Editorial

Intravenous Lipid Emulsion as an Immediate Antidote for Carbamazepine Toxicity: Tick-Tock Tick-Tock Tick-Tock! -

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Submitted: 19 November 2015; Approved: 22 December 2015; Published: 31 December 2015

Citation this article: Baek WS. Intravenous Lipid Emulsion as an Immediate Antidote for Carbamazepine Toxicity: Tick-Tock Tick-Tock Tick-Tock! Scientific Journal of Neurology & Neurosurgery. 2015;1(1): 001-002.

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ABSTRACT
Carbamazepine (CBZ) is a tricyclic compound, structurally similar to imipramine as well as phenytoin, with a ureide moiety (-N-CO-NH2) present in its heterocyclic ring.

Symptoms of toxicity include diplopia (at levels above 7μg/ml in the majority of patients), ataxia, and dysarthria. Coma, hypotension, respiratory depression, cardiac arrhythmias, and seizures may occur.

Peak levels are usually achieved 6-8 hours after administration. Distribution is slow, and the volume of distribution is roughly 1L/kg with a low systemic clearance of approximately 1L/kg/d. The half-life in subjects following an initial single dose is 36 hours but with continuous therapy decreases to less than 20 hours. CBZ is about 80% to 85% protein-bound and has a large volume of distribution estimated between 0.5 to 2 L/kg [2] [3].

Both multiple dose activated charcoal and whole bowel irrigation have been implemented for CBZ overdose [4], but these may be ineffective in reducing absorption and enhancing elimination in overdose of slow-release CBZ. Hence extracorporeal treatment has been recommended in treating CBZ poisoning [5], but this requires the ER physician to request for additional services such as Nephrology with urgent hemodialysis service, which can delay treatment. Moreover, the Log P value of CBZ is 2.5, making this a lipophilic drug and less amenable to hemodialysis.

Intravenous lipid emulsion (ILE) is an established, effective treatment for local anesthetic-induced cardiovascular collapse. By creating an expanded, intravascular lipid phase, an equilibrium which drives the offending drug from the target tissues towards the newly formed ‘lipid sink’ is established. Hence, lipid emulsion has been considered a potential antidote for any lipophilic drug overdose, such as beta blockers, calcium channel blockers, and tricyclic antidepressants (TCAs) [6]. CBZ is lipophilic and structurally resembles TCAs, hence one would presume that ILE could be used in cases of CBZ toxicity. However, to date no standardized protocols of ILE therapy exist [6], and survival benefits have not been established in animal studies. Its safety been not established, either.

Hirose et al. have reported an interesting case where ILE was used as rescue therapy in a 15-year-old female with acute carbamazepine toxicity manifesting as respiratory depression and seizures [7]. She ingested approximately 2000mg of carbamazepine 11 hours prior to admission. She developed respiratory depression 12 hours post-ingestion, which was beyond the known time of 6-8 hours to reach peak concentration, generalized seizures(15 hours post-ingestion), mydriasis, oliguria, and gastrointestinal hypomotility, all of which improved by decreasing levels of carbamazepine.

The patient did not receive hemodialysis. She was given 100ml of 20% lipid emulsion therapy intravenously as bolus. CBZ reached peak levels of 104.5 μg/mL 20 hours later therefore 31 hours post-ingestion, not the 6-8 hours known to be the peak concentration time, and took 67 hours (78 hours post-ingestion) to come down below toxicity range (20 μg/mL), reflecting its gradual absorption. She was discharged 8 days later without any sequelae.

ILE may be an attractive alternative, as this could be more effective than hemodialysis and deliverable by the ER physician himself without any need for consulting additional services, especially when time is of essence. Randomized, large-scale, placebo-controlled studies are warranted to establish the potential role of ILE in treating carbamazepine toxicity.

REFERENCES