Therapeutic Drug Monitoring of Carbamazepine

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Abstract

Carbamazepine is one of the classical antiepileptic drugs, chemically related to the Tricyclic Antidepressants. There are different methods to detect Carbamazepine in plasma i.e. Therapeutic Drug monitoring (TDM). Various studies claim the usefulness of TDM of Carbamazepine but clear-cut guidelines for TDM are still lacking. This article is authors’ endeavour to summarize facts in different publications on TDM of Carbamazepine. Electronic databases MEDLINE/PubMed, Google Scholar, IMSEAR (Index Medicus for South-East Asia Region) and Scopemed were extensively searched with Mesh (Medical Subject Headings) terms “Carbamazepine” AND “drug monitoring” from earliest possible date (1966) to December, 2016. Articles in any language especially those published in recent years were given preference. For non-English articles, Google translation was used and only abstracts were included. Review is mostly centred on toxic effects, poorly adjusted therapies and poor seizure control. Individualization of drug dose with the help of plasma level detection is a must in case of Carbamazepine therapy. TDM helps better outcome by minimizing the risk of under or overdosing due to drug/food interaction or genetic polymorphism of enzymes and transporters involved in the metabolism of Carbamazepine.

Keywords: Anticonvulsants; Drug monitoring; Epilepsy; High pressure liquid chromatography

Introduction

Carbamazepine is an antiepileptic drug, chemically related to the Tricyclic Antidepressants. It is an iminostilbene-derivative with a carbamyl moiety at the 5th position of the molecule. This moiety is essential for its anti-seizure activity [1].

High-performance liquid chromatography (HPLC) with diode array detector, gas chromatography mass spectrometry [2], are few methods to detect Carbamazepine in plasma. HPLC is a simple, sensitive, accurate and cost-effective method [3,4] and it gives high recovery with exact precision [5].

There are also other methods to detect Carbamazepine in plasma. Some of them are:

- Micellar electrokinetic capillary chromatography [6]
- Microextraction by packed sorbent method [7]
- Fluorescence polarization assays [8]

Many reports claim the usefulness of TDM of Carbamazepine but clear-cut guidelines for TDM are still lacking. This article is authors’ endeavor to summarize facts in different publications on TDM of Carbamazepine.

Methods

Electronic databases MEDLINE/PubMed, Google Scholar, IMSEAR (Index Medicus for South-East Asia Region) and Scopemed were extensively searched with Mesh (Medical Subject Headings) terms “Carbamazepine” AND “drug monitoring” from earliest possible date (1966) to December, 2016. Articles in any language especially those published in recent years were given preference. For articles published in non-English, only abstracts were reviewed.

Discussion

Metabolism and interaction

Carbamazepine plasma level is affected by several factors [9]. It is altered by age and pregnancy status including several other factors [10].

Carbamazepine is primarily metabolized by Cytochrome P4503A4 in the liver. Its major metabolite is Carbamazepine-10,11-epoxide, which also retains anti-epileptic and toxic property. Routine TDM of Carbamazepine-10,11-epoxide is not considered necessary. However, it might be beneficial in patients taking Carbamazepine with other anti-epileptic drugs susceptible to pharmacokinetic interaction, in suspected toxicity and renal insufficiency [11-14].

Again, Carbamazepine is a potent inducer of its metabolizer, Cytochrome P4503A4, i.e., it is an auto-inducer. Therefore, there is significant decrease in plasma drug levels during the first few weeks due to auto-induction [15,16]. Hence, timing of TDM is very important in case of Carbamazepine because there is significant
decrease in plasma drug levels during the first few weeks due to auto-induction [15,16].

After some time, with a single extended-release dose of Carbamazepine, the average half-life range from 35–40 h [17].

The free fraction Carbamazepine ranges shows considerable inter-individual variability, especially in the presence of associated disease or drug interactions and multiplicity of variables [18]. Abruptly low plasma levels are more likely due to surreptitious noncompliance or drug interactions with enzyme inducers [19].

Being a potent Cytochrome P4503A4 inducer, it also decreases the plasma concentration of many psychotropic, immunosuppressant, antineoplastic, antimicrobial, and cardiovascular drugs, as well as oral contraceptive steroids which are metabolized by the same cytochrome isomorph. On the other hand, certain macrolide antibiotics, azole antifungals and isoniazid inhibit this isomorph, thereby, enhancing its plasma half-life and serum concentration [20,21].

As anticipated, Fluvoxamine, inhibitor of CYP4503A4, significantly increases plasma levels of Carbamazepine [22]. However, fluoxetine, primarily metabolized by CYP2D6, does not interact with Carbamazepine [23]. Similarly, pomegranate juice, which inhibits cytochrome P4503A4, significantly increases the AUC of orally administered Carbamazepine in rats [24].

**Interaction with anti-epileptics**

 Plasma concentration of Carbamazepine is significantly lower in polytherapy than in monotherapy [25]. Vigabatrin decreases plasma concentration of Carbamazepine by increasing its clearance not catabolism [26]. Topiramate interferes Carbamazepine plasma level [27]. Zonisamide may increase its serum levels of Carbamazepine in some patients [28] and not alter the level of Carbamazepine or Carbamazepine-10,11-epoxide in other [29]. Topiramide Clearance was 70% higher in patients co-treated with Carbamazepine and was found to increase with patient age [30].

 However, all interaction is not pharmacokinetic. Carbamazepine plus Stiripentol (a newer anticonvulsant) interact pharmacodynamically and the benefits may outweigh the usual disadvantages of polytherapy [31].

**Interaction with CNS drugs**

 Haloperidol increases the serum Carbamazepine level [32] but Carbamazepine decreases the concentration of Haloperidol by 37% [33].

 When Carbamazepine was co-administered with quetiapine, the clearance of quetiapine was significantly higher (p=0.01) [34-36].

 Carbamazepine co-medication with Pregabalin, can moderately decrease Pregabalin serum concentrations by about 20% to 30% [37].

 Patients co-medicated with Carbamazepine had a 71% lower median concentration/dose (C/D) ratio for Olanzapine than patients on Olanzapine monotherapy [38].

 Comedication with the CYP3A4 inducer Carbamazepine lowered the dose-adjusted aripiprazole concentration by 88% [39].

 Carbamazepine decreases Methadone blood concentrations, probably by induction of CYP3A4 activity, which can result in severe withdrawal symptoms [40].

The mean C/D of both Amitriptyline and Nortriptyline in patients on Carbamazepine was about 50% lower than in those treated with the antidepressant only [41].

**Interaction with cardiovascular drug**

 Amlodipine decreases the metabolism of Carbamazepine [42]. Similarly, a potentially harmful drug-drug interaction may occur if Carbamazepine and Diltiazem or Verapamil are administered concurrently [43,44]. Some of these interactions may have potential implication for pharmacological basis of rational polytherapy. Similarly, Flunarizine Nicardipine distinctly increases the level of Carbamazepine in plasma [45]. On the other hand, Caffeine diminishes the efficacy of Carbamazepine [45].

**Uses and advantages of carbamazepine**

 Carbamazepine has been successfully employed in a variety of neurological and psychiatric disorders [9]. Carbamazepine monotherapy is one of the most frequently prescribed antiepileptic drug therapy [46]. It is the drug of choice (DOC) or first line drug for partial seizures and most grand mal seizure [47–49]. It even shows usefulness in refractory partial epilepsy [50]. It has also been tried in alcohol withdrawal seizures [51,52]. It is specially preferred for not being problematic in terms of weight gain and adverse metabolic concerns [53]. Moreover, it is a preferred antiepileptic for those with intellectual disability, balance disturbances and cognitive dysfunction [54]. Together with ethosuximide, it is used to treat epileptic mixed-seizure patterns [55]. It also has mood-stabilizing and anti-manic effect. The antimanic response is significantly correlated with the plasma levels of both Carbamazepine and its epoxide metabolite [56]. One preliminary study shows that Carbamazepine may be an effective anticonvulsant for neonatal seizures [57]. Carbamazepine is one of the time-tested drugs of Trigeminal Neuralgia [58,59].

**Importance of TDM**

 Carbamazepine plasma level is directly correlated with dose, therapeutic effect and side effects [50,60,61]. A study revealed that with Carbamazepine, there is non-linear relationship between the dose and the plasma concentration even within the range of therapeutic doses [62]. Normally for any drug, TDM (measurement of serum drug concentrations) is meaningful in three conditions

1. When drug interactions are expected
2. When toxicity suspected
3. When drugs have nonlinear pharmacokinetics [63].

Many times pharmacodynamic resistance rather than pharmacokinetic, is responsible for lack of efficacy of Carbamazepine in non-responding epileptic patients [64]. This is revealed by serum plasma level of the drug. At times plasma level of Carbamazepine helps us to rule out toxicity from idiosyncratic reaction like Carbamazepine encephalopathy [65].

Efficiency of learning new information and memory-scanning rate displays a concentration-dependent relationship with Carbamazepine level, with poor performance significantly associated with its higher plasma concentrations therefore plasma level monitoring may help prevent unnecessary concentration dependent cognitive decline by keeping plasma level at the lower therapeutic range [66,67].

Carbamazepine elimination is related to genetic polymorphisms of drug metabolizing enzymes and transporters. It adds another reason
for plasma monitoring and individualization as the drug level may become unpredictable in them [68]. Literature says once seizures are controlled, plasma levels of the drug should be measured to establish optimum levels for individual patients being treated. Most studies emphasize the importance of early diagnosis of the condition and early treatment aided with frequent plasma level monitoring [69,70].

**Recommended plasma level of carbamazepine**

Therapeutic range of Carbamazepine in plasma is 5 to 10 μg/ml [10]; more specifically, 7.4 μg/ml for adults and 8.2 μg/ml for children [71]. In bipolar patients, mean values of Brief Psychiatric Rating Scale (BPRS) scores were better when plasma Carbamazepine concentrations was 7 μg/ml. [72]. Literature shows during Plasma drug level monitoring, trough levels, should provisionally be aimed at between 6 to 8 μg/mL and in order to avoid toxic effects, peak levels should not exceed 12 or even 10 μg/mL [73].

In a study done in Patan Hospital, Nepal, Carbamazepine level was tested in 241 patients and it was found that 79.3% of them had at therapeutic drug level, 15.8% had sub-therapeutic drug level and 4.9% had toxic level. Study concluded that monitoring of Carbamazepine is helpful when their toxicity and efficacy are doubtful [74].

In an Indian study, 15 out of 25 on Carbamazepine had plasma levels within the therapeutic range [75].

**Features of toxicity**

There is a correlation between plasma free Carbamazepine levels and manifestations of toxicity [18]. Acute intoxication causes neurologic and cardiovascular dysfunction. Neurologic manifestations may range from mild ataxia to profound coma with respiratory failure. Cardiovascular effects appear primarily as conduction system disturbances [76]. Coma, somnolence, cerebellar syndrome and epileptic seizures are often seen in its overdose survivors [9]. Blood Levels of alkaline phosphatase were significantly more in patients compared to controls [77]. Carbamazepine plasma level determinations can at times provide explanation for toxicity [78]. Few anti-epileptics like Carbamazepine meet the theoretical criteria justifying free drug level monitoring [79].

**Carbamazepine and pregnancy**

Carbamazepine is FDA pregnancy category D drug. However, it is considered that the teratogenicity of Carbamazepine is significantly lower than other classical antiepileptics [80]. Therefore, during pregnancy, it is one of the most preferred anticonvulsant. However, altered body physiology during pregnancy remarkably twists its metabolism [10,81]. Total Carbamazepine concentration is slightly lower during the third trimester as compared with baseline, whereas free concentration is unchanged [60].

**Alternative to plasma for carbamazepine level detection**

Various studies suggest a possibility of using saliva as an alternative biological material for determination of Carbamazepine concentrations in therapeutic application as well as in acute poisoning and a possible extrapolation of the results obtained in saliva to serum concentrations of Carbamazepine [82-85]. Again although it had been suggested by several authors that the measurement of Carbamazepine in hair might provide a better index of individual dosage history than the plasma level assays, the deviations observed in the study led by Kintz et al. [86] concluded that hair samples are not suitable for evaluating the quantity of drug consumed. The Carbamazepine concentration in breast milk ranged from 0.34-0.86 mg/L [87].

**Conclusion**

Individualization of drug dose with the help of Plasma level detection is a must in case of Carbamazepine therapy. It helps to minimize the risk of under or overdosing due to drug/food interaction or genetic polymorphism of enzymes and transporters involved in the metabolism of Carbamazepine.

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**References**


