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CARBAMAZEPINE FOR MANAGEMENT OF SEIZURE DISORDERS AND ITS INTERACTION: A REVIEW

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ABSTRACT

Carbamazepine (CZ) is an anticonvulsant drug is used for management of seizure disorders. It is a mood stabilizer to treat combined episodes, manic episodes, and bipolar disorder. It is also recommended for use in treatment trigeminal neuralgia, generalized tonic-clonic attacks, temporal lobe seizures, and multiple psychiatric problems. CZ gets broken down in the liver by the enzyme CYP450 3A4. Carbamazepine epoxide is the most essential metabolite. The metabolic routes of CZ include oxidation, hydroxylation, deamination, and esterification with glucuronic acid. CZ has a 75–80% high affinity for plasma proteins. The bioavailability can vary from 75 to 85%. Consuming food did not seem to have any effect on the rate or degree of absorption. It exhibits its effects via decreasing dopamine turnover, raising brain levels of -aminobutyric acid (GABA) through several kinds of synthesis and degradation processes, and altering a series of neurotransmitters, extra hypothalamic neuropeptides, voltage-sensitive Na^+ channels, secondary messenger systems, and neuro protection. Despite triacetyloleandomycin, erythromycin, propoxyphene, isoniazid, and cimetidine minimize the metabolism of CZ, it facilitates the metabolism of phenytoin, primidone, valproic acid, phenobarbital, and warfarin. The most common adverse reactions include ataxia, nausea, vomiting, constipation, diarrhea, a lack of appetite, and sleepiness. Skin rashes, weakened bone marrow function, and confusion are the main negative consequences.

Keywords: Carbamazepine, Seizure disorders, Metabolism, Liver, Bioavailability, Ataxia

INTRODUCTION

Swiss chemist Walter Schindler in 1953 first discovered and synthesized Carbamazepine (CZ) **[1]**. Carbamazepine was initially used to treat trigeminal neuralgia **[2]**. Anticonvulsant property of CZ was obtained from animal experiments, and also from clinical studies in humans **[3]**. CZ is effective well for stabilizing the mood. It has been approved for the management of manic episodes and for contributing in the treatment of bipolar illness **[4]**. The other applications include treatment of behaviorally labile patients, and mental illness. That is why CZ is becoming popular to psychiatrists **[5]**.

The chemical formula for CZ is $C_{15}H_{12}N_2O$, and its molecular name is (5H-dibenz [b,f] azepine-5-carboxamid. It is a member of a class of compounds known as dibenzoazepines that have a tricyclic ring structure. A white, crystalline powder known as CZ is available. A small amount of it dissolves in water. Its structural similarities to tricyclic antidepressants can be compared. Blood-brain barrier (BBB)-crossing CZ has a lipophilic character **[6]**.
The initial dose of CZ used in treatment is very little. Later, the dose is gradually increased to an effective dose depending on each individual. It is recommended to gradually reduce the CZ dose after the completion of the prescribed period of treatment. CZ and its metabolites can be identified in breast milk and may penetrate the blood-brain barrier and the placenta **[7]**. The liver's CYP isoenzymes primarily metabolize carbamazepine and its metabolites that eventually get eliminated in the urine (which is frequently as glucuronide conjugates). The metabolic pathways of CZ are oxidation, hydroxylation, deamination, and esterification with glucuronic acid **[8]**. The liver enzyme cytochrome P450 3A4 is the main enzyme that breaks down carbamazepine to its active metabolite, carbamazepine-10,11-epoxide, which follows by being further broken down by the enzyme epoxide hydrolase **[9]**. Other metabolites which have been identified are Carbamazepine-10,11-epoxide are: 10,11 Dihydroxycarbamazepin 2,3-exposid Carbamazepine oxycarbamazepine 2 Carbamazepine-iminoquinone containing 2 hydroxyiminostibene Carbamazepine-O-quinone, 3-hydroxycarbamazepine 2,3, Dihydroxycarbamazepine. Some CZ parameters are depicted in **Table 1**.

Table 1: Data of Carbamazepine [10]

S. No.	Parameter	Data
1	Bioavailability	75-85% for extended-release tablets 90% for non-extended-release tablets
2	Volume of distribution	0.7-1.4 L/kg
3	Elimination half-life	35- 40 hours
4	Protein binding	70-80%
5	Excretion	Urine (72%), Feces (28%)
6	Clearance	25 ± 5 mL/min per single dose; 80 ± 30 mL/ min per multiple dose
7	Metabolism	Liver
8	Metabolites	carbamazepine-10,11-epoxide (Active)
9	Therapeutic index	narrow

Mechanism action of CZ

The sodium (Na+) channels of the excitatory nervous system are obstructed by CZ. As a result, the generation of action potentials decreases, resulting in decreased high frequency activity in neurons **[11]**. The electrical stimulation of the neurons is inhibited as a result of the interaction among voltage-dependent calcium (Ca2+) and potassium (K+) channels **[12]**. In accordance with Van Calker D *et al*. (1991), CZ interactions with adenosine binding sites in the brain resulting in an anticonvulsant effect **[13]**. GABA levels are decreased in individuals with bipolar disorder. The medication CZ enhances GABA transmission and dopamine turnover **[14]**.

By inhibiting sodium channels, CZ improves trigeminal neuralgia symptoms and seizures. According to the Young Mania Rating Scale, CZ reduces the symptoms underlying bipolar 1 illness.

Medical Uses

In accordance with studies by Ceron-Litvoc D *et al*. (2009), Owen RT *et al*. (2006), and Gierbolini J *et al*. (2016), CZ is a drug approved by the FDA for the management of epilepsy, trigeminal neuralgia, and acute manic and mixed episodes in bipolar I disorder **[15-17]**. Partial convulsions with multiple manifestations (psychomotor, temporal lobe), mixed types of seizures, and generalized tonic-clonic convulsions (grand mal) may all be specific symptoms of epilepsy. In addition, CZ is used to treat fibromyalgia **[18]**, neuropathic pain **[19]**, and refractory schizophrenia. The research of Latifi S *et al*. (2019), CZ is an effective treatment for those with moderate to severe alcohol withdrawal syndrome **[20]**.

There are also several forms of CZ available, such as sustained-release pills (100 mg, 200 mg), normal tablets (100 mg, 200 mg), solutions, and suspensions. Tablets for sustained release can't be crushed, broken or masticated. It can be administered along with food.

CZ is initially administered to pediatric patients at a dose of 5–10 mg/kg/day, and when required, the dose is increased every 5-7 days. Children usually respond to dosages of 20–30 mg/kg/day, divided into 2-3 doses/day. For children below the age of 16, a daily maximum dose of 1 g is recommended, regardless of the fact that treatment should be followed by monitoring levels in the blood and patient response. Therapy is often started with 200 mg given twice daily to elder children and adults, after which it is titrated to a daily maintenance dose of 800 to 1,200 mg (WHO, 2019) **[21]**. The dose formulation being used determines the dosing frequency range, which ranges from 2 - 4 times per day. The same total daily dose (in mg), separated into two doses, should be administered to patients moving from a steady-release to an extended-release medicine. Patients are advised and given directions and advised to properly shake the suspension just before administration. To prevent stomach upset or distress, carbamazepine may be taken with food. The research of Seetharam MN *et al*. (1991), administering CZ with enteric feedings can result in a delay in its absorption **[22]**.

Carbamazepine Warnings

Individuals who are hypersensitive to CZ or ingredients of the medication's constituents cannot take CZ medications. Patients having a history of liver disease, acute intermittent porphyria, critical blood disorder, severe heart disease (heart block), kidney disease, glaucoma, heart rhythm problems, an intolerance to fructose, bone marrow suppression, and taking antifungal drugs. It is harmful to administer CZ to pregnant women. The growing foetus might suffer harm as a result. Before administering CZ to patients of Asian descent, the doctor can examine the patient for any severe skin reactions.

Patients are warned not to suddenly discontinue taking CZ. Before completely discontinuing the medication, the doctor will need to gradually decrease the amount **[23]**. CZ could end up in the following health problems: Aplastic anaemia, severe skin reactions, or other blood-related disorders. Suicidal thoughts or changes in behaviour can result from DRESS, or drug response with eosinophilia and systemic side effects, which may damage the liver, heart, or kidney.

Direction for taking Carbamazepine

This drug may be administered either on its own or in combination with other medications for seizures **[24]**.

Chewable tablet: It is preferred to take this medication with food or milk when it is administered orally. Before ingesting the tablet, be sure that you completely chew it.

Extended-release capsule: swallow the entire extended-release capsule. Do not break, ingest or crush it.

Liquid used orally (orally): The medicine is best to be administered with food or milk. Make use of the appropriate measuring spoon, oral syringe, or medicine cup for measuring the oral medication that is liquid. Before every use, give the bottle a thorough shaking. Take this medication apart from other oral liquid medications.

Tablet (Oral route): It is recommended to take this medication by tablet (orally) with food or milk. Completely swallow the tablet. Do not eat it, break it, or crush it. Do not use a cracked or broken extended-release tablet.

Interactions

CZ involves in a number of drug interactions. Absorption, metabolism, and protein binding are all modified, changed, or manipulated as part of the reaction's mechanism. In the end, it largely impacts interactions which are clinically important. As a consequence, CZ affects the cytochrome P450 enzyme in the system, which in turn affects metabolism. Delavirdine, nefazodone, and other specific HIV/AIDS medications (including etravirine and efavirenz) should not be taken with CZ. This drug should not be taken with a medication called a MAO inhibitor (MAOI) within 14 days of each other's administration. CZ interacts with blood thinners and HIV protease inhibitor anti-HIV drugs, including Fos amprenavir, atazanavir, darunavir, indinavir, lopinavir, ritonavir, and saquinavir, as well as blood diluents like apixaban, dabigatran, edoxaban, and rivaroxaban. Medications that treat fungi, such as fluconazole, itraconazole, ketoconazole, and voriconazole, and also steroids, such as dexamethasone, prednisolone, and prednisone

The following tables list **(Table 2 and 3)** clinically significant interactions with carbamazepine **[25]**.

Table 2: Drugs that change Carbamazepine Concentrations

Drugs	Concentrations of Carbamazepine	Drugs	Concentrations of Carbamazepine
Clarithromycin, Danazol, Niacinamide, Diltiazem, Cimetidine, Erythromycin, Fluoxetine, Fluvoxamine, Isoniazid, Itraconazole,	**Increased**	**Phenytoin, Charcoal, Doxorubicin, Theophylline, Felbamate, Phenobarbital Primidone, Cisplatin, Rifampin, Tricyclic Antidepressant, etc.**	**Decreased**

Ketoconazole, Loratadine, Nicotinamide, Terfenadine, Valproic Acid, Verapamil, Propoxyphene, etc.			

Table 3: Drugs which are affected by Carbamazepine Drug

S. No.	Drug	Effect
1	Acetaminophen	Improves metabolism
2	Clonazepam	Reduces concentrations
3	Alprazolam	Reduces concentrations
4	Clozapine	Reduces concentrations
5	Cyclosporine	Reduces concentrations
6	Doxycycline	Reduces concentrations
7	Haloperidol	Reduces concentrations
8	Ethosuximide	Reduces concentrations
9	Felbamate	Reduces concentrations
10	Valproic Acid	Reduces concentrations
11	Pancuronium	Reduces efficacy
12	Oral Contraceptives	Reduces efficacy
13	Lithium	Increase in CNS toxicity

Drugs like abiraterone, acetazolamide, alcohol, allopurinol, aliskiren, antipsychotic drugs (examples- aripiprazole, chlorpromazine, clozapine, haloperidol, olanzapine, quetiapine, risperidone), antiarrhythmic drugs (examples: amiodarone, disopyramide, dronedarone, propafenone, quinidine), antineoplastic drugs antineoplastic drugs (examples- cabazitaxel, docetaxel; doxorubicin; etoposide, ifosfamide, irinotecan, vincristine), alpha-blockers (examples: alfuzosin, doxazosin, silodosin, tamsulosin), antiseizure drugs (examples- levetirace , phenobarbital, primidone, clobazam, topiramate, phenytoin, valproic acid, zonisamide) etc. (Thus, proper advice should be adopted. CZ may interact with medications like dabigatran, deferasirox, desmopressin, dapsone, dexmethylphenidate, digoxin, dronedarone, echinacea, cyclosporine, edoxaban, elagolix, eliglustat, enzalutamide, eplerenone, estrogens (examples conjugated estradiol, ethinyl estradiol), everolimus, exemestane, , fexofenadine, fingolimod, flibanserin, fesoterodine , maraviroc, mebendazole, mefloquine, modafinil, mesalamine, methadone, methylphenidate, gingko biloba, mifepristone, mirabegron, mirtazapine, etc. CZ also may interact with drugs like, tamoxifen, sulfasalazine, tacrolimus, stiripentol, tenofovir, tetracyclines (minocycline, doxycycline, tetracycline), theophyllines (e.g., aminophylline, theophylline, oxtriphylline,), thalidomide, thiazide diuretics (certain water pills; e.g., hydrochlorothiazide, indapamide), thyroid replacements (e.g., desiccated thyroid, levothyroxine), tofacitinib, tolvaptan, trazodone, tocilizumab, tyrosine kinase

inhibitors (e.g., dasatinib, imatinib, nilotinib, sunitinib), ulipristal, warfarin, zolpidem, zopiclone etc. CZ interacts with drugs like apixaban, aprepitant, "azole" antifungals (e.g., fluconazole, itraconazole, ketoconazole, voriconazole), benzodiazepines (e.g., alprazolam, clonazepam, midazolam, triazolam), calcium channel blockers (e.g., amlodipine, felodipine, diltiazem, verapamil), ciprofloxacin, clindamycin, cobicistat, conivaptan, cannabis, monoamine oxidase inhibitors (MAOIs; e.g., rasagiline, moclobemide, phenelzine, selegiline, tranylcypromine),narcotic pain relievers (e.g., codeine, fentanyl, morphine, oxycodone, tramadol), phosphodiesterase 5 inhibitors (e.g., sildenafil, tadalafil), selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, citalopram, fluvoxamine, sertraline), St. John's wort etc **[26]**.

Side effects

According to Gilman AG *et al*. (1985) a side effect is an unfavourable reaction to a medication when it is taken in the recommended dosages **[27]**. Side effects could be mild or severe, transient or long-lasting. Every individual who uses this medicine experiences the adverse effects described below. At least 1% (less often) of individuals using this medicine has had the negative effects listed below. Abdominal pain, acne, clumsiness, constipation, confusion, diarrhoea, dizziness, falls, fatigue, changes in hair or nails, headache, increased oversensitivity of skin to sunlight (skin rash, itching, redness, or serious sunburn), increased sweating/ perspiration, loss of appetite, memory loss, mouth ulcers, muscle or joint pain, nausea, red eyes, dryness of mouth or throat, sore tongue, and sexual complications (men) are some of the side effects **[28]**. According to Ballenger JC *et al*. (1980), CZ may cause major side effects including unusual thoughts or actions, feeling chilly, coughing, fever, sore throat, or mouth ulcers as well as confusion, memory-related issues, extreme exhaustion, muscle spasms or weakness, and unusual bleeding, bruising, or weakening, Itching or rashes, swelling in the face, arms, or hands, swelling or numbness in the mouth or throat, chest constriction, trouble in breathing, burning, peeling, red skin rash, blurred vision, visual changes, frequent urination, and chest pain/discomfort are all indications of hypersensitive allergic reaction, difficulty breathing, bluish skin, cold chills, a rapidly beating or pounding heartbeat, painful or expanded lymph nodes in the groyne, armpits, or neck, dark-coloured urine, vomiting, a lack of appetite, discomfort and pain in the stomach, yellow skin or eyes,

feeling lightheaded, or fainting, among other symptoms **[29, 30]**.

CONCLUSION

The drug carbamazepine is beneficial for treating various seizure types including epilepsy. It can be used to treat certain mental illnesses and neuropathic pain. Treatment for CZ needs to be closely monitored as there are several interactions between medications.

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