**Introduction:**

Carbamazepine(CBZ) is an iminostilbene derivative related to the tricyclic antidepressants. CBZ is the most commonly used and effective clinical anti-epileptic drug, the safety range of anti-epileptic drugs (AEDs) is narrow, the anti-epileptic effect and toxicity is closely related to plasma concentration. However, there are large individual differences between the dosage and plasma concentration. Therefore, it is essential for monitoring these drugs applications, anti-epileptic drugs are often monitored drugs in Therapeutic drug monitoring (TDM).

**Indications:**

CBZ, an antiepileptic, is used in the treatment of patients who experience partial seizures with complex symptoms, generalized tonic-clonic seizures (grand mal) seizures, mixed seizure patterns, and other partial or generalized seizures. It is also used for control of pain experienced in trigeminal neuralgia, and treatment of bipolar disorder. Successful unlabeled uses include treatment of resistent schizophrenia, ethanol withdrawal, restless leg syndrome, and post-traumatic stress disorders.**1**

**Pharmacodynamics/Kinetics:**

Absorption: Slow

Distribution: Vd: Neonates: 1.5 L/kg; Children: 1.9 L/kg; Adults: 0.59-2 L/kg

Protein binding: Carbamazepine: 75% to 90%, may be decreased in newborns; Epoxide metabolite: 50%

Metabolism: Hepatic via CYP3A4 to active epoxide metabolite; induces hepatic enzymes to increase metabolism

Bioavailability: 85%

Half-life elimination: Note: Half-life is variable because of autoinduction which is usually complete 3-5 weeks after initiation of a fixed carbamazepine regimen.

Carbamazepine: Initial: 25-65 hours; Extended release: 35-40 hours;

Multiple doses: Children: 8-14 hours; Adults: 12-17 hours

Epoxide metabolite: Initial: 25-43 hours

Time to peak, serum: Unpredictable:

Immediate release: Suspension: 1.5 hour; tablet: 4-5 hours

Extended release: 12-26 hours (single dose), 4-8 hours (multiple doses); 3-12 hours

Excretion: Urine 72% (1% to 3% as unchanged drug); feces (28%)**1**

**Dose: Adults:** Oral: 0.8-1.2 g/day maintenance for seizure control for anxiety

0.2-1.2 g/day for neuralgia

**Pediatrics**: Oral: 10-20 mg/kg/day for seizures1

**Therapeutic and Toxic Levels:**

The monitoring of carbamazepine levels in the blood is critical. Common toxic reaction seen with this drug includes drowsiness, dizziness, nausea with vomiting, light headedness, skin rash, ataxia (uncoordinated muscle movement in the absence of other symptoms and spasticity) alopecia, and photosensitivity. Extreme toxicity can cause hepatitis, rare hematologic reactions, aplastic anemia, thrombocytopenia, and agranulocytosis and death due to cardiorespiratory arrest.

As with all AEDs, there are no prospective controlled trials that define the reference range for carbamazepine. Retrospective and observational studies suggest that optimal seizure control in patients on monotherapy is most likely to occur between 4 and 12 mcg/L (17–51 *μ*mol/L). In patients taking other AEDs, lower serum carbamazepine concentrations may be required, particularly with respect to the need to minimize toxicity.**2**

Therapeutic Levels:

4-12 μg/mL; with other anticonvulsants: 4-8 μg/mL. Patients requiring higher levels (ie, 8-12 μg/mL) should be watched closely. Patients on multiple drugs may experience toxicity at levels within the therapeutic range.

Possible Toxic level: >12 μg/mL

Critical level: > 20 μg/mL**3**

**Assay Parameters:**

Sample:

1 mL serum or plasma (0.5 mL minimum)

Container:

Red top (no additive) tube, lavender top (EDTA) tube, or green top (heparin) tube. Do **not** use a serum separator tube. Containers are laboratory and methodology specific.

Collection:

Routine venipuncture. Separate serum or plasma from cells as soon as possible. A consistent sampling time, ideally a trough level 30 minutes prior to next dose should be used to monitor patients on chronic therapy.

Storage Instructions:

Maintain sample at room temperature or refrigerate. 3

**Analytical Methods:**

Commercial reagent-based techniques represent the primary methodology for the analysis of carbamazepine such as serum Enzyme immunoassay (EIA); enzyme multiplied immunoassay technique (EMIT); fluorescence polarization immunoassay (FPIA); gas-liquid chromatography (GLC); high performance liquid chromatography (HPLC); turbidimetric inhibition immunoassay; liquid chromatography/tandem mass spectrometry (LC/MS-MS).

**GLC:**

Although numerous GLC procedures have been developed, which measures either intact drug or variety of derivative or degradation product. None is satisfactory as CBZ undergoes partial degradation during GLC. The best approach is to analyze the intact drug and to use C13 CBZ as an internal standard, but this approach requires spectrometric detection.

**HPLC:**

This is done using 50% Methanol-water mobile phase, symmetry C18 and detection at 212nm. This method allows quantitative analysis of CBZ and epoxide metabolite in serum and plasma.

**EMIT and FPIA:**

Both are widely used for CBZ analysis. One disadvantage about both of these methods is it cannot measure epoxide metabolite separately.**4**

However, GLC and HPLC techniques have the advantage of simultaneously measuring other AEDs and the active metabolite carbamazepine-10,11-epoxide and also availability of test and cost, rapid results would give the edge over other analytical methods in Indian setup.**5**

**Conclusion:**

The unpredictable relationship between dose and CBZ concentration, its narrow therapeutic index, and the presence of numerous clinically significant drug interactions support the need to individualize and maintain therapy using TDM. The accepted therapeutic range for CBZ is 4–12 μg/mL when the drug is used for the treatment of seizures and neuralgia. Because CBZ has a relatively short half-life, sampling time in relation to dose ingestion is important for the interpretation of the drug concentration. Ideally samples for carbamazepine measurements should be drawn 30 minutes before the morning dose. HPLC is the method of choice for analysis of CBZ sample in Indian setup.

**References:**

1. Lacy CF, Armstrong LL, Goldman MP, et al editors. Drug Information Handbook, 18th ed, Hudson OH: Lexi-Comp [serial online] 2009 [cited 2010 Aug 15] Available from: URL: <http://online.lexi.com/crlsql/servlet/crlonline>
2. Patsalos NP, Berry JD, et al editors. Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring. Epilepsia [serial online] 2008 Jan 28 [cited 2010 Aug 15] Available from: URL: <http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2008.01561.x/full>
3. Carbamazepine level. Lab tests and Diagnostic Procedures. [serial online] 2008 July 15 [cited 2010 Aug 15] Available from: URL: <http://online.lexi.com/crlsql/servlet/crlonline?a=tox>
4. Zheng H, Zheng J, et al editors. Determination of Carbamazepine in Human Serum by HPLC. MPR [serial online] 2008 Nov 01 [cited 2010 Aug 15] Available from: URL: <http://tasusa.org/Documents/mpr_2009_02_2.pdf>
5. Nadkarni VV, Dalvi SS, Khare SD. TDM using rapid HPLC. NA [serial online] 2004 [cited 2010 Aug 15] Available from: URL:

<http://www.neurology-asia.org/articles/20043_120.pdf>