Acute hepatitis due to poisoning

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The term "liver poisoning" mainly applies to hepatic damage related to acetaminophen overdose, amanita mushroom, chlorinated hydrocarbons, arsenic and various non orthodox compounds such as vegetal substances or herbal remedies.

Acetaminophen "overdose"

Acetaminophen (paracetamol) overdose remains one of the most common intoxications, especially in United Kingdom. Acute liver failure related to paracetamol results from accidental ingestion or suicidal attempt. On the physiopathological point of view, acetaminophen is metabolised in the liver into various sulfo- and glucurono-conjugates, catechol metabolites, N-acetyl-p-benzoquinone imine (NAPQI) and p-aminophenol. NAPQI is likely the major cytotoxic and hepatotoxic metabolite and its production as that of catechol metabolites is closely dependent of Cytochrome P450 function. The alcohol inducible CYP 2E1 is mainly involved in this oxydative process and its induction such as that observed in chronic alcohol abuse results in an increased production of NAPQI and an increased risk of liver toxicity. The detoxification pathway of NAPQI involves glutathione conjugation and all circumstances in which glutathione depletion occurs may be associated with a higher susceptibility to toxicity. Among others, denutrition, chronic alcoholism and morbid obesity may thus promote toxicity and liver injury (1). Conversely, N-Acetyl-L-Cysteine exerts a protective effect primarily by the elevation of intracellular glutathione concentrations in situations where it becomes depleted. On a clinical point of view, paracetamol hepatotoxicity rarely occurs in adults taking less than 12 g of the compound. However, in situations in which NAPQI is increased and/or detoxification is reduced, severe hepatotoxicity may occur following the administration of doses as low as 3.5 g/day. In a recent study of prevalence and characteristics of acetaminophen-associated liver injury in hospitalized patients mortality was higher in accidental overdose (19%) than in suicidal attempts (2%) and was observed in 5 cases (7%) who had taken 4 g of acetaminophen or less (2). Great care should thus be taken in patients with increased susceptibility due to CYP 2EI induction and/or glugathione depletion in whom doses considered in the therapeutic range by most physicians may induce severe liver necrosis. Early recognition is of obvious utmost importance since urgent (within 15 hours) I.V. N-Acetyl-L-Cysteine administration nearly suppresses mortality.

Amanita mushroom poisoning

Amanita mushroom poisoning mainly occurs with Amanita species (*A. Phalloides, Verna, Virosa*). In adults, the consumption of 50 g of Amanita (about 3 full mushrooms) may lead to severe liver toxicity.

Toxicity is related to amatoxins (mainly amanitin) which are heat-stable, have an enterohepatic circulation and bind to cellular proteins.

On a clinical point of view, ingestion of Amanita is followed after a latent period of 6 to 24 hours by a gastrointestinal phase (vomiting and diarrhea) lasting for 2 or 3 days and which may induce dehydratation, hypotension and acute renal failure. A cytolytic hepatitis develops within 36 to 48 hours following ingestion. The prognostic evaluation of acute liver failure resulting from Amanita poisoning is exceedingly difficult, death being observed in 84% of cases with PTT below 10%. Plasma amanitin determinations show low plasma concentrations during a short period of time (24-48 hours) while high urine concentrations are eliminated during 3-4 days. Treatment is now that of acute liver failure of other origin and good results of liver transplantation are increasingly reported (3,4).

Industrial solvents

Several industrial solvents, mainly chlorinated hydrocarbons are highly toxic to the liver. Acute carbon tetrachloride (CCl_4) poisoning is now very uncommon since its industrial use was prohibited. Hepatotoxicity is caused by reactive species which results from CYP 450 primary metabolism and ensuing secondary metabolism leading to lipid peroxydation. As with that of acetaminophen, liver toxicity may be increased by CYP 450 induction and/or glutathione depletion (5).

On a clinical point of view, CCL_4 may induce fulminant liver failure which is frequently associated with acute renal failure related to acute tubular necrosis. Early treatment with N-Acetyl-L-Cysteine may decrease the formation of toxic metabolites and thus reduce the extend of liver necrosis. The intrinsic liver toxicity of trichloroethylene is low and liver toxicity reported in sniffers of solvants containing the compound were likely related to fraudulent addition of CCl_4 to trichloroethylene.

Other industrial hepatotoxic agents include 2-nitropropane, dimethylformamide and monochlorobenzene.

Arsenic

Arsenic (especially AS_2O_3) is a highly toxic compound which causes a spectrum of systemic toxicities among which digestive, neurologic and hemodynamic (especially vasoplegy) features. Due to the lack of specificity of the clinical symptoms the diagnosis may be extremely difficult and even overlooked if the determination of urinary arsenic is not performed. Due to its X-Ray radioopaqueness AS_2O_3 a gastric precipitate may be readily visible on a plain X-ray of the abdomen also suggesting the diagnosis. Liver dysfunction is usually present together with increased liver enzymes resulting from mild associated hepatitis. Liver biopsy shows a stricking increase in mitotic figures, a feature which may proof of high diagnostic value (6).

Other non orthodox medicines and herbal remedies

An increasing number of vegetal substances have been recognized as potentially hepatotoxic. The main herbal substances implicated in hepatotoxicity include *Teucrium chamaedrys* (Germander), plants containing pyrrolizidine alkaloids (*crotalaria, senecio, heliotropium, ...*) *atractylis gummifera*, chinese herbs, *senna* and *valeriane officinalis*. The best known substance toxic to the liver is Germander which has been used for more than 2 000 years for relieving fever and abdominal disorders. The compound has been largely used in the recent years for its diuretic, choleretic and healing properties. The implication of Germander in more than 30 cases of liver injury in France led to withdrawal from the market in this country in 1992 as in Belgium. However, the substance remains available in a number of pharmacies as well as in specialized stores. Mechanism of Germander liver toxicity which involves CYP3A has been recently identified (7). Other vegetal compounds have been shown to induce various types of liver injury, pyrrolizidine alkaloids such as that contained in *heliotropium* having been implicated in veno-occlusive disease.

In conclusion, liver poisoning remains a challenge for clinicians, toxicologists and researchers. Early clinical recognition and diagnosis are of utmost therapeutic importance and may be extremely difficult. The help of an expert toxicological laboratory is mandatory as well as the proximity of liver transplant facilities.

On a pathophysiological point of view, advances made during the recent years in the understanding of the mechanisms of toxicity have been considerable allowing for better management and therapy.

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