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Antiepileptic drugs and liver disease

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Summary Antiepileptic drugs (AEDs) are no longer restricted to the treatment of epilepsy. These are widely used in a broad spectrum of psychiatric and neurological disorders. Liver plays a major role in the metabolism of a majority of these drugs. Hepatotoxicity is rare, but a real concern when initiating therapy. Likewise, liver disease can adversely affect the biotransformation of some of these drugs.

This manuscript addresses the significance of elevated liver enzymes associated with AED use, the role of therapeutic drug monitoring, pharmacokinetics during liver disease and potential risk of hepatotoxicity.

Hepatic biotransformation of AEDs in health and liver disease

Almost all antiepileptic drugs (AEDs) with the exception of Gabapentin and Vigabatrin undergo hepatic biotransformation (Table 1).

Lipophilic AEDs require conversion to a hydrophilic/water-soluble state for renal excretion. This process comprises phase-I and -II reactions. Phase-I reactions include oxidation, reduction and hydroxylation, whereas phase-II reactions imply conjugation. Glucoronidation is a common phase-II reaction, leading to active and inactive metabolites.

Liver disease can affect the metabolism of AEDs in several ways and due to different underlying etiologies. Drug metabolism depends on hepatic blood flow, albumin binding, the degree of drug uptake by the hepatocyte, the functional integrity of the hepatocytes and finally the patency of the hepatobiliary system. A functional compromise at any level can potentially impair biotransformation, causing parent compounds to accumulate or the generation of active metabolites to be interrupted.

The decision to continue or withdraw drug therapy depends on the underlying pathology, the extent of hepatic insult, the role of the AED in potentially accentuating the insult and finally the risks (status epilepticus) of discontinuing this agent. In some instances, it is safe to continue the drug at a lower dose and, in others, it is not safe to continue the drug at all. Impaired biotransformation can lead to an alternative route of metabolism and, the generation of hepatotoxic metabolites, as in Valproic acid (VPA)-induced hepatotoxicity.

The Child—Pugh classification for alcoholic liver disease and portal hypertension[1] classifies liver

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Table 1 Metabolism of AEDs

Predominantly metabolized by the liver	Partially metabolized by the liver	Extrahepatic metabolism or excretion
Benzodiazepines	Leviteracetam	Gabapentin
Carbamazepine	Topiramate	Vigabatrin
Ethosuximide	Zonisamide	
Felbamate		
Lamotrigine		
Oxcarbazepine		
Phenobarbital		
Phenytoin		
Tiagabine		
Valproate		

disease as mild, moderate and severe (Child—Pugh Grade A, B and C, respectively), and is useful when considering the pharmacokinetics of a drug in the presence of liver disease. This classification considers five parameters: bilirubin; albumin; prothrombin time; and the presence of encephalopathy and ascites. The number of abnormal variables determines the score, with a higher score representing a more severe disease.

The assessment of liver functions and hepatotoxicity during AED therapy

Liver enzymes can serve as markers of hepatocellular injury (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) or of an obstruction in the bile flow—cholestasis (alkaline phosphatase [ALP] and gamma-glutamyl transferase [GGT]). Although these enzymes are elevated in liver disease, the elevation can also be secondary to enzyme induction in the absence of hepatic pathology. An elevated partial thromboplastin time (PTT) or decrease in albumin along with elevated liver enzymes is a more specific marker of liver dysfunction.

Carbamazepine (CBZ), Phenobarbital (PB) and Phenytoin (PHT) are potent enzyme inducers. On the other hand, Topiramate (TPM) has weak enzyme-inducing characteristics. A few weeks to a month's therapy with one of the enzyme inducers, leads to a modest elevation of ALT, AST, ALP and GGT, whereas a less than two fold increase in ALT, AST and ALP is usually insignificant. GGT is a non-specific marker of liver disease and often elevated during AED therapy. Because ALP can originate from both the liver and bone, an elevated ALP, in the absence of elevated GGT, points to an extrahepatic origin. Hyperammonemia is also a marker of liver disease, and a four to five fold increase in levels is associated with central nervous system (CNS) manifestations. With the exception of VPA, AEDs typically do not lead to elevated ammonia levels. A two to three fold elevation in serum ammonia can result during VPA therapy and is usually insignificant. This elevation probably results from a decreased synthesis of mitochondrial acetyl CoA, leading to a decrease in *N*-acetylglutamate, an activator of carbamoyl phosphate synthetase.[2] A more than two to three fold increase in liver enzymes during AED therapy should caution the physician of a potential of coexistent liver disease. If subsequent follow-up reveals a progressive increase in the values of the enzymes, investigations for coexistent liver disease are warranted, and may require a switch to an alternative AED.

AED-induced liver disease can be a part of a generalized hypersensitivity reaction, as is recognized with CBZ, lamotrigine (LTG), PB and PHT. Cases of hypersensitivity reaction with other AEDs are also reported. Fever, transient skin rash, eosinophilia and lympadenopathy are associated features.

Characteristics specific to individual drugs

The following section deals with individual medications. Drugs with predominantly extrahepatic metabolism/clearance are grouped together.

Benzodiazepines

Clobazam, clonazepam, diazepam, lorazepam and midazolam are commonly used benzodiazepines (BDZ) in the treatment of epilepsy, alcohol withdrawal seizures and status epilepticus.[3—7]

As a group, BDZs are highly protein bound in plasma, and undergo extensive hepatic biotransformation. Renal excretion of the parent compound is minimal. Due to a predominant hepatic metabolism, liver disease can significantly affect the metabolism of various BDZ. For example, liver cirrhosis can markedly increase the elimination half-life of diazepam and lorazepam.[8—10] The elimination of lorazepam was not significantly impaired in patients with viral hepatitis.[11] We were unable to identify established cases of BDZ-induced hepatotoxicity in the span of last 30 years.

In summary, the literature recommends reducing the dose of BDZs in the presence of liver disease. Clinical response and dose-dependent side effects are useful measures for making this change. Hepatotoxicity is not a major concern and sequential blood testing is not necessary, provided the baseline liver function tests are normal.

Carbamazepine

Carbamazepine (CBZ) is effective for the treatment of partial and secondarily generalized tonic–clonic seizures. Hepatic biotransformation is the main route of elimination.[12,13] Epoxidation and hydroxylation are the main metabolic pathways though conjugation reactions may also have a role.[12] The most important metabolic product is 10,11-CBZ epoxide, which has been shown to be pharmacologically active.[12] CBZ induces its own metabolism (autoinduction) that starts within 24 h of the initiation of therapy and is completed after 3–5 weeks of treatment.[14] Therefore, when measuring CBZ drug levels it is worth delaying the first measure until 4–5 weeks to find steady state level following autoinduction. Therapy with other AEDs and several other classes of medications also induces CBZ metabolism (heteroinduction). Due to these interactions, higher doses of CBZ are required to maintain a steady concentration in the blood.

A transient and asymptomatic elevation of liver enzymes occurs in 25–61% of patients receiving CBZ.[15,16] Serious CBZ-associated hepatotoxicity takes two forms: a hypersensitive reaction in the form of granulomatous hepatitis that presents with fever and abnormal liver functions tests; and an acute hepatitis and hepatocellular necrosis with fever, rash, hepatitis and lymphadenopathy simulating biliary tract infection,[17] which may result from direct drug toxicity.

Hepatotoxic reactions of CBZ usually occur within 3–4 weeks after the initiation of therapy and are independent of serum CBZ levels. Symptoms usually resolve after the drug is discontinued; however, fatal hepatotoxicity can occur even after early intervention and discontinuation of the drug.[18] The profile of patients susceptible to serious hepatotoxicity is not established.

Ethosuximide

Ethosuximide (ESM) is an effective treatment for absence (*petit mal*) seizures. It has a half-life of 40–60 h and is not protein bound. It is extensively metabolized in the liver and only a small percent of the drug is excreted unchanged in the urine.[19,20] Since ESM undergoes significant liver metabolism, it has potential interactions with other enzyme-inducing AEDs, though the clinical importance of these drug–drug interactions is unclear. ESM is not associated with enzyme induction or hepatotoxicity.[21] One case of ESM-induced liver dysfunction is reported in a 13-month-old child manifested by increased enzymatic activity, but the enzymes reverted to normal when the therapy was discontinued. Since this patient was concurrently being treated with Acetazolamide and PB and, had been treated with VPA two months previously,[22] it was hard to establish if ESM was solely responsible for the abnormal liver functions. Although hepatotoxicity is not a recognized adverse effect from ESM, the product monograph recommends using "extreme caution" in its administration in patients with known liver disease.

Felbamate

Felbamate (FBM) is a broad-spectrum antiepileptic medication, approved for marketing in the US in 1993, which was found to be effective against both partial and generalized seizures. It undergoes biotransformation by phase-I and -II reactions, hydroxylation and glucoronidation, respectively. The metabolites and the parent compound are excreted through the kidneys. It inhibits the cytochrome P-450 system thus resulting in significant interactions with other AEDs and in most instances increasing the levels of PHT, CBZ epoxide and VPA. In 1994, several cases of aplastic anemia and serious hepatotoxicity were noted which led to the gradual discontinuation of this drug from a vast patient population. The estimated incidence of hepatic failure is 164 per million patients treated.[23]

The American Academy of Neurology has issued a practice guideline for the use of FBM, reserving it for medically refractory epilepsy such as Lennox Gastaut syndrome. Emphasis is also placed on an informed consent, a detailed past history of cytopenia, drug-induced allergic reactions and immune disorders.[24]

Lamotrigine

Lamotrigine (LTG) is an effective treatment both for focal and generalized epilepsies. It primarily undergoes hepatic metabolism. Human experiments demonstrate that the clearance of LTG depends on the severity of hepatic impairment.[25] One group noted the need to reduce the dose by 50–75% in patients with liver cirrhosis corresponding to Child–Pugh Grade B or C, respectively.[26] In vitro experiments by Furlan et al.[27] demonstrated no significant changes in the metabolic clearance of LTG in the presence of liver disease. This discrepancy between in vivo and in vitro experiments, suggests the need for extreme caution when generalizing laboratory results to human therapeutics.

Although no changes were reported in routine laboratory tests of hepatic function in the phase-III/IV studies, hepatic failure and multiorgan failure has been described in adult and pediatric patients

taking LTG.[28–31] Sauve et al.[29] note that the hepatotoxicity often seems associated with other symptoms such as hyperthermia, cutaneous rash, rhabdomyolysis, and coagulopathy.

Based on human studies, the dose of LTG needs adjustment in the presence of liver disease. This adjustment should be based on therapeutic response rather merely on serum levels. Reports of LTG-related liver disease is rare, with suboptimal data to establish causality between this drug and hepatotoxicity.

Oxcarbazepine

Oxcarbazepine (OXC) is effective for partial and secondarily generalized tonic–clonic seizures. Its spectrum of action is quite similar to CBZ. Like CBZ, it is predominantly metabolized through the liver. It is a less potent enzyme inducer with relatively less prominent interaction with other AEDs. Furthermore, it is not biotransformed to CBZ epoxide, and therefore is better tolerated than the first generation CBZ. Hepatic metabolism converts OXC to its active metabolite monohydroxylated derivative.[32] Liver disease has no effect on the pharmacokinetics of OXC and monohydroxylated derivative.[33] OXC has not been associated with hepatotoxicity except for anecdotal case reports, but it can cause a modest elevation of liver enzymes.[34–36]

Phenobarbital (PB)

Phenobarbital (PB) was introduced as an AED in 1912. It is the oldest AED still in use and is effective in partial and secondarily generalized tonic–clonic seizures, in the control of status epilepticus and in the prevention of febrile seizures.[37]

PB is metabolized by hydroxylation in the hepatic mixed function oxidase system. *p*-Hydroxyphenobarbital (PBOH) is the major metabolite, which is subsequently conjugated to glucuronic acid to form PBOH glucuronide. Nine to 33% of the dose is excreted unchanged in the urine, and the renal clearance depends on the urine flow and pH. The half-life of PB ranges from 75 to 126 h in healthy subjects and is significantly prolonged in patients with liver cirrhosis. In patients with acute viral hepatitis, the prolongation of elimination half-life is not statistically significant.[38] PB is a potent inducer of hepatic microsomal enzymes and can enhance the metabolism of several drugs, including AEDs, steroids and anticoagulants. It also increases the hepatic metabolism of sex hormones that may lead to the failure of oral contraceptives. Dose-dependent hepatotoxicity is a rare occurrence: only a minority of susceptible patients with a defect in drug detoxification develops hepatotoxicity.[39,40] A more common occurrence is an asymptomatic and clinically insignificant elevation of ALP and GGT.[41]

Alternately, hepatic involvement may occur as part of a generalized hypersensitivity or idiosyncratic reaction seen in about 9% of patients, an incidence that is similar in patients taking CBZ and PHT.[42] Fever, transient skin rash, eosinophilia, and lymphadenopathy are the other features of this reaction. The hepatic involvement may present with a hepatotoxic, cholestatic or a mixed picture. Granulomatous inflammatory changes develop in the liver and are reversible on discontinuation of the drug.

Phenytoin (PHT)

Merritt and Putnam introduced PHT as an anticonvulsant in 1938.[43] It is one of the most commonly used compounds for treating secondarily generalized tonic–clonic seizures and status epilepticus.[44] Ninety-five percent of PHT is bio-transformed by the liver and less than 5% is eliminated unchanged in the urine.[45] PHT at clinically accepted doses can saturate the hepatic enzymatic system that metabolizes the drug (zero-order kinetics). This is particularly significant in the presence of liver disease, and the dose increment should be gradual.

GGT is elevated in 50–90% of patients on PHT therapy.[46] Although a number of studies have found elevated ALP with PHT therapy[46,47] these numbers have not been reproduced in age- and sex-matched studies.[48] Elevation of AST and ALP are considered as more specific markers of liver disease than ALT and GGT.[48] In the absence of primary hepatic disease and drug hypersensitivity syndrome, a mild elevation in enzymes is clinically insignificant.

Hepatic injury due to PHT is an infrequent occurrence, but once it develops, 10–38% of cases will progress to a fatal outcome.[17] The interval between the initiation of PHT therapy and the onset of clinical abnormalities ranges from 1 to 6 weeks in the vast majority of patients.[49] The most common presenting symptoms were fever, rash and lymph-adenopathy. Jaundice and hepato-splenomagaly were common findings as well, and a substantial proportion of patients experienced hemorrhagic complication.[50] Biochemical features of PHT hepatotoxicity are variable but generally include abnormal serum bilirubin, transaminases, and ALP levels, as well as eosinophilia and leukocytosis. The morphologic and pathologic abnormalities are non-specific, including, but not limited to, primary hepatocellular degeneration and/or necrosis.[49]

The clinical course of PHT hepatotoxicity ranges from prompt resolution on drug withdrawal to fatal hepatic injury.[50] Hepatic injury with PHT is most likely secondary to a hypersensitivity reaction rather than a direct hepatotoxic effect. Clinicopathological studies looking at liver biopsies are in keeping with this hypothesis.[50] Toxicity after drug overdose primarily affects the central nervous system with signs of neurotoxicity rather than hepatotoxicity.[51] When clinical and biochemical picture is suggestive of hepatotoxicity prompt discontinuation of the drug is essential.

Tiagabine

Tiagabine is an effective add-on treatment for partial seizures with or without secondary generalization.[52–54] It is highly protein bound and predominantly metabolized by the liver by the 3A family of cytochrome P450 (CYP). It does not seem to induce or inhibit hepatic microsomal enzymes.[55] Liver disease is shown to attenuate its metabolism. Based on this finding the recommendations are to consider reducing the dosage and increasing the dosing intervals to minimize neurotoxicity.[56] Its use is discouraged in patients with severely impaired liver functions.[57] Our Medline search did not demonstrate established cases of Tiagabine-induced liver disease.

Topiramate

Topiramate (TPM) is effective for partial and generalized seizures.[58] It is minimally bound to plasma proteins (15%) and has a half-life of about 21 h. In healthy volunteers, 20% of the dose is metabolized, and about 40% is excreted unchanged via the kidney. Biliary excretion plays a minor role in TPM metabolism.[59] The mean plasma concentration of TPM was found to be 40–50% when it was used as an adjunct therapy with liver enzyme inducing AEDs. The product monograph reports a 30% increase in the drug concentration associated with moderate to severe liver disease.[60] In such cases, monitoring central nervous system side effects such as, psychomotor slowing, speech problems, confusion and mood alterations, can help in deciding dosage adjustment. TPM can infrequently lead to elevated liver enzymes. We came across two possible cases of TPM-induced hepatotoxicity[61,62] in the literature, and one case report suggesting reversible hepatic failure after adding TPM to VPA.[63] These are isolated case reports requiring further corroborating evidence. Routine monitoring of liver function tests is not recommended during TPM therapy.[64]

Valproic acid (VPA)

VPA has a broad spectrum of activity against both focal and generalized epilepsies. It is 80–90% protein bound. Hepatic biotransformation is the main route of elimination and involves glucuronidation, β-oxidation and ω-oxidation.[65,66] Retrospective studies have demonstrated a transient elevation of liver aminotransferases in up to 10–15% of patients on VPA[67,68] but these finding were not reproduced in a prospective study with a relatively small sample size.[69] Rarely, levels of other liver enzymes including ALP, lactic dehydrogenase (LDH) and GGT may also rise in the serum.[70] The medication can be continued if the rise in enzyme levels is moderate: up to two to three times the baseline levels and the patient has remained asymptomatic. If the changes in hepatic functions are clinically symptomatic it is recommended to discontinue the drug with supportive therapy such as maintaining serum glucose, Vitamin K supplement and carnitine therapy.[71,72]

A rare, idiosyncratic reaction to VPA therapy is irreversible hepatic failure.[73] The incidence of VPA-induced fatal hepatic dysfunction is highest, 1/500, in children under 2 years of age, treated with polypharmacy.[73,74] The risk declines with age with a rate of 1/12,000 when used in polytherapy and 1/37,000 when used in monotherapy after the first 2 years of life.[74,75] Certain risk factors for VPA-induced liver failure have been identified and include: Younger age, mental retardation, history of metabolic disorders or inborn error of metabolism, polypharmacy, stressful condition such as infection and underlying liver disease.[76] In adults, the risk of an idiosyncratic reaction is much less than in children. König et al.[77] critically reviewed 26 fatalities in adult patients from hepatotoxicity from 1980 to 1996. Three patients were on monotherapy and 12 had no concurrent illnesses. The authors therefore advised vigilance even when adults with no underlying illness receive VPA monotherapy. VPA therapy can be associated with hyperammonemia in the presence of normal AST, ALT and ALP.[78] The mechanism of hyperammonemia therefore is independent of the acute hepatic injury but can be seen in acute VPA overdose.[79] In vitro studies have shown causality between VPA and oxidative stress, especially in the presence of glutathione deficiency.[80,81] These findings support the previous observations, linking inborn errors of metabolism with a higher incidence of VPA associated toxicity in humans.[82,83]

The idiosyncratic hepatic toxicity to VPA usually occurs during the first 2–3 months of therapy and leads to reduced alertness, vomiting, hemorrhage, increased seizures, anorexia, jaundice, edema, and ascites. The most frequently reported hepatic his-

topathological findings were necrosis and steatosis.[82] Laboratory tests are poor predictors of heptotoxicity with VPA because hepatotoxic reactions have occurred even after a protracted period of normal liver enzymes levels while on therapy. Furthermore, clinical parameters are known to precede laboratory abnormalities in most patients who had adverse hepatic reactions to VPA. A shift from β-oxidation to ω-oxidation is a probable trigger in the pathogenesis. This leads to the formation of 4-en VPA, the compound leading to microvesicular steatosis, which is a hallmark of VPA-induced hepatic injury.[17] The depletion of L-carnitine, a co-factor in the beta-oxidation of fatty acids, is another postulated mechanism.[72] The initial observation that concomitant therapy with VPA and ketogenic diet can predispose the patient to hepatotoxicity[84] was not substantiated in a recent review.[85] A recent study demonstrated the presence of non-alcoholic fatty liver disease in 61% of VPA-treated patients as compared to 23% receiving CBZ therapy.[86] Given the significant number developing the fatty change and a very small fraction developing liver toxicity, a cause-and-effect relationship cannot be established.

In summary, VPA associated hepatotoxicity in adults is a rare but potentially serious diagnosis. Routine biochemical monitoring does not reduce the risk; therefore patient education to identify early clinical manifestations is important. A moderate elevation of liver enzymes (less than two times of baseline) is usually insignificant but requires vigilance. The use of VPA with co-existent liver disease is discouraged.

Zonisamide

Zonisamide is a broad-spectrum antiepileptic drug with efficacy against partial and generalized seizures.[87,88] Hepatic biotransformation accounts for 70% clearance and the rest is excreted unchanged by the kidneys.[89] CYP 3A seems to be the principal family of the cytochrome P-450 involved in its metabolism. Elevated liver enzymes are found in 2—4% of the patients with chronic therapy[90] but no significant heptotoxicity has been reported. In the presence of underlying liver disease, considering the long half-life, clinical and biochemical monitoring is advisable.

Antiepileptic drugs with predominant extrahepatic clearance

This group includes Gabapentin, levetiracetam and vigabatrin.

Gabapentin is excreted unchanged in the urine. It does not affect the liver enzymes and has not been associated with hepatotoxicity.[91]

Vigabatrin (VBN) is excreted unchanged by the kidneys without undergoing hepatic metabolism.[92] A case of fatal hepatotoxicity is reported in a 3-year-old child treated with VBN for 9 months along with PB,[93] with an underlying history of prematurity, perinatal cerebral hemorrhage and leukomalacia. A definite cause-and-effect relationship could not be established.

Levetiracetam (LEV) is predominantly (66%) excreted unchanged by the kidneys, with a smaller amount (27%) metabolized to three inactive compounds.[94] It does not bind to plasma proteins. The pharmacokinetics of LEV are not affected by mild to moderate liver impairment.[95] In patients with severe liver cirrhosis (Child—Pugh Class C) total clearance was reduced by 57% and a reduction in dose by 50% is recommended.[96] We did not come across any report of LEV-induced hepatotoxicity on a Medline search.

Conclusion

With the ever-increasing indications and markets for AEDs, the need for a better understanding of their pharmacokinetics and potential toxicity is imperative. Based on our extensive literature review we would like to make the following concluding remarks:

1. There is no proven value of routine blood testing for monitoring liver functions in asymptomatic patients.[97] We do recommend a baseline test to identify an existing problem.
2. The presence of underlying liver disease may require dose adjustment and not necessarily the discontinuation of the medication. Exceptions apply to FBM, VPA and possibly CBZ.
3. In most established cases hepatic toxicity is idiosyncratic or part of a hypersensitivity reaction. Dose dependent hepatotoxicity is rare and usually reversible with prompt discontinuation of the offending agent.

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