Physiologically-based pharmacokinetic modeling of acetaminophen metabolism and toxicity

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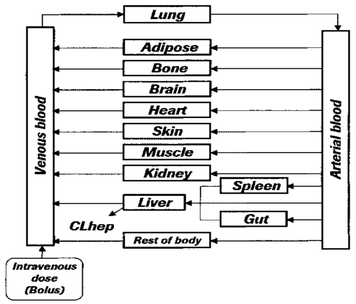
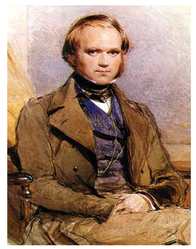
Abstract

Acetaminophen is a common analgesic and antipyretic. Metabolism of acetaminophen and acetaminophen-induced liver necrosis are predicted using physiologically-based pharmacokinetic (PBPK) modeling. *Pharmacokinetic* means the model determines where the drug is distributed in the body over time. *Physiologically-based* means the anatomy and physiology of the human body is reflected in the structure and functioning of the model. Acetaminophen is usually safe and effective when taken as recommended, but consumption at higher levels may lead to liver damage. Additionally, other factors such as alcoholic liver disease, smoking, and malnutrition affect the maximum safe dose of acetaminophen.

Physiologically-based pharmacokinetic (PBPK) modeling[1]



Example PBPK model[2]



Example human (Charles Darwin)

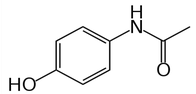
The block diagram (left) is an example of how a human (right) can be modeled:

- Organs appear as *compartments (*blocks) connected by blood flow (arrows).
- The model is described using mathematics (differential equations).

Pharmacokinetics is divided into several processes:

- Absorption: Drugs can enter the body through various portals such as intravenous or oral routes.
- Distribution: Drugs circulate through the body via blood flow, or accumulate in tissue.
- Metabolism: Drugs may be changed or broken down into other substances.
- Elimination: Drugs or their metabolic products are eliminated from the body through various routes including the kidney (urine), liver, or lungs.

Acetaminophen



... is also known as paracetamol and APAP.
... is a common analgesic (pain reliever) and antipyretic (fever reducer).
... has molecular formula $C_8H_9NO_2$ (figures at left).
... is sold under brand names including Anacin-3, Panadol, and Tylenol (figures at right); it may be combined with other ingredients such as codeine.

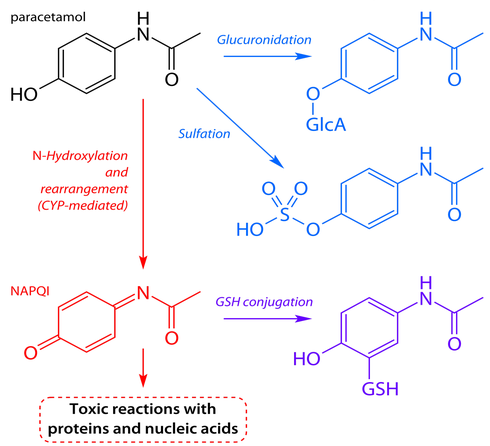
Clinical Significance in U.S.[3]

- Over 370 million packages of acetaminophen sold in 2008.
- Average 44,000+ emergency department visits annually (2000-2007).
- Average 33,500+ hospitalizations annually related to overdose (2000-2006).

Acetaminophen metabolism, detoxification, and toxicity[4]

Metabolism: Acetaminophen (black in figure) is metabolized in the liver into:

- Acetaminophen glucuronide (blue) — nontoxic.
- Acetaminophen sulfate (blue) — nontoxic.
- NAPQI (*N*-acetyl-p-benzoquinone imine), catalyzed by CYP (cytochrome P450) enzymes (red) — toxic.



Detoxification

- NAPQI is rapidly detoxified via combination with GSH (glutathione) (purple).
- The level of GSH may be reduced due to medical conditions or xenobiotics (substances found in the body but not expected to be present).

Toxicity: Toxic levels of NAPQI may be caused by:

- Overdose of acetaminophen (more than 10-15 g) overwhelming the detoxification process.
- Depletion of GSH preventing detoxification of NAPQI (possibly caused by alcohol or malnutrition).
- Excessive CYP activation producing too much NAPQI (possibly caused by smoking or other medications).

Liver necrosis (cell death) occurs when GSH is depleted to ~70% of normal levels[5].

Results

- A PBPK model of acetaminophen metabolism was implemented using the *Mathematica* program.
- Figure 1 shows good correspondence between the model's predictions (blue) with experimental data[6] (red).

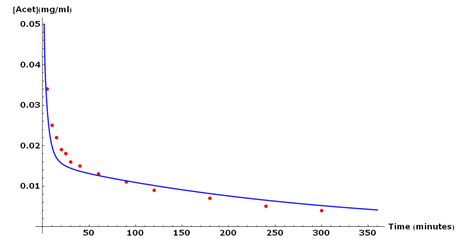


Figure 1: Concentration of acetaminophen in the venous system: model prediction in blue, experimental data in red. Initial acetaminophen dose: 1000 mg. RMSD = 0.0029.

- Susceptibility to acetaminophen-induced liver necrosis depends on the initial concentration of GSH and metabolic activity.
- Figure 2 shows the model's prediction of concentrations of GSH vs. acetaminophen dose for patients under different conditions.
- Table 1 lists the acetaminophen dose that depletes GSH concentration to 70% of normal under different conditions.
- Patients who enter the toxicity region at a lower drug dose are more subject to acetaminophen poisoning.

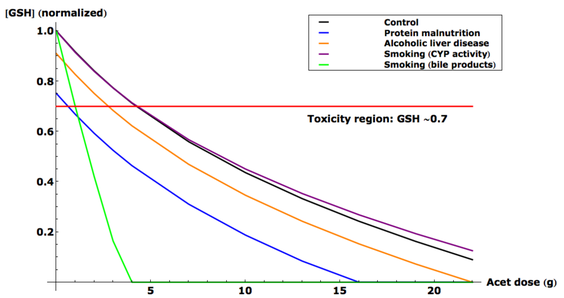


Figure 2: Predicted concentration of antioxidant GSH as a function of acetaminophen dose, for different subject conditions. Liver necrosis occurs when GSH is depleted to ~70% of normal (red).

Condition	Dose (g)	Notes	Ref
Maximum safe dosage	4.00	Maximum safe dosage should be no greater than 4 g in a 24-hour period.	4
Model control	4.22	Model predicts dose greater than maximum safe dosage to deplete GSH to 70% of normal.	n/a
Smoking	4.26	Based on benzothiazole exposure in rats, with metabolism in model tuned to match reported enzyme activities.	7
Smoking	1.00	Based on benzothiazole exposure in rats, with metabolism in model tuned to match reported metabolite levels in bile.	7
Protein malnourishment	0.61	Malnourishment defined as intake of protein less than 20 g/day for at least one week. Initial GSH level is reduced to 75% of normal.	8
Alcoholic liver disease	2.75	Initial GSH level is reduced to 91% of normal (mitochondrial GSH is depleted by 45-60%; mitochondrial GSH makes up 10-15% of total cellular GSH).	9

Table 1: Predicted acetaminophen dose that depletes GSH level to 70% of normal for different patient conditions.

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