

Letter to the editor

How safe is intravenous N-acetylcysteine for the treatment of paracetamol poisoning? (Hong Kong J Emerg Med 2007;14:198-203)

Dear Editor,

We read with interest Merl et al's article "How safe is intravenous N-acetylcysteine for the treatment of paracetamol poisoning?" and would like to raise comment on the statistical analysis method adopted in the article.

The authors have applied chi-square test to analyse the association between the rates of N-acetylcysteine (NAC) infusion and frequency of adverse drug reaction (ADR). The authors concluded that they "found no association between the rate of infusion and likelihood of ADR". We beg to differ from this opinion. We would like to point out that at least two values of expected

frequency were less than 5 and one expected value of frequency was even less than 1. Therefore to apply chi-square test could be inappropriate and introduce significant bias (Table 1).

To elaborate it further, if this study could have enough sample size (say three times of the present sample size but with the same proportionate outcome so that above 80% of the values of expected frequency would be greater than 5 and no value less than 1), the p-value would change dramatically from not significant to "very" significant (Table 2).

We believe that combining the categories could be one possible solution to the problem of inadequate sample size for this study. If the four categories were combined into two categories for analysis, the statistical result would be totally different as shown in Table 3. Of course, one could argue that this may lead to loss of

Table 1. Contingency table of original data

Rate of initial NAC infusion	No ADR		ADR		p-value
	Observed	Expected	Observed	Expected	
15 min	108	113.5	20	14.5	p=0.122
30 min	15	16.0	3	2.05	
60 min	142	136.5	12	17.5	
>120 min	8	7.09	0	0.909	
Total	273		35		

ADR = adverse drug reaction; NAC = N-acetylcysteine

Table 2. Contingency table of hypothetical case (3 times the sample size but same proportionate outcome as the data in Table 1)

Rate of initial NAC infusion	No ADR	ADR	p-value
15 min	324	60	p=0.0006
30 min	45	9	
60 min	426	36	
>120 min	24	0	
Total	819	105	

ADR = adverse drug reaction; NAC = N-acetylcysteine

Table 3. Contingency table of combined categories of data

Rate of initial NAC infusion	No ADR		ADR		p-value
	Observed	Expected	Observed	Expected	
30 min or below	123	129.4	23	16.6	p=0.034 (with Yates' correction)
60 min or above	150	143.6	12	18.4	
Total	273		35		

ADR = adverse drug reaction; NAC = N-acetylcysteine

useful information. However, we believe that this approach should be acceptable because the total number of observations in the groups of 30 min and >120 min were much smaller than the other two groups.

The logical fallacy in this scenario has reminded us that chi-square procedures are computationally simple,

but they actually rest upon a complex logical substructure.

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Authors' reply

Dear Editor,

We thank Dr Tsui and Dr Kam for their interest in this work and the obviously thorough attention that they have paid to the data.

We chose an omnibus chi-square approach to test the association between infusion rate and the rate of adverse drug reactions, as this can be applied to 4 x 2 tables such as this and we had some concerns about treating infusion rate as accurate continuous data, based on our clinical experience. P values calculated by Pearson's method and the exact [i.e. Fisher's] method using STATA on this data give very similar results [p=0.122 and p=0.118 respectively]. Thus we do not accept that suggestion of significant bias. We do not agree that post hoc combination of categories is appropriate, as this in itself adds bias. We do however wish to point out that this does not mean that there is no association between these variables. Failure to find a p<0.05 does not mean the variables are not related.

Given Dr Tsui and Dr Kam's concerns, we have sought an independent expert statistical review of the analysis.

Professor Damien Jolley [Monash University] suggested that logistic regression analysis using values for infusion rate rather than categories and analysing for the risk of ADR might be an alternative way of addressing this question. He calculated that the risk of ADR decreased with OR=0.32 (95% CI: 0.12 to 0.83, p=0.02) for every hour increase in infusion time – a significant relationship. That said, as we all know in emergency medicine, the accuracy of actual rather than prescribed infusion times is unclear, which confounds analysis using infusion times as continuous data. It is possible that the approach we adopted was overcautious.

On the question of sample size, we do not agree with Dr Tsui and Dr Kam. Every observed table can be made 'significant' by increasing the sample size. All this proves that a P-value is an imperfect measure of association and that where there are appropriate alternative methods of analysis, these should be employed.

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