Background. Adverse effects to N-acetylcysteine (NAC) are well recognized, but their etiology and incidence are unclear. Methods. The nature and severity of adverse effects were prospectively studied in 169 patients and potential reaction mediators studied in 22 patients.

Results. Adverse effects were minimal in 101 (59.8%), moderate in 51 (30.2%), and severe in 17 (10.1%). Features were nausea (70.4%), vomiting (60.4%), flushing (24.9%), pruritus (20.1%), dyspnea (13.6%), chest pain (7.1%), dizziness (7.7%), fever (4.7%), wheeze and bronchospasm (7.1%), and rash and urticaria (3.6%). Serum acetaminophen concentration was lower in patients with severe adverse effects: median (IQR) 46 mg/L (0 to 101 mg/L), moderate 108 mg/L (54 to 178 mg/L), and minimal 119 mg/L (77 to 174 mg/L), p = 0.002. Family history of allergy and female gender were independent risk factors for adverse effects. Severity of adverse effects was associated with histamine release: AUC for change from baseline histamine was $-6$ ng/mL min ($-60$ to $11$ ng/mL min) in the minimal group, $26$ ng/mL min ($3$–$129$ ng/mL min) in the moderate group, and $49$ ng/mL min ($21$–$68$ ng/mL min) in the severe group ($p = 0.01$). There was no increase in tryptase and no differences between groups for NAC concentrations or hemostatic and inflammatory variables (factors II, VII, IX, X, vWF, tPA, IL6, and CRP).

Conclusion. Severity of adverse effects correlates with the extent of histamine release. Histamine release appears independent of tryptase suggesting a non-mast cell source. Acetaminophen is protective against adverse effects of NAC, and mechanisms by which acetaminophen might lessen histamine release require further attention.

Keywords Acetaminophen; Antidote; N-acetylcysteine; Adverse effects

Introduction

Acetaminophen is the main cause of fulminant hepatic failure in the United Kingdom and elsewhere (1). In overdose, acetaminophen is converted to a reactive metabolite (N-acetyl-p-benzo-quinone imine), which may cause hepatic necrosis. N-acetylcysteine (NAC) has long been used as an effective antidote in acetaminophen overdose. The current protocol in the United Kingdom involves a step-down intravenous infusion of 150 mg/kg in 200 mL 5% dextrose over 15 min, followed by 50 mg/kg in 500 mL 5% dextrose over 4 h, and 100 mg/kg in 1,000 mL 5% dextrose over 16 h (2). Since its introduction in 1979, there have been reports of anaphylactoid adverse reactions to this regimen with rates of occurrence variously estimated between 3 and 9% in retrospective studies and 40–50% in prospective studies (3–8). The full profile of adverse reactions reported includes rash, pruritus, flushing, nausea and vomiting, coughing, dyspnea, chest pain, bronchospasm, wheezing, angioedema, hypotension, hypertension, tachycardia, electrocardiograph abnormalities, and fever (3–9). Asthma is a risk factor for adverse effects of NAC (10,11), and death has been reported in a patient with asthma (12).

The mechanistic basis of adverse reactions to NAC remains unclear. NAC is capable of stimulating histamine release in vitro, and dose-dependent histamine-mediated weal and flare responses in susceptible individuals (13,14). Adverse reactions in healthy people after antidotal doses of NAC are associated with a rapid increase of circulating factor VIII and von Willebrand factor (vWF) concentrations (within 1 h of commencing infusion), thought due to inflammation of the vascular endothelium (15). In contrast to anaphylactoid reactions, acute allergy and anaphylactic shock have been intensively studied. The latter are associated with increased circulating concentrations of histamine and tryptase due to mast cell degranulation, and altered concentrations of vWF and tissue plasminogen activator (tPA) due to impaired endothelial function (16–18). Interleukin-6 (IL-6) is secreted by mast cells and basophils and may contribute to the inflammatory component of allergic reactions (19–21). IL-6 has a longer half-life (48 h) than either...
serum histamine and tryptase and has been suggested as a biomarker in the setting of anaphylactoid reactions (20).

The extent to which these mechanisms are relevant to patients with acetaminophen overdose is unknown. The present study prospectively examined the rate of occurrence of adverse effects of NAC, including clinical features and possible risk factors. In a subset of these patients, circulating markers of mast cell degranulation, inflammation, and endothelial function were examined to better understand the underlying mechanisms of adverse effects of NAC.

Methods

A prospective study included patients admitted to the Royal Infirmary of Edinburgh for NAC treatment after acetaminophen overdose between July 2006 and May 2007. The study protocol was approved by the local research ethics committee, and informed consent form was obtained from all patients. All patients who received NAC were carefully monitored for adverse effects. Patients were seen during their hospital stay, with case note review and telephone follow up of patients discharged from hospital over night, at weekends, or public holidays. Data collected were age, gender, quantity of acetaminophen ingested, date and time of ingestion, plasma acetaminophen concentration, alcohol history, history of allergy (atopy, asthma, drug allergy), family history of allergy, previous NAC treatment, history of adverse reactions to NAC, nature of any reaction to NAC in the current admission, together with treatments given and if it was necessary to interrupt the NAC infusion, and risk categorization based on chronic excess ethanol consumption, malnutrition, or prior use of enzyme-inducing medications (22).

Classification of adverse effects

The precise details of any reactions, including time of onset, additional treatment, or NAC discontinuation, were recorded. Predefined clinical categories were used: minimal if patients had no reaction or mild gastrointestinal symptoms only without any specific treatment; moderate if patients had gastrointestinal symptoms requiring temporary NAC infusion cessation, mild flushing, pruritus, mild chest pain, breathlessness, or peak expiratory flow rate (PEFR) 25–50% less than baseline (where available); severe if NAC was stopped due to severe flushing, respiratory distress, moderate to severe chest pain, >50% reduction in PEFR from baseline (where available), or hypotension (systolic blood pressure <90 mmHg or diastolic blood pressure <50 mmHg).

Intensive study protocol

A subset gave additional informed consent to participate in a more detailed study. There was a strict protocol for specimen sampling and handling, which forced recruitment of patients that presented only during office hours, and therefore, this subset represents a convenience group. Venous blood was collected from the non-infused forearm immediately prior to NAC and at 0.5, 1, 2, 4, and 20 h after commencing infusion for determination of NAC, tryptase, tPA, IL6, C-reactive protein, clotting factors II, V, VII, VIII, IX, X, XI, XII, and vWF, histamine (0, 0.5, 1, and 2 h only), and acetaminophen (0 and 4 h only). Samples were placed immediately into ice and separated within 30 min, then stored at −80°C prior to analyses. Blood pressure, temperature, oxygen saturation, and PEFR were recorded at the same time points.

Laboratory analyses

Plasma histamine was determined using an enzyme immunoassay (EIA, BioSource Europe S.A.), and the sensitivity of the assay was 0.1 ng/mL. NAC was determined by high-performance liquid chromatography with a fluorescence detector (Agilent 1200, Agilent Technologies, South Queensferry, UK) using an established method (23,24). Tryptase was determined using a fluoroenzyme immunoassay (UNICAP Tryptase; Pharmacia Diagnostics, Freiburg, Germany), which detects both α- and β-tryptase. Plasma tPA antigen, clotting factors and vWF antigen, and IL-6 were determined using enzyme-linked immunosorbent assays (tPA Combi Actibind, Technoclone, Vienna, Austria; Dako, Glostrup, Denmark; Quantikin Human IL-6, R&D Systems, Minneapolis, MN, USA). Serum C-reactive protein was determined using an immunoturbidimetric technique and acetaminophen concentrations determined using an automated enzymatic dry slide method (Vitros system, Ortho Clinical Diagnostics, UK).

Statistical analyses

Analysis in the total cohort focused on the pattern of adverse effects and potential risk factors. In the more intensive study, the relationship between adverse reaction severity and the changes in the various biological markers were examined. Data are presented as mean and 95% confidence intervals or median and inter-quartile range and, where appropriate, comparisons between groups were made using Mann–Whitney tests. AUC analyses of the change from baseline histamine concentration was undertaken between 0 and 120 min, and a simple linear imputation method was used to minimize the potential effects of missing data on AUC analyses. Kruskal–Wallis H test was used for multiple group comparisons of continuous data, a chi-square test used to compare categorical data. Univariate analyses were performed using Spearman’s rank correlation, and possible risk factors were examined using binary logistic regression (step-wise backward) with exclusion of factors if p > 0.1.

Results

There were 193 patients that required NAC administration after acetaminophen overdose. Data were not available in 24
cases because the patients had absconded from the ward or were discharged against medical advice and could not be interviewed. Therefore, the study population consisted of 169 patients (71 men, 42.0%) with mean (95% confidence interval) age of 37 years (35–39 years). Reported adverse effects were nausea (70.4%), vomiting (60.4%), flushing (24.9%), pruritus (20.1%), dyspnoea (13.6%), chest pain (7.1%), dizziness (7.7%), fever (4.7%), wheezing and bronchospasm (7.1%), and rash and urticaria (3.6%). None of the patients developed hypotension. Severity was minimal in 101 (59.8%), moderate in 51 (30.2%), and severe in 17 (10.1%), whereas there were no adverse effects in 39 patients (Fig. 1 and Table 1). NAC infusion was stopped temporarily due to adverse effects in 18 patients.

Serum acetaminophen concentration was lower in patients with severe adverse effects: median (IQR) 46 mg/L (0–101 mg/L), moderate 108 mg/L (54–178 mg/L), minimal 119 mg/L (77–174 mg/L), p = 0.002 by three-way comparison. Concentrations were undetectable in four patients; two had taken a staggered overdose, and two had presented late (at 21 h and at 48 h after ingestion). Logistic stepwise backward regression analyses of possible risk factors for moderate to severe adverse effects are presented in Table 2. This found that moderate to severe adverse effects were correlated inversely with serum acetaminophen concentration, odds ratio 0.99 (95% confidence interval 0.99–1.00) and male gender, odds ratio 0.45 (95% confidence interval 0.22–0.92), and correlated positively with a family history of allergy, odds ratio 2.89 (95% confidence interval 1.39–5.99). No significant correlations were found with age, gender, history of asthma, or previous drug allergy (Table 2).

The intensive study recruited 22 patients (11 men, 50.0%), with mean (95% confidence interval) age 35 years (21 to 45 years). All patients completed the first 2 h of the study; histamine data were missing at the 30 min time point in one patient. Only 18 completed the first 4 h, and 16 the full study because some did not require a full course of NAC treatment, self-discharged, or withdrew from the study. Severity of adverse effects was minimal in 10 (45%), moderate in 5 (23%), and severe in 7 (32%). There was no significant difference in age, gender, blood pressure, or pulse rate between groups. Onset of adverse effects was between 15 and 60 min after commencing infusion in most patients. In this subset, serum acetaminophen concentrations were lower in patients...

**Table 1.** Occurrence of adverse reactions to intravenous N-acetylcysteine (NAC) in patients with acetaminophen overdose (n = 169)

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>119 (70.4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>102 (60.4%)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>8 (4.7%)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>42 (24.9%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>34 (20.1%)</td>
</tr>
<tr>
<td>Rash and urticaria</td>
<td>6 (3.6%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>23 (13.6%)</td>
</tr>
<tr>
<td>Wheeze and bronchospasm</td>
<td>12 (7.1%)</td>
</tr>
<tr>
<td>Coughing</td>
<td>4 (2.4%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>13 (7.7%)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>12 (7.1%)</td>
</tr>
<tr>
<td>Fever (temperature ≥38°C)</td>
<td>8 (4.7%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

**Table 2.** Stepwise backward logistic regression for possible variables associated with moderate to severe adverse effects of N-acetylcysteine (NAC)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wald statistic</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>5.82</td>
<td>0.40 (0.19 to 0.84)</td>
<td>0.016</td>
</tr>
<tr>
<td>Age (years)</td>
<td>2.67</td>
<td>0.98 (0.95 to 1.00)</td>
<td>0.102</td>
</tr>
<tr>
<td>Acetaminophen (mg/L)</td>
<td>3.47</td>
<td>1.00 (0.99 to 1.00)</td>
<td>0.062</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.03</td>
<td>1.09 (0.42 to 2.83)</td>
<td>0.867</td>
</tr>
<tr>
<td>Drug allergy</td>
<td>1.64</td>
<td>1.82 (0.73 to 4.52)</td>
<td>0.200</td>
</tr>
<tr>
<td>Family history of allergy</td>
<td>4.78</td>
<td>2.36 (1.09 to 5.08)</td>
<td>0.029</td>
</tr>
<tr>
<td>Constant</td>
<td>4.59</td>
<td>6.02</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Univariate analyses:

- Male gender: 5.82, Odds ratio 0.40 (0.19 to 0.84), p-value 0.016
- Age (years): 2.67, Odds ratio 0.98 (0.95 to 1.00), p-value 0.102
- Acetaminophen (mg/L): 3.47, Odds ratio 1.00 (0.99 to 1.00), p-value 0.062
- Asthma: 0.03, Odds ratio 1.09 (0.42 to 2.83), p-value 0.867
- Drug allergy: 1.64, Odds ratio 1.82 (0.73 to 4.52), p-value 0.200
- Family history of allergy: 4.78, Odds ratio 2.36 (1.09 to 5.08), p-value 0.029
- Constant: 4.59, Odds ratio 6.02, p-value 0.032

Logistic stepwise regression analysis:

- Male gender: 4.80, Odds ratio 0.45 (0.22 to 0.92), p-value 0.028
- Acetaminophen: 4.11, Odds ratio 0.99 (0.99 to 1.00), p-value 0.043
- Family history of allergy: 8.14, Odds ratio 2.89 (1.39 to 5.99), p-value 0.004
- Constant: 2.11, Odds ratio 2.452, p-value 0.147

*aChange in risk related to each year of life and each mg/L increase in acetaminophen concentration, other variables are treated as categorical data.

![Fig. 1. Diagrammatic representation of adverse effect profiles in patients treated with acetylcysteine for acetaminophen poisoning, categorized by adverse effect severity: minimal–moderate–severe (n = 169, including 39 patients with no adverse effects).](image-url)
with severe rather than minimal adverse effects: 0 mg/L (0 to 41 mg/L) versus 138 mg/L (60 to 230 mg/L) (p = 0.02). The highest NAC concentrations were recorded at 30 min after commencing the infusion, and there were no differences between the groups (Fig. 2).

Plasma histamine concentrations were similar between groups at baseline but increased 2.5-fold in patients with moderate and severe adverse effects to peak concentrations at around 30–60 min. Maximum histamine concentrations in the minimal severity group were 0.83 ng/mL (0.69–0.98 ng/mL), moderate severity group were 1.38 ng/mL (0.96–2.54 ng/mL), and severe group were 1.53 ng/mL (1.38–1.81 ng/mL) (p = 0.003 by three-way comparison). Histamine concentrations expressed as the AUC for change from baseline also showed differences between the groups: minimal –6 ng/mL min (−60 to 11 ng/mL min), moderate 26 ng/mL min (3–129 ng/mL min), and severe 49 ng/mL min (21–68 ng/mL min) (p = 0.01, Fig. 3). There were no significant differences in plasma tryptase, CRP, IL-6, or t-PA concentrations between groups.

Clotting factors II, VII, IX, and X decreased within 4 h of commencing NAC infusion; maximum derangement in factors II, IX, and X occurred at 1 h and factor VII at 4 h (Fig. 4). However, there was no association between any clotting factors or vWF concentrations and severity of adverse effects. Significant correlations were noted between plasma factor VIII and vWF concentrations at baseline (r = 0.4, p = 0.05, n = 22), 1 h (r = 0.6, p = 0.01, n = 18), and 2 h (r = 0.6, p = 0.006, n = 21).

Discussion

This study found that moderate and severe adverse reactions to NAC occurred in 40.2% (severe in 10.1%), which is broadly in keeping with existing reports (3–50%) (5–8). Discrepancies between existing reports are likely due to different case definitions, retrospective versus prospective data collection, and different study populations. Predisposing factors for anaphylactoid reactions to NAC are a history of atopy and asthma (3,10), drug allergy (11), and low plasma acetaminophen concentrations (5,7,8,11). This study identified family history of allergy and low acetaminophen concentrations as important but had insufficient power to address other factors adequately.

Systemic histamine concentrations were significantly higher in patients with moderate or severe adverse effects of NAC. Existing data show that intradermal NAC provokes a dose-dependent weal and flare response that is suppressed by pretreatment with a specific histamine-1 receptor antagonist (14). Taken together, the present findings strongly implicate histamine as a systemic mediator of adverse effects of NAC administration. Importantly, the occurrence of severe adverse effects cannot be explained by differences in NAC concentration alone because this was similar in the three groups. True anaphylaxis is associated with elevated histamine and tryptase concentrations, which correlate with clinical severity (17). Mast cell degranulation causes elevated histamine and tryptase concentrations that are detectable within 1–2 h, and tryptase has been suggested as a diagnostic test for anaphylaxis (25,26). In contrast, this study found that although histamine concentrations increased in patients with severe adverse effects, there was a lack of effect on tryptase concentrations.
Therefore, non-mast cell sources of histamine might be important. For example, NAC is capable of provoking dose-dependent release of histamine from basophils and neutrophils (13,27). The authors propose that NAC-associated basophil degranulation might be important because this is not normally accompanied by significant tryptase release (28).

True anaphylaxis is associated with endothelial impairment and activation of the coagulation and fibrinolytic systems, including increased vWF and t-PA concentrations (18,29,30). Anaphylactoid reactions to therapeutic doses of NAC are accompanied by increasing factor VIII and vWF concentrations in healthy people (15). This study found that NAC administration led to a decrease of vitamin K-dependent clotting factors (II, VII, IX, and X), and there was a correlation between factor VIII and vWF, as noted elsewhere (15,30). However, there were no significant differences in any hemostatic variable between patient groups, suggesting that these do not contribute to adverse effects of NAC or to histamine release.

An inverse correlation was found between serum acetaminophen concentrations and severity of adverse effects, as reported elsewhere (5,7,8,11). A high incidence of adverse reactions to NAC (50%) in healthy people not receiving acetaminophen is further evidence that acetaminophen itself may have some protective effect against adverse effects of NAC (15).

NAC interferes with prostaglandin synthesis, resulting in increased PGF2 alpha and reduced PGE, thereby promoting bronchoconstriction (27). Supra-therapeutic concentrations of acetaminophen inhibit leukocytes and platelets via reversible cyclo-oxygenase inhibition and reduce prostaglandin and thromboxane synthesis (31,32). Therefore, acetaminophen might minimize the severity of NAC adverse effects by inhibiting the inflammatory cascade, as previously suggested (8). More studies are required to better understand the effect of acetaminophen in preventing adverse effects of NAC.

A limitation is that the adverse effects cannot be attributed solely to NAC, and effects of ingested acetaminophen, co-ingested drugs, and ethanol might have contributed. A further limitation is that the classification tended to segregate patients with anaphylactoid reactions into the moderate and severe groups, whereas the minimal group mainly consisted of patients with gastrointestinal symptoms; these distinct clinical phenotypes might have separate underlying mechanisms. A further limitation is that the sample collection, storage, and processing might have had an impact on assay performance, thereby limiting the ability to interpret a lack of effect of NAC. This does not appear relevant to the clotting factor assays, which were sufficiently sensitive to detect a fall in factor II, VII, IX, and X concentrations.

NAC-induced histamine release in acetaminophen overdose occurs in the absence of release of other markers of mast cell degranulation or endothelial dysfunction. The broad range of adverse effect profiles illustrate the variability in inter-individual susceptibility to the adverse effects of NAC. The reasons for this variability also require to be understood to minimize the incidence of adverse reactions to NAC. The rates of nausea and vomiting we have observed are high, and this raises the issue of whether routine anti-emetic prophylaxis with an antihistamine would be effective and if histamine release is involved in their causation. There appear to be other individual factors that underlie the risk of having an adverse effect to NAC, and family history of allergy suggests that genetic factors may be relevant here. Whether reducing the initial bolus dose of NAC would reduce the incidence of adverse effects without impairing efficacy is another key question.

**Conclusion**

Anaphylactoid reactions to NAC are common after acetaminophen overdose. Low acetaminophen concentration is a risk factor for developing adverse reactions, and clinical severity is associated with the extent of systemic histamine release. Future studies need to address the mechanisms by which NAC is capable of stimulating histamine release, and mechanisms by which acetaminophen itself is capable of altering this process.

**Acknowledgment**

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**References**