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REVIEW ON ANTI EPILEPTIC DRUG CARBAMAZAPINE

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Abstract

Carbamazepine is the drug of choice in the treatment of simple and complex partial seizures,Trigeminal neuralgia and glossopharyngeal neuralgia. It is often preferred over phenobarbital Or phenytoin because of its anti-inflammatory properties and fewer side effects. This article Provides an overview of the mechanism of action and medicinal properties of carbamazepine To explain the most common side effects and toxic effects of the disease. Most of these effects, That is those affecting the nervous system or cardiovascular system, are related to increased use of the drug in plasma and disappear rapidly after treatment. Other less toxic conditions, such as aplastic anaemia or fatal liver disease, can be attributed to the unexpected. Carbamazepine Poisoning causes clinical symptoms with neurological and cardiovascular symptoms, usually Accidental and sometimes secondary to a combination of other drugs. The results are generally good, sometimes spontaneous recovery and the mortality rate is very Low. There is no specific antibiotic. Oral activated charcoal has been shown to be an effective Treatment that reduces the plasma half-life of the drug.

Keywords: epilepsy, carbamazepine glossopharyngeal neuralgias, idiosyncratic reactions

Introduction

Epilepsy Definition

Epilepsy is a brain condition characterized by the rush of unprovoked seizures. Generally, prognostic refers to the probability of attaining seizure freedom on treatment and Little is known about the natural history of the undressed condition. Then, we epitomize aspects of the prognostic and prognostic predictors of treated and undressed epilepsy and of its different Runs. generally, epilepsy is a fairly benign condition.[(1)]

Generally, epilepsy is a fairly benign condition. utmost epilepsies have a good prognostic for full Seizure control and eventual termination of AEDs, but epilepsy runs have differing issues and responses to treatment. Prognostic factors include aetiology, EEG abnormalities, Type of seizures and the number of seizures endured before

treatment onset, and poor early goods of medicines. Early response to treatment is an important positive predictor of long- term prognostic, while the history of a high number of seizures at the time of opinion, intellectual Disability, and characteristic aetiology are negative predictors. Different prognostic patterns can Be linked, suggesting that the epileptogenic process isn't stationary. Epilepsy carries a lesser Than anticipated threat of unseasonable death. Aetiology is the single most important threat factor for unseasonable death.[1]

Causes of Epilepsy

The development of the unique population- grounded medical records- relation resource is told, and the measures of circumstance and association used in epidemiologic study designs to assess the causes of epilepsy are presented. The literal cohort design is optimal for the study of the relationship between common central nervous system cuts and seizures, and case-control studies are stylish used for analysis of fairly rare seizure diseases. The major Findings about the etiologic places of traumatic brain injuries, central nervous system infections, Cerebrovascular complaint, brain excrescences, neurodegenerative conditions, experimental disabilities, Perinatal cuts, and domestic factors are bandied. The part of inheritable factors in epilepsy has Been controversial, maybe because of the multitudinous causes of seizures and their episodic nature.[2]

Classification of Seizures and Epilepsy

In all bracket systems, the distinction between seizures primarily relies on whether the commencement of these events in the cerebral cortex is of a focal or generalized origin. thus, all bracket systems begin with a division of seizures between focal and generalized Seizures. This is important because the choice of medical and surgical interventions will be Dependent on the applicable bracket The subtypes for generalized and focal seizures are Displayed in Tables 1 and 2. [3]

Types	Other names
Focal seizures without impairment of consciousness Autonomic Clonic Hemiconvulsive Subjective sensory/psychic	Simple partial
Focal dyscognitive seizures with impairment of consciousness	Complex partial
Focal seizure evolving to a bilateral convulsive seizure	Secondary generalized

Table .1 - Focal seizures—three subtypes

Primary tonic–clonic
Absence
Typical
Atypical
Absence with special features
Myoclonic absence
Eyelid myoclonia
Myoclonic
Tonic
Clonic
Atonic

Table no. 2 - Generalized seizures—six subtypes

Treatment

Valproate was treatment of choice for characteristic myoclonic and generalized alcohol- clonic Seizures. For original monotherapy for complex partial seizures, carbamazepine and Oxcarbazepine were treatments of choice, with valproate also first line. As original remedy for immature spasms caused by tuberous sclerosis, viagabatrin was treatment of choice. As original remedy for immature spasms that are characteristic in etiology, vigabatrin was also treatment of Choice, with adrenocorticotropic hormone (ACTH) and prednisone other first-line options. As original remedy for Lennox- Gastaut pattern, valproate was treatment of choice. For acute Treatment of a prolonged febrile seizure or cluster of seizures, rectal diazepam was treatment of choice. Valproate was treatment of choice as preventative remedy for febrile seizures. For Benign nonage epilepsy with centro-temporal harpoons, valproate was treatment of choice. For Nonage and juvenile absence epilepsy, valproate was treatment of choice, with lamotrigine

Another first- line option (ethosuximide was another first- line option for nonage absence Epilepsy). For juvenile myoclonic epilepsy in adolescent males, valproate was treatment of Choice, with lamotrigine another first- line option; for juvenile myoclonic epilepsy in adolescent Ladies, lamotrigine was treatment of choice, with valproate another firstline option. As original remedy for neonatal status epilepticus, intravenous (IV) phenobarbital was treatment of choice. As original remedy for all types of paediatric status epilepticus, IV diazepam was treatment of Choice. For generalized alcohol- clonic status epilepticus, rectal diazepam and IV lorazepam were Also treatments of choice; for complex partial status epilepticus, IV lorazepam was another First- line option.[4]

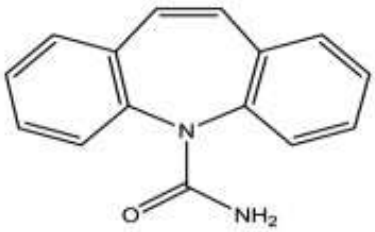
Carbamazepine Use in Epilepsy

Epilepsy is one of the most common neurological diseases, affecting roughly 50 million People worldwide. Despite a dramatic increase in treatment options over the once 30 times, it Still ranks fourth in the world's complaint burden. There are now close to 30 antiepileptic medicines AEDs), with further than two thirds introduced to the request after carbamazepine (CBZ) and one third after its outgrowth, oxcarbazepine (OXC). Following the preface of these newer AEDs, the part of CBZ and OXC in the remedial armamentarium for seizure control and Effective epilepsy operation needs to be reviewed. The main guidelines list both CBZ and OXC as first- line options or alternate- line druthers for the treatment of focal- onset epilepsy and primary generalized alcohol- clonic seizures. While substantiation suggests that overall AEDs have analogous efficacity, some newer AEDs may be better permitted than CBZ. In line with this, there Have been changes in treatment patterns, with numerous variations across different countries. still, CBZ remains among the two or three most

prescribed medicines for focal epilepsy in numerous countries, and is extensively used across Europe, Africa, South America, and Asia, where it Represents a good concession between cost, vacuity, and effectiveness. OXC is among the First- choice options for the original treatment of focal- onset seizures in several countries, Including the US and China, where the oral suspense is generally specified. This review guidance on the optimal use of these two medicines in clinical practice, including in Children, the senior, and in gestation.[5]

Drug Profile

Structure of Carbamazepine



5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide
Chemical Formula: $C_{15}H_{12}N_2O$
Molecular Weight: 236.27

Figure 1- Structure of Carbamazepine

History of Carbamazepine

CBZ was first discovered and synthesized by Swiss druggist Walter Schindler in 1953 and was originally developed to treat trigeminal neuralgia (1,2). In the early 1960s, carbamazepine's Anticonvulsant parcels were observed in beast trials and latterly in mortal clinical Studies (3,4). As a result, CBZ was also approved as antiepileptic medicine in Great Britain and Switzerland in 1963. [6]

CBZ (5H- dibenz (b, f) azepine-5-carboxamid; C15H12N2O) belongs to the class of Dibenzazepines and consists of a tricyclic ring structure (Figure 1). CBZ is available as white liquid greasepaint, which is hardly answerable in water. The structural parallels of CBZ Compared to tricyclic antidepressants may explain its broad exertion diapason as well as its Antiepileptic and psychoactive properties. [7]

Chemical Properties of carbamazepine

The influence of hydroxypropyl methylcellulose (HPMC) on the demitasse habit parcels of carbamazepine in sustained release matrix tablets and in waterless results was delved Using discriminational scanning calorimetry (DSC), X-ray greasepaint diffraction and surveying electron Microscopy (SEM). The results suggest that HPMC inhibits the metamorphosis of Carbamazepine- to- carbamazepine dihydrate in the gel subcaste of doused tablets and in waterless results (depending on HPMC attention), participates in its crystallization process and induces amorphism of carbamazepine chargers. The medium which explains these goods envisages the polymer serving as a template or micro substrate for nucleation in the Crystallization process. We assume that the commerce between the medicine and polymer occurs by hydrogen cling. The hydroxyl groups of the polymer may attach to the medicine at the point of Water list, and therefore its metamorphosis to the dihydrate form, is inhibited. A more specific Interaction involves structural matching (analogous bond distance distances) betweeninter-atomic Distances in the demitasse chassis of carbamazepine dimer andintra-atomic distances along the Polymer chain.[8]

Solubility

Soluble in alcohol, acetone, propylene glycol; virtually undoable in water Soluble in chloroform, dimethylformamide, ethylene glycol monomethyl ether, or methanol; Only slightly answerable in ethanol or glacial acetic acid.(9)

Pharmacological Properties Of carbamazepine

Route of administration

Carbamazepine comes as a tablet, a chewable tablet, an extended- release (long- amusement) tablet, an extended- release capsule, and as a suspense (liquid) to take by mouth. The regular tablet, Chewable tablet, and suspense are generally taken two to four times a day with meals. The Extended- release tablet (Tegretol XR) is generally taken twice a day with meals. The extended release capsule (Carbatrol, Equetrol) is generally taken twice a day with or without meals.(10)

Absorption

Carbamazepine is fairly sluggishly but virtually fully absorbed after administration by mouth. Loftiest attention in the blood tube are reached after 4 to 24 hours depending on the lozenge form. Slow release tablets affect in about 15 lower immersion and 25 lower peak tube attention than ordinary tablets, as well as in lower change of the attention, but not In significantly lower minimum attention.

Carbamazepine crosses perfectly through the blood- brain hedge. Carbamazepine is 75- 80 Bound to tube proteins. One pharmacokinetic study indicates that it's 72 bound to tube Proteins. Carbamazepine is largely metabolized in the liver.(11)

Volume of distribution

Carbamazepine (2.7- 3 mg/ kg) was administered orally as an alcoholic result (50 v/ v) to Eight healthy levies. Two of the subjects were also given 50 mg and 100 mg of Carbamazepine in alcoholic result and 200 mg as a tablet.

The volume of distribution is roughly0.8-1.2 L/ kg, which can increase to over to 3 L/ kg in cases of carbamazepine overdose. Carbamazepine is metabolized by the cytochrome P- 450 System enzymes 2D6 and 3A4.

The pharmacokinetic parameters calculated from single oral boluses were used to prognosticate the Steady-state tube attention anticipated after treatment with multiple boluses of 200 mg three Times daily. The prognosticated steady- state attention was 2- 3 times advanced than that reported In cases witnessing habitual treatment with carbamazepine at this cure position, i.e. the Pharmacokinetics of carbamazepine supposedly change during multiple dosing.(12)

Metabolism

Carbamazepine is largely metabolized in the liver. CYP3A4 hepatic enzyme is the major Enzyme that metabolizes carbamazepine to its active metabolite, carbamazepine- 10,11- Epoxide 12, which is farther metabolized to its trans- diol form by the enzyme epoxide Hydrolase.

Two metabolic processes by CYP3A4 were enforced, as carbamazepine is metabolized By CYP3A4 to carbamazepine -10,11-epoxide as well as to hydroxylated metabolites.

Carbamazepine induces its own metabolism, leading to increased concurrence, docked serum Half- life, and progressive drop in serum situations. Increases in diurnal lozenge are necessary to Maintain tube attention. Severe liver dysfunction may beget disordered Pharmacokinetics.(13)

Route of Elimination

After single boluses of carbamazepine, elimination follows cure-dependent first order kinetics. Carbamazepine is metabolised by oxidation before excretion in the urine. In experimental creatures, the metabolite carbamazepine -10,11-epoxide has anticonvulsant exertion similar With that of the parent medicine.(14)

Half Life

After single oral boluses of carbamazepine, the immersion is fairly complete and the elimination Half- life is about 35 hours (range 18 to 65 hours).(15)

Clearance

In a pharmacokinetic study, the apparent oral concurrence of carbamazepine was 25 ± 5 mL/ min 11,16 after one cure of carbamazepine and 80 ± 30 mL/ min after several boluses. The original signs of carbamazepine overdose do 1- 3 hours post ingestion.(16)

Mechanism of Action

Carbamazepine's medium of action isn't completely illustrated and is extensively batted. One major thesis is that carbamazepine inhibits sodium channel blasting, treating seizure exertion. Beast exploration studies have demonstrated that carbamazepine exerts its goods by lowering Polysynaptic whim-whams response and inhibitingpost-tetanic potentiation. In both pussycats and rats, Carbamazepine was shown to drop pain caused by infraorbital whim-whams stimulation. A drop in the action eventuality in the nexus ventralis of the thalamus in the brain and Inhibition of the lingual mandibular kickback were observed in other studies after carbamazepine Use. Carbamazepine causes the below goods by binding to voltage-dependent sodium channels and precluding action capabilities, which typically lead to stimulator goods on jitters. In Bipolar complaint, carbamazepine is allowed to increase dopamine development and increase GABA Transmission, treating manic and depressive symptoms.

A common issue that has arisen is resistance to this medicine in over to 30 of epileptic cases, which may do to altered metabolism in cases with variant genotypes. A implicit remedial target to combat carbamazepine resistance has lately been linked as the EPHX1 gene protagonist, potentially conferring resistance to carbamazepine through Methylation.(17)

Therapeutic Use

Carbamazepine is FDA indicated for epilepsy, trigeminal neuralgia, and acute manic and Mixed occurrences in bipolar I complaint. suggestions for epilepsy are specifically for partial Seizures with complex symptomatology (psychomotor, temporal lobe), generalized alcohol Seizures (grand mal), and mixed seizure patterns. Carbamazepine isn't indicated for absence Seizures. Carbamazepine is FDA indicated as a first- line treatment for trigeminal neuralgia or Tic douloureux. A systemic review shows the efficacity of carbamazepine extended- release in Bipolar I mania in cases with acute manic or mixed occurrences.

Carbamazepine is used off- marker for refractory schizophrenia. Simple well- designed trials have Shown efficacity in cases with schizophrenia with EEG abnormalities, schizophrenia with Violent occurrences, and schizoaffective complaint. It improves both positive and negative Symptoms in schizophrenic cases. Other off- marker uses of this medicine include treating restless Leg pattern and dwindling agitation and aggression in cases with madness. Another Prominent off- marker use of this medicine is the treatment of neuropathic pain and fibromyalgia. In Cases with moderate to severe alcohol pullout pattern, carbamazepine has shown Clinical efficacity in treatment. still, this suggestion doesn't have blessing from the FDA, And it has not been shown to help alcohol pullout seizures compared to benzodiazepines.(18)

Side Effects

• Feeling sleepy, dizzy or tired. Don't drive, cycle or use tools or ministry if you 're Feeling sleepy, tired or dizzy.

• or being sick (nausea or vomiting) Stick to simple meals and don't eat rich or racy Food.

• Headaches.

• Sot mouth.

• Putting on weight.

Carbamazepine may cause life-hanging antipathetic responses called **Stevens-Johnson Syndrome (SJS)** or poisonous epidermal necrolysis (TEN). These antipathetic responses may cause Severe damage to the skin and internal organs. The threat of SJS or TEN is loftiest in people of Asian ancestary who have a inheritable (inherited) threatfactor.However, your doctor will If you're Asian. Generally order a test to see if you have the inheritable threat factor before defining carbamazepine. If you don't have this inheritable threat factor.(19)

Contraindications

Carbamazepine is contraindicated in cases with bone gist depression and Acuity to this medicine or tricyclic composites similar as amitriptyline. S Before Administration, monoamine oxidase impediments should be discontinued for a minimum of 14 Days. operation carbamazepine and nefazodone together may affect in inadequate tube attention of nefazodone. Carbamazepine is contraindicated in use with nefazodone.(20)

Toxicity

Carbamazepine overdose has a predictable cure-dependent CNS depression and Anticholinergic goods. Carbamazepine if unique in the anticonvulsants that's also has sodium Channel blocking goods and can act also in overdose to a tricyclic antidepressant and the part of sodium bicarbonate should be flashed back.

Toxicokinetics

Slow and erratic immersion, this is important in a large overdose due to the ineluctable ileus that will form due to the anticholinergic goods. The case also has a large tablet bezoar that has Continued erratic immersion potentially performing in a shifting GCS/ recovery. immersion Can last for several days

Small volume of distribution0.8 –1.2 L/ kg

Hepatic metabolism to the active metabolite carbamazepine 10,11 epoxide which is also Metabolised to an inactive form and excreted in the urine.(21)

Adverse Effects

The most common adverse goods of carbamazepine include dizziness, doziness, ataxia, Nausea, and puking. Although rarer in circumstance, this comes with a black box warning for Several severe dermatologic responses. In cases of Han Chinese strain, studies have Indicated a strong association between the HLA- B * 1502 gene and Steven Johnson Pattern/ poisonous epidermal necrolysis (SJS/ TEN). Studies have shown no increased threat with This gene and SJS/ TEN in Iranian cases. A meta- analysis of 11 studies with 343 cases of Carbamazepine-convinced SJS/ TEN showed HLB- B * 4001, HLB * 4601, and HLB * 5801 genes Were strong defensive factors. Cases of Han Chinese strain should suffer testing for the HLA- B * 1502 gene. Up to 90 of cases on carbamazepine who have this response Experience it within the first many months of treatment. Another important allele to consider with this drug is HLA * 3101. This allele is present in Japanese, Korean, and European strain. Retrospective studies show a significantly increased prevalence of dermatologic responses similar as Stevens- Johnson pattern, poisonous epidemic necrolysis, maculopapular Eruptions, and medicine response with eosinophilia and systemic symptoms (DRESS syndrome).

Carbamazepine has another black box warning on agranulocytosis and aplastic anaemia. Other Serious side goods include central nervous system depression, hepatotoxicity, confusion, renal toxin, suicidal creativity, and hyponatremia. Hyponatremia is mild, flash, and reversible.[22]

Conclusion and discussion-

Carbamazepine is an effective drug for the treatment of certain types of epilepsy, particularly partial onset seizures and generalized alcohol- clonic seizures, as well as some types of mood diseases and pain.Carbamazepine shows variability due to its narrow remedial window. thus, clinical operation in a3n Iranian epileptic population should concentrate on results deduced from remedial medicine monitoring in order to reduce inter and intra-individual variability in tube medicine attention.

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