

Oral or Intravenous *N*-Acetylcysteine for Acetaminophen Poisoning?

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Acetaminophen (paracetamol, *N*-acetyl-*p*-aminophenol) is an effective, mild analgesic, antipyretic agent and is probably the most widely used of all drugs in the world. It does not share the formidable prostaglandin-dependent toxicity of aspirin and other conventional nonsteroidal anti-inflammatory agents, and when used properly, it has an excellent safety record. In many countries, it is fashionable to misuse over-the-counter analgesics for self-poisoning. As a result, acetaminophen has become a victim of its own success, and it is now one of the most commonly encountered substances to be taken deliberately in overdose. The most important complication of a major overdose of acetaminophen is acute centrilobular hepatic necrosis, but only a small minority of patients is at risk. Before effective antidotal therapy became generally available some 25 years ago, less than 10% of unselected patients referred to the hospital with acetaminophen poisoning suffered severe liver damage (defined as maximum plasma alanine or aspartate aminotransferase exceeding 1,000 IU/L), and 1% to 3% developed fulminant hepatic failure, which in the absence of liver transplantation programs, was often fatal.¹ There were particular problems with acetaminophen overdose at that time. The severity of poisoning could not be judged initially on clinical grounds because there were no specific symptoms or signs, consciousness was not usually impaired unless other drugs had also been taken, and the maximum abnormalities of liver function tests were delayed for at least 3 days. The severity of poisoning could only be established reliably by measurement of the plasma concentration of acetaminophen in relation to the time since ingestion.² In most cases, an overdose of acetaminophen was taken on impulse with no real intention of ending life. It was distressing to care for a young patient who was fully conscious, not appearing to be ill and now wanting to live, who several days later suffered an unpleasant death in hepatic failure.

The availability of *N*-acetylcysteine has transformed the management of severe acetaminophen poisoning. Initial studies with intravenous *N*-acetylcysteine in the United Kingdom in 100 severely poisoned patients showed that, in comparison with 57 similarly poisoned control patients receiving only supportive therapy, it was virtually 100% effective in preventing severe liver damage, renal failure, and death, provided that it was given

within 8 to 10 hours of the ingestion of the overdose. After this time, its efficacy fell off rapidly, and when treatment was delayed beyond 15 hours, it seemed to have no useful effect.^{3,4} Similar dramatic results were obtained with oral *N*-acetylcysteine in a large national multicenter study in the United States. Again, it was most effective when given within 10 hours, but it seemed to have some effect even when given as late as 16 to 24 hours after ingestion.⁵⁻⁷ Although the efficacy of *N*-acetylcysteine declines progressively with increasing delay in treatment after 8 hours, it is still recommended for patients who present late (>12 hours) after taking an overdose of acetaminophen. Such individuals are usually severely poisoned with a poor prognosis, and even minor benefit from treatment with *N*-acetylcysteine could ultimately tip the balance between life and death.

Acetaminophen causes liver toxicity through the generation of a reactive intermediate metabolite (*N*-acetyl-*p*-benzoquinoneimine) formed by its oxidation via hepatic cytochrome P450 enzymes. This metabolite damages essential mitochondrial and other cellular enzymes by binding covalently to and arylating their protein sulphhydryl groups. Hepatic reduced glutathione has a vital protective role. Acetaminophen hepatotoxicity is invariably associated with major depletion of glutathione, and liver injury can be prevented if hepatic glutathione concentrations can be maintained. L-cysteine is essential for glutathione production, and its availability is rate-limiting; *N*-acetylcysteine probably acts primarily by providing L-cysteine for the stimulation of glutathione synthesis. The critical arylation of sulphhydryl groups by acetaminophen can be reversed by excess glutathione, but only for a limited time after exposure to the toxic metabolite. The changes then become permanent, leading to irreversible hepatic damage and necrosis. *N*-acetylcysteine has several other actions that may be relevant to protection against liver damage after overdose of acetaminophen.^{8,9}

Acetaminophen hepatotoxicity can be seen as the consequence of 2 independent time-related processes: (1) its conversion to the toxic metabolite *N*-acetyl-*p*-benzoquinoneimine and subsequent depletion of hepatic glutathione with arylation of vital sulphhydryl groups and (2) the limited time window during which this lethal arylation can be reversed by restoration of effective concentrations of hepatic glutathione. In practical terms, this "period of grace" in which serious

hepatotoxicity can be prevented by administration of sulphhydryl donors such as *N*-acetylcysteine seems to be about 8 hours from the time of ingestion of the overdose of acetaminophen. In patients with acetaminophen poisoning, every effort must therefore be made to start *N*-acetylcysteine as soon as possible. Treatment must never be withheld if the critical time limit of 8 hours since ingestion is running out, and it must not be delayed beyond this time while awaiting laboratory confirmation of ingestion of a toxic dose of acetaminophen.

Oral *N*-acetylcysteine is used in the United States, whereas intravenous *N*-acetylcysteine is used in Europe, Canada, and Australasia. The intravenous route was developed in the 1970s in the United Kingdom. A loading dose of 150 mg/kg in 5% dextrose is given over a 15-minute period followed by 50 mg/kg in 4 hours and 100 mg/kg in 16 hours. The total dose is 300 mg/kg in 20 and one quarter hours.^{3,4} Oral *N*-acetylcysteine was introduced in the United States at about the same time. An initial dose of 140 mg/kg is followed by 17 doses of 70 mg/kg every 4 hours to give a total dose of 1,330 mg/kg over 3 days. If vomiting occurred within 1 hour of a dose, it was repeated and administration was attempted by nasogastric tube if vomiting persisted.⁵⁻⁷ It was claimed that the results of treatment by the oral route were superior to those following intravenous administration.^{7,10} However, the overall outcomes cannot be compared directly because in all but the earliest oral studies a lower plasma acetaminophen concentration was used to set the threshold for treatment. Thus, the patients treated with oral *N*-acetylcysteine were less severely poisoned than those treated with intravenous *N*-acetylcysteine. In addition, ethical considerations of withholding the drug precluded the use of control patients in the patients treated with oral *N*-acetylcysteine.

One reason why the oral regimen might have seemed to be better than the intravenous when treatment was delayed is that the dose of oral *N*-acetylcysteine was much higher and it was continued for 72 hours instead of 20 hours. Further studies were therefore conducted with intravenous *N*-acetylcysteine given in the same high dose as in the original oral studies and continued for 48 hours. It was concluded that this 48-hour intravenous protocol was as effective as standard 72-hour oral *N*-acetylcysteine and 20-hour intravenous *N*-acetylcysteine when given early and was more effective than the latter when treatment was delayed.¹⁰ The results of other studies with different regimens were generally similar.¹¹⁻¹³ Reports of the use of oral and intravenous *N*-acetylcysteine in patients with acetaminophen poisoning are summarized in the Table. In all studies, *N*-acetylcysteine was very effective in preventing severe liver damage when given within 10 hours, irrespective of dose, route of administration, or duration of therapy. However, the incidence of severe liver damage varied from 8% to 53% when treatment was delayed for 10 to 24 hours. The most important factors that determine the efficacy of *N*-acetylcysteine are individual susceptibility, the severity of poisoning (as shown by the plasma acetaminophen concentration related to time since ingestion), and the critical interval between ingestion and the start of treatment with *N*-acetylcysteine. The reason for these

major discrepancies is not clear, but there are important deficiencies in some studies and direct comparison of the results is clearly not possible. The differences claimed between different regimes were probably artifactual and related more to inappropriate analysis of subgroups.¹⁴ On balance, oral and intravenous *N*-acetylcysteine seem to be equally effective.

The major disadvantage of oral *N*-acetylcysteine is difficulty of administration and the risk of therapeutic failure in patients who develop nausea and vomiting. Unfortunately, these complications occur in most patients who are severely poisoned with acetaminophen and thus at greatest risk of severe hepatotoxicity. Oral *N*-acetylcysteine may therefore fail in the very patients who need effective treatment the most.^{4,11,15-17} Aside from the problems with nausea and vomiting, there is inevitably some delay between the administration of oral *N*-acetylcysteine and absorption of an effective dose. This could be significant in patients who take drugs such as anticholinergics and narcotic analgesics together with acetaminophen in overdose. These drugs inhibit gastric emptying, and this would seriously delay the absorption of oral *N*-acetylcysteine. In addition, there are unresolved questions about interference by oral *N*-acetylcysteine with the ability of activated charcoal to adsorb acetaminophen after an overdose and also the adverse effects of activated charcoal on the absorption of the *N*-acetylcysteine itself.¹⁸ Problems with the absorption of oral *N*-acetylcysteine are particularly important when the critical time limit of 8 hours required for effective hepatoprotection is approaching or has passed. Attempts have been made to overcome the problems of nausea and vomiting by administration of *N*-acetylcysteine via nasogastric tube⁷ and by high-dose anti-emetic therapy, but these measures can cause further complications and could hardly be described as successful.¹⁹⁻²¹ One possible advantage of the oral route is that the whole absorbed dose passes through the liver, producing very high local concentrations precisely where required at the primary site of action in the liver.³

Protection against liver damage is one side of the *N*-acetylcysteine coin, but the other side concerns the relative risks of oral versus intravenous administration. Serious life-threatening reactions to *N*-acetylcysteine are uncommon in patients with acetaminophen poisoning, but rare fatalities have been reported after intravenous administration, and patients with asthma seem to be at particular risk.²²⁻²⁵ In other reports, serious and fatal reactions have been caused by gross iatrogenic overdosage of intravenous *N*-acetylcysteine.^{10,26} Most reactions to intravenous *N*-acetylcysteine are described as "anaphylactoid" and include nausea, vomiting, flushing, urticaria, and pruritus. They are usually minor and usually subside rapidly on temporarily discontinuing the *N*-acetylcysteine or reducing the rate of infusion. These anaphylactoid reactions are thought to be dose-related and mediated by histamine release.²⁷ More severe manifestations involve bronchospasm, angioedema, and hypotension.^{10,28-31}

The reported incidence of anaphylactoid reactions to intravenous *N*-acetylcysteine in patients with acetaminophen

Table. Efficacy of treatment with oral and intravenous *N*-acetylcysteine in combined probable and high-risk* patients with acetaminophen poisoning.[†]

Source Reference	NAC Schedule	Treatment Delay of 0–10 h (%)	% Patients at High Risk	Treatment Delay of 10–24 h (%)	% Patients at High Risk	Total (%)
Prescott et al ⁴	20 h IV	1/62 (2)	53	20/38 (53)	71	21/100 (21)
Buckley et al ¹⁴	20 h IV	2/49 (4)	10	3/37 (8)	16	5/86 (6)
Dawson et al ³¹	20 h IV			7/20 (35) [‡]	95	7/20 (35)
Kerr et al ³⁹	20/21 h IV	0/58 (0) [§]	NS	11/112 (10) [¶]	NS	11/170 (6)
Smilkstein et al ¹⁰	48 h IV	6/74 (8)	32	39/135 (29)	37	45/209 (22)
Perry and Shannon ¹¹	52 h IV [#]	0/?	NS	2/?	NS	2/25 (8)
Smilkstein et al ⁷	72 h oral	49/733 (7)	28	446/1,513 (29)	38	495/2,246 (22)
Perry and Shannon ¹¹	52 h oral [#]	0/?	NS	2/?	NS	2/29 (7)
Woo et al ¹³	24–64 h oral	NS**	NS	NS**	NS	6/75 (8)

NAC, *N*-acetylcysteine; IV, intravenous; NS, not specified.

*Plasma acetaminophen above lines joining 200 and 300 mg/L at 4 h and 25 and 37.5 mg/L, respectively, on a semilog plot.

[†]Values given are the number of patients with severe liver damage (aminotransferases >1,000 IU/L)/the total number of patients.

[‡]Delay of 12 to 24 h.

[§]Delay of 0 to 8 h.

^{||}Severity of poisoning not specified.

[¶]Delay >8 h.

[#]Children; numbers of patients treated within 10 h and between 10 and 24 h not specified.

**Treatment delay not specified other than <24 h.

poisoning has varied widely from well under 10% to almost 50%.^{11,12,14,16,28,32-35} These differences presumably reflect different selection criteria, and the rates will obviously be higher if all events such as nausea, headache, and flushing are included. The oral route is clearly much safer, and adverse reactions are rarely mentioned with this route of administration. Nausea and vomiting may occur, but rashes, erythema, angioedema, and anaphylaxis seem to be very rare.^{5,11,36,37}

Most reactions to intravenous *N*-acetylcysteine occur during the first hour, when the initial rate of infusion is greatest and the plasma concentrations are highest.³⁸ Many investigators have suggested that the incidence and severity of these reactions could be reduced simply by slowing the initial rate of infusion.^{10,11,14,16,30,33,35} Although in practice the initial dose of intravenous *N*-acetylcysteine is often given over 60 rather than 15 minutes, it is not known whether this actually reduces the incidence and severity of reactions. In this issue of *Annals*, Kerr et al³⁹ attempt to answer this question with a prospective multicenter trial in which patients with acetaminophen overdose were given intravenous *N*-acetylcysteine according to the standard 20-hour protocol, with the initial dose infused over either a 15-minute or 60-minute period. *N*-acetylcysteine-related adverse events were observed in 49 (45%) of 109 patients receiving the initial dose over 15 minutes and in 21 (38%) of 71 patients receiving it over 60 minutes. The corresponding rates of severe liver damage as shown by the maximum plasma alanine aminotransferase activity were 6.8% and 8.7%, respectively. Unfortunately, the authors did not specify the severity of poisoning, and the delay to treatment was only given as less than 8 and more than 8 hours. These differences are not statistically significant, and it seems unlikely that any important advantage would be demonstrated by a larger, more disciplined study. Where does all this leave us? Regrettably, we still do not know the optimum dose, duration of treatment, and route of administration of *N*-acetylcysteine in

patients with acetaminophen poisoning. These questions can only be answered by properly controlled prospective clinical trials, and such studies are long overdue.

Until recently, only the oral form of *N*-acetylcysteine was available in the United States. However, the US Food and Drug Administration has given approval for the use of intravenous *N*-acetylcysteine. This is now available as Acetadote, and the recommended dosage schedule is the same as that used for intravenous *N*-acetylcysteine in the United Kingdom and other countries. Clinicians will now need to make up their minds concerning the best route of administration of *N*-acetylcysteine for individual patients. Unfortunately, there are no data from head-to-head trials of the oral or intravenous routes of administration. This information is needed for physicians in the United States to make an informed decision regarding the best formulation for their patients. In terms of efficacy, intravenous *N*-acetylcysteine might be preferred in patients who are seriously poisoned, patients who present late, patients who are thought to be particularly susceptible to acetaminophen hepatotoxicity, patients with nausea and vomiting, patients who have been given activated charcoal or who have taken other drugs that could interfere with the absorption of oral *N*-acetylcysteine, patients with impaired consciousness, and patients who are unable to take *N*-acetylcysteine orally for whatever reason. The 8-hour time window does not apply to patients who have taken slow- or extended-release dosage forms of acetaminophen or to patients who have taken several (staggered) overdoses over a period of hours or days. Because of the uncertainty of the timing of absorption of the acetaminophen and poor prognosis in some of these cases, intravenous *N*-acetylcysteine would probably be a better choice. A shorter stay in the hospital with reduced costs,³³ less inconvenience for patients and hospital staff, and the avoidance of problems with the absorption of oral *N*-acetylcysteine by vomiting or previous administration of charcoal should make intravenous

N-acetylcysteine an attractive option for most patients with acetaminophen overdose. Oral *N*-acetylcysteine might be preferred for patients seen early with uncomplicated mild to moderate poisoning, patients with a history of previous reactions to *N*-acetylcysteine, and patients with asthma. Another approach might be to give oral *N*-acetylcysteine immediately to all patients who have taken an overdose of acetaminophen pending assessment. This could subsequently be switched to intravenous *N*-acetylcysteine if indicated as above. In any case, only direct comparative evidence will be sufficient to determine whether oral or intravenous *N*-acetylcysteine is appropriate.

Whatever route is chosen, the single most important factor for the prevention of severe liver damage is the interval between ingestion of the acetaminophen and treatment with *N*-acetylcysteine. Efficacy decreases progressively when treatment is delayed beyond 8 hours, and speed is of the essence.

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