Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning

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Purpose. The efficacy, safety, and cost issues that should be considered when deciding on the appropriate route of acetylcysteine for the treatment of patients with acetaminophen poisoning are reviewed.

Summary. Oral and i.v. acetylcysteine appear to be equally effective when given within 8–10 hours of acetaminophen overdose. Anaphylactoid reactions to i.v. acetylcysteine have generally been reported in 3–6% of acetaminophen-poisoned patients. Dosing errors and hyponatremia have occurred in pediatric patients receiving i.v. acetylcysteine. Several investigators found an increased rate of anaphylactoid reactions in patients treated with i.v. acetylcysteine whose pretreatment serum acetaminophen levels were nontoxic. Compounding i.v. acetylcysteine from the oral preparation is less expensive than using premade i.v. solution. State pharmacy laws dictate whether extemporaneous compounding of acetylcysteine from the oral formulation is allowed. Oral acetylcysteine administration has resulted in minimal anaphylactoid reactions and is safer than i.v. acetylcysteine. Oral therapy should preferentially be considered in patients with asthma or atopic histories. The most important factors to consider when selecting the route of acetylcysteine administration include individual susceptibility, the severity of acetaminophen toxicity, and the time interval between acetaminophen ingestion and initiation of acetylcysteine therapy.

Conclusion. Oral acetylcysteine administered within 8–10 hours of acetaminophen overdose prevents liver toxicity in the majority of patients who tolerate it and have no contraindications to therapy. I.V. acetylcysteine should be administered when patients are treated more than 10 hours postingestion of acetaminophen overdose or have underlying conditions preventing oral treatment. Anaphylactoid reactions are rare and occur more frequently in patients treated with the i.v. preparation.

Index terms: Acetaminophen; Acetylcysteine; Allergies; Analgesics and antipyretics; Anaphylaxis; Antidotes; Blood levels; Contraindications; Costs; Dosage; Dosage schedules; Drug administration routes; Drugs, adverse reactions; Liver diseases; Pediatrics; Pharmacoeconomics; Placental transfer; Poisoning; Pregnancy; Protocols; Toxicity

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Dissatisfied with the unavailability of cysteamine, Prescott and Matthew1 first suggested using acetylcysteine as an antidote for acetaminophen-induced hepatotoxicity in 1974. In 1977, Prescott et al.2 described the treatment of 15 patients with acetaminophen poisoning with i.v. acetylcysteine using a sterile 20% aqueous solution, suggesting that oral administration may improve the drug’s efficacy, “since most of the dose should pass through the liver.” Thus the debate began of whether acetylcysteine should be administered orally or intravenously and continues to this day.

The debate was fueled by the marketing approval by the Food and Drug Administration in early 2004 of Acetadote (Cumberland Pharmaceuticals, Nashville, TN), an i.v. acetylcysteine preparation. Clinicians now have a choice of using a premade i.v. acetylcysteine product, compounding an i.v. product from an oral acetylcysteine preparation, or administering the oral form that has been used for over 25 years. Deciding on the most appropriate formulation for an individual patient can be difficult, and many factors, including efficacy, safety, and cost, need to be considered before choosing a specific product. This article reviews the issues that should be considered when deciding on the appropriate route of acetylcysteine for treating acetaminophen-poisoned patients.

Mechanism of action

About 4% of acetaminophen is metabolized to N-acetyl-p-benzoquinoneimine (NAPQI) via the cytochrome P-450 (CYP) isoenzyme mixed-function oxidase system.3 This potentially toxic intermediate conjugates with glutathione, forming the nontoxic metabolites cysteine and...
Acetylcysteine as an antidote

Prescott et al.7 and Smilkstein and colleagues8 published landmark papers demonstrating the efficacy of i.v. and oral acetylcysteine, respectively, in patients with acetaminophen poisoning. Prescott et al.7 found that the administration of acetylcysteine 300 mg/kg i.v. over 20 hours (using a loading dose of 150 mg/kg infused over 15 minutes, followed by 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours) prevented liver toxicity in all patients with acetaminophen poisoning who received treatment within 8 hours of the overdose.

Smilkstein et al.8 conducted a large prospective study of oral acetylcysteine for acetaminophen overdose. A loading dose of 140 mg/kg was given, followed 4 hours later by 70 mg/kg every 4 hours for 17 doses. They found the 72-hour oral acetylcysteine regimen to be as effective as Prescott et al.’s7 20-hour i.v. protocol and speculated that oral acetylcysteine may have greater efficacy than i.v. therapy when treatment is delayed beyond 10 hours. Prescott9 recently speculated that oral acetylcysteine was more efficacious in patients who sought treatment more than 10 hours after overdose because the dosage of the oral preparation was higher and the regimen was continued for a longer period of time compared with the i.v. protocol.

Smilkstein and colleagues10 studied the efficacy of a high-dose (140 mg/kg i.v. loading dose, followed by 12 70-mg/kg i.v. doses every 4 hours), 48-hour acetylcysteine protocol. This protocol was as effective as the 72-hour oral and 20-hour i.v. protocols when started within 10 hours of acetaminophen overdose. The 48-hour i.v. protocol was more effective than the 20-hour i.v. protocol when treatment was delayed.

Woo et al.11 conducted a retrospective study of 75 patients with acetaminophen poisoning to determine the safety and efficacy of oral acetylcysteine until serum acetaminophen levels were not detectable. All patients had toxic serum acetaminophen levels and were treated within 24 hours of overdose. Oral acetylcysteine was administered using a loading dose of 140 mg/kg, followed by maintenance doses of 70 mg/kg every 4 hours until serum acetaminophen was not detectable. One third of the patients were treated for less than 24 hours, one third for 24–36 hours, and one third for 37–64 hours. Six patients developed hepatotoxicity (i.e., aminotransferase concentration of >1000 IU/L), 2 in the 24–36-hour group and 4 in the 37–64-hour group. Three of these patients were treated at least 13 hours after ingest- ing acetaminophen. The occurrence of hepatotoxicity in this study was similar to the rates reported in the previously mentioned studies.7,10

Oral versus i.v. acetylcysteine

Oral and i.v. acetylcysteine appear to be equally effective when given within 8–10 hours of acetaminophen overdose and when the oral route is tolerated. Perry and Shannon12 compared a 52-hour i.v. acetylcysteine protocol (140-mg/kg loading dose, followed by 70 mg/kg every 4 hours for 12 maintenance doses) with historical control pediatric patients treated using Smilkstein et al.’s8 72-hour oral acetylcysteine protocol. They found the 52-hour i.v. protocol to be as effective as the 72-hour oral protocol. The mean time to treatment was significantly longer in the i.v. treatment group (14.4 versus 10.4 hours for the oral treatment group) (p = 0.001). Hepatotoxicity did not occur in patients treated within 10 hours of ingestion. The rate of hepatotoxicity was the same for both groups when treatment was delayed 10–24 hours after acetaminophen overdose.

In another study, Buckley et al.13 retrospectively analyzed a series of acetaminophen poisonings treated with an i.v. acetylcysteine protocol (300 mg/kg was administered over 20 hours). These retrospective data were derived from the investigators’ poison center database. Patients were assessed for adverse effects, including hepatotoxicity. The authors then incorporated their results in a meta-analysis of previously reported studies of both i.v. and oral acetylcysteine. During the retrospective portion of the study, 3% of patients were noted to have developed hepatotoxicity. Compared with patients without hepatotoxicity, these patients ingested larger quantities of acetaminophen, sought treatment later, had higher serum acetaminophen levels, and received acetylcysteine later.

The meta-analysis indicated that patients with probable or high-risk serum acetaminophen concentrations (defined using the Rumack et al.14 nomogram for treating acetaminophen poisoning) had similar outcomes regardless of whether they were treated with oral or i.v. acetylcysteine.13 Rates of hepatotoxicity were similar in patients who were treated within 10 and 10–24 hours postingestion (regardless of route of administration). The authors concluded that any differences in studies comparing outcomes with i.v. and oral acetylcysteine were artificial and likely the result of inappropriate subgroup analysis. They recommended treating patients with acetaminophen poisoning with i.v. acetylcysteine because it requires shorter hospitalization times.

Compounded i.v. acetylcysteine versus Acetadote

According to the American As-
sociation of Poison Control Centers, 1886 patients were treated with i.v. acetylcysteine in 2003.\textsuperscript{15} The next year, a commercially prepared i.v. formulation of acetylcysteine (Acetadote) received FDA-approved labeling. Clinicians treating acetaminophen poisoning suddenly had a choice: use Acetadote or continue compounding the i.v. acetylcysteine preparation from the oral solution. However, the cost of Acetadote far exceeded that of compounded i.v. acetylcysteine. According to Lavonas et al.,\textsuperscript{16} the treatment of a 70-kg patient for 20 hours cost the pharmacy $416 for Acetadote, $57 for Mucomyst (Bristol-Myers Squibb), and $32 for generic acetylcysteine. These authors concluded that the compounded product and Acetadote were appropriate for treating acetaminophen overdose, considering that Acetadote has thus far not been shown to be safer than the compounded product.

Preparation of i.v. acetylcysteine from the oral product is considered compounding and, according to Crouch and Rusho,\textsuperscript{17} is governed by state law. Clinicians treating patients with compounded acetylcysteine should consult their state pharmacy board to determine the legality of this process in their state now that an i.v. preparation is commercially available.

**Pediatric concerns**

Hyponatremia and seizures may occur in pediatric patients if they are treated according to standard acetylcysteine i.v. dosing guidelines for adults.\textsuperscript{18} This is primarily due to the excess free water they will receive with the medication. The authors of one case report described a 3-year-old girl whose serum sodium concentration dropped from 141 to 118 mmol/L after 9 hours of i.v. acetylcysteine therapy. Had the 20-hour protocol been completed, she would have received 1540 mL of i.v. fluid. As a result, the authors developed a treatment protocol for pediatric patients weighing less than 40 kg to avoid this potentially life-threatening situation. This protocol incorporates a final acetylcysteine concentration of 40 mg/mL, thereby minimizing the risk of hyponatremia and hypervolemia in young children.\textsuperscript{18}

**Use in pregnancy**

Acetylcysteine has been detected in cord blood.\textsuperscript{19} Riggs et al.\textsuperscript{20} conducted a prospective study evaluating oral acetylcysteine for the treatment of acetaminophen toxicity. Of the 60 pregnant patients studied who ingested acetaminophen, 24 had plasma concentrations exceeding therapeutic values (using Rumack et al.’s\textsuperscript{21} nomogram). Ten patients received oral acetylcysteine within 10 hours of acetaminophen ingestion, 10 were treated 10–16 hours after ingestion, and 4 were treated 16–24 hours after ingestion.\textsuperscript{20} Multiple logistic regression analyses showed significant correlation between the risk of fetal death and the delay in initiating acetylcysteine therapy. The benefits of using acetylcysteine early in the management of acetaminophen poisoning in pregnancy outweigh the risks of no treatment.

**Adverse effects**

Anaphylactoid reactions after acetaminophen poisoning. Anaphylactoid reactions to i.v. acetylcysteine, which likely result from histamine release,\textsuperscript{21} have generally been reported in 3–6% of acetaminophen-poisoned patients,\textsuperscript{22,23} although a recent study reported the rate to be as high as 48%.\textsuperscript{24} Symptoms may include pruritis, rash, angioedema, bronchospasm, tachycardia, hypotension, nausea, and vomiting. Anaphylactoid reactions generally occur within 30 minutes after infusion of the loading dose. Oral acetylcysteine administration has resulted in minimal anaphylactoid reactions.\textsuperscript{25-27}

Sunman et al.\textsuperscript{28} found that the rate of anaphylactoid reactions to i.v. acetylcysteine was higher in patients who received iatrogenic overdoses of acetylcysteine (73%) compared with patients who did not receive overdoses (up to 3%). They also found the rate of hypotension to be higher in acetylcysteine overdose patients (6 of 11) compared with those who did not receive an overdose (6 of 38). Pruritis, angioedema, and bronchospasm occurred more frequently in patients who did not receive an overdose.

Dawson et al.\textsuperscript{29} reported on 29 cases of adverse reactions to i.v. acetylcysteine that were reported to the Adverse Drug Reactions Advisory Committee in Australia over an eight-year period. All adverse reactions were anaphylactoid in nature, and all patients had good outcomes.

There are reports of fatalities from overdoses of i.v. acetylcysteine. In one study, a follow-up questionnaire was sent to physicians who had consulted (over a 2.5-year period) with the National Poisons Information Service regarding patients who overdosed on acetaminophen.\textsuperscript{22} The authors reported 19 cases of acetylcysteine overdose, 15 of which had sufficient clinical information to be evaluated. Two patients died after receiving between 2.5 and 10 times the recommended loading dose of i.v. acetylcysteine. It was not clear whether acetylcysteine contributed to these deaths. In addition, there is a case report of a four-year-old child who received twice the recommended dose of i.v. acetylcysteine despite a nontoxic acetaminophen level.\textsuperscript{30} This child had an anaphylactic reaction without bronchospasm and could not be resuscitated. Autopsy results revealed circulatory congestion and small bilateral subdural hematomas.

Kao et al.\textsuperscript{31} conducted a survey over a six-year period to determine the rate of adverse events with i.v. acetylcysteine compounded from the oral preparation. Medical records of all patients who received compounded i.v. acetylcysteine were retrospec-
Adverse reactions from acetylcysteine may result from the rate at which the infusion is administered (i.e., the faster the infusion rate, the greater the rate of adverse effects).10,12,13,24,32 Kerr et al.23 recently studied the effect of the loading-dose infusion rate on the frequency of adverse effects in patients with acetaminophen poisoning. In this two-year, multicenter, randomized trial, the i.v. acetylcysteine loading dose was infused over 15 or 60 minutes. There was no significant difference in the rates of anaphylactoid reactions (18% versus 14%, respectively) and overall adverse events (45% versus 38%, respectively) between the two groups. Horowitz et al.33 commented on this study, indicating that although there was no statistically significant difference in the rates of anaphylactoid reactions between the two groups, the reported rates of 18% and 14% were still higher than what is usually reported. They noticed an increase in anaphylactoid reactions in their practice since using Acetadote and attributed the increase to the preparation of acetylcysteine in 200 mL of 5% dextrose injection regardless of the patient’s weight. In doing this, a 70-kg patient would receive a final concentration of acetylcysteine of 5.25%, while a 100-kg patient would receive 7.5%. In Kao et al.31 study, a final concentration of 3% resulted when i.v. acetylcysteine was compounded from the oral preparation, and anaphylactoid reactions occurred in only 3.7% of patients. It is not evident from Kerr et al.23 data whether there was a difference in the rate of anaphylactoid reactions in patients who received more concentrated acetylcysteine solutions.

Another group contended that Kerr et al.’s study was biased, did not use a blocked randomization process, and was underpowered and therefore unable to show a difference in the rates of adverse events in the two groups, even if a difference did exist.24 Gawarammana et al.35 commented that Kerr et al.23 study did not mention the number of atopic or asthmatic patients. This is important, since these patients are at higher risk for developing reactions to acetylcysteine. There was no mention of patients’ acetaminophen levels in Kerr et al.23 study and whether adverse events occurred more frequently with lower levels.

**Anaphylactoid reactions to nontoxic levels of acetaminophen.** Several investigators found an increased rate of anaphylactoid reactions in patients treated with i.v. acetylcysteine whose pretreatment serum acetaminophen levels were below the nomogram treatment line (defined by an acetaminophen level of <150 mg/L at 4 hours and <37.5 mg/L at 12 hours.)24,29,36,37 Lynch and Robertson24 conducted a prospective case–control study to determine if there are predictive factors for acetylcysteine-induced anaphylactoid reactions. Of the 31 patients who developed anaphylactoid reactions, 13 (42%) had acetaminophen concentrations below the treatment line on Rumack et al.14 nomogram. Lynch and Robertson suggested that patients who had nontoxic acetaminophen levels, had nondetectable acetaminophen levels, or were treated more than 8 hours after ingestion had an increased likelihood of developing an anaphylactoid reaction to acetylcysteine.

Bailey and McGuigan37 evaluated the efficacy of an institution-specific treatment guideline in patients who had developed anaphylactoid reactions to i.v. acetylcysteine. Of the 22 patients with urticaria, 5 had nontoxic levels of acetaminophen. Two of the 8 patients with facial edema and 3 of the 19 patients with respiratory symptoms had nontoxic levels of acetaminophen.

Dawson et al.29 reported that most of their patients (26 of 29) had blood acetaminophen levels below the nomogram treatment line. Nonetheless, these patients received i.v. acetylcysteine and subsequently developed adverse reactions. The authors did not give information on the specific adverse effects exhibited.

There was a significant correlation (p = 0.00006) between low serum acetaminophen levels and the development of adverse effects to acetylcysteine in Schmidt and Dalhoff’s36 retrospective review. This prompted the authors to speculate that toxic serum acetaminophen levels may be autoprotective against acetylcysteine-induced toxicity.

Other researchers have found that lymphocytes, neutrophils, and thrombocytes are functionally inhibited by toxic acetaminophen levels but not by therapeutic levels.38-40 This is thought to be due to acetaminophen-induced inhibition of cyclooxygenase and the subsequent inhibition of prostaglandin and thromboxane synthesis. Schmidt and Dalhoff36 postulated that acetaminophen inhibits the function of basophils and mast cells, resulting in decreased anaphylactoid reactions to acetylcysteine in patients with toxic acetaminophen serum levels.

**Bronchospasm.** Acetylcysteine-induced bronchospasm in asthmatic patients may be due to local histamine release or inhibition of allergen tachyphylaxis.41 Allergen tachyphylaxis is defined as a decrease in asthma severity after patients are sequentially challenged by allergen
inhalation. Dorsch et al.\textsuperscript{41} studied the effect of inhaled acetylcysteine on allergen tachyphylaxis in six asthmatic patients. Allergen tachyphylaxis was inhibited by inhaled acetylcysteine in two patients, prompting the authors to caution against acetylcysteine use in asthmatic patients. Schmidt and Dalhoff\textsuperscript{48} performed a retrospective chart review of 529 patients with acetaminophen poisoning to determine the risk factors for developing adverse reactions to acetylcysteine. Of the 529 patients, 33 (6.2\%) had a history of asthma. Multiple-regression analyses showed that adverse reactions occurred 2.8 times more frequently in asthmatic patients than those without asthma ($p = 0.004$). Systemic adverse reactions occurred 4.3 times more frequently in asthmatic patients (95\% CI, 2.8–8.7).

In the study conducted by Mant et al.,\textsuperscript{22} 5 of the 38 patients who had anaphylactoid reactions after receiving appropriate doses of i.v. acetylcysteine developed bronchospasm. In addition, 2 patients who received overdoses of acetylcysteine had bronchospasm, and 1 developed respiratory depression. Of the 30 patients who developed adverse reactions to i.v. acetylcysteine in Dawson et al.'s study, 8 had bronchospasm. It is unclear whether any patients from either study had a history of asthma. All patients had good outcomes.

Ho and Beilin\textsuperscript{42} described two cases of acetaminophen poisoning in which one patient had a nontoxic level of acetaminophen and the other had a level that was not interpretable. Both patients had a history of asthma and developed wheezing and worsening of asthma after receiving loading doses of i.v. acetylcysteine over 15 minutes. Acetylcysteine was discontinued in both patients, who then received i.v. aminophylline without sequelae.

Appelboam and colleagues\textsuperscript{43} described a 40-year-old woman with a history of severe asthma who had a fatal reaction to a therapeutic dose of i.v. acetylcysteine given for acetaminophen poisoning. No serum acetaminophen value was reported, but the patient admitted to ingesting about 15 g of acetaminophen over 48 hours. The patient developed shortness of breath and bilateral wheezing five minutes after acetylcysteine was initiated. Acetylcysteine was immediately discontinued, and the patient’s condition rapidly deteriorated despite appropriate therapy. She experienced respiratory arrest followed by cardiac arrest and was resuscitated but died one week later. The authors recommended exercising extreme caution when administering i.v. acetylcysteine to patients with severe asthma.

**Status epilepticus.** Two case reports of status epilepticus associated with i.v. acetylcysteine have been published.\textsuperscript{44,45} A previously healthy 30-month-old girl developed status epilepticus after receiving more than a 10-fold cumulative overdose of i.v. acetylcysteine.\textsuperscript{44} She was administered 44 mL/kg of 5\% dextrose injection during the acetylcysteine infusion. She developed intracranial hypertension and subsequently died. Her serum sodium concentration was within normal limits, and the hypotonic fluid that she received was not thought to have contributed to her seizures. The authors postulated that the intracranial hypertension might have resulted from a direct toxic effect of acetylcysteine, free-water overload, hypoxia from the seizure activity, or any combination of these.

In the second case, a 30-month-old girl who potentially ingested acetaminophen 220 mg/kg developed status epilepticus and cortical blindness after 16 hours of i.v. acetylcysteine therapy.\textsuperscript{45} Her vision was almost completely recovered after 18 months.

**Effects on International Normalized Ratio.** Jepsen and Hansen\textsuperscript{46} reported a significant decrease in prothrombin time and clotting factors II, VII, and X in healthy volunteers who received i.v. acetylcysteine. Wasserman and Garg\textsuperscript{47} noted prolonged prothrombin times, especially after receiving the loading dose, in 19 of 30 pediatric patients who received i.v. acetylcysteine for acetaminophen toxicity. These patients had no signs of hepatotoxicity.

Kao and Furbee\textsuperscript{48} reexamined the data from their previous study\textsuperscript{31} and found that 63 patients treated with i.v. acetylcysteine had measured International Normalized Ratios (INRs) during treatment. These patients had no evidence of hepatotoxicity. The INR values in these patients ranged from 0.93 to 2.84, with 28 patients (44\%) having INR values of 1.2 or greater. The increase in INRs may have resulted from the destabilization of the disulfide bonds in clotting factors by the thiol group in acetylcysteine.\textsuperscript{49} However, Whyte et al.\textsuperscript{50} found that acetaminophen overdose itself causes a functional (but not antigenic) factor VII deficiency and is associated with a prolonged INR without hepatotoxicity.

**Selecting the appropriate route of administration**

Clinicians unfamiliar with acetylcysteine therapy may find the treatment options confusing because of the various protocols for i.v. and oral formulations. Acetylcysteine administration within the United States generally occurs via the oral route unless underlying patient conditions (e.g., refractory vomiting) dictate i.v. administration. I.V. acetylcysteine administration has been routinely used in other countries. Controversy exists regarding which route of administration is safer and more efficacious. Until Acetadote’s recent marketing approval, all intravenously administered acetylcysteine in the United States had to be compounded using the oral preparation.

The most important factors to consider when selecting the route of acetylcysteine administration include individual susceptibility, the
Adverse effects to oral therapy have been mild. Therefore, acetylsalicylic acid- or n-acetylcysteine who do not have toxic acetaminophen-poisoned patients with a history of asthma or hypersensitivity reactions should receive oral acetylcysteine unless circumstances preclude this route of therapy.

**Considerations with oral acetylcysteine.** Acetylcysteine has a putrid odor, and its taste is very difficult to mask. Because oral acetylcysteine is unpalatable, patient adherence to mask. Because oral acetylcysteine is unpalatable, patient adherence becomes an issue. Many patients develop nausea and vomiting after the administration of oral acetylcysteine. This delays acetylcysteine administration when time is of the essence. Absorption time is critical because of the narrow 8–10-hour window in which acetylcysteine is most effective in preventing acetaminophen-induced hepatotoxicity. Acetylcysteine absorption may be further delayed if the patient is receiving any concomitant drugs with anticholinergic properties.

Investigators have studied whether oral acetylcysteine reduces activated charcoal’s ability to adsorb acetaminophen. The results of one in vitro study showed that acetylcysteine significantly decreased the binding of activated charcoal to acetaminophen (p < 0.005). Oral administration of acetylcysteine undergoes a first-pass effect so that the entire dose passes through the liver, resulting in high concentrations and the potential for hepatotoxicity. This may be advantageous in poisoned patients who present within 8–10 hours postingestion.

Acetylcysteine for oral administration is less expensive than both compounded i.v. acetylcysteine and Acetadote. However, this cost saving may be lost because patients may spend less time in the hospital receiving i.v. acetylcysteine compared with the oral preparation, even if an abbreviated oral acetylcysteine protocol is followed. However, it is easier to prepare the oral product than to extemporaneously prepare the i.v. product.

**Conclusion**

Oral acetylcysteine administered within 8–10 hours of acetaminophen overdose prevents liver toxicity in the majority of patients who tolerate it and have no contraindications to therapy. I.V. acetylcysteine should be administered when patients are treated more than 10 hours postingestion of acetaminophen overdose or have underlying conditions preventing oral treatment. Anaphylactoid reactions are rare and occur more frequently in patients treated with the i.v. preparation.

**References**