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Single Case

Non-Intentional N-Acetylcysteine Overdose Associated with Cerebral Edema and Brain Death

Emma E.M. Spence[a] Sey Shwetz[b] Lauren Ryan[c] Natalie Anton[c] Ari R. Joffe[c]

[a]Internal Medicine Residency Program, University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [b]Department of Emergency Medicine, University of Saskatchewan, Saskatoon, SK, Canada; [c]Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Alberta and Stollery Children's Hospital, Edmonton, AB, Canada

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Abstract
N-acetylcysteine is the established treatment for acetaminophen toxicity. This medication's complex dosing schedule engenders a high incidence of medication errors. While nuisance side effects are common, only rare case reports describe serious outcomes associated with N-acetylcysteine administration, all of which take place in the setting of non-intentional N-acetylcysteine overdose. This case report contributes to a small but growing literature that suggests that large N-acetylcysteine overdose may have devastating outcomes. We describe a 15-year-old female who presented with stage III acetaminophen toxicity and who received a non-intentional 6-fold overdose of intravenous N-acetylcysteine due to a medication prescribing error. During the N-acetylcysteine infusion dosing error, the patient had clinical deterioration including seizure followed by cerebral edema and brain herniation that progressed to brain death. She developed agitation and worsening headache within 2 h of the dosing error, which progressed to seizure and intubation 14 h into the dosing error. Although possibly due to hepatic encephalopathy, at the time she developed fixed dilated pupils, her lactate, international normalized ratio, aspartate aminotransferase, and alanine aminotransferase had all improved. On review of the literature, other case reports of seizures (n = 4) and cerebral edema with brain herniation (n = 3) were found, suggesting our patient was not an isolated case. Clinicians need to be aware of the common occurrence of dosing errors for N-acetylcysteine infusions. We suggest institutions review their N-acetylcysteine ordering, dosing, and mixing protocols in order to avoid similar rare errors in the future. Iatrogenic overdose of N-acetylcysteine can cause seizure, cerebral edema, and brain death.

Correspondence to:
Ari R. Joffe, ari.joffe@ahs.ca

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Introduction

Acetaminophen is the most used non-prescription analgesic and antipyretic agent worldwide [1]. In many developed countries, acetaminophen toxicity is the leading cause of acute liver failure [1]. Severe hepatotoxicity, renal failure, and death can result from overdose [1]. For decades, N-acetylcysteine (NAC) has remained the recommended treatment for acute acetaminophen poisoning [1]. NAC works as an antidote by detoxifying N-acetyl-p-benzoquinoneimine, a hepatotoxic metabolite produced in acetaminophen overdose [2]. The decision to initiate management with NAC ideally relies on blood acetaminophen concentration at an early time since ingestion, plotted on the Rumack-Matthew acetaminophen nomogram equipped with risk and treatment thresholds [2].

While NAC is generally considered a safe medication, its use is not without risk. Nausea, vomiting, and cutaneous reactions are the most common adverse events associated with intravenous administration [3]. Anaphylactoid reactions to NAC treatment have been reported in up to 48% of patients, including symptoms of flushing, pruritis, rash, angioedema, bronchospasm, hypotension, and rarely death [3]. A small number of case reports describe serious outcomes not related to anaphylactoid reactions (Table 1) [4–10]. Herein we aim to add to this literature to describe a patient who developed seizure, cerebral edema, and brain death in the context of acetaminophen poisoning, acute liver failure, and 6-fold NAC overdose that occurred due to a medication prescribing error.

The patient's mother signed informed consent to publish this case report. Ethics committee review is not required for case reports at our institution as long as there is a signed informed consent form. This report was written in accordance with the CARE case report guidelines. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529169).

Case Presentation

A 15-year-old female with a history of substance use was evaluated at a rural hospital 48 h after ingesting approximately 15 g of acetaminophen. Clinical and laboratory findings revealed acute hepatic toxicity. A 3-bag intravenous NAC infusion protocol was initiated, and the patient was transferred to our tertiary care pediatric intensive care unit (PICU) for consideration of liver transplant. On day one in the PICU, the patient did not meet criteria for liver transplantation based on King's College Criteria. While the patient endorsed ongoing abdominal discomfort and nausea, she maintained a Glasgow Coma Scale of 15 with appropriate mentation and behavior. Repeat laboratory investigations found some improvement in liver function (shown in Fig. 1). Hepatology consultation recommended continuation of the NAC infusion due to persistently prolonged international normalized ratio (INR).

Despite adequate fluid resuscitation, the patient developed oliguria with increasing creatinine levels. The patient also complained of new headache. In order to limit fluid input, a fluid-restricted higher concentration of NAC was ordered at 23:00 h on day one in PICU. Up until this point, the patient had been receiving an appropriate weight-based NAC dose of 12.5 mg/kg/h using a 30 mg/mL concentration. The electronic medical record medication ordering platform prompted default concentrations for NAC that did not include the new desired concentration of 40 mg/mL. As such, the new NAC concentration, dilution instructions, and infusion rate were input manually into the ordering platform by the physician team; unfortunately, the infusion rate was input at an incorrectly high rate. The patient subsequently received 72 mg/kg/h of NAC, representing a 6-fold overdose. Failure to

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Table 1. Case reports of NAC infusion overdose associated with non-anaphylactoid adverse outcomes [4–10]

Reference	Age	Sex	Acetaminophen overdose presentation	Prescribing error: amount, duration	Severe outcome
Bailey et al., (2004) [4]	30 months	F	Acute. Circumstances of ingestion not provided. The ingested dose of acetaminophen was determined (after death) to have been nontoxic	11.8-fold overdose administered over 6 h 45 min	Status epilepticus, intracranial hypertension, cerebral edema, uncal herniation, and brain death. Normal liver on autopsy
Heard and Schaeffer, (2011) [5]	21 years	F	Acute. Unintentional overdose. Presented with vomiting	16-fold overdose administered over 32 h	Agitation, status epilepticus, cerebral edema, uncal herniation, and severe neurological injury
Bronstein et al., (2009) [6] (Addendum case)	18 years	F	Acute. Circumstances of ingestion not provided	4-fold overdose administered over 4 h, then 16-fold overdose administered over 16 h	Status epilepticus, aspiration pneumonia, cerebral edema, brain herniation, and brain death. No liver necrosis on autopsy
Razlansari et al., (2017) [7]	2.5 years	M	Acute. Circumstances of ingestion not provided	10-fold overdose administered as loading dose over unspecified time	"Immediate" status epilepticus leading to intensive care transfer and 3 day hospitalization
Mullins and Vitkovitsky (2011) [8]	21 years	F	Acute, with ethanol. Intentional overdose (suicide attempt)	5-fold overdose administered over 1 h 20 min	Atypical hemolytic uremic syndrome requiring hemodialysis, blood transfusion, and plasmapheresis. Survived with no significant adverse effects at 6-month follow-up
Mahmoudi et al., (2015) [9]	23 years	F	Acute. Intentional overdose (suicide attempt)	10-fold overdose administered over 30 min	Initial hypotension, periorbital edema, and dyspnea (anaphylactoid reaction). CT of the "brain showed signs of edema." By day 2, developed severe hemolytic uremic syndrome, requiring hemodialysis and plasmapheresis. Death from HUS on day 12. Liver function recovered and histology normal on autopsy

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Table 1 (continued)

Reference	Age	Sex	Acetaminophen overdose presentation	Prescribing error: amount, duration	Severe outcome
Srinivasan et al., (2015) [10]	20 years	F	Acute. Intentional overdose (suicide attempt)	10-fold overdose administered over 14 h	Mild hemolysis not requiring transfusion. Survived with full recovery
Current case	15 years	F	Delayed – after unknown prior acute overdose. Presented with acute liver failure. Intentional impulsive overdose	6-fold overdose administered over 57 h	Seizure, cerebral edema, brain herniation, and brain death

recognize the dosing error resulted in the patient receiving the incorrect dose for 57 h prior to the diagnosis of brain death, and for a total of 78 h as described below (shown in Fig. 2).

Early during day two in the PICU, the patient endorsed worsening of her headache and became increasingly agitated. This mental status change was attributed to a combination of uremic encephalopathy, hepatic encephalopathy, possible drug-use withdrawal, and possible posterior reversible encephalopathy syndrome. A CT scan of the brain was normal. Her mental status and level of consciousness continued to deteriorate over the course of the day. That afternoon, she experienced a generalized seizure and was intubated. Continuous renal replacement therapy was initiated. She was listed for liver transplant. On the morning of day 3 in PICU, she had fixed dilated pupils. Although initially attributed to hypothermia (her core temperature was unintentionally low at 32–33˚C), a repeat CT scan showed diffuse cerebral edema and transforaminal herniation of the cerebellar tonsils. Over the next 17 h two clinical examinations by two pediatric intensivists, an electroencephalogram showing electrocerebral silence, and a diffusible radionuclide test showing lack of intracranial blood flow and uptake, confirmed the diagnosis of brain death. The family consented to organ donation. In discussion with the organ procurement organization, the decision was made to continue the NAC infusion while the patient was worked up for organ transplantation. On the morning she was scheduled for organ retrieval, the dosage error of NAC was identified by the bedside nurse.

On review of the literature, we found case reports suggesting that NAC overdose may cause cerebral edema and brain herniation (Table 1) [5–7]. During the dosing error infusion of NAC, her lactate, INR, and ammonia initially worsened, reflecting worsening liver injury. By the time she had fixed dilated pupils, her lactate, INR, aspartate aminotransferase, and alanine aminotransferase had all improved. The improvement in ammonia and creatinine was likely due to the continuous renal replacement therapy. She developed agitation and worsening headache within 2 h of the dosing error, and these progressed to seizure and intubation 14 h into the dosing error (shown in Fig. 2). Based on this, we are unsure whether the cerebral edema was due to hepatic encephalopathy, prolonged NAC overdose, or a combination of both. The medication error was disclosed to the family, and its potential contribution to her clinical course was explained.

Discussion and Conclusions

Acetaminophen toxicity has classically been divided into four stages that are defined by time elapsed since ingestion. Peak hepatotoxicity tends to occur in stage III between 72 and

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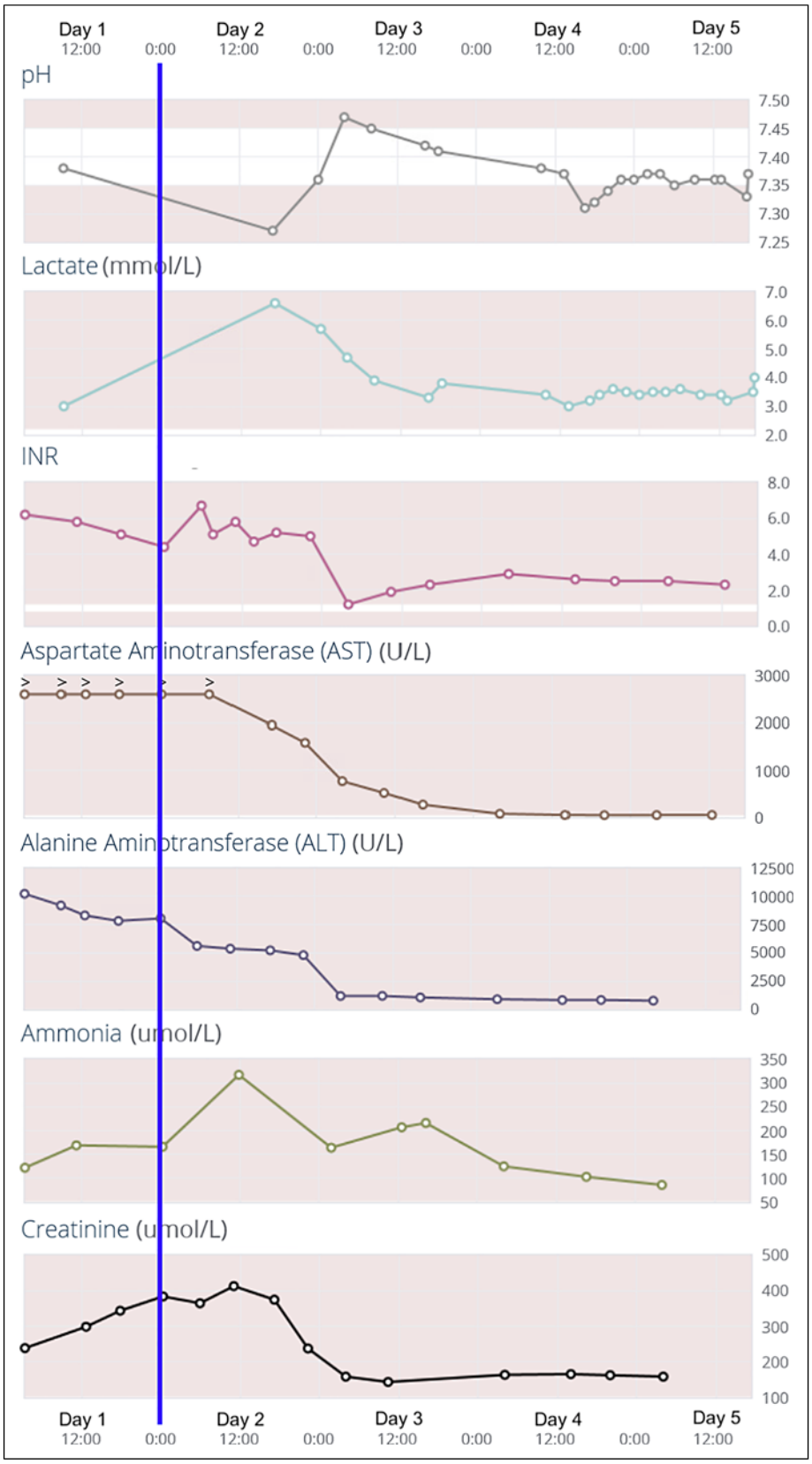

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96 h, the time frame corresponding to our patient's presentation. Stage IV, defined as >5 days since ingestion, can be characterized by resolution of hepatotoxicity, typically with no long-term liver sequelae, provided the patient received treatment at least early during stage II (24–72 h since ingestion). Alternatively, stage IV can involve progression to hepatic failure characterized by hepatic encephalopathy, cerebral edema, coma, coagulopathy, gastrointestinal bleeding, and death. Multiple organ dysfunction, including acute kidney injury, can also occur [2].

Our patient's clinical deterioration may be due to Stage III and IV symptoms of acetaminophen toxicity. It is impossible to determine whether the prolonged 6-fold overdose of NAC running for 57 h impacted the patient's clinical deterioration; however, our literature review suggests NAC may have contributed. Three previous case reports described the development of cerebral edema in patients who were non-intentionally prescribed large NAC overdoses while treating acetaminophen overdose; in these cases, NAC initiation occurred within 8 h of ingestion and there was no acute liver failure [4–6]. Similarities between our patient and previous case reports included the development of seizure [4, 5, 7], uncal herniation [5, 6], and death [4, 9]. Even if the clinical outcome was solely due to acute liver failure with hepatic encephalopathy, we believe there are several reasons to report our consideration of NAC overdose in this patient.

First, from a patient safety and quality improvement perspective, the steps leading to this error must be examined and addressed in order to prevent recurrence. Due to the complex dosing regimen and infrequent use, there is a relatively high incidence of medication dosing errors during NAC administration [11, 12]. In our case, the incorrect infusion administered to the patient occurred due to a combination of human error and limitations of the automated medical record ordering system. The electronic medical record ordering system at our institution, which had been in place for 4 months prior to our case, has been revised to not allow changing the concentration of NAC infusions (always 30 mg/mL) manually. In addition, a two-bag system for dosing of NAC is now used, with loading dose of 200 mg/kg over 4 h (50 mg/kg/h for 4 h), followed by 100 mg/kg over 16 h (6.25 mg/kg/h for 16 h), with accompanying dilution instructions and infusion rates. We recommend centers with electronic medical record ordering systems, whether recently implemented or not, review their NAC ordering protocols.

Second, our case and those of others (Table 1) highlight the serious and, although rare, potentially lethal risk associated with non-intentional NAC overdose. Systematic reviews find established benefit to administering NAC for acetaminophen overdose, with much higher impact if started within 8–10 h of ingestion [1, 2]. However, systematic reviews evaluating NAC administration in non-acetaminophen-related hepatotoxicity come to differing conclusions, and data based on randomized controlled trials in non-acetaminophen-related liver failure find no statistically significant effect of using NAC in children or adults [13, 14]. We recommend all centers review their written NAC protocols to be sure instructions on dosing and mixing of infusions are very clear and readily available at the bedside to avoid this rare error in the future.

The limitation of this case report is that we cannot know whether NAC contributed to our patient's cerebral edema and brain herniation. The patient's clinical course may be attributable to the NAC overdose, the natural history of hepatic encephalopathy progression in

Fig. 1. Laboratory results during the patient's admission to the pediatric intensive care unit. Trends in pH, lactate, INR, aspartate aminotransferase (AST), alanine aminotransferase (ALT), ammonia, and creatinine over the course of the patient's admission. Pink shaded areas on each graph represent values that fall outside of the normal range for that blood test. Blue line indicates the timepoint where the N-acetylcysteine (NAC) infusion was increased to six-times the intended dose (72 mg/kg/h).

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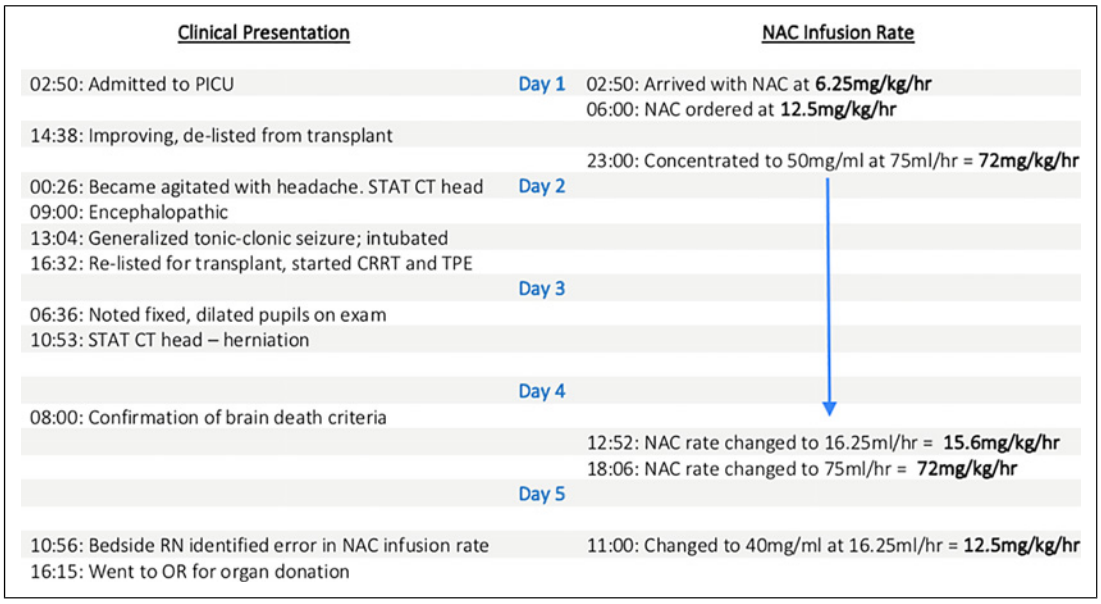

Fig. 2. Timelines of clinical and therapeutic events during the patient's admission to the pediatric intensive care unit. Timeline of events showing the patient's clinical findings, alongside changes to the N-acetylcysteine (NAC) infusion rate. The arrow highlights the duration of time during which the NAC infusion ran at six-times the intended dose (72 mg/kg/h) prior to declaration of brain death. CRRT, continuous renal replacement therapy; TPE, total plasma exchange.

acetaminophen toxicity (particularly given the delayed presentation to care), or both. Nevertheless, this case report draws attention to both individual- and system-level problems as well as potential solutions associated with NAC administration. This case adds to the literature on NAC overdose, being a reminder of important safety considerations pertinent to current and potential future indications for clinical use of this medication. We suggest institutions review their NAC ordering, dosing, and mixing protocols in order to avoid similar rare errors in the future.

Acknowledgments

We thank the patient's mother for allowing us to publish this case report.

Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the parent of the patient for publication of the details of their medical case and accompanying images.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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There was no funding of any research relevant to this study.

Author Contributions

E.E.M.S., S.S., L.R., N.A., and A.R.J. contributed to conception and design of the work, acquisition and interpretation of the data, and substantial critical revisions of the manuscript for important intellectual content, have approved the submitted version, and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. E.E.M.S. wrote the first draft of the article. L.R. prepared the two figures. All authors have read and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Chiew AL, Gluud C, Brok J, Buckley NA. Interventions for paracetamol (acetaminophen) overdose. Cochrane Database Syst Rev. 2018;2:CD003328.
2 Yoon E, Babar A, Choudhary M, Kutner M, Pyrsopoulos N. Acetaminophen-Induced hepatotoxicity: a comprehensive update. J Clin Transl Hepatol. 2016;4(2):131–42.
3 Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. Clin Toxicol. 2009;47(2):81–8.
4 Bailey B, Blais R, Letarte A. Status epilepticus after a massive intravenous N-acetylcysteine overdose leading to intracranial hypertension and death. Ann Emerg Med. 2004;44(4):401–6.
5 Heard K, Schaeffer TH. Massive acetylcysteine overdose associated with cerebral edema and seizures. Clin Toxicol. 2011;49(5):423–5.
6 Bronstein AC, Spyker DA, Cantilena LR, 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. 2009;47(10):911–1084.
7 Razlansari AA, Jafrasteh A, Garmsiri M. N-Acetylcysteine overdose after acetaminophen poisoning. Int J Adv Biol Biomed Res. 2017;5(2):69–72.
8 Mullins ME, Vitkovitsky IV. Hemolysis and hemolytic uremic syndrome following 5-fold N-acetylcysteine overdose. Clin Toxicol. 2011;49(8):755–9.
9 Mahmoudi GA, Astaraki P, Mohtashami AZ, Ahadi M. N-acetylcysteine overdose after acetaminophen poisoning. Int Med Case Rep J. 2015;8:65–9.
10 Srinivasan V, Corwin D, Verceles AC. An accidental overdose of N-acetylcysteine during treatment for acetaminophen toxicity. Clin Toxicol. 2015;53(5):500.
11 Hayes BD, Klein-Schwartz W, Doyon S. Frequency of medication errors with intravenous acetylcysteine for acetaminophen overdose. Ann Pharmacother. 2008;42(6):766–70.
12 Ferner RE, Langford NJ, Anton C, Hutchings A, Bateman DN, Routledge PA. Random and systematic medication errors in routine clinical practice: a multicentre study of infusions, using acetylcysteine as an example. Br J Clin Pharmacol. 2001;52(5):573–7.
13 Siu JTP, Nguyen T, Turgeon RD. N-acetylcysteine for non-paracetamol (acetaminophen)-related acute live failure. Cochrane Database Syst Rev. 2020;12:CD012123.
14 Shrestha DB, Budhathoki P, Sedhai YR, Adhikari A, Poudel A, Aryal B, et al. N-acetyl cysteine versus standard of care for non-acetaminophen induced acute liver injury: a systematic review and meta-analysis. Ann Hepatol. 2021;24:100340.