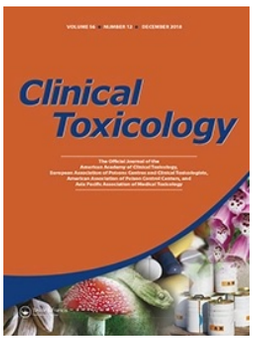

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CLINICAL RESEARCH

Two-bag intravenous N-acetylcysteine, antihistamine pretreatment and high plasma paracetamol levels are associated with a lower incidence of anaphylactoid reactions to N-acetylcysteine

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ABSTRACT

Context: *N*-acetylcysteine (NAC) is used worldwide to prevent liver injury after paracetamol overdoses. Anaphylactoid reactions to NAC occur frequently and often lead to treatment interruptions or discontinuations. In Denmark in 2013, the NAC treatment regimen was simplified from a three-bag to a two-bag NAC regimen. Factors of importance for the development of anaphylactoid reaction to this new regimen are poorly explored. Previous studies have suggested a protective effect of high plasma levels of paracetamol on the development of anaphylactoid reactions. Likewise, exposure to antihistamines prior to NAC treatment may protect against these reactions.

Methods: This is a retrospective cohort study of patients treated with NAC and with at least one plasma paracetamol sample performed in the Capital Region of Denmark from 2010 to 2017. The primary outcome was the incidence of anaphylactoid reactions to NAC requiring intravenous treatment with antihistamines and/or glucocorticoids. Logistic regression analyses were carried out to identify the risk of developing an anaphylactoid reaction to NAC affected by influencing factors.

Results: Of 4315 admissions included in the study, 259 (6.0%) developed an anaphylactoid reaction to NAC. The two-bag regimen (adjusted OR 0.44 [95%CI: 0.32–0.60]), increasing age (adjusted OR 0.84 [95%CI: 0.78–0.90] per 10-year increase) or children <10 years (adjusted OR 0.14 [95%CI: 0.04–0.36]) and antihistamine co-ingestion in overdose (adjusted OR 0.17 [95%CI: 0.02–0.64]) were associated with significantly fewer anaphylactoid reactions. High plasma paracetamol concentrations protected against development of anaphylactoid reactions during the two-bag regimen (adjusted OR 0.59 [95%CI: 0.47–0.71] and three-bag regimen 0.82 [95%CI: 0.72–0.94] per doubling of paracetamol concentration). The effect differed between the two regimens ($p = .004$ for interaction).

Conclusion: In this retrospective cohort, a high peak plasma paracetamol concentration, age, antihistamine co-ingestion and use of the two-bag NAC regimen were associated with fewer anaphylactoid reactions to NAC.

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Introduction

Paracetamol is a widely used analgesic drug due to its perceived efficacy and safety at therapeutic doses. However, in overdose, paracetamol has an unwanted safety profile making it the leading cause of fulminant hepatic failure in the Western world [1]. *N*-acetylcysteine (NAC) is the antidote of choice for paracetamol poisoning due to its efficacy in preventing hepatotoxicity and its relatively safe profile regarding adverse drug reactions [2,3].

The intravenous NAC regimen was proposed nearly 40 years ago in Edinburgh by Prescott and colleagues and involved three different infusions intended to deliver half the total dose of NAC (a bolus of 150 mg/kg) over no more than 15 min. The remaining two parts of the dose consisted of a continuous infusion of 50 mg/kg over 4 h followed by a continuous infusion of 100 mg/kg over 16 h [4]. In Denmark, it was recommended that an additional infusion of 100 mg/kg over 16 h were given for a total duration of 36 h until the guideline was changed in 2013 [5].

The complexity of the Prescott regimen resulted in a high rate of medication errors [6], which were potentially lethal [7]. In addition, the treatment was often delayed due to a high rate of anaphylactoid reactions occurring mostly in relation to the initial infusion because of the high peak NAC concentration [8,9]. Thus, slowing the initial infusion rate is associated with a significantly reduced frequency of anaphylactoid reactions. The interest in reducing the anaphylactoid reactions, the medication errors, the duration and complexity of the treatment has recently led to various modifications of the original Prescott regimen replacing it with more

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Supplemental data for this article can be accessed here.

simplistic two-bag regimens in Australia [10,11] and Denmark [12]. Even shorter regimens have been introduced, e.g., the 12-h SNAP protocol in the UK [13,14] and NACSTOP protocol in Australia [15]. In Denmark, the current guideline is based on a two-bag regimen with an initial 4 h infusion of 200 mg/kg followed by an infusion of 100 mg/kg over 16 h [12]. The regimen has been used as the standard regimen since 2013 with the intention of reducing the rate of anaphylactoid reactions and shortening the duration of NAC treatment. The latter is important since all patients in Denmark with suspected paracetamol overdose are treated with NAC regardless of plasma paracetamol concentration [5].

The incidence and severity of the anaphylactoid reactions to NAC are related to a dose-dependent histamine release [16,17]. Thus, theoretically pretreatment with antihistamines may be used to prevent the anaphylactoid reactions. Further, high concentrations of paracetamol have been associated with a reduced frequency of anaphylactoid reactions [5,11,17,18]. This was recently supported by a large retrospective study of patients treated with the three-bag regimen [19]. However, there is inconsistent evidence and still some doubt to which degree higher paracetamol concentrations and antihistamine pretreatment protect against anaphylactoid reactions to NAC when delivered by the two-bag regimen. The aim of this study was to examine whether antihistamine pretreatment, the two-bag regimen or high plasma paracetamol concentrations were associated with fewer anaphylactoid reactions to NAC.

Materials and methods

Study design, population and setting

This was a retrospective cohort study of patients treated with NAC and at least one hospital laboratory measurement of plasma paracetamol concentration in the Capital Region of Denmark in the period 2010–2017. The study is reported according to the STROBE statement [20]. The population of the Capital Region of Denmark is ~1.7 million. In Denmark, all residents with paracetamol poisoning are admitted to hospitals in their local region. The only tertiary center for liver transplantation is located in the Capital Region and accepts patients with severe liver failure from the other regions of Denmark as well.

Data collection and outcome

Information about prescribed drugs was obtained from The Electronic Patient Medication (EPM) module which is a database for in-hospital drug-use in the Capital Region of Denmark [21]. Age, gender, year of hospitalization, duration of stay and prior diagnostic codes were obtained from a regional version of The Danish National Patient Register via the Danish unique personal identification number given to all Danish residents at birth or upon immigration [22]. The Charlson Comorbidity index was calculated from prior diagnoses [23]. Measurements of plasma paracetamol were collected from the Clinical Laboratory Information System using the personalized identification number [24]. Anaphylactoid reaction was defined as a reaction requiring treatment with intravenous antihistamine (clemastine) and/or glucocorticoids (methylprednisolone or hydrocortisone) during treatment with NAC. A full-text search of the medical charts was performed to identify cases where treatment with intravenous antihistamines or glucocorticoids were not documented in the EPM by searching for the brand names and generic names including spelling variations of the drugs in the medical charts. Afterwards, the medical charts of all cases identified in EPM and in the full-text search were reviewed to access if the treatment was given prior to initiation of NAC and to register the type and severity of anaphylactoid reaction to NAC and time from initiation of NAC to start of the anaphylactoid reaction. Exposure to an antihistamine, defined as drugs known to antagonize the H1-histamine receptor, either as a co-ingestant or used daily prior to admission was defined as one of the following drugs/therapeutic groups in the Anatomical Therapeutic Chemical (ATC) classification system: N05BB01 (hydroxyzine), N05AA02 (levomepromazine), N05AF01 (flupentixol), N05AF03 (chlorprothixene), N05AF05 (zuclopenthixol), N05AH (loxapine, clozapine, olanzapine, quetiapine, clotiapine) N06AA (nonselective monoamine reuptake inhibitors), N06AX03 (mianserin), N06AX11 (mirtazapine) and R06A (antihistamines for systemic use). Additional data on co-ingestion were obtained from the Danish Poison Information Centre (DPIC) from the subset of patients with a contact to DPIC during or before the admission. The NAC treatment regimen was defined from the admission date (two-bag regimen after May 1, 2013, three-bag regimen prior to this date) based on the length of stay in the study period (Supplementary Figure S1).

Ethics

The study was approved by the Danish Patient Safety Authority (No. 3-3013-1884/1/) and the Danish Data Protection Agency (No. BFH-2016-058).

Statistical analysis

Data are reported as median and interquartile range or count and percentages with 95% CI. Continuous data were compared using nonparametric Mann–Whitney or Kruskal–Wallis test and categorical data with the Pearson's $\Χ^2$ or Fisher's exact test respectively, when comparing 2 or more unpaired groups. Due to complete separation in the dataset, univariate and multiple Firth's bias-reduced penalized logistic regression analyses were used to predict the influencing factors that will affect the risk of developing an anaphylactoid reaction to NAC [25]. Stepwise multiple regression analyses were performed to identify variables associated with anaphylactoid reactions which was used in the adjusted analysis. As a sensitivity analysis, the regression analysis was repeated with two different dates for the implementation of the two-bag regimen (January 1, 2013 and December 31, 2013).

All available data were used for analyses performed with R version 3.5.1 [26]. The null-hypothesis was rejected if two-tailed p value $\leq$.05.

Results

In total, we identified 3,570 patients with 4,315 admissions where NAC was administered and with at least one plasma paracetamol sample (Figure 1, Table 1). Of these, 544 were also present in the DPIC database. In 205 cases, clemastine or methylprednisolone or hydrocortisone was administered according to the EPM. The full-text search identified an additional 124 cases. The medical charts were reviewed leaving 259 (6.0%) patients, who developed an anaphylactoid reaction (Figure 1). Most anaphylactoid cases (73%) had cutaneous involvement (Table 2).

There were 151 admissions (3.5%) of children (<10 years old). Three (2.0%) of those developed an anaphylactoid reaction to NAC. There were 680 admissions (16%) with adolescents (10–18 years old). Sixty (8.8%) of those developed an anaphylactoid reaction to NAC. The risk of developing an anaphylactoid reaction declined with increasing age (Figure 2(A)). Anaphylactoid reactions were less common in cases treated with the two-bag regimen (4.0%) compared to the three-bag regimen (10.4%).

Pretreatment with clemastine was administered in 40 cases mainly due to previous anaphylactoid reactions to NAC. In these pretreated patients, one developed a minor anaphylactoid reaction that was managed by temporary cessation of the NAC infusion and one developed an anaphylactoid reaction requiring intravenous clemastine 5 h after initiation of the NAC infusion. Quetiapine was both the most common medication with antihistamine activity ingested in overdose ($n = 36$) and most common medication with antihistamine activity used daily prior to admission ($n = 329$).

A total of 2104 (48.8%) patients had a plasma paracetamol below the lower limit of quantification (<130 μmol/L) (Figure 3 and Table 1), and of these 148 (7.0%) developed anaphylactoid reactions. We found a significant negative correlation ($p < .0001$) between highest measured plasma paracetamol and the development of anaphylactoid reactions. The association was most pronounced in patients treated with the two-bag regimen (Figure 2(B)). Univariate and multiple logistic regression analyses identified plasma paracetamol, two-bag regimen (vs three-bag regimen), age and co-ingestion of medication with antihistamine activity as factors significantly associated with a reduced risk of developing anaphylactoid reactions (Table 3). The effect of higher plasma paracetamol levels differed between the two-bag and three-bag regimen (adjusted OR 0.59 [95%CI: 0.47, 0.71]

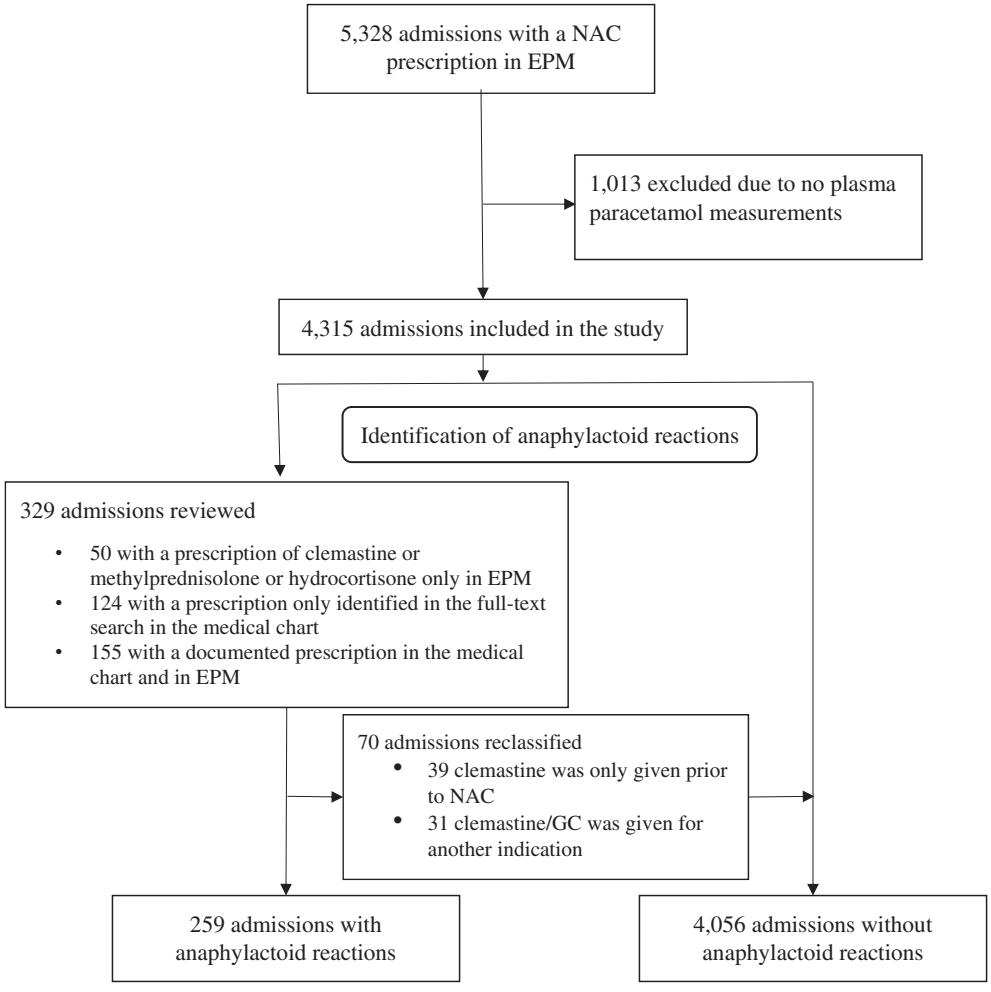

Figure 1. Study flow diagram.

Table 1. Demographics and outcomes grouped by anaphylactoid vs non-anaphylactoid reactions.

	Anaphylactoid, 259 (6.0%)	Nonanaphylactoid, 4056 (94%)	All, 4315	*p* value
Female gender, *n* (%)	199 (6.4%)	2895 (94%)	3094 (72%)	.064
Age, years	25 (18–41)	30 (19–52)	29 (19–51)	.0005
Paracetamol concentration, µmol/L	130 (130–397)	151 (130–610)	145 (130–600)	<0.0001
Paracetamol concentration BLLQ, *n* (%)	148 (7.0%)	1956 (93%)	2104 (49%)	.006
NAC-regimen[a]				
Two-bag, *n* (%)	117 (4.0%)	2834 (96%)	2951 (68%)	
Three-bag, *n* (%)	142 (10.4%)	1222 (90%)	1364 (32%)	<.0001
Antihistamine overdose, *n* (%)	1 (0.9%)	108 (99%)	109 (2.5%)	.021
Daily use of antihistamines, *n* (%)	29 (3.8%)	735 (96%)	764 (18%)	.004
Length of stay, hours	41 (27-53)	34 (24–73)	34 (24–50)	.030
Charlson Comorbidity index	0 (0–0)	0 (0–1)	0 (0–1)	.017

BLLQ: below the lower limit of quantification (<130 µmol/L).
[a]All treatments prior to May 1, 2013 was defined as following the three-bag regimen.
Data are reported as median and interquartile range or count and percentages.

Table 2. Description of anaphylactoid reactions.

Characteristic	Two-bag, *n* (%) *N* = 117 out of 2951 (4.0%)	Three-bag, *n* (%) *N* = 142 out of 1364 (10.4%)
Type of reaction:		
Cutaneous	85 (72.6%)	105 (73.9%)
Respiratory symptoms	10 (8.5%)	20 (14.1%)
Cardiovascular (e.g., hypotension)	2 (1.7%)	3 (2.1%)
Gastrointestinal symptoms	7 (5.9%)	7 (4.9%)
Severe[a]	4 (3.4%)	8 (5.6%)
Unspecified/Other	21 (17.9%)	31 (21.8%)
Time from start of NAC to reaction:		
<1 h	28 (23.9%)	92 (64.8%)
1–4 h	54 (46.2%)	44 (31.0%)
4–8 h	26 (22.2%)	3 (2.1%)
>8 h	8 (6.8%)	3 (2.1%)
Unspecified/Other	1 (0.9%)	
Medications administered:		
Clemastine	114 (97.4%)	140 (98.6%)
Methylprednisolone or hydrocortisone	86 (73.5%)	120 (84.5%)
Β$_2$-agonists inhalation	4 (3.4%)	5 (3.5%)
Adrenaline inhalation	0 (0%)	4 (2.8%)

Data are reported as count and percentages.
[a]Severe reactions were defined as life-threatening reactions (severe hypotension or angioedema threatening the airway) not controlled with only clemastine/glucocorticoids.

vs 0.82 [95%CI: 0.72, 0.94] per doubling of paracetamol concentration, $p = .004$ for interaction). Hence, the analysis confirmed the interaction between the NAC treatment regimen and the effect of the peak plasma paracetamol concentration in predicting the risk of developing an anaphylactoid reaction. The sensitivity analysis did not reveal any significant effect of changing the implementation date of the two-bag NAC regimen to the beginning or end of 2013 (Supplementary Tables S1 and S2).

Discussion

In this study, we identified several factors associated with a lower risk for anaphylactoid reactions to NAC treatment: A high peak plasma paracetamol concentration, age, antihistamine co-ingestion and use of the most recent two-bag NAC regimen. In addition, we found that the association between plasma paracetamol and anaphylactoid reactions was more pronounced with the two-bag regimen.

Previous studies, including one randomized controlled trial, have found a lower incidence of anaphylactoid reactions in patients receiving a two-bag regimen compared to the three-bag regimen. The studies are summarized in Figure 4 [10–12,14,27]. The reported event rates of anaphylactoid reaction with the two-bag regimen (ranging from 2% to 4.6%) were lower than with the three-bag regimen (ranging from 10% to 31%). The overall OR for the studies are 0.24 [95%CI: 0.16, 0.36] but with significant heterogenicity (I^2 70%). This was primarily due to a more pronounced reduction in anaphylactoid reaction with the two-bag regimen in two studies from UK compared to two Australian and two Danish studies. This can partly be explained by the lower plasma paracetamol concentrations in Denmark as the Matthew–Rumack nomogram is not used which leads to more patients treated with low or undetectable plasma paracetamol concentrations. As high paracetamol concentration is required to protect against anaphylactoid reactions with the three-bag regimen, which is rarely encountered. Consequently, the incidence of anaphylactoid reactions would be expected to be comparable in the UK and Denmark with the three-bag regimen. However, with the two-bag regimen, the protective effect of paracetamol occurs at a concentration close to the treatment threshold on the nomogram (Figure 2(B)). Most treated patients in the UK have concentration of paracetamol at levels expected to protect against anaphylactoid reactions, while half of patients treated in this study have undetectable levels of paracetamol. Hence the rate of anaphylactoid reactions is higher and the advantage of the two-bag regimen is less evident. However, this does not explain the higher rate observed in Australia compared to the UK as the treatment threshold is higher in Australia compared to the UK.

None of the studies have so far shown any apparent difference in development of hepatotoxicity, deaths and/or liver transplants between various NAC-regimens. Isbister et al. [28] and Pauley et al. [29] also reported a reduced incidence of anaphylactoid reactions compared to prior published data in a prospective and retrospective study, respectively.

Few studies have investigated the effect of plasma paracetamol on the risk of developing anaphylactoid reactions with the two-bag regimen [10–12,28]. Only one of four studies found significant lower plasma paracetamol concentrations in patients with anaphylactoid reactions compared to patients without reactions [11], while the remaining studies failed to show a difference [10,12,28]. In contrast, all four

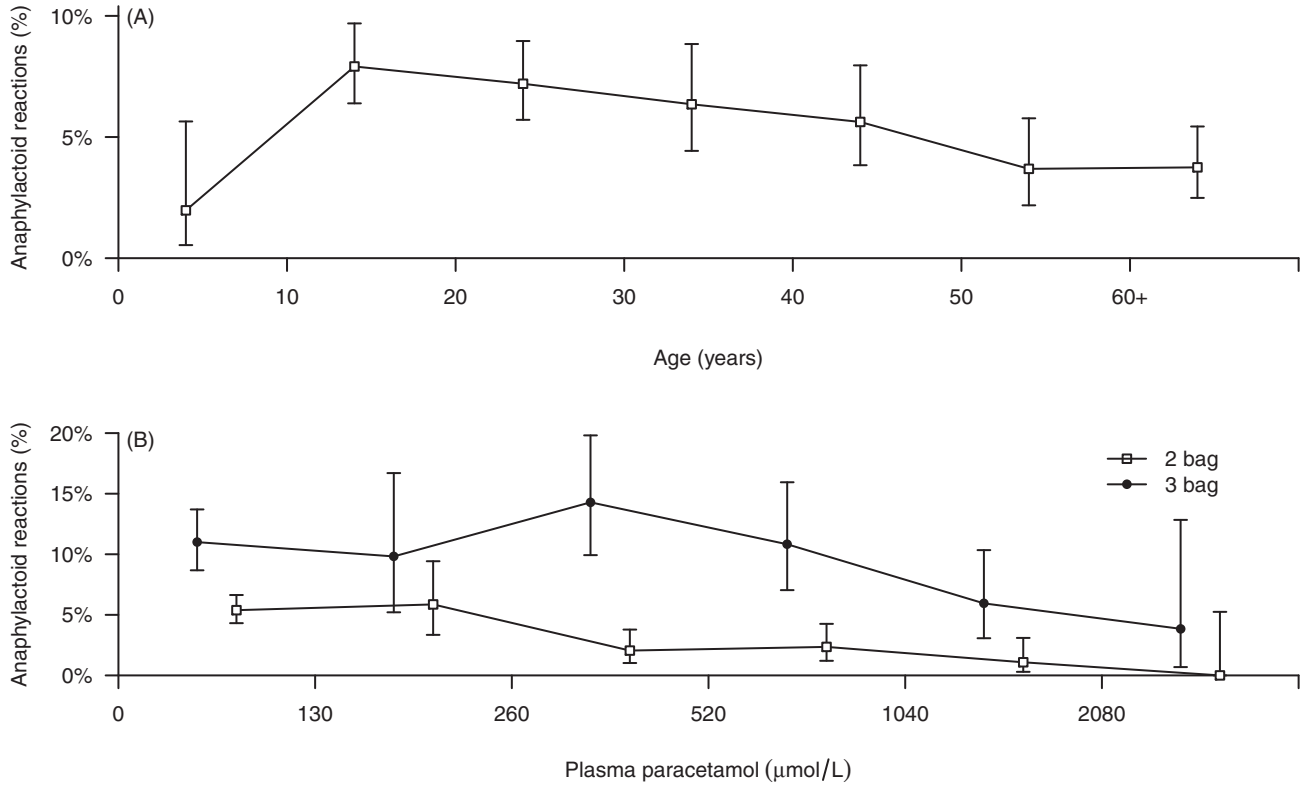

Figure 2. Anaphylactoid reactions to NAC in relation to age (A) and the highest measured paracetamol concentration stratified by NAC treatment regimen (B). Error bars indicate 95% confidence interval.

studies did find a significant lower plasma paracetamol concentration in patients with anaphylactoid reactions treated with the three-bag regimen and the difference in concentration between patients with and without anaphylactoid reactions was more pronounced with the three-bag regimen compared to the two-bag regimen.

We found that the apparent protective effect of plasma paracetamol on preventing anaphylactoid reactions occurred at lower concentrations with the two-bag regimen (Figure 3), which again may be due to the lower peak concentrations of NAC in the two-bag regimen. Because of the Danish recommendations to treat all adult patients with a suspected intake of more than 6 g regardless of the measured plasma paracetamol, a high proportion of patients had a highest measured plasma paracetamol below the lower limit of quantification. Likewise, the Danish recommendation of continuing the NAC treatment for at least 20 h (disregarding plasma paracetamol) may have resulted in a higher incidence of anaphylactoid reactions. This increases the sensitivity to detect a significant correlation between anaphylactoid reactions and plasma paracetamol compared to most countries where the practice is based on the Matthew–Rumack nomogram. This may also explain the lack of interaction between plasma paracetamol level and NAC regimen observed in previous studies, where cessation or lack of initiation of NAC infusion were frequent for patients with nontoxic paracetamol concentrations. Hence, fewer patients with lower paracetamol concentrations were included in these studies, which limit the ability to show that the incidence of anaphylactoid reactions is relative higher with the two-bag regimen when the paracetamol

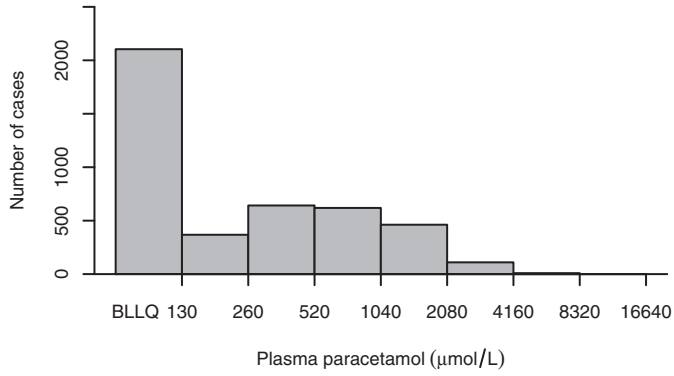

Figure 3. Distribution of peak paracetamol levels. BLLQ: below lower level of quantification (<130 μmol/L).

Table 3. Variables associated with development of anaphylactoid reactions requiring treatment.

	Anaphylactoid Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Paracetamol concentration[b]	0.81 [0.73, 0.90]	–
Two-bag regimen	0.64 [0.52, 0.77]	0.59 [0.47, 0.71]
Three-bag regimen	0.89 [0.78, 1.00]	0.82 [0.72, 0.94]
Paracetamol concentration BLLQ	1.43 [1.11, 1.84]	0.88 [0.58, 1.37]
Two-bag regimen	0.36 [0.28, 0.46]	0.44 [0.32, 0.60]
Antihistamine overdose	0.21 [0.02, 0.77]	0.17 [0.02, 0.64]
Daily use of antihistamines	0.60 [0.40, 0.87]	0.77 [0.50, 1.12]
Age, per 10-year increase	0.89 [0.84, 0.95]	0.84 [0.78, 0.90]
Age, 0–9 years of age	0.36 [0.10, 0.89]	0.14 [0.04, 0.36]
Length of stay, per day	0.97 [0.93, 1.00]	0.97 [0.92, 1.00]
Charlson Comorbidity index	0.89 [0.80, 0.98]	0.96 [0.85, 1.06]

BLLQ: below the lower limit of quantification.
[a]Adjusted for NAC regimen, plasma paracetamol concentration, interaction between plasma paracetamol and NAC regimen, antihistamine poisoning and age.
[b]Log2 transformed, i.e., the odds ratio corresponds to a doubling of the plasma concentration. Plasma concentrations BLLQ were set to 130 μmol/L.

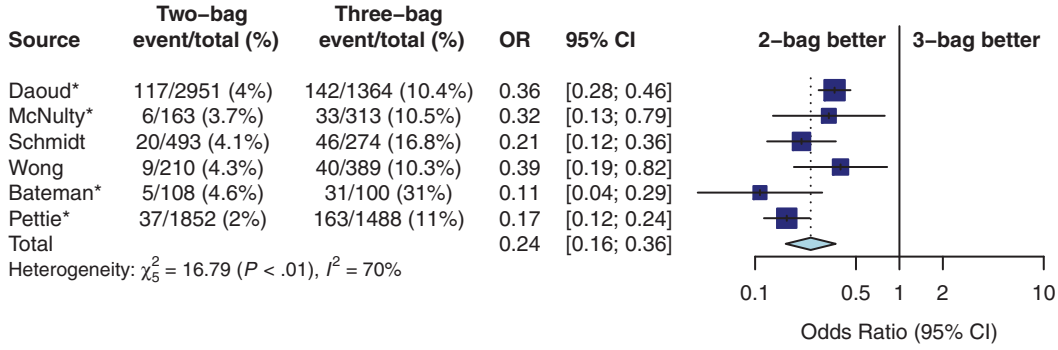

Figure 4. Meta-analysis of the occurrence of anaphylactoid reactions with the two-bag NAC regime versus the three-bag regime. *Only reactions requiring medical treatment are included. A random effect model was used for the total estimate. References: Daoud [Current study], McNulty [10], Schmidt [12], Wong [11], Bateman [27], Pettie [14].

concentration is low compared to patients with higher paracetamol concentrations.

Our study suggests that higher plasma paracetamol concentrations protect against the development of anaphylactoid reactions to NAC, and that it occurs at a lower plasma paracetamol concentration with the two-bag regimen. The mechanism behind this effect is not known, but it has been shown in vitro that paracetamol attenuates NAC-induced histamine release [30].

The low occurrence of anaphylactoid reactions in younger children despite low plasma paracetamol concentration has previous been observed in a study of 176 children aged 0–6 years where only two patients developed cutaneous reaction requiring treatment with systemic corticosteroid and antihistamines [31]. The lower incidence of anaphylactoid reactions in older patients has been described previously [19,32]. A good explanation for the low rate of anaphylactoid reactions in children and elderly is missing. It may be due to differences in the pharmacokinetics of NAC, but insufficient data exist to support this hypothesis.

We found that exposure to medications with antihistamine activity prior to NAC are associated with a lower incidence of anaphylactoid reactions. Few studies have examined the effect of prior antihistamine intake on the incidence of anaphylactoid reactions. A small retrospective study by Kao et al. found a numerically smaller incidence of anaphylactoid reactions in 110 patients exposed to antihistamine. In this study only 3 developed an anaphylactoid reaction compared to 4 reactions in 77 patients unexposed to antihistamines [33]. However, limited details on antihistamine exposure were reported and the small patient sample may have underpowered the findings. In another Danish study predating this cohort, the effect of prophylactic antihistamines were examined in patients with prior reactions to NAC [32]. In 39 patients exposed to antihistamine with or without corticosteroids before the NAC infusion only 6 (15%) developed an anaphylactoid reaction compared to 20 reactions in 48 (42%) patients unexposed to antihistamines. Hence, it may be warranted to administer antihistamine to patients with previous anaphylactoid reactions to NAC before initiating NAC or in the cases where a low concentration of plasma paracetamol is expected, i.e., staggered overdose.

This study has some limitations. First, the retrospective nature of the study leads to confounding bias. Second, it may underestimate the incidence of anaphylactoid reactions to NAC since only reactions severe enough to warrant antihistamine/glucocorticoid treatment were included. This notion is supported by the higher reported rates among prospective studies [28]. However, by inclusion of only anaphylactoid cases that necessitated treatment, it is likely that we mainly included clinically relevant severe anaphylactoid reactions. Third, as often is the case in retrospective studies, data on patient's medication and co-ingestion of antihistamines prior to admission are incomplete. This could lead to misclassification of the NAC treatment regimen, although it did not seem to significantly affect the outcome of the sensitivity analysis. Not all patients contacted DPIC during or before admission. In the aggregated data set, some patients could have been included or excluded in error. However, we thoroughly reviewed the medical charts of the patients identified to minimize this risk. Further, if anaphylactoid reactions were identified, they were usually described in detail and treated by the attending physician. It is important to notice that this study was not designed to evaluate the efficacy of the two-bag regimen in preventing liver injury compared to the three-bag regimen which is why no data are presented on liver function.

Conclusion

We found that the two-bag NAC regimen, being a child or increasing age, coingestion of antihistaminergic medication and high plasma paracetamol levels were associated with lower incidence of anaphylactoid reactions to NAC. However, a randomized clinical trial is warranted to establish the usefulness of pretreatment with antihistamine in high-risk patients prior to NAC treatment for reducing the occurrence of anaphylactoid reactions.

Declaration of interests

We declare no competing interests.

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