Certain portions of this correspondence have been omitted pursuant to a request
for confidential treatment which has been filed separately with the SEC.

June 22, 2007

United States Securities and Exchange Commission
100 F Street, N.E.
Washington, D.C. 20549
Attention: Mr. Jeffrey P. Riedler
Assistant Director

Re: Cumberland Pharmaceuticals Inc.
Form S-1 Registration Statement
File No. 333-142535

Ladies and Gentlemen:

We are responding supplementally to comments received in a letter dated June 8, 2007 from Mr. Jeffrey P. Riedler to Mr. A.J. Kazimi with respect to the Form S-1 Registration Statement of Cumberland Pharmaceuticals Inc. filed on May 1, 2007.

1) To fulfill our response to your Comment No. 8, we hereby provide the Commission a copy of the article entitled "An update of *N*- acetylcysteine treatment for acute acetaminophen toxicity in children" by Laurie Marzullo, published by Lippincott Williams & Wilkins, Curr Opin Pediatr 17:239-245, 2005.

2) To fulfill our response to your Comment No. 28, we hereby advise the Commission Staff that the Company considers the following public companies to be its peers: Myriad Genetics, Inc. ("MYGN"), Bradley Pharmaceuticals, Inc. ("BDY"), Nabi Biopharmaceuticals ("NABI"), Forest Laboratories, Inc. ("FRX") and Salix Pharmaceuticals, Ltd ("SLXP").

3) To fulfill our response to your Comment No. 48, we hereby provide the following itemized chronological schedule covering all equity instruments issued by the Company since January 1, 2006:

CUMBERLAND PHARMACEUTICALS INC

COMMON STOCK CERTIFICATES

Certificate Number	Name	Related Party	Issued Price	Number of Shares	Issue Date	Value of Shares Transacted	Nature of Grant
389	[***]	Board member	$18.00	6,000	2/1/2006	108,000.00	Services
390	[***]	Sr V.P. and Medical Director	$18.00	1,350	2/1/2006	24,300.00	Services
415	[***]	Board member	$22.00	1,091	12/29/2006	24,002.00	Services
416	[***]	Board member	$22.00	1,091	12/29/2006	24,002.00	Services
417	[***]	Board member	$22.00	1,091	12/29/2006	24,002.00	Services
418	[***]	Board member	$22.00	3,136	12/29/2006	68,992.00	Services
425	[***]	Board member	$22.00	2,200	2/1/2007	48,400.00	Services
426	[***]	Board member	$22.00	3,318	2/1/2007	72,996.00	Services
427	[***]	Consultant	$22.00	2,500	2/1/2007	55,000.00	Services
428	[***]	Sr V.P. and Medical Director	$22.00	2,600	2/1/2007	57,200.00	Services
429	[***]	HR Consultant	$22.00	1,000	2/1/2007	22,000.00	Services

OPTIONS GRANTED

Number	Name	Related Party	Underlying Stock Value	Exercise price Stock Value	Number of Shares	Grant Date	Term (in years)	Nature of Grant
N-104	[***]	Consultant	$18.00	$18.00	10,000	1/31/2006	60 days after vest	Services
N-105	[***]	CET consultant	$18.00	$18.00	2,000	1/31/2006	10	Services
I-45	[***]	employee	$18.00	$19.80	10,000	6/30/2006	5	Employee incentives
I-46	[***]	employee	$18.00	$18.00	6,500	6/30/2006	10	Employee incentives
I-47	[***]	employee	$18.00	$18.00	5,500	6/30/2006	10	Employee incentives
I-48	[***]	employee	$18.00	$18.00	1,300	6/30/2006	10	Employee incentives
I-49	[***]	employee	$18.00	$18.00	1,000	6/30/2006	10	Employee incentives
I-50	[***]	employee	$18.00	$18.00	7,500	7/17/2006	10	Employee incentives
I-51	[***]	employee	$18.00	$18.00	1,575	9/1/2006	10	Employee incentives
I-52	[***]	employee	$18.00	$18.00	1,200	10/15/2006	10	Employee incentives
I-53	[***]	employee	$18.00	$18.00	1,400	10/15/2006	10	Employee incentives
I-54	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-55	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-56	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-57	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-58	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-59	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-60	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-61	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-62	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives

Number	Name	Related Party	Underlying Stock Value	Exercise price Stock Value	Number of Shares	Grant Date	Term (in years)	Nature of Grant
I-63	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-64	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-65	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-66	[***]	employee	$22.00	$22.00	500	1/1/2007	10	Employee incentives
I-67	[***]	employee	$22.00	$22.00	6,000	2/2/2007	10	Employee incentives
I-68	[***]	employee	$22.00	$22.00	6,000	2/2/2007	10	Employee incentives
I-69	[***]	employee	$22.00	$22.00	5,000	2/2/2007	10	Employee incentives
I-70	[***]	employee	$22.00	$22.00	5,000	2/2/2007	10	Employee incentives
I-71	[***]	employee	$22.00	$22.00	4,000	2/2/2007	10	Employee incentives
I-72	[***]	employee	$22.00	$22.00	3,000	2/2/2007	10	Employee incentives
I-73	[***]	employee	$22.00	$22.00	2,000	2/2/2007	10	Employee incentives
I-74	[***]	employee	$22.00	$22.00	500	2/2/2007	10	Employee incentives
N-106	[***]	CET consultant	$22.00	$22.00	7,000	2/2/2007	10	Services
I-75	[***]	employee	$22.00	$22.00	460	2/26/2007	10	Employee incentives

WARRANTS GRANTED

Number	Name	Related Party	Underlying Stock Value	Exercise price Stock Value	Number of Shares	Grant Date	Term (in years)	Nature of Grant
W-3	Bank of America, N.A.	NO	$18.00	$18.00	1,979	4/6/2006	10	Loan Agreement Fee

If you have any additional questions, please call the undersigned at (615) 259-1479.

Sincerely yours,

ADAMS AND REESE LLP

/s/ Martin S. Brown, Jr.

cc: Mary K. Fraser, Esq., United States Securities and Exchange Commission
A.J. Kazimi, Cumberland Pharmaceuticals Inc.
Donald J. Murray, Esq., Dewey Ballantine LLP, Counsel to the underwriters

Enclosure

An update of *N*-acetylcysteine treatment for acute acetaminophen toxicity in children

Laurie Marzullo

Purpose of review

Acetaminophen poisoning accounts for a disproportionate percentage of all toxic ingestions, and can be life-threatening. This article reviews the mechanism and presentation of acetaminophen toxicity, as well as its treatment, including current thinking and treatment recommendations.

Recent findings

N-acetylcysteine acts to detoxify acetaminophen in several ways, but primarily by increasing the synthesis and availability of glutathione, which binds and inactivates the highly reactive and hepatotoxic acetaminophen metabolite *N*-acetyl-*p*-benzoquinoneimine. The US Food and Drug Administration has approved an intravenous formulation of *N*-acetylcysteine, thus allowing the treatment time to be decreased from the 72 hr most commonly used for the oral regimen, to only 20 hr. This comes after many years of accepted intravenous *N*-acetylcysteine use in Europe and Canada, and much controversy as to the superiority of both treatments. This review summarizes this controversy, and offers a framework to develop a safe treatment plan that has the optimal outcome for the patient, as well as reflecting knowledge of the potential caveats at work. It describes side effects of *N*-acetylcysteine treatment, as well as relative indications to choose one route of treatment over the other.

Summary

Acetaminophen can lead to irreversible liver damage and even death in acute overdose. Outcome is related to the swiftness in which the antidote (*N*-acetylcysteine) is provided. In the United States, there are now available both the oral and intravenous forms of *N*-acetylcysteine, and pros and cons exist for each. With brisk and adequate treatment using either route, recovery can be complete, and liver function can be restored.

Keywords

acetaminophen toxicity, anaphylaxis, centrilobular necrosis, glutathione, *N*-acetylcysteine

Curr Opin Pediatr 17:239–245. © 2005 Lippincott Williams & Wilkins.

Division of Pediatric Emergency Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence to Laurie Marzullo, University of Alabama at Birmingham, 1600 7th Avenue South, Midtown Center suite 205, Birmingham, AL 35233, USA
Tel: 205 939 9587; fax: 205 975 4623; e-mail: lmarzullo@peds.uab.edu

Current Opinion in Pediatrics 2005, 17:239–245

Abbreviations

AST	aspartate aminotransferase
NAC	*N*-acetylcysteine
NAPQI	*N*-acetyl-*p*-benzoquinoneimine

1040-8703

Introduction

Acetaminophen is a well-known, long trusted, and exceedingly available over-the-counter analgesic and antipyretic. Since its availability in the 1950s, its use has become very widespread, because of its efficacy, as well as its high toxic-to-therapeutic ratio, and its availability in liquid, tablet, and suppository preparations. Perhaps in part because of its ubiquity in medicine chests, it is an extremely frequently reported agent of toxic ingestions, both accidental and intentional. It accounted for 147 deaths reported to the American Association of Poison Control Centers in 2003 [1]. Damage to the liver is the most common cause of serious morbidity and death. Acetaminophen is metabolized almost exclusively in the liver, with more than 90% being converted to the nontoxic glucuronide and sulfate conjugates, and less than 5% being excreted unchanged in the urine. The remaining 5% is metabolized by various cytochrome P450 enzymes, and thus the highly reactive *N*-acetyl-*p*-benzoquinoneimine (NAPQI) is formed [2–4].

The generally accepted potential risk of toxicity in previously healthy, nonfasted patients occurs with acute ingestion of more that 150 mg/kg in children (although recent studies indicate that doses up to 200 mg/kg may be safe) and 7.5 g total ingestion in adults [2]. Fasted patients, those with chronic liver disease or a history of excessive alcohol use, and those who take drugs that induce the cytochrome P450 system are at greater risk from lower ingestions. The therapeutic range in the plasma is 10–20 μg/ml, all preparations are readily absorbed, and even the extended release compounds reach peak concentrations by 4 hr after ingestion.

Mechanism of toxicity

In the usual nontoxic acetaminophen doses, NAPQI combines with the sulfhydryl group of endogenous glutathione to form a nontoxic mercaptide conjugate. In toxic doses, excessive NAPQI is formed, and glutathione stores are depleted. There is observable NAPQI-induced liver toxicity if the glutathione supply falls below 30% of normal.

Centrilobular necrosis in the liver cells predominates as the cellular mechanism of acetaminophen toxicity, because of covalent binding of NAPQI to cysteinyl sulfhydryl groups in the liver cells. How the actual injury occurs remains under study, but possible mechanisms include damage to mitochondrial function, inhibition of Krebs cycle enzymes, and disruption of calcium gradients that are involved with various cellular functions [2–4].

Clinical features of toxicity

Treatment of acetaminophen toxicity needs to be aggressive and early to avoid the significant morbidity and even mortality associated with overdose, and this is often complicated by the fact that early recognition of the ingestion is easily missed.

There are four main stages of toxicity:

(I) (0.5–24 hr after ingestion): Symptoms may include anorexia, nausea, vomiting, malaise, pallor, and diaphoresis. This stage may be completely asymptomatic, and all laboratory studies (but acetaminophen concentration) are normal. If there are other signs or symptoms at this stage, a thorough investigation for possible co-ingestants should be made.

(II) (24–48 hr after ingestion): Symptoms and signs may include right upper quadrant pain, jaundice, elevated laboratory values (bilirubin, PT, hepatic enzymes), and oliguria. Aspartate aminotransferase (AST) is the most sensitive measure of liver toxicity in this scenario, and always precedes actual liver dysfunction. Resolution of the vague stage I symptoms may occur.

(III) (72–96 hr after ingestion): This is the time of maximal hepatotoxicity. Findings may vary from the complete lack of symptoms to fulminant hepatic failure, with coma and life-threatening hemorrhage. Transaminases may surpass 10 000, even with no objective signs of liver dysfunction. If liver injury is significant, hyperbilirubinemia, prolonged PT, acidosis, and other findings referable to liver dysfunction may be present. If fatality is the outcome, it usually occurs at 3–5 days.

(IV) (4 days–2 weeks): This is the recovery phase. In survivors, hepatic regeneration of function is complete.

In severely poisoned patients, renal dysfunction is common (up to 25%), because of direct, in situ NAPQI toxicity in the kidney analogous to that in the liver, as well as secondary renal failure related to the primary hepatic insult (hepatorenal syndrome).

Laboratory evaluation

The measured acetaminophen level at 4 hr after ingestion or longer predicts the possibility of liver injury when plotted on the accepted acetaminophen nomogram.

The original study that predicted liver toxicity as it related to acetaminophen level and time since ingestion (done by Rumack and Matthew, 1975) [5] depicted a treatable 4-hr level at 200 μg/ml. However, a lower line, the 'possible hepatotoxicity line' (25% under the upper one), indicating a 4-hr level of 150 μg/ml, was subsequently established to prevent undertreatment. Special care must be given to interpreting the level with knowledge of the correct units. In addition, the nomogram cannot be used to interpret chronic ingestions.

In general, the same 4-hr postingestion level can be used for treatment decisions concerning extended-release acetaminophen products, but some conservative practitioners advocate the measurement of 4-hr and 6-hr levels in large ingestions of extended-release products, and treating if either value is in the toxic range.

In the previously healthy patient with no baseline liver dysfunction, further diagnostic evaluation is guided by the presence of a toxic acetaminophen concentration. If laboratory evaluation is triggered, then liver function tests, electrolytes, glucose, and pH determinations should be done.

General treatment guidelines

The accepted antidote for ingestion of toxic levels of acetaminophen is *N*-acetylcysteine (NAC), as published by Prescott *et al.* [6,7]. In addition to a number of extrahepatic and microcirculatory effects, NAC works in the liver by a number of proposed mechanisms, described as follows (Fig. 1).

(1) NAC increases the synthesis and availability of glutathione, being converted to cysteine and then to glutathione.

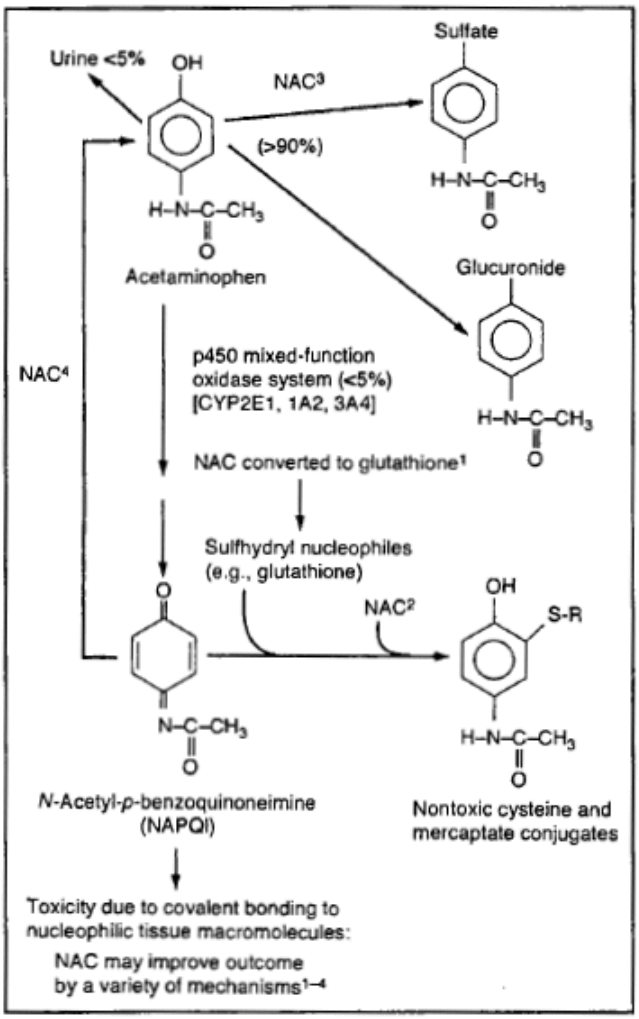
(2) NAC (via its reduced sulfur group) can substitute for glutathione and directly bind, and thus detoxify, NAPQI.

(3) NAC can supply a substrate for sulfation, increasing the percentage of nontoxic metabolism.

Gastric decontamination with activated charcoal is recommended, but its usefulness is limited if given more than 2 hr after ingestion, because acetaminophen is rapidly absorbed.

Acetaminophen is rapidly adsorbed by activated charcoal, and its administration is especially important if the overdose involves multiple compounds. The decision to use activated charcoal should not be affected by considerations of the use of NAC, but the evidence remains controversial as to whether charcoal adsorption of NAC is clinically significant. The most likely hypothesis is that the amount of NAC used in acetaminophen toxicity so greatly exceeds that needed to prevent liver cell damage,

Figure 1. Mechanisms by which *N*-acetylcysteine (NAC) works in the liver



NAC increases the synthesis and availability of glutathione, being converted to cysteine and then to glutathione. NAC (via its reduced sulfur group) can substitute for glutathione and directly bind, and thus detoxify, *N*-acetyl-*p*-benzoquinoneimine. NAC can supply a substrate for sulfation, increasing the percentage of nontoxic metabolism. Reproduced with permission [2].

that a small decrease in NAC bioavailability by activated charcoal adsorption is not clinically significant [3]. In addition, it is often possible to temporally separate the activated charcoal from the first dose of oral NAC, because outcome is not affected as long as NAC is started within 8 hr of acetaminophen ingestion [8].

Considerations for the use of oral *N*-acetylcysteine

The use of an oral protocol for NAC therapy for acetaminophen toxicity has long accepted the dosing schedule to include a 140 mg/kg loading dose, followed by an additional 17 doses of 70 mg/kg every 4 hr (for a total of 1330 mg/kg NAC over 72 hr) [6]. Smilkstein *et al.*, 1988 [8] conducted a study to define the efficacy of oral NAC in this setting, and its relation to the initial plasma APAP concentration and to the delay before treatment is initiated. The evaluated patients met inclusion criteria of a single, acute acetaminophen overdose, at least one APAP measurement between 4 and 24 hr after ingestion, at least 17 doses (unless they died first) of enterally administered NAC (orally or enteral tube), and availability of serial AST measurements to assess liver toxicity. Those chosen for treatment had APAP levels that were stratified, but all had levels that were at or above a point on the nomogram corresponding to 150 μg/ml at 4 hr after ingestion, previously described by Rumack and Matthew [5]. Also treated were those whose levels were not available until after treatment was initiated, if ingestion was more than 140 mg/kg in a child or 7.5 g in an adult. As with previous studies, it was shown that hepatotoxicity was minimal regardless of the initial APAP concentration *if* NAC was started within 8 hr of ingestion. This suggests that treatment delays due to factors that delay gastric emptying or to the administration of activated to charcoal should not adversely impact the outcome, if NAC is started within 8 hr of ingestion. There was, however, an increase in hepatotoxicity with treatment delays within 8–16 hr after ingestion.

Woo *et al.* (2000) [9] did an observational study to assess whether the oral dosing of NAC could be implemented for less than 72 hr and keep the same efficacy as the originally recommended 72-hr regimen. The study was done as a retrospective chart review of acetaminophen ingestions at one hospital, with therapy being initiated if serum APAP levels were above a modified Rumack-Matthew line extending from 140 μg/ml at 4 hr to 50 μg/ml at 10 hr. The regional poison control center recommended instituting the oral NAC regimen at the usual 140 mg/kg loading dose, followed by 70 mg/kg q4h dosing, until the serum APAP level was undetectable. This study demonstrated as high an efficacy in the shorter regimens of oral NAC use as compared with the 72-hour oral protocol described in the Smilkstein study (1988) [8] discussed earlier. Smilkstein's group showed an incidence of hepatotoxicity of 6.1% if NAC was initiated within 10 hr of ingestion, and 26.4% if treated after 10 hr. The present study showed analogous incidences of hepatotoxicity of 3% and 21%, respectively. The authors suggesting the adoption of a time of 36 hr after ingestion as a time to discontinue NAC therapy, if the acetaminophen level is no longer detectable and if AST/ALT levels are normal.

Considerations for the use of intravenous *N*-acetylcysteine

In Europe and Canada, the 20-hr intravenous NAC regimen for acetaminophen overdose has long been used, with a cumulative dose of 300 mg/kg, even as the oral regimen was the only one approved in the United States for this

purpose. In 1991, Smilkstein's group [10] published a study aimed at describing an effective and shorter alternative to the oral regimen using an investigational, pyrogen-free form of intravenous NAC, and the 48-hr, intermittent dosing protocol was described. The dosing included a 140 mg/kg loading dose, followed by 12 maintenance doses of 70 mg/kg, every 4 hr. All doses were infused over 1 hr, and each subsequent dose was started 4 hr after the previous one (i.e., 3-hr 'off' per time period). The total treatment dose was 980 mg/kg over 48 hr. The inclusion criteria were the same as Smilkstein's 1988 oral NAC study [8]. This study produced results similar to those of the studies describing the 72-hr oral NAC protocol and the 20-hr continuous intravenous NAC protocol, in acutely poisoned patients treated within 10 hr of ingestion.

The incidence of hepatotoxicity in the 48-hr intravenous protocol was comparable to previously noted percentages for treatment groups before and after 10 hr of ingestion in the 72-hr oral protocol as well as the 20-hr intravenous protocol. There was 10% hepatotoxicity if treatment was initiated within 10 hr of ingestion, and 27.1% if initiated within 24 hr of ingestion. It was deemed 'hepatoprotective' and resulted in no deaths in all risk groups.

Perry and Shannon [11] made the comparison of intravenous versus oral NAC, in an open-label clinical trial in a pediatric population. The study group was similar to that in other studies, in that patients had an acute ingestion, a 4-hr level that placed them at least above the 'possible toxicity' line on the nomogram, and presented no later than 24 hr after overdose. The intravenous NAC regimen was 140 mg/kg loading dose followed by 12 doses of 70 mg/kg, all during 1 hr, 4 hr apart. The historical control subjects were those treated with oral NAC in the accepted regimen, with the same eligibility requirements as the intravenous NAC group. Mean treatment delay was significantly longer in the intravenous group, as was peak prothrombin time values. All other laboratory values had no significant differences between groups.

In Perry's study, there were no patients in the intravenous protocol who had hepatotoxicity if treated within 10 hr, and 9.8% if treated within 10–24 hr. The authors of this paper gave several reasons why the results might be better in the pediatric population, including sulfation playing a more important role in acetaminophen metabolism before age 12, the possibility (untested) of age playing a role in the elaboration of the toxic NAPQI, the capacity for glutathione regeneration possibly being greater in children, and the prevalence of ETOH likely being lower in the pediatric population. The mean age of patients in this study was 15.6 ± 3.2, as compared with 21.3 ± 9.3 in the 48-hr intravenous protocol study by Smilkstein *et al.* previously described [10].

The US Food and Drug Administration approved an intravenous formulation of NAC in early 2004 (Acetadote ®, Cumberland Pharmaceuticals, Nashville, Tennessee, USA) using the 20-hr, continuous-infusion protocol. In regard to adult intravenous dosing, the loading dose is 150 mg/kg in 200 ml of D5 for 15 min, followed by 50 mg/kg in 500 ml of D5 for 4 hr, and 100 mg/kg in 1000 ml of D5 for 16 hr [12].

In regard to pediatric intravenous dosing, it has been shown [13] that standard intravenous dosing can cause hyponatremia and secondary seizures because of the free water load (see later section on adverse events). Therefore, the convention is to dilute 20% NAC to a final concentration of 40 mg/ml. See Table 1 for a depiction of the usual pediatric dosing schedule. The final milligrams per kilogram dosing (150 mg/kg loading dose, 50 mg/kg for 4 hr, and 100 mg/kg for 16 hr) is the same; the free water is less than in the adult schedule.

One suggested practice guideline is outlined below (E. L. Liebelt, 2004, personal communication).

(1) Draw an acetaminophen level and plot on the Rumack-Matthew nomogram.
(2) If the level (according to time since ingestion) falls above the 'possible hepatotoxicity' line, begin therapy.
(3) Draw aspartate aminotransferase/alanine aminotransferase, prothrombin time/international normalized ratio, electrolytes, blood urea nitrogen/creatinine, and CBC.
(4) At the end of infusion, redraw the prothrombin time/international normalized ratio, aspartate aminotransferase/alanine aminotransferase, blood urea nitrogen/creatinine. If any laboratory studies are abnormal, continue the infusion. In the setting of liver dysfunction, continue until liver function improves.

We are only beginning our American experience on the widespread use of this protocol, although for years the off-label use of intravenous *N*-acetylcysteine has been used at the discretion of US clinicians. The potential for a shorter hospital stay using the intravenous protocol has the promise of reducing the overall treatment costs, but the comparison of actual costs between the treatment types has yet to be formally compared. Some indications of when intravenous *N*-acetylcysteine might be preferable are in cases of refractory vomiting, despite use of antiemetics; bowel obstruction; or other cause of a surgical abdomen in which the gastrointestinal tract should not be used, gastrointestinal bleeding, and in cases of neonatal acetaminophen toxicity.

Adverse events after *N*-acetylcysteine administration

Refractory nausea and vomiting have long been described after acetaminophen ingestion. The exacerbation of these

Table 1. Pediatric intravenous dosing

Body weight		Loading infusion (15 min)–150 mg/kg		
Kg	lb	NAC 20% (mL)	Diluent volume D5W (mL)	Final volume (mL)
30	66	22.5	90	112.5
25	55	18.75	75	93.75
20	44	15	60	75
15	33	11.25	45	56.25
10	22	7.5	30	37.5
Body weight		Second infusion (4 HR)–50 mg/kg		
Kg	lb	NAC 20% (mL)	Diluent volume D5W (mL)	Final volume (mL)
30	66	7.5	30	37.5
25	55	6.25	25	31.25
20	44	5	20	25
15	33	3.75	15	18.75
10	22	2.5	10	12.5
Body weight		Third infusion (16 HR)–100 mg/kg		
Kg	lb	NAC 20% (mL)	Diluent volume D5W (mL)	Final volume (mL)
30	66	15	60	75
25	55	12.5	50	62.5
20	44	10	40	50
15	33	7.5	30	37.5
10	22	5	20	25

Mix 50 mL of Acetadote® (20% solution, 30 mL each vial) with 200 mL of D5W (remove 50 mL from a 250 mL bag of D5W) to obtain 40 mg/mL concentration. Loading dose–150 mg/kg infused over 15 minutes–Infuse 3.75 mL/kg over 15 minutes, Second infusion–50 mg/kg infused over 4 hours–Infuse 1.25 mL/kg over 4 hours (0.31 mL/kg/hr), Third infusion–100 mg/kg infused over 16 hours–Infuse 2.5 mL/kg over 16 hours (0.16 mL/kg/hr), from [13].

symptoms has often been attributed to the foul, rotten-egg odor and taste of the oral NAC antidote. Many have suggested that this is an indication to administer NAC via the intravenous route. In addition, because of the partial binding of NAC by activated charcoal and thus its decreased bioavailability, others have promulgated this as another reason to use the intravenous route. However, the need or requirement to resort to intravenous dosing in these or other situations has remained equivocal.

Before a sterile, pyrogen-free intravenous NAC product was available in the United States, oral NAC (administered intravenously) was used in many study protocols [14•,15]. Most of the adverse events associated with intravenous NAC use have been anaphylactoid in nature, including rash, pruritus, wheeze, throat tightening, and sometimes hypotension [10,11,15]. Of note, there have not been reports of anaphylactoid reactions to oral NAC administration. These adverse reactions were almost always seen with the loading dose, and were assumed to be dose-related and infusion-rate related, histamine dependent, but not IgE mediated as in true anaphylaxis. In most cases, antihistamine therapy has been effective, and the transient reactions did not prelude the completion of the NAC courses. Appelboam *et al.* [16] reported a fatal anaphylactoid reaction to intravenous NAC in an asthmatic patient, suggesting that preexisting asthma be an indication to use special caution in the use of intravenous NAC.

Kao *et al.* [14•], in a retrospective study of the use of oral NAC for intravenous administration in acetaminophen toxicity, sought to analyze the adverse events associated with its use, using the European standard of 300 mg/kg NAC during 20 hr. The infusion was stopped when the transaminases were less than 1000 IU/l and the patient was clinically improving. The loading dose of 150 mg/kg was infused during 1 hr, instead of the previously described 15-min loading dose infusion time [3]. Adverse events were defined as any cutaneous, systemic (such as wheeze, transient hypotension), or life-threatening (respiratory or cardiac arrest, or hypotension requiring intervention) reaction. Of the 10 deaths in the study population, none occurred during the NAC loading dose or were tied to the use of NAC by the intravenous route. The study showed a 3.7% (7/187) rate of adverse events. Of the seven adverse events, six were cutaneous and responded rapidly to antihistamines, and the one life-threatening event (apnea and junctional bradycardia) was not clearly linked to the use of intravenous NAC. This study offered support to the common suggestion to increase the infusion time for the intravenous loading dose to 1 hr.

Bailey and McGuigan [17] did a review of acetaminophen toxicity charts in an attempt to analyze the treatment of NAC-induced anaphylactoid reactions and to develop treatment guidelines addressing whether or not to continue the therapy that was clearly indicated and needed. They saw a 23% reaction rate in the 20-hr intravenous protocol, 20% rate in the 48-hr intravenous protocol, and no reactions in the 72-hr oral protocol. Treatment guidelines were developed and then applied prospectively in the setting of NAC treatment for acetaminophen ingestion. The treatment paradigm ranged from no intervention for simple flushing, to attendance to ABCs, intravenous diphenhydramine, oral cimetidine and ephedrine in the cases of respiratory symptoms or hypotension. Even in these cases, NAC was restarted in 1 hr if no symptoms recurred. In summary, the guidelines were successfully applied, with no poor outcomes. This study had a limitation of a small number of subjects; 33 were treated according to the guidelines prospectively. Another limitation of this study was that no life-threatening reactions occurred. Interventions and techniques of slowing the infusion rate, and so on, therefore, could not be evaluated on these subjects.

Lynch and Robertson [18] conducted a prospective, case-controlled study to investigate the predictive factors of developing an anaphylactoid reaction to intravenous NAC. Of the 64 patients who received the infusion,

48.4% developed an anaphylactoid reaction, and 71% of these were in the first 15 min of infusion. They note that this incidence of reaction is much higher than in previous studies. There findings suggested that patients were more likely to react to intravenous NAC if they had low APAP levels, zero levels, were classified as high risk, or presented late (>8 hr after ingestion). The authors concluded that it might minimize reactions if treatment was delayed until the APAP level was known in early presenters (<8 hr), and if the loading dose was given during 60 instead of 15 min.

A case report by Bonfiglio *et al.* [19] described a 20-year-old woman with a polyingestion (including 16 g of acetaminophen), presenting at least 16 hr afterward. Immediately after the 150 mg/kg loading dose, she experienced chest pain, dyspnea, tachycardia, ST depression, and T-wave inversion in electrocardiogram leads V2–V5 (the events of which have not been described for her co-ingestants). Nitroglycerin and antacid gave no relief, but she was relieved within 2 min of antihistamine administration. The electrocardiogram abnormalities were persistent, and deemed to likely predate the ingestion, but she clinically returned to normal.

Another case study done in Canada by Sung *et al.* [13] described a 3-year-old girl who, 9 hr into intravenous NAC therapy, had tonic–clonic seizure activity and a serum sodium level of 118 mmol/L (documented at 141 mmol/L prior to initiation of treatment). It was theorized that an excess of free water delivery associated with the treatment protocol was to blame, causing an exaggerated dilutional response because the patient was a small child. The authors suggested an alternate dilution method for the intravenous NAC, which decreased unnecessary free water delivery to small patients.

In 1994, Mohammed [20] reported a case of serum sickness in a man given oral NAC at an unclear dose (unknown milligrams per kilogram), every 6 hr; the protocol used was unclear. His reactions started 60 hr after NAC exposure, and included fever, rash, arthralgia, adenopathy, abdominal pain, and a decrease in platelet count. In addition to stopping the NAC, he was given methylprednisolone and diphenhydramine, and was significantly better within 12 hr.

Conclusion

We are at a state of maximal knowledge of the mechanisms of and treatment for acetaminophen toxicity, and in the United States we now have the ability to make a choice between the use of oral versus intravenous NAC formulations. However, the responsibility belongs to the practitioner to weigh the variables in this decision, taking into account the relative risk of hepatotoxicity given the magnitude of the ingestion, as well as other factors. Patient characteristics, such as age, preexisting morbidity, other medication exposure, nutritional state, atopic tendency, and even genetic factors may culminate in a milieu that will swing the balance toward increased acetaminophen-induced toxicity or toward increased iatrogenic morbidity from its treatment.

The oral NAC regimen has been used for more than 20 years in the United States, and has been shown to be as effective as the intravenous protocols, especially in early treatment. Many have touted that the intravenous form is indicated if there is intractable vomiting, but we still do not know whether this is a valid argument. Antiemetics have been used extensively in this setting, and the use of a transpyloric feeding tube to support enteral NAC administration may have a role in this setting. As for the negative effect on NAC bioavailability from adsorption by activated charcoal, the argument for this is also weak. Efficacy of the oral protocol has not been shown to be decreased, despite the decrease in NAC bioavailability.

The intravenous formulation is much more expensive, but the oral regimen raises healthcare costs in this setting because hospital stays potentially may be much longer. The oral regimen has fewer side effects, but the vast majority of the side effects to intravenous NAC area easily treated and do not preclude finishing of the course.

Clinicians need to assess their risk tolerance in this setting, and make decisions on a case-by-case basis. Hopefully study in this area will continue, and case-controlled studies between the available treatments, with special attention to differing patient characteristics, will be forthcoming.

As a final note, this paper has not addressed the concept that late NAC treatment, by microcirculatory, antioxidant, or other effects, may have a restorative effect on acetaminophen-induced hepatotoxicity, and certainly more work is needed to address this possibility.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 Watson WA, Litovitz TL, Klein-Schwartz W, *et al.* Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2004; 22:335–366.

2 Anker A. Toxins in depth: acetaminophen. In: Ford MD, Delaney KA, Ling LJ, Erickson T, editors. Clinical toxicology. 1st ed. Philadelphia: W.B. Saunders; 2001. pp. 265–274.

3 Anker AL, Smilkstein MJ. Acetaminophen: concepts and controversies. Emerg Clin North Am 1994; 12:335–349.

4 Kozer E, Koren G. Management of paracetamol overdose: current controversies. Drug Saf 2001; 24:503–512.

5 Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics 1975; 55:871–876.

6 Prescott LF, Park J, Ballantyne A, *et al.* Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. Lancet 1977; 2:432–434.

7 Prescott LF, Illingworth RN, Critchley JA, *et al.* Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. BMJ 1979; 2:1097–1100.

8 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 (1976-1985). N Engl J Med 1988; 319:1557–1562.

9 Woo OF, Mueller PD, Olson KR, *et al.* Shorter duration of oral N-acetylcysteine therapy for acute acetaminophen overdose. Ann Emerg Med 2000; 35:363–368.

10 Smilkstein MJ, Bronstein AC, Linden C, *et al.* Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. Ann Emerg Med 1991; 20:1058–1063.

11 Perry HE, Shannon MW. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label, clinical trial. J Pediatr 1998; 132:149–152.

12 Acetadote: (acetylcysteine) injection. Package insert. Cumberland Pharmaceuticals Inc., Nashville, Tennessee. 2004.

13 Sung L, Simons JA, Dayneka NL. Dilution of intravenous N-acetylcysteine as a cause of hyponatremia. Pediatrics 1997; 100:389–391.

14 • Kao LW, Kirk MA, Furbee RB, *et al.* What is the rate of adverse events after oral N-acetylcysteine administered by the intravenous route to patients with suspected acetaminophen poisoning? Ann Emerg Med 2003; 42:741–750.
Studies rate of adverse events with the intravenous use of the oral N-acetylcysteine solution, and suggests guidelines for its use.

15 Yip L, Dart RC, Hurlbut KM: Intravenous administration of N-acetylcysteine. Crit Care Med 1998; 26:40–43.

16 Appelboam AV, Dargan PI, Knighton J: Fatal anaphylactoid reaction to N-acetylcysteine: caution in patients with asthma. Emerg Med J 2002; 19:594–595.

17 Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. Ann Emerg Med 1998; 31:710–715.

18 Lynch RM, Robertson R. Anaphylactoid reactions to intravenous N-acetylcysteine: a prospective case controlled study. Accid Emerg Nurs 2004; 12:10–15.

19 Bonfiglio MF, Traeger SM, Hulisz DT, Martin BR. Anaphylactoid reaction to intravenous N-acetylcysteine associated with electrocardiographic abnormalities. Ann Pharmacother 1992; 26:22–25.

20 Mohammed S. Serum sickness-like illness associated with N-acetylcysteine therapy. Ann Pharmacother 1994; 28:285.