Editorial

Iatrogenic Toxic Liver Disease

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Important factors for toxic injuries of the liver are route of application, binding rate to plasma proteins elimination rates, biotransformation, enzyme induction, covalent binding to macromolecules and lipid peroxidation. The concurrence of these factors in the production of toxic liver injury is demonstrated in paracetamol-poisoning and isoniazid-hepatitis. In order to avoid misunderstanding and nomenclatory difficulties it is recommended to distinguish between obligatory and facultative hepatotoxins (or toxic hepatic reactions).

The liver is the main site of metabolism of environmental chemical agents and drugs. Therefore, it is often damaged by toxins. Several factors contribute to the variety of these toxic injuries (Table 1).

ROUTE OF APPLICATION, BINDING CAPACITY
AND ELIMINATION RATES

Parenterally administered substances are distributed evenly in the body. Only 30% pass the liver in the first circulation. Substances having an alimentary portal of entry behave differently. Their total amount passes the liver before entering systemic circulation (Fig. 1). However, the hepatic elimination rate varies. Some substances are mostly or almost completely extracted while others have a low first pass-elimination rate (Table 2). The importance of these mechanisms becomes obvious when the circulation in the liver or the metabolic capacity of the liver is impaired (1). A further factor of importance is the binding rate of substances to plasma proteins since, generally, only their free fraction is able to penetrate the liver.

BIOTRANSFORMATION

Most of the environmental agents and drugs are lipid-soluble and almost insoluble in water. Therefore, they easily pass the cell membranes and cumulate within the cells. The liver converts these substances to more polar (water-soluble) metabolites for excretion into bile or urine.

Biotransformation is largely a function of the smooth endoplasmic reticulum (microsomes), which contains the necessary enzymes. Key-enzymes are found in a system of related mixed-function oxidases. Their most important component is called cytochrome P-450. It has a very low substrate specificity and readily metabolizes most lipid-soluble substances. This first step of metabolism involves oxidation, reduction or hydrolysis, and

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Table 1  Important factors influencing hepatotoxicity

<table>
<thead>
<tr>
<th>Route of application</th>
<th>Binding rate to plasma proteins</th>
<th>Elimination rate</th>
<th>Steric configuration</th>
<th>Biotransformation</th>
<th>Enzyme induction</th>
<th>Covalent binding to macromolecules</th>
<th>Lipid peroxidation</th>
</tr>
</thead>
</table>

Fig. 1  Distribution of a drug according to the route of application.  
(After Münst and Bircher (3))

Table 2  Hepatic elimination rates of some important drugs

<table>
<thead>
<tr>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprenolol</td>
<td>Antipyrine</td>
</tr>
<tr>
<td>Clinnarizine</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Clomethiazol</td>
<td>Meprobamate</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Opiates</td>
<td>Pentobarbital</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Phenytoine</td>
</tr>
<tr>
<td>Salicylamide</td>
<td>Procainamide</td>
</tr>
<tr>
<td></td>
<td>Rifampicine</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
</tr>
</tbody>
</table>

(After (3))
the metabolites can be highly active and therefore toxic. In a second step, many metabolites are neutralized by conjugation with weak acids like glucuronic or sulfuric acids (Fig. 2).

Only polar substances with a molecular weight of less than 200 pass the cellular membrane freely. The molecular weight of most of the metabolites is higher. In order to be excreted from the cell they need an active transport system.

**ENZYME INDUCTION**

The decreasing effectiveness of barbiturates with repeated use is a well-known fact. Experimental studies delineated to elucidate this phenomenon revealed an active response of the metabolizing cell: Enzyme induction (4). Many lipid-soluble drugs and environmental chemical agents cause an increase of the smooth endoplasmic reticulum of the hepatocyte as well as a selective increase in the amount of its enzymes. Enzyme induction is, in general, a beneficial reaction which facilitates the metabolism and the excretion of foreign, lipid-soluble substances. However, enzyme induction may become dangerous when toxic metabolites are produced.

**COVALENT BINDING TO MACROMOLECULES**

Biotransformation often results in the activation of chemically stable substances to potent alkylating, arylating, or acylating agents. They are positively charged either because of the loss of electrons or because of the formation of free radicals.

If such highly reactive agents are not immediately broken down or conjugated they attack macromolecules (cell proteins) which are rich in electrons and therefore negatively charged. This covalent binding is an irreversible and, in its initial interaction, a physicochemical reaction.

Regarding the toxicity of reactive metabolites, at least four kinetic determinants must be considered (2): (1) the proportion of the dose of the toxicant that is converted to a chemically reactive metabolite;

(2) The proportion of the reactive metabolite that becomes covalently bound to cellular components;

(3) The proportion of the covalently bound metabolite that is attached to important cellular components;

(4) The proportion of vitally important structures that cannot be replaced or repaired rapidly by the cell.

Covalent binding to different hepatocellular macromolecules partly explains the morphologic variety of toxic hepatopathies. Since the smooth
endoplasmic reticulum is the main side of biotransformation, it frequently is the target of reactive agents. Due to the vital importance of this organelle, the damaged cells become necrotic. A model hepatotoxin of this kind is carbon tetrachloride.

The hepatocellular microtubular system is not of vital importance but it is essential for biliary secretion. When the affinity of the reactive metabolite (e.g., 17α-methyltestosterone) causes covalent binding to pericanalicular microtubules, cholestasis is the consequence. Jaundice lasts until the damaged microtubular system has been replaced.

Small molecules such as the reactive metabolites of drugs may serve as haptnens and elicit an antibody response only after they become covalently bound to macromolecules (2). Examples are the halothane-induced and the oxyphensatine-induced hypersensitivity reaction. Antigens may become attached to the cell membrane of hepatocytes by a mechanism similar to the incorporation of the hepatitis B-surface antigen. This explains why allergic hepatitis can closely resemble acute viral hepatitis or chronic aggressive viral hepatitis.

Most alkylating agents (e.g., cyclophosphamide, vinylchloride, aflatoxins) are carcinogenic for humans if ingested for a sufficient period of time, the latent period being 10 - 30 years before the neoplasia is expressed. Probably, the covalent binding to the DNA-molecule causes breaks in the nucleotide-chain resulting in the loss of fragments or the incorporation of "false" nucleotides, giving the DNA mutagenic properties.

Besides covalent binding, lipid peroxidation is another possibility of a damaging action: The peroxidative degradation of polyunsaturated fatty acids starts with an initiating reaction leading to the formation of the polyunsaturated fatty acid free radical, which reacts with oxygen to yield a peroxy radical. The peroxy radical reacts with a second molecule of polyunsaturated fatty acid, and so on. This chain reaction may be terminated in a variety of ways, e.g. by formation of aldehyde products or ethane (Table 3). The peroxidative degradation of polyunsaturated fatty acids may cause substantial damage to the structure and metabolic functions of biomembranes such as the endoplasmic reticulum of the hepatocyte.

### Table 3 Lipid peroxidation

| (i)  | PUFA (H) + R'  | PUFA' + RH |
| (ii) | PUFA' + O₂  | PUFA O₂' |
| (iii) | PUFA O₂' + PUFA (H) | → PUFA₂⁺H + PUFA' |
| (iv) | PUFA O₂' | diene conjugation |
| (v)  | PUFA O₂' | aldehydes, hydroxy-alkenals, ethane |

(PUFA = polyunsaturated fatty acid)  
(Slater (5))

**CONCURRENCE OF THE VARIOUS FACTORS IN THE PRODUCTION OF TOXIC LIVER INJURY**

Recent studies revealed the initiating events of many toxic hepato-pathies. Paracetamolpoisoning and isoniazid-hepatitis are instructive examples (2).
Paracetamol (acetaminophen, acetyl-p-aminophenol) was considered to be one of the safest of all analgetics and antipyretics until its suicidal possibilities where discovered. When oral overdoses of more than 15 gms. are taken, fulminant necrosis of the liver follows after a latent period of 24 to 48 hours.

Some fractions of acetaminophen are conjugated with sulfuric acid or with glucuronic acid and excreted in the urine. A third part is oxidized by a cytochrome-p-450-dependent, mixed function oxidase to an arylating metabolite which is detoxified by reacting with glutathione. The conjugate forms of readily excreted mercapturic acid. After the liver is depleted of glutathion, the metabolite combines with essential liver macromolecules and necrosis occurs (Fig. 3).

![Fig. 3 Pathways of acetaminophen metabolism. (Mitchell and Coll. (2))](image_url)

Inducers of cytochrome P-450 enzymes potentiate the hepatic injury caused by paracetamol. A phenobarbital addict dies after a dose of only 7.5 g (7).

Toxicity may apply not only to drugs given in large overdoses but also after therapeutic doses of drugs. Isoniazid is hepatotoxic in 23% of the patients, but overt isoniazid-hepatitis only occurs in 0.7%.

The rate of acetylation of isoniazid has been shown to be under genetic control. The metabolism of isoniazid and acetylisoniazid was recently reexamined (4). In patients who are rapid acetylators (about 45% of the population of Central Europe), 94% of the isoniazid was mainly converted
to the atoxic metabolite diacetylisoniazid and 6% was excreted either unchanged or as hydrazone conjugates. Slow acetylators, on the other hand, excreted almost 37% of the drug in the urine but 63% was converted to acetylisoniazid.

Acetylisoniazid, however, is oxidized by cytochrome P-450 oxidases to reactive acylating intermediates which either react with water and produce acetate or bind to macromolecules (Fig. 4).

In chemotherapy for tuberculosis a combination of isoniazid and rifampicin is preferred. Rifampicin again is a potent enzyme-inducer which increases the metabolic activation of acetyl-isoniazid. Therefore, this combined therapy can become dangerous when slow acetylators are involved (Dengler H., personal communication).

Fig. 4 Pathways of isoniazid metabolism.
OBLIGATORY AND FACULTATIVE HEPATOTOXICITY

Formerly, hepatotoxins were divided into direct (absolute) and indirect (relative) toxins. However, it may only be a matter of the dosage whether a substance is a safe and harmless drug or a deadly poison (paracetamol). On the other hand we have learned that many so-called direct hepatotoxins are chemically stable and only become toxic by metabolic activation (carbon tetrachloride).

Toxic hepatic reactions were divided into predictable and unpredictable reactions, but it was shown that unpredictable reactions, e.g. the isoniazid-hepatitis, become predictable in special groups of genetically determined individuals, especially after pretreatment with enzyme-inducers.

These difficulties are avoided when a simple classification of obligatory and facultative hepatotoxins or toxic hepatic reactions is used (6) (Table 4).

<table>
<thead>
<tr>
<th>Obligatory</th>
<th>Facultative</th>
</tr>
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<tbody>
<tr>
<td>Predictable</td>
<td>Unpredictable or limited predictability</td>
</tr>
<tr>
<td>Reproducible</td>
<td>Not always reproducible</td>
</tr>
<tr>
<td>Dose dependent</td>
<td>Dose independent</td>
</tr>
<tr>
<td>Not influenced by age and sex</td>
<td>Very rare in children</td>
</tr>
<tr>
<td>Short latency period</td>
<td>Long and varying latency periods</td>
</tr>
<tr>
<td>Animal models with characteristic lesions</td>
<td>Rare animal models with uncharacteristic lesions</td>
</tr>
</tbody>
</table>

(Thaler (6))

REFERENCES


