International Journal of Neurorehabilitation

Panday et al., Int J Neurorehabilitation Eng 2017, 4:1
DOI: 10.4172/2376-0281.1000245

Research Article Open Access

Therapeutic Drug Monitoring of Carbamazepine

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Received date: February 02, 2017; **Accepted date:** February 11, 2017; **Published date:** February 18, 2017

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 (1965) 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]. Aberrantly 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 isoform. On the otherhand, certain macrolide antibiotics, azole antifungals and isoniazid inhibit this isoform, 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 pharmaco dynamically 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-maniac 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.

Acknowledgement

Authors will like to acknowledge Professor Dr. Bishnu Hari Paudel for going through the manuscript and giving his expert opinion on the matter.

References

1. Katzung B, Masters S, Trevor A (2011) Basic and clinical pharmacology. McGraw-Hill, USA.
2. Hallbach J, Vogel H, Guder WG (1997) Determination of lamotrigine, carbamazepine and carbamazepine epoxide in human serum by gas chromatography mass spectrometry. Eur J Clin Chem Clin Biochem 35: 755-759.
3. Domingues DS, Pinto MAL, de Souza ID, Hallak JEC, Crippa JA de S, et al. (2016) Determination of drugs in plasma samples by high-performance liquid chromatography-tandem mass spectrometry for therapeutic drug monitoring of schizophrenic patients. J Anal Toxicol 40: 28-36.
4. Deeb S, McKeown DA, Torrance HJ, Wylie FM, Logan BK, et al. (2014) Simultaneous analysis of 22 antiepileptic drugs in postmortem blood, serum and plasma using LC-MS-MS with a focus on their role in forensic cases. J Anal Toxicol 38: 485-494.
5. Zhu XP, Zhao YD, Cheng Z, Zhao NM, Li H (2015) The establish of the HPLC method to examine the plasma concentration of lamotrigine and oxcarbazepine. Pak J Pharm Sci 28: 1121-1125.
6. Makino K, Goto Y, Sueyasu M, Futagami K, Kataoka Y, et al. (1997) Micellar electrokinetic capillary chromatography for therapeutic drug monitoring of zonisamide. J Chromatogr B Biomed Sci Appl 695: 417-425.
7. Ferreira A, Rodrigues M, Oliveira P, Francisco J, Fortuna A, et al. (2014) Liquid chromatographic assay based on microextraction by packed sorbent for therapeutic drug monitoring of carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin and the active metabolites carbamazepine-10,11-epoxide and licarbazepine. J Chromatogr B Anal Technol Biomed life Sci 971: 20-29.
8. Steijns LSW, Bouw J, van der Weide J (2002) Evaluation of fluorescence polarization assays for measuring valproic acid, phenytoin, carbamazepine and phenobarbital in serum. Ther Drug Monit 24: 432-435.
9. Schmidt S, Schmitz-Buhl M (1995) Signs and symptoms of carbamazepine overdose. J Neurol 242: 169-173.
10. Bertilsson L (1978) Clinical pharmacokinetics of carbamazepine. Clin Pharmacokinet 3: 128-143.
11. Mittag N, Meister S, Berg AM, Walther UI (2016) A case report of a carbamazepine overdose with focus on pharmacokinetic aspects. Pharmacopsychiatry 49: 76-78.
12. Tutor-Crespo MJ, Hermida J, Tutor JC (2008) Relative proportions of serum carbamazepine and its pharmacologically active 10,11-epoxy derivative: Effect of polytherapy and renal insufficiency. Ups J Med Sci 113: 171-180.

13. Burianova I, Borecka K (2015) Routine therapeutic monitoring of the active metabolite of carbamazepine: Is it really necessary? Clin Biochem 48: 866-869.
14. Hermida J, Boveda MD, Vadillo FJ, Tutor JC (2002) Comparison between the Cobas Integra immunoassay and high-performance liquid chromatography for therapeutic monitoring of carbamazepine. Clin Biochem 35: 251-254.
15. Pynnönen S, Sillanpää M, Frey H, Iisalo E (1977) Carbamazepine and its 10,11-epoxide in children and adults with epilepsy. Eur J Clin Pharmacol 11: 129-133.
16. Kanarkowski R, Wankiewicz G, Lehmann W, Rybakowski J (1988) Pharmacokinetics of carbamazepine in psychiatric patients. Pol J Pharmacol Pharm 40: 55-61.
17. Brunton L, Chabner B, Knollman B (2010) Goodman and Gilman's: The pharmacological basis of therapeutics. Mcgraw-hill, USA.
18. Riva R, Albani F, Ambrosetto G, Contin M, Cortelli P, et al. (1984) Diurnal fluctuations in free and total steady-state plasma levels of carbamazepine and correlation with intermittent side effects. Epilepsia 25: 476-481.
19. Van Putten T, Marder SR, Wirshing WC, Aravagiri M, Chabert N (1991) Neuroleptic plasma levels. Schizophr Bull 17: 197-216.
20. Patsalos PN, Perucca E (2003) Clinically important drug interactions in epilepsy: Interactions between antiepileptic drugs and other drugs. Lancet Neurol 2: 473-481.
21. Spina E, Arena D, Scordo MG, Fazio A, Pisani F, et al. (1997) Elevation of plasma carbamazepine concentrations by ketoconazole in patients with epilepsy. Ther Drug Monit 19: 535-538.
22. Cottencin O, Regnaut N, Thevenon-Gignac C, Thomas P, Goudemand M, et al. (1995) Carbamazepine-fluvoxamine interaction. Consequences for the carbamazepine plasma level. Encephale 21: 141-145.
23. Sproule BA, Naranjo CA, Brenmer KE, Hassan PC (1997) Selective serotonin reuptake inhibitors and CNS drug interactions. A critical review of the evidence. Clin Pharmacokinet 33: 454-471.
24. Misaka S, Nakamura R, Uchida S, Takeuchi K, Takahashi N, et al. (2011) Effect of 2 weeks' consumption of pomegranate juice on the pharmacokinetics of a single dose of midazolam: an open-label, randomized, single-center, 2-period crossover study in healthy Japanese volunteers. Clin Ther 33: 246-252.
25. Koristkova B, Bergman U, Grundmann M, Brozmanova H, Sjoqvist F (2006) Therapeutic monitoring of antiepileptic drugs: A comparison between a Czech and a Swedish University Hospital. Ther Drug Monit 28: 594-598.
26. Sánchez-Alcaraz A, Quintana MB, López E, Rodríguez I, Llopis P (2002) Effect of vigabatrin on the pharmacokinetics of carbamazepine. J Clin Pharm Ther 27: 427-430.
27. Grunze HC, Normann C, Langosch J, Schaefer M, Amann B, et al. (2001) Antimanic efficacy of topiramate in 11 patients in an open trial with an on-off-on design. J Clin Psychiatry 62: 464-468.
28. Mimaki T (1998) Clinical pharmacology and therapeutic drug monitoring of zonisamide. Ther Drug Monit 20: 593-597.
29. Miura H (2000) Developmental and therapeutic pharmacology of antiepileptic drugs. Epilepsia 9: 2-6.
30. Vovk T, Jakovljevic MB, Kos MK, Jankovic SM, Mrhar A, et al. (2010) A nonlinear mixed effects modelling analysis of topiramate pharmacokinetics in patients with epilepsy. Biol Pharm Bull 33: 1176-1182.
31. Lockard JS, Levy RH (1988) Carbamazepine plus stiripentol: is polytherapy by design possible? Epilepsia 29: 476-481.
32. Iwahashi K, Miyatake R, Suwaki H, Hosokawa K, Ichikawa Y (1995) The drug-drug interaction effects of haloperidol on plasma carbamazepine levels. Clin Neuropharmacol 18: 233-236.
33. Hirokane G, Someya T, Takahashi S, Morita S, Shimoda K (1999) Interindividual variation of plasma haloperidol concentrations and the impact of concomitant medications: The analysis of therapeutic drug monitoring data. Ther Drug Monit 21: 82-86.
34. Wittmann M, Hausner H, Kostlbacher A, Hajak G, Haen E (2010) Individual clearance and therapeutic drug monitoring of quetiapine in clinical practice. Neuro Endocrinol Lett 31: 203-207.
35. McGrane IR, Loveland JG, Zaluski HJ, Foster KD (2015) Serum quetiapine concentration changes with concomitant oxcarbazepine therapy in a boy with autism spectrum disorder. J Child Adolesc Psychopharmacol 25: 729-730.
36. Castberg I, Skogvoll E, Spigset O (2007) Quetiapine and drug interactions: Evidence from a routine therapeutic drug monitoring service. J Clin Psychiatry 68: 1540-1545.
37. May TW, Rambeck B, Neb R, Jürgens U (2007) Serum concentrations of pregabalin in patients with epilepsy: The influence of dose, age and comedication. Ther Drug Monit 29: 789-794.
38. Skogh E, Reis M, Dahl ML, Lundmark J, Bengtsson F (2002) Therapeutic drug monitoring data on olanzapine and its N-demethyl metabolite in the naturalistic clinical setting. Ther Drug Monit 24: 518-526.
39. Castberg I, Spigset O (2007) Effects of comedication on the serum levels of aripiprazole: Evidence from a routine therapeutic drug monitoring service. Pharmacopsychiatry 40: 107-110.
40. Eap CB, Buclin T, Baumann P (2002) Interindividual variability of the clinical pharmacokinetics of methadone: Implications for the treatment of opioid dependence. Clin Pharmacokinet 41: 1153-1193.
41. Jerling M, Bertilsson L, Sjöqvist F (1994) The use of therapeutic drug monitoring data to document kinetic drug interactions: An example with amitriptyline and nortriptyline. Ther Drug Monit 16: 1-12.
42. Kaminski R, Jasinski M, Jagiello-Wojtowicz E, Kleinrok Z, Czuczwar SJ (1999) Effect of amlodipine upon the protective activity of antiepileptic drugs against maximal electroshock-induced seizures in mice. Pharmacol Res 40: 319-325.
43. Al-Humayyd MS (1990) Elevation of carbamazepine plasma levels by diltiazem in rabbits: A potentially important drug interaction. Biopharm Drug Dispos 11: 411-417.
44. Beattie B, Biller J, Mehlhaus B, Murray M (1988) Verapamil-induced carbamazepine neurotoxicity. A report of two cases. Eur Neurol 28: 104-105.
45. Czuczwar SJ, Gasior M, Janusz W, Szczepanik B, Wlodarczyk D, et al. (1990) Influence of different methylxanthines on the anticonvulsant action of common antiepileptic drugs in mice. Epilepsia 31: 318-323.
46. Rwiza HT, Keyser A, Hekster YA, Pool M, Verwey H (1989) Retrospective analysis of drug treatment in epileptic patients. Pharm Weekbl Sci 11: 50-55.
47. Berkovic SF (2005) Treatment with anti-epileptic drugs. Aust Fam Physician 34: 1017-1020.
48. Breton H, Cociglio M, Bressolle F, Peyriere H, Blayac JP, et al. (2005) Liquid chromatography-electrospray mass spectrometry determination of carbamazepine, oxcarbazepine and eight of their metabolites in human plasma. J Chromatogr B Anal Technol Biomed life Sci 828: 80-90.
49. Stogmann W (1986) Epileptic seizures in childhood: Classification, diagnosis, therapy. Padiatr Padol 21: 303-316.
50. Semah F, Gimenez F, Longer E, Laplane D, Thuillier A, et al. (1994) Carbamazepine and its epoxide: an open study of efficacy and side effects after carbamazepine dose increment in refractory partial epilepsy. Ther Drug Monit 16: 537-540.
51. Chu NS (1979) Carbamazepine: Prevention of alcohol withdrawal seizures. Neurology 29: 1397-1401.
52. Barrons R, Roberts N (2010) The role of carbamazepine and oxcarbazepine in alcohol withdrawal syndrome. J Clin Pharm Ther 35: 153-167.
53. Ketter TA, Haupt DW (2006) Perceptions of weight gain and bipolar pharmacotherapy: Results of a 2005 survey of physicians in clinical practice. Curr Med Res Opin 22: 2345-2353.
54. Iivanainen M (1998) Phenytoin: Effective but insidious therapy for epilepsy in people with intellectual disability. J Intellect Disabil Res 1: 24-31.

55. Warren JW Jr, Benmaman JD, Wannamaker BB, Levy RH (1980) Kinetics of a carbamazepine-ethosuximide interaction. Clin Pharmacol Ther 28: 646-651.
56. Petit P, Lonjon R, Cociglio M, Sluzewska A, Blayac JP, et al. (1991) Carbamazepine and its 10,11-epoxide metabolite in acute mania: Clinical and pharmacokinetic correlates. Eur J Clin Pharmacol 41: 541-546.
57. Singh B, Singh P, al Hifzi I, Khan M, Majeed-Saidan M (1996) Treatment of neonatal seizures with carbamazepine. J Child Neurol 11: 378-382.
58. Burke WJ, Grant JM, Selby G (1965) The treatment of trigeminal neuralgia: A clinical trial of carbamazepine ("Tegretol"). Med J Aust 1: 494-498.
59. Benoliel R, Zini A, Khan J, Almoznino G, Sharav Y, et al. (2016) Trigeminal neuralgia (part II): Factors affecting early pharmacotherapeutic outcome. Cephalalgia 36: 747-759.
60. Tomson T, Lindbom U, Ekqvist B, Sundqvist A (1994) Epilepsy and pregnancy: A prospective study of seizure control in relation to free and total plasma concentrations of carbamazepine and phenytoin. Epilepsia 35: 122-130.
61. Krasniqi S, Neziri B, Islami H, Bauer S (2010) Carbamazepine and lamotrigine plasma concentrations in epileptic patients during optimising therapy. Med Arh Bosnia and Herzegovina 64: 80-83.
62. Miyakoshi M (1986) Aging variabilities of level-dose relationship in antiepileptic monopharmacy-with reference to drug interaction between mono and bipharmacy. Jpn J Psychiatry Neurol 40: 329-335.
63. Perucca E, Dulac O, Shorvon S, Tomson T (2001) Harnessing the clinical potential of antiepileptic drug therapy: Dosage optimisation. CNS Drugs 15: 609-621.
64. Vasudev A, Tripathi KD, Puri V (2000) Association of drug levels and pharmacokinetics of carbamazepine with seizure control. Indian J Med Res 112: 218-223.
65. Duche B, Louiset P, Demotes-Mainard J, Loiseau P (1987) Subacute encephalopathy. Idiosyncratic reaction to carbamazepine? Rev Neurol 143: 211-213.
66. O'Dougherty M, Wright FS, Cox S, Walson P (1987) Carbamazepine plasma concentration. Relationship to cognitive impairment. Arch Neurol 44: 863-867.
67. Smith KRJ, Goulding PM, Wilderman D, Goldfader PR, Holterman-Hommes P, et al. (1994) Neurobehavioral effects of phenytoin and carbamazepine in patients recovering from brain trauma: A comparative study. Arch Neurol 51: 653-660.
68. Yeap LL, Lim KS, Ng CC, Hui-Ping KA, Lo YL (2014) Slow carbamazepine clearance in a nonadherent Malay woman with epilepsy and thyrotoxicosis. Ther Drug Monit 36: 3-9.
69. Porter RJ (1987) How to initiate and maintain carbamazepine therapy in children and adults. Epilepsia 28 Suppl 3: S59-63.
70. Dasgupta A, Reyes MA, Davis BG, Marlow AM, Johnson M (2010) Analytical performance evaluation of ADVIA Chemistry Carbamazepine_2 assay: Minimal cross-reactivity with carbamazepine 10, 11-epoxide and none with hydroxyzine or cetirizine. J Clin Lab Anal 24: 278-282.
71. Samaei A, Nobahar M, Vafaei AA (2009) An experimental design for finding of minimum dosage of carbamazepine and valproate in preventing of seizure attacks. Pak J Pharm Sci 22: 180-183.
72. Chbili C, Bannour S, Khlifi S, Ben H, Ali B, et al. (2014) Relationships between pharmacokinetic parameters of carbamazepine and therapeutic response in patients with bipolar disease. Ann Biol Clin 72: 453-459.
73. Nolen WA, Jansen GS, Broekman M (1988) Measuring plasma levels of carbamazepine. A pharmacokinetic study in patients with affective disorders. Pharmacopsychiatry 21: 252-254.
74. Shakya G, Malla S, Shakya KN, Shrestha R (2008) Therapeutic drug monitoring of antiepileptic drugs. J Nepal Med Assoc 47: 94-97.
75. Karande SC, Dalvi SS, Kshirsagar NA (1995) Shortcomings in the pharmacotherapy of epileptic children in Bombay, India. J Trop Pediatr 41: 247-249.
76. May DC (1984) Acute carbamazepine intoxication: Clinical spectrum and management. South Med J 77: 24-26.
77. Aggarwal A, Kumar M, Faridi MM (2005) Effect of carbamazepine on serum lipids and liver function tests. Indian Pediatr 42: 913-918.
78. Tomson T, Tybring G, Bertilsson L, Ekbom K, Rane A (1980) Carbamazepine therapy in trigeminal neuralgia: Clinical effects in relation to plasma concentration. Arch Neurol 37: 699-703.
79. Barre J, Didey F, Delion F, Tillement JP (1988) Problems in therapeutic drug monitoring: Free drug level monitoring. Ther Drug Monit 10: 133-143.
80. Finnell RH, Mohl VK, Bennett GD, Taylor SM (1986) Failure of epoxide formation to influence carbamazepine-induced teratogenesis in a mouse model. Teratog Carcinog Mutagen 6: 393-401.
81. Lanchote VL, Bonato PS, Campos GM, Rodrigues I (1995) Factors influencing plasma concentrations of carbamazepine and carbamazepine-10,11-epoxide in epileptic children and adults. Ther Drug Monit 17: 47-52.
82. Djordjevic S, Kilibarda V, Vucinic S, Stojanovic T, Antonijevic B (2012) Toxicokinetics and correlation of carbamazepine salivary and serum concentrations in acute poisonings. Vojnosanit Pregl Serbia 69: 389-393.
83. Al Za'abi M, Deleu D, Batchelor C (2003) Salivary free concentrations of anti-epileptic drugs: An evaluation in a routine clinical setting. Acta Neurol Belg 103: 19-23.
84. Vasudev A, Tripathi KD, Puri V (2002) Correlation of serum and salivary carbamazepine concentration in epileptic patients: Implications for therapeutic drug monitoring. Neurol India 50: 60-62.
85. Rosenthal E, Hoffer E, Ben-Aryeh H, Badarni S, Benderly A, et al. (1995) Use of saliva in home monitoring of carbamazepine levels. Epilepsia 36: 72-74.
86. Kintz P, Marescaux C, Mangin P (1995) Testing human hair for carbamazepine in epileptic patients: Is hair investigation suitable for drug monitoring? Hum Exp Toxicol 14: 812-815.
87. Zhao M, Yang L, Wei Y, Xiong X, Zhou Y, et al. (2010) A case report of monitoring on carbamazepine in breast feeding woman. Beijing Da Xue Xue Bao 42: 602-603.