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Australian clinical toxicology investigators collaboration randomized trial of different loading infusion rates of N-acetylcysteine [6]

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Abstract

Adverse reactions to N-acetylcysteine are reported in 6% to 23% of patients who are administered the antidote for treatment of paracetamol poisoning.1 Because paracetamol is the most common pharmaceutical product taken in overdose in many countries, it is essential that attempts be made to prevent or minimize adverse effects caused by N-acetylcysteine. We congratulate Kerr et al2 on their attempt to address this important issue.

Keywords

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Australian Clinical Toxicology Investigators Collaboration Randomized Trial of Different Loading Infusion Rates of *N*-Acetylcysteine

To the Editor:

Adverse reactions to *N*-acetylcysteine are reported in 6% to 23% of patients who are administered the antidote for treatment of paracetamol poisoning.1 Because paracetamol is the most common pharmaceutical product taken in overdose in many countries, it is essential that attempts be made to prevent or minimize adverse effects caused by *N*-acetylcysteine. We congratulate Kerr et al2 on their attempt to address this important issue.

We would like to comment on the following.

Previous studies have shown that atopic individuals, and particularly asthmatic individuals, are more likely to develop reactions to *N*-acetylcysteine.3 We do not know from the study how many individuals in this study were atopic or asthmatic. The incidence of asthma in Australia is recognized to be amongst the highest in world.4

Adverse reactions to *N*-acetylcysteine are more prevalent with low concentrations of paracetamol in the blood of the patient being treated.3 Analysis of this risk factor for anaphylactoid reactions would have been helpful in the study. The reactions to *N*-acetylcysteine would also depend on the plasma *N*-acetylcysteine concentration,5 which was not estimated in this study. A further reason for determining plasma *N*-acetylcysteine concentrations is that previous studies have shown that there are often large variations in the dose of *N*-acetylcysteine to patients with paracetamol poisoning caused by administration errors.6

The endpoints measured in the study comprise various adverse events as recorded by the treating physician. Yet classification of the reaction and whether the reaction was drug related or not was decided independently by 2 investigators at a later date. The potential ‘‘subjective’’ nature of this assessment is a possible source of bias. Actions taken to treat an event have been taken into account when such classification was made. It is not unusual for different physicians to treat the same condition differently. Furthermore, the classification system used was one designed for adverse events associated with long-term drug administration.

The best indicator of hepatotoxicity caused by paracetamol is International Normalized Ratio (INR). Though measurement of alanine amino transferase (ALT) and INR was made, maximum measured values of ALT were used to assess the efficacy of the 2 treatment arms. The baseline ALT concentration has a bearing on the maximum level reached, and therefore the degree of increase in ALT from baseline might have been a better indicator.

N-acetylcysteine has an elimination half-life of 5.7 hours. Adverse events were observed every 30 minutes during the first 4 hours and at 2-, 4-, and 8-hour intervals subsequently. Given a half-life of almost 6 hours, the results may have been different if the observations had been made more frequently, especially in the early part of the infusion. It would have been helpful if the adverse events after the first 15 minutes were compared between the 2 groups because most adverse reactions seem to occur during the first 15 minutes.5

The study on *N*-acetylcysteine use and infusion rates probably needs to be repeated over a long loading time and with detailed study of adverse events.

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