A BRIEF DISCUSSION OF EPILEPSY WITH SPECIAL REFERENCE TO CARBAMAZEPINE

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ABSTRACT

Epilepsy is becoming the most serious disorder of brain function and affects 40 million people worldwide. The prevalence rate of epilepsy is 4 to 10 per thousand population. The incidence of epilepsy is less in most developed countries than developing countries. Epilepsy can result form brain injuries caused by blows to the head, stroke, infections, high fever or tumors. Some cases of epilepsy are induced by genetic factors. Several factors are proved to be responsible for precipitating seizures in susceptible individual these include hormonal changes during menstruation, puberty or pregnancy, drugs like theophylline, alcohol, high dose phenothiazines, antidepressants and anti-epileptics in toxic concentration. Some seizure may occur as single event resulting from withdrawal of CNS depressant , during acute illness or toxic conditions. Carbamazepine is a tricyclic iminostilbene derivative, widely used antiepileptic drugs and used in the treatment of epilepsy, trigeminal neuralgia and bipolar disorders. It belongs to the class II biopharmaceutical classification system. Compounds in this category have high intestinal permeability and low water solubility subsequently the bioavailability of such compound is limited by their solubility in water. Carbamazepine is also characterized short half life on chronic dosing because of the auto-induction of hepatic metabolism. The initial half life is about 24 hrs falling to approximately 12 hrs with chronic mono-therapy and 8 hrs in those patients a receiving other enzyme inducing drugs. This review reflects general discussion of epilepsy and analytical information, mechanism of action, pharmacokinetics, indication, adverse effects and drug interaction of mostly used antiepileptic drug, carbamazepine.

Keywords: Carbamazepine, epilepsy, antiepileptic drugs, brain disorder.

INTRODUCTION

Epilepsy is a chronic brain disorder and characterized by the periodic and unpredictable occurrence of seizures with or without convulsions [1]. Seizures can vary widely in their clinical presentation, depending on site, extent and mode of propagation of the paroxysmal discharge of impulses by a group of neurons in the brain [2]. A seizure involving motor cortex is associated with clonic jerking of the body part controlled by this region of cortex. Involvement of hypothalamus causes peripheral autonomic discharge and involvement of the reticular formation in the upper brain stem leads to loss of consciousness [1]. Epilepsy may result form brain injury, chemical imbalance, poisoning, stress, head trauma, stroke, infection, genetic factors etc and are not restricted to

any age group, sex or race.

About 50 million people worldwide have epilepsy, and nearly 90% of epilepsy occurs in developing countries. In Western countries, it is recognized that the incidence rate of epilepsy is higher in elderly as compared to young children. Higher prevalence rates ranging from 14 to 57 per thousand have been reported from some African and South American countries [3]. In India, approximately 5.5 million people suffer from epilepsy, among whom approximately 4.1 million people are inhabitant of rural areas [4, 5]. The incidence of epilepsy ranges from 40 to 70 per 100,000 in most developed countries and from 100 to 190 per 100,000 in developing countries and in India the estimated rate of incidence is 49.3 per 100,000 persons each year [6-10]

Management of epilepsy involves the treatment of causative factors, proper education to the patient regarding disease, duration of treatment and need for compliance and avoidance of precipitating factors like alcohol, sleep deprivation, emotional stress etc[11]. Effective management of a patient with epilepsy requires a detailed and accurate classification of seizure types. The epileptic seizures are mainly classified into four major groups e.g., partial seizures (seizures begin locally), generalized seizures (bilaterally symmetrical and without local onset), unclassified seizures and status epileptics. partial seizures are further classified as simple (without impairment of consciousness), complex (with impairment of consciousness) and secondarily generalized (partial onset evolving to generalized tonic clonic seizures). Similarly, generalized seizures are categorized into absence, myoclonic, clonic, tonic, tonic-clonic, atonic and infantile seizures [11].

Epilepsy is usually controlled, but not cured, with available medication [12, 13]. Therefore, the primary objective of management of epilepsy with antiepileptic drug is to achieve complete control of seizure with no side effects [11]. The drugs currently used not only fail to control seizure in some patients but they frequently cause unwanted effects. So in order to minimize toxicity, treatment starts with a single drug and if seizures are not controlled even at its adequate plasma concentration, the concurrent use of second drug is usually preferred [1]. The commonly used antiepileptic drugs include phenytoin, carbamazepine, valproate, ethosuccimide and phenobarbital together with various benzodiazepines, such as diazepam, clonazepam and clobazam. Several new drugs have been recently introduced for clinical use they include vigabatrin, gabapentin, lamotrigine, felbamate, tiagabine and topiramate [14]. Antiepileptic drugs are effective in controlling seizures in 50 -80% of the patients [2] and 8% patients are taking atleast one antiepileptic drug for long term therapy [11]. Carbamazepine being prototype drug and is used extensively for the treatment of epilepsy, therefore, our present study is restricted in general discussion of epilepsy with special reference to carbamazepine.

Carbamazepine, tricyclic iminostilbene derivative, is one of the most important drugs for the therapy of psychomotor epilepsy, used to control grandmal and also in the treatment of trigeminal neuralgia. It belongs to the class II biopharmaceutical classification system. Compounds in this category are characterized by high membrane permeability, irregular and delayed gastro-intestinal absorption due to their low water solubility [15]. Carbamazepine is also characterized short half life on chronic dosing because of the auto-induction of hepatic metabolism. The initial half life is about 24 hrs falling to approximately 12 hrs with chronic mono-therapy and 8 hrs in those patients a receiving other enzyme inducing drugs [16]. It is now considered to be a primary drug for the treatment of all types of epilepsy except absence seizures [17].

History [18, 19]

Carbamazepine was discovered by chemist Walter Schindler at J.R. Geigy AG (now part of Novartis) in Basel, Switzerland in 1953.

In 1971, Drs. Takezaki and Hanaoka first used carbamazepine to control mania in patient's refractory to antipsychotic. Carbamazepine was studied for bipolar disorder throughout 1970s.

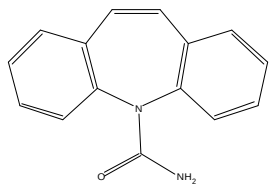
ANALYTICAL INFORMATIONS

A) Description [20-23]

Carbamazepine is 5H-dibenz [b,f] azepine–5–carboxamide carbamazepine contain not less than 97.0 percent and not more than 103.0 percent of $C_{15}H_{12}N_2O$, calculated on the dried basis.

Generic Name: Carbamazepine

Formulae: $C_{15}H_{12}N_2O$



5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide

Figure 3.1. Structure of carbamazepine

Molecular weight: 236.30

Elemental composition: C–76.25%, H-5.12%, N-11.86%, O-6.77%.

Appearance: A white or yellowish–white crystalline powder; almost odorless; exhibit polymorphism.

Melting point: Melts within a range of between 187°C and 193°C.

Solubility: Freely soluble in dichloromethane; sparingly soluble in ethanol (95%) and in acetone; practically insoluble in water and in ether.

***Storage*:** Store protected from moisture.

B) Identification [24]

***Infrared Spectroscopic test*:** USP XIX cites the use of Infra-red absorption spectrum of carbamazepine in methylene chloride as a mean of identification comparing some characteristic adsorption bands of the drug. This is given in infra-red spectral properties of the drug.

Color test: Carbamazepine can be identified by color test with ammonium molybdate. A faint to blue color is produced (sensitivity 1.0 µg). B.P. 1973 describes a color test in which 0.1 gm of the drug is treated with 2 ml. nitric acid in a water bath for 3 minutes where an orange color is produced.

Crystal test: Carbamazepine can be identified by forming crystals with lead iodide solutions where needles are formed.

C) Spectral properties

***Ultraviolet spectrum*:** Carbamazepine in neutral methanol solution shows maxima at 212 nm, an inflection at 236 nm, 283 nm; and a minimum at 256 nm. Carbamazepine in ethanol shows maxima at 250 nm and at 285 nm, minimum at about 257 nm. In 0.1 N sulphuric acid, the drug shows maxima at 283 nm (E 1%, 1 cm 147) and an inflection at about 255 nm (E 1%, 1cm 274). The ultraviolet absorption spectrum of the drug is used as a mean of identification of carbamazepine in B.P. 1973. A 2 cm layer of 0.001 w/v solution in alcohol (95%) exhibit a maximum only at 285 nm; extinction at 285 nm, about 0.98. The drug also exhibits an intense blue fluorescence in the ultraviolet light at 366 nm.

***Infra-red spectrum*:** The infra-red spectrum was obtained from nujol mull. The structural assignments have been correlated with the following band frequencies:

Frequency (cm^{-1})	Assignments
3470	NH_2
1680	C = O
1600 shoulder and 1590	Aromatic C = C

Clarke cited the following band as characteristic principal peaks for carbamazepine when determined in potassium bromide; 1678, 1388 and 1594 cm^{-1}.

Mechanism of action

Like phenytoin, carbamazepine limits the repetitive firing of action potential evoked by a sustained depolarization. This appeared to be mediated by slowing of rate of recovery of voltage-activated sodium channel from inactivation. Voltage–activated sodium channel are the molecular pores that allow brain cells (neurons) to generate action potentials, after the sodium channels open to start the action potentials, they inactivate, essentially closing the channel. Carbamazepine stabilizes the inactivated state of sodium channel [1]. It has also been shown to potentiate GABA receptors made up of alpha 1, beta 2, Gamma 2 subunits [25].

It also acts presynaptically to decrease synaptic transmission. These effects probably account for the anticonvulsant action of carbamazepine [26].

Pharmacokinetics

The absorption of carbamazepine from immediate–release tablets is slow and erratic because of its low water solubility. Carbamazepine is widely distributed throughout the body (volume of distribution is roughly 1L/Kg) [26]. Carbamazepine crosses the placental barrier and is distributed into breast milk [21]. It is 75% bound to plasma protein, primarily to albumin [27]. Carbamazepine has the unique ability to induce its own metabolism. It increases the activity of hepatic microsomal enzyme system CYP3A4 which metabolizes carbamazepine it self. Most (98% to 99%) of an administered carbamazepine is metabolized by the liver, primarily by CYP3A4 [21]. Initially its plasma t½ is 20-40 hours but decreases to 10-20 hours on chronic medication due to enzyme induction [14]. Increase in does at a rate of 200 mg every 1-2 weeks may be required to achieve a stable seizure threshold. Stable carbamazepine concentrations occur usually within 2-3 weeks after initiation of therapy [28]. Carbamazepine 10-11-epoxide is one of the primary metabolized of carbamazepine and is active. Carbamazepine is excreted in the urine and in the faeces almost entirely in the form of its inactive metabolites. The pharmacokinetics of carbamazepine is affected by the concomitant administration of other antiepileptic.

Therapeutic uses [1]

1) Carbamazepine is used in generalized tonic-clonic and both simple and complex partial seizures.
2) It is also used in the treatment of trigeminal and glossopharyngeal neuralgias.
3) It is also useful in tabetic pain.

Dose [21]

The dose of carbamazepine will range from 400 to 1200 mg per day, the average being 600 mg per day. One third of usual maintenance dose should be given initially, when the anticonvulsant therapy is being started in a previous untreated woman. It should be increased weekly over a period of three to four weeks until the mean daily maintenance dose is reached.

1) The usual oral dose in children based on the body weight is 10 to 20 mg per kg daily in divided doses.
2) In the treatment of trigeminal the initial dose of carbamazepine is 100 mg once or twice daily by month increased gradually as necessary; the usual maintenance dose of 400 to 800 mg daily in two to four daily divided doses but up to 1.6 gm daily may be required.
3) For prophylaxis of bipolar disorder, an initial oral dose of 400 mg in daily divided doses as necessary up to a maximum of 1.6 gm daily; the usual maintenance dose range is 400 to 600 mg daily.

Table 1: Dosage forms and route of administration [29]

Following are some of the preparation of carbamazepine currently available in India:

Sl No	Brand Name	Dosage forms	Amount in mg.	Routes of Administration	Name of the Manufacturer
1	Mazetol	Tablet,SR-Tablet,Chw-Tablet,Syrup	100, 200, 300, 400	Oral	Piramal HC
2	Carbatol	Tablet,CR-Tablet	100, 200, 300, 400	Oral	Torrent
3	Zeptol, Carmaz, Carmaz Kid	Tablet, CR-Tablet, DT-Tablet	100, 200, 400	Oral	Sun.Pharma
4	Zen, Zen Retard	Tablet, CR-Tablet	100, 200, 300, 400	Oral	Intas
5	Tegretol	Tablet, Syrup Chew-Tablet,	100, 200, 400	Oral	Novartis India
6	Carbadac	Tablet,	200	Oral	Zydus Cadila
7	Versizur	Tablet	200	Oral	Micro lab
8	Tegrital	Tablet, Syrup	100, 200, 300, 400	Oral	Novartis Pharma
9	Zepcar	DT-Tablet, CR-Tablet	100, 200, 300, 400	Oral	Alkem (Pentacare)
10	Antilep	Tablet, CR-Tablet	100, 200, 300, 400	Oral	Psycorem

Adverse effects

Carbamazepine produces dose related neurotoxicity–sedation, dizziness, drowsiness, diplopia, blurred vision [30-32]. Other does related complaints include mild gastrointestinal upset, unsteadiness, nausea, vomiting, diarrhoea etc.

Agranulocytosis and aplastic anemia are rare but very serious adverse effects.

A mild transient leucopenia occurs in about 10% of patients, but usually disappears in first four months of treatment.

Hyponatremia and sometimes odema have occurred. Other adverse effects reported include headache, arrhythmias, heart block, heart failure, rashes, impotence, weight gain, tremors [27, 33], gynaecomastia, photosensitivity reaction, urticaria, rashes etc. Carbamazepine increases the risk of developing lupus by 1.88 [34].

Drug interaction

Carbamazepine has a very high potential for drug interactions; caution should be taken in combining other medicines with-it. Including other antiepileptic and mood stabilizers [35]. When administered with phenobarbital, phenytoin, or primidone, methosuximide, cisplatin, doxorubicin HCl, rifampicin, theophyline and valproate may increase the metabolism of carbamazepine by inducing CYP3A4 and decrease its plasma level. Carbamazepine may increase the biotransformation of phenytoin as well as conversion of primidone to Phenobarbital. Carbamazepine as a CYP450 inducer may increase clearance of many drugs decreasing their blood levels [36]. Drugs like erythromycin [37], cimetidine, proporyphene and calcium channel blockers may decrease the metabolism of carbamazepine and increase its plasma level. Carbamazepine also increases the metabolism of the hormones in birth control pills and can reduce their effectiveness, potentially leading to unexpected pregnancies [35]. Carbamazepine is an enzyme inducer; can reduce efficacy of haloperidol lamotrigine and topiramate [14].

Valproic acid and valnoctamide inhibits microsomal epoxide hydrolase (mEH); thereby inhibiting breakdown of carbamazepine-10-11-epoxide into inactive metabolites [38], prolonging the effects of carbamazepine and delaying its excretion.

Contraindication

Carbamazepine should not be used in patients with history of previous bone narrow depression. Hypersensitivity to the drug or known sensitivity to any of the tricyclic compound, such as amitriptylene, desipramine, imipramine, nortryptylene etc.

Use with MAO inhibitors is not recommended. Carbamazepine should be given with caution to patients with a history of blood disorders or of cardiac, hepatic or renal disease. Since carbamazepine has mild antimuscarinic properties caution should be observed in patients with glaucoma or raised intra ocular pressure.

CONCLUSION

Now a day, epilepsy is becoming a social burden and affecting from children to elder persons. Since epilepsy can be controlled but not cured, therefore it is very much essential to have a detailed and accurate classification of seizure types to select appropriate antiepileptic drug(s). Advances in clinical and basic science are increasing our understanding of epilepsy mechanisms. New information from molecular genetics, imaging techniques, and cellular physiology are creating conditions whereby these advances will translate into therapeutic relevances. There is a continuing need for new antiepileptic drugs and more research in the area. The researchers are eager to find out the links between the different levels of pathophysiology in epilepsy, and translate these into beneficial therapies.

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