

## Should N-acetylcysteine be administered orally or intravenously for the treatment of paracetamol overdose?

治理撲熱息痛劑量過度，乙醯半胱氨酸應以口服或靜脈內施與？

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**Introduction:** Paracetamol is the most commonly used drug in deliberate poisoning. N-acetylcysteine is the standard antidote for significant acute paracetamol overdose, but the route of administration varies between countries. This review aimed to find and appraise those comparative studies which would help answer the following question: in patients who have taken an overdose of paracetamol requiring antidote, is there any difference between intravenous and oral N-acetylcysteine in mortality, hepatotoxicity, adverse drug reactions or cost? **Methods:** A literature search was conducted using Medline and other databases. Relevant papers were identified and appraised. **Results:** One animal study and seven comparative clinical studies were identified and appraised. The quality of the evidence was generally poor, and there was no clear difference in outcomes between the two routes of administration. **Conclusions:** Without evidence of advantage for one route over the other, routine practice should not be changed. However, after 30 years experience, both routes appear to be effective and safe, and in countries where intravenous administration is the standard, it would be reasonable to consider the oral route as an alternative when intravenous access is problematic. There is a need for prospective, randomised trials to determine the relative effectiveness, safety and cost of intravenous and oral formulations of N-acetylcysteine. (*Hong Kong j.emerg.med.* 2009;16:106-116)

**導言：**撲熱息痛是蓄意服毒中最普遍使用的藥物。在嚴重的急性撲熱息痛過量，乙醯半胱氨酸是標準的解毒劑，但在不同國家有不同的施藥途徑。本評論文章旨在尋找及鑑定那些可以幫助解答以下問題的比較性研究：服食過量撲熱息痛而需要解毒劑的病人，口服或靜脈內施用乙醯半胱氨酸對死亡率、肝毒害性、藥物副作用或成本有否分別？**方法：**使用醫學文獻及其他的資料庫進行文獻搜索。識別及評估有關的文章。**結果：**識別及評估一個動物的研究及7個比較性臨床研究。證據的質素一般上很差，而兩種施藥途徑在結果上沒有清晰的分別。**結論：**在沒有證據顯示一個途徑較優下，不應改變慣常的做法。然而經過30年的經驗後，兩種途徑看來有效及安全，在以靜脈施藥為標準的國家中，當靜脈內通道有困難時，考慮口服途徑作另一選擇是合理的。有需要進行前瞻性隨機化的試驗，以確定靜脈內及口服乙醯半胱氨酸配方的相對有效性，安全性及成本。

**Keywords:** Acetaminophen, acetylcysteine, intravenous infusions, oral administration

**關鍵詞：**醋氨酚，乙醯半胱氨酸，靜脈內輸注，口服

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## Introduction

Paracetamol (acetaminophen, N-acetyl-p-aminophenol, APAP) is the most commonly used drug in the world,<sup>1</sup> and the most commonly used drug for deliberate self poisoning in the United Kingdom (UK), United States (US) and Hong Kong.<sup>2-4</sup> From 1993 to 2002 there were approximately 30,000 admissions each year for paracetamol overdose in England.<sup>5</sup> In Hong Kong, paracetamol poisoning is less common than in the UK but the incidence is rising. A total of 222 Chinese patients presented to the Prince of Wales Hospital with paracetamol poisoning over the six years from 1988 to 1993, which suggests an annual incidence less than 10% of that in the UK.<sup>6</sup> In 2001 across six Hong Kong emergency departments, paracetamol was the most common drug used in deliberate poisoning, and N-acetylcysteine (NAC) the most frequently used antidote. In the six months of the study, 109 patients received NAC.<sup>4</sup>

Before the availability of effective antidotes in the 1970s, about 10% of all paracetamol overdoses referred to hospital resulted in severe hepatotoxicity, defined as a peak plasma aspartate or alanine aminotransferase (AST or ALT) >1000 iu/l.<sup>2</sup> Between 1-3.5% developed fulminant, and often fatal, hepatic failure.<sup>1,7</sup> Plasma paracetamol levels taken at least 4 hours after a single acute ingestion indicate the need for antidote to prevent these sequelae. In the UK and Hong Kong, treatment nomograms are based on semi-logarithmic plots connecting plasma paracetamol levels of 200 mg/l at 4 hr with 30 mg/l at 15 hr.<sup>8,9</sup> Those presenting with paracetamol levels above this line are considered to have a "probable risk" of hepatotoxicity (60% if untreated). The US adapted Prescott's nomogram by adding a "possible" risk line from 150 mg/l, 25% lower, in view of the uncertainty over the exact time of overdose and the reliability of laboratory assays.<sup>10</sup> In the UK, if patients are considered to be high risk because of glutathione depletion or enzyme induction (e.g. alcoholism, eating disorders, enzyme inducing drugs, human immunodeficiency virus) a line from 100 mg/l is used.

Consensus opinion is that NAC is the antidote of choice.<sup>11,12</sup> Oral methionine can also be used as an

antidote, and is considered a second-line treatment.<sup>13</sup> However, it is rarely used. In the Hong Kong epidemiological studies referred to above, of several hundred paracetamol overdoses, NAC was administered in 133 cases. Methionine was not mentioned as a treatment option.<sup>4,7,9</sup>

NAC is converted to glutathione in hepatocytes, as well as acting like glutathione directly to detoxify N-acetyl-p-benzo-quinone imine, a toxic metabolite of paracetamol. However, there is disagreement over which route of administration is best. In Europe, Australasia and Canada, intravenous (IV) NAC is the standard antidote for significant acute paracetamol poisoning.<sup>1</sup> In the US, although the Food and Drug Administration (FDA) approved the use of an IV formulation of NAC in 2004, oral (PO) NAC is still often used.<sup>1</sup> IV NAC is recommended in Hong Kong<sup>8</sup> and most of Asia<sup>13</sup> although PO NAC is used in Taiwan<sup>3</sup> and Vietnam, according to information from their National Poison Control Centre (Nguyen TN, 30th June 2008, email communication). For adults, IV NAC is administered in the UK and Hong Kong at a total of 300 mg/kg over 20 hours: 150 mg/kg in 200 ml of 5% dextrose over 15 minutes, then 500 mg/kg in 500 ml over 4 hours, then 1000 mg/kg in 1000 ml over 16 hours.<sup>1</sup> More recently in Australia, the first dose of 150 mg/kg has been given over 60 minutes rather than 15 minutes.<sup>14</sup> In children, smaller volumes of 5% dextrose are recommended to avoid the risk of hyponatraemia: for children over 20 kg, half the adult volumes are used; for children under 20 kg, the three doses are administered respectively in 3 ml/kg, 7 ml/kg and 14 ml/kg of 5% dextrose.<sup>13</sup> The traditional PO regime in the US administers a total of 1330 mg/kg over 72 hours: 140 mg/kg loading dose, then 70 mg/kg every 4 hours for 17 more doses.<sup>1</sup> Some centres use an abbreviated form of this regime according to paracetamol and AST levels.<sup>15</sup>

This variety in treatment regimes for such an important problem as paracetamol overdose implies a lack of evidence-based consensus. Two evidence-based reviews conducted in 2005, which shared a co-author, found no clear difference between PO and IV NAC (nor between different IV protocols) regarding mortality or hepatotoxicity. No good quality randomised trials were

identified, and their conclusions were drawn from case-series alone.<sup>2,11</sup> Nonetheless, proponents of each route of administration claim advantages in effectiveness, cost and safety.

PO NAC, which is said to provide an early high concentration to the liver through the portal venous system, is claimed to be more effective than IV NAC, especially for those presenting after 15 hours, with allegedly fewer serious adverse reactions.<sup>1,16-19</sup> The drug itself is often cheaper. Inadvertent NAC overdose, which has caused two deaths with IV administration,<sup>20</sup> is supposed to be less likely when given PO. PO NAC can also be used in those with difficult or refused IV access.

Proponents of IV NAC claim increased effectiveness, in part because the dose is more predictable, especially as there should be less vomiting and no adsorption by oral charcoal.<sup>9,12,14,19</sup> The usual dosing regime is shorter and should allow earlier discharge and lower costs.<sup>18,21</sup> IV NAC is the only route shown to benefit patients in established hepatic failure following a paracetamol overdose.<sup>11</sup> Lastly, in Hong Kong, UK and Australasia, IV administration is more familiar to staff.

With FDA approval of the IV formulation of NAC in 2004, it seemed there was a fresh opportunity for trials to be conducted in the US directly comparing IV and PO NAC. Such studies would be unlikely to have been published in time for the Cochrane review. Comparative studies published previously but not included in Cochrane because of insufficient quality, might also be of use in view of the otherwise limited evidence.

The purpose of this paper therefore is to find and appraise those studies which compare IV and PO NAC in order to answer the following three-part question: in patients who have taken an overdose of paracetamol requiring antidote, is there any difference between intravenous and oral NAC in mortality, hepatotoxicity, adverse drug reactions, or cost?

## Methods

The Ovid interface was used to conduct a literature

search using Medline (1950 to present), Embase (1947-2008 week 26), Cinahl (1982-2008 June) and EBM Reviews (to second quarter 2008).

The search strategy used the following terms: [exp Acetaminophen/ OR (acetaminophen OR paracetamol OR APAP).mp] AND [exp Acetylcysteine/OR (acetylcystein\$ OR n-acetylcystein\$ OR NAC).mp] AND [exp Administration, Oral/OR oral\$.mp] AND [exp Infusions, Intravenous/OR (intravenous\$ OR IV).mp]

The toxicological abstract database Current Awareness in Clinical Toxicology (CACT) 1997-2008 was also searched ([www.npis.org/archive.htm](http://www.npis.org/archive.htm)).

The abstracts of all identified references were assessed by the reviewer for relevance to the three-part question, and relevant papers critically appraised.

## Results

The search strategies found 51 references in Medline, 138 in Embase, 12 in Cinahl and 3 in EBM reviews. The CACT database identified one abstract not found in the other searches.<sup>22</sup>

From the abstracts of these papers seven clinical comparative studies<sup>8,15,19,22-25</sup> and one laboratory animal randomised controlled trial (RCT)<sup>26</sup> were identified. These were appraised and summarised in Table 1.

## Discussion

The animal study is of pharmacological interest but not clinically relevant, especially because cats respond metabolically to paracetamol very differently from humans. Paracetamol is extremely toxic to cats as they lack glucuronyl transferase.<sup>26</sup>

From the summaries of the clinical studies in the table, it is clear that comparative evidence of benefit of one route of NAC over the other is lacking. Two of the studies were not strictly comparative at all.<sup>15,23</sup> Four of the other studies were so limited by potential confounding, bias or chance that any suggestion of

Table 1. Summary of appraisal

Author, date, country	Subject group	Study type	Outcomes	Key results	Study weaknesses
Savides, 1985, US <sup>26</sup>	Laboratory cats 6 study animals (IV & PO) 6 controls (no antidote)	Randomised controlled crossover trial	Clinical signs and biochemistry	No difference between IV and PO; both IV and PO were better than controls.	Very small, laboratory animal study Cats lack glucuronyl transferase
					<b>Conclusion:</b> Not clinically relevant
Perry, 1998, US <sup>7</sup>	Paediatric patients (<16 years) presenting within 24 hours of an acute single "possibly hepatotoxic" paracetamol overdose  25 IV NAC over 52 hours (1986-1996)  29 historical controls from that hospital; PO NAC over 72 hours (1989-1996)	Prospective observational study; retrospectively determined control group	<b>Primary</b>  Hepatotoxicity      <b>Coagulopathy (clinical; fresh frozen plasma need)</b>  <b>Encephalopathy (clinical; electroencephalogram)</b>  <b>ADR (including hives, erythema)</b>  <b>Other</b>  Vomiting (delaying therapy; need for antiemesis)	No significant difference  IV 2 patients (8.0%) PO 2 patients (6.9%)  Zero in either group treated within 10 hours of ingestion  IV 2 patients with minimal symptoms (8%) PO zero  IV zero PO 1 patient (3.4%)  IV 2 patients PO 2 patients	Paediatric only  Manufacturer supplied IV NAC  Small numbers, no power-calculation  Non-randomised, treatment allocation at physician's discretion  Historical controls, slightly different time period  Unknown number in IV group were PO treatment failures. Not "intention to treat" analysis  Significantly longer delay to treatment in IV group  More vomiting in IV group possibly related to earlier PO treatment-failure  Only p-values to compare groups, but no comparison for ADR or vomiting
					<b>Conclusion:</b> Level of evidence 2-

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Table 1. Summary of appraisal (cont'd)

Author, date, country	Subject group	Study type	Outcomes	Key results	Study weaknesses
Buckley, 1999, Australia <sup>19</sup>	1. 981 patients in one hospital with paracetamol overdose (1987-1996), 205 given IV NAC 2. 86 patients from this study and 255 patients from 3 other studies, with "probably hepatotoxic" paracetamol ingestion given IV NAC <sup>9,17,27</sup> 1462 "probably hepatotoxic" patients given PO NAC over 72 hours <sup>10,15,16</sup>	1. Prospective observational study 2. Incorporated into meta-analysis of IV or PO NAC case-series	Primary Hepatotoxicity	1. 14/205 (30/981) with hepatotoxicity, associated with larger ingestion dose, higher paracetamol levels, delayed presentation 2. Total hepatotoxicity rate: IV 16% PO 19% (No significant difference)	No power-calculation Criteria for NAC changed during the study from <15 to <24 hr post-ingestion Only included series which measured AST/ALT, to determine hepatotoxicity Heterogeneity of studies Different IV NAC protocols used No statistical analysis performed comparing IV and PO NAC
Lifshitz, 2000, Israel <sup>23</sup>	All patients with paracetamol overdose treated with IV NAC in one hospital (1994-1998) 92 patients aged 18-52 years hospital stay	Retrospective observational study; cost comparison evaluated according to average rates for drugs and hospital stay	ADR ADR Cost	1. 12/205 (6%) ADR mostly flushing and urticaria, two anaphylactoid reactions 2. Not compared 3/92 (3.3%) ADR, mild urticaria or pruritic rash PO costs are three times greater than IV	Patients from one IV study not included in the total, which would change the pooled IV NAC hepatotoxicity rate to 19% Conclusion: Level of evidence 2+
			Other		Retrospective No controls No comparison for ADR Cost comparison theoretical only Conclusion: Level of evidence 3

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Table 1. Summary of appraisal (cont'd)

Author, date, country	Subject group	Study type	Outcomes	Key results	Study weaknesses
Mullins, 2004, US <sup>24</sup>	Patients treated at children's hospital (<19 years) for single acute paracetamol poisoning (1997-2003) 17 IV NAC 72 PO NAC	Retrospective observational comparative study	ADR	IV 6 patients (35%) including 2 nausea, 2 vomiting, 2 rash PO 40 patients (56%) including 29 (40%) vomiting, 10 (14%) nausea, 2 (3%) abdominal pain	Limited details, published as letter/abstract Paediatric only Hepatotoxicity not studied Small numbers, no power-calculation
			Hospital stay	IV median 1 day (range 1-4) PO median 3 days (range 1-10)	Non-randomised, not clear why patients received which protocol Two patients changed from PO to IV, analysed in IV NAC group
			Hospital charges	IV \$5634.63 PO \$5261.54	<b>Conclusion:</b> <b>Level of evidence 2-</b>
Tsai, 2005, Taiwan <sup>15</sup>	Study group: ED presentations of an at least "possibly hepatotoxic" paracetamol overdose (1997-2002) 27 patients given "patient-tailored" PO NAC protocol, variable duration until paracetamol <10 mg/l and AST <40 iu/l Historical controls: 1462 PO NAC (72 hours) <sup>16</sup> 100 IV NAC (20 hours) <sup>9</sup>	Retrospective observational study; historical controls from the literature	Hepatotoxicity	<b>Treatment delay &lt;10 hours</b> Study group: 5% (95% CI 0.1-24.9) Historical groups: PO 6.1% (4-8) IV 1.6% (0-9) <b>Treatment delay &gt;10 hours</b> Study group: 25% (8.7-49.1) Historical groups: PO 26.4% (24-30) IV 52.6% (36-69)	Study patients identified from codings 30 patients excluded because of missing data Historical controls, based on only two papers, from different times/countries, no attempt at systematic review or matching controls Comparative statistical analysis not done because of small sample size, no power-calculation <b>Conclusion:</b> <b>Level of evidence 3</b>

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Table 1. Summary of appraisal (cont'd)

Author, date, country	Subject group	Study type	Outcomes	Key results	Study weaknesses
Yarema, 2006, Canada/US <sup>22</sup>	PO group (72 hours): 2022 patients from the 1976-85 US National Multicenter Study  IV group (20 hours): 1813 patients treated in 34 Canadian hospitals 1980-2005	Retrospective observational comparative study	Hepatotoxicity	PO: 15.4%; IV: 7.3%  Absolute difference 8.1% (95% CI 6%-10.1%)  The difference was greatest for those treated between 4-13 hours post-ingestion	Limited details, published only as abstract  Retrospective  Compared cohorts from different countries and different time periods  <b>Conclusion:</b> <b>Level of evidence 2-</b>
Miller, 2007, US <sup>25</sup>	Patients admitted for paracetamol overdose at one hospital, who received a full course of NAC  20 PO NAC (72 hours), from 2002-2004  17 IV NAC (20 hours) from 2004-2006	Retrospective observational comparative study	Percentage of patients given anti-emetics   Anti-emetic doses given per patient treated with NAC  Cost of anti-emetics (US\$)  IV: \$14.7 (SE 4.92) (p=0.1)	PO: 75% IV: 58.8% Relative risk 0.78 (95% CI 0.48-1.25, p=0.48)   PO: 2.8 (SE 0.7) IV: 1.1 (SE 0.2) (p=0.04)  PO: \$49.31 (SE 19.64) IV: \$14.7 (SE 4.92) (p=0.1)	Retrospective  Small numbers, no power-calculation  Excluded 74 patients treated with NAC who did not complete the course  IV was only used for fulminant hepatic failure, patient intolerance of oral NAC or concurrent gastrointestinal bleeding  Cost analysis did not include costs other than anti-emetics  Reasons for anti-emetic prescription were not standardised and could have been influenced by physician expectation of NAC route rather than patient nausea  Compared cohorts from different time periods  <b>Conclusion:</b> <b>Level of evidence 2-</b>

Note: Levels of evidence are as used by the National Institute for Health and Clinical Excellence (UK), and the Scottish Intercollegiate Guidelines Network.<sup>27</sup>

ADR=adverse drug reaction; ALT=alanine aminotransaminase; AST=aspartate aminotransaminase; IV=intravenous; NAC=N-acetylcysteine; PO=oral

causality in detected differences cannot be relied on.<sup>7,22,24,25,27</sup> In addition, two of the studies were paediatric. As children may metabolise paracetamol differently, and tend not to use alcohol, extrapolation to an adult population would be difficult.<sup>7,24</sup>

In view of the weakness of these comparative studies, the best evidence available seems to be that from pooling and comparing case-series.<sup>2,11,19</sup> This evidence is not level 1, which requires at least one RCT.<sup>27</sup> These reviews of case-series excluded those with too few or selected patients, but there are still large risks of bias, and not just because the case-series were not directly controlled. There is the possibility of incorrect timings, especially when associated with serious intent and alcohol ingestion. Some PO NAC patients may be identified as "hepatotoxic" on the basis of a later, slight elevation which would be missed had they been discharged earlier after the shorter IV NAC protocol. Some studies used non-standard protocols of IV or PO NAC, which also makes comparison difficult. The authors acknowledge the very high risk of bias in these studies, and find no evidence for one route over the other. However, they conclude that IV is the treatment of choice "until evidence... that oral NAC is as effective".<sup>11</sup>

In terms of mortality and hepatotoxicity, the Cochrane review<sup>11</sup> pooled data from 9 case-series including 1614 PO patients and 637 IV.<sup>9,12,14,17-19,21,28,29</sup> Because of the heterogeneity of the series, no comparative statistical analysis was made. Different studies used different definitions of adverse drug reactions, and pooling this data would be misleading. Mortality was very low, with no deaths at all in those treated with NAC within 10 hours of paracetamol ingestion, and only 1% (PO) and 2% (IV) between 10-24 hours. Mortality overall was 0.6% (PO) and 0.9% (IV). Hepatotoxicity was much higher when NAC was started late. At 0-10 hours, hepatotoxicity was 7% (PO) and 4% (IV); at 10-24 hours 27% (PO) and 21% (IV). In the previous edition of the Cochrane review,<sup>11</sup> which didn't include the two IV studies from 2005,<sup>14,29</sup> hepatotoxicity in the 10-24 hour IV group was 29%. In the 2002 Cochrane issue there appeared to be little difference between the two routes; in the 2006 issue it appears possible that IV

NAC might have a lower hepatotoxicity rate in the later treatment group.

This however does not take into account a potential time bias. Table 2 presents hepatotoxicity data from the case-series used by Cochrane. The original papers were consulted for hepatotoxicity rates for patients with "probably hepatotoxic" paracetamol levels who were treated with NAC 10-24 hours post-ingestion. This group was chosen as it represents clearly defined patients at highest risk of poor outcomes for whom prompt antidote treatment is most important. One study did not present sufficient detail to determine how many patients belonged to this group.<sup>29</sup> Smilkstein's study<sup>17</sup> included data from the two earlier papers from the ongoing National Multicenter Study,<sup>10,16</sup> and the figures presented in Table 2 have adjusted the data accordingly. From the data presented in the papers, 95% confidence intervals were calculated by this author. There is no significant difference between the routes of NAC administration.

As well as demonstrating similar results for each route, there appears to be a trend of improvement from the late 1970s for both IV and PO NAC, although the heterogeneity of these studies precludes formal analysis. Several reasons could be hypothesised: the general care of patients may have improved; there might be less co-ingestion of other more hepatotoxic drugs; overdose patients might be younger; there might be more awareness of paracetamol overdose among ED staff and therefore earlier treatment. Whatever the reason, a time bias would prevent reliable conclusions being drawn from studies that compare new data with historical controls. A decreasing trend in mortality rates from poisoning with other drugs (excluding opiates and drugs of abuse) has also been documented.<sup>5</sup>

In terms of adverse reactions to NAC, there is no good evidence either from the comparative papers presented here, nor from any reviews of case-series. In one such review, 3-48% of patients treated with IV NAC experienced some degree of anaphylactoid reaction with histamine release, including pruritus, rash, nausea and vomiting, through to angio-oedema, bronchospasm and

**Table 2.** Hepatotoxicity rates in high risk paracetamol overdose treated with PO and IV N-acetylcysteine

Author, country	Date	PO NAC	% (95%CI)	IV NAC	% (95%CI)	Notes
Rumack, US <sup>16</sup>	78	23/51	45 (31-59)	–	–	
Prescott, UK <sup>9</sup>	79	–	–	20/38	53 (37-69)	
Rumack, US <sup>10</sup>	81	16/40	40 (25-55)	–	–	Having subtracted data from Rumack 78 <sup>16</sup>
Smilkstein, US <sup>17</sup>	88	208/844	25 (22-28)	–	–	Having subtracted data from Rumack 78 and 81 <sup>10,16</sup>
Parker, UK <sup>28</sup>	90	–	–	7/20	35 (14-56)	
Smilkstein, US <sup>18</sup>	91	–	–	23/85	27 (18-37)	Used 48 hour IV NAC protocol
Spiller, US <sup>12</sup>	94	6/36	17 (4-29)	–	–	9-16 hours post-ingestion; "possibly hepatotoxic" paracetamol levels
Buckley, Australia <sup>19</sup>	99	–	–	3/37	8 (0-17)	
Woo, US <sup>21</sup>	00	4/19	21 (3-39)	–	–	Some patients received shorter PO protocols if not hepatotoxic
Kerr, Australia <sup>14</sup>	05	–	–	11/112	10 (4-15)	Including both 15 min and 60 min loading doses IV NAC; may have included some patients with lower paracetamol levels
<b>Total</b>		<b>257/990</b>	<b>26.0</b> (23.3-28.8)	<b>64/292</b>	<b>21.9</b> (17.4-27.2)	<b>P = 0.16</b>

IV=intravenous; NAC=N-acetylcysteine; PO=oral

shock.<sup>30</sup> Merl et al noted that adverse drug reaction (ADR) rates were higher (42-48%) in prospective studies than in retrospective studies (4-9%). In their own study, the rate was 12%, with "major" ADR 0.6% (hypotension and angio-oedema).<sup>20</sup> There are also two case-reports of death occurring from inadvertent over-administration of IV NAC, and one in an asthmatic.<sup>2</sup> PO NAC is most commonly associated with vomiting and abdominal pain, up to 63% in one series, as well as rarer anaphylactoid reactions.<sup>31</sup>

It seems reasonable to accept that there might be increased vomiting with PO NAC, and more anaphylactoid reactions with IV NAC. As the Cochrane review suggested, PO NAC has more risk of less significant reactions, and IV NAC a much smaller risk of much more significant reactions.<sup>11</sup> However, without knowing how frequent and severe these

reactions are, we cannot conclude that one route is preferable or cheaper.

Cost is also an important factor in the decision to use one or the other route for administration of NAC. The studies presented in this review were not of sufficient quality to determine whether one route is more cost-effective.<sup>23-25</sup> In the US, the IV formulation is more expensive than PO. However, the total IV dose administered is usually less, as is the duration of treatment with possible savings from reduced bed-stay. Costs of treating adverse reactions must also be considered.<sup>30</sup>

Ideally, an RCT would establish the best route and regime for NAC administration. In those treated early, the very low incidences of death and hepatotoxicity would require very large numbers of patients to power

such a study. It would be difficult to achieve this in Europe or Australia where IV treatment is well established, and the recent Australian RCT demonstrated the difficulty of recruiting even 200 patients over a few years.<sup>14</sup> However, it should still be feasible to conduct a RCT comparing ADRs and cost-effectiveness.

It is an important question to answer, as PO NAC might be a welcome addition to our armamentarium in Hong Kong and elsewhere. If both routes were safe and effective, it might allow the occasional use of PO NAC in cases of difficult or refused IV access, or when IV NAC might be a particular risk. In a questionnaire survey of all Emergency Medicine specialists and senior trainees in Wales in June 2006, only 57% had heard of PO NAC and 4% had seen it used. If it were available however, 71% said they would consider using it. The most commonly suggested advantages for PO NAC were ease of administration and avoidance of IV cannulation in difficult cases such as patient refusal, needlephobia, or poor access.<sup>32</sup>

Lastly, comment must be made regarding the option of methionine. Although methionine is an accepted second-line oral alternative to NAC, there is little experience of its use. There has been no randomised controlled trial comparing methionine with NAC, and the Cochrane review found only four case series of treatment with methionine. These dated from the late 1970s and early 1980s, and demonstrated very similar efficacy to NAC in terms of mortality and hepatotoxicity, but included a total of only 197 patients.<sup>11</sup> Rather than recommending as second-line a drug for which there is little international experience, and for which the evidence of effectiveness is based on a small series of patients from nearly 30 years ago, it would seem more prudent to use PO NAC which has been used extensively as first-line treatment in the US and elsewhere with similar results to IV NAC, in case series now totalling nearly 4000 patients.<sup>22</sup>

## Conclusion

There is insufficient evidence to decide between the IV and PO routes for the administration of NAC, in

terms of effectiveness, safety or cost. Lack of evidence of difference does not mean there is no difference, but any difference is unlikely to be large. After 30 years of US experience, it does seem clear that the PO regime is also effective and safe. It would seem reasonable to use PO NAC when IV access is problematic, or there is concern about possible severe reactions. It could also be considered for units that do not use IV infusions, such as psychiatric wards. However, without good evidence to change we should continue to use IV NAC as our usual, standard practice for most patients. There is a need for good prospective, randomised trials to determine the relative effectiveness, safety and cost of intravenous and oral formulations of N-acetylcysteine.

## References

1. Prescott L. Oral or intravenous N-acetylcysteine for acetaminophen poisoning? *Ann Emerg Med* 2005;45(4):409-13.
2. Buckley N, Eddlestone M. Paracetamol (acetaminophen) poisoning. *Clin Evid* 2005;14:1738-44.
3. Tsai CL, Chang WT, Weng TI, Fang CC, Chen WJ. Acute acetaminophen intoxication in Taiwan: outcomes and risk factors. *J Formos Med Assoc* 2004;103(11):830-5.
4. Chan YC, Fung HT, Lee CK, Tsui SH, Ngan HK, Sy MY, et al. A prospective epidemiological study of acute poisoning in Hong Kong. *Hong Kong J Emerg Med* 2005;12(3):156-61.
5. Morgan O, Griffiths C, Majeed A. Impact of paracetamol pack size restrictions on poisoning from paracetamol in England and Wales: an observational study. *J Public Health (Oxf)* 2005;27(1):19-24.
6. Chan TY, Chan AY, Critchley JA. Factors responsible for continuing morbidity after paracetamol poisoning in Chinese patients in Hong Kong. *Singapore Med J* 1996;37(3):275-7.
7. Perry HE, Shannon MW. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label, clinical trial. *J Pediatr* 1998;132(1):149-52.
8. Chan TY, Chan AY, Critchley JA. Paracetamol poisoning and hepatotoxicity in Chinese - the Prince of Wales Hospital (Hong Kong) experience. *Singapore Med J* 1993;34(4):299-302.
9. Prescott LF, Illingworth RN, Critchley JA, Stewart MJ, Adam RD, Proudfoot AT. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *BMJ* 1979;2(6198):1097-100.
10. Rumack BH, Peterson RC, Koch GG, Amara IA. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med* 1981; 141(3 Spec No):380-5.

11. Brok J, Buckley N, Gluud C. Interventions for paracetamol (acetaminophen) overdoses. *Cochrane Database Syst Rev* 2006;(2):CD003328. [2002;(3):CD003328].
12. Spiller HA, Krenzelok EP, Grande GA, Safir EF, Diamond JJ. A prospective evaluation of the effect of activated charcoal before oral N-acetylcysteine in acetaminophen overdose. *Ann Emerg Med* 1994;23(3):519-23.
13. Joint Formulary Committee. *British National Formulary*, 51st ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2006. p. 30.
14. Kerr F, Dawson A, Whyte IM, Buckley N, Murray L, Graudins A, et al. The Australasian clinical toxicology investigators collaboration randomized controlled trial of different loading infusion rates of N-acetylcysteine. *Ann Emerg Med* 2005;45(4):402-8.
15. Tsai CL, Chang WT, Weng TI, Fang CC, Walson PD. A patient-tailored N-acetylcysteine protocol for acute acetaminophen intoxication. *Clin Ther* 2005;27(3):336-41.
16. Rumack BH, Peterson RG. Acetaminophen overdose: incidence, diagnosis, and management in 416 patients. *Pediatrics* 1978;62(5 Pt 2 Suppl):898-903.
17. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *New Engl J Med* 1988;319(24):1557-62.
18. Smilkstein MJ, Bronstein AC, Linden C, Augenstein WL, Kulig KW, Rumack BH. Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. *Ann Emerg Med* 1991;20(10):1058-63.
19. Buckley NA, Whyte IM, O'Connell DL, Dawson AH. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol* 1999;37(6):759-67.
20. Merl W, Koutsogiannis Z, Kerr D, Kelly AM. How safe is intravenous N-acetylcysteine for the treatment of paracetamol poisoning? *Hong Kong J Emerg Med* 2007;14(4):198-203.
21. Woo OF, Mueller PD, Olson KR, Anderson IB, Kim SY. Shorter duration of oral N-acetylcysteine therapy for acute acetaminophen overdose. *Ann Emerg Med* 2000;35(4):363-8.
22. Yarema MC, Johnson DW, Berlin R, Nettel-Aguirre A, Brant R, Sivilotti M, et al. The 72 hour oral versus the 20 hour intravenous N-acetylcysteine protocols for treatment of acute acetaminophen overdose. *Clin Toxicol (Phila)* 2006;44(5):782.
23. Lifshitz M, Kornmehl P, Reuveni H. The incidence and nature of adverse reactions during intravenous acetylcysteine therapy for acetaminophen overdose. *J Pharm Technol* 2000;16(2):44-9.
24. Mullins ME, Schmidt RU, Jang TB. What is the rate of adverse events with intravenous versus oral N-acetylcysteine in pediatric patients? *Ann Emerg Med* 2004;44(5):547-8.
25. Miller MA, Navarro M, Bird SB, Donovan JL. Antiemetic use in acetaminophen poisoning: how does the route of N-acetylcysteine administration affect utilization? *J Med Toxicol* 2007;3(4):152-6.
26. Savides MC, Oehme FW, Leipold HW. Effects of various antidotal treatments on acetaminophen toxicosis and biotransformation in cats. *Am J Vet Res* 1985;46(7):1485-9.
27. National Institute for Health and Clinical Excellence. *The guidelines manual*. London: National Institute for Health and Clinical Excellence; 2007. p. 45-6. Available from: [www.nice.org.uk](http://www.nice.org.uk)
28. Parker D, White JP, Paton D, Routledge PA. Safety of late acetylcysteine treatment in paracetamol poisoning. *Hum Exp Toxicol* 1990;9(1):25-7.
29. Ayonrinde OT, Phelps GJ, Hurley JC, Ayonrinde OA. Paracetamol overdose and hepatotoxicity at a regional Australian hospital: a 4-year experience. *Intern Med J* 2005;35(11):655-60.
30. Kanter MZ. Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. *Am J Health Syst Pharm* 2006;63(19):1821-7.
31. Wright RO, Anderson AC, Lesko SL, Woolf AD, Linakis JG, Lewander WJ. Effect of metoclopramide dose on preventing emesis after oral administration of N-acetylcysteine for acetaminophen overdose. *J Toxicol Clin Toxicol* 1999;37(1):35-42.
32. Cattermole GN. Oral N-acetylcysteine for acute paracetamol poisoning. [Letter] *Emerg Med J* 2007;24(12):866.