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Original Article

Atopic diseases: Risk factor in developing adverse reaction to intravenous N-Acetylcysteine

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ABSTRACT

Background: N-acetylcysteine (NAC) is the choice treatment for acetaminophen overdose. The main side effect of intravenous NAC therapy is anaphylaxis or anaphylactoid reactions. We investigated the prevalence of anaphylactoid or anaphylaxis reactions to IV-NAC therapy in acetaminophen poisoned patients with atopic disease.

Methods: A case series antrograde and descriptive–analytic study was done on acetaminophen poisoned patients who treated with IV-NAC from September 2003 to September 2004 in Isfahan, Iran.

Results: Of 173 infused IV-NAC patients, 77 patients (44.5%) developed an anaphylactoid reaction. Its side effects was nausea and vomiting (n=49, 63.15%), flashing (n=23, 30.26%), bronchospasm (n=20, 26.31%), vertigo (n=18, 23.68%), skin rash (n=25, 32.36%) and hypotension (n=12, 15.75%). Also, 71 patients (41%) had history of atopic disease. Atopic diseases were asthma (n=12, 6.9%), atopic dermatitis (n=7, 4%), allergic rhinitis (n=5, 2.8%) and allergic conjunctivitis (n=1, 0.5%). Among 71 atopic patients, 59 patients (83.13 %) developed side effects to NAC. There was a relation between previous history of atopic disease and anaphylactoid reaction to NAC.

Conclusions: We report substantially higher incidence of anaphylactoid reactions to IV-NAC than previous studies. Different atopic diseases must be considered as a risk factor in the development of side effects to IV-NAC-therapy.

Keywords: Poisoning, Acetaminophen, Anaphylactoid reaction, N-acetylcysteine, Atopic disease

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Acetaminophen poisoning is the forth cause of drug poisoning in poisoning emergency department of Noor hospital, Isfahan, Iran [1], and also accounting for 108,066 exposures and 156 deaths reported to the American association of poison control centers in 2000 [2].

Acetaminophen poisoning produces hepatotoxicity via toxic metabolite N-acetyl-p-benzoquinonimine. N-acetylcysteine (NAC) is recommended for treatment of acetaminophen poisoning and within 8 hours of acetaminophen ingestion, NAC therapy significantly reduces the risk of serious hepatotoxicity [4-6]. Intravenous NAC (20 to 21 hours infusion or a 48 hour protocol) [3, 8], was considered as a standard care for acetaminophen poisoning [5].

Most commonly adverse events associated with IV-NAC is an anaphylactoid reaction, including rash, wheezing, itching, and in some cases hypotension [4,9,10.12]. These reactions are dose related and therefore are most common with loading dose. Anaphylactoid reactions may be more common in patients with atopic diseases and less common in patients with high acetaminophen levels [11]. Atopic diseases include allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and allergic [extrinsic] asthma and some cases of urticaria and GI food reactions [13]. As in many other countries, we use NAC intravenously due to existing facilities & situations (unavailability of oral form of NAC, and limited beds for hospitalization).

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Therefore, we studied the prevalence of adverse reactions to IV-NAC in acetaminophen poisoned patients with history of atopic diseases.

Subjects and Methods

In a case series antrograde and descriptive–analytic study, 173 hospitalized acetaminophen poisoned patients who had ingested toxic doses (5 g or more) and had not used any other drug were evaluated from September 2003 to September 2004 and received IV-NAC.

After gastric lavage and administration of activated charcoal, IV-NAC was administered as 20 hours protocol: 150 mg/kg in 200 ml of DW 5% (loading dose), 50 mg/kg in 500 ml DW 5% in 4 hours (maintenance dose), and a later dose of 100 mg/kg in 1000ml DW 5% in 16 hours [6]. Then, anaphylactoid reaction (rash, wheezing, itching, nausea and vomiting, bronchspasm, dizziness, flashing and hypotension) were checked. In the case of allergy, NAC infusion was promptly ceased and appropriate treatment started as needed. Demographic factors and past history of atopic disease were checked for each patient. The history is more valuable than tests in determining whether a patient is allergic [13].

Then, atopic diseases were diagnosed via its symptoms, their relation to environment and to seasonal and situational variations, clinical course, and family history of similar problems [13]. The results were analyzed by SPSS software, using Chi- square test.

Results

Most patients were 15-30 years old (75.7%), and were women (60.12%). After administration of IV-NAC, 44.5% of patients have an adverse reaction which was more common in women (76.6%). All patients who showed adverse reactions received IV antihistamines and corticosteroids. Then, re- infusion of NAC with decreased rate was started without any complications. No patient needed ICU admission. The most frequent adverse reaction was nausea and vomiting (63.15%) (Table 1). Some patients had several signs and symptoms at a same time. Adverse reaction more frequently occurred in the first stage of NAC administration (63.15%). Table 2 shows frequency distribution of previous allergies in the patients. Among atopic patients, 83.33% showed adverse reactions to NAC, and 54.23% of patients without history of atopic disease showed adverse reactions to NAC (Table 3). X^2 test reveals this to be a significant difference (p- value < 0.05).

Table 1. Frequency distribution of IV-NAC hypersensitivity reactions

Reaction (sign or symptom)	Frequency (%)
Nausea& Vomiting	49 (63.15)
Flashing	23 (30.26)
Bronchospasm	20 (26.31)
Dizziness	18 (23.68)
Rash	17 (22.36)
Hypotention	12 (15.78)

Table 2. Frequency distribution of previous allergies in acetaminophen poisoned patients treated with NAC

Type of Atopic diseae	Frequency (%)
Asthma	12(6.9)
Atopic dermatitis	7 (4)
Allergic rhinitis	5 (2.8)
Allergic conjunctivitis	1 (0.5)

Table 3. Frequency distribution of hypersensitivity reactions to IV NAC according to allergy history

Reaction to IV-NAC	History of Atopic disease (%)	
	Yes	**No**
Yes	83.33	54.23
No	16.66	45.76

Discussion

Frequency distribution of allergy to IV-NAC was 44.5% which is much higher than of others (3-14%) [3,7,10]. This might be due to the type of purchased NAC from a certain company that must be investigated. Another important factor is infusion rate, as the hospitalized patients receive NAC via ordinary infusion set, which is apt to maladjustment of drops.

So IV NAC should be administered via infusion pump providing precise adjustment of drops. Finally, high prevalence of adverse reaction to NAC might be due to higher prevalence of atopic disease in the patients. There is a positive relation between history of atopic disease and adverse reaction to IV-NAC.

However, one study at 2000 concluded that previous drug allergy is not a risk factor [11]. They studied only previous drug allergy and asthma. But, we showed that allergy to NAC is associated to all kinds of atopic disease. In other similar studies, allergic and asthmatic patients are at risk for developing allergy in response to IV NAC administration [7, 10, 11].

The most frequent adverse reaction was nausea and vomiting in our study, and cutaneous reactions (rash, pruritus and flashing) in others [12]. Nausea and vomiting could not be due to acetaminophen poisoning, because it started after NAC administration, and stopped after NAC cessation or after using antihistamines and slow restart of NAC. Lack of anaphylactic shock and death probably implies lower risk of serious complications due to IV NAC administration.

In conclusion, atopic history (asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis) is supposed as a risk factor for the occurrence of adverse reactions to IV-NAC. We recommend case-control studies on pre-treatment with antihistamines in patients with history of atopic disease.

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