Clinical Aspects of Liver Diseases

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1 Drugs as foreign substances

Xenobiotics: Xenobiotics are defined as exogenously administered or endogenously produced foreign substances that impair and ultimately damage the ecology and homoeostasis of cellular systems. This definition also includes medicinal preparations. (s. p. 52)

All orally or parenterally administered drugs enter the liver and from here, after passing through **biotransformation systems,** are released into the cardiovascular system in an unconverted or a metabolically converted state. In addition, systemic effects have to be anticipated in cases of topical administration (cutaneous, inhalant). • Metabolic processes generate **metabolites,** more specifically *catabolites* (= degradation products) and *anabolites* (= synthesis products). These biochemical processes are catalyzed or controlled inside and outside the cell by enzymes, hormones and the neurovegetative system. • Exogenous substances may also be metabolized and excreted without enzymatic processing by spontaneous chemical conversion (= **metabonates**).

► Of the many different xenobiotics, only a small fraction are sufficiently water-soluble to be excreted in an unchanged state via the kidneys or the bile. These are strongly polar groups such as penicillin, cephalosporin, tetracycline, thiazide, amiloride and cromoglycic acid; so far, no metabolites of these substances have been found. The phase-I reaction comprises non-synthetic processes such as the oxidation, reduction or hydrolysis of medicinal products. This largely takes place in the endoplasmic reticulum via the cytochrome P-450 isoenzyme system. For the metabolism of foreign substances, CYP 3 A 4 is quantitatively important. • The mainly lipophilic foreign substances can only be eliminated by **biotransformation,** i. e. by the metabolic production of water-soluble compounds. Phase-II reactions also occur due to specific transferases. The medicinal preparation as well as its metabolites are conjugated by various substances; this mainly takes place in the cytosol of the hepatocytes. These conjugation processes develop slowly during the first weeks of life. The metabolization of drugs via the kidneys, intestinal mucosa, muscles, lungs and skin is of minor importance in this context. (s. pp 52–55) **Biotoxometabolites** (or biotoxometabonates) may occur as a result of faulty biochemical reactions. (s. fig. 3.11) • The metabolization of medicaments also involves *antioxidants* (s. p. 67) as well as some functions of the *hepatic RES*. (s. pp 64–66) • The biochemical mechanisms related to the metabolism of xenobiotics may be affected by **non-variable factors** such as genetics, gender and age, or by **variable factors**. In individual cases, such factors may be of crucial importance. (s. tab. 3.18) (s. fig. 3.11) • The pharmacokinetic characteristics of a certain drug may be largely determined by the *pharmacogenetics* of the single patient. The enzymes responsible for biotransformation are also influenced by *genetics*; this affects largely the phase-II reactions (and occasionally the oxidation process in phase I). *Genetic polymorphism* prevails if a certain enzyme variant is found in ≥ 1% of the population. (9, 29, 65, 96)

Medicaments that have a hepatic clearance of > 60% when passing through the liver (bioavailability = 30–40%) are termed "high clearance substances". This rate of clearance depends on the hepatic circulation. • Medicaments with a hepatic clearance rate of < 30% (bioavailability = 70–80%) are termed "low clearance substances". The clearance process itself largely depends on the metabolic function of the liver. • With increasing age and/or with the existence of liver disease, hepatic clearance and the biotransformation of medicaments decline, whereby phase I is predominantly affected. Thus medicinal products that are mainly metabolized during phase II are not impaired. *(see chapter 3.12)*.

The recognition that a system which metabolizes drug products can also produce highly reactive **toxic metabolites** has proved crucial. As the liver has the highest number of enzyme biotransformation systems, it is the main site of production of such reactive metabolites and is thus more susceptible to damage. • Medicaments must therefore be regarded as **potentially hepatotoxic substances.** Basically, they can trigger a vast range of functional and morphological changes in the liver. The resulting hepatic damage can mimic almost any acute or chronic liver disease. *This means that in terms of function, morphology and clinical presentation, it is virtually impossible to differentiate between drug-induced liver diseases and the non-iatrogenic liver diseases they mimic.*

Drugs always have to be considered in the differential diagnosis of any case of liver disease lacking unequivocal clarification. The diagnosis of a pharmacon-related liver disease depends on the reliable exclusion of other potential causes of the existing disease as well as on the so-called withdrawal trial.

2 Frequency

Quantification: With regard to their frequency, adverse side effects are classified as (*1.*) *frequent* (>10%), (*2.*) *occasional* (1–10%), (*3.*) *rare* (<1%), (*4.*) *very rare* (<0.1%), and (*5.*) *isolated cases* (not yet quantifiable).

Surprisingly – but also understandably, given the great difficulties related to any reliable quantification – very little information is available regarding the **frequency** of adverse side effects in patients taking medication. A total of 2.3% or 1.9–6.2%, sometimes even up to 20%, of all hospitalizations has been attributed to drug-related diseases; 2–5% of all hospitalized types of jaundice and 25% of all patients with acute necrotizing hepatitis have been diagnosed as medication-induced toxicosis. • A ten-year study carried out in Sweden between 1966 and 1975 listed 274 deaths due to pharmaceutical preparations, 23 (9%) of them with toxic liver damage. (11) In Denmark, the incidence of drug-induced side effects doubled within the space of ten years (1978–1987). (32) In Japan, there was an 11-