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**REVIEW OF N-ACETYLCYSTEINE FOR THE TREATMENT OF
ACETAMINOPHEN (PARACETAMOL) TOXICITY IN PEDIATRICS**

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EXECUTIVE SUMMARY

Acetaminophen (paracetamol) toxicity is a common cause of drug-induced hepatotoxicity in children and adults. N-acetylcysteine (NAC) has been used for several decades and has proven to be the antidote of choice in treating acetaminophen-induced hepatotoxicity. There is significant clinical evidence to support that oral and intravenous NAC are equally efficacious in the prevention of hepatotoxicity. An important factor in assessing the efficacy of NAC is the timing of therapy initiation in relation to the ingestion. Patients that ingest an acute overdose and have NAC therapy initiated within 8 hours do well and have less than a 10% incidence of hepatotoxicity and generally do not develop liver failure or die. Those patients that chronically ingest excessive doses of acetaminophen over many hours and/or have NAC therapy initiated more than 8 hours after an acute overdose have an approximately 8-50% incidence of hepatotoxicity. Unlike clinical scenarios in which NAC therapy is initiated early, patients that have administration delayed are at risk of developing fulminant hepatic failure and death.

Oral administration is the preferred route for NAC therapy unless contraindications exist (e.g aspiration, persistent vomiting). The usual recommended loading dose is 140 mg/kg followed in 4 hours by a maintenance dose of 70 mg/kg orally given every 4 hours. This dosing is commonly recommended to be continued for 72 hours; however more recent clinical experience supports tailoring the duration of therapy to the patient's clinical condition. Intravenous NAC is recommended in situations in which the patient is not able to tolerate oral administration of NAC or has fulminant hepatic failure. The most commonly used IV protocol is to administer 150 mg/kg IV over 1 hour, followed by 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours. A modified intravenous dosing formulation for pediatric patients (weighing less than 40 kg) is recommended to prevent excessive fluid administration.

The antidotal efficacy of NAC is determined by great extent to the time that treatment is initiated after an overdose of acetaminophen. NAC therapy should be initiated within 8 hours of an acute ingestion and otherwise as soon as possible. While many protocols have defined lengths of treatment, it is generally recommended that NAC be administered until the serum acetaminophen concentration is undetectable (<10 mcg/ml) and the patient is clinically well with normal liver function tests. In cases of hepatotoxicity, NAC should be continued until: 1) the serum liver transaminases fall to less than 1000 IU/L, bilirubin and coagulation studies are normal, and the patient is clinically well; 2) the patient receives a liver transplant; or 3) the patient dies.

Both oral and intravenous NAC are well tolerated. Nausea and vomiting are common with oral administration. Intravenous use has been associated with the development of anaphylactoid reactions. Generally these reactions are characterized by the development of a mild rash or urticaria. They typically respond to antihistamines and often the infusion is able to be completed. Life-threatening anaphylactoid reactions and deaths have been reported, but are uncommon.

PROPOSAL

The World Health Organization Model List of Essential Medicines and Model Formulary of 2006 lists acetylcysteine (NAC) as an antidote for use in the treatment of acetaminophen (paracetamol) overdose.^{1,2} It is proposed that acetylcysteine be considered the antidote of choice in the treatment of acetaminophen toxicity. Acetylcysteine is widely available and can be administered by both oral and intravenous (IV) routes. Both oral and IV use of NAC in this setting have proven to be safe and effective.

INTRODUCTION

Acetaminophen (Paracetamol) is used worldwide for its analgesic and antipyretic properties. It is widely available and present in many prescription and non-prescription medications. Unfortunately, however, acetaminophen toxicity remains the most common cause of drug-induced hepatic failure. Repeated supratherapeutic misuse, non-intentional misuse, and intentional ingestion may all result in hepatic toxicity.

The mechanism of acetaminophen toxicity has been well studied. Following ingestion a majority (>90%) of acetaminophen undergoes phase II metabolism (via glucuronidation and sulfation) to produce non-toxic metabolites. A small fraction (<5-10%) of acetaminophen is metabolized by CYP450 isoforms (predominately CYP2E1) to N-acetyl-p-benzoquinoneimine (NAPQI), a toxic metabolite. Under normal conditions NAPQI is detoxified through conjugation with glutathione. With acetaminophen toxicity, cellular glutathione is depleted resulting in the availability of NAPQI to bind to cellular macromolecules, the consequences of which are hepatocellular injury and cell death. Hepatic toxicity is generally thought to occur when glutathione stores are depleted to less than 30% of normal.³ Children may be less susceptible to acetaminophen toxicity^{4,5} consequent to a developmentally associated increase in sulfation ability.⁶

Certain factors can place patients at higher risk of acetaminophen toxicity. Diseases, such as alcoholism, malnutrition, HIV and cancer are associated with glutathione deficiency. This could result in a decreased ability to detoxify NAPQI. Concurrent use of drugs or ethanol that induce CYP2E1 and potentially, other CYP450 enzymes involved in NAPQI production (eg. CYP1A2, CYP3A4) could result in an increase in the amount of acetaminophen that is metabolized to NAPQI. Chronic ethanol use has been associated with an increased risk of acetaminophen hepatotoxicity.

In the first 4 to 6 hours following an acetaminophen ingestion, patients may be asymptomatic or may have mild symptoms such as nausea or vomiting. A latent period may then ensue in which the patient appears clinically well. However, with the development of NAPQI and depletion of hepatic glutathione stores to a critical level, hepatotoxicity ensues. Most patients will develop elevations of the AST and ALT within 24 hours of an ingestion, and almost all will have elevations at 36 hours.⁷ Occasionally, there is a delay in rise of the transaminases. Generally, maximal hepatotoxicity occurs at 72-96 hours. Progression to hepatic failure is characterized by development of encephalopathy, coma, cerebral edema, coagulopathy, gastrointestinal bleeding, and sepsis. Most deaths from hepatic failure occur within the first week following an acetaminophen overdose. Patients that recover do well and do not develop chronic liver dysfunction.

Following an acute acetaminophen ingestion, current recommendations are to obtain a serum acetaminophen level 4 hours following the ingestion. This level can then be plotted on the Rumack-Matthew nomogram to determine the patient's risk of hepatotoxicity. There is limited evidence that following an ingestion of acetaminophen elixir that a serum level obtained two hours post-ingestion can determine children at risk for hepatotoxicity.⁸ Obtaining a serum acetaminophen level prior to complete absorption of an ingested dose limits the predictive ability of the nomogram. Finally, the rate of decline for a serum acetaminophen level following overdose can not be predicted using the Rumack-Matthew nomogram.

An alternative approach to laboratory testing is warranted in cases of chronic acetaminophen ingestion or repeated suprathreshold dosing. A chronic ingestion is generally defined as occurring over more than 4-8 hours. In such cases an acetaminophen level should be obtained along with liver function and coagulation profiles. If the acetaminophen level is >10mcg/ml or the AST or ALT are >50 IU/L, then NAC therapy is recommended.^{9,10} This approach has been evaluated in a prospective case series of 249 patients. No patient that was below the recommended laboratory parameters subsequently developed hepatotoxicity.⁹

An acute acetaminophen ingestion of ≥ 150 mg/kg is potentially toxic. Several studies have reviewed the incidence of hepatotoxicity in patients who present within the "possible" hepatotoxicity range when plotted on the Rumack-Matthew nomogram. Brandwene et al. retrospectively identified 23 patients (15 were <18 years old) that had acetaminophen serum levels in the "possibly" toxic range that did not develop hepatotoxicity when NAC was withheld.¹¹ Some evidence suggests that the threshold dose of 150 mg/kg is too conservative and that up to 200 mg/kg may be ingested without development of toxicity (especially in children). Caravati assessed the risk of children having a toxic (possible and probable) acetaminophen level according to the Rumack-Matthew nomogram following an acute, unintentional ingestion. A total of 1,015 patients (mean age 28 ± 12 months) were identified that ingested a mean APAP dose of 213 ± 148 mg/kg. Six patients were identified with potentially or probably toxic acetaminophen ingestions. In three cases, the amount ingested was >200 mg/kg, and in the remaining three the amount ingested was undetermined.¹² Subsequently, Mohler and colleagues prospectively assessed for hepatotoxicity in pediatric patients that ingested up to 200 mg/kg of acetaminophen. They identified 1,039 patients that met the inclusion criteria. Follow up data was not available for 20 of these patients. Of the remaining 1,019 patients all were asymptomatic and without evidence of hepatotoxicity at 72 hour follow up.¹³

Several decades of experience have proven that NAC is the treatment of choice for acetaminophen poisoning. Prior to the introduction of NAC, L-methionine was used as a treatment for hepatotoxicity, however NAC has subsequently proven to be more efficacious^{14,15} and easier to administer given the availability of commercial dosing forms. NAC has several mechanisms of action that are beneficial in the treatment of acetaminophen poisoning which include serving as a glutathione replacement and a free radical scavenger, binding NAPQI directly and increasing microcirculatory oxygenation.¹⁶

Efficacy of NAC and prognosis are associated with the type of acetaminophen ingestion (acute vs chronic) and the time from ingestion to the initiation of NAC treatment. Those patients that present early following a single, acute ingestion or those patients that have normal liver functions tests on admission are probably at lower risk and do well with NAC therapy. The definition of APAP-induced hepatotoxicity most commonly reported in

clinical studies is an AST and/or ALT >1000 IU/L, or other evidence of hepatic failure. Any reference to hepatotoxicity in this report is based on this definition.

Multiple series in adults and children have demonstrated that patients who have taken multiple ingestions of acetaminophen and/or have a delayed presentation and treatment are at higher risk for severe hepatotoxicity.¹⁷⁻¹⁹ Thus, it is recommended that caution be exercised when administering >90 mg/kg/day of acetaminophen to a “sick” child (vomiting, diarrhea, poor oral intake) younger than 2 years of age, especially when acetaminophen is required for more than 1 day.²⁰ Generally speaking, data supporting the dosing regimens and efficacy of NAC in treating an acute ingestion of acetaminophen can not be extrapolated to the treatment of chronic acetaminophen ingestion and/or cases of protracted supratherapeutic administration of the drug.

While NAC is generally accepted across the developed world as the preferable antidote, its broader acceptance must be predicated upon information which demonstrates not only its therapeutic superiority to other treatments but also, clear and current evidence that supports its global adoption as the antidote of choice for this condition. This report will review and summarize the available evidence regarding:

- a) The efficacy of oral and IV NAC for the treatment of acetaminophen toxicity.
- b) The safety of oral and IV NAC for the treatment of acetaminophen toxicity.
- c) Side effect profile of oral and IV NAC.
- d) Duration of treatment and follow up laboratory testing in those receiving NAC therapy.
- e) Formulations and recommended dosage.

LITERATURE REVIEW

The studies for this review were identified by performing a search of the PubMed and Medline databases using the search terms: “acetaminophen” and “poisoning”, “acetaminophen” and “toxicity”, and “acetaminophen” and “acetylcysteine”. The dates included 1966-2007. The Cochrane Database for Systematic Reviews was also searched and a relevant data for review were identified.²¹ The bibliographies of selected articles were also reviewed to identify any studies not found by the original literature search.

CURRENT LISTING OF ACETYLCYSTEINE

The WHO Model list for 2006 currently lists only the intravenous formulation of acetylcysteine (200 mg/ml, 10 ml ampoule). For both adults and children the recommended dose is 150mg/kg IV over 15 minutes followed by 50 mg/kg over 4 hours then 100 mg/kg over 16 hours. Administration and preparation is determined by the age of the patient. In the those >12 years old, the recommended total volume (NAC and IV fluid) for the bolus, 4 hour infusion, and 16 hours infusion are 200 ml, 500 ml, and 1 liter, respectively. In children <12 years of age (but over 20 kg) the recommended volumes are 100 ml, 250 ml, and 500ml, respectively. In those children under 20 kg it is recommended to administer 3ml/kg, 7ml/kg, and 14ml/kg, respectively. It is noted that hypersensitivity reactions may be managed by decreasing the infusion rate or discontinuing the infusion. Use of medications, such as inhaled beta agonists or antihistamines, may also be necessary.

EFFICACY

The use of NAC for the treatment of acetaminophen poisoning originated in England in the 1970's. Subsequently, multiple studies have proven NAC to be efficacious in the treatment of acetaminophen poisoning. Early animal studies demonstrated the ability of NAC to attenuate or prevent hepatotoxicity.²² One randomized trial evaluated efficacy of NAC in the treatment of patients with acetaminophen-induced fulminant hepatic failure.²³ After several early NAC trials showed promising results, subsequent human investigations have consisted mostly of observational studies due to ethical concerns of withholding a potential lifesaving treatment. Thus, there are no randomized controlled trials that evaluate NAC therapy for prevention of acetaminophen-induced hepatotoxicity. Likewise, no randomized efficacy trials have been conducted in children. Many of the trials evaluate efficacy based on the outcomes of historical control patients.

In the only randomized trial reported in the literature, patients with acetaminophen-induced fulminant hepatic failure were assigned to receive IV NAC treatment versus standard supportive/intensive care. The mean age of the treatment patients was 33 yr (range 17-60). The treatment and control group had similar baseline characteristics and severity of illness. NAC treatment was associated with 48% (12/25 patients) survival compared to 20% (5/25 patients) survival in the control group ($p=0.037$). Patients treated with NAC had a lower incidence of cerebral edema (40% vs. 68% $p=0.047$).²³

Several early case series also examined the utility of NAC. One series reported the use of IV NAC in 15 patients.²⁴ One patient was 16 years old; the remaining 14 patients were all adults. Twelve patients were treated within 10 hours of their ingestion. The remaining patients had NAC initiated at a mean of 15.1 hours (10.2-23.5 hours) following ingestion. Those patients treated within 10 hours did well; one patient developed hepatotoxicity. No patients developed encephalopathy or hepatic failure. The 3 patients treated after 10 hours all developed hepatotoxicity, however all recovered without sequelae.²⁴

Prescott, et al. later reported their experience with the use of IV NAC for the prevention and treatment of acetaminophen hepatotoxicity in 100 patients.²⁵ The mean age of their cases was 33 years (range 13-82). Only one of 62 patients treated within 10 hours of ingestion developed hepatotoxicity. In those patients that were treated with NAC between 10-24 hours (mean 15 hours) of ingestion hepatotoxicity occurred in 53%. There were no deaths in those treated within 10 hours, and two deaths related to hepatic failure in those patients treated after 10 hours. The incidence of hepatotoxicity in their historical controls was 52-58% (3 deaths).²⁵

Rumack and colleagues reviewed the use of oral NAC in two observational studies.²⁶ Of those patients confirmed to have toxic acetaminophen levels two were less than age 5, 78 patients were between the ages of 12 and 21, and the remainder of the patients (20) were adults. No cases of hepatotoxicity developed in those that had NAC initiated within 10 hours (49 patients). However, there was a 45% incidence of hepatotoxicity in those that had a delay to initiation of NAC therapy >10 hours.²⁶ The two children that were younger than 5 years old did not develop hepatotoxicity. In this study, the time of NAC initiation relative to the acetaminophen overdose and specific pediatric data were not otherwise reported. A follow up study by the same investigators assessed the use of oral NAC in 662 patients.²⁷ Twenty three patients were younger than age 13; patient ages were not further specified. Patients (all ages included) treated with oral NAC within 10 hours of ingestion had a 7% incidence of

hepatotoxicity. Hepatotoxicity increased to 29% and 62% in those treated between 10-16 hours and >24 hours, respectively.²⁷ No specific adverse effects related to NAC administration were reported.

The largest study to evaluate the efficacy of NAC was a national multi-center study that reported data collected from 1976-1985.²⁸ A total of 2,023 patients had toxic acetaminophen concentrations based on the nomogram. A majority (78%) of the patients were between 10 and 30 years of age. Only 3% of patients were younger than five years old. Specific data regarding the pediatric patients was not reported further. Those patients treated within 8-10 hours of ingestion had a 6-8% incidence of hepatotoxicity compared to 26-34% in those treated 10-24 hours after ingestion. Hepatotoxicity was noted in 41% of patients that had NAC initiated between 16 and 24 hours. There were 10 acetaminophen-related hepatic failure deaths in patients that were treated with NAC within 24 hours. There were no deaths in those treated within 8-10 hours and only one death of a patient treated within 16 hours (this patient had significantly elevated liver transaminases at the time of NAC initiation suggesting that there have been an error in the history of the time of ingestion.²⁸ Unlike previous studies that cast doubt on the efficacy of delayed NAC therapy, this trial was able to show efficacy (compared to historical controls) up to 24 hours following ingestion.

An observational trial was conducted to assess efficacy of a 48 hour IV NAC protocol (compared to the previously studied 20 hour protocol) in 179 patients presenting within 24 hours of an acute APAP overdose.²⁹ The mean (\pm SD) age of the subjects was 21 ± 9 years. A majority (55%) were between 10 and 20 years old. Six patients were younger than 5 years old. Hepatotoxicity was observed in 7/97 (7%) of patients treated within 10 hours. If NAC therapy was initiated greater than 10 hours following the ingestion the incidence of hepatotoxicity increased to 40/156 (26%).²⁹ Two acetaminophen-related deaths were reported in those treated with NAC within 24 hours. Both of these subjects had elevated transaminases on presentation and had a delay in initiation of NAC therapy (13.5 hours and 22 hours).

Burkhart, et al. conducted an investigation to assess the utility of cimetidine in addition to normal antidotal therapy in those with acetaminophen toxicity.³⁰ Although the primary purpose of this study was not to evaluate NAC, all patients were treated with NAC. Thus, it provided data that can be compared to historical controls. The mean age of the 107 study subjects was 23 years (range 12-70). Forty seven patients were under 18 years of age. The mean time of initiation of NAC was 14.5 hours after ingestion. Subjects treated within 16 hours (12/74 patients) of ingestion had a 16% incidence of hepatotoxicity compared to 35% (11/31 patients) in those treated after 16 hours. There were no cases of hepatic failure or death.³⁰

The use of late NAC administration in patients with acetaminophen-induced fulminant hepatic failure also appears to be beneficial.³¹ The 43 study subjects were compared to 57 control patients. Mean (\pm SD) age of the study and control groups were 28.6 ± 10.7 and 33.4 ± 13.5 years, respectively. Pediatric data were not specifically reported. Although not specifically stated, it is presumed that the NAC was administered IV as this was the most popular route of administration in the country where this study was conducted (England). Median delay to hospital presentation was approximately 16.5 hours in both groups. Two patients were treated within 10 hours. Neither patient developed hepatotoxicity. In those treated after 10 hours, 21/41 (51%) developed hepatic failure and 15 died. The control group progressed to hepatic failure in 75% of cases and 33 died.³¹

Additional case series also support late administration of NAC.³² Twenty subjects (mean age 36 years, range 18-76 years) were treated a median of 15.5 (range 12-24) hours following ingestion. Again, the route of NAC administration was not specified, but is presumed to have been IV. Hepatotoxicity developed in 30% of those treated between 12 and 15 hours of ingestion and 40% of subjects treated between 15 and 24 hours. Those with delays in time to treatment had higher peaks in their liver transaminases and coagulation parameters. No subjects developed hepatic failure and no deaths occurred.³²

Perry and Shannon evaluated the efficacy of oral versus intravenous (IV) NAC in pediatric patients.³³ Intravenous NAC therapy was administered to children that presented within 24 hours of an acute overdose. These patients (29 cases) were compared to control patients (25 cases) treated with oral NAC. The mean age of the treatment and control groups was both 15 years. Two patients were younger than 5. The incidence of hepatotoxicity was comparable between IV (8%) and oral (6.9%) NAC.³³ The IV NAC treatment group had a higher incidence of coagulopathy (8% vs. 0%); however, there were no episodes of clinically significant bleeding. It was not reported if the patients who developed coagulopathy had other evidence of hepatotoxicity. Abnormal coagulation parameters have been subsequently reported by others and it is thought that IV NAC can interfere with the laboratory testing for coagulopathy.³⁴ Data from this study supports a conclusion that IV and oral NAC are of comparable efficacy in children.

Buckley and colleagues reviewed their experience with the use of IV NAC in the treatment of 205 patients.³⁵ Median age of the patients was 24 years (range 0-89). Of 162 patients with potentially toxic serum acetaminophen levels, 137 (85%) were treated with NAC. The remaining patients that were treated presented >24 hours following ingestion or had a non-toxic acetaminophen level. The incidence of hepatotoxicity in those patients with toxic APAP concentrations was 8%, compared to 20% in those with a delayed presentation or unknown time of ingestion.³⁵ Two patients, both of whom presented >24 hours following ingestion, died from hepatic failure. Data specific to children was not further reported in their results. Like other studies, a delay in initiation of NAC was associated with a higher incidence of hepatotoxicity.

Yip and Dart briefly summarized their experience with the use of the recently approved IV NAC formulation. They included 33 patients ranging in age from 13-48. Two children were included (ages 13 and 14). All patients had potentially toxic serum acetaminophen concentrations based on the nomogram. All were treated with a 20 hour IV NAC protocol that was begun within 4-8 hours of ingestion. There were no cases of hepatotoxicity or death reported.³⁶ Most recently, Whyte et al. reviewed their 16 year experience with the use of IV NAC in a cohort of 399 patients.³⁷ Most patients were between 16 and 40 years old and the youngest was 4 years old. Pediatric specific data were not reported further in their results. Patients treated within 8 hours (n=64) had a lower incidence (3% vs 25%) of hepatotoxicity compared to those that were treated later than 8 hours (n=32). There were five deaths of which two were judged to have resulted from APAP-induced hepatic failure.³⁷

Lastly, the effect of gastrointestinal decontamination on preventing acetaminophen toxicity can not be ignored when examining the literature evaluating the efficacy of NAC. Most of studies assessing efficacy of NAC have occurred in patients that have received various forms of gastrointestinal decontamination performed at different time intervals from ingestion. Gastrointestinal decontamination is certainly a potential confounder in evaluating

the existing literature on the efficacy of NAC. A detailed discussion of gastrointestinal decontamination is beyond the scope of this review; however the reader is referred to several recent evidence based guidelines.³⁸⁻⁴¹ There is concern about concomitant administration of oral NAC and activated charcoal. It is generally recommended that oral NAC and activated charcoal administration be separated by one hour if feasible. Some have recommended increasing the dose of NAC when co-administered with activated charcoal.⁴² However, there is a volunteer study as well as observational evidence that demonstrate co-administration of NAC and activated charcoal is safe and does not decrease the efficacy of NAC or result in poorer clinical outcomes.^{43,44} Recent evidence suggests that administration of activated charcoal is associated with a decreased incidence of hepatotoxicity in those individuals that have NAC therapy initiated within 24 hours.^{45,46}

ADVERSE EFFECTS/SAFETY

Oral administration of NAC is usually well tolerated. The most common side effects are nausea, vomiting, and abdominal pain.⁴⁷ The distasteful odor of NAC (eg. akin to rotten eggs) may contribute to intolerance and vomiting of the administered dose. Concomitant use of antiemetics can help decrease NAC-associated nausea and vomiting. Serious adverse effects related to oral NAC use are rare. There is one report in the literature of a patient that developed an anaphylactoid reaction (tongue swelling and rash) after administration of the 8th dose of NAC in a treatment regimen.⁴⁸ The patient was treated with methylprednisolone and diphenhydramine and was able to complete all 17 doses of NAC. It is not reported if any other medications were administered that could have been responsible for this patient's symptoms. There are two other reports published in abstract form of rash associated with oral NAC therapy.^{49,50}

Intravenous use of NAC is associated with a higher incidence of adverse reactions. Nausea and vomiting are the most common adverse effects reported.^{37,47} The most serious adverse effects are anaphylactoid reactions. Most commonly these reactions are characterized by the development of rash, urticaria, and pruritis. However, more serious and potentially fatal reactions can occur and manifest with bronchospasm and hypotension. Patients with asthma appear to be at higher risk for developing serious anaphylactoid reactions.⁵¹⁻⁵⁴ Numerous case reports and case series have examined the incidence of anaphylactoid reactions and other adverse effects associated with IV NAC. The incidence of anaphylactoid reactions varied from 0-48%.^{23-25, 29, 31-33, 35, 37, 47, 51, 55-58} The wide variability in the incidence of adverse effects reported is likely multifactorial (definition, prospective vs retrospective data collection, etc). Serious or life threatening reactions appear to be uncommon (<5% incidence). Many anaphylactoid reactions appear to be related to the rapid initial infusion over 15 minutes.^{35, 55, 58} Thus, it is generally recommended that an initial IV dose of NAC be infused over 60 minutes. Kerr, et al. prospectively evaluated the relationship between IV NAC infusion rate and incidence of adverse effects. They randomized 109 patients to receive the 15 minute infusion and 71 patients to receive a 60 minute infusion. While the incidence of adverse effects was similar between the groups (45% vs 38%), there was a trend toward fewer adverse effects in the 60 minute group.⁵⁹ Management of anaphylactoid reactions typically involves discontinuing the infusion and providing symptomatic treatment such as administration of antihistamines, corticosteroids and rarely (ie., when hypotension is present) epinephrine. In most instances, the infusion can be restarted at a slower infusion rate and be completed without further problems.⁶⁰

IV NAC administration has also been reported to result in hyponatremia (with resultant seizures) as a result of administration of large volumes of hypotonic fluid.⁶¹ This is most likely to occur in small children because early IV NAC protocols did not adjust the volume of IV fluid to account for patient weight. More recently, however, the manufacturer has updated its guidelines for the use of NAC in children weighing less than 40 kg to prevent excessive fluid administration. Finally, published information pertaining to overdose of IV NAC is scant. In a single case report, a massive IV NAC dose (2,450 mg/kg) in a 30 month old patient resulted in status epilepticus, intracranial hypertension, and death.⁶² Information contained in the report could not differentiate a direct effect of NAC vs. fluid and electrolyte complications of treatment as being associated with the demise of the patient.

DURATION OF TREATMENT/FOLLOW UP LABORATORY TESTING

The duration of a course of NAC treatment should consider not only the APAP dose (and time course) but also, a given patient's clinical and laboratory findings. In those patients with evidence of hepatotoxicity (AST or ALT >1000 IU/L), NAC treatment should be continued until one of the following occurs: 1) The patient has a drop in AST and ALT below 1000 IU/L and other laboratory studies (bilirubin and coagulation parameters) and clinical status confirm the patient's toxicity is resolving, 2) the patient receives a liver transplant, or 3) the patient dies from fulminant hepatic failure.

The duration of treatment in those without clinical or laboratory evidence of hepatotoxicity is increasingly debated. The original oral NAC protocol approved by the Food and Drug Administration called for the administration of oral NAC for 72 hours (17 doses). This is in contrast to the recently approved IV NAC that specifies a 20 hour treatment protocol. The continued administration of oral NAC for 72 hours in an asymptomatic patient with normal laboratory studies after 36 hours of treatment is probably unwarranted. Identifying patients at minimal risk for subsequent development of hepatotoxicity is critical to determining who requires NAC treatment. James, et al. were able to determine in a retrospective review of cases that patients with normal LFT's at 48 hours or normal LFT's at 24 hours with an acetaminophen serum level under the "probable" toxicity line on the Rumack-Matthew nomogram following an acute ingestion were at low risk for the development of hepatotoxicity.⁶³

Patient-tailored NAC therapy would allow individualization of treatment and early discontinuation of NAC at a time when the patient was determined to not be at further risk for toxicity. Several investigators have examined outcomes in patients treated with shortened courses of oral NAC. Woo, et al. reported their experience with shortened course oral NAC therapy in the treatment of acute acetaminophen overdoses.⁶⁴ They identified 75 patients with possible hepatotoxicity (based on the Rumack-Matthew nomogram) that had NAC started within 24 hours of their ingestion. The duration of therapy ranged from less than 24 hours to 64 hours. The mean and median duration of therapy was 31 hours. Overall, 6 patients developed laboratory evidence of hepatotoxicity (AST or ALT >1000 IU/L).⁶⁴ This was more common (4/6 patients) in those that had NAC initiated >10 hours following their ingestion. No patient required liver transplantation and no deaths occurred. The incidence of hepatotoxicity in this study is comparable to other studies evaluating oral NAC therapy. Patient-tailored NAC treatment was also evaluated in a series of 27 patients, 21 of whom received NAC for less than 72 hours.⁶⁵ None of the patients treated with a shortened course of NAC developed hepatotoxicity. Most recently, use of a shortened course of NAC was evaluated in 205 patients.⁶⁶ No patient in this series developed hepatotoxicity. Thus, there is

increasing evidence to support shortening the duration of oral NAC therapy to 36 hours in cases in which the patient is asymptomatic with normal liver function tests at 36 hours.⁶⁷

Based on an assessment of the recent literature, patients that are receiving NAC therapy should receive at least daily laboratory studies including the following: serum APAP level (until less than 10 mcg/ml), serum chemistries (including creatinine), liver function tests (eg., ALT, AST, total and direct bilirubin), and coagulation studies (eg., INR, prothrombin time).

FORMULATION AND RECOMMENDED DOSAGE

NAC is available as a solution for oral administration. Additionally, there is a sterile, pyrogen-free commercially available solution for intravenous administration. Clinical experience and the available literature also provide support for the administration of the oral form of NAC after passing it through a 0.22 micron sterilizing filter (which does not remove all pyrogens). When the oral formulation of NAC is prepared for intravenous administration, it should be used within 60 hours. When used within this timeframe there is less than 10% decomposition and the prepared solutions remain free of bacterial growth.⁶⁸ Administration of oral NAC solution intravenously is less costly than using the commercially available sterile solution.

Oral NAC is initiated with a loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours. The most commonly cited protocol recommends continued administration for 72 hours; however duration of therapy should be individualized to each patient as described above. If vomiting occurs within 1 hour of administration the dose should be repeated.

Intravenous NAC should be used when contraindications to oral therapy exist (e.g. risk of aspiration, persistent vomiting) or in cases of fulminant hepatic failure. In adults the dose is 150 mg/kg administered over 60 minutes, followed by 50mg/kg over 4 hours, then 100 mg/kg over 16 hours. In children weighing less than 30kg the final concentration of the IV solution requires modification (to a final concentration of 40mg/ml) so that an excessive amount of fluid is not required. The manufacturer of IV NAC recommends it be administered with dextrose 5%, but it is also compatible with ½ normal saline. The manufacturer has a recommended dosing schedule for patients less than 40 kg (Table).⁶⁹

Table. Dosing of IV NAC in Patients Weighing less than 40 kg.

| Body Weight | | LOADING Dose 150 mg/kg over 60 minutes | | SECOND Dose 50 mg/kg over 4 hours | | THIRD Dose 100 mg/kg over 16 hours | |
|-------------|------|-------------------------------------------|------------------------|--------------------------------------|------------------------|---------------------------------------|------------------------|
| (kg) | (lb) | NAC (mL) | 5% Dextrose (mL) | NAC (mL) | 5% Dextrose (mL) | NAC (mL) | 5% Dextrose (mL) |
| 30 | 66 | 22.5 | 100 | 7.5 | 250 | 15 | 500 |
| 25 | 55 | 18.75 | 100 | 6.25 | 250 | 12.5 | 500 |
| 20 | 44 | 15 | 60 | 5 | 140 | 10 | 280 |
| 15 | 33 | 11.25 | 45 | 3.75 | 105 | 7.5 | 210 |
| 10 | 22 | 7.5 | 30 | 2.5 | 70 | 5 | 140 |

SUMMARY

NAC should be considered the antidote of choice for the prevention and treatment of acetaminophen-induced hepatotoxicity. Both oral and IV NAC are acceptable and appear to be equally efficacious. Oral NAC should be considered the preferred treatment unless the patient is at risk of aspirating, has persistent vomiting, or develops hepatic failure. Both oral and IV NAC are generally well tolerated. IV NAC is associated with anaphylactoid reactions, most of which are mild and easily treated. Life-threatening reactions appear to be uncommon. Intravenous NAC is well tolerated in children, however in those weighing less than 40 kg it is recommended that the concentration/formulation be modified to prevent excessive fluid administration. Recent evidence supports tailoring the duration of therapy depending on the patient's clinical status and laboratory data.

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FORMULARY

Uses: Acetaminophen (paracetamol) overdose/toxicity

As little as 10–15 g or 150 mg/kg of acetaminophen taken within 24 hours may cause severe hepatocellular necrosis. Early features of poisoning, nausea and vomiting, usually resolve within 24 hours. Persistence symptoms (vomiting, abdominal pain, jaundice) suggest the development of liver injury which is maximal 3–4 days after ingestion. In spite of a lack of significant early symptoms, patients who have taken an acute overdose (>150 mg/kg) of acetaminophen should be transferred to hospital urgently.

Administration of activated charcoal should be considered if acetaminophen in excess of 150 mg/kg or 12 g, whichever is smaller, is thought to have been ingested. If administered, activated charcoal should be given as soon as possible (ideally within 1 hour) following the ingestion. The activated charcoal and N-acetylcysteine (NAC) dose should be separated by one hour if feasible

NAC is most effective within 8 hours of overdose after which its effectiveness declines. However, delayed administration is still beneficial. The need for NAC therapy is dependent on the type of ingestion (acute vs chronic). In the setting of an acute overdose a 4-24 hour serum APAP level can be plotted on the nomogram to determine the risk of hepatotoxicity and the need for NAC therapy. In chronic ingestions liberal use of NAC is recommended if the serum APAP is > 10mcg/ml, the AST or ALT are abnormal, or if the patient has clinical evidence of liver injury.

Dose—Oral: Adults and children—140 mg/kg then 70 mg/kg orally every 4 hours.
Intravenous: Adults---- initially 150 mg/kg over 60 minutes then 50 mg/kg over 4 hours then 100 mg/kg over 16 hours. Children under 40kg--- Mix 50 ml of 20%NAC with with 200 ml of 5% dextrose to create a 40 mg/ml solution. The loading dose is 150 mg/kg (3.75 ml/kg) over 60 minutes, then 50 mg/kg (1.25 ml/kg) over 4 hours, followed by 100 mg/kg (2.5ml/kg) over the remaining 16 hours.

Dextrose 5% is the manufacturer recommended fluid for IV administration however NAC is also compatible with ½ normal saline.

Adverse-effects: Anaphylactoid hypersensitivity-like reactions have been reported with IV use. Patients with asthma may be at higher risk to have a serious reaction. Generally these reactions may be managed by reducing infusion rate or suspending infusion until reaction has resolved—specialist advice may be needed (rash may be managed with an antihistamine, for example diphenhydramine or chlorphenamine, and acute asthma managed with a short-acting beta₂ agonist (such as albuterol or salbutamol).