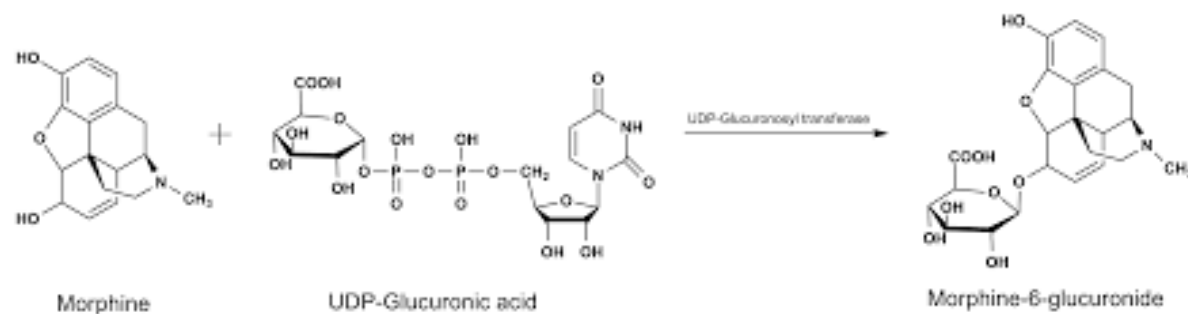


Figure 9. The structures of morphine, UDPGA, and morphine-6-glucuronide

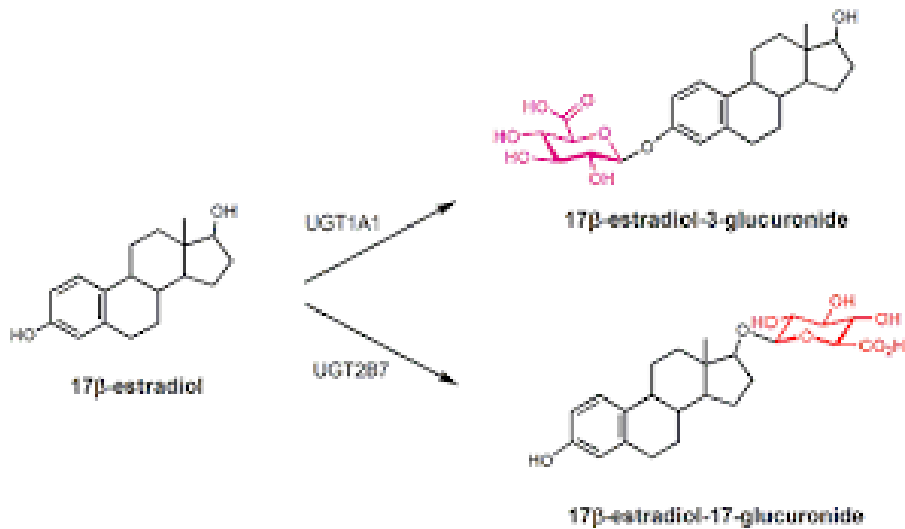


Figure 10. The structures of 17β-estradiol as well as the 3-glucuronide and the 17-glucuronide

Antibody metabolism and elimination

Antibodies (including monoclonal antibodies) are much larger than small molecule drugs. The molecular weight of small molecule drugs ranges from about 150-500 g/mole. The weight of therapeutic antibodies ranges from 100,000 to 500,000 g/mole.

The elimination of antibodies occurs through intracellular metabolism mainly by lysosomal degradation to amino acids. The metabolism/catabolism of large proteins to amino acids is hydrolytic. This metabolism occurs after uptake of the antibodies by cells such as macrophages through pinocytosis (non-specific fluid phase uptake), or by receptor-mediated endocytosis.

Several receptors regulate the metabolism of antibodies. These receptors include FcRn and Fc Rn, and their subtypes. We continue to learn more about the metabolic breakdown of antibodies but understand that their metabolism is quite different than that of small molecules.

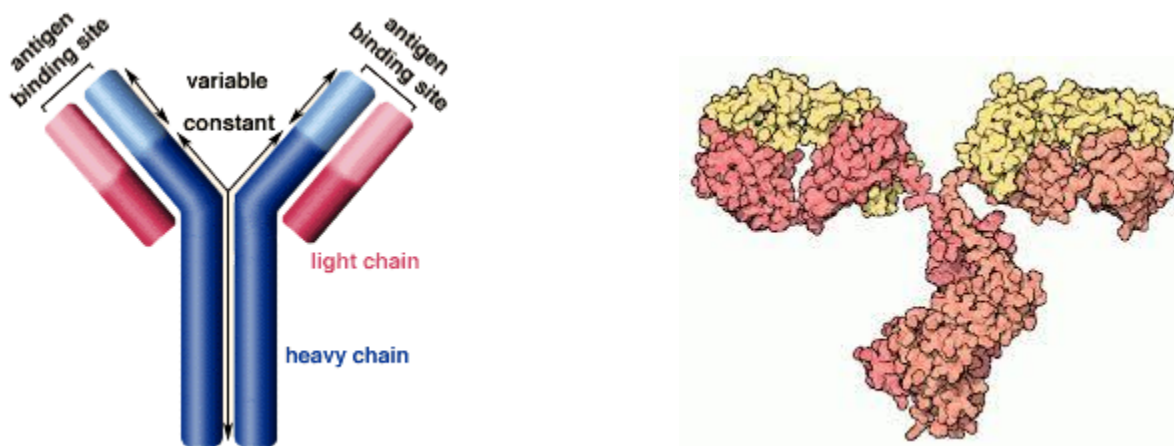


Figure 11. Depiction of the typical antibody structure in two dimensions (left) and space-filling three dimensions (right)