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 metabolites in the liver or other organs.
- Excretion: Drugs or their metabolites are eliminated from the body through various routes including bile, sweat, urine, and breath.

The block diagram (left) is an example of how a human body distributes drugs over time.

Clinical Significance in U.S.³

- Average 44,000+ emergency department visits annually (2000-2007).
- Average 33,500+ hospitalizations annually related to overdose (2000-2006).

Abstract

Acetaminophen is a common analgesic and antipyretic. Over 370 million packages of acetaminophen are sold in the U.S. annually. Overdose of acetaminophen is a significant health concern, particularly in patients consuming only acetaminophen and not an opioid analgesic. Overdose of acetaminophen can result in hepatotoxicity, which is the leading cause of acute liver failure in the U.S. In the U.S., more than 10,000 cases of acetaminophen overdose are reported each year, with 1000-3000 cases requiring hospitalization. Acetaminophen overdose is associated with a high mortality rate, with approximately 1% of overdose patients dying. Mortality is dependent on the amount of acetaminophen consumed and the presence or absence of other co-ingested substances.

Acetaminophen metabolism, detoxification, and toxicity⁴

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 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.

Test conditions and results are provided in Table 1. A PBPK model of acetaminophen metabolism was developed using the Mathematica program. Figure 1 shows good correspondence between the model’s predictions (blue) with experimental data (red).

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug mg</th>
<th>Dose (mg)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy patient</td>
<td>2.75</td>
<td>1000</td>
<td>RMSD = 0.0029.</td>
</tr>
<tr>
<td>Malnourished patient</td>
<td>2.75</td>
<td>1000</td>
<td>RMSD = 0.0029.</td>
</tr>
<tr>
<td>Smoking patient</td>
<td>4.26</td>
<td>1000</td>
<td>RMSD = 0.0029.</td>
</tr>
<tr>
<td>Smaller CYP acv. patient</td>
<td>4.26</td>
<td>1000</td>
<td>RMSD = 0.0029.</td>
</tr>
<tr>
<td>Smaller GSH deplet. patient</td>
<td>4.26</td>
<td>1000</td>
<td>RMSD = 0.0029.</td>
</tr>
<tr>
<td>Match reported met. levels</td>
<td>6.93</td>
<td>1000</td>
<td>RMSD = 0.0029.</td>
</tr>
<tr>
<td>Match reported enzym. acv.</td>
<td>6.93</td>
<td>1000</td>
<td>RMSD = 0.0029.</td>
</tr>
<tr>
<td>Match reported metabolite levels</td>
<td>6.93</td>
<td>1000</td>
<td>RMSD = 0.0029.</td>
</tr>
<tr>
<td>Match reported other conditions</td>
<td>6.93</td>
<td>1000</td>
<td>RMSD = 0.0029.</td>
</tr>
</tbody>
</table>

References