Carbamazepine Toxicity

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Background

Carbamazepine (5H-dibenzazepine-5-carboxamide) is an iminostilbene derivative with a tricyclic structure. It is an antiepileptic drug widely used for treatment of simple partial seizures and complex partial seizures, trigeminal neuralgia, and bipolar affective disorder.

Carbamazepine selectively inhibits high frequency epileptic foci while normal neuronal activity remains undisturbed. Carbamazepine is absorbed erratically after oral administration because of its lipophilic nature. It has a large volume of distribution; peak plasma levels occur 4-8 hours postingestion but may take up to 24 hours to peak. The primary site of metabolism is the liver; its metabolite also is active, which may increase duration of the symptoms of toxicity.

Pathophysiology

Carbamazepine reduces the propagation of abnormal impulses in the brain by blocking sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus. Carbamazepine is absorbed slowly and distributed erratically following oral administration. It enters the brain rapidly because of its high lipid solubility.

Carbamazepine is metabolized primarily in the liver by oxidative enzymes, then is conjugated with glucuronic acid, and finally is excreted in the urine. Its metabolite, carbamazepine-10,11-epoxide, is active and may achieve up to 50% concentration of the parent compound.

The elimination of carbamazepine increases over the first few weeks because of autoinduction. Carbamazepine also enhances the metabolism of phenytoin, causing its levels to fall. Erythromycin, isoniazid, and propoxyphene (withdrawn from US market) inhibit the hepatic metabolism of carbamazepine; therefore, the dose of carbamazepine may need to be adjusted in patients taking multiple medications.

Carbamazepine induces the hepatic cytochrome P-450 system and its half-life decreases with chronic administration. The enhanced cytochrome P-450 system increases metabolism of other antiepileptic drugs.

Epidemiology

Frequency

United States

According to the Annual Report of the American Association of Poison Control Centers' National Poison Data System, 2330 carbamazepine single exposures were reported in 2008. Of these, 1517 patients sought treatment in a health care facility.[1]

Mortality/Morbidity

Of the exposures to carbamazepine reported to the American Association of Poison Control Centers in 2008, 389 resulted in no significant outcome and 69 had a significant consequence. No deaths were reported.[1]

- Montgomery et al reports that severity of symptoms at the time of initial contact with the poison control center correlates with outcome severity for children and adults.[2] However, the amount of time between ingestion and poison control center contact did not alter the correlation between initial severity of symptoms and final outcome severity.
- Far more exposures to the drug are unintentional (57.2%) than intentional (37.6%). A small number of people experienced the effects of toxicity secondary to adverse reactions rather than true poisonings (4%). Montgomery et al found that the reason for ingestion was correlated significantly with outcome. Carbamazepine levels greater than 85 mg/L were associated with severe toxicity.[2]
- The new drug oxcarbazepine is structural derivative of carbamazepine. It is metabolized to a product called 10-monohydrate derivate (MHD); this is the pharmacologically effective compound. van Optstal et al reported a case when a patient ingested more than 100 tablets of oxcarbazepine.[3] The serum level of the parent compound was 10-fold higher than the therapeutic dosage of 31.6 mg/L. However, the concentration of MHD was only 2-fold higher. MHD levels peaked 7 hours after intake. The patient survived without an adverse outcome. The authors concluded that since oxcarbazepine is a prodrug, formation of the active MHD metabolite is a rate-limiting process contributing to low overall toxicity of this drug.

Age

Roughly one third of carbamazepine exposures occur in children younger than 6 years. Pediatric patients with carbamazepine ingestion are at higher risk for dystonic reactions, coma, and apnea if serum levels exceed 28 mg/L. Children eliminate the drug more rapidly than adults.

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References

1. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Giffin SL. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. *Clin Toxicol (Phila)*. Dec 2009;47(10):911-1084. [Medline].
2. Montgomery VL, Richman BJ, Goldsmith LJ, Rodgers GC Jr. Severity and carbamazepine level at time of initial poison center contact correlate with outcome in carbamazepine poisoning. *J Toxicol Clin Toxicol*. 1995;33(4):311-23. [Medline].
3. van Opstal JM, Janknegt R, Cilissen J, L'Ortije WH, Nel JE, De Heer F. Severe overdosage with the antiepileptic drug oxcarbazepine. *Br J Clin Pharmacol*. Sep 2004;58(3):329-31. [Medline]. [Full Text].
4. Fischer M, Hamm H, Wirbelauer J. [Severe drug-related skin reaction: toxic epidermal necrolysis caused by carbamazepine]. *Klin Padiatr*. Sep-Oct 2004;216(5):288-93. [Medline].
5. Allam JP, Paus T, Reichel C, Bieber T, Novak N. DRESS syndrome associated with carbamazepine and phenytoin. *Eur J Dermatol*. Sep-Oct 2004;14(5):339-42. [Medline].
6. Vander T, Odi H, Bluvstein V, Ronen J, Catz A. Carbamazepine toxicity following Oxybutynin and Dantrolene administration: a case report. *Spinal Cord*. Apr 2005;43(4):252-5. [Medline].
7. Apfelbaum JD, Caravati EM, Kerns WP 2nd, Bossart PJ, Larsen G. Cardiovascular effects of carbamazepine toxicity. *Ann Emerg Med*. May 1995;25(5):631-5. [Medline].
8. Bass J, Miles MV, Tennison MB, Holcombe BJ, Thorn MD. Effects of enteral tube feeding on the absorption and pharmacokinetic profile of carbamazepine suspension. *Epilepsia*. May-Jun 1989;30(3):364-9. [Medline].
9. Goldfrank L, Flomenbaum NE, Lewin NA. Carbamazepine. In: *Goldfrank's Toxicologic Emergencies*. Appleton & Lange; 1994:594-5.
10. Graudins A, Peden G, Dowsett RP. Massive overdose with controlled-release carbamazepine resulting in delayed peak serum concentrations and life-threatening toxicity. *Emerg Med (Fremantle)*. Mar 2002;14 (1):89-94. [Medline].
11. Klimaszyk D, Lukasik-GLebocka M. [Cardiac toxicity of carbamazepine]. *Przegl Lek*. 2002;59(4-5):384-5. [Medline].
12. Micromedex. Toxicologic Managements of Carbamazepine. *Healthcare Series Micromedex*. 95.
13. Miles MV, Lawless ST, Tennison MB, Zaritsky AL, Greenwood RS. Rapid loading of critically ill patients with carbamazepine suspension. *Pediatrics*. Aug 1990;86(2):263-6. [Medline].

14. Riva R, Contin M, Albani F, et al. Free and total plasma concentrations of carbamazepine and carbamazepine-10,11-epoxide in epileptic patients: diurnal fluctuations and relationship with side effects. *Ther Drug Monit*. 1984;6(4):408-13. [Medline].

15. Romero Maldonado N, Sendra Tello J, Raboso Garcia-Baquero E, Harto Castano A. Anticonvulsant hypersensitivity syndrome with fatal outcome. *Eur J Dermatol*. Sep-Oct 2002;12(5):503-5. [Medline].

16. Stremski ES, Brady WB, Prasad K, Hennes HA. Pediatric carbamazepine intoxication. *Ann Emerg Med*. May 1995;25(5):624-30. [Medline].

17. Van Der Meyden CH, Kruger AJ, Muller FO, Rabie W, Schall R. Acute oral loading of carbamazepine-CR and phenytoin in a double-blind randomized study of patients at risk of seizures. *Epilepsia*. Jan-Feb 1994;35 (1):189-94. [Medline].

18. Wada JA, Troupin AS, Friel P, Remick R, Leal K, Pearmain J. Pharmacokinetic comparison of tablet and suspension dosage forms of carbamazepine. *Epilepsia*. Jun 1978;19(3):251-5. [Medline].