Hepatotoxicity of Psychotropic Drugs

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Psychotropic drugs with hepatotoxic potential can be classified based on their intended use: 1) antipsychotics-neuroleptics including phenothiazines, butyrophenones, and clozapine; 2) antidepressants including tricyclics, serotonin reuptake inhibitors, and monoamine oxidase (MAO) inhibitors; 3) anti-anxiety drugs such as benzodiazepines; 4) acetylcholinesterase inhibitors such as tacrine; and 5) drugs of abuse including cocaine and ecstasy. Antiseizure drugs represent another class of central nervous system (CNS) drugs, but will not be considered here. Hepatotoxicity of psychotropic drugs occurs in a variable but small proportion of users and therefore can be considered unpredictable or idiosyncratic. When these uncommon adverse events occur in association with rash, eosinophilia, and/or a rapid positive rechallenge, sufficient circumstantial evidence exists to ascribe the mechanism to an immune-mediated hypersensitivity reaction. Acute overt reactions to drugs tend to have clinicopathological features of hepatitis (destruction of liver parenchyma), cholestasis (impaired bile secretion), or both.

The hepatotoxic reactions to psychotropic drugs conform to these general patterns. Furthermore, as with most hepatotoxic drugs, individual psychotropic drugs have a characteristic pattern of injury, *i.e.*, cholestatic for some (*e.g.*, chlorpromazine, haloperidol, tricyclics), hepatitic for others (*e.g.*, hydrazines, MAO inhibitors, cocaine, ecstasy) (see Table 1).

NEUROLEPTICS

Phenothiazines. Phenothiazines, although no longer in widespread use, typify numerous drugs associated with liver injury. There is a high background of asymptomatic liver test abnormalities (>20%) and a lower incidence of overt liver disease (0.1%-1%). Features of hypersensitivity are seen in about half the phenothiazine cases (including positive rechallenge).[1-4] Chlorpromazine has been the most extensively studied. The clinical features appear to be accounted for by a mix of hypersensitivity reaction and metabolite toxicity. The bile ductule may be an important target, and a ductopenic syndrome is the most severe, although uncommon, consequence.

The classic description of the clinicopathological picture of phenothiazine-induced hepatic injury, written by Ishak and Irey in 1972,[3] remains the standard in the field. It describes 36 validated cases, of which 33 had received chlorpromazine. A prodrome of nonspecific symptoms lasting 1 to 2 weeks was common. Eosinophilia was observed in three quarters. Four developed a chronic ductopenic syndrome (over 30 have been reported in all; 3 progressed to cirrhosis, although many lacked long-term follow-up). A survey of prescriptions in the United Kingdom from 1985 to 1991 revealed an overall incidence of chlorpromazine jaundice of 0.16%, increasing to 0.3% over age 70, more than 10 times higher than in those below age 50.[4] Cross-reactivity among phenothiazines is extremely rare,[17] but avoidance of this class of compound is probably prudent in any patient with suspected history of an overt hepatic reaction to chlorpromazine.

Most of the work on pathophysiology of experimental chlorpromazine cholestasis dates back about 20 years, implicating reactive metabolites, with damage to membranes and the cytoskeleton, and prostaglandin-induced sinusoidal perfusion abnormalities.[5-8] Chlorpromazine metabolism is very complex. Experimentally, it produces a dose-related impairment in bile secretion, inhibiting NaK adenosine triphosphatase and altering membrane fluidity.[9-11] Ring-hydroxylated products are more potent and the sulfoxidation product less potent.[12,13] In experimental animals, dose-related cholestasis is induced within minutes. Chlorpromazine is a cationic amphiphile with detergent properties; it binds to and precipitates bile acids and phospholipids. It is, however, unclear if these effects are responsible for cholestasis. In monkeys, phospholipid secretion is decreased much more significantly than is bile acid secretion.[13] Although the drug's use has declined, it would be of interest to re-examine the pathogenesis of its cholestatic effects in light of the recent advances in the knowledge of molecular mechanisms of bile secretion and drug metabolism.

Attempts to identify genetic factors in chlorpromazine hepatitis have been interesting, though limited and of uncertain significance. Because the sulfoxide seems less toxic, a genetic defect in sulfoxidation was sought.[12] The phenotyping employed *S*-carboxymethyl-L-cysteine, which presumably undergoes sulfoxidation as cysteine does,[14-16] in the pathway to sulfate formation. Thus, this test should not reflect CYP-mediated metabolism of chlorpromazine. However, all 12 patients recovering from chlorpromazine jaundice were deficient in sulfoxidation.[12] Could this indicate a defect in a pathway for detoxification of hydroxylation products (sulfation) or other endogenous substances? Certainly, the finding that 100% were deficient in cysteine sulfoxidation compared with 22% and 23.8%, respectively, of normal and liver disease controls may provide a clue as to factors that determine susceptibility.[12] However, questions about the methodology for phenotyping (paper chromatography) has cast doubt on the entire thesis.[15]

The mechanism of phenothiazine-induced cholestatic disease remains uncertain. In favor of a hypersensitivity mechanism is the early onset (<1 month), presence of rash and eosinophilia in some cases, and the lack of a dose-relationship in humans. However, a metabolic idiosyncratic reaction based on individual susceptibility cannot be excluded and is supported by an extensive experimental literature.

Butyrophenones. Haloperidol, while structurally similar to phenothiazines, is a very rare cause of overt liver disease. The features resemble phenothiazine-induced cholestatic injury.[18]

Abbreviations: MAO, monoamine oxidase; ALT, alanine aminotransferase; MDMA, 3,4-methylenedioxymethamphetamine.

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TABLE 1. Hepatotoxicity Caused by Psychotropic Drugs

Drug	Type of Injury	Incidence	Latency	Probable Mechanism
Phenothiazines				
Chlorpromazine	CH	0.1%-1% (↑ALT only 25%-50%)	1-5 weeks	Hypersensitivity idiosyncratic?
Butyrophenones				
Haloperidol	CH	0.002% (↑ALT only 16%)	4-5 weeks	Hypersensitivity
Misc. neuroleptics				
Clozapine	HC	rare (↑ALT only 37%)	5 weeks	unclear
Benzodiazepines				
Diazepam	CH or HC	rare	days-months	Hypersensitivity
Chlordiazepoxide			2-6 weeks	
Barbiturates				
Phenobarbital	CH or HC	rare	1-8 weeks	Hypersensitivity
MAO inhibitors				
Phenelzine	HC	rare	weeks	unclear
Tricyclic antidepressant				
Amitriptyline	CH or HC	0.5%-1% (↑ALT only 10%)	8 weeks	Hypersensitivity
Imipramine			1-3 weeks	
Desipramine			1-3 weeks	
Amineptine	HC	rare	2-3 months	Hypersensitivity
Other antidepressants				
Trazodone	HC or CH	rare	2-20 weeks	unclear
Nefazodone	HC	rare	14-28 weeks	unclear
Acetylcholinesterase inhibitors				
Tacrine	HC	ALT > 3-fold 20% ALT > 20-fold 2%	up to 12 weeks	idiosyncratic
SSRI Fluoxetine				
Fluoxetine	HC	rare	4 weeks	unclear
Drugs of abuse				
Cocaine	HC	unknown	hours to days	ischemic vs. toxic metabolite
Ecstasy	HC	unknown	hours to weeks	unclear

NOTE. Rare = one or few isolated reports. Hypersensitivity based on presence of clinical features.

Abbreviations: CH, cholestatic; HC, hepatocellular.

One case of ductopenic chronic cholestatic liver disease has been reported.[19] Liver test abnormalities from bromperidol also have been reported.[20]

Other. Clozapine is an "atypical" neuroleptic; an increase in alanine transaminase (ALT), which was mild and transient, occurred in 37% of recipients.[21] While this appears benign, toxic hepatitis also has been described.[22]

ANTIDEPRESSANTS

Tricyclics. Most tricyclic antidepressants are potentially hepatotoxic. Amineptine, which is not used in the United States, is the most extensively studied. Amineptine-induced liver disease is mainly cholestatic, although moderate necrosis may be seen. An immunoallergic mechanism is suggested by the occurrence of fever, rash, eosinophilia, and positive rechallenge. Amineptine is converted by microsomes into an epoxide that is detoxified by GSH.[23,24] Although poor hydroxylators are at decreased risk, 90% of whites are rapid hydroxylators (CYP2D6).[23] Thus, hydroxylator status is not a useful predictor of toxicity, although it points to the role of reactive metabolites capable of eliciting an immune response. *In vitro* cytotoxicity testing indicates that lymphocytes from patients and their first-degree relatives exhibit an increased susceptibility to killing by amineptine metabolites, suggesting an important genetic factor. The basis for the latter is unknown; it does not involve altered GSH or epoxide hydrase,[23] although impaired detoxification presumably could be responsible for exposure and sensitization to amineptine metabolites. The metabolism of tianeptine is similar to that of amineptine. The two compounds have an identical heptanoic acid side chain and, rarely, have been associated with microvesicular steatosis.[25] The side chain is metabolized by β-oxidation, leading to inhibition of medium- and short-chain fatty acid β-oxidation.[26,45] Thus, both drugs are converted by P450 to reactive metabolites that can induce a hypersensitivity reaction in genetically susceptible individuals. Less commonly, they induce a microvesicular steatosis; in mice, this requires much higher doses than those used therapeutically,[27] although one wonders if impaired oxidation of these drugs (in the presence of a competing P450 substrate or in a poor metabolizer) might lead, at least rarely, to the accumulation of sufficient levels of the parent drug to impair β-oxidation.

Imipramine can induce a cholestatic jaundice that generally is not progressive.[28] Although other tricyclics (including amitriptyline, desipramine, doxepin) rarely cause liver disease, the reported cross-reactivity should preclude their use when sensitivity to one has been suspected.[29] Occasionally, hepatitis-like injury has been reported with tricyclics.[30,31]

MAO Inhibitors. MAO inhibitors, which derive from hydrazine, are all potential hepatotoxins. The experience with one, iproniazid, was disastrous: overt hepatitis occurred in 1% with case fatalities approaching 20%,[32] and the drug was withdrawn. Hydrazines can be metabolized by P450 to toxic intermediates. Their metabolism and mechanism resemble that of isoniazid, also a hydrazine. One substituted hydrazine MAO inhibitor remains available, namely phenelzine; there have been case reports of hepatitis.[33]

Other Antidepressants. Trazodone has been implicated as the cause of a lesion with elements of both hepatitis and cholestasis; the problem appears to be uncommon.[34-36] Hepatotoxicity from serotonin reuptake inhibitors inhibitors such as fluoxetine and paroxetine is reported but very rare.[37,38] Nefazodone has been associated with three cases of fulminant hepatic failure within 14 to 28 weeks of starting the drug.[38a]

Anti-anxiety Drugs. Benzodiazepines, such as chlordiazepoxide, diazepam, and flurazepam, have very low hepatotoxic potential, with only case reports in the literature, usually with a cholestatic pattern.[39,40]

ACETYLCHOLINESTERASE INHIBITORS

Tacrine is a reversible cholinesterase inhibitor used for Alzheimer's disease. Remarkably, in about 50% of recipients, the ALT exceeds the upper limit of normal; in 25%, the value is more than three times the upper limit, and in 2%, it is 20-fold increased.[41] Nearly all the toxicity is seen in the first 12 weeks. Only a few instances of jaundice have been reported. The level of eosinophilia and the ALT are related, the toxicity is not clearly dose-related, and positive rechallenges have been described. On the other hand, ALT levels with rechallenge were lower than those associated with the

initial drug exposure. Thus, although a hypersensitivity mechanism is possible, the reaction is sufficiently atypical as to support the possibility of metabolic idiosyncracy. Tacrine is metabolized by CYP1A2 to reactive metabolites that may be damaging.[42] However, CYP1A2 activity, as inferred from a caffeine breath test, does not predict toxicity.[43]

Alternative hypotheses have been put forward to explain the mechanism of tacrine-induced hepatotoxicity. Tacrine is a lipophilic amine (weak base) that may exert a protonophoric effect in mitochondria, *i.e.*, protonation in the intermembranous space with diffusion into the matrix, followed by deprotonation and recycling of the drug. This movement of cationic drug and its deprotonation in the matrix depolarizes the mitochondria, resulting in decreased adenosine triphosphate formation.[44] Similar uncoupling effects have been seen with amiodarone and perhexiline, but accumulation of the latter in mitochondria also inhibits β-oxidation, leading to fatty liver and inhibition of the respiratory chain.[45] These two effects are not seen with tacrine. Another potential mechanism is based on the inhibition by tacrine of acetylcholinesterase, leading to a cholinergic coeliac ganglion-induced stimulation of an afferent sympathetic pathway, resulting in vasoconstriction, leading to impaired perfusion of the sinusoids and reperfusion injury mediated by reactive oxygen metabolites.[46] These are not mutually exclusive hypotheses in that the former mechanism may sensitize to the latter. Thus, tacrine undergoes high extraction, suggesting that periportal hepatocytes may take up a large proportion of the drug; the uncoupling effect would increase respiration and O_2 consumption in periportal hepatocytes, thus limiting O_2 availability in the more distally perfused perivenular cells; superimposition of decreased O_2 delivery as a result of the effect on the microcirculation would further limit O_2 in the perivenular zone.

The extremely high incidence of ALT elevation caused by tacrine, despite the rare occurrence of overt liver disease, was sufficiently worrisome to lead to a very rigorous surveillance recommendation by the FDA. The concerns about hepatotoxicity and the cumbersome nature of the required surveillance (weekly ALT for 16 weeks, then monthly for 2 months, and finally every 3 months) have limited the use of tacrine.

DRUGS OF ABUSE

Cocaine. Cocaine hepatotoxicity has been studied experimentally in considerable detail. Toxicity is dose-related. In naive mice, coagulative necrosis is localized to the midzonal or the centrilobular zone depending on the strain.[47-49] In mice pretreated with phenobarbital, the toxicity is increased and shifts to the periportal zone.[48,49] β-Naphthoflavone and chronic ethanol pretreatment produce sharply localized centrilobular damage and increased liver injury.[49] The presence of covalent adducts of cocaine metabolites defines the site of injury,[49] and localizes P450 mediated toxic metabolite production. However, this does not necessarily prove that covalent binding is responsible for the observed toxicity.

Toxicity seems to depend on P450 catalyzed *N*-demethylation to norcocaine, which then is converted to *N*-hydroxynorcocaine by flavin mono-oxygenase or P450.[50] The latter redox cycles to norcocaine nitroxide by receipt of an electron from NADPH, and the latter transfers electrons to O_2, generating oxidative stress. Covalent binding of metabolites (*e.g.*, norcocaine nitrosonium) may also be important and can be detected by immunochemical staining of histological sections or Western blotting.[51] The presence of covalent adducts is P450-dependent and colocalizes with the zone of necrosis. It would be of interest to apply this type of immunohistochemistry to liver sections of patients with suspected cocaine hepatotoxicity. Mitochondria are key targets of the oxidative stress and may further contribute to the generation of reactive oxygen intermediates.[52] An alternative route of metabolism through hydrolysis by esterases in plasma and liver is actually the predominant route of metabolism and generates nontoxic metabolites.[48,49,53,54] Esterase inhibitors potentiate hepatotoxicity by routing more parent drug through P450 pathways. Conversely, induction of esterases (*e.g.* dexamethasone) prevents toxicity.[54a] Because cocaine is a sympathomimetic, impaired hepatic perfusion theoretically may be a contributing factor, the presence or absence of generalized systemic effects notwithstanding (*e.g.*, hypotension and hyperthermia).

Although cocaine induces oxidative stress in hepatocytes, its mechanism is controversial. As noted above, futile redox cycling between *N*-hydroxynorcocaine and norcocaine nitroxide, consuming NADPH and generating O_2 and H_2O_2, has been proposed. However, because the drug exhibits a type I binding spectrum to P450, one might predict metabolic uncoupling, with cocaine causing P450 to function more as an oxidase than an oxygenase,[54] and thus generating reactive oxygen metabolites.

Cocaine induces its own metabolism, principally by increasing expression of CYP3A.[47] Norcocaine nitroxide, when administered to mice, induces hepatotoxicity that is P450-dependent and morphologically identical to that of the parent compound,[55] including the fact that pretreatment of animals with phenobarbital shifts the zone of injury from midzonal to periportal. Thus, this sheds no light on whether the injury mechanism involves redox cycling oxidative stress or covalent binding of a toxic metabolite (Fig. 1).

Reports in humans have documented a very small number of patients in whom cocaine seems to be an unequivocal cause of hepatotoxicity; the most convincing of these was a case with periportal necrosis.[56] However, most of the cases in the literature and in our clinical experience occur in the setting of rhadomyolysis (which itself can increase both aspartate aminotransferase and ALT), disseminated intravascular coagulopathy (DIC), hypotension, hypoxemia, and/or hyperpyrexia and are associated with centrilobular necrosis when histology is available.[53,57,58] A common additional feature has been microvesicular steatosis in the zones spared of necrosis,[57] which may reflect the mitochondrial toxicity noted above. The study of Silva et al. is most informative[58]: of

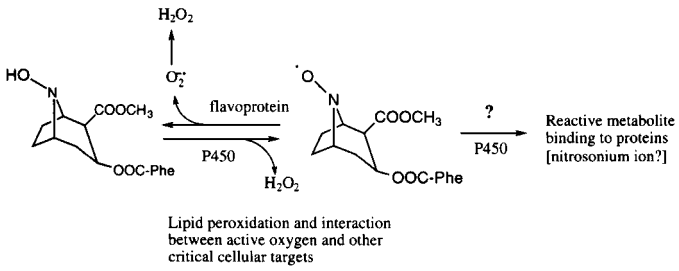

FIG. 1. Oxidative metabolism of cocaine and toxicity. *N*-Hydroxynorcocaine (*left*) can cycle with norcocaine nitroxide (*middle*) or undergo further metabolism by unspecified P450 to reactive alkylating species (nitrosonium ion?). Reprinted with permission.[55]

39 consecutive cases of cocaine-associated rhadomyolysis, 23 had liver abnormalities (of which the ALT in 16 was more than 10-fold increased). Hypotension and DIC were seen in 50% of cases with liver abnormalities, and hyperpyrexia was seen in 75%. Of note, 13 of 16 cases with a marked elevation of ALT (at least 10-fold increased) developed renal failure, whereas none of the others did, suggesting relatively severe rhabdomyolysis and systemic effects. It should be noted that heatstroke is a cause of hepatic necrosis, presumably as a result of impaired hepatic perfusion.[59] Thus, despite the well-documented characterization of cocaine hepatotoxicity in mice, it remains uncertain if this is more than a rarity in humans.

Ecstasy. Ecstasy, which is 3,4-methylenedioxymethamphetamine (MDMA), produces a syndrome similar to cocaine with fulminant hyperthermia, DIC, rhabdomyolysis, and acute renal failure. Severe hepatotoxicity may be a concomitant.[60-64] MDMA is metabolized by CYP2D6; a rat model with deficient enzyme exhibited an elevated thermal response to MDMA,[65] suggesting that genetically poor hydroxylators (≈5% of whites) with decreased CYP2D6 may be predisposed to MDMA-related hyperthermia and possibly hepatotoxicity. However, human data to support this hypothesis are lacking.

A number of case reports and small series describe severe acute hepatotoxicity in response to MDMA.[60-64] These occurred after incidental or regular ingestion with variable latency of days to weeks. An eosinophilic infiltrate was seen occasionally in the portal tracts. Repeat episodes, associated with progressive fibrosis in one case, have been described.[64] Two patterns emerge: one similar to cocaine with acute profound systemic effects accompanied by severe liver injury shortly after ingestion (hyperthermia, etc.), and the other with variably delayed, sometimes fulminant hepatitis in the absence of the systemic features and apparently unrelated to hyperthermia because of the latent period. MDMA will be found in toxicology screening of the acute, but not the delayed, cases. In the latter, it is uncertain if MDMA, its metabolites, or drug contaminants are responsible. Although tissue eosinophilia is seen in some of the cases, suggesting an immune mechanism, one should bear in mind that other chemicals with direct toxicity also are associated with eosinophilia, *e.g.*, methylene dianiline (Epping jaundice)[66] and aniline-denatured rapeseed cooking oil (toxic epidemic syndrome).[67]

The widespread abuse of MDMA makes it an important cause of toxic hepatitis. Because the presentation with liver injury may be delayed and may not be accompanied by the systemic features of MDMA use, toxicity of the drug should be suspected in young adults presenting with a hepatitis-like illness with negative viral studies.[68]

THE USE OF PSYCHOTROPIC DRUGS IN PATIENTS WITH LIVER DISEASE

A full discussion is beyond the scope of this article. Benzodiazepines illustrate the complexities of the question: some exhibit altered clearance in liver disease, *e.g.*, diazepam and chlordiazepoxide, whereas others are unaffected, such as lorazepam, oxazepam, and temazepam. Most psychotropic drugs that have been studied have decreased clearance and increased half-life in patients with liver disease, including midazolam, triazolam, barbiturates, tricyclics, and fluoxetine.[69] However, even if hepatic metabolism is not changed, effects of increased volume of distribution (low albumin and ascites) and increased brain sensitivity to sedation cannot be ignored, so that dose adjustments must be made on an individual basis. However, the low risk of hepatotoxicity with this class of drugs, coupled with a lack of evidence that underlying liver disease would increase susceptibility to hepatotoxicity, should provide reassurance that their use can follow the usual indications. The major concern is oversedation, which must be avoided.

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