Silvio Garattini
Editor

POST-MARKETING SURVEILLANCE OF DRUGS
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POST-MARKETING SURVEILLANCE OF HEPATOTOXICITY

Niels Tygstrup & Henrik Enghusen Poulsen
Med.Dept.A, Rigshospitalet, Copenhagen, Denmark.

Adverse hepatic reactions to drugs have been ascribed to a large number of drugs (more than 600) of almost any type (1). In many cases, however, the casual relation is not directly proven, and this together with the large variety of hepatic drug reactions, makes detection of hepatotoxicity by surveillance programmes difficult.

Several definitions of hepatotoxic reactions are possible, depending both on the purpose of using the term, and the methodology applied.

Four types of observations, here ranked according to their sensitivity, may be used: 1) liver morphology (liver biopsy), 2) serum markers of liver cell damage, 3) changes in the function of the liver, and 4) symptoms and signs of clinical liver disease. In phase I, II and III premarketing studies morphology and markers of liver cell damage are most commonly used, in phase IV (surveillance) programmes liver function and clinical liver disease are of major importance, but morphology and markers of liver cell damage may be of interest for early detection. In post-marketing surveillance spontaneous reporting, in many cases by general practitioners, is most important.

Morphology:

Focal sinusoidal cell activation, small foci of necrosis, slight inflammatory infiltrates in the portal tracts, scattered fat droplets in liver cells, mild ductular proliferation and pigment accumulation may be due to drug intake, but may also be seen in individuals not taking drugs, and these changes are rarely accompanied by changes in liver function of clinical liver disease.

The acute morphological changes are of two types, one characterized by liver cell necrosis and the other by accumulation of bile in bile canaliculi (cholestasis). In most cases both changes can be found; a clear distinction between

them is not possible, but some drug reactions are typically dominated by liver cell necrosis and others by cholestasis. The distinction has some practical implications in that cholestatic reactions may be more benign, and may be misdiagnosed as biliary disease.

A separate change is acute fatty metamorphosis, occasionally seen after treatment with tetracyclin (2).

Chronic changes may be in the form of fibrosis, chronic active hepatitis, cirrhosis, steatosis, vascular changes, and benign and malignant tumors.

Some morphological drug reactions may include special features which will give the trained histopathologist suspicion of drug reaction, but in general they are unspecific and similar to the changes seen in other types of liver disease. However, necrosis in the centrilobular region should always raise suspicion of drug-induced liver injury.

Markers of liver cell damage:

If the liver cell dies, or the cell membrane is damaged, intracellular substances may be found in the blood in increased concentrations. This applies especially to aminotransferases which are considered sensitive markers of liver cell damage (3). Increased serum enzymes may, however, be caused by chlofibrate (4), without other signs of hepatotoxicity. The enzyme elevations are not very specific, especially when moderate. Alkaline phosphatases are markers of cholestasis (3). The ratio between aminotransferases and alkaline phosphatases is often used to distinguish between necrotic and cholestatic drug reactions, a high ratio suggesting parenchymal damage and a low ratio cholestasis, but as with liver morphology they do not provide a clear distinction.

Changes in liver function:

Among the common liver tests only serum bilirubin and prothrombin time are associated with liver function. They are both insensitive indices of liver cell function. Prolonged prothrombin time will usually indicate a severe decrease of liver cell function, whereas hyperbilirubinemia will also be present in cholestasis with fairly well preserved liver function. Certain drugs, e.g. novobiocin (5) and cholegraphic contrast media (6) specifically interfere with the excretion of bilirubin and cause slight hyperbilirubinemia.

Acute clinical liver disease:

Drug-induced liver disease in most cases is of the hepatocellular necrotic or the cholestatic type. Furthermore, they are divided into two pathogenetic types, I and II. It should be noted that this distinction is mainly based on our present knowledge. As an example the anaesthetic halothane can be characterized as a type I reaction in animal experiments (7), but as a type II in clinical situations (8).

Type I ('direct') hepatotoxic reactions are characterized by being dose-dependent and are usually reproducible in animals. Classical examples are carbon-tetrachloride (9) and acetaminophen (10). In most cases not the substance itself, but its metabolites, formed in the drug metabolizing mixed function oxidase system in the liver cells, are assumed to be the cause of liver cell damage. Free radicals or epoxides may react with macromolecules in the liver cell and thereby destroy different organelles.

Type II ('indirect') hepatotoxic reactions are not dose-dependent, most of them are rare and unpredictable, and they cannot be reproduced in animal experiments. They have also been called hypersensitivity reactions, but it is uncertain whether the immune system is involved. It cannot be excluded that the mechanism of hepatotoxicity is similar to that of the type I reactions. The drugs are often metabolized by cascade reactions, with a large number of secondary and tertiary metabolites, of which one or a few may be highly reactive. In most cases they are formed in such small amounts that they are readily detoxified and therefore harmless, but many factors - genetic, environmental or interaction with other drugs (11) - may change the pattern of metabolism and detoxification in such a way that the threshold for the toxic metabolite(s) is exceeded. The system is sufficiently complicated and unknown to make such reactions unpredictable.

The large list of known or possible hepatotoxic drugs mostly belong to this category. Classical examples are disulfiram (12) and chlorpromazine (13).

Chronic liver disease is rare, perhaps because the association with drug intake is less easily recognized. Cirrhosis due to treatment with methotrexate is well documented (14) and chronic active hepatitis or cirrhosis after long-term treatment with oxiphenisatin (15) and alpha-methyldopa (16) are also likely.

Other types of drug reactions in the liver are hepatoma and liver thrombosis caused by contraceptive steroids (18), and hepatocellular carcinoma caused by synthetic anabolic steroids (18). A variety of malignant tumours are caused by thorium dioxide (19) and arsenicals, which also cause portal hypertension (10).

The significance of hepatotoxic drug reactions:

In order to evaluate the magnitude of this problem Martin Døssing and Per Buch Andreasen from our unit made an analysis of liver-related drug reactions based on reports of a decade to the Danish Board of Adverse Reaction to Drugs (21). Six percent of the reports were related to hepatotoxicity, and this group accounted for 12 percent of the fatal drug reactions. Age and sex distribution corresponded to the general pattern of drugs used, i.e. with preponderance of the older age groups and of females. The most common causes were halothane (25%), chlorpromazine (16%), oral contraceptives (9%), and the combination trimethroprim-sulfamethoxazol (7%), but antiinflammatory, tuberculostatic, laxative, antiepileptic,. and antihypertensive drugs were also relatively frequent causes.

Halothane-induced acute liver damage was characterized as cholestatic in only 2 percent, it was fatal in 13 percent and severe in half of the remaining cases. In contrast chlorpromazine-induced liver damage was cholestatic in 80 percent, and severe in 31 percent of surviving cases. Oral contraceptives caused no death, and trimethoprim-sulfamethoxazol one death.

Chronic liver disease (chronic active hepatitis or cirrhosis, verified by biopsy) was found in 28 cases, the most frequently recorded cause (8 cases) being oxiphenisatin.

The latency period, from when the drug was given to when the hepatotoxic reaction was recorded, varied from 1 day (halothane and chlorpromazine) to 13 years (oxyphenisatin). For halothane (repeated anaesthesias), trimethoprim-sulfamethoxazol and nitrofurantoin, the median was 4 days, for halothane (first anaesthesia) 10 days, for chlorpromazine 14 days, for alpha-methyldopa 38 days, for oral contraceptives 225 days, for androgenic and anabolic steroids 1 year, and for oxyphenisatin 3 years.

Unfortunately, it was only possible in a few cases to relate the number of reactions to the usage of the drug. It was estimated, however, that there was one halothane reaction per 600 anaesthesias (=0.17 promille). For trimethoprim--sulphamethoxazol the reations were 3.5 times more frequent in relation to doses given than for sulphamethizol.

It can be questioned whether this is a true picture of hepatic adverse drug reaction in Denmark. There are several reasons to doubt this. Firstly notification is known to be quantitively unreliable. Some diseases, like meningococcal meningitis, is probably reported in almost any case, whereas other diseases, like rubella, are reported only sporadically. It is estimated that virus hepatitis is reported in less than

half of the cases, even if the correct diagnosis is made, and it may well be even less for hepatotoxic reactions.

More important, however, is that hepatotoxic reactions are not always recognized as such. As mentioned, they are usually unspecific and may be diagnosed as independent liver disease, if the physician does not a priori suspect a relation. This will often be the case if the reaction is rare or has a long latency period. The high frequency of reported reactions to halothane, trimethoprim-sulphamethoxazol and contraceptive steroids may be due to a special interest in these reactions, resulting in several publications in the national medical press. This tendency to focus on special drugs may result in over-reporting, when drug administration coincides with non-drug induced liver disease.

In the case of the infrequent type II reactions a causal relation only can be confirmed by challenge with the drug under careful supervision. Challenge may be unintended, i.e. the reaction reappears each time the drug is given. Intended challenge is only warranted if the reaction is acute, relatively mild, and fully reversible. This was how hepatotoxicity due to disulfiram (antabuse) was detected (12). This is an example of a difficult case, because the drug is usually given to patients who may suffer from liver disease due to alcohol abuse. Fortunately the reaction of the patient who was challenged was mild. Later on 4 fatal reactions were notified to the Danish Board of Adverse Reaction to Drugs.

Surveillance:

Surveillance is particularly important concerning type II hepatotoxic reactions and chronic liver disease. Due to their low frequency, type II reactions are rarely detected in pre-marketing studies. The probability of relating such reactions to a drug depends mainly on the frequency of the reaction (the disease provoked by the drug), the frequency of the disease which the reaction simulates (e.g. virus hepatitis), and the number of people exposed to the drug. Theoretical considerations are given elsewhere (22).

Notification is a necessary measure, but not sufficient, partly because of the inherent defects, discussed above, partly because they rarely can be analyzed in relation to the usage and benefits of the drug. Health authorities and physicians cannot make sound decisions on the significance of hepatotoxic reactions without detailed knowledge of the exposure of the population to the drug, and the benefits it has. Halothane is an example of a drug in which hepatotoxicity, even though often severe, is so rare, and other benefits so great, that it is not withdrawn from the market. On the other hand oxyphenisatin is withdrawn in most countries, even if

the proof of hepatotoxicity is circumstantial (23), because this drug is easily replaced by other innocent ones.

Cohort studies may reveal an association between a given drug under suspicion and liver disease, whereas case-control studies may also incriminate other drugs. In chronic liver disease of unknown etiology, i.e. when drug reactions are a possible cause, case-control studies probably will be most useful. In any case, however, studies will have to include large numbers of patients due to the unpredictable manifestations of hepatotoxic reactions.

Complete registration of all drugs administered to a population and of all patients with signs of liver disease is the most informative and most certain form of surveillance. It is theoretically feasible, but extremely expensive and probably not acceptable. To be effective, it should include drug-store preparations obtained without prescription, herbal drugs and other 'natural medicines' which enjoy great popularity in large groups which would probably resent systematic registration.

Patients with liver diseases:

Where health authorities or drug companies suspect hepatotoxic reactions it is customary to warn against the use in patients with liver disease. It is not known whether hepatotoxic type II reactions are more frequent in liver patients than in patients with normal liver. With regard to type I reactions, however, it is possible that decreased metabolization of the drug in the patient's liver may protect against hepatotoxicity, since most reactions are caused be metabolites (24). Therefore, in these patients, as in others, the usual risk/benefit considerations should apply. It may be more important to keep in mind that drugs eliminated by the liver may reach higher levels in liver patients and that their risk of unwanted and general toxic reactions therefore is high if conventional doses are given.

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