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Lower incidence of anaphylactoid reactions to N-acetylcysteine in patients with high acetaminophen concentrations after overdose

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Lower incidence of anaphylactoid reactions to N-acetylcysteine in patients with high acetaminophen concentrations after overdose

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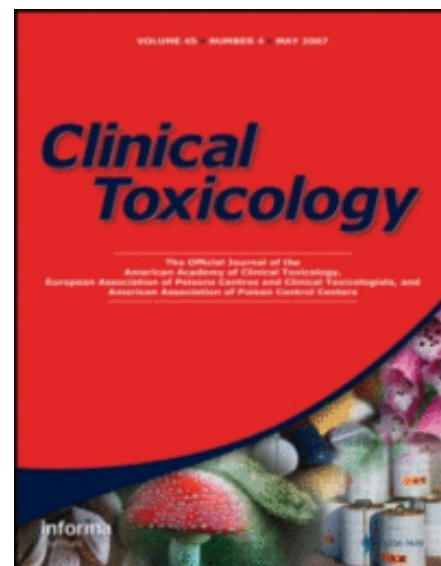
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Abstract

Background. Mechanisms responsible for anaphylactoid reactions to N-acetylcysteine (NAC) are poorly understood, and acetaminophen itself may play an important role. The present study examined the relationship between serum acetaminophen concentrations and risk of anaphylactoid reactions. **Methods.** Prospective study of adverse reactions to NAC administered according to standardized clinical protocols in patients who present to hospital after acute acetaminophen overdose. Subgroups were defined by serum acetaminophen concentrations 0 to 100 mg/L, 101 to 150 mg/L, 151 to 200 mg/L, 201 to 300 mg/L, and >300 mg/L. **Results.** There were 362 patients, and anaphylactoid reactions occurred in 14.9%. Anaphylactoid reactions occurred less commonly in patients with high serum acetaminophen concentrations ($p = 0.046$ by Cochran-Armitage trend test) and high equivalent 4 h acetaminophen concentrations ($p = 0.004$). **Discussion.** High serum acetaminophen concentrations were associated with fewer anaphylactoid reactions, suggesting that these might in some way be protective. The biological basis needs further exploration so as to allow a better



understanding of the mechanisms responsible for adverse reactions to NAC treatment.

Keywords: Acetaminophen; Adverse drug reaction; Overdose; Poisoning; Toxicity

Introduction

N-acetylcysteine (NAC) minimizes the risk of hepatotoxicity after acute acetaminophen overdose.

However, a high proportion of patients experience adverse reactions to NAC, which are variably reported to occur in 5-15% of patients in retrospective studies, and 40-56% in prospective studies [1-5].

Anaphylactoid reactions to NAC are characterized by erythema, urticaria, flushing, bronchospasm, wheeze, and hypotension [6,7]. Around 15-30% of patients develop a diffuse erythematous or urticarial rash, which typically affects the upper trunk, neck, and face [8,9]. While the clinical presentation is similar to true anaphylaxis, anaphylactoid reactions differ because prior exposure to NAC is not required, and treatment can normally be reintroduced without provoking a further reaction [7]. Features typically occur 20-60 min after commencing intravenous NAC, and subside quickly after the infusion is stopped [10]. Onset coincides with expected peak serum NAC concentrations during the standard intravenous loading regimen [11], and inadvertent administration of very high dosages is associated with severe anaphylactoid reactions [10]. Localized wheal and flare responses to NAC are concentration-dependent [12]. The incidence of anaphylactoid reactions may be reduced when the initial loading dose of NAC 150 mg/kg is administered over 60 or 90 min instead of the standard 15 min regimen [5, 13, 14]. For example, adverse reactions occurred in 49 of 109 (45%) after 15 min infusion, versus 27 of 71 (38%) after 60 min infusion, although the difference was not statistically significant [13].

Existing data suggest that anaphylactoid reactions are directly related to serum concentrations of NAC, and that risk is dose-dependent [5,13,14]. Nonetheless, the basic biological mechanisms of anaphylactoid reactions remain unclear. Histamine appears to be an important mediator, and wheal responses to localized NAC can be abolished by prior treatment with a selective histamine-1 receptor antagonist [12]. NAC is also capable of evoking endothelium-independent vasodilatation, possibly due to a direct relaxant effect on vascular smooth muscle [15]. Preliminary clinical data indicate fewer

anaphylactoid reactions in patients with high serum acetaminophen concentrations, suggesting that acetaminophen itself might be capable of conferring protective effects [16,17]. However, these data involve comparatively small numbers, and might be confounded by delayed presentation to hospital. The present study was designed to prospectively address whether high acetaminophen concentrations might be protective against anaphylactoid reactions after acute acetaminophen overdose in patients who are managed in a consistent setting using standardized clinical protocols.

Methods

The study protocol was reviewed and approved by the local research ethics committee, and specific consent was not required from participants. This was a prospective, observational study of consecutive patients presenting to the Emergency Department after acute acetaminophen overdose between March 2005 and June 2006. Exclusion criteria were presentation >24 h after overdose, uncertainty about the timing of ingestion, and ingestion staggered over 2 h or more. This institution serves a catchment population of around 600 thousand, and approximately 3 thousand poisoned patients are admitted via the Emergency Department annually. Local policies mean that all patients with suspected poisoning are brought directly to our hospital if >13 y age, whereas patients ≤ 13 y are directed to a regional pediatric center. A standard operating procedure is used in management of acetaminophen overdose patients to ensure consistency between the Emergency Department and Toxicology Unit, and is in accordance with TOXBASE®, the standard resource for poisoning management advice in the United Kingdom [18]. In brief, intravenous N-acetylcysteine is indicated after acute ingestion if serum acetaminophen concentration is above the Rumack-Matthew '200-line' nomogram, or above the '100-line' and the patient is considered at high risk due to chronic ethanol excess, enzyme inducing drugs (carbamazepine, phenobarbital, phenytoin, rifampicin, St John's wort), chronic liver disease, or malnutrition [19]. Chronic ethanol excess is defined by regular consumption of >21 units (168 g) per week in men or >14 units (112 g) in women [20]. If more than 8 h have elapsed after ingestion and the patient is thought to have ingested >12 g or >150 mg/kg, then N-acetylcysteine may be initiated before acetaminophen concentrations become available. Intravenous N-acetylcysteine 150 mg/kg is infused

over 15 min, followed by 50 mg/kg over 4 h, followed by 100 mg/kg over 16 h, and serum creatinine, prothrombin time ratio, and liver biochemistry are monitored.

Data collection

A study-specific data collection sheet was used to record patient age, gender, stated date and time of overdose, quantity of acetaminophen ingested, whether other drugs had been co-ingested, the presence of risk factors for hepatotoxicity, serum acetaminophen concentration, and interval between ingestion and blood sample collection. This was separate from the main medical casenotes, and data were collected by staff that were blinded to the study hypothesis. The administration of NAC and subsequent occurrence of adverse effects were recorded. Anaphylactoid reactions may be minor (e.g., flushing), moderate (e.g., urticaria), or severe (e.g., angioedema or respiratory symptoms). Nausea or vomiting alone do not constitute an anaphylactoid reaction, and are recognized adverse effects of thiol donors and 'sulpha' drugs. Our experience indicates that adverse reactions to NAC fall into discrete clinical phenotypes, and predefined criteria for anaphylactoid reactions were new-onset itch, flushing, oedema, stridor, urticarial rash, or wheeze, and criteria for gastrointestinal adverse reactions were abdominal pain, nausea, or vomiting.

Data analyses

Demographic data were not expected to be normally distributed and are presented as median and interquartile ranges. Serum acetaminophen concentration and equivalent 4 h concentration were both considered, and patients were categorized into convenience groups based on multiples of the standard Rumack-Matthew '200-line' nomogram, namely 0 to 100 mg/L, 101 to 150 mg/L, 151 to 200 mg/L, 201 to 300 mg/L, and >300 mg/L. Appropriate nomograms were constructed using the formula $C_t = C_4 \times 2 \times e^{-(0.693/4)t}$ where C_t is the acetaminophen concentration determined at interval after ingestion in hours (t), and C_4 is the equivalent 4 h acetaminophen concentration.

The occurrence of anaphylactoid reactions was expressed as a proportion of treated patients and 95%

confidence intervals were constructed using the modified Wald method [22]. Cochran-Armitage tests were used to examine the relationship between adverse reactions and categories of serum acetaminophen concentration and equivalent 4 h concentration using SPSS statistical software (version 11.5, SPSS Inc., Chicago, USA). P-values <0.05 were accepted as statistically significant.

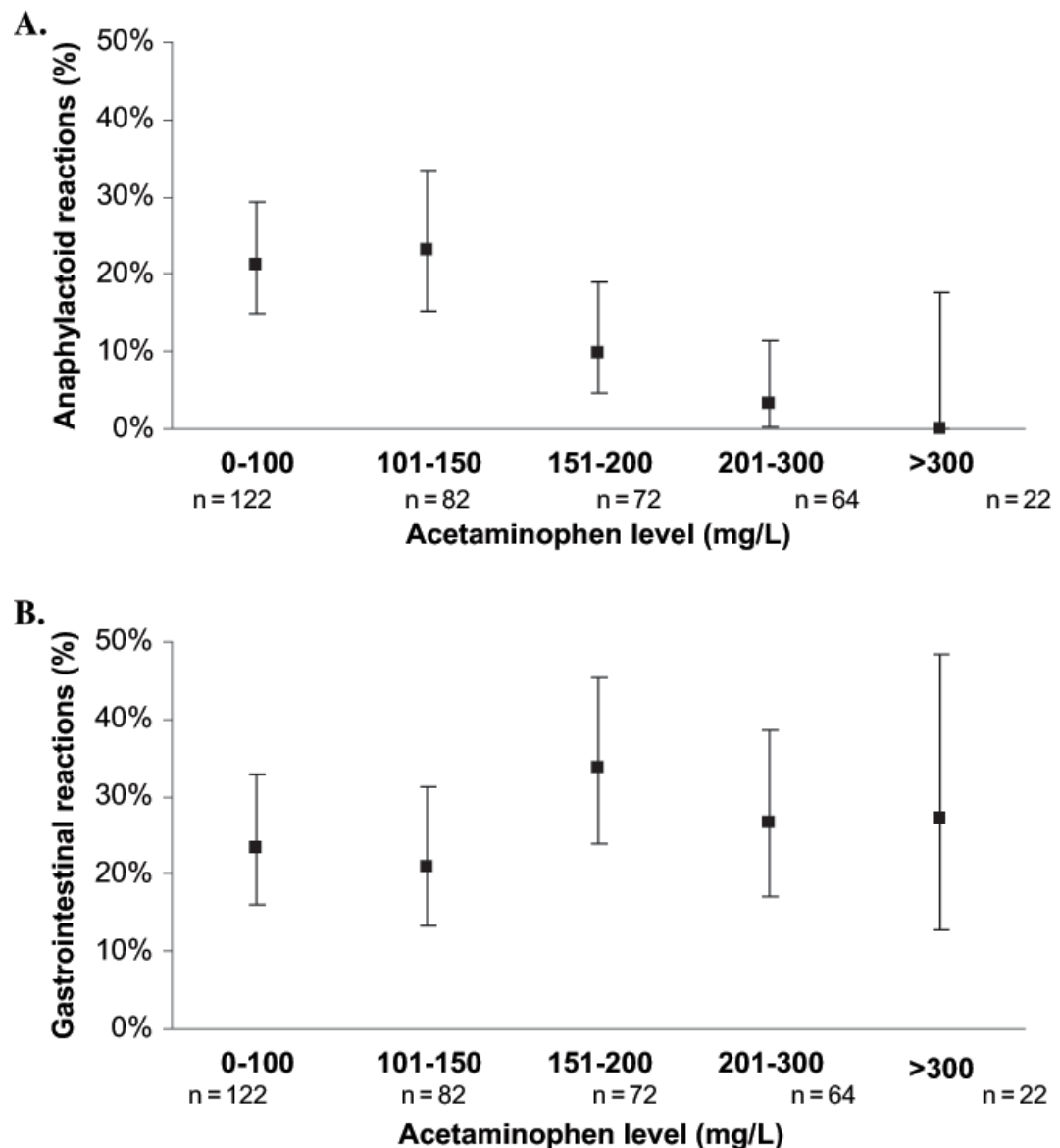
Results

During the study period, 1091 patients presented to the Emergency Department after acetaminophen overdose. Twenty-three patients were excluded due to staggered ingestion over >2 h, and 23 additional patients were excluded because they presented >24 h after ingestion. NAC was not indicated in 683 patients and, therefore, the study population consisted of 362 patients (122 men, 33.7%). Median (interquartile range) age was 35 y (22-44 y), and weight 66.0 kg (56.5-75.0 kg). The stated quantity of ingested acetaminophen was 17 g (13-25 g), and the interval between ingestion and determination of serum acetaminophen concentration was 4.9 h (4.2-8.3 h). 194 patients (53.6%) were considered to be at high risk of hepatotoxicity due to chronic alcohol excess (151), malnutrition [33], prior use of enzyme inducing drugs [8], recent acetaminophen ingestion [1], and the presence of established liver disease [1].

Adverse reactions to NAC occurred in 147 patients (40.6%), including anaphylactoid reactions in 54 (14.9%), gastrointestinal reactions in 90 (24.9%), and localized skin reactions at the infusion site in 3 patients (0.8%). The median (interquartile range) time to onset of anaphylactoid reactions was 75 min (50 to 112 min) after commencing infusion. NAC was temporarily discontinued, and antiemetics administered to 74 patients (50.3%), antihistamines to 51 (34.7%), corticosteroids to 4 (2.7%), and inhaled albuterol to 2 (1.4%). In 9 patients (6.1%), NAC was not restarted because acetaminophen concentrations were below the appropriate treatment line. In the remaining 138 patients (93.9%), reinstitution of intravenous NAC caused no further adverse effects. No fatalities or other serious effects were observed.

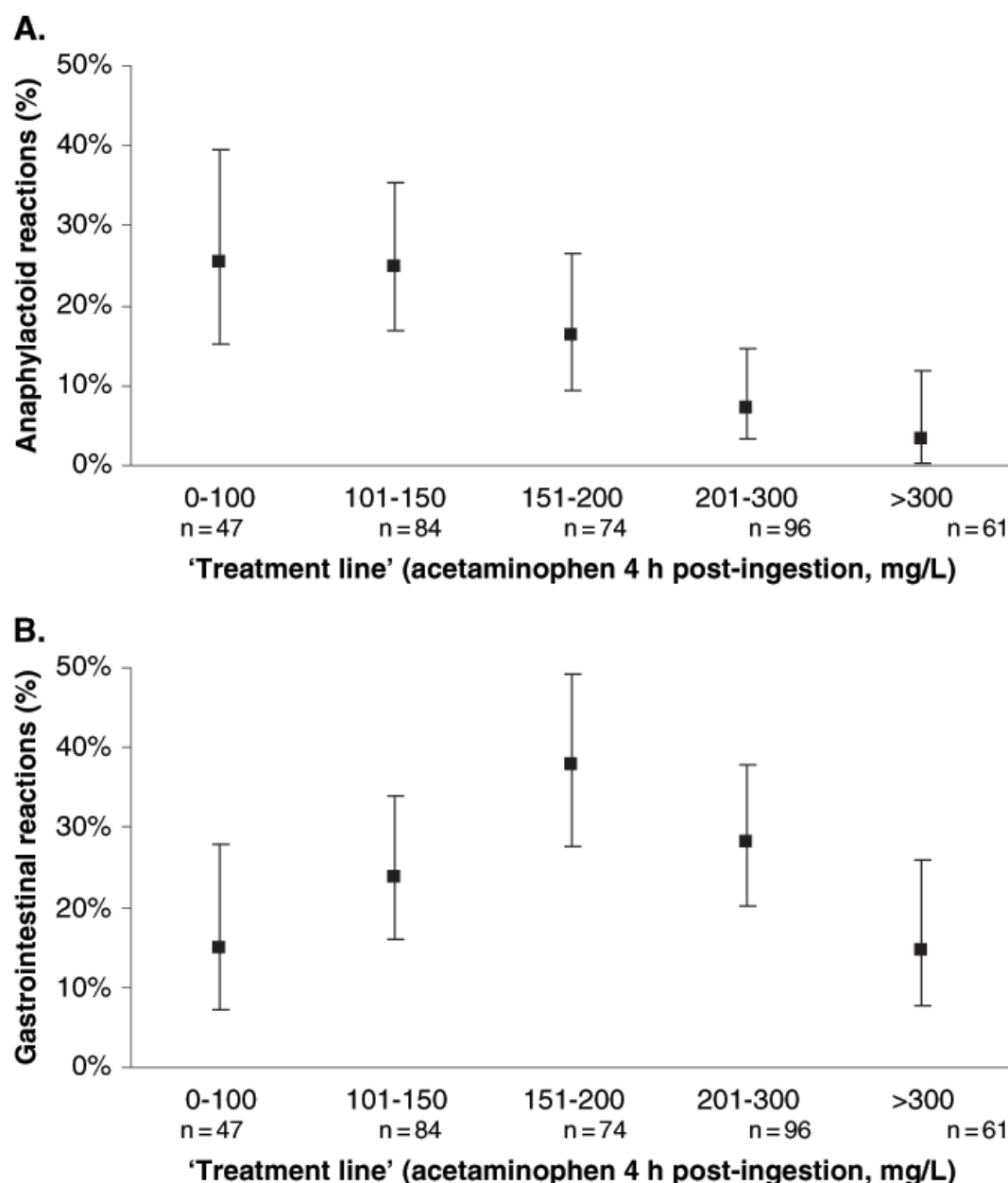
Anaphylactoid reactions occurred less often in patients who had high serum acetaminophen

concentrations ($p = 0.047$ by Cochran-Armitage test with 4 degrees of freedom) (Figure 1). A similar pattern was observed when equivalent 4 h acetaminophen concentrations were considered ($p = 0.004$) (Figure 2). No such relationships were noted for gastrointestinal adverse reactions.



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Fig. 1. Proportion of patients with (A) anaphylactoid, (B) gastrointestinal adverse reactions to NAC with respect to serum acetaminophen concentration, shown with 95% confidence intervals. $p = 0.047$ for anaphylactoid reactions, $p = 0.138$ for gastrointestinal reactions by Cochran-Armitage tests.



[Enlarge Image]

Fig. 2. Proportion of patients with (A) anaphylactoid, (B) gastrointestinal adverse reactions to NAC with respect to equivalent 4 h acetaminophen concentration, shown with 95% confidence intervals. $p = 0.004$ for anaphylactoid reactions, $p = 0.052$ for gastrointestinal reactions by Cochran-Armitage tests.

Discussion

NAC treatment caused adverse effects in around 40% of patients, including anaphylactoid reactions in almost 15%, which are similar to the rates reported in other prospective studies. None of the patients suffered severe or prolonged adverse effects, and the infusion could be safely restarted when symptoms had resolved, as reported elsewhere [1]. The study design included equivalent 4 h concentrations, so as to partially compensate for the confounding effect of interval between ingestion

and presentation. Both high serum acetaminophen concentrations and overall acetaminophen exposure were associated with a lower risk of anaphylactoid reactions.

NAC is capable of stimulating free radical generation, which might contribute to acute inflammation in anaphylactoid reactions [23]. Arachadonic acid is sequentially metabolized to prostaglandin G2 by cyclooxygenase (COX), prostaglandin H2 by peroxidase, and prostaglandin E2 by cytosolic and membrane-bound synthases. Acetaminophen is capable of inhibiting COX isoenzymes 1a, 1b, and 2 and, therefore, might be expected to suppress inflammation [24]. Therapeutic concentrations inhibit COX only weakly, whereas concentrations between 500-3000 $\mu\text{mol/L}$ (76-453 mg/L) inhibit prostaglandin E2 synthesis in a dose-dependent manner [25, 26]. Such concentrations are in keeping with those observed after acetaminophen overdose. Therefore, COX-dependent mechanisms might be important in anaphylactoid reactions to NAC.

NAC is capable of enhancing intracellular glutathione concentrations, and this may provoke inflammation and free radical liberation [27]. In contrast, glutathione depletion is associated with down-regulation of the inflammatory cascade, and suppression of cytokines [28-30]. Therefore, suppression of anaphylactoid reactions might simply be a marker of glutathione depletion, which would be anticipated in patients exposed to the highest acetaminophen concentrations. Such a mechanism would require biochemical confirmation of reduced hepatic glutathione stores, which were not measured in the present study [31]. High acetaminophen concentrations might also exert redox effects relevant to anaphylactoid reactions. For example, the liver is an important source of oxygen-derived free radicals that may promote systemic hypotension [32]. Acetaminophen possesses antioxidant properties that might be capable of attenuating the hypotensive effect of oxidative stress [33], and supra-therapeutic acetaminophen concentrations of 100 to 1000 $\mu\text{mol/L}$ (15-151 mg/L) can directly inhibit the vasodilator responses to arachadonic acid *in vivo* [34].

A limitation is that the study design does not address the biological basis for an association between acetaminophen concentrations and anaphylactoid reactions. We propose to address the potential

underlying mechanisms in a program of basic and clinical research.

In conclusion, patients with high acetaminophen concentrations are associated with fewer

anaphylactoid reactions to NAC in the context of acute acetaminophen overdose. Further work is

required to elucidate the mechanisms that underlie this association in order to develop appropriate

strategies for preventing adverse reactions to NAC.

Disclosures

There were no specific sources of funding associated with this study.

References

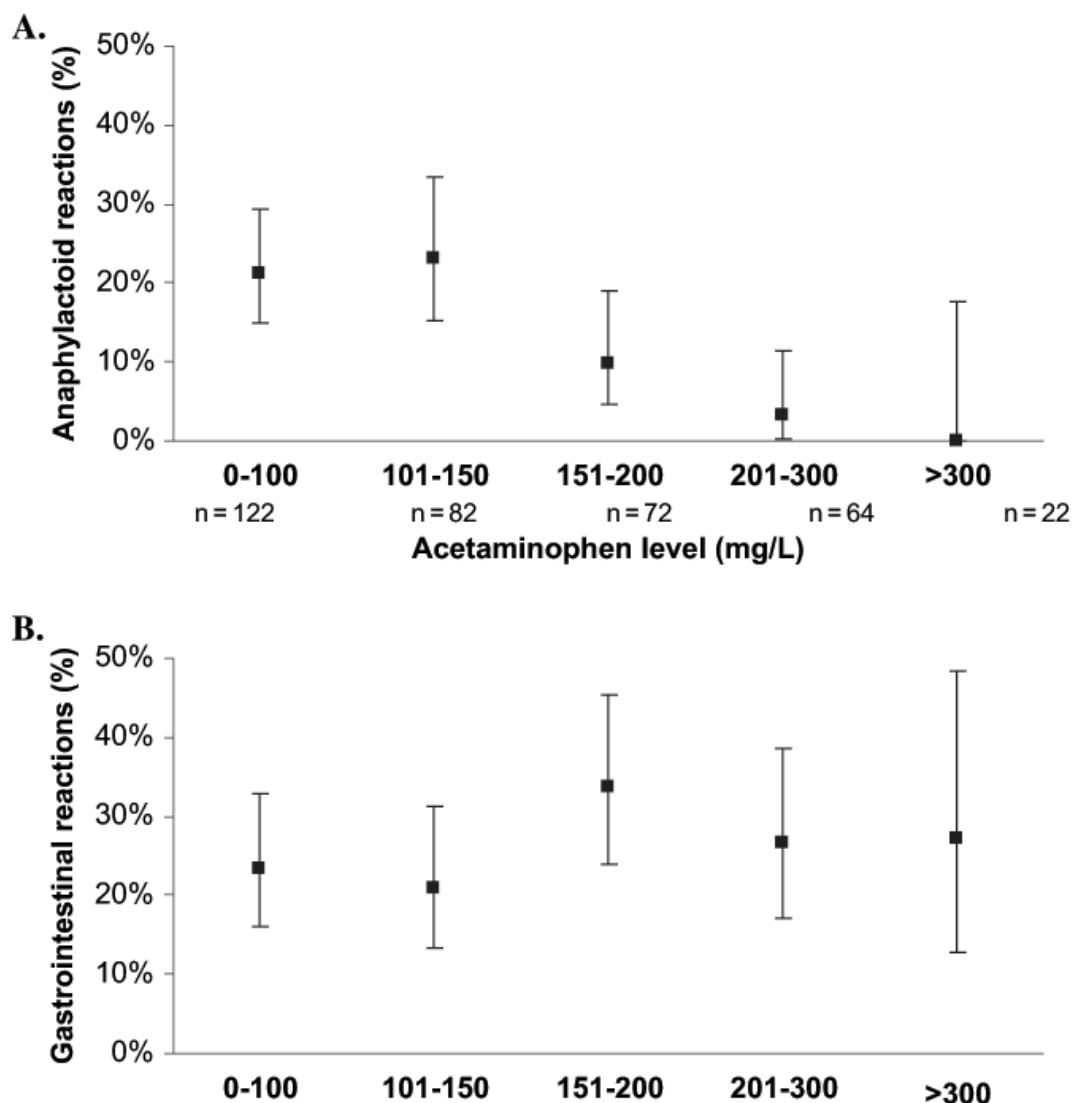
- 1. Bailey, B. and McGuigan, MA (1998) Management of anaphylactoid reactions to intravenous N-acetylcysteine. *Ann Emerg Med* 31 , pp. 710-715. [[crossref](#)]
- 2. Schmidt, LE and Dalhoff, K. (2001) Risk factors in the development of adverse reactions to N-acetylcysteine in patients with paracetamol poisoning. *Br J Clin Pharmacol* 51 , pp. 87-91. [[crossref](#)]
- 3. Lynch, RM and Robertson, R. (2004) Anaphylactoid reactions to intravenous N-acetylcysteine: a prospective case controlled study. *Accid Emerg Nurs* 12 , pp. 10-15. [[crossref](#)]
- 4. Knudsen, TT, Thorsen, S., Jensen, SA, Dalhoff, K., Schmidt, LE, Becker, U. and Bendtsen, F. (2005) Effect of intravenous N-acetylcysteine infusion on haemostatic parameters in healthy subjects. *Gut* 54 , pp. 515-521. [[pubmed](#)] [[csa](#)] [[crossref](#)]
- 5. Butera, R., Georgatos, J., Arrigoni, S., Lonati, D., Petrolini, V., Locatelli, C. and Manzo, L. (2005) Adverse reactions to intravenous acetylcysteine: effects of reducing the infusion rate of the loading dose. *Clin Toxicol* 43 , pp. 437-438.
- 6. Lieberman, P., Kemp, SF, Oppenheimer, J., Lang, DM, Bernstein, L. and Nicklas, RA (2005) The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 115 , pp. S483-523. [[crossref](#)]
- 7. Sampson, HA, Munoz-Furlong, A., Campbell, RL, Adkinson Jr, NF, Bock, SA, Branum, A., Brown, SG, Camargo Jr, CA, Cydulka, R., Galli, SJ, Gidudu, J., Gruchalla, RS, Harlor Jr, AD, Hepner, DL, Lewis, LM, Lieberman, PL, Metcalfe, DD, O'Connor, R., Muraro, A., Rudman, A., Schmitt, C., Scherrer, D., Simons, FE, Thomas, S., Wood, JP and Decker, WW (2006) Second symposium on the definition and management of anaphylaxis: summary reportdSecond National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 117 , pp. 391-397. [[crossref](#)]
- 8. Gheshlagi, F., Izadi-Mood, N., Amini, R. and Montazeri, G. (2005) Prevalence of hypersensitivity reactions to intravenous n-acetylcysteine in acetaminophen poisoned patients. *Clin Toxicol* 43 , pp. 514-515.
- 9. Smilkstein, MJ, Bronstein, AC, Linden, C., Augenstein, WL, Kulig, KW and Rumack, BH (1991) Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. *Ann Emerg Med* 20 , pp. 1058-1063. [[crossref](#)]
- 10. Mant, TG, Tempowski, JH, Volans, GN and Talbot, JC (1984) Adverse reactions to

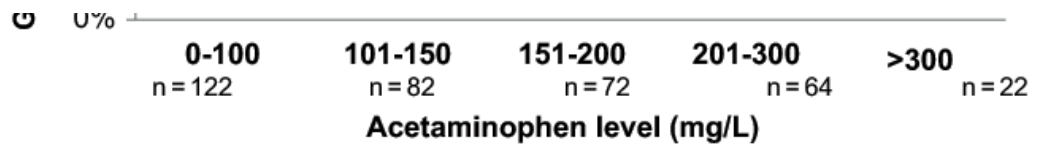
acetylcysteine and effects of overdose. *BMJ* 289 , pp. 217-219. [[pubmed](#)]

- 11. Prescott, LF, Donovan, JW, Jarvie, DR and Proudfoot, AT (1989) The disposition and kinetics of intravenous N-acetylcysteine in patients with paracetamol overdosage. *Eur J Clin Pharmacol* 37 , pp. 501-506. [[crossref](#)]
- 12. Bateman, DN, Woodhouse, KW and Rawlins, MD (1984) Adverse reactions to N-acetylcysteine. *Lancet* 2 , p. 228. [[pubmed](#)] [[crossref](#)]
- 13. Kerr, F., Dawson, A., Whyte, IM, Buckley, N., Murray, L., Graudins, A., Chan, B. and Trudinger, B. (2005) The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. *Ann Emerg Med* 45 , pp. 402-408. [[crossref](#)]
- 14. Jepsen, S. and Hansen, AB (1994) The influence of N-acetylcysteine on the measurement of prothrombin time and activated partial thromboplastin time in healthy subjects. *Scand J Clin Lab Invest* 54 , pp. 543-547. [informaworld]
- 15. Sunman, W., Hughes, AD and Sever, PS (1992) Anaphylactoid response to intravenous acetylcysteine. *Lancet* 339 , pp. 1231-1232. [[pubmed](#)] [[crossref](#)]
- 16. Waring, WS, Pettie, JM, Dow, MA and Bateman, DN (2006) Paracetamol appears to protect against N-acetylcysteine-induced anaphylactoid reactions. *Clin Toxicol* 44 , pp. 441-442.
- 17. Newton, PJ and Thomas, SHL (2006) Anaphylactoid reactions to intravenous acetylcysteine, frequency, risk factors and outcome. *Clin Toxicol* 44 , p. 432.
- 18. Bateman, DN and Good, AM (2006) Five years of poisons information on the internet: the UK experience of TOXBASE. *Emerg Med J* 23 , pp. 614-617. [[crossref](#)]
- 19. Buckley, N. and Eddleston, M. (2005) Paracetamol (acetaminophen) poisoning. *Clin Evid* 14 , pp. 1738-1744.
- 20. (2001) Report of a Working Party of the Royal College of Physicians. Alcohol- can the NHS afford it? Recommendations for a coherent alcohol strategy for hospitals. *Royal College of Physicians of London*
- 21. Rumack, BH, Peterson, RC, Koch, GG and Amara, IA (1981) Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med* 141 , pp. 380-385.
- 22. Zou, G. and Klar, N. (2005) A non-iterative confidence interval estimating procedure for the intraclass kappa statistic with multinomial outcomes. *Biom J* 47 , pp. 682-690. [[crossref](#)]
- 23. Sprong, RC, Winkelhuyzen-Janssen, AM, Aarsman, CJ, van Oirschot, JF, van der Bruggen, T. and van Asbeck, BS (1998) Low-dose N-acetylcysteine protects rats against endotoxin-mediated oxidative stress, but high-dose increases mortality. *Am J Respir Crit Care Med* 157 , pp. 1283-1293.
- 24. Graham, GG and Scott, KF (2005) Mechanism of action of paracetamol. *Am J Ther* 12 , pp. 46-55. [[crossref](#)]
- 25. Nossaman, BD, Baber, SR, Nazim, MM, Waldron, PR, Hyman, AL and Kadowitz, PJ (2007) Acetaminophen, Phenacetin and Dipyrone Do Not Modulate Pressor Responses to Arachidonic Acid or to Pressor Agents. *Pharmacology* 80 , pp. 249-260. [[pubmed](#)] [[crossref](#)]
- 26. Robak, J., Wieckowski, A. and Gryglewski, R. (1978) The effect of 4-acetamidophenol on prostaglandin synthetase activity in bovine and ram seminal vesicle microsomes. *Biochem Pharmacol* 27 , pp. 393-396. [[crossref](#)]
- 27. Mukherjee, TK, Mishra, AK, Mukhopadhyay, S. and Hoidal, JR (2007) High concentration of antioxidants N-acetylcysteine and mitoquinone-Q induces intercellular adhesion molecule 1 and oxidative stress by increasing intracellular glutathione. *J Immunol* 178 , pp. 1835-1844. [[pubmed](#)]

- 28. Lou, H. and Kaplowitz, N. (2007) Glutathione depletion down-regulates tumor necrosis factor (TNF) alpha -induced NF-kappa B activity via Ikappa B Kinase (IKK)-dependent and - independent mechanisms. *J Biol Chem.* — [Epub ahead of print].
- 29. Dimova, S., Hoet, PH, Dinsdale, D. and Nemery, B. (2005) Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *Int J Biochem Cell Biol* 37 , pp. 1727-1737. [[crossref](#)]
- 30. Szaszi, K., Jones, JJ, Nathens, AB, Lo, AY, Marsden, PA, Kapus, A. and Rotstein, OD (2005) Glutathione depletion inhibits lipopolysaccharide-induced intercellular adhesion molecule 1 synthesis. *Free Radic Biol Med* 38 , pp. 1333-1343. [[crossref](#)]
- 31. Sakhi, AK, Blomhoff, R. and Gundersen, TE (2007) Simultaneous and trace determination of reduced and oxidized glutathione in minute plasma samples using dual mode fluorescence detection and column switching high performance liquid chromatography. *J Chromatogr A* 1142 , pp. 178-184. [[crossref](#)]
- 32. Sakaguchi, S. and Furusawa, S. (2006) Oxidative stress and septic shock: metabolic aspects of oxygen-derived free radicals generated in the liver during endotoxemia. *FEMS Immunol Med Microbiol* 47 , pp. 167-177. [[crossref](#)]
- 33. Rork, TH, Hadzimichalis, NM, Kappil, MA and Merrill, GF (2006) Acetaminophen attenuates peroxynitrite-activated matrix metalloproteinase-2-mediated troponin I cleavage in the isolated guinea pig myocardium. *J Mol Cell Cardiol* 40 , pp. 553-561. [[crossref](#)]
- 34. Shaffer, JE, Cagen, LM and Malik, KU (1981) Attenuation by acetaminophen or arachidonic acid-induced coronary vasodilation and output of prostaglandins in the isolated rat heart. *Eur J Pharmacol* 72 , pp. 57-61. [[crossref](#)]

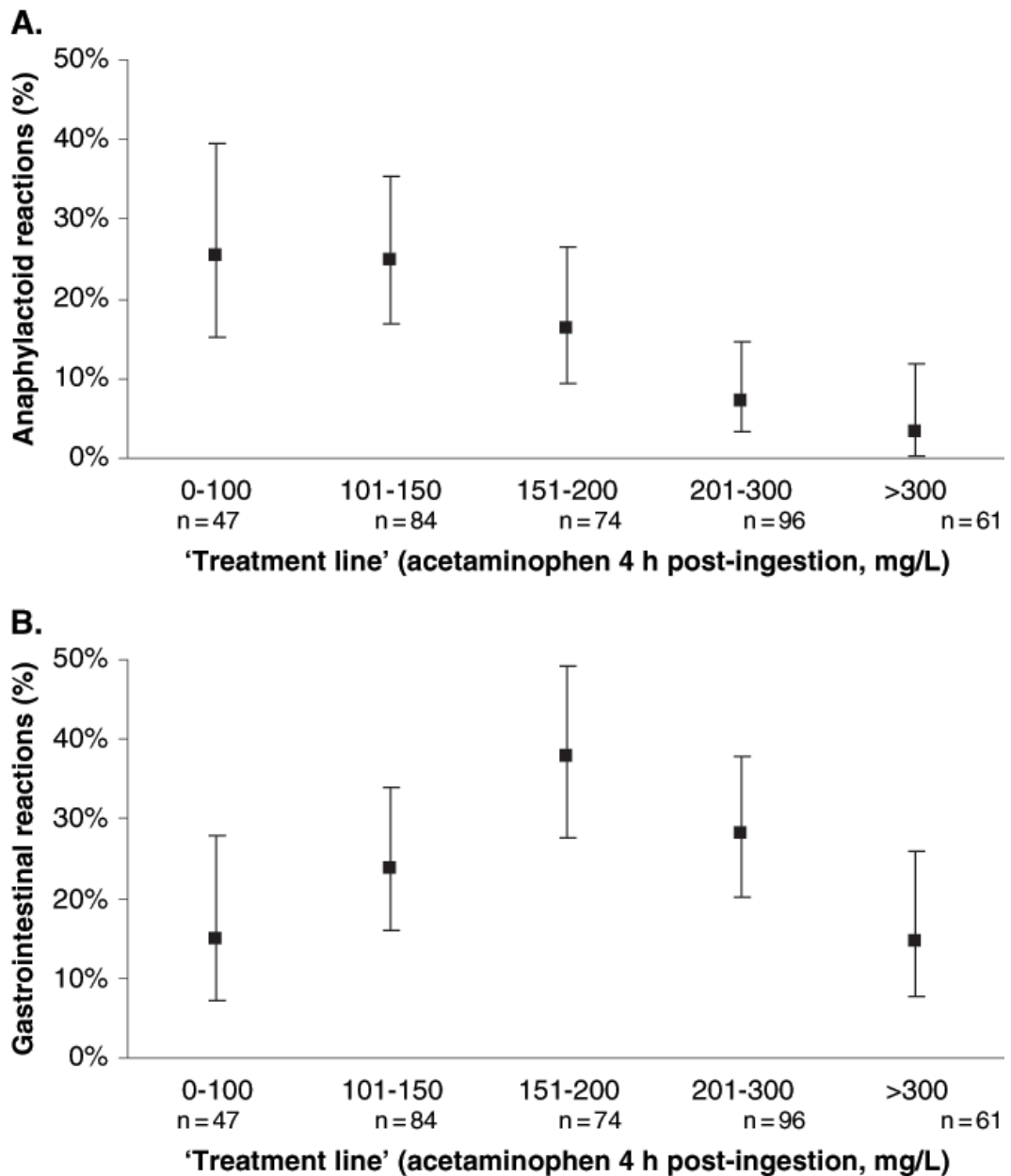
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Fig. 1. Proportion of patients with (A) anaphylactoid, (B) gastrointestinal adverse reactions to NAC with respect to serum acetaminophen concentration, shown with 95% confidence intervals. $p = 0.047$ for anaphylactoid reactions, $p = 0.138$ for gastrointestinal reactions by Cochran-Armitage tests.



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Fig. 2. Proportion of patients with (A) anaphylactoid, (B) gastrointestinal adverse reactions to NAC with respect to equivalent 4 h acetaminophen concentration, shown with 95% confidence intervals. $p = 0.004$ for anaphylactoid reactions, $p =$

0.052 for gastrointestinal reactions by Cochran-Armitage tests.

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