

Bipolar Disorders and Carbamazepine: Pharmacokinetics, Pharmacodynamics, Therapeutic Effects and Indications of Carbamazepine: Review of Articles

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Abstract

Carbamazepine is a mood stabilizer which is approved for use in bipolar disorder with manic and mixed episodes. It is also approved for use for the treatment of trigeminal neuralgia, temporal lobe epilepsy (complex partial seizures) and generalized tonic-clonic seizure. It is metabolized in the liver, primarily by CYP450 3A4 and is an inducer of CYP450 3A4 enzyme. The specific mechanism of action of carbamazepine in stabilizing mood is unknown. It exerts effects by decreasing dopamine turn over, enhancement of brain γ -aminobutyric acid (GABA) levels via multiple actions of synthesis and degradation, and modulation of other neurotransmitters, voltage sensitive Na^+ channels, extra hypothalamic neuropeptides, secondary messenger systems, and neuro protection. The most common side effects are nausea, vomiting, constipation, diarrhea, loss of appetite, sedation, dizziness and ataxia. Serious side effects may include skin rashes, decreased bone marrow function and confusion. It should not be used in those with a history of bone marrow problems. Routine blood level monitoring is necessary. There is an increased risk of fetal abnormalities if carbamazepine taken in pregnancy. Carbamazepine concentrations are known to be increased with concurrent use of antidepressants (such as fluoxetine, fluvoxamine, nefazodone), omeperazole, efavirnaz, ratirovir, valproate, cimetidine and erythromycin. Its level decrease when administered with Rifampin and Cisplatin.

Keywords: Carbamazepine; Pharmacokinetics; Pharmacodynamics; Side effects; Drug interactions

Introduction

Carbamazepine was first synthesized as a potential antidepressant. It is an effective mood stabilizer, is approved for the treatment of mania and the maintenance treatment of bipolar disorder. It is now recognized in most guidelines as a second-line mood stabilizer useful in the treatment and prevention of both phases of bipolar affective disorder. Carbamazepine (CBZ) is a medication used primarily in the treatment of epilepsy and neuropathic pain [1]. For seizures it is effective as phenytoin and valproate. It is not effective for absence seizures or myoclonic seizures where valproate is effective and the drug of choice. It may be used in augmentation for inadequately responding schizophrenia along with other medications and as a second line agent in bipolar disorder [2-4].

Carbamazepine (Tegretol) has structural similarity with tricyclic antidepressant imipramine (Tofranil). It is FDA approved medication for the treatment of acute mania in 2002. Carbamazepine is also FDA approved for use for the treatment of trigeminal neuralgia, temporal lobe epilepsy (complex partial seizures), generalized tonic-clonic seizure and bipolar disorder with manic and mixed episodes [4-6].

Common side effects include nausea, constipations, diarrhea, and loss of appetite, sedation and drowsiness. Serious side effects may include skin rashes, decreased bone marrow function and confusion. It should not be used in those with a history of bone marrow problems. Use during pregnancy may cause harm to the baby; however stopping it in pregnant women with seizures is not recommended. Its use during

breastfeeding is not recommended. Care should be taken in those with either kidney or liver problems [1,6].

Mechanism of Action of Carbamazepine (Pharmacodynamics)

GABA neurotransmission

GABA is an inhibitory neurotransmitter that plays an important role in regulating dopamine and glutamate neurotransmission. It was found that patients with bipolar disorder had lower GABA levels, which results in excitotoxicity and can cause apoptosis (cell loss). It is also of interest that chronic but not acute administration of Carbamazepine are associated with up regulation of GABA_B receptors in the hippocampus, yielding this action as a potential convergent mechanism for mood stabilization. Carbamazepine is a GABA receptor agonist, as it has also been shown to potentiate GABA receptors made up of $\alpha 1$, $\beta 2$, and $\gamma 2$ subunits. This mechanism may contribute to its efficacy in neuropathic pain and bipolar disorder [7,8].

Glutamate neurotransmission

Glutamate is the universal excitatory neurotransmitter. Carbamazepines are able to weakly block calcium influx through glutamate receptors of the NMDA subtype. Carbamazepine could exert anti glutamatergic effects both by decreased release of glutamate as well as by relative decreases in glutamate's postsynaptic efficacy by inhibiting calcium influx. Antidepressant and mood-stabilizing effects of carbamazepine is linked to its glutamate antagonism [8-10].

Dopaminergic transmission

Dopamines are major neurotransmitters involved in the patho-physiologic mechanism of bipolar disorders. Antimanic and mood-stabilizing properties of carbamazepine could be related decrease dopamine turnover. Carbamazepine is not a direct antagonist at dopamine receptors and exerts its actions on the dopamine system through some other series of mechanisms. Chronic administration of carbamazepine reduced D₂ receptor density and D₂-like receptor phosphorylation. Dopamine levels have been reported to be increased in the prefrontal cortex after chronic Carbamazepine administration. Carbamazepine does decrease levels of the dopamine metabolite homovanillic acid (HVA) in the CSF of affectively ill patients following probenecid administration, consistent with its ability to decrease dopamine turnover in animals [8-10].

Serotonergic transmission

Serotonin are another major neurotransmitters involved in the patho-physiologic mechanism of bipolar disorders. Carbamazepine is a serotonin releasing agent and possibly even a serotonin reuptake inhibitor [10-15].

Effects of carbamazepine on G-proteins and inositol transporter

Carbamazepine blocks cyclic adenosine monophosphate (cAMP) and G proteins. Carbamazepine may also enhance several inositol phosphatases. It modalities increase brain-derived neurotrophic factor (BDNF) Chronic administration of carbamazepine increased levels in rat brain of GRK3, which is involved in homologous desensitization of agonist-activated G-protein coupled receptors. GRK3 is reduced in the post-mortem study of bipolar disorders brain [8,10].

Noradnergic transmission (NE, norepinephrine)

Norepinephrine's are major neurotransmitters involved in the patho-physiologic mechanism of bipolar disorders. Studies demonstrated that carbamazepine decreases the release of norepinephrine [10].

Effects on voltage-gated sodium channels

Carbamazepine stabilizes the inactivated state of voltage-gated sodium channels, making fewer of these channels available to subsequently open. This leaves the affected cells less excitable until the drug dissociates. By doing this carbamazepine like vaproate decreases influx of sodium ion and increases efflux of potassium ion [8,10].

Pharmacokinetics of Carbamazepine

Metabolized in the liver, primarily by CYP450 3A4. It is renal excreted. The active metabolite is (carbamazepine-10,11 epoxide). Initial half-life 26–65 h (35–40 h for extended release formulation); half-life 12–17 h with repeated doses Half-life of active metabolite is approximately 34 h. It is not only a substrate for CYP450 3A4, but also an inducer of CYP450 3A4. Thus, carbamazepine induces its own metabolism, often requiring an upward dosage adjustment.

Carbamazepine is well absorbed after oral administration. Its plasma half-life is about 30 h when it is given as single dose, but it is a

strong inducer of hepatic enzymes and the plasma half-life shortens to about 15 h when it is given repeatedly [10].

Bioavailability is 80% and its peak plasma levels are reached 2-8 h after a single dose. Carbamazepine is 70-80% bound to plasma protein. The average half-life after a single dose is 26 h, with a range of 18-54 h. However, with long-term administration, the half-life decreases to approximately 12 h (range, 10-25 h). This change occurs with the induction of hepatic P450 enzymes, which increase the rate of metabolism of Carbamazepine itself (auto induction) [10,11]. The degree of Carbamazepine auto induction is somewhat dose dependent but is usually complete after 3-5 weeks of treatment [10,11,13].

Carbamazepine is metabolized in the liver and then excreted by the kidneys, as only 1 percent is eliminated by biliary excretion [10,11,13].

Pre-carbamazepine work up and monitoring

Before starting carbamazepine treatments other causes of mood disorder or manic symptoms, including medical disorders, medications and substances of abuse, should be excluded. Screening laboratory exams should include liver function tests, thyroid function tests, CBC and ECG in patients over 40 years old or with pre-existing cardiac disease. In females of childbearing age, pregnancy should be excluded due to carbamazepine use during the first trimester is associated with teratogenic effect (especially neural tube defect) (Table 1). Start folic acid supplement in women (pregnant) who are carbamazepine [10,16-23].

Predictors of good carbamazepine response

Factors predicting positive response to carbamazepine includes past history of good carbamazepine response or family member with good response, co morbid anxiety or panic attack, mixed mania and depression is followed by Mania [10,16-23].

Summary of predictors for good carbamazepine response

- 1) Past history of good carbamazepine response (personal or family).
- 2) History of alcoholism.
- 3) Comorbid post-traumatic stress disorders.
- 4) History of trigeminal neuralgia.
- 5) Irritable mania.
- 6) Comorbid substance issues.
- 7) Sequence: Depression-Mania-Euthymia.
- 8) Severe mania (severe mania with psychosis).
- 9) Mixed mania.
- 10) Secondary mania.
- 11) Co morbid anxiety and panic attack.
- 12) Co morbid migraine headache.

Initial Monitoring	1) Liver function tests (LFTs): Carbamazepine use may associate with severe liver damage especially after 6 month. In cases of aggravated liver dysfunction or acute liver disease discontinue carbamazepine. Frequent monitoring and considering discontinuing carbamazepine is advised in case of emergent of signs and symptoms of liver disease
	2) CBC
	3) Weight and height
	4) Carbamazepine levels
Six months after starting	1) CBC
	2) LFTs
	3) Weight and height if patient gains weight rapidly (to check for weight gain or obesity)
	4) Carbamazepine levels
Routine Monitoring	1) Carbamazepine levels
	2) Urine analysis and RFT(BUN)
Additional Monitoring	1) Carbamazepine level At any time check carbamazepine level if you consider if toxicity suspected (>12 mg/L) or possible noncompliance. or If adequate response not obtained. Trough levels >7 mg/L are associated with therapeutic response in bipolar disorder.
	2) CBC If patient develop fever, sore throat, etc. while on carbamazepine treatment

Table 1: Summary of pre carbamazepine work up and monitoring.

Side Effects of Carbamazepine

Common side effects of carbamazepine

The most common side effects are nausea, vomiting, constipation, diarrhea, loss of appetite, sedation, dizziness, ataxia, confusion. These can be prevented or significantly reduced by increasing the daily dosage slowly [10,19,22-26].

Hematological side effects

- Carbamazepine may cause life-threatening thrombocytopenia, agranulocytosis, and aplastic anemia in 0.005% of patients. Carbamazepine should be discontinued if the WBC declines to less than 3000 mm, absolute neutrophil count <1500 mm or platelet count decreases to <100,000 cells per mm [10,19].
- In the early phase of treatment transient and minor decreases in blood cell indices may occur and do not warrant discontinuation of carbamazepine [10,19,22].

Liver (hepatic side effects)

Carbamazepine has been associated with rare reports of severe hepatitis and cholestatic jaundice has been associated with enzyme elevations. If patient develop hepatitis the medication should be discontinued immediately [10].

Skin (dermatologic side effects)

Rash and urticaria are relatively common. Potentially dangerous, but very rare, dermatological side effects include exfoliative dermatitis and toxic epidermal necrolysis (Stevens-Johnson syndrome), requiring immediate discontinuation often drug [10,19,22,27-30].

Weight gain and carbamazepine

Long-term treatment with carbamazepine is associated with small degrees of weight gain, which are significantly less than those observed on valproate [10].

Cardiac side effects

Uncommon side effects include AV conduction defects, arrhythmias, and congestive heart failure [10,22].

Metabolic/Endocrine side effects

SIADH with hyponatremia has been reported [10].

Genitourinary side effects

Urinary frequency, urinary retention, azotemia, renal failure and impotence are uncommon [10,19].

Pregnancy and carbamazepine

Use of carbamazepine during pregnancy especially associated with teratogenic effect including neural tube defects, such as spina bifida. Preconceptional education and folate- vitamin b complex supplementation for all for pregnant women is necessary. The teratogenic side effect less in carbamazepine as compared to valproate but higher than lithium [10,24].

Overdose and toxicity of carbamazepine

In overdose, carbamazepine produces seizures, confusion, stupor, motor restlessness, drowsiness, ataxia, dilated pupils, muscle twitching, tremor, hypotension or hypertension, athetoid movements, nystagmus, abnormal reflexes, oliguria, nausea and vomiting. Cardiac arrhythmias do not generally occur unless very large doses are ingested and few fatalities have been reported even after ingestion of as high as 10-20 g of carbamazepine [10,19,22].

Drug Interactions

Carbamazepine is a potent inducer of cytochrome P450 oxidase enzymes, particularly of the 3A4 category so that it reduces in the levels of a variety of other compounds concurrently used with it [31]. Carbamazepine concentrations are known to be increased with concurrent use of antidepressants (such as fluoxetine, fluvoxamine, nefazodone), omeperazole, efavirnaz, ratirovir, valproatecarthromycin, cemitidine and erythrmycin [32]. Its level decrease when administrated with rifampicin. Here are common drug interactions of carbamazepine [10,31,32].

Anticonvulsant interactions with carbamazepine

1. Decrease the levels of phenytoin and carbamazepine when given at the sometime.
2. Phenobarbital will lower carbamazepine levels because of microsomal enzyme induction.
3. Decreased ethosuximide levels because of cytochromeP450 enzyme induction.
4. Felbamate can increase the active metabolite of carbamazepine resulting intoxicities but decrease carbamazepine levels.
5. Lamotrigine and valproate can increase levels of the active metabolite. Patients may have signs of toxicity with normal carbamazepine levels. Carbamazepine will cause decreased valproate levels.

Drug interactions which increase serum levels of carbamazepine

Medications such as erythromycin, fluoxetine, cimetidine, isoniazid, ketoconazole, loratadine, verapamil, diltiazem and danazol inhibit the metabolism of carbamazepine with resultant increase in serum levels and neurotoxicity.

Drug interactions which in decrease serum levels of carbamazepine: Rifampin and Cisplatin cause cytochrome P450 enzyme induction and decreased carbamazepine levels.

Drug interactions of carbamazepine which increase serum levels of other drugs: Carbamazepine will induce hepatic microsomal enzymes and enhance the metabolism (decrease serum levels and decrease the effectiveness) of drugs such as acetaminophen, clozapine haloperidol, benzodiazepines (especially alprazolam, triazolam), oral

contraceptives, corticosteroids, cyclosporine, doxycycline, mebendazole, methadone, theophylline, thyroid supplements, valproate and warfarin.

Other Interactions

1) Diuretics may cause hypo natremia can occur with carbamazepine alone.

2) MAOI need to be given after minimum 14-day washout due to the molecular similarity between tricyclic antidepressants and carbamazepine.

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