Has naloxone a role in treating carbamazepine overdose?

Abdel Melik A. Abdel Razik, MBBS, FRCPCH, Rubia Shahzadi, MBBS, MRCPCH.

ABSTRACT

A nine year old girl who took an overdose of carbamazepine presented with coma, arrhythmias, hypotension and respiratory depression. She made a prompt recovery following intravenous administration of naloxone.

Keywords: Carbamazepine, naloxone.


Since its introduction 30 years ago, carbamazepine is increasingly used as an anticonvulsant in the treatment of trigeminal neuralgia and other medical conditions.\(^1\) Being available in many households, this drug poses a potential risk of overdose. Carbamazepine poisoning has been reported by many authors in both epileptics and non-epileptics. It is a significant problem for emergency physicians and its management remains far from satisfactory in the absence of a specific antidote.\(^2\)

We report here a case of carbamazepine poisoning in a 9 year old epileptic girl, who presented with several of the toxic manifestations of the drug including cardiotoxicity, respiratory depression, electrolyte disturbances and coma. After receiving supportive management without significant response, she made a prompt improvement when given naloxone.

Case Report.

A 9 year old known epileptic girl was brought to the Accident and Emergency department 30 minutes after deliberate ingestion of carbamazepine syrup (2 bottles). The exact size of the dose was not known.

She was drowsy on arrival and soon she lapsed into coma. On examination, she was unresponsive to verbal and deep painful stimuli, markedly hypotonic with absent deep tendon reflexes and equivocal plantars. Pupils were dilated and poorly reactive to light. She had good and effective respiratory effort with respiratory rate 20/min, the cardiovascular status was stable with a heart rate of 82/min and satisfactory blood pressure of 115/70 mm Hg.

The rest of the physical examination was unremarkable. After securing an airway, gastric lavage was performed and activated charcoal given via the nasogastric tube in adequate doses.

Blood specimens for full blood count and differential, urea, electrolytes, blood sugar and liver function test as well as for carbamazepine level were collected at about 45 minutes after ingestion. All the tests yielded normal results. The carbamazepine level was determined by using Fluorescence Polarization Immunoassay (FPIA) (Abbott Laboratories). The patient’s carbamazepine level 45 minutes after ingestion was 37mg/L (Therapeutic level 4 - 12 mg/L).

Two hours after admission and initial management, she was still deeply comatose, and her

From the Department of Pediatrics, Fujairah Hospital, Fujairah, U.A.E.

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Address correspondence and reprint request to: Dr. Abdel Melik A. Abdel Razik, PO Box 872, Fujairah, United Arab Emirates. Tel. No. 00971 9 222428. Fax No. 00971 9 229077.
general condition deteriorated. Cardiac monitoring showed variability of cardiac rate and rhythm; heart rate ranging between 80-140/min with wide QRS complexes and atrial plus ventricular extrasystoles. She also developed hypokalemia (serum potassium 2.8 mmol/L - initial potassium on admission was normal). Her breathing became markedly shallow and blood gases and pH showed respiratory acidosis. Oxygenation, however, was maintained as she was given Oxygen by mask. Blood pressure remained fairly stable at around 115/70 for the first 2 hours following admission then it steadily dropped to 85/50 at 5 hours of admission.

When the patient developed more marked respiratory depression while comatose, a 0.4 mg bolus of naloxone was administered intravenously in an attempt to combat her deteriorating condition. The response was dramatic with immediate improvement in blood pressure and respiratory effort and there was a favourable change in the level of consciousness. The same dose of naloxone was repeated 30 minutes later and further improvement was noticed; when the patient opened up her eyes in response to command. One hour after the first dose she regained full consciousness. Slight residual nystagmus and mild ataxic gait remained but both disappeared completely by the next day. Ingestion of other drugs was denied by the mother and later by the patient.

Blood toxology showed only the presence of carbamazepine at a serum level of 37 mg/L.

**Discussion.** Carbamazepine is a broad-spectrum anticonvulsant used primarily in the treatment of many types of epilepsy in both adults and children.

With increasing prescriptions, there is a potential risk of overdosing and drug toxicity in epileptics and non-epileptics especially children. Carbamazepine poisoning, therefore, is a significant problem for emergency physicians.

Carbamazepine is structurally related to tricyclic antidepressants. It is slowly and erratically absorbed through the gastrointestinal tract, metabolised in the liver and excreted in urine and feces. The peak level may be delayed for 6-72 hours.

One of the drug metabolites, carbamazepine 10-11 epoxide is equally active. Up to 28% is eliminated in feces and there is an enterohepatic recycling that may be responsible of cases of relapsing symptoms should poisoning occurs.

The clinical manifestations of toxicity form a recognisable clinical picture of diminished conscious state, respiratory depression, cardiotoxicity, abnormal muscle tone, ataxia, nystagmus, mydriasis, electrolyte disturbances and seizures. Fatalities due to carbamazepine poisoning were reported usually resulting from toxic brain damage, aspiration pneumonia, respiratory failure, or cardiotoxicity. The severity of toxicity is usually correlated with the serum carbamazepine level, but at least in one study, this correlation was lacking.

In the absence of a specific antidote the management of carbamazepine, overdose is largely supportive, aiming at safeguarding the airway, maintaining vital functions, in addition to preventing further absorption, promoting its elimination and dealing with other complications such as electrolyte disturbances, arrhythmias and respiratory depression.

Gastric lavage is particularly useful as the anticholinergic effect of the drug delays gastric emptying. Activated charcoal was found to be beneficial provided that it is given in large doses. It binds the unabsorbed drug, thus reducing its enterohepatic circulation, prevents further absorption and facilitates its excretion in faeces. Care, however, should be exercised when using large doses of charcoal as bowel obstruction due to coagulum of charcoal tablets has been reported. Forced diuresis and hemodialysis have not been shown to be effective in increasing carbamazepine clearance.

On the other hand, results of charcoal hemoperfusion have been inconsistent with significant toxicity and mortality associated to it. Plasmapheresis also gave mixed results and it is not strongly recommended.

Naloxone is a specific opiate antagonist. It reverses respiratory depression by competing for the central nervous system (CNS) narcotic receptor sites. In addition to CNS manifestations and signs of cardiotoxicity our patient developed marked respiratory depression with shallow breathing and mixed acidosis. Although there was no evidence of concomitant ingestion of an opioid, the deteriorating respiratory status prompted us to try naloxone in an attempt to reverse the respiratory depression and obviate the need for mechanical ventilation. The response to the first dose was surprisingly dramatic and following the second dose the patient made a speedy recovery without relapse of symptoms.

The precise mechanism of naloxone action in reversing the manifestation of carbamazepine toxicity is not clear. To our knowledge this is the first case of carbamazepine poisoning in which naloxone was used and found to be very helpful. It is difficult to recommend routine use of naloxone in the management of carbamazepine poisoning until further studies are carried out to prove its effectiveness and delineate its mode of action.

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References