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Case Report: N-Acetylcysteine Overdose: A Case Report

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ABSTRACT

Background: N-Acetylcysteine (NAC) is a cost-effective antioxidant and very useful treatment for several diseases.

Methods: Here we report a rare case of iatrogenic NAC overdose following the mistake in calculation of the loading dose.

Results: The patient was 14 years old girl referred to a local hospital due to history of intentional ingesting about 7grams acetaminophen. The physician prescribed her 6 grams NAC as a loading dose but 42grams NAC were infused by mistake. After infusion, the patient showed signs of anaphylactic shock and then transferred to Imam Reza toxicology-unite with weakness, lethargy, extreme fatigue, nausea, and dizziness. NAC overdosing, in a short period of time, led to coagulopathy, reduced platelet count, acute renal failure and metabolic acidosis. After 24 h, the patient died. The Medical forensic examination showed minor lung hemorrhage and presence of little amount of Aluminum phosphide in tissues they did not find no vital organ hemorrhage. It is unclear related to NAC overdose, phosphine intoxication or synergic effects.

Conclusion: Massive transfusion of NAC was associated with impairment of coagulation factors, intracranial hypertension, renal failure and metabolic acidosis. Thus, NAC administration should be with caution. The medical history of patients committed suicide are not always accurate and complete evaluation are recommended.

1. Introduction

Acetaminophen (APAP), also known as paracetamol, is a popular analgesic. APAP overdose can often occur because it is a common medication [1]. The liver metabolizes APAP to a hepatotoxic metabolite, N-acetyl-p-benzoquinone imine (NAPBQI) [2].

N-Acetylcysteine (NAC) is a cost-effective antioxidant and proper treatment for the patient with fibrosis, chronic obstructive pulmonary disease, acetaminophen-induced hepatotoxicity [3] and several other conditions. NAC is a cysteine precursor that activates the cysteine-glutamate exchanger, stimulates glutathione biosynthesis, increases detoxification, and directly scavenges free radicals [4]. These properties make NAC a well-known

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antioxidant. In this case report, we present a rare case of iatrogenic NAC overdose following the mistake in calculating infused dose.

2. Case Report

A 14-year-old girl was referred to the local hospital 2 h after her suicidal attempt. She said that she intentionally ingested 7 g of acetaminophen. She had no history of hospitalizations, liver disease, seizures, drug or ethanol abuse, and psychiatric problem. Her body weight was about 50 kg. As the local hospital could not assess the acetaminophen serum level, the infusion of 6 g NAC over one hour was ordered. Each NAC ampoule in Iranian pharmacopeia contains 2 g/10 mL (200 mg).

3. Result

Because of a wrong assumption of 200 mg in each vial, about 42 g of NAC (21 vials) were infused into the patient. During the infusion, an NAC hypersensitivity reaction occurred because the patient showed drowsiness, nausea, vomiting, respiratory distress, and tachypnea. Thus the NAC infusion was discontinued, and she received chlorphenamine, hydrocortisone, and epinephrine. After 8 h of stay in the local hospital, she referred to the tertiary poisoning department (at 8 am) due to an NAC overdose. Her initial assessment in the poisoning ward was as follows: Glasgow Coma Scale=13, blood pressure: 90/50 mm Hg, heart rate: 130 beats/min, respiratory rare: 20 breaths/min, SpO2: 87%, temperature: 37.2°C, and blood sugar: 86 mg/dL. The electrocardiogram showed sinus tachycardia with normal QRS and corrected QT (QTc) intervals. The patient was monitored and received oxygen 6-8 L/min by a mask. The routine toxicology evaluation, including acetaminophen serum level and urine immunoassay screen tests, were negative. Table 1 summarized the lab test results.

The Venous Blood Gas (VBG) revealed metabolic acidosis with high base excess. Therefore, she was treated with sodium bicarbonate 7.5%, 100 mL as a loading dose, and an infusion of 150 mL every 8 h. A single dose of 2.5 mg oral tablet of vitamin K was given because of the increased International Normalized Ratio (INR) and Prothrombin Time (PT). She was admitted to the Intensive Care Unit (ICU) 5 h after her admission (1 pm). Her vital signs were normal till 5 pm, but her arterial blood gas measurements indicated an unknown source of metabolic acidosis. Her hemoglobin level and platelet counts decreased. She became hypotensive (70/40 mm), and her metabolic acidosis deteriorated. She was treated with 100 mL of sodium bicarbonate 7.5% and an infusion of norepinephrine (2-5 µg/kg/min). She developed tachypnea (RR=30), and her level of consciousness decreased to a GCS of 7/15; therefore, she was intubated at 8 pm. During her stay in the ICU, the patient became oliguric, with less than 100 mL of urine in 12 h. At 9 pm, her respiratory tract secretions significantly increased, and the bloody discharge was seen in the tracheal tube. Then her radial pulse became impalpable, and biochemistry assays showed increased blood urea nitrogen and creatinine. The vital signs during ICU admission are presented in Table 2.

At 10 pm, she became bradycardic, which lead to asystole, and then Cardiopulmonary Resuscitation (CPR) was immediately performed. After 10 minutes, spontaneous heartbeats were detected. Metabolic acidosis was seen again, and 100 mL sodium bicarbonate was infused. Thirty minutes later, at 11 pm, asystole was detected again, and 30 minutes of CPR was done successfully. Ten minutes later, she became asystole for the third time. Unfortunately, 45 minutes of standard CRP was unable to resuscitate her, and she died. The corpse was transferred to the Forensic Medical Organization for further evaluation. The organization reported minor pulmonary hemorrhage and no bleeding in other vital organs. Also, they found a small amount of Aluminum Phosphide (ALP) in the stomach contents.

4. Discussion

We reported a 14-year-old girl who received 42 g NAC instead of 6 g because of the total dose miscalculation. She received 21 vials, seven times more than the prescribed dose. In APAP overdose, NAC is loaded 150 mg/kg in 200 mL over 60 min followed by 50 mg/kg in 500 mL over 4 h and, 100 mg/kg in 1000 mL over the next 16 h [5]. NAC has been introduced as an antidote and treatment of APAP intoxication to prevent hepatotoxicity [6]. The most common reported NAC adverse effects in therapeutic doses are rash, pruritus, angioedema, bronchospasm, tachycardia, and hypotension [7-9]. The current case manifested drowsiness, nausea, vomiting, respiratory distress, and tachypnea during the NAC infusion. She developed metabolic acidosis, severe hypotension, and renal failure during her hospitalization. Also, her lab tests showed increased PT and INR and decreased platelet count.

There are some case reports about NAC overdose that all of them were secondary to miscalculation. Mahmoudi et al. [10] reported a case of NAC overdose (100 g) in a 23-year-old female following intentional ingestion of 16 g of acetaminophen. She was intubated due to a decreased level of consciousness, severe hypotension, and

Table 1. The lab test results of patient intoxicated by N Acetyl Cysteine referred to Imam Reza Hospital Toxicology Department.

Time	Local Clinic Lab Tests	After Admission			
Lab test (unite)		9 am	17 pm	21 pm	23 pm
White blood cells (×1,000)	-	30.8	34	-	44
Hemoglobin (mg/dL)	-	14	12.2	-	12
Platelets (×1,000)	-	144	114	-	120
Urea (mg/dl)	25	30	-	-	55
Creatinine (mg/dl)	0.70	1.4	-	-	3.4
Sodium (mEq/L)	139	144	-	145	-
Potassium (mEq/L)	3.5	3.4	-	4	-
Aspartate aminotransferase (U/L)	13	28	-	-	-
Alanine aminotransferase (U/L)	10	8	-	-	-
Alkaline phosphatase (U/L)	540	206	-	-	-
Lactate dehydrogenase (U/L)	-	668	-	-	-
Creatine phosphokinase (U/L)	-	642	-	-	-
prothrombin time (seconds)	-	22	-	18	-
international normalized ratio (INR)	-	2.68	-	2.05	-
partial thromboplastin time(seconds)	-	76	-	55	-
pH	-	7.18	7.25	7.06	-
PCO2(mmHg)	-	40	31	54	-
HCO3 (mEq/L)	-	14	13	15.4	-
O2 sat(%)	-	47.4	36.5	40.6	-
Pco2 (mmHg)	-	27.1	31.7	54.6	-
Base excess	-	-8.1	-6.7	-15.7	-

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Table 2. The vital sings of the patient intoxicated by N-Acetyl Cysteine

Time Parameter (unite)	13 pm	15 pm	17 pm	19 pm	21 pm	23 pm
Glasgow Coma Scale	13	13	12	9	8	6
Blood pressure (mmHg)	100/60	105/65	95/60	87/55	80/53	85/58
Respiratory rate (cycle / min)	24	25	30	32	32	35
Heart rate (beat/ min)	130	128	133	125	135	145
Spo2 (%)	92 %	93 %	92 %	89 %	86 %	84 %

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tachypnea. The error in calculating the prescribed dose leads to death in ICU 12 days later due to hemolysis, thrombocytopenia, renal failure, and metabolic acidosis. In another case, a 2.5 years old boy developed delirium and seizures that progressed to cerebral edema and ultimately, severe brain injury due to an iatrogenic overdose of NAC [11]. The impaired consciousness, reduced visual acuity, and repetitive intractable focal and generalized convulsions have been reported secondary to the NAC overdose after the infusion of 20 g instead of 2 g. The child was discharged in good condition after 3 days [12]. Our patient died just 2 days after admission, and it is unclear whether it was related to NAC overdose, phosphine intoxication, or synergic effects.

Although our patient showed some coagulopathy level (INR=2.6), the corps laparotomy did not find any vital organ hemorrhage or coagulopathy evidence. However, impairment of coagulation factors can be related to severe liver injures secondary to APAP toxicity; previous studies demonstrated NAC-induced coagulopathy. Intravenous NAC administration, 150 mg/kg, resulted in impaired blood clotting and attenuated platelet aggregation in patients undergoing repair of abdominal aortic aneurysm [13]. Wijeysundera et al. (2009) reported that the administration of NAC to patients who underwent cardiac surgery with moderate preoperative renal insufficiency induced more blood lost and increased the amount of blood product transfused [14]. In vitro study has shown that PT increases with increasing dose of NAC [15]. NAC infusion (10 mg/kg as a loading dose and 10 mg/kg/h as continuous doses for 32 h) could decrease the activity of coagulating factors, including VII, and IX without any effect on Activated Partial Thromboplastin time (APTT) [16]. Decreasing in plasma levels of other vitamin K dependent proteins participating in the coagulation cascade, such as factor IX, protein C and free protein S, were also reported as a consequence of NAC administration [16, 17]. NAC could reversibly reduce disulfide bonds required for maintenance coagulation factors structure and function [18]. Also, NAC reduces the activity of the vitamin K dependent proteins through denitrosylating [19].

Our patient became drowsy, and her cognition was impaired without any seizures. Animal studies and case reports suggested that NAC overdose causes increased internal cranial pressure leading to edema and seizure [12, 20].

ALP intoxication was reported as the main cause of her death by the Legal Medical Organization (LMO). They found the ALP in her tissues and pulmonary hemorrhage, similar to AIP intoxication [21]. ALP is a cheap and effective pesticide that, unfortunately, is used for suicide [22]. ALP inhibits cytochrome c oxidase (complex IV) [23]. The main complications of ALP intoxication are hypotension and metabolic acidosis [24, 25], as in our case. Disseminated Intravascular Coagulation (DIC), coagulopathy, and renal failure are not common in ALP toxicity [26] except in end stages and very severe cases. Our patient had evidence of coagulopathy, a renal failure that seems both are not related to ALP intoxication.

3. Conclusion

In conclusion, massive transfusion of NAC was associated with the impairment of coagulation factors, intracranial hypertension, renal failure, and metabolic acidosis. The additional doses of NAC should be administered with caution. The medical history of patients who committed suicide is not always accurate, and a complete evaluation is recommended.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. Also, Informed consent was obtained from the parents of the deceased child.

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Author's contributions

Conceptualization and Supervision: Mohammad Moshiri; Methodology: Leila Etemad; Investigation, Writing original draft, and Writing review & editing: All authors; Data collection: Seyed Hadi Mousavi, Seyed Mohsen Rezazadeh-Shojaie, Toktam Sadeghi, and Mohammad Moshiri; Funding acquisition and Resources: Mohammad Moshiri.

Conflict of interest

The authors declared no conflict of interests.

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