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Relationship between Serum Acetaminophen Concentration and *N*-Acetylcysteine-Induced Adverse Drug Reactions

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Abstract: Intravenous *N*-acetylcysteine is usually regarded as a safe antidote. However, during the infusion of the loading dose, different types of adverse drug reactions (ADR) may occur. The objective of this study was to investigate the relation between the incidence of different types of ADR and serum acetaminophen concentration in patients presenting to the hospital with acetaminophen overdose. This is a retrospective study of patients admitted to the hospital for acute acetaminophen overdose over a period of 5 years (1 January 2004 to 31 December 2008). Parametric and non-parametric tests were used to test differences between groups depending on the normality of the data. SPSS 15 was used for data analysis. Of 305 patients with acetaminophen overdose, 146 (47.9%) were treated with intravenous *N*-acetylcysteine and 139 (45.6%) were included in this study. Different types of ADR were observed in 94 (67.6%) patients. Low serum acetaminophen concentrations were significantly associated with cutaneous anaphylactoid reactions but not other types of ADR. Low serum acetaminophen concentration was significantly associated with flushing ($p < 0.001$), rash ($p < 0.001$) and pruritus ($p < 0.001$). However, there were no significant differences in serum acetaminophen concentrations between patients with and without the following ADR: gastrointestinal reactions ($p = 0.77$), respiratory reactions ($p = 0.96$), central nervous reactions ($p = 0.82$) and cardiovascular reactions ($p = 0.37$). In conclusion, low serum acetaminophen concentrations were associated with higher cutaneous anaphylactoid reactions. Such high serum acetaminophen concentrations may be protective against *N*-acetylcysteine-induced cutaneous ADR.

Acetaminophen (paracetamol) is one of the most widely used drugs worldwide [1]. In therapeutic doses, acetaminophen has an excellent safety profile. However, in large doses, acetaminophen can cause liver impairment [1–3]. *N*-acetylcysteine is the recommended antidote for acetaminophen overdose. It has been shown to be effective especially when administered early following ingestion [4,5]. Intravenous *N*-acetylcysteine has been the standard treatment for acetaminophen overdose in Europe, Canada, Asia and Australia [3,4,6–8]. The current protocol in Malaysia for the management of acetaminophen overdose involves an 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 hr, and 100 mg⁄kg in 1000 ml 5% dextrose over 16 hr.

In the literature, adverse drug reactions (ADR) to intravenous *N*-acetylcysteine are described as being common, but rarely serious [9–25]. Nausea and vomiting [23–25] and cutaneous anaphylactoid reactions [6,17,19,20,22] are the most common ADR associated with intravenous *N*-acetylcysteine. Preliminary clinical data indicate fewer anaphylactoid reactions induced by *N*-acetylcysteine in patients with high serum acetaminophen concentrations, suggesting that acetaminophen itself might be capable of conferring protective effects [24,26,27]. Anaphylactoid reactions to *N*-acetylcysteine are characterized by erythema, urticaria, flushing, hypotension, brochospasm and wheeze [28]. Around 15–30% of patients develop a diffuse urticarial rash or erythematous, which typically affects the upper trunk, neck and face [20].

To further investigate potential ADR associated with *N*-acetylcysteine, we carried out this 5-year, hospital-based, retrospective study to investigate the relationship between different types of ADR and serum acetaminophen concentration in patients presenting to the hospital with acetaminophen overdose.

Materials and Methods

Settings and study design. This is an observational retrospective case review of all patients with acute acetaminophen overdose admitted to a 1200-bed hospital located in the Northern region of Malaysia. The hospital provides health care and emergency treatment for all illnesses and accidents. All aspects of the study protocol, including access to and use of the patients' clinical information, were authorized by the local health authorities before the initiation of this study.

Data collection. Data were collected from 1 January 2004 to 31 December 2008. A computer-generated list was obtained from the Hospital Record Office. We identified our cases according to the

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T-codes of the International Classification of Diseases-Tenth revision (ICD-10). All patients with diagnostic codes T 39.1 (acetaminophen overdose) were included in the study. Patients' records were traced according to their identification card and hospital registration numbers. Acute acetaminophen overdose cases were identified according to the discharge diagnosis documented in their medical records. Also, the list of patients was modified according to the coding on the entire hospital record dependent on emergency department.

Specially designed data collection forms were used to collect data and included age, gender, ethnicity, date and time of overdose to calculate the *latency time* (the time of ingestion to the time the patient presented at the hospital), quantity of acetaminophen ingested, serum acetaminophen concentration, nature of any reaction to *N*-acetylcysteine in each admission, together with treatment given and if it was necessary to interrupt the *N*-acetylcysteine infusion.

The primary outcome of interest was the incidence rate and types of ADR, and the secondary outcome were the relationship between ADR and serum acetaminophen concentration. The diagnosis of ADR was based on the attending physicians' and nurses' assessment of patients during hospitalization, as reported in the medical records. Such ADR included rash, pruritus, flushing, nausea and vomiting, coughing, dyspnoea, chest pain, bronchospasm, wheezing, angioedema, hypotension, hypertension, tachycardia, electrocardiograph abnormalities, headache, dizziness, convulsion and fever [6,9–25]. The exact details of any reactions, including time of onset, *N*-acetylcysteine discontinuation or additional treatment, were recorded. Data on serum acetaminophen concentration measurements were obtained from the hospital's therapeutic drug monitoring laboratory service. Hypotension was defined as systolic blood pressure <90 mmHg or diastolic blood pressure <50 mmHg.

The charts of all patients identified through the search were reviewed and the data were collected. Charts of patients who had a serum acetaminophen concentration at or more than 4 hr post-ingestion and who were treated with intravenous *N*-acetylcysteine were extracted for further analysis. Charts were excluded from analysis for the following reasons: (1) the drug concentration on the acetaminophen nomogram was not measured, (2) the time of ingestion was not known or (3) the time interval between ingestion and determination of serum acetaminophen concentration was more than 24 hr.

Statistical analysis. Data were entered and analysed using the Statistical Package for Social Sciences programme version 15 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± S.D. for continuous variables and as frequency for categorical variables. Variables were tested for normality using the Kolmogorov-Smirnov test. Variables that were not normally distributed were expressed as the median (lower–upper quartiles). The Mann-Whitney U test was used to test differences between groups since the data were not normally distributed. Patients were categorized into two groups based on whether ADR were present or absent.

Results

A total of 305 patients with a diagnosis of acetaminophen overdose were admitted to the hospital during the study period. Of these, 146 patients (47.9%) were treated with intravenous *N*-acetylcysteine. Seven patients were excluded because their acetaminophen concentration was measured after 24 hr post-ingestion and, therefore, the study population consisted of 139 patients (fig. 1).

One hundred and twelve (80.6%) patients of the study population were females. The average age of the study population was 23.67 ± 7.47 years (range: 14–53 years). The majority (68.3%) of patients in the study population were presented within 8 hr from acetaminophen ingestion. The

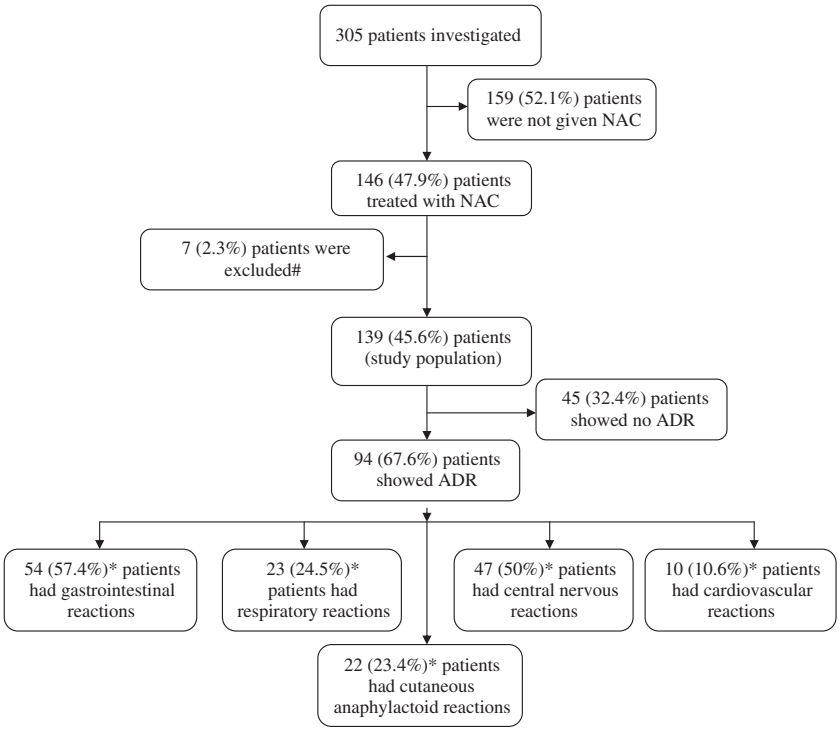

Fig. 1. Diagrammatic representation of adverse drug reaction (ADR) profiles in patients treated with *N*-acetylcysteine (NAC). # Seven patients were excluded because their acetaminophen concentration was measured after 24 hr post-ingestion; *total exceeds 100% as data are overlapping due to multiple ADR.

median (interquartile range) quantity of acetaminophen ingested was 15 g (10–17.63 g) and the time between ingestion and determination of serum acetaminophen concentration was 7 hr (4.75–11 hr). The median (interquartile range) serum acetaminophen concentration was 128.4 mg/l (66–173 mg/l). Overall, two patients were admitted to the intensive care unit but no patient died or needed liver transplant as a result of acetaminophen overdose. Also, only two patients with acetaminophen overdose presented to the hospital with impairment in level of consciousness upon admission.

Of the 139 patients in the study population, 94 (67.6%) developed different types of ADR which included gastrointestinal reactions in 54 (38.8%), central nervous reactions in 47 (33.8%), respiratory reactions in 23 (16.5%), cutaneous anaphylactoid reactions in 22 (15.8%) and cardiovascular reactions in 10 (7.2%). These findings are summarized in fig. 1.

The reactions to *N*-acetylcysteine occurred within the first hour after administration. Infusion of *N*-acetylcysteine was stopped temporarily and the rate of infusion was reduced due to ADR in 30 patients who had cutaneous (skin) anaphylactoid reactions and bronchospasm. Twenty-two patients received treatment with intravenous hydrocortisone and 12 patients with intravenous chlorpheniramine following skin reactions. All 10 patients who developed bronchospasm required an oxygen nebulizer. Fifty-four patients who developed nausea and vomiting were treated by intravenous metoclopramide. All patients received a complete course of *N*-acetylcysteine; however, in one patient, *N*-acetylcysteine was not restarted because serum acetaminophen concentration was below the toxic level.

We further analysed and compared the serum acetaminophen concentration associated with the presence or absence of different types of ADR induced by *N*-acetylcysteine. Significantly lower serum acetaminophen concentrations were associated with the presence of flushing ($p < 0.001$), rash ($p < 0.001$), and pruritus ($p < 0.001$), but not with nausea ($p = 0.07$), vomiting ($p = 0.51$), chest pain ($p = 0.76$), bronchospasm ($p = 0.48$), coughing ($p = 0.48$), headache ($p = 0.89$), dizziness ($p = 0.92$), convulsion ($p = 0.81$) and hypotension ($p = 0.37$) (table 1).

Although some types of *N*-acetylcysteine-induced ADR were significantly associated with acetaminophen serum concentration, the results showed that there was no significant difference between serum acetaminophen concentration in patients with and without ADR ($p = 0.70$). The median (interquartile range) values of acetaminophen concentration in the presence or absence of ADR were 130 mg/l (65.7–178.4 mg/l) and 116 mg/l (65–166.1 mg/l), respectively. As shown in fig. 2, the median serum acetaminophen concentration was significantly lower in patients with cutaneous (skin) anaphylactoid reactions when compared to patients without this type of ADR ($p < 0.001$). There were no significant differences in median serum acetaminophen concentrations noted in patients with gastrointestinal reactions ($p = 0.77$), respiratory reactions ($p = 0.96$), central nervous reaction ($p = 0.82$) and cardiovascular reactions ($p = 0.37$).

Thirty-seven (26.62%) patients reported having only one type of ADR, 20.86% of patients reported having two different types of ADR and 20.15% reported having three or more different types of ADR (fig. 3). A total of 214 ADR episodes were reported by all the patients, giving a median (interquartile range) 1 (0–2, range: 0–8) ADR per patient. There were

Table 1.
Serum acetaminophen concentration and adverse drug reaction patterns of the study subjects in the two groups (n = 139).

Signs and symptoms	Total, n (%) n = 139	Median (Q1–Q3) of serum acetaminophen concentration		*p*-value
		Presence ADR[1]	Absence ADR[1]	
Gastrointestinal	54 (38.8)			
Nausea	32 (23)	100.5 (51.6–145.5)	142.6 (71–178)	0.07
Vomiting	29 (20.9)	139 (77.5–194.3)	126.7 (64.9–200)	0.51
Skin (cutaneous)	22 (15.8)			
Flushing	22 (15.8)	51 (25.5–75.1)	144.3 (87–185.5)	<0.001
Rash	17 (12.2	43.7 (22–60.6)	143.5 (87.5–181)	<0.001
Pruritus	12 (8.6)	41.1 (14.7–56.2)	141 (82.5–178)	<0.001
Respiratory	23 (16.5)			
Chest pain	14 (10.1)	126.9 (77.6–175.8)	128.4 (64.8–174.5)	0.76
Bronchospasm	10 (7.2)	154.8 (44.7–200)	125 (68–167.9)	0.48
Coughing	9 (6.5)	167.7 (46.9–194.9)	126.7 (69–168.5)	0.48
Central nervous	47 (33.8)			
Headache	32 (23)	131.3 (53.8–175.5)	123 (70–173)	0.89
Dizziness	24 (17.3)	136.8 (57.5–183.7)	123 (70–170)	0.92
Convulsion	3 (2.2)	55 (52.7–171.5)	129.2 (70–172.3)	0.81
Cardiovascular	10 (7.2)			
Hypotension	10 (7.2)	126.7 (23.9–170.4)	130 (70–174.5)	0.37

ADR, adverse drug reactions; Q1–Q3, lower quartile–upper quartile.
[1]This comparison between the serum acetaminophen concentrations related to the presence of different ADR subgroups and the serum acetaminophen concentration related to the absence of this type of ADR.

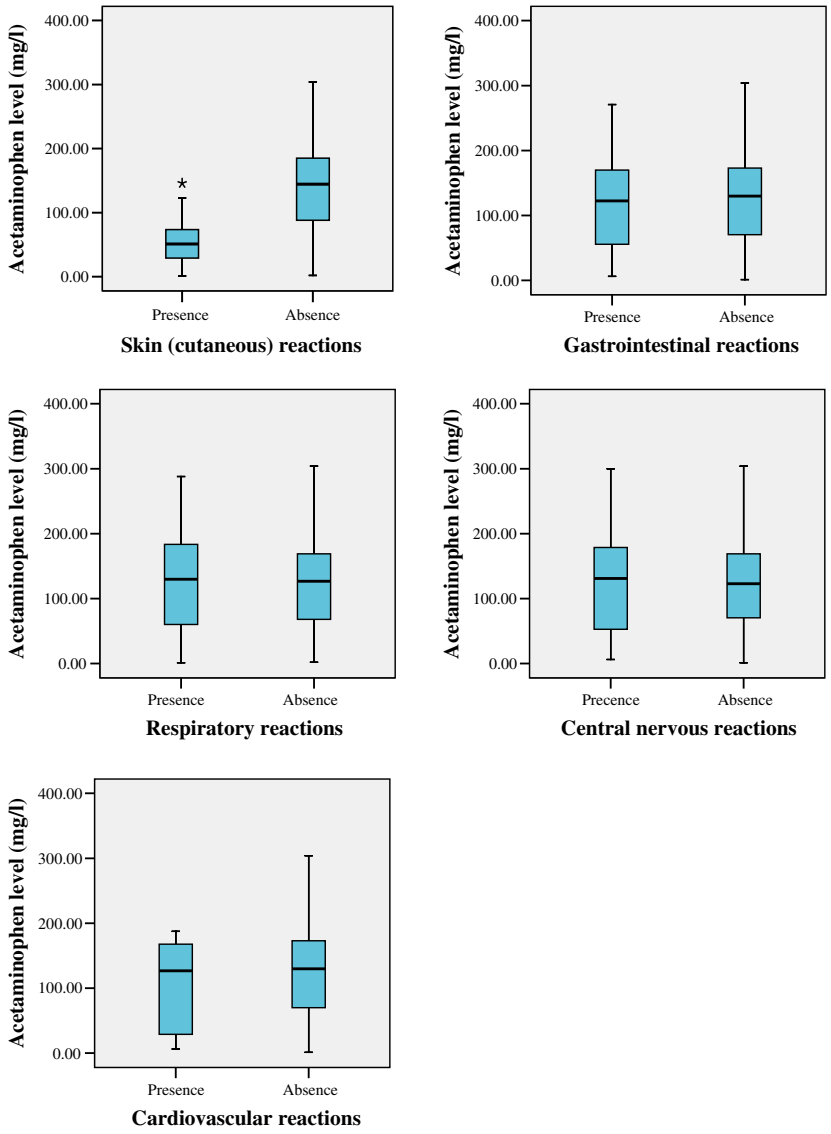

Fig. 2. Boxplot (A, B, C, D, and E) of serum acetaminophen concentration for different types of adverse reaction according to the system. *They were significantly different ($p < 0.001$) for skin (cutaneous) reactions.

no significant differences ($p = 0.08$) between serum acetaminophen concentration and number of ADR.

Discussion

The present study was conducted to investigate the relationships between the incidence of different types of *N*-acetylcysteine-induced ADR and serum acetaminophen concentration in patients presenting to the hospital with acetaminophen overdose. Intravenous *N*-acetylcysteine has been the standard treatment for acetaminophen overdose in Europe, Canada, Asia and Australia. There are reports of ADR to *N*-acetylcysteine with incidence ranging from 3% to 77% [6,20–25]. The incidence rate of ADR to *N*-acetylcysteine reported in our study was within the range of incidence reported in other countries. We found an adverse reaction incidence rate of 67.6%. A study in the UK showed that the incidence of ADR was revealed in 76.9% of acetaminophen overdose cases [25]. Among Iranian patients with acetaminophen overdose, the incidence rate of ADR was 44.5% [21]. A Chinese study showed that the incidence of ADR to *N*-acetylcysteine among patients with acetaminophen overdose was 11.2% [22]. It is likely that the differences in the incidence of ADR reported are due to different study populations, differences in the inclusion criteria, differences in definition and interpretation of ADR (e.g. inclusion or exclusion of nausea and vomiting as ADR or inclusion of new ADR such as headache and coughing) and oversight or accuracy in documentation in the medical records. For example, in our study, no restriction was made in the inclusion of nausea while in Merl *et al.,* patients with nausea were excluded [22].

In our study, no patients developed life-threatening ADR or prolonged ADR. All cases of ADR were easily managed and the infusion of *N*-acetylcysteine could be safely restarted

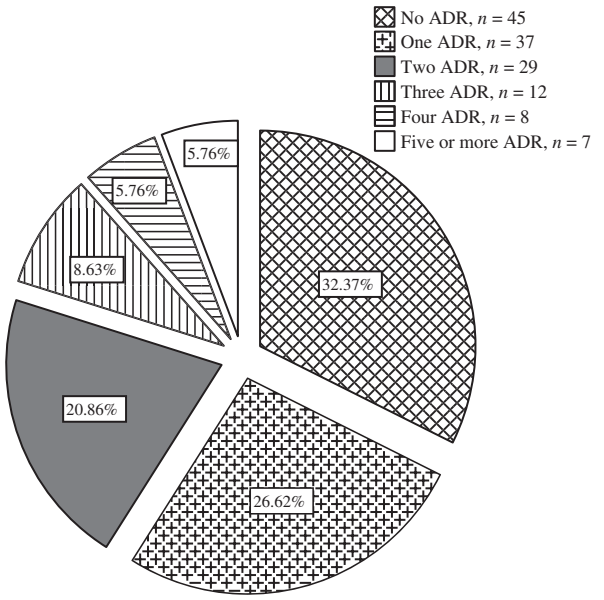

Fig. 3. Number of different adverse drug reactions (ADR) occurred after receiving the recommended dose of intravenous *N*-acetylcysteine among patients with acetaminophen overdose (n = 139). There were no significant differences ($p = 0.08$) between serum acetaminophen concentration and number of ADR.

when symptoms had resolved, as reported in previous studies [24,29].

In the current study, a low serum acetaminophen concentration was associated with higher risk of cutaneous anaphylactoid reactions induced by *N*-acetylcysteine infusion. Interestingly, it appears that acetaminophen itself may play a role in protection against *N*-acetylcysteine-induced cutaneous anaphylactoid reactions. An increased rate of anaphylactoid reactions has been observed among patients who received *N*-acetylcysteine and had low acetaminophen concentrations [6,20,24]. A similar study in the UK showed that anaphylactoid skin reactions occurred less often in patients who had high serum acetaminophen concentrations ($p = 0.047$). No such relationships were noted for gastrointestinal adverse reactions [24]. Another study in the UK showed that 42% of patients who developed anaphylactoid reactions to *N*-acetylcysteine had acetaminophen levels below the treatment line [20]. On the contrary, high serum acetaminophen concentrations have been associated with a low frequency of anaphylactoid reactions, suggesting a protective effect [6,24,27].

The mechanism by which this occurs is unclear. *N*-acetylcysteine has been shown to stimulate the production of free radicals which might contribute to inflammation and anaphylactoid reactions [30]. Acetaminophen is associated with inhibiting cyclooxygenase (COX) isoenzymes and thus might be expected to suppress inflammation [31]. Therapeutic acetaminophen concentrations weakly inhibit COX, while concentrations between 76 and 453 mg/l inhibit prostaglandin E2 synthesis [32,33]. Therefore, COX dose-dependent mechanism might be important in cutaneous anaphylactoid reactions induced by *N*-acetylcysteine infusion.

Although this study is the first of its type in Malaysia, it suffers from a few limitations. Further risk factors for ADR occurrence were not taken into account in the analysis. Further research is needed to determine other risk factors associated with *N*-acetylcysteine-induced ADR in patients with acetaminophen overdose in the future.

Conclusion

Adverse drug reactions to *N*-acetylcysteine infusion are common after acetaminophen overdose and are easily managed. No fatalities were observed. Low acetaminophen concentration is a risk factor for developing cutaneous anaphylactoid reactions, suggesting that high serum acetaminophen concentration may be protective against this type of ADR.

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Conflict of interest

We wish to declare that there was no conflict of interest in conducting this research.

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