Risk factors in the development of adverse reactions to *N*-acetylcysteine in patients with paracetamol poisoning

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Aims To identify risk factors in the development of side-effects to *N*-acetylcysteine (NAC) in patients with paracetamol poisoning.

Methods A retrospective study was carried out based upon the hospital charts of 529 consecutive patients admitted with paracetamol poisoning, all treated with NAC, at the Department of Hepatology, Copenhagen University Hospital (the tertiary care centre of liver disease in Denmark).

Results Forty-five patients (8.5%; 95% confidence intervals (CI) 6.4, 11%) developed side-effects to NAC and 18 patients (3.4%; 95% CI 2.1, 5.4%) developed systemic side-effects. Asthmatics were 2.9 times (95% CI 2.1, 4.7) more likely to develop side-effects (Chi-square: $P=0.004$). Side-effects were of similar severity in asthmatics and nonasthmatics. A history of medical allergy was not a risk factor. Serum paracetamol was lower in patients with side-effects than in those without (Mann–Whitney: $P=0.00006$).

Conclusions Asthma must be considered a risk factor in the development of side-effects to NAC. However, the side-effects are easily managed and there is no reason to withhold NAC from any patient with paracetamol poisoning. Paracetamol itself seems to offer some protection against the development of side-effects to NAC.

Keywords: acetaminophen, asthma, atopy, drug interaction, *N*-acetylcysteine, paracetamol, poisoning, risk factor, side-effects

Introduction

N-acetylcysteine (NAC) is an effective antidote in the treatment of paracetamol toxicity [1]. In 1996, it was recommended by the Danish Association for the Study of the Liver (DASL) that all patients suspected of having overdosed on paracetamol should receive a 36 h standard i.v. treatment with NAC immediately after hospital admission [2]. The use of treatment guidelines, which assess the risk of developing liver failure from blood paracetamol concentrations corrected for time to NAC treatment, is questionable due to the unreliability of histories obtained from overdosed patients [1, 3]. Furthermore, such treatment guidelines do not account for the patients at special risk, i.e. chronic alcoholics and patients receiving enzyme-inducing anticonvulsants [4]. Reports of patients dying from paracetamol poisoning without NAC treatment have been published [5].

A consequence of the recommendation by DASL has been a prolonged treatment of an increasing number of patients. To justify the use of such guidelines, the risk/benefit of NAC treatment has to be very small. This prompted us to look at the side-effects of NAC in patients with paracetamol overdose [6]. In the literature, adverse reactions to NAC are described as being common, but are rarely serious [7–11]. Case reports have suggested that patients with atopy (asthma and allergy) are a special risk group [7, 12–15]. However, this has not been confirmed in any observational study investigating the side-effects to NAC.

Methods

The charts of all patients admitted with paracetamol poisoning between 1 January 1994 and 30 June 1999 were

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reviewed in order to identify adverse reactions to intravenous NAC and the possible risk factors for the development of adverse reactions to NAC. The patients were identified by a computer search of the hospital registration of diagnoses. The following information was recorded for each case: year of admission, duration of hospitalization, age, gender, whether the patient had been transferred from another hospital, dose of paracetamol ingested, time from paracetamol ingestion to commencement of NAC ('time to NAC'), ingestion of other medication or drugs on an acute or regular basis, ingestion of alcohol on an acute or regular basis, medical history of asthma, history of medical allergy, adverse reactions to NAC, minimum prothrombin (pp) and platelet count, maximum bilirubin, alanine transaminase (ALT), creatinine, and serum paracetamol, coma at the time of admission, hepatic encephalopathy (HE), treatment with plasma exchange or haemodialysis, liver transplant, and death. The diagnosis of asthma was based on information given by the patients themselves. A diagnosis of COPD was not regarded as being synonymous with asthma.

The Danish standard NAC regimen consists of an infusion of NAC 150 mg kg^{-1} i.v. over 15 min followed by 50 mg kg^{-1} over 4 h and 100 mg kg^{-1} over 16 h with repetition of the last phase until three consecutive increasing values of prothrombin have been demonstrated. The Department of Hepatology at the Copenhagen University Hospital is the tertiary care centre for liver disease in Denmark. The most severely ill patients are closely monitored within the department in a specialized liver intensive care unit, where treatments such as dialysis, plasmapheresis, mechanical ventilation, and liver transplantation may be employed. The majority of the patients are transferred from other Danish hospitals. However, some are admitted primarily from the locality, typically via the emergency room. Indications for considering transfer of a patient to the tertiary care centre are prothrombin <0.40, creatinine >300 μmol l^{-1}, platelets $<100\times10^{9}$ l^{-1}, arterial pH <7.30, or the development of hepatic encephalopathy.

Statistics

The statistical significance between variables was determined by the Mann–Whitney test, while the chi-square test was used for the comparison of frequencies. For the multivariate analysis a backward, stepwise multiple regression analysis (STATISTICA version 5.1, 1997 edition) was applied. The general level of significance was set at $P<0.05$, which was also applied for elimination of variables in the stepwise regression. Frequencies are given as percentages with 95% confidence intervals (CI).

Similar analyses were performed on a subset of 473 patients, omitting 56 comatose patients in whom side-effects were likely to have been overlooked (see Discussion).

Results

Over the 5½ years covered by the study, 529 patients were admitted with paracetamol poisoning (101 in 1994; 90 in 1995; 74 in 1996; 99 in 1997; 106 in 1998; 59 in 1999 (first 6 months)). The charts of all patients identified by the computer search were retrieved and were complete, i.e. including doctors' and nurses' notes, registration of administered medication, laboratory results, and in the case of transfers, copies of the chart from the transferring hospital. Information on medication, alcohol, allergy, asthma, adverse reactions, and outcome parameters were 100%, biochemical variables were 99 to 100%, time to NAC 97%, and paracetamol dose 93% complete. For the latter two variables, the information was deemed to have been unobtainable. Table 1 shows the demographic and anamnestic data of the patients. The drugs most frequently taken together with paracetamol included benzodiazepines, aspirin, and other analgesics. Predominant regular medication included benzodiazepines, antidepressants, and neuroleptics. Regular abuse of alcohol has been defined by the Danish National Board of Health as an excess of 14 units weekly for women and 21 units for men. When medical allergy was mentioned, it was almost exclusively to penicillin. All patients were treated with

Table 1 Demographic and anamnestic data of 529 patients admitted with paracetamol poisoning

Age (years)	31 (22–45; 12–88)
Female/male	361 (68.2%)/168 (31.8%)
Number of patients transferred from other hospital	382 (72.2%)
Duration of hospitalization (days)	4 (3–5; 1–48)
Dose of paracetamol (g)	25 (16–50; 2.5–150)
Time to NAC (hours)	15 (5–36; 0.5–192)
Number of patients cointoxicated with other drugs	159 (30.1%)
Number of patients with a regular use of other medication	229 (43.3%)
Number of patients cointoxicated with alcohol	123 (23.3%)
Number of patients with a regular abuse of alcohol	136 (25.7%)
Number of patients with a history of asthma	33 (6.2%)
Number of patients with a history of medical allergy	45 (8.5%)

Values are given as median (1st quartile–3rd quartile; minimum–maximum).

NAC in accordance with the Danish guidelines, despite the fact that these were not formally published until 1996.

Adverse reactions to NAC were observed in 45 patients (8.5%, CI 6.4–11%), hereafter referred to as the reaction group. Cutaneous reactions (rash, pruritus, flushing) were present in 42 patients and thus by far the most common. Non dermal systemic reactions (e.g. bronchospasm, angioedema, and nausea) developed in 18 patients (3.45; 95% CI 2.1, 5.4%) as shown in Table 2. Twenty-seven patients had only cutaneous reactions while three had systemic reactions only. All the side-effects were easily managed by the use of antihistamines ($n=42$), corticosteroids ($n=34$), adrenaline ($n=1$), and inhaled β_2-adrenoceptor agonists ($n=1$). In two patients, the side-effects had disappeared before treatment was administered. No patients (0/529 (0%, CI 0, 0.56%)) developed any serious side-effects requiring intensive care. A multiple regression analysis was performed using adverse reactions as the dependent variable, and age, gender, paracetamol dose, time to NAC, cointoxication (drugs or alcohol), regular ingestion of medication, regular alcohol abuse, asthma, medical allergy, and serum-paracetamol as the independent variables. After stepwise deletion of variables (see the Statistics section), only serum paracetamol, asthma, and age remained ($\beta=-0.14$, $P=0.002$; $\beta=+0.12$, $P=0.009$; and $\beta=-0.10$, $P=0.03$, respectively). Adverse reactions were 2.8 (95% CI 2.0,4.6) times more frequent in asthmatics than in nonasthmatics (7/33 (21%, 95% CI 9.8, 39%)) *vs* 38/496 (7.7%, 95% CI 5.6, 10%); Chi-square: $P=0.006$), whereas non dermal systemic reactions were 4.3 (95% CI 2.8,8.7) times more frequent in asthmatics than in nonasthmatics (4/33 (12%, 95% CI 4.2, 9%)) *vs* 14/496 (2.8%, 95% CI 1.6, 4.8%); Chi-square: $P=0.004$). However, within the reaction group systemic side-effects did not occur more frequently in asthmatics than in nonasthmatics (4/7 (57%, 95% CI 21, 88%)) *vs* 14/38 (37%, 95% CI 22, 54%); Fisher: nonsignificant). In particular, medical allergy was not associated with adverse reactions (4/45 (8.9%, 95% CI 3.0, 22%)) in allergic patients *vs* 41/484 (8.5%, 95% CI 6, 2, 11%) in nonallergic patients; Chi-square: nonsignificant).

The prognosis in the reaction group was significantly better than in the nonreaction group as shown in Table 3. For example, HE was more frequent in the nonreaction group (80/484 (17%, 95 % CI 13, 20%)) *vs* 2/45 (4.4%, 95% CI 0.54–15%); ratio 3.7 (95% CI 1.5–3.9); Chi-square: $P=0.03$ and there were no fatalities (0/45 (95% CI 0–8.9%)) in the reaction group (*vs* 32/484 (6.6%, 95% CI 4.7, 9.3%); Chi-square: $P=0.07$ (nonsignificant). Fifty-five patients were comatose at the time of admittance (from HE ($n=42$), cointoxication without hepatic failure ($n=11$), epileptic status ($n=1$), and diabetic ketoacidosis ($n=1$)). One patient with a history of 'allergy' to NAC was treated with antihistamine and corticosteroid prior to NAC treatment and therefore was not considered to be susceptible to developing adverse reactions. The omission of these 56 patients resulted in a subset of 473 patients (see the statistics section). Within this subset, no significant differences remained between the reaction and nonreaction groups regarding HE or death. When the multiple regression analysis was performed on the subset, only serum-paracetamol and asthma remained as significant

Table 2 Details of the 18 patients who developed systemic (nondermal) side-effects to *N*-acetylcysteine

Number	*F/M*	*Age (years)*	*Dose*	*TNAC*	*Asthma*	*Allergy*	*Side-effects*
1	F	21	13 g	3 h	0	0	Rash, pruritus, bronchospasm
2	F	17	20 g	6 h	0	0	Rash, bronchospasm
3	F	19	20 g	27 h	0	0	Rash, flushing, nausea, vomiting
4	M	36	28 g	60 h	0	0	Nausea, discomfort
5	M	27	25 g	20 h	0	0	Flushing, nausea, bronchospasm
6	F	16	10 g	10 h	0	0	Pruritus, angioedema
7	M	44	60 g	67 h	0	0	Pruritus, vomiting, dizziness, local pain
8	F	18	23 g	15 h	0	+	Pruritus, flushing, vomiting
9	F	16	15 g	48 h	+	+	Pruritus, flushing, nausea, angioedema, sneezing
10	F	34	18 g	9 h	0	0	Rash, pruritus, flushing, angioedema
11	F	14	20 g	45 h	+	0	Nausea, bronchospasm
12	F	18	5 g	17 h	0	0	Rash, pruritus, flushing, hypotension, bronchospasm
13	F	49	50 g	60 h	0	0	Rash, burning sensation, fever
14	M	38	5 g	18 h	0	0	Flushing, nausea, sweating, chest pain
15	F	26	20 g	5 h	+	0	Rash, flushing, coughing
16	M	49	25 g	42 h	0	0	Rash, angioedema
17	F	19	10 g	38 h	+	0	Chest pain
18	F	33	25 g	32 h	0	0	Rash, pruritus, angioedema

TNAC = time to *N*-acetylcysteine.

Table 3 Biochemical and clinical data in all patients admitted with paracetamol poisoning. A subset of patients who were not comatose upon admittance was constructed

	Total (n = 529)		*Subset (n = 473)*	
	Side-effects (n = 45)	*No side-effects (n = 484)*	*Side-effects (n = 44)*	*No side-effects (n = 429)*
Prothrombin (arbitary units)	0.29 (0.21–0.50)	0.24 (0.13–0.48)	0.29 (0.21–0.53)	0.27 (0.14–0.53)
ALT (units l^{-1})	2510 (28–66400	3085 (29–9635)	2760 (29–7145)	2660 (26–9750)
Bilirubin (μmol l^{-1})	26 (13–45)	33 (14–85)*	27 (13–47)	30 (13–73)
Platelets ($\times 109$ l^{-1})	198 (129–227)	150 (83–208)*	200 (130–227)	161 (96–214)*
Creatinine (μmol l^{-1})	87 (74–98)	91 (77–166)	88 (75–103)	87 (76–121)
S-paracetamol (mmol l^{-1})	0.07 (0.01–0.63)	0.51 (0.09–1.26)*	0.07 (0.01–0.63)	0.52 (0.10–1.24)*
Coma on admission	1/45 (2.2%)	54/484 (11%)	–	–
Hepatic encephalopathy	2/45 (4.4%)	80/484 (17%)†	1/44 (2.3%)	40/429 (9.3%)
Plasmapheresis	0/45 (0%)	37/484 (7.6%)	0/44 (0%)	19/429 (4.4%)
Haemodialysis	3/45 (6.7%)	35/484 (7.2%)	3/44 (6.8%)	27/429 (6.3%)
Liver transplant	0/45 (0%)	5/484 (1.0%)	0/44 (0%)	4/429 (0.9%)
Death	0/45 (0%)	32/484 (6.6%)	0/44 (0%)	16/429 (3.7%)

Values are given as median (1st quartile-3rd quartile). * Mann–Whitney: $P<0.05$ † Chi-square: $P<0.05$.

determinants. In this subset of patients asthmatics were 2.9 (95% CI 2.1, 4.7) times more likely to develop adverse reactions than nonasthmatics (7/29 (24.1%, 955 CI 10–44%)) *vs* 37/444 (8.3%, 95% CI 6.0, 11%); Chi-square: $P=0.004$. Serum paracetamol remained significantly lower in the reaction group compared with the nonreaction group (Mann–Whitney: $P=0.00006$).

Discussion

Our data confirm that asthma, as previously suspected, is a risk factor in the development of side-effects to NAC in patients with paracetamol poisoning [6]. Systemic side-effects were also more frequent in asthmatics, but within the reaction group side-effects were of similar severity in asthmatics and in nonasthmatics. Side-effects to NAC are suspected of being caused by a nonallergic release of histamine; this is thought to be a direct and dose dependent pharmacological effect of NAC [16]. Since asthmatics are characterized by hyper-reactivity to histamine this corresponds well with our findings. A history of drug allergy did not seem be a risk factor in the development of side-effects to NAC.

In addition, the reaction group unexpectedly differed from the nonreaction group in having a better prognosis. Many side-effects to NAC are completely or partly subjective (e.g. pruritus (with or without a transitory rash), chest pain, dyspnoea, general discomfort) and are not likely to have been registered in a comatose, perhaps even sedated and mechanically ventilated patient. Thus, in patients initially presenting with coma, the frequency of adverse reactions was probably underestimated resulting in bias. A similar bias was suggested by a study performed in Australia, which showed that side-effects were reported only in cases of mild paracetamol poisoning [8]. Since comatose patients are likely to differ from noncomatose patients regarding age and serum paracetamol, the demonstration of these variables as predictors of side-effects in the multivariate analysis could be ascribed to such a bias. In attempting to eliminate this bias, a subset of patients was constructed omitting the 55 patients who were comatose at the time of admission when side-effects are most likely to occur, plus the one patient who was treated prior to NAC to avoid side-effects. Within this subset, deletion of the variable age from the multivariate analysis was rendered possible, suggesting that its previous status as a predictor could be ascribed to this bias.

A strong correlation was demonstrated between a low serum paracetamol at the time of treatment and the development of side-effects to NAC. Even when we tried eliminating the above described bias, this finding was highly significant suggesting an interaction of paracetamol and NAC in the sense that paracetamol itself might actually offer some protection against the development of side-effects to NAC. In this context, the time to NAC was not found to be important and it seemed of no relevance whether the low serum paracetamol concentration was due to low dose paracetamol ingestion combined with a short time to NAC, or from a high paracetamol ingestion with a correspondingly longer time to NAC. *In vitro* studies have demonstrated that the function of lymphocytes, neutrophils, and thrombocytes is inhibited by toxic, but not therapeutic levels of paracetamol [17-19]. The effect is probably caused by a reversible inhibition by paracetamol of cyclo-oxygenase leading to a reduced synthesis of prostaglandins and thromboxanes. The toxic

derivative of paracetamol, *N*-acetyl-*p*-benzoquinone imine, does not have this effect on thrombocytes [20]. It is likely that paracetamol similarly inhibits the function of basophils/mast cells, and since prostaglandins are major contributors to the anaphylactic reaction, this would explain the apparent protection from adverse reactions by high serum levels of paracetamol. Indeed a case has previously been described in whom severe asthma was actually relieved by ingestion of 3 g of paracetamol [21].

The retrospective design may be considered a weakness of the study. Since 72% of the patients were transferred from other hospitals, it would have been impossible to conduct a prospective study of this size. However, probably because we see a large number of patients with paracetamol poisoning, documentation was consistent and complete, with the necessary information being almost invariably available.

In our study, no patients developed life-threatening side-effects. All cases of side-effects were easily managed and all patients received a complete course of NAC.

In conclusion, asthmatics should be considered to be at special risk of developing side-effects to NAC. With as many as one in four asthmatics developing side-effects, treating all paracetamol poisoned asthmatics prophylactically with antihistamines, e.g. 15 min prior to NAC-infusion, might be considered. However, since the side-effects are usually mild and easily treated, even in asthmatics, it does not seem reasonable to delay NAC on this account. Because of the dose dependent effect of NAC, it ought to be considered, especially in asthmatics, to infuse the NAC bolus over a slightly longer period of time, e.g. 30–60 min instead of the conventional 15 min. There is no reason to withhold NAC from any patient in whom paracetamol poisoning is demonstrated or suspected.

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