The Mechanism and Management of Carbamazepine-Induced Hepatotoxicity

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Carbamazepine (CBZ) is a frequently prescribed antiepileptic drug (AED), used in the treatment of epilepsy, neuropathic pain and psychiatric disorders. CBZ was the 176th most commonly prescribed medication in 2017 across the United States, with a total of 3,516,204 prescriptions written that year. CBZ is predominantly metabolised hepatically, subsequently increasing the risk of a CBZ-induced liver injury or CBZ-induced hepatotoxicity; with hepatotoxicity being defined as drug induced liver damage. Deviation beyond the therapeutic range of CBZ is consistent with toxicity, which combined with abnormal liver function tests, would be indicative of CBZ-induced hepatotoxicity. The liver is the leading organ for the maintenance of the body's internal environment, therefore obstruction of the liver's ability to conduct its regular function can carry a number of consequences. With a large number of patients receiving CBZ therapy worldwide, it is of absolute importance to understand the best clinical approach to the treatment of CBZ-induced hepatotoxicity. There have been a number of studies reviewing the type of liver damage that occurs in cases of hepatotoxicity, classified as either a hypersensitivity reaction or acute hepatitis, and how different methods of treatment specific to CBZ-induced hepatoxicity directly correlate with a successful outcome. Treatment of CBZ-induced hepatotoxicity can consist of recording serum levels of the drug whilst administering intravenous fluids and continuing CBZ therapy. A different approach would be that of primary gut decontamination with activated charcoal which has proven to be very effective, whilst various means of dialysis have been considered to have a limited ability to remove CBZ from the blood serum alone. This review will assess the mechanism of CBZ-induced hepatotoxicity alongside the most effective clinical management.

Introduction

Carbamazepine (CBZ) is an antiepileptic drug (AED) that is used in the treatment of several types of epilepsy and in the management of intermittent severe pain in trigeminal neuralgia. CBZ can also be used to stabilise mood in bipolar disorder, to reduce urine output in diabetes insipidus and to relieve pain in patients presenting with diabetic neuropathy (1). From a pharmacological perspective, CBZ is chemically related to tricyclic antidepressants, such as amitriptyline, and differs in its structure to other anticonvulsants. CBZ was the 176th most commonly prescribed medication in 2017 across the United States, with a total of 3,516,204 prescriptions written that year (2). The majority of patients receiving CBZ therapy will experience very few adverse drug reactions (ADRs), however the incidence of ADRs becomes more common with increased CBZ serum levels (1). CBZ hypersensitivity affects ~10% of patients receiving the therapy, whilst antiepileptic hypersensitivity syndrome affects ~1 in 5000 people taking CBZ or phenytoin (3). CBZ is almost entirely metabolised in the liver with only approximately 5% of the drug excreted in its original unchanged form. CBZ is a well-known cause of clinically apparent liver injury which can range in severity from acute to fatal (4). It is also an established cause of hepatotoxicity; the capability of a drug or chemical to produce toxic damage to the liver (5).

This review article will focus on the incidence of CBZ-induced hepatotoxicity in epileptic patients taking CBZ to manage focal seizures with and without secondary generalised seizures or to manage primary generalised tonic-clonic seizures (4). Various studies into CBZ-induced hepatotoxicity are indicative of a vast proportion of patients experiencing transient serum aminotransferase elevations (ranging from 1 to 22%), these elevations are typically benign and not correlated with any form of hepatic histological abnormality and as such will frequently resolve despite the continuation of CBZ therapy (7). Clinically apparent CBZ-induced hepatoxicity, although uncommon, is well described. CBZ hepatotoxicity typically occurs in the jurisdiction of anticonvulsant hypersensitivity syndrome with the onset of a fever, typically followed by a rash, facial oedema, lymphadenopathy, an elevated white blood cell (WBC) count as well as eosinophilia or atypical lymphocytosis; this frequently occurs 1 to 8 weeks after commencing CBZ therapy (7). This hypersensitivity syndrome is often referred to by the acronym DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), with the most persistent form of systemic involvement being that of liver injury (7). The hepatic involvement varies from mild or transient elevations in the patient's serum enzymes, to the abrupt onset of an acute hepatitis-

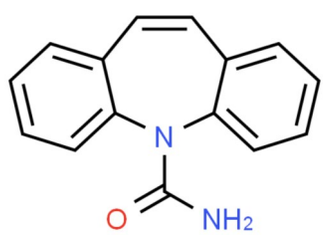

Figure 1. The molecular structure of CBZ, an aromatic anticonvulsant with a molecular formula of $C_{15}H_{12}N_{2O}$ and an average molecular mass of 236.269 Da (6).

like syndrome that can be severe and even fatal. As a result of this, CBZ is a commonly listed agent in cases of acute liver failure (8).

Mechanism of Drug Action

Antiepileptic drugs are pleiotropic; they have multiple effects on different ion channels (9). The mechanism of action of CBZ is not entirely understood. It is thought to inhibit neuronal sodium channels, stabilise resting membrane potentials and reduce neuronal excitability (3). CBZ prolongs the inactivated state of the sodium channel, halting action potential propagation. As a result, sodium channel inhibitors such as CBZ show a degree of specificity for the treatment of partial and secondary generalised seizure activity (9). Ultimately this can inhibit the spread of seizure activity within the brain of epileptic patients or block synaptic transmission in the trigeminal nucleus to control neuropathic pain, such as that present in patients with trigeminal neuralgia (3).

Mechanisms of Hepatic Injury

The mechanism of CBZ-induced hepatotoxicity typically occurs in two forms; a hypersensitivity reaction in the form of granulomatous hepatitis that presents clinically with a fever and abnormal liver function tests (LFT) or an acute hepatitis and hepatocellular necrosis accompanied by fever, rash, hepatitis and lymphadenopathy simulating a biliary tract infection (10). The association of liver injury with the human leukocyte antigen (HLA) haplotypes, a gene complex that encodes the major histocompatibility complex (HMC) proteins in humans, hasn't been as well demonstrated as the link between CBZ associated severe cutaneous ADRs, such as that of Stevens-Johnson Syndrome with HLA-B*1502 across Southeast Asian populations (5). Carbamazepine is highly bound to plasma proteins in patients. Metabolism is believed to play a fundamental role in the pathogenesis of CBZ hypersensitivity and hepatotoxicity. Although the mechanism of toxicity is poorly understood, it had been inferred that reactive metabolites are generally accepted as the causal agents of hepatic injury. The major route of metabolism is primarily via CYP450 oxidation, producing a pharmacologically active metabolite CBZ 10,11-epoxide. Following this, CBZ 10,11-epoxide is further metabolised by epoxide hydrolase 1; however, this is not the major metabolite. Several different variations of reactive metabolites have been postulated; the production of these reactive metabolites is dependent on oxidative metabolism by cytochrome P450 (CYP) enzymes (11). Similarly, minor metabolic pathways look at ring-hydroxylation producing 2-hydroxy-CBZ (2-OH-CBZ) as well as 3-hydroxy CBZ (3-OH -CBZ), with the production of each likely to be proceeded by an arene oxide (epoxide) intermediate.

Diagnosis of Carbamazepine-Induced Hepatotoxicity

The diagnosis of CBZ-induced hepatotoxicity is vastly a clinical diagnosis. As such, both the onset and offset of hepatic injury evidenced by the patient's liver function tests (LFTs), are fundamental factors to take into consideration when contemplating the diagnosis. Liver enzymes can serve as markers of hepatocellular injury e.g. aspartate aminotransferase (AST) with a reference range of 10 – 55 and alanine aminotransferase (ALT) with a reference range of 10 – 40 U/L (12).

Prospective studies are indicative of a sizeable proportion of patients taking CBZ displaying transient serum aminotransferase elevations (ranging from 1% to 22%); these are typically benign in nature and will resolve despite drug continuation (7). Additionally, most patients on CBZ therapy will develop mild-to-moderate elevations in gamma glutamyltranspeptidase (GGT) levels, that are likely indicative of hepatic enzyme induction as opposed to liver injury. However, a marked increase in aminotransferase (> 5-fold increase) occur less frequently and are indicative of hepatotoxicity or an alternative type of liver injury (7).

There are no specific diagnostic laboratory tests to identify CBZ-induced hepatotoxicity (8), however if CBZ toxicity is suspected, serum concentration will be measured, alongside the LFTs, and compared to that of the therapeutic reference range of CBZ which ranges from 4-12 mg/L. When doing so, blood should be taken immediately prior to the next dose when the serum level should be within the therapeutic range. Serial CBZ levels must be repeated every 4 hours. From a toxicokinetic viewpoint, the majority of CBZ will remain bound to plasma protein due to the high protein binding affinity, the drug will also enter the bloodstream from tissue stores. CBZ toxicity can be classified into three categories:

1. Disorientation and ataxia at serum levels of 11 - 15 mg/L;
2. Aggression and hallucinations at serum levels of 15 - 25 mg/L;
3. Seizures and coma at serum levels above 25 mg/L;
    a. A serum CBZ concentration of 40 mg/L is typically fatal even with clinical intervention.

CBZ is eliminated with a half-life of about 30 hours after the initial dosage; typically inducing the cytochrome P450 enzyme for subsequent doses, with increased elimination (13). Patients presenting with CBZ-induced hepatotoxicity may present with a variety of symptoms, subject to the severity of ingestion or toxicity. Mild toxicity may present with vomiting, ataxia, slurred speech, drowsiness, nystagmus, hallucinations and dystonic reactions or repetitive muscle contraction. Whilst severe toxicity may result in coma, seizures, hypotension and respiratory depression, potentially resulting in respiratory arrest (14). A number of biochemical indicators can be used in the diagnosis of hepatoxicity subject to whether the predicted level present is either abnormally high or low, indicating possible hepatotoxicity; these indicators are explored in Fig. 1.

Treatment of Carbamazepine-Induced Hepatotoxicity

There is no clear line of treatment for the management of CBZ-induced hepatotoxicity. The treatment protocol followed typically varies subject to the treating Trust's own protocols and the leading clinician's degree of experience or the country in which the patient is being treated. In

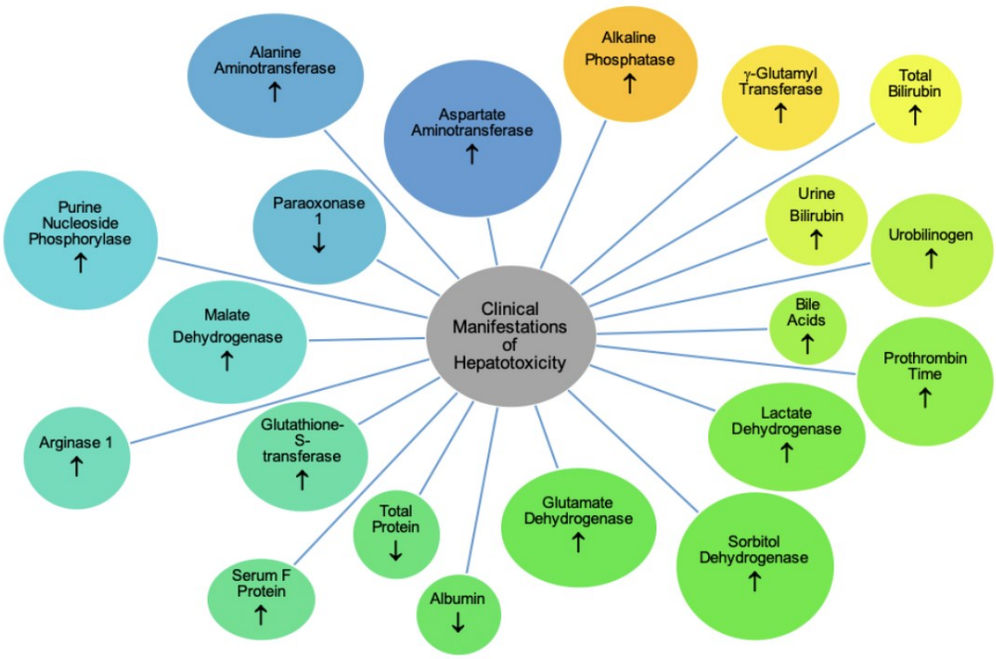

Figure 2. The clinical-biochemical indicators of hepatotoxicity in patients presenting with hepatotoxicity as a result of a drug overload or xenobiotics. Where ↑ indicates an increased value during hepatotoxicity whilst ↓ indicates a decreased value during hepatoxicity. Adapted from (15).

patient's presenting with CBZ toxicity, treatment can consist of monitoring serum levels of the drug alongside supportive care with the administration of intravenous fluids to manage hypotension whilst diluting the plasma concentration of the drug present in the blood. This line of treatment also typically incorporates the continuation of benzodiazepine treatment to manage epileptic seizure activity (16). Patients should have serial CBZ serum levels taken every 4 hours to monitor toxicity, with particular focus on a serum level taken immediately prior to the administration of the next dosage of CBZ; as this is when it is most likely for the levels to be back within the therapeutic range (14). An alternative line of treatment in CBZ-induced hepatotoxicity is that of primary gut decontamination with activated charcoal (17). There is a preference for this line of treatment as charcoal adsorption decreases CBZ enteral absorption subsequently reducing its plasma half-life. Gastrointestinal (GI) absorption of CBZ is unpredictable in nature and peak plasma concentration can be observed from 2-18 hours after a single dose has been administered. The plasma half-life ranges from 8-19 hours in continually treated, known epileptic patients (17). This half-life range is significantly lower than that of normal volunteers who possess a predicted half-life value of 21 to 55 hours (17). The increased plasma protein binding of CBZ is thought to be around 70-80%, and is fundamentally the reason as to why haemodialysis, peritoneal dialysis and alkaline diuresis are believed to have a very restricted ability in removing CBZ from the blood plasma, and subsequently treating the toxicity (18). In the case of an adult female presenting to medics having overdosed on CBZ; LFTs, routine bloods, GCS monitoring, ECG and routine observations were ordered. The leading clinicians on this case declared the management of the toxicity successful by combining intravenous fluid therapy, activated charcoal and haemodialysis with one another (19). A haemodialysis catheter was attached to the right femoral artery and two consecutive rounds of haemodialysis were conducted; due to the absence of carbon hemoperfusion. The CBZ serum levels were measured throughout, via high-pressure liquid chromatography. Prior to haemodialysis the serum level of CBZ measured at 57.7 µg/ml, following haemodialysis the serum level of CBZ was 28.9 µg/ml. By day three the patient was conscious and maintaining a GCS of 15, a significant improvement on the GCS 7 the patient were on presentation to the department; the patient's CBZ serum level had also dropped to 6.8 µg/ml (19). Fluid therapy earlier in the treatment protocol alongside activated charcoal and haemodialysis were administered in conjunction to encourage drug elimination. Due to the high mortality of CBZ toxicity, fluid therapy alongside activated charcoal treatment must be started as a matter of urgency, with haemodialysis being performed even in the absence of carbon hemoperfusion (19).

Discussion

Due to the frequency of prescription and subsequent administration of CBZ, an in-depth understanding of the pharmacokinetics and potential for hepatotoxicity is imperative for the improvement of the care of patients receiving CBZ therapy. Having reviewed the literature available around this subject, several fundamental conclusions can be drawn:

1. The routine monitoring of liver function in asymptomatic patients is unlikely to be of any merit as elevations in LFTs are to be expected whilst on

CBZ, but are typically not of concern until the patient is symptomatic;

2. Baseline testing of liver function and liver enzymes prior to the commencement of CBZ therapy would be of benefit to establish a comparative point, should the patient later become symptomatic;
3. CBZ should not be advised in the treatment of patients with a known history of liver disease or hepatic injury, unless it is the only viable course of treatment, as elevations in LFTs and liver enzymes are to be expected following the commencement of CBZ therapy.

CBZ hepatotoxicity is typically associated with elevated serum levels of CBZ in the blood. Elevated serum levels are those beyond the therapeutic range, which is 4-12 mg/L for CBZ. Symptoms of hepatotoxicity vary with the extent of CBZ toxicity in the blood plasma. Patients will present with predominantly CNS symptoms including ataxia, nystagmus, convulsions, myoclonus, coma and ophthalmoplegia. Other symptoms can include sinus tachycardia, hyperthermia, respiratory depression and even respiratory arrest. CBZ-induced hepatotoxicity is a known cause of death, with a 13% mortality rate observed in a study conducted on 307 patients presenting with CBZ toxicity (20). As a result of this relatively high incidence of mortality, it is vital that intravenous fluid therapy and activated charcoal treatment must be commenced urgently on admission by the clinicians responsible for the patient. Haemodialysis must then be subsequently implemented even in the absence of carbon hemoperfusion, in order to reduce the extent of toxicity present in the bloodstream and provide the patient with the best possible chance of survival (19).

Conclusion

With CBZ being the 176th most commonly prescribed medication in 2017 across the US, with a total of 3,516,204 prescriptions written that year (2), alongside the statistical knowledge that ~10% of patients receiving this therapy experience CBZ hypersensitivity, whilst antiepileptic hypersensitivity syndrome affects ~1 in 5000 people taking CBZ or phenytoin (3); the need for an awareness of identifying when and how to best treat patients experiencing CBZ-induced hepatotoxicity is truly emphasised. However, when it comes to CBZ-hepatotoxicity there is no specific antidote or designated treatment protocol; multiple dose activated charcoal or haemodialysis are the main lines of treatment but are often used in competition as opposed to in collaboration; which, as mentioned beforehand, is known to be an effective course of treatment for patients experiencing toxicity. Deaths as a result of CBZ hepatotoxicity have been reported, with a 13% mortality rate noted in a study of 307 patients presenting with CBZ hepatotoxicity; further emphasising the need for routine serum monitoring whilst being treated with CBZ therapy as well as the need for an established treatment protocol should toxicity occur (20).

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