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Heamatobiochemical Alterations Induced by Carbamazepine and Phenytoin: Mini Review

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Abstract

This review was carried out to conduct a literature survey of the effects of anticonvulsants carbamazepine (CBZ), phenytoin (PHT) and their combination on haematological and serum biochemical parameters. CBZ and PHT are among the oldest AEDs and usually the first line of treatment in epilepsy, being prescribed alone or sometimes in combination for retractable epilepsy. AEDs have been associated with different side effects which could be deleterious to the haemopoietic, nervous and/or hepatic systems. However, these effects may subside with the discontinuation of the medication(s). Side effects are prominent with the older AEDs such as CBZ, PHT, valproic acid (VPA) and phenobarbital (PB).

Keywords: Side effects; AEDs; Red blood cells; Platelets; White blood cells; Liver enzymes

Introduction

Epilepsy is considered a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and (3) Diagnosis of an epilepsy syndrome [1]. Epilepsy is a syndrome of different cerebral disorders which is characterized by excessive discharges of large numbers of neurons [2]. It is a disabling condition, rendered especially disturbing because of its unpredictability and its being a common neurological disorder worldwide [3]. Carbamazepine (CBZ) and phenytoin (PHT) were amongst the most prescribed antiepileptic drugs (AEDs) as monotherapy and as combination therapy as well as valproic acid (VPA); while levetiracetam (LEV) and lamotrigine (LTG) were found frequently prescribed amongst newer AEDs [4]. AEDs act either by increasing inhibition through sustaining the release of GABA or glycine, or decreasing excitation by inhibiting glutamate release. However, some AEDs reduce membrane excitability by interrelating with neurotransmitter receptors or ion channels (CBZ, VPA) but the methods of action for most of them are not fully understood (LEV, zonisamide) [5]. Although, CBZ and PHT are frequently prescribed for the treatment of epilepsy, there are some biochemical side effects that must be addressed. Therefore, in this mini-review, available informations on CBZ, PHT and their effects on biochemical parameters in epileptic individuals were compiled from electronic data bases.

Aetiology and Diagnosis of Epilepsy

Disruptions of GABAergic neurotransmission have been implicated in numerous central nervous system disorders, including epilepsy, depression, bipolar disorder and neuropathic pain [6]. The aetiology commonly consists of a lesion in some parts of the cortex such as a tumour, developmental malformation, and damage due to trauma or stroke. Such lesions are often evident on brain magnetic resonance imaging. Alternatively, the aetiology may be genetic [7]. Once epileptic seizures have been diagnosed, the determination of the epileptic syndrome follows and then the seizure type. The first issue that arises is whether and when to initiate treatment, for instance, it may not be necessary to initiate antiseizure therapy after an isolated tonic-clonic seizure in a healthy young adult, who lacks a familial history of epilepsy and who has a normal neurological examination, a normal EEG and a normal magnetic resonance imaging scan. That is the probability of recurrence of another episode of seizure in the next 1 year is 15% and the risk of unwanted side effects associated with AEDs administration could be severe as to result in the discontinuation of medication [8].

Therapy of Epilepsy

Therapy is symptomatic because the available drugs will only inhibit seizure, and neither effective prophylaxis nor cure is available [7]. The choice of an antiepileptic drug for any individual should take into cognizance information about seizure control, adverse effects and cost [9]. It was initially assumed that a single drug could treat all forms of epilepsy, but the causes of epilepsy are extremely diverse, encompassing genetic and developmental defects, traumatic, neoplastic and degenerative disease processes [10]. Rational polypharmacy aims at interacting with multiple receptors or ion channels to increase inhibition and simultaneously reduce excitation [5].

Antiepileptic Drugs (AEDs)

The term antiepileptic is used synonymously with anticonvulsant to describe drugs that are used to treat "epilepsy" (which does not

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necessarily cause convulsions) as well as "non-epileptic" convulsive disorders [11]. They include the hydantoins (PHT) and succinimides, the chemically distinct structures of the benzodiazepines, an iminostilbene (CBZ) and a branched-chain acid (VPA). Others are phenyltriazine (lamotrigine), a cyclic analogue of GABA (gabapentine), a sulphamate-substituted monosaccharide (topiramate), a nipecotic acid derivative (tiagabine) and a pyrrolidine derivative (LEV) [7]. Existing antiseizure drugs provide adequate seizure control in about two-thirds of patients, they exhibit similar pharmacokinetic properties including those with diverse structural and chemical properties because most have been selected for oral activity and all must enter the central nervous system [10].

Phenytoin (PHT)

It was first synthesized in 1908 by Biltz, but its anticonvulsant activity was not discovered until 1938 [7]. PHT, known for decades as diphenylhydantoin is the oldest non-sedative antiseizure drug, introduced in 1938 after a systematic evaluation of compounds such as phenobarbital that altered electrically-induced seizures in laboratory animals [10]. Phenytoin sodium is an anticonvulsant used to control grand mal and psychomotor seizures. Systemic administration induces anticonvulsant effect in humans and experimental animals [12]. The most significant effect of PHT is its ability to alter membrane potential [10] by blocking sodium ion channels and inhibiting neuronal firing in the brain [12].

Carbamazepine

Carbamazepine was discovered by a chemist, Walter Schindler at J.R. Geigy AG (now part of Novartis) in Basel, Switzerland in 1953, he then synthesized the drug in 1960, before its antiepileptic properties had been discovered [13]. Carbamazepine is an iminostilbene, a dibenzepine derivative that is chemically and pharmacologically related to tricyclic antidepressant agents [14]. It was approved for the management of seizures in 1974, although, it had been introduced a decade earlier for the management of trigeminal neuralgia [15]. Carbamazepine is a highly conventional antiepileptic drug, which has efficacy in attenuating picrotoxin-induced convulsion [16]. It acts by sodium-dependent channel blockade, weak GABAergic and antiglutamatergic effects [17]. Carbamazepine is the usual drug of choice for patients with newly diagnosed partial onset seizure [9]. It is effective against maximal electroshock seizures and exhibits autoinduction by inducing the hepatic microsomal enzyme system, CYP3A4 which metabolizes carbamazepine itself [18].

Side effects

Antiepileptic drugs are known to cause a variety of adverse effects; such as idiosyncratic bone marrow suppression or dose-related bone marrow suppression or aplastic anaemia with the exception of gabapentine [19,20]. Decreased immunoglobulins A and G were reported following CBZ and PHE administration [21]; this may cause reduced serum globulin and make patients susceptible to infections. Phenytoin sodium has been implicated in gingival hyperplasia, agranulocytosis and aplastic anaemia. It produces chromosomal anomalies and increased incidence of malignant melanoma [22]. Antiseizure drugs are eliminated chiefly by hepatic mechanisms although; many are converted to active metabolites that are also eliminated by the liver [10]. CBZ has been reported in an earlier study to cause decrease RBC counts, apparently due to isolated cessation of RBC production, as a result of pure RBC aplasia [23].

Effects on haematological parameters: All AEDs are potential toxic drugs; as all have significantly impaired lipid and hematological profile of the epileptics [4]. PHT, PB and CBZ are highly toxic to the haemopoietic system [24]. Platelet count was significantly reduced in epileptics treated with CBZ, PHT, PB and VPA as monotherapy or combination therapy compared to newer AEDs combination therapy. This toxicity was prominent in VPA, PHE and PB treated epileptics singly or as combination, similarly, leucopenia was significant in PHT and CBZ treated monotherapy group patients [4]. Antiepileptic drugs are hematotoxic with decreased haemoglobin concentration, RBC and WBC counts after long term antiepileptic therapy [25]. In contrast to these findings some scientists opined that AEDs do not have any effect on the biochemical and hematological parameters of epileptic patients [26]. Some of the AEDs implicated in pure red blood cell (RBC) aplasia include diphenylhydantoin, sodium valproate and CBZ [27]. Aliyu et al. [23] reported a decrease in RBC count and neutrophilia following the administration of CBZ and PHT; a non-significant decrease in RBC counts with co-administration of CBZ and PHT and lymphocytosis with CBZ administration. McNamara [7], reported that the prevalence of aplastic anaemia appears to be 1 in 200,000 patients, treated with CBZ monotherapy. Therefore, the concern that aplastic anaemia may be a frequent complication following CBZ therapy remains controversial. PHE administration has been known to cause lymphopenia because it was suspected to suppress mitogen-induced activation of lymphocytes [28]. The insignificant effects observed with the co-administration of CBZ and PHT on haematological parameters compared to the monotherapy groups may be attributed to CBZ ability to reduce the bioavailability of serum PHE [29]. Fever, transient skin rash, eosinophilia and lympadenopathy were associated features with the administration of CBZ and PHT. PHT has also been implicated in abnormal serum bilirubin, transaminases, eosinophilia and leukocytosis [30].

Effects on serum biochemical parameters: Hepatotoxicity refers to the destruction of the liver cells due to the presence of drugs or chemicals (hepatotoxins) caused by the generation of free radicals [31]. The liver being the primary organ of drug metabolism and elimination including AEDs is subjected to drug-induced toxicity from mild and transient elevations of the hepatic enzymes to fatal hepatic failure. PHT, PB and CBZ are potent enzyme inducers and induce cytochrome P_{450} system [32,33]. The hepatotoxicity induced by antiepileptic drugs occurs either as a result of the production of reactive toxic metabolites, immune-allergic reactions or obstruction in bile flow, cholestasis [4]. Liver enzymes such as, aspartate aminotransferase (AST), alanine aminotransferase (ALT) alkaline phosphatase (ALP) and gammaglutamyl transferase (GGT) can serve as markers of hepatocellular injury. CBZ, PHT and sodium valproate are associated with mild elevation of liver enzymes, hepatotoxicity induced by antiepileptic drug can lead to death or an acute liver failure [4]. Raghda et al. [2] conducted a study to assess the effect of CBZ, sodium valproate and PHT on liver enzymes; aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) in epileptic patients at the neurology outpatient clinic of Beni-Suef University, Beni-Suef, Egypt between February 2010 and June 2011. It was observed that sodium valproate was more hepatotoxic than carbamazepine which was more hepatotoxic than phenytoin also, the higher the dose of sodium valproate, the higher the AST level and the higher the dose of carbamazepine the higher the serum level. Syed and Zaeem [30] observed that administration of carbamazepine and phenytoin resulted in a modest elevation of ALT, AST, ALP and GGT. GGT was elevated in 50-90% of patients on PHT therapy. Elevation of AST and ALP were considered more specific markers of liver disease than ALT and GGT. The idiosyncratic hepatic toxicity to VPA

occurred during the first 2-3 months of therapy and lead to reduced alertness, vomiting, haemorrhage, increased seizures, anorexia, jaundice, edema, and ascites. VPA associated hepatotoxicity in adults was rare but potentially serious. Mostly, 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. Kashinath et al. [34] conducted a study to evaluate the effect of Phenytoin sodium on liver function tests on patients suffering from Grandmal epilepsy between the ages of 20 and 30 years. Ten healthy volunteers of same age group served as the control for the study. The period of exposure to drug varied from one year to five years. An increase in ALP activity in the epileptic patients on Phenytoin sodium was observed. Metabolic side effects of antiepileptic medications have been the cause of debate, whether these drugs require monitoring to assess and interventions to rectify the altered metabolic markers, antiepileptics may cause mild increase in liver function tests that tend to resolve over time [5]. Increased liver enzymes activities have been reported with PHT administration, it has been known that serum activities of liver enzymes in patients receiving a long-term anticonvulsant monotherapy showed a predominant elevation of GGT and ALP and that all enzymes were more often raised and attained higher values with phenytoin than with carbamazepine [35-37]. Except in the case of ALT activity, which was highest in the CBZ group, the AST and ALP activities were highest in the PHE group [7,23]. Ekaidem et al. [38] also reported increased activities of ALT, AST and ALP with long-term PHT therapy in rats. There was an increase in ALT with CBZ+PHT administration and increased LDH activity in all the AED-treated groups, with PHE having the highest activity [23]. There is a controversy regarding the exact mechanism for increased enzyme activities. Some investigators are of the opinion that increase occurs due to enzyme induction along with liver cell damage [39], while others maintain that increase is due to enzyme induction and is mostly mild and clinically insignificant [40]. Naithani et al. [41] reported a mild increase in liver enzyme levels and it was attributed to enzyme induction and not hepatocellular damage. The pre-disposition to the toxic effects of PHT and CBZ is presumed to be a consequence of an inherited deficiency in the detoxifying enzyme, epoxide hydrolase [42]. Ashrafi et al. [21] reported a decrease in immunoglobulins A and G following CBZ administration and this may cause decreased globulin concentration. Increased ALP activity following CBZ therapy was thought to be associated with an effect on bone formation possibly related to increased bone turnover [43].

Conclusion

The administration of carbamazepine and/or phenytoin caused alterations in haemato-biochemical parameters. Interactions between AEDs based on kinetics and rate of elimination from the liver appear to be accountable for the greater efficiency or adverse effects [5]. Therefore, a patient undergoing carbamazepine therapy should be carefully monitored, especially for serious adverse reactions, including pure red cell aplasia [44].

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