Poison Centre®
Centre Anti-Poison

Attention: Pharmacy, Internal Medicine, Intensive Care, Emergency Medicine
Nurse Managers, Educators and Physicians

IMPORTANT: PLEASE DISTRIBUTE TO ALL STAKEHOLDERS

February 28, 2019

Re: CARE OF THE ACETAMINOPHEN POISONED PATIENT

Dear Health Care Provider,

As an important stakeholder in the care of the poisoned patient and a partner of the Ontario/Manitoba or Nunavut Poison Centre, I am writing to inform you of the imminent change in the care of the acetaminophen poisoned patient. On April 2, 2019, the Specialists and Toxicologists at the Poison Centre will be advising n-acetylcysteine (NAC) treatment, for those for whom it is indicated, based on a new, simplified acetaminophen protocol.

Approximately 10% of the calls to the Ontario/Manitoba/Nunavut Poison Centre are in regards to acetaminophen exposures.

Since the 1970's, n-acetylcysteine, (NAC, Mucomyst®, Parvolex®) has been used for the prevention of toxicity from, and for the treatment of, acetaminophen overdoses. Based on early research, intravenous and oral treatment protocols were developed to fit most overdose scenarios, recognizing that, for the most part, acetaminophen causes damage once metabolized to NAPQI (n-acetyl-para-quinonimine). It has been recognized that an early load of NAC and early treatment initiation are the most important aspects of treatment to prevent fulminant hepatotoxicity.

Over the subsequent, almost 50 years, acetaminophen has become the most published toxin in the English language literature. Indeed, with experience and as science evolves, it has been noted that

1. One dose does not fit all. There are some patients who may need more or less NAC depending on their time of presentation following an exposure, the dose of acetaminophen taken, underlying pre-morbid state and risk factors for hepatotoxicity.
2. Drug errors are common including excessive free fluid administration, excessive sodium administration, delay in administration of each "bag" of the protocol.
3. Anaphylactoid reactions occur especially with the rapid rate of infusion of the one hour loading dose.

When NAC administration is deemed to be necessary following an acetaminophen exposure, based on consultation with the Poison Centre, a 3% NAC solution will be recommended. The loading dose will be administered over 4 hours at one rate, and the subsequent maintenance dose administered at a different rate until it is recommended by the Poison Centre that NAC can be stopped, based on rigid "Stopping Rules". The prolonged loading dose hopes to reduce the histamine release reactions that have occurred from NAC in the past. Fluid requirements are adjusted for patient weight to reduce the risk of hyper or hyponatremia.

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Faxable Sheet

Intravenous *n-a*cetylcysteine (NAC) Dosing Scenario for **High Risk Patients**

For those patients who have taken a potentially toxic amount of acetaminophen, intravenous *N*-acetylcysteine is the recommended treatment. The literature has identified that certain patients require greater amounts of *N*-acetylcysteine following their acetaminophen exposure. Through consultation with the Poison Centre, your patient has been identified as one of these patients. Using a 3% solution, the following dosing schedule is recommended for your patient. Please refer to and follow the Poison Centre's recommendations on how to prepare this 3% solution.

LOADING DOSE:	**2 mL/kg/hr** (maximum 200 mL/hr) of 3% *N*-Acetylcysteine IV infusion X 4 hours
MAINTENANCE DOSE:	**0.4 mL/kg/hr** (maximum of 40 mL/hr) of 3% *N*-Acetylcysteine IV continuously until advised to STOP by the Poison Centre

SMART PUMP DOSING:

For those institutions whose SMART PUMPS are unable to be programmed in mL/kg/hr the doses above have been adjusted accordingly:

LOADING DOSE:	**60mg/kg/hr** (maximum of 6000 mg/hr) of 3% *N*-Acetylcysteine X 4 hours
MAINTENANCE DOSE:	**12 mg/kg/hr** (maximum of 1200 mg/hr) of 3% *N*-Acetylcysteine continuously until advised to STOP by the Poison Centre

Additional Notes:

This dosing gives 240 mg/kg NAC over the first 4 hours and, at least, an additional 48 mg/kg NAC in the next 8 hours before the first reassessment at 12 hours; similar to the 300 mg/kg total that a patient received with the old 21 hour protocol.

Do not order intravenous *n*-acetylcysteine to run over a fixed duration (e.g. 21 hours) or a fixed dose (e.g. 100mg/kg over 16 hours), but instead order as an open-ended hourly infusion, with reassessment at least q12 hours based on serial laboratory testing as recommended by the Poison Centre.

Assume a maximum lean body weight of 100 kg.

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GUIDELINES TO PREPARE A 3% INTRAVENOUS *N*-ACETYLCYSTEINE BAG

As part of the Poison Centre's treatment recommendations for the acetaminophen-poisoned patient, a 3 % *n*-acetylcysteine solution will need to be prepared. The following are instructions on how to prepare this solution in **D5W**.

Patient is <20kg:

Remove 37.5 mL from a 250 mL bag of D5W

Add 37.5 mL of 20% IV *N*-Acetylcysteine to the remaining 212.5 mL in the D5W bag

37.5 mL X 200 mg/mL = 7 500 mg of *N*-Acetylcysteine

7500 mg in 250 mL yields a final solution with 30 mg/mL or 3%

Patient is 21 – 40 kg:

Remove 75 mL from a 500 mL bag of D5W

Add 75 mL of 20% IV *N*-Acetylcysteine to the remaining 425 mL in the D5W bag

75 mL X 200 mg/mL = 15 000 mg of N-Acetylcysteine

15 000 mg in 500 mL yields a final solution with 30 mg/mL or 3%

Patient is >41 kg:

Remove 150 mL from a 1000 mL bag of D5W

Add 150 mL of 20% IV *N*-Acetylcysteine to the remaining 850 mL in the D5W bag

150 mL X 200 mg/mL = 30 000 mg of *N*-Acetylcysteine

30 000 mg in 1000 mL yields a final solution with 30 mg/mL or 3%

Notes:

1. 20% IV *N*-Acetylcysteine is equivalent to 200 mg/mL
2. The 3% solution is slightly hyperosmolar but still within the safety margin for administration via a peripheral vein.
3. It is recognized that any particular bag of IV fluid could have excessive fluid more than advertised. It is of little consequence when making this 3% solution. Assume a finished volume as advertised on the bag.

Mixing is important to ensure uniform distribution of *N*-Acetylcysteine in infusion solution.

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Faxable Sheet

Intravenous n-acetylcysteine (NAC) Typical Dosing Scenario

For those patients who have taken a potentially toxic amount of acetaminophen, intravenous *n*-acetylcysteine is the recommended treatment. Using a 3% solution, the following dosing schedule is recommended for your patient. Please refer to and follow the Poison Centre's recommendations on how to prepare this 3% solution.

LOADING DOSE: **2 mL/kg/hr** (to a maximum of 20 mL/hr) of 3% *n-a*cetylcysteine X 4 hours

MAINTENANCE DOSE: **0.2 mL/kg/hr** (Maximum of 20 mL/hr) of 3% *n-a*cetylcysteine continuously until advised to STOP by the Poison Centre

SMART PUMP DOSING:

For those institutions whose SMART PUMPS are unable to be programmed in mL/kg/hr the doses above have been adjusted accordingly:

LOADING DOSE: **60mg/kg/hr** (maximum of 6000 mg/hr) of 3% *n-a*cetylcysteine X 4 hours

MAINTENANCE DOSE: **6 mg/kg/hr** (maximum of 600 mg/hr) of 3% *n-a*cetylcysteine continuously until advised to STOP by the Poison Centre

Additional Notes:

This dosing gives 240 mg/kg NAC over the first 4 hours and, at least, an additional 24 mg/kg NAC in the next 8 hours before the first reassessment at 12 hours, similar to the 300 mg/kg NAC total that a patient receives with the old 21 hour protocol.

Do not order intravenous n-acetylcysteine to run over a fixed duration (e.g. 21 hours) or a fixed dose (e.g. 100mg/kg over 16 hours), but instead order as an open-ended hourly infusion, with reassessment at least q12 hours based on serial laboratory testing as recommended by the Poison Centre.

Assume a lean body mass of 100 kg maximum.

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Recommended Investigations for Acetaminophen-Overdose Patients

For those patients who have taken (or are suspected to have taken) an acetaminophen overdose the following laboratory results will be requested. As a general principle, at a minimum, the Poison Centre recommends bloodwork to be drawn 4 hours post-ingestion and every 12 hours afterward. Additional testing may be recommended by the Poison Specialist on an "as needed" basis. It is important to note that from the perspective of the Poison Centre, acetaminophen is considered undetectable if it is less than 66 µmol/L (10 µg/dL).

On initial presentation of all suspected acetaminophen overdoses:

- Acetaminophen level (at least 4 hours post END of ingestion), ASA level
- Venous gases, electrolytes (Na, K, Cl, HCO_3), glucose, BUN, creatinine, osmolality
- AST, ALT, INR
- Ethanol level depending on clinical scenario

For Sustained Release preparations OR when co-ingestants are opioid or anticholinergic:

- Repeat acetaminophen level every 4 hours until level peaks, then every 12 hours until undetectable

For patients receiving N-Acetylcysteine:

- Repeat venous gases, electrolytes, glucose, BUN, creatinine, AST, ALT, INR every 12 hours
- Repeat acetaminophen level every 12 hours until undetectable

For certain cases determined by the Poison Centre to be severe risk:

- Lactate, lipase
- Phosphate (PO_4) if liver enzymes are elevated
- Repeat acetaminophen level, venous gases, electrolytes, glucose, BUN, creatinine, AST, ALT, INR every 4 hours until acetaminophen level peaks, then every 12 hours until undetectable