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Adverse Effects of Intravenous N-Acetylcysteine

Prospective Study on 206 Patients with Paracetamol Poisoning

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Paracetamol (acetaminophen) consumption is one of the most common causes of drug poisoning in the world.[1] In the US in 1998 and 1999, 203 930 cases of paracetamol overdose were reported to US poison centres, making it the leading pharmacological agent associated with toxicity.[2] Various kinds of drugs have been evaluated as a paracetamol antidote; the most important of them is N-acetylcysteine (NAC), which serves as an available precursor for glutathione synthesis, thus replenishing glutathione stores and preventing the reaction of N-acetyl-p-benzoquinoneimine (NAPQI) with hepatocytes.[1]

The optimal route, dose and duration of administration for NAC in the management of paracetamol poisoning is controversial. Different therapeutic programmes are implemented throughout the world. In England, Canada and Australia, NAC is administered in a continuous and non-interrupted manner in the form of intravenous infusion for a period of 20 hours. Currently, in the US, oral administration for 72 hours is the only US FDA-approved treatment for paracetamol poisoning. However, an ongoing clinical trial of intravenous NAC is currently being conducted in that country.[1]

Nausea and vomiting are among the most common early symptoms of paracetamol poisoning and may be exacerbated by oral administration of NAC because of its disagreeable taste and smell. However, either coingestants or syrup of ipecac may result in nausea and vomiting. In these conditions, in spite of treatment with antiemetic medications, nausea and vomiting may be persistent and intractable, precluding oral therapy. Also, in some cases, there may be a possibility of concurrent consumption of drugs with high mortality and morbidity risk, necessitating immediate decontamination of the gastrointestinal tract. As a result, these conditions would reduce the bioavailability of oral NAC, and in such cases intravenous administration of NAC is potentially life-saving.[1,3]

Furthermore, there are advantages of intravenous administration: firstly, to lessen the total dosage of the drug compared with oral regimens and, secondly, to shorten the hospital stay needed for receiving antidote therapy.[1,4]

Various anecdotal reports have claimed development of adverse events following intravenous NAC therapy that have restricted this form of usage.[5-10] In Iran, it is unclear whether the use of intravenous NAC is associated with a significant incidence of adverse events. We conducted this study to investigate the frequency of adverse effects of intravenous NAC therapy, to compare them with previous reports, and to assess the safety of intravenous NAC therapy. We included patients who were referred to our hospital as a result of an overdose of paracetamol, who were being treated with intravenous NAC.

Patients and Methods

This was a descriptive and prospective study, aimed at determining the frequency of adverse effects resulting from intravenous NAC in the management of paracetamol poisoning. It was conducted at Loghman-Hakim Hospital in Tehran, Iran, during a 1-year period (from 21 March 2001 to 21 March 2002). We included all adult patients who had a history of one toxic dose of paracetamol ingestion (defined as an intake of 7.5g or more[1]) reported by either the patient or the family, and presenting fewer than 12 hours after consumption. These patients were treated regardless of the serum levels of paracetamol.[11] Patients with concurrent intoxication (as a possible confounding factor), coma and hepatic encephalopathy (because of the underestimation of adverse reactions[12]) were excluded from the study. The diagnosis of acute consumption of other drugs or chemicals was based on information given by the patients or their families. Hepatic encephalopathy was defined as hepatic coma grade II or more.

Initial therapeutic measures including gastrointestinal decontamination with syrup of ipecac or gastric lavage[13] and other supportive measures were performed. We found no study in the published literature that reported that syrup of ipecac or gastric lavage had any significant influence on the occurrence of adverse effects associated with intravenous administration of NAC.

Treatment of these patients was carried out using a 20-hour therapeutic protocol,[1] where 150 mg/kg bodyweight of NAC in 200mL of glucose 5% over 15–20 minutes, 50 mg/kg in 500mL of glucose 5% during 4 hours, and 100 mg/kg in 1L during the next 16 hours were given intravenously. The administered NAC was of the commercial form, in preparations of 200 mg/mL per 10ml ampoule. Intravenous NAC was delivered without an infusion pump.

During the course of treatment, a single dose of activated charcoal was given to poisoned patients who presented to the hospital within 2 hours of intoxication.[14,15] We also measured the serum concentrations of aminotransferases to identify the occurrence of hepatotoxicity.[16]

A structured data collection form was submitted to all patients prospectively. This form included the patient's age and sex, medical history of asthma and allergy, cause of poisoning, serum concentrations of aminotransferases, type and time of onset of adverse effects, and administered medication for control of these effects. Patients with asthma were identified through history taking and physical examination, either by the resident physicians or by the study investigators.

Signs and symptoms were recorded every 5 minutes during infusion of the first dose of NAC, every hour during the second, and every 2 hours during the third dose of NAC. The observers were one of the study investigators and/or the resident physicians as well as nurses. Patients were discharged after a full course of NAC if liver and renal function tests were normal or improving, and after a psychiatric evaluation, if needed.

Statistical Analysis

To evaluate the association between age, sex, asthma, medical allergy and the development of adverse effects of intravenous NAC, the study population was divided into two groups: patients who developed adverse reactions and those who did not. A logistic regression analysis (based on the stepwise variable selection method) was carried out using SPSS Software version 8.0 (SPSS Inc., Chicago, Illinois, USA), with the adverse reactions as the dependent variable and age, sex, asthma and medical allergy as the independent variables. A probability value of less than 0.05 ($p < 0.05$) was considered to be significant.

The study was approved by the local ethics committee and was in accordance with the Declaration of Helsinki.

Results

Intravenous NAC was administered to 206 adults who had been referred to Loghman-Hakim Hospital in Tehran, Iran, during the research period. Of these, 126 (61.2%) were female and 80

Table I. Number of patients in whom adverse reactions occurred after receiving intravenous N-acetylcysteine (most patients experienced more than one reaction)

Type of reaction	No. of patients (n = 48)
Facial flushing	41
Pruritus	30
Dyspnoea	23
Rash	18
Coughing	13
Tachycardia	11
Wheezing	5
Bronchospasm	4
Hypotension	3
Angioedema	1

(38.8%) were male. The age range was 14–70 years (mean 21.4 years). The cause of poisoning in 99.51% of patients was attempted suicide. Adverse reactions to NAC were observed in 48 patients (23.3%) [table I]. The most common adverse reaction was facial flushing.

The time of occurrence of these reactions in 75% of cases (36 patients) was during infusion of the first NAC dose. In 20.8% of cases (10 patients) they occurred during the second dose (with an occurrence of 10.8% of the reactions [five patients] in the first 30 minutes of this infusion), and in 4.2% of cases (two patients) reactions occurred during the third dose. Of the 48 patients who developed these reactions, 22 became asymptomatic after reduction of the infusion rate or temporary discontinuation of the antidote.

Twenty-six poisoned individuals (54.2%) who developed reactions did not respond to temporary discontinuation of intravenous NAC administration, and were controlled by a single intravenous dose of hydrocortisone or antihistamine. The NAC infusion was restarted after administration of these medications and adverse effects did not recur when treatment was restarted.

Of the 48 patients who experienced adverse reactions, 2.9% were true asthmatic patients and 8.3% had a positive history of medical allergy to penicillin or cotrimoxazole. Five patients (2.42% of the 206 poisoned patients) developed a significant increase in serum transaminases (>1000 IU/L).

Age, sex, asthma and medical allergy were not observed to have a significant relationship with adverse effects (see Statistical Analysis section).

It was unnecessary to completely stop the intravenous NAC infusion in any of the symptomatic poisoned individuals. No patients developed any serious adverse effects requiring intensive care and there were no deaths.

Discussion

Various studies have suggested that the frequency of adverse effects from intravenous NAC is 0.2–20.8%.[5-10,12,17] However, the frequency of these reactions was found to be greater in the present study (23.3%). Adverse effects of intravenous NAC appear to be dose related.[5,6,18] One group estimated that when intravenous NAC was administered correctly the frequency of these reactions was 0.3–3%, whereas 11 of 15 patients who had received an overdose experienced an adverse reaction.[19] In our study, we did not use an automatic infusion pump and this probably resulted in inconsistent administration of intravenous NAC (i.e. accidental too rapid administration of the doses), which may have accounted for the high frequency of adverse events. Therefore, using an infusion pump might possibly reduce the rate of these adverse effects.

In addition, this high frequency may have been, to some extent, attributable to infrequent factors such as variability in drug response due to genetic factors in the Iranian population,[20,21] or hypersensitivity to paracetamol.[22-24]

Side effects of intravenous NAC are suspected of being caused by nonallergic release of histamine.[5] Furthermore, a strong association between low serum paracetamol levels at the time of treatment and the development of adverse reactions to intravenous NAC has been demonstrated, suggesting that a high paracetamol concentration may protect against the release of histamine.[12] In contrast to this, it has been stated that some of these adverse effects may have been due to paracetamol poison-

ing itself.[6] Determination of the plasma paracetamol levels was not performed in our study (which may be considered a weakness of the study). We have therefore been unable to confirm or refute these relationships; the observed low rate of hepatotoxicity (2.42%) would be expected to correspond with a high frequency of adverse effects.

The administration of NAC without reference to blood paracetamol levels is a novel feature of this study. This is a situation faced by many clinicians in developing countries with limited access to laboratory tests. However, in some centres patients who have ingested 150 mg/kg or more of paracetamol are treated regardless of plasma paracetamol levels.[11]

It has been stated that the risk of NAC adverse effects is associated with asthma.[12] In this study, there was no significant relationship between asthma, age, sex or medical allergy and the development of adverse effects.

Previous studies have shown that these reactions often occur during or shortly after the administration of the initial dose of intravenous NAC and usually respond to reducing the rate or temporary discontinuation of intravenous infusions.[6,7,18,25,26] In our study, these reactions most frequently occurred at the first dose of intravenous NAC therapy, and in 45.8% of these patients, slowing of the infusion rate or temporary discontinuation of intravenous NAC administration stopped the reactions. With respect to the occurrence of 10.8% of these reactions in the first 30 minutes of the second dose, it seems likely that this percentage relates to the initial loading dose, where a high dose is given over a short time (i.e. due to the dose-dependent effect of NAC). Therefore, to decrease its adverse effects, the initial loading dose could be given over 60 rather than 15 minutes.

One study evaluated the use of intravenous NAC in patients presenting early to hospital. It found that patients treated within 10 hours of paracetamol overdose were less likely to develop liver damage than untreated historical controls (1.6% vs 57.9%).[27] Furthermore, for intravenous NAC, the overall rate of hepatotoxicity was worse if treatment was delayed beyond 8–10 hours (1% in those treated within 8 hours versus 46% in those treated after 16 hours).[4,25] Therefore, the fact that we observed a 2.4% rate of hepatotoxicity can be explained by possible inaccurate patient histories related to the time from overdose to presentation at hospital.

Conclusion

On the basis of our findings in this study we concluded that the low rate of hepatotoxicity would be expected to correspond with a high frequency of adverse effects. Despite the high frequency of adverse effects, they were transient, not life-threatening, easily treated, and all patients received a complete course of intravenous NAC. Therefore, the treatment can be considered relatively safe in the management of paracetamol poisoning.

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