Influence of liver impairment on the action of thiopental sodium

San-Hua Fang, Yun-Bi Lu, Wei-Wei Hu, Yan-Ying Fan

Department of Pharmacology
School of Medicine
Zhejiang University
2008.03.25
Backgrand

1. Drug Metabolism and the Liver
2. Effects and Metabolism of thiopental
3. Liver injury model
Drug at site of administration

1. Absorption
   (input)

Drug in plasma

2. Distribution

Drug in tissues

3. Metabolism
   Metabolite(s) in tissues

4. Elimination
   (output)

Drug and / or metabolite(s)
In urine, feces, bile
1. Drug Metabolism and the Liver

The liver is the main organ for drug metabolism but other sites include:

GI tract, skin, lungs, and kidneys
1. Drug Metabolism and the Liver

Significance of drug metabolism

(1) Drug inactivation: Drugs are often inactivated after biotransformation.

(2) Drug activation: some biotransformation products have enhanced activity or toxic properties.
Lipid-soluble agents are metabolized by the liver using two general sets of reactions, called phase I and phase II. Phase I reactions frequently involved the P-450 system. Phase II reactions are conjugation, mostly with glucuronide.
1. Drug Metabolism and the Liver

Drug

Phase I:
- Oxidation
- Reduction
- and/or hydrolysis

Phase II:
- Conjugation

Following Phase I, the drug may be activated, unchanged, or most often, inactivated.

Some drugs directly enter Phase II metabolism.

Conjugated drug is usually inactive.
Phase I reactions are the basis of one mechanism of drug interaction. Most of these reactions utilize the microsomal P-450 enzymes.

PYP3A4 plays role in the metabolism of about 35% of the drugs that are currently prescribed. Enhancement or inhibition of PYP3A4 by onedrug will affect the levels of any other drug that is also metabolized by CYP3A4.
2. Effect and Metabolism of thiopental

(1) Classification of barbiturates

According to their action duration, barbiturates are classified into:

**Long acting barbiturates**: such as phenobarbital, 1-2 days

**Short acting barbiturates**: such as pentobarbital, secobarbital and amobarbital, 3-8 hours

**Ultra-short-acting barbiturates**: such as thiopental, 20 minutes
(2) Action of barbiturates

Most drugs: dose from small to large, its effect:

- ▲ sedation
- ▲ hypnosis
- ▲ anesthesia
- ▲ Coma

Dose-response curves for two hypothetical sedative-hypnotics.
(3) Characteristics of thiopental

1. Thiopental is very lipid-soluble, penetrating brain tissue rapidly following intravenous administration, so it is used for induction of the anesthetic state.

2. Thiopental rapidly redistribute in the body from brain to skeletal muscle, and finally to adipose tissue, so it causes short duration of anaesthetic action. The feature is useful in recovery from anesthesia.
(4) Metabolism of thiopental

Because thiopental is a very lipid-soluble, the majority of the drug binds plasma proteins and is not easily infiltrate from glomerular. Moreover, it easily absorbs from renal tubule. So very few original thiopental is eliminated from kidney. It must be biotransformed by the liver, and eliminated by the kidney. So the liver damage will affect the biotransformation of thiopental and prolong the anaesthetic time of the drugs.
3. Liver injury model

1) Chemical liver injury

   Carbon tetrachloride
   galactosamine (D-GalN)
   Thioacetamide (TAA)
   Acetaminophen

2) Liver injury followed viral infection

3) Liver injury induced by Ischemia / reperfusion
3. Liver injury model

Carbon tetrachloride is a kind of hepatotoxic chemical and used to build liver injury model and hepatic fibrosis model.

Molecular formula: CCl₄
Objective: To observe the influence of liver impairment in the anesthetic action of thiopental sodium

Materials

1. Animals: 24 ICR mice, 6 mice each group, weight 25-30 g.

2. Drugs: 5% carbon tetrachloride, 0.5% thiopental sodium, normal saline.

3. Instrument: balance, surgical scissors, syringe (1 ml), stopwatch
Methods

1. Take 6 mice and mark (No. 1, 2, 3, 4, 5 and 6). Ten percentage of carbon tetrachloride (0.2 ml/10 g) is subcutaneously injected for No. 1, 2 and 3 to create the model of liver impairment. For No 4, 5, and 6 saline as a control.

2. After 24 hours of carbon tetrachloride administration, 0.5% thiopental sodium (0.1 ml/10 g) is intraperitoneally injected for No. 1, 2, 3, 4, 5 and 6. Then observe the response of mice. Record the time of disappearance and recovery of righting reflex, respectively.
Methods

3. At last, execute mice by dislocation of the cervical vertebra, and then open the abdomen to take out the livers and compare the difference between them. *(The liver of mouse injected with carbon tetrachloride will be swollen largely)*
### Results

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight (g)</th>
<th>Carbon Tetracholide (0.2 ml/10g)</th>
<th>Thiopental sodium (0.1 ml/10g)</th>
<th>Anesthetic action</th>
<th>Appearance of livers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Latent period</td>
<td>Anesthetic duration</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table: Influence of liver impairment on the action of thiopental sodium*
Discussion

1. What change will happen to the anesthetizing action time of thiopental sodium when the liver function is impaired?

2. What is the clinical significance of the results gained from the experiment?