N-acetylcysteine overdose after acetaminophen poisoning

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Abstract: N-acetylcysteine (NAC) is used widely and effectively in oral and intravenous forms as a specific antidote for acetaminophen poisoning. Here we report a rare case of iatrogenic NAC overdose following an error in preparation of the solution, and describe its clinical symptoms. Laboratory results and are presented and examined. A 23-year-old alert female patient weighing 65 kg presented to the emergency ward with weakness, lethargy, extreme fatigue, nausea, and dizziness. She had normal arterial blood gas and vital signs. An excessive dosage of NAC over a short period of time can lead to hemolysis, thrombocytopenia, and acute renal failure in patients with normal glucose-6-phosphate dehydrogenase, and finally to death. Considering the similarity between some of the clinical symptoms of acetaminophen overdose and NAC overdose, it is vitally important for the administration phases and checking of the patient’s symptoms to be carried out attentively and cautiously.

Keywords: N-acetylcysteine, overdose, acetaminophen poisoning, medication error

Introduction
Acetaminophen is a widely used analgesic and antipyretic agent. However, acetaminophen overdose is common in patients who present to hospital emergency rooms, and in many cases causes liver and renal necrosis.1–3 Previous studies reported that a sterile 20% solution of N-acetylcysteine (NAC) administered intravenously was effective in the treatment of acetaminophen overdose.4–6 Their NAC regimen was 150 mg/kg body weight given over 15–30 minutes, 50 mg/kg over 4 hours, and 100 mg/kg over 16 hours, with the final dose of 100 mg/kg repeated three times until liver aminotransferase levels reverted to normal.7–9 NAC solution has been used for over two decades in emergency wards in Iran. However, despite its efficacy in reducing mortality due to acetaminophen poisoning, intravenous NAC can cause anaphylactoid reactions.6–8 Due to the complexity of preparation of NAC as well as its side effects, mistakes are possible. Here we report a rare case of iatrogenic NAC overdose due to an error made during preparation of the solution. Clinical symptoms, laboratory test results, are presented and discussed.

Case report
Four hours after taking 50 acetaminophen 325 mg tablets, a 23-year-old alert female patient weighing 65 kg presented to the emergency ward with weakness, lethargy, nausea, and dizziness. She had normal arterial blood gas and vital signs. Following administration of activated charcoal, in view of the toxic dose of acetaminophen ingested, treatment with NAC was started, with a 10 g loading dose of NAC 150 mg/kg
given over 30 minutes, followed by a 9.5 g maintenance dose with 500 mL of 5% dextrose water administered over 20 hours. The patient developed agitation, nausea, vomiting, dyspnea, tachypnea, hypotension (blood pressure 80 mmHg), drowsiness, and periorbital edema. Suspecting a drug allergy, the physician stopped administration of NAC, but further investigation revealed that a nurse had administered NAC 100 g (instead of 10 g) as the loading dose. After administration of NAC 100 g, the patient’s pupils were normal, symmetric, and reactive to light. However, her level of consciousness decreased to 7/15 on the Glasgow Coma Scale, her hypotension became severe, her radial pulse became unpalpable, and her respiratory rate increased to 32 per minute. She was intubated and transferred to the intensive care unit, where she died 12 days later.

According to the clinical evaluations, the patient’s pupils were normal, symmetric, and reactive to light until the third day, when they became mydriatic and reacted slowly to light thereafter. Computed tomography of the brain showed signs of edema. Respiratory tract secretions increased significantly, and the patient had dyspnea, tachypnea, and shallow breathing early on. Her breath sounds were decreased on auscultation of the lungs. Her arterial blood gas measurements indicated metabolic acidosis and respiratory alkalosis that was resistant to treatment in the first 18 hours, but was controlled by ventilation and infusion of sodium bicarbonate.

On the first day, there was a gradual increase in edema around the eyes and face. The patient also became oliguric, with a urine output of less than 250 mL in 24 hours. On the second day, generalized edema was observed. Biochemistry showed hypernatremia and increased blood urine and creatinine from the first day onward (Table 1).

Liver function tests showed elevated alanine aminotransferase and aspartate aminotransferase (22 and 12 times the upper limit of normal, respectively) until the second day of poisoning and a gradual decrease to normal by the seventh day. Partial thromboplastin time, international normalized ratio, prothrombin time, and total bilirubin levels were within normal limits during hospitalization (Table 1).

Between the first and second day of NAC administration, the patient’s hemoglobin and hematocrit levels decreased markedly from 12.6 g/dL and 35% to 4.5 g/dL and 13%, respectively. Her hemoglobin continued to decrease steadily, despite administration of a peak cell injection. Her platelet level was 70×1,000/mm³ in the first 24 hours after the poisoning and 29×1,000/mm³ on the second day. As with her hemoglobin levels, an intermittent decrease in platelets was observed, prompting administration of platelets and fresh frozen plasma (Table 1). Schistocytes peripheral blood film slide by thrombotic thrombocytopenic purpura and hemolytic anemia diagnosis; plasmapheresis was also performed 7 days after taking acetaminophen.

### Table 1 Trends of cell blood count, and renal and liver function tests

| Cell blood count/days | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|-----------------------|---|---|---|---|---|---|---|---|---|----|----|----|
| White blood cells x1,000 | 33.7 | 18 | 10.1 | 12.9 | 8.6 | 9.1 | 9.5 | 10.3 | 11 | 11 | 14 | 10 |
| Red blood cells (mil/mic) | 3.79 | 1.3 | 2.2 | 3.01 | 2.42 | 2.26 | 2.39 | 3.06 | 4.4 | 3.5 | 3 | 2.55 |
| Hemoglobin (mg/dL) | 12.6 | 4.5 | 7.5 | 8.9 | 7.9 | 8.1 | 12.2 | 15.8 | 14 | 9.7 | 7.7 | 7.8 |
| Hematocrit (%) | 35.9 | 13 | 20.5 | 26.7 | 21.5 | 23.9 | 35.5 | 46.1 | 39 | 55 | 28 | 23.6 |
| Platelets x1,000 | 70 | 29 | 63 | 20 | 43 | 36 | 43 | 169 | 54 | 34 | 22 | 73 |

**Renal function**

| Urea (mg/dL) | 62 | 55 | 143 | 101 | 87.9 | 140 | 152 | 155 | 175 | 234 | 260 | 323 |
| Creatinine (mg/dL) | 1.98 | 3.8 | 5.1 | 5.8 | 4.49 | 5.7 | 3.9 | 3.81 | 4.5 | 5.7 | 5.1 | 5.87 |
| Sodium (mEq/L) | 152 | 146 | 145 | 147 | 151 | 130 | 146 | 153 | 153 | 151 | 148 |
| Potassium (mEq/L) | 3.78 | 3.5 | 3.45 | 3.2 | 3.3 | 3.5 | 3.22 | 3.5 | 3.2 | 3.5 | 4 |
| Blood glucose | 121 | 140 | 139 | 139 | 139 | 140 | 140 | 140 | 140 | 140 | 140 |

**Liver function**

| SGOT (U/L) | 576 | 689 | 672 | 481 | 339 | 162 | 128 | 77 | 55 | 39 | 46 | 46 |
| SGPT (U/L) | 437 | 506 | 480 | 349 | 221 | 132 | 110 | 92 | 65 | 47 | 45 | 45 |
| ALKP (U/L) | 19 | 15 | 16.5 | 13.2 | 12.9 | 129 | 13 | 14 | 14 | 13 | 13.2 |
| PT/INR | 1.2 | 1.6 | 1.83 | 1.1 | 1.2 | 1.2 | 1.2 | 1.1 | 1 | 1 | 1.21 |
| PTT (seconds) | 2.3 | 60 | 50.8 | 35 | 27.6 | 31 | 37.5 | 29 | 33 | 36 | 37.1 |
| Bilirubin total (mg/dL) | 1.22 | 1.2 | 1.29 | 1.31 | 1.6 | 1.15 | 1.28 | 1.1 | 1 | 1.1 | 1.08 |
| Bilirubin direct (mg/dL) | 0.2 | 0.4 | 0.4 | 0.5 | 0.5 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |

**Abbreviations:** INR, international normalized ratio; PTT, partial thromboplastin time; PT, prothrombin time; ALKP, alkaline phosphatase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.
Discussion
The issue of patient health is a priority in medicine and is paramount in research. Each year, a large number of patients are harmed as a result of medical errors, many of which are preventable.10–12 The risk of such events occurring can be greatly reduced by identifying and understanding their causes. Hepatotoxicity is a well-known side effect of acetaminophen poisoning.13–15 Acetaminophen toxicity was recognized in our patient, who presented to the emergency ward after taking 16.25 g of acetaminophen in an attempt to commit suicide. She was complaining of peptic stomach pain, dizziness, and headache. Her serum aminotransferases indicated phase 2 toxicity; they remained elevated for 48 hours, then decreased and finally reverted to normal level on the third day of hospitalization. Other liver function tests, including international normalized ratio, prothrombin time, alkaline phosphatase, and bilirubin were reported to be normal. These findings and normal liver histology (Lam liver) represents a slight injury to hepatocytes and no liver failure and encephalopathy in the patient’s NAC seemed effective to prevent liver damage due to the poisoning.

NAC is derived from the amino acid, L-cysteine, oral and intravenous formulations of which are used widely and effectively as an antidote for acetaminophen poisoning (especially during the first 10 hours after poisoning) to prevent hepatotoxicity.16–19 Acetylcysteine is rapidly absorbed from the gastrointestinal tract, with maximal plasma concentrations achieved within half an hour of administration of a therapeutic dose.20,21 The mechanism via which acetylcysteine works in acetaminophen poisoning is not clear. At least four mechanisms have been proposed, including: intracellular activity of NAC as a substitute for glutathione, its combination with toxic metabolites, and elimination of their toxic effects (ie, a direct antidotal effect); stimulation of glutathione synthesis; stimulation of acetaminophen sulfate and antioxidant effects; and decreasing the effects of the inflammatory response induced in the liver.22–25

The most commonly reported adverse effects of intravenous acetylcysteine are anaphylactic reactions, including rash, pruritus, angioedema, bronchospasm, tachycardia, and hypotension.26–29 A previous study reported that approximately 15% of patients treated with intravenous acetylcysteine had an anaphylactic reaction within 2 hours after the initial infusion, and that increasing the infusion time from 15 minutes to 60 minutes did not alter the rate of adverse events.30–32 Other common adverse effects included vomiting and flushing. Further, retrospective studies have identified adverse effects in approximately 5% of cases.33–34

Considering the toxic dose of acetaminophen ingested by this patient, the physician prescribed intravenous NAC. Because of a mistake made by a nurse, the patient received seven times more NAC over 20 minutes that she should have. A number of clinical symptoms were reported following NAC overdose, including vomiting, nausea, exacerbation of respiratory distress (bronchospasm), periorbital angioedema, and hypotension while receiving the antidote.

Some studies reported that administration of NAC 63.6% and even 50% is associated with mild to life-threateningly severe side effects; these are quite prevalent when using oral treatment, and there is always a risk of iatrogenic overdose when using intravenous NAC. More serious side effects have been observed during actual administration of NAC and in the first hour following the dose.9,18,19

The most common side effects of treatment with intravenous NAC are anaphylactic reactions, including nausea, vomiting, flushing, hives, and rashes in non-severe cases, and bronchospasm, angioedema, and hypotension in severe cases. These reactions are dose-dependent and preceded by release of histamine. Usually the side effects are mild and resolve rapidly after discontinuation of the drug or a reduction in the injection rate.19,21,23,24 Regarding the allergic reactions in this case, the physician stopped the intravenous NAC and administered chlorphenamine and hydrocortisone.

Hypotension is reported to be an unusual symptom of acetaminophen. NAC has a nitrate-based vasodilating effect, and is commonly used to prevent nephropathy associated with radiocontrast agents. Our patient’s blood pressure was normal until the NAC overdose occurred, after which time her systolic pressure decreased to 60 mmHg. Normal saline solution was administered to increase her blood pressure, but without success. Her hypotension was controlled by administration of dopamine at a maximum dose of 15 mg/kg/h.25

In a previous paper, a cumulative intravenous NAC dose of 2,450 mg/kg was reported to be associated with status epilepticus, intracranial hypertension, and death in a child. Anuria, uremia, edema, loss of consciousness, and a decrease in glomerular filtration rate to approximately 40% of normal was seen within the first day after NAC overdose, and intensifying the process in the days after acetaminophen poisoning (Table 1), suggesting acute renal failure. Decreased hemoglobin, hematocrit, and platelet levels, the presence of schistocytes on a peripheral blood smear, along with other examinations on hematology, a negative Coombs test, hemolytic anemia, and thrombotic thrombocytopenic
purpura or immune thrombocytopenia caused by drug overdose suggested hemolytic uremic syndrome caused by NAC overdose.

Acute tubular necrosis and nephrotoxicity are reported in 1%–2% of cases of acetaminophen poisoning, and can occur in isolation or along with hepatotoxicity caused by NAC overdose. Its created metabolism is said to be dependent on toxic metabolite from renal cells’ cytochrome P450 activities and prostaglandin reactions. In many cases, renal failure due to acetaminophen ingestion develops after liver poisoning. It should be distinguished from hepatorenal symptoms caused by rapid liver failure. None of the liver function tests in our patient were in favor of liver failure or hepatorenal syndrome. Severe hypotension seen in NAC overdose due to a vasodilatory effect and the consequent oliguria raises the issue of prerenal pathophysiology and acute renal failure. Administration of 700 mL of NAC within 20 minutes, blood osmolality changes, and changes in glomerular filtration made renal failure possible. Unfortunately after the patient’s anuria and poor response to fluid therapy of sedimenteration, urinary test was not possible, and differentiation between prerenal and postrenal failure was not carried out.

The patient was treated with daily hemodialysis. Hemolysis is not a common side effect of acetaminophen poisoning. Some papers have reported hemolytic anemia due to glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficiency was not confirmed in our patient. A justifiable mechanism and cause for hemolysis and thrombocytopenia are not known. In the current case, daily plasmapheresis, administration of fresh frozen plasma, and platelet injections were also performed. Regrettably, the patient died as a result of hemolytic uremic syndrome after 12 days of treatment.

Animal studies and previous case reports strongly suggest that NAC overdose causes cerebral edema and seizures. To minimize the possibility of dosing errors, intravenous NAC should be administered as 12.5 mg/kg/h for 4 hours followed by 6.25 mg/kg/h for 16 hours.

Conclusion
An excessive dosage of NAC over a short period of time can lead to hemolysis, thrombocytopenia, acute renal failure, and death in patients with normal G6PD. Considering the similarity between some of the clinical symptoms of acetaminophen overdose and NAC overdose, it is important to carry out the administration phases and check the patient’s symptoms more attentively and cautiously.

Disclosure
The authors report no conflicts of interest in this work.

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