***N*-Acetylcysteine (NAC)-Induced Hyponatremia Caused by an Electronic Medical Record (EMR) Order Error**

Jakub Furmaga · Paul Wax · Kurt Kleinschmidt

Published online: 29 January 2015
© American College of Medical Toxicology 2015

Abstract

Introduction Intravenous *N*-acetylcysteine (NAC) causes few adverse drug events, with mild anaphylactoid reactions being the most common. Hyponatremia as a complication of hypoosmolar NAC solution has been reported. We describe how a locally constructed electronic medical record (EMR) order set for IV NAC resulted in a seizure from hyponatremia due to excess free water administration.

Case Report A 13-month-old female with no past medical history presented to a hospital after ingesting an unknown number of acetaminophen 500 mg tablets. The 4-h acetaminophen concentration was 343 mcg/mL, and she was started on IV NAC. 8.2 h into her 21-h IV NAC protocol, she developed a tonic-clonic seizure. Repeat serum sodium was 124 mEq/L, a decrease from 142 mEq/L at the time of admission. She was treated with hypertonic saline, lorazepam, and levetiracetam and had no further seizures. A brain MRI and EEG were both normal. After the seizure was stabilized, the providers noticed that the patient had received a total of 900 mL of D5W (112.5 mL/kg) in the first 9 h of hospitalization. This was caused by a poorly constructed, restrictive, EMR order set that did not allow customization of the IV NAC preparation.

Discussion Because the 21-h IV NAC administration involves preparation of 3 different doses infused over 3 different time intervals, an order set was developed to reduce ordering errors. However, error in its construction caused the pharmacist to prepare a solution containing too much free water,

decreasing patient's intravascular sodium and resulting in a seizure.

Conclusion The purposes of our case report were to highlight the dangers of overreliance on EMR order sets and to recognize hyponatremic seizures as an adverse reaction of an inappropriately prepared IV NAC.

Keywords *N*-Acetylcysteine · Hyponatremia · Electronic medical records · Seizure · Acetaminophen

Introduction

Intravenous *N*-acetylcysteine (NAC) causes uncommon adverse drug events. The most common are anaphylactoid reactions that include nausea, vomiting, rash, flushing, pruritis, bronchospasm, and angioedema. Serious adverse events occur even less frequently with few case reports describing hypotension, status epilepticus, and serum sickness-like illness [1]. Bailey et al. described a massive (2450 mg/kg) IV NAC overdose leading to status epilepticus, intracranial hypertension, edema, herniation, and eventually brain death [2]. However, IV NAC may also cause seizures through a different mechanism involving the diluent rather than the medication itself. Per package insert IV NAC should be administered with D5W, 0.45 % NaCl, or sterile water [3]. Because of the hypoosmolar nature of these solvents, hyponatremia and subsequent seizures can develop if the standard 200-, 500-, and 1000-mL volumes are not modified for a smaller patient (Acetadote® manufacturer defines them as <40 kg). A Maryland Poison Center study suggested that intravenous NAC administration errors for acetaminophen poisoning occur in approximately one third of cases, and they include incorrect doses, incorrect rate, interruption of therapy, and unnecessary

J. Furmaga (✉)
Parkland Health and Hospital System, Dallas, TX, USA
e-mail: jfurmaga@gmail.com

P. Wax
University of Texas Southwestern, Dallas, TX, USA

K. Kleinschmidt
University of Texas Southwestern, Dallas, TX, USA

administration of NAC [4]. Despite these glitches, weight-based dilution miscalculations rarely occur as evidenced by the lack of case reports describing them. To our knowledge, there are only two previous reports of IV NAC-induced hyponatremic seizure and they were caused by human miscalculations [5, 6]. The goal of this case report was to describe how a poorly designed electronic medical record (EMR) order set led to faulty preparation of IV NAC and resulted in a hyponatremic seizure.

Case Presentation

A 13-month-old female with no past medical history presented after ingesting unknown number of acetaminophen 500 mg tablets. The 4-h acetaminophen concentration was 343 mcg/mL, and she was started on IV NAC. 8.2 h into her 21-h NAC protocol, she developed a tonic-clonic seizure which was initially treated with lorazepam and levetiracetam. Immediately after the seizure was controlled, her electrolytes revealed sodium of 124 mEq/L, an 18 mEq/L decrease from 142 mEq/L at the time of admission (Fig. 1). All infusions were then discontinued, and she received 24 mL of 3 % hypertonic saline. The treatment team at that time realized the error in the NAC pharmacy order, with the volume of solvent dosed for an adult and not an 8-kg child. The NAC order was 150 mg/kg NAC in 200 mL of D5W for the first hour, 50 mg/kg in 500 mL of D5W over the next 4 h, and then 100 mg/kg in 1000 mL of D5W over 16 h. At the time of her seizure, she had received 900 mL of free water or 112.5 mL/kg over 8.2 hours. She subsequently had a normal brain MRI and EEG and had a complete recovery

with no sequelae. She also had appropriate IV NAC preparation restarted and never developed transaminitis. Siemens Dimension Vista® System urine drug screen was negative for amphetamine, opiates, methylenedioxymethamphetamine (MDMA), barbiturates, benzodiazepines, phencyclidine, cocaine, and cannabinoids, supporting the conclusion that the seizure was solely due to dilutional hyponatremia.

Discussion

The FDA-approved 21-h IV NAC protocol involves preparation of three different-size bags that have two different concentrations of NAC, which are weight based so are different for every patient (i.e., there is no universal concentration), and are administered at three different infusion rates over nonstandard time intervals (1, 4, and 16 h). Because of this complexity, a locally constructed order set was developed within Epic®, the EMR used at Children's Medical Center of Dallas. Per FDA-approved dosing, for a patient weighing 5–20 kg, Acetadote® should be prepared in the following way: the first dose should be 150 mg/kg of NAC dissolved in 3 mL/kg of diluent, the second should be 50 mg/kg of NAC in 7 mL/kg of diluent, and the third should be 100 mg/kg of NAC in 14 mL/kg of diluent [3]. This means that at the time of the seizure, the patient should have received only 12.8 mL/kg of D5W and not the 112.5 mL/kg that she was administered. This tenfold error was caused by a faulty order set which was designed to accept patient's weight and then auto-populated the quantity of NAC, the solvent type, the volume, and the infusion rate, with both

Fig. 1 Serum sodium concentration vs time

the physician and the pharmacist digitally prohibited from altering these parameters to minimize human error. Ironically, it was this read-only restriction that resulted in both the physician and the pharmacist accepting the computer's miscalculations (which would have been correct for an adult but not for a child) without manually doing the arithmetic (Fig. 2). When Acetadote® is

prepared for administration, it comes in a concentrated stock solution that needs to be extracted and dissolved in three appropriate bags of solvent. It is therefore also important to emphasize that both the preparing pharmacist as well as the administering nurse failed to identify the volume of drug (200 mL bag+500 mL bag+1000 mL bag) as too large for an 8-kg patient.

Fig. 2 Copy of the erroneous order set

ACETYLCSYSTEINE (ACETADOTE) INFUSION PANEL

acetylcysteine (ACETADOTE) 1,200 mg in D5W 250 mL Accept Cancel Remove

150 mg/kg × 8 kg (Order-specific weight) = 1,200 mg, INTRAVENOUS, ONCE, For 1 dose, Today at

Order Inst: Loading dose: 150 mg/kg (maximum: 15 gram) infused over 60 minutes

Reference Links: 1. Lexi-Comp

Dose: 150 mg/kg 150 mg/kg

Weight Type: Actual Ideal Adjusted **Order-Specific**

Weight: 8 kg

Administer Dose: **1,200 mg** 150 mg/kg × 8 kg [Order-specific weight as of 1531]
 = 1,200 mg × 100 mL/20,000 mg
 = 6 mL × 20,000 mg/100 mL
 = 1,200 mg

Administer Amount: **1,200 mg**

Route: INTRAVENO **INTRAVENOUS**

Frequency: ONCE **ONCE**

Starting: Today Tomorrow At:

First Dose: **Today** Number of doses: **1**

Scheduled Times: [Hide Schedule](#)

Linked Order Details: [Show Details](#)

Duration: 60 Minutes

Admin. Inst.: [Dose 1 of 3. Infuse entire contents of bag.](#)

Comments (F6): [Click to add text](#) (300 char max.)

Class: Normal

Exception Code:

☐ Self Administered ☐ Patient supplied for Doses

Rate: mL/hr

Medications

☒ acetylcysteine 150 mg/kg 150 mg/kg

Dose calculation will be based on order-specific weight for all ingredients. [Jump to weight selection](#)

Calc. Dose = 1,200 mg
 150 mg/kg × 8 kg [Order-specific weight as of]
 = 1,200 mg × 100 mL/20,000 mg
 = 6 mL × 20,000 mg/100 mL
 = 1,200 mg

Base (Selection Required)

☒ D5W 250 mL

Priority: Routine **Routine** STAT

Product: **ACETYLCSYSTEINE MPB LOADING DOSE**

Volume: 250 mL

Routing:

Department:

Phase of Care:

Indications:

☐ Additional clinical indications

Accept Cancel Remove

Could not be changed

One way to reduce such errors from happening in the future would be to institute an easier dosing regiment for IV NAC such as the one-bag system used at the Barnes-Jewish Hospital [7]. However, this one-bag system is an off-label infusion protocol some institutions may be reluctant to adopt. Another strategy would be to create a centralized location for EMR order sets (similar to the App Store® or Google Play®) where institutions can download pretested order sets. This too, however, has limitations as most EMRs are not compatible and handle electronic ordering differently. Our institution responded to this incident by having both the pharmacy and the information technology departments meet and correct the culpable order set to prevent such errors from occurring in the future.

Conclusion

Based on complete recovery with correction of hyponatremia and normal brain testing, neurology ruled out new onset epilepsy. Given that the patient was not on any medications, had a negative urine toxicology screen, and did not receive any other IV solution, it is unlikely that anything other than the free water administered with the IV NAC caused her hyponatremia. To our knowledge, this is the first reported case of dilutional hyponatremia due to a poorly constructed IV NAC electronic order set despite several retrospective evaluations of EMRs praising them for reducing prescription/medication errors [8, 9]. The purposes of our case were to highlight dangers of over-reliance on EMR order sets and to recognize hyponatremic

seizures as an adverse reaction of inappropriately prepared IV NAC.

References

1. Sandilands EA, Bateman DN (2009) Adverse reactions associated with acetylcysteine. *Clin Toxicol* 47(2):81–8
2. Bailey B, Blais R, Letarte A (2004) Status epilepticus after a massive intravenous N-acetylcysteine overdose leading to intracranial hypertension and death. *Ann Emerg Med* 44(4):401–6
3. Acetadote (acetylcysteine) Injection Initial U.S. Approval: 2004. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021539s012lbl.pdf. Accessed 21 Dec 2013.
4. Hayes BD, Klein-Schwartz W, Doyon S (2008) Frequency of medication errors with intravenous acetylcysteine for acetaminophen overdose. *Ann Pharmacother* 42(6):766–70
5. Sung L, Simons JA, Dayneka NL, PharmD P (1997) Dilution of Intravenous N-Acetylcysteine as a Cause of Hyponatremia. *Pediatrics* 100(3):389
6. Mayordomo-Colunga J, Larrea E, García M, Suárez S, Rodríguez J (2009) Life-threatening hyponatremia due to intravenous n-acetylcysteine treatment in an infant: a case report. *Cases J* 2(1):8347
7. Johnson MT, McCammon CA, Mullins ME, Halcomb SE (2011) Evaluation of a simplified N-acetylcysteine dosing regimen for the treatment of acetaminophen toxicity. *Ann Pharmacother* 45(6):713–20
8. Abramson EL, Malhotra S, Osorio SN et al (2013) A long-term follow-up evaluation of electronic health record prescribing safety. *J Am Med Inform Assoc* 20(e1):e52–8
9. Anderson JG, Jay SJ, Anderson M, Hunt TJ (2002) Evaluating the capability of information technology to prevent adverse drug events: a computer simulation approach. *J Am Med Inform Assoc* 9(5):479–90