Georgia Poison Center GUIDELINE for ACETAMINOPHEN INGESTION

Purpose

The Georgia Poison Center may be contacted for assistance in the management of ingestions of acetaminophen. This document outlines the basic approach which should be followed in these circumstances, unless extenuating factors dictate otherwise. If the SPI believes that extenuating circumstances may exist, medical backup should be consulted promptly.

Procedure

I. OBTAIN INITIAL HISTORY INCLUDING:

a. Time of exposure, current symptoms if any, existing medical problems and medications in use, previous therapy, exact name of product and concentrations and quantities involved, age(s) and weight(s) of victim(s).

b. Determine potential for toxicity. Risk is increased by:

Intent=	Suicide
Age=	More than 6 years
Dose ingested=	More than 200 mg/kg or 7.5 gm
Time elapsed=	More than 16 hours
Dose pattern=	Chronic or repetitive, rather than single dose
Past medical history=	Frequent EtOH use and/or prior hepatic disease

Also determine:
Drug level and time obtained, preferably at 4 hours or more after ingestion following a single dose
Recent or chronic use of EtOH or other medication
Presence of other possible toxins

II. SINGLE ACUTE/CHRONIC DOSE INGESTED:

A. CALLER IS A LAYMAN:

1. Patient allowed to remain at home IF:
   a. Intent is not suicide, **AND**
   b. Maximum possible dose is <200 mg/kg OR < 7.5 gm total dose, **AND**
   c. Patient is not at increased risk (not alcoholic, no preexisting liver disease, not malnourished) and maximum possible dose is <140 mg/kg or 4 gm total dose

2. Patient should be referred for treatment in a medical care facility if ***any*** of the exacerbating factors in (1) immediately above are present

B. CALLER IS MEDICAL:

1. DECONTAMINATION by activated charcoal if within 1 hr of ingestion should be done if ingested dose exceeds 200 mg/kg or 7.5 gm total dose, or 140 mg/kg or 4 gm total dose if patient is at increased risk (such as alcoholic, preexisting liver disease, malnutrition). If activated charcoal is to be given (due to acetaminophen combined with other co-ingestants) within 4 hr or less since acetaminophen ingestion, activated charcoal may be used with IV NAC, or before oral NAC is administered; if more than 8 hr after acetaminophen, give NAC intravenously or give oral NAC first and wait 1-2 hours, then give activated charcoal.

   (example: APAP and theophylline and phenobarb ingested at 12 N
   Charcoal given at 5 PM
   Oral NAC given at 7 PM)

2. LABORATORY: A blood level drawn 4 or more hours after a single acute ingestion is
   i. required. *Levels obtained less than 3.5 hr after ingestion are poorly predictive, and therefore should be repeated.* There is little toxicity associated with the antidote. If the lab turn-around time will delay treatment to more than 8 hours post ingestion, do not wait for the lab result. Instead, begin treatment and reserve the option to discontinue NAC if subsequent information justifies this.

   ii. If extended-release acetaminophen tablets are included among the ingested products, see the guidance section for extended-release acetaminophen.

3. THERAPY: Where indicated, start NAC as soon as decision has been made to start NAC therapy.

4. **SINGLE ACUTE INGESTION: Following a single ingestion, which has occurred within 24 hours before the patient's arrival at a health care facility**, NAC therapy is generally indicated when serum acetaminophen concentration exceeds the "150" line on the Rumack-Matthew nomogram (i.e., the line passing through the 150 *mcg/mL* point at 4 hours following ingestion). If patient is at increased risk (alcoholic, preexisting liver disease, malnutrition), NAC therapy may be indicated at a lower concentration; consult medical backup for further guidance. If extended-release acetaminophen, or acetaminophen mixed with an antimuscarinic or opioids is included among the ingested products, see the **guidance section below**.

5. NAC optimally should be started within 8 hours following ingestion in the setting of an acute single ingestion, or within 8 hours of the initial dose in the setting of a repeated supra-therapeutic ingestion. If the patient receives hemodialysis for any reason, NAC should be administered at twice the rate indicated for patients not on hemodialysis. This increase in dosing is not needed for patients on continuous renal replacement therapy.

    a. <u>If giving NAC orally:</u>

Oral NAC is available in various oral formulations. Effervescent Tablets are designed to dissolve in water, creating a solution that's easier to ingest. An example is Cetylev, approved by the FDA for the treatment of acetaminophen overdose. Alternatively, liquid formulations intended for dilution or bronchial inhalation can be used PO.

i. Loading dose is 140 mg/kg PO or NG tube.
ii. Continue with 70 mg/kg PO/ NGT every 4 hours, until 17 doses have been given over 72 hr AND liver enzymes (AST and/or ALT) AND liver function (INR) are within normal limits, **OR**
iii. 36 hr of therapy have been given under situations discussed elsewhere in this document AND liver enzymes AND liver function is within normal limits, **OR**
iv. more than the minimum course of therapy as per 4 or 5 above has been given and liver enzymes and liver function has returned to normal or to patient's baseline

    b. <u>If giving NAC intravenously:</u>

NAC IV is supplied by a number of generic companies as well as brand Acetadote®, all approved by the FDA. Other formulations of NAC are currently FDA approved for use orally and/or instillation into bronchi, but are not labeled for use intravenously. In regards to dosing, *many institutions have used both FDA approved and non-FDA approved dosing for IV NAC*. "Off-label" or non-FDA dosing of an approved drug in a manner different than approved, whether for a different indication and/or a different means of administration, is within the legal purview of a licensed physician even though the FDA has not ruled on the merits of such use, provided that appropriate techniques are used for its preparation pursuant to applicable regulatory requirements.

There are 2 FDA approved dosing regimens for NAC IV. The total recommended dosage of NAC IV is 300 mg/kg given intravenously as either a three-bag regimen or a two-bag regimen.

<u>FDA Approved Three-Bag Regimen</u>

i. **Dose:** Loading dose infusion of 150 mg/kg in 200 mL of diluent over 60 minutes, then immediately start maintenance infusions of 50 mg/kg in 500 mL over 4 hrs (12.5 mg/kg/hr) then 100 mg/kg in 1000 mL over 16 hrs (6.25

mg/kg/hr). The total infusion time should be 21 hours. ***Dose is calculated using total body weight up to a maximum of 100 kg.***

ii. If therapy is continued for any reason beyond the total of 21 hours, continue at 6.25 mg/kg/hr.

iii. The three-bag regimen administers more NAC IV in the first three hours and may be preferred for patients with early signs of severe liver injury or history of a large acetaminophen ingestion; however, there is the potential for a higher incidence of hypersensitivity reactions.

FDA Approved Two-Bag Regimen

i. **Dose**: Loading dose infusion of 200 mg/kg in 1000 mL of diluent over 4 hours (50mg/kg/hr), then immediately start the maintenance infusion 100 mg/kg in 500 mL over 16 hrs (6.25 mg/kg/hr). The total infusion time should be 20 hours. ***Dose is calculated using total body weight up to a maximum of 100 kg.***

ii. If therapy is continued for any reason beyond the total of 20 hours, continue at 6.25 mg/kg/hr.

iii. The two-bag regimen delivers a lower amount of NAC IV over the first three hours and may be associated with fewer hypersensitivity reactions than the three bag regimen

c. Preferred IV Diluent

The choice of diluent should be based on the individual patient's clinical status, concurrent medical conditions, and institutional protocols. In general, **0.45% normal saline** is the preferred diluent because it provides a more consistent osmolarity profile, reduces the amount of free water delivered to the patient, and better approximate physiologic fluids than 5% dextrose in water (D5W) or sterile water for injection. However, consider D5W or sterile water for injection if sodium load is a concern for the patient.

d. Three-Bag Recommendation for NAC IV Dosage and Dilution for Patients 5kg or greater

Body Weight	Bag 1 (Loading Dose)			Bag 2 (Second Dose)			Bag 3 (Third Dose)		
	Loading Dose	Diluent Volume*	Infusion time	Second Dose	Diluent Volume*	Infusion time	Third Dose	Diluent Volume*	Infusion time
5 kg** to 20 kg	150 mg/kg	3 mL/kg	Infused over 1 hour	50 mg/kg	7 mL/kg	Infused over 4 hours	100 mg/kg	14 mL/kg	Infused over 16 hours
21 kg to 40 kg	150 mg/kg	100 mL		50 mg/kg	250 mL		100 mg/kg	500 mL	
41 kg to 99 kg	150 mg/kg	200 mL		50 mg/kg	500 mL		100 mg/kg	1,000 mL	
100 kg or greater***	15,000 mg	200 mL		5,000 mg	500 mL		10,000 mg	1,000 mL	

* Dilute ACETADOTE in one of the following three solutions: sterile water for injection, 0.45% sodium chloride injection, or 5% dextrose in water.

** Recommended dosing for those less than 5 kg has not been studied.

*** No specific studies have been conducted to evaluate the necessity of dose adjustments in patients weighing over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg.

e. Two-Bag Recommendation for NAC IV Dosage and Dilution for Patients 41kg or greater

Body Weight	Bag 1 (Loading Dose)			Bag 2 (Second Dose)		
	Loading Dose	Diluent Volume*	Infusion time	Second Dose	Diluent Volume*	Infusion time
41 kg to 99 kg	200 mg/kg	1,000 mL	Infused over 4 hours	100 mg/kg	500 mL	Infused over 16 hours
100 kg or greater**	20,000 mg	1,000 mL		10,000 mg	500 mL	

* Dilute ACETADOTE in one of the following three solutions: sterile water for injection, 0.45% sodium chloride injection, or 5% dextrose in water.

** No specific studies have been conducted to evaluate the necessity of dose adjustments in patients weighing over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg.

f. Adverse Effects
    i. There are no medications known to be incompatible with IV NAC.
    ii. If utilizing a preparation of NAC not labeled for IV use (ie not Acetadote or generic IV NAC), administer the diluted IV NAC through an in-line 0.22 (or 0.2) micron filter. The manufacturer of Acetadote does not indicate in the package insert that a filter is necessary for administration of that product.
    iii. The most common presentation of an adverse reaction to intravenous NAC has been a cutaneous reaction (rash and urticaria on face and trunk). In published studies, these reactions all resolved after antihistamine use. Life threatening adverse events have been reported in the literature rarely; their true incidence is undetermined. Patients with asthma have been reported in some sources to be at potentially higher risk of anaphylactoid reactions, but other sources disagree.
    iv. In one Australian series comparing the incidence of anaphylactoid events in patients receiving their initial dose of IV NAC over 15 minutes or 60 minutes, both groups displayed moderate to severe anaphylactoid reactions in 10% of all patients (18 of 180 total of both groups, 12/109 15-minute group, 6/70 60 minute infusion group) [Kao et al, 2003].
    v. Other adverse effects (including vomiting, rash, hypotension, wheezing, flushing, and facial swelling) each occurred in less than 10% of patients [Acetadote Package Insert].

g. Management of Anaphylactoid Reactions
    i. Patients who develop findings suggestive of an anaphylactoid reaction or other dermatologic reactions such as urticaria should have the infusion stopped for at least one hour. Treat the allergic reaction with diphenhydramine or similar agents; use of ranitidine (or similar agent) should also be considered. Use albuterol inhalation or similar beta2 agonists for bronchospasm.
    ii. With serious reactions (hypotension, bronchospasm, or no response to diphenhydramine in other suspected adverse reactions), consider adding a histamine-2 receptor blocker (such as ranitidine), parenteral glucocorticoid (such as methylprednisolone) and parenteral epinephrine. Support ventilation as necessary, including endotracheal intubation and mechanical ventilation if needed. Reassess the need for IV NAC.

6. **UNKNOWN TIME of INGESTION: Where the patient has ingested a potentially toxic single dose based on history of amount ingested, but has presented for medical care more than 24 hour after ingestion**, **or if the time of ingestion is unknown,** the Rumack - Matthew nomogram may or may not apply. We recommend obtaining a serum acetaminophen level, serum AST, and serum ALT and beginning NAC therapy. When lab tests are completed a decision can be made about further NAC therapy.

    a. If serum acetaminophen level > 10 *mcg/mL* and/or AST >normal and/or ALT > normal, administer NAC . In general, the three-bag IV NAC dose should be given for the 21 hour infusion. If using oral NAC, it should be continued for at least 24 hours of dosing. Discontinuation of NAC is outlined below.

    b. If serum acetaminophen <10 *mcg/mL* and AST, ALT, and INR all within normal limits, and time since last ingestion is greater than 24 hr, we recommend that NAC therapy probably does not need to be initiated in this circumstance.

7. **DISCONTINUATION OF NAC**:

Once NAC has been started, regardless of the protocol length or route of delivery, NAC therapy should be continued until APAP metabolism is complete (the APAP is below detection or < 10 mcg/mL), the AST is normal or at patient's baseline and there are no signs of hepatotoxicity. NAC should be continued beyond the "protocol length" if the APAP remains detectable or the AST is significantly elevated.

After NAC therapy is extended beyond a set-length protocol, the decision to discontinue NAC therapy should be based on the patient's condition. For patients **without hepatic failure** but with an elevated AST, NAC should be continued until the following conditions are met.

1. The APAP is undetectable or <10 mcg/mL.
2. There is no evidence of hepatic failure (INR <2.0).
3. If the AST was elevated, it has significantly decreased. There is limited data defining a significant decrease in AST, but two consecutive decreasing AST values and an AST less than 1,000 IU/L, or an AST/ALT ratio of < 0.4 or are reasonable and are commonly used.

The AST should be used to determine whether to stop NAC, as the AST decreases earlier upon recovery than ALT (half-life of 15 h for AST and 40 h for ALT).

In patients **who developed hepatic failure** NAC can be discontinued when the following conditions are met.

1. The patient should have a normal mental status and/or is recovered from hepatic encephalopathy.
2. The INR decreases below 2.0.
3. Hepatic abnormalities have improved: AST is decreasing and < 1,000 IU/L or the AST/ALT ratio < 0.4.
4. NAC should be stopped when the patient receives a liver transplant.

III. HIGH SERUM LEVEL OR THERAPY DELAYED

In situations where the serum acetaminophen level measured at 4 hours or later after a single ingestion exceeds the 300 *mcg/mL* line when plotted on the Rumack-Matthew nomogram, consideration should be given to administering the same initial dose but then providing a larger dose of NAC over the ensuing 16 hours.

A. Consult with the toxicologist on call to determine if an increased dose of NAC is warranted. This is accomplished via doubling the maintenance rate of the final bag of whichever protocol is being used. The final maintenance rate should be at least 12.5 mg/kg/hr. (see Hendrickson Clin Tox 2019 and Washington State Poison Center analysis)

B. The acetaminophen X aminotransferase product (APAP x AT) has been suggested as a prognostic indicator for hepatotoxicity in acute and chronic acetaminophen ingestions.

1. This number is calculated by multiplying the [APAP] by the higher of AST or ALT. If greater than 10,000, this may indicate the patient is at high risk for development of hepatotoxicity irrespective of NAC administration. This parameter has been increasingly utilized as an indicator to initiate fomepizole (4MP).
2. 4MP may aid in preventing NAPQI formation via CYP2E1 inhibition and inhibit JNK-pathway mediated hepatocellular death
3. Indications:
    i. APAP x AT >10,000
    ii. AGMA secondary to APAP
    iii. Lactatemia secondary to APAP
    iv. Fulminant hepatic failure
    v. APAP >700 mcg/mL

C. 4MP dosing has not been prospectively studied. Case report level data indicates either **one dose of 15 mg/kg IV** may be used. Continuation of therapy should be determined on a case-by-case basis in conjunction with the on-call toxicologist. Subsequent doses should be the same as those

used in the management of toxic alcohols: **10 mg/kg IV every 12 hours for 4 doses and then increase to 15 mg/kg IV every 12 hours until discontinued.**

D. Hemodialysis is recommended for situations where:
   1. the serum concentration of acetaminophen is more than 1000 mcg/mL and NAC has NOT been administered within 6 hour after ingestion, and/or
   2. the patient presents with altered mental status, metabolic acidosis, with an elevated lactate, acetaminophen concentration is more than 700 mcg/mL, and NAC has not been administered within 6 hour after ingestion, and/or
   3. the patient presents with an altered mental status, metabolic acidosis, an elevated lactate, and acetaminophen concentration is more than 900 mcg/mL, even if NAC has been administered within 6 hour after ingestion

E. When a patient receiving IV NAC is placed on intermittent hemodialysis, the current rate of IV NAC infusion should be doubled during the time that hemodialysis is in process on the patient. If the patient is receiving Continuous Renal Replacement Therapy (CRRT), the IV rate may not need adjusted.

IV. POTENTIALLY TOXIC DOSE DIVIDED OVER A PERIOD OF TIME:

A. If total dose exceeds 200 mg/kg or 7.5 gm total dose in any 24 hr period within the last 72 hr, or if patient is at increased risk (such as alcoholic, preexisting liver disease, malnutrition) and total dose in any 24 hr period within the last 72 hr exceeds 150 mg/kg or 7.5 gm total dose, refer to ED for evaluation and care.

B. DECONTAMINATION by activated charcoal if within 1 hour of last dose, or if indicated based on co-ingestants. If activated charcoal is to be given (due to acetaminophen dose and/or other co-ingestants), intravenous NAC may be preferable to oral NAC. If NAC orally is preferred due to circumstances, and it is 8 hr or less since ***first*** acetaminophen ingestion, activated charcoal may be used before NAC is administered; if more than 8 hr after acetaminophen, give NAC first and wait 2 hours, then give activated charcoal.

C. LABORATORY: If acetaminophen has been ingested in a repetitive dosing pattern, a blood level cannot be interpreted using the Rumack- Matthew nomogram. Given the increased risk (based on previous patient data) of hepatotoxicity in these situations, we recommend that NAC be started and continued IV for the 21 hour infusion, or orally or nasogastrically for at least 24 hours after ingestion.

D. THERAPY: We recommend that, in this setting, NAC be started according to the usual dosing strategy and continued until **ALL** of the following conditions are met:

1. If time since first dose is <24 hr, then plot on Rumack-Matthew nomogram based on time of first dose. If plotted point falls above "Possible Toxicity" line, start NAC. If plotted point is below this line, check AST and ALT. If either is more than 50 IU/L, start NAC.

2. If time since first dose is 24 hours or more, then start NAC while awaiting lab results. Obtain AST, ALT, INR, and serum acetaminophen level. If most recent dose is within 6 hr and serum acetaminophen level is >20 µg/mL, or most recent dose is >6 hr ago and acetaminophen level is >10 µg/mL, or if AST or ALT or INR abnormal, continue treatment with NAC.

E. DISCONTINUATION OF NAC: See above recommendations on page 7 and 8.

IV. COMMENTS ABOUT ADMINISTRATION OF ORAL NAC:

Much of the difficulty in administering this drug is caused by its odor. Following are suggestions for oral administration:

1. Do not mix the drug in the patient's room.
2. Use a carbonated drink with a strong flavor as the vehicle.
3. Serve ice cold in a covered cup to be drunk through a straw.

If patient refuses, administer by NG tube. Any dose which is vomited within one hour after administration should be repeated. If vomiting is a continuing problem, metoclopramide, ondansetron, or the placement of a trans-pyloric tube into the duodenum may be used to obviate vomiting. If vomiting continues to be a problem despite these measures, consult medical backup for additional suggestions, possibly including the intravenous use (off-label) of N-acetylcysteine.

Dosing guidelines for these anti-emetics:

metoclopramide: usual starting dose 0.1 mg/kg/dose q6h, up to 10 mg /dose q6h, but may increase up to 0.15 mg/kg/dose q6h not to exceed 15 mg q6h if needed for better effectiveness

ondansetron: 0.15 mg/dose IV up to 8 mg/dose 30 min before NAC dose, may repeat before each dose if needed

If charcoal has been used as a bolus dose, the NAC dose should follow charcoal by 2 hours and should be staggered with charcoal where a multi-dose charcoal care plan is being utilized.

V. APPROPRIATE REMINDERS FOR MEDICAL CALLERS

It is generally appropriate to remind the medical caller that:

1. symptoms and laboratory evidence of clinically significant toxicity may be delayed up to 24 hr, with the usual peak of enzyme elevation 36-72 hours post exposure.

2. Use of hepatic enzyme inducers may enhance the toxic potential of acetaminophen by increasing the rate of production of the toxic metabolite. However, there is no data to demonstrate whether or not this hypothesized effect is clinically significant in people.

3. Use of cimetidine (Tagamet® and others) does not reduce risk of hepatotoxicity when administered following acetaminophen overdose, and its impact on toxicity when used chronically prior to acetaminophen overdose is uncertain.

4. Chronic alcoholism may increase risk of hepatotoxicity following acetaminophen overdose, probably due to preexisting impaired hepatocellular function combined with poor nutritional stores.

VI. EXTENTED RELEASE and COINGESTION with ANTIMUSCARINIC or OPIOID AGENT

Clinical Pharmacology – Extended-Release

Extended-release acetaminophen is acetaminophen which has been formulated to be released in the digestive tract over a prolonged period.

Procedure

Recognizing this prolonged release and the toxicokinetics of acetaminophen, we will utilize the following approach to the triage and management of ingestions of extended-release acetaminophen:

1. We will utilize the same criteria for triage of extended-release acetaminophen as for standard acetaminophen, as above.
2. When extended-release acetaminophen is ingested, we will recommend that initial serum acetaminophen levels be obtained between 4 to 12 hours following ingestion. If level exceeds 150 mcg/mL, we will recommend that N-acetylcysteine therapy be employed either by the standard 21 hour IV regimen or the standard oral NAC dosing strategy for at least 24 hours and continued until the guidelines for stopping NAC above have been met.
    - If the level is undetectable (<10 mcg/dL), do not repeat APAP and NAC is not indicated.
    - If the level is detectable (>10 mcg/dL) but below the 150-line, a level should be repeated 4 to 6 hours after the first measurement. If this subsequent level is below the 150-line no NAC is indicated. If it is above the 150-line, administer NAC.

Clinical Pharmacology – Antimuscarinic or Opioid Agent

Recognizing that coingestion of antimuscarinic or opioid agonists with APAP may delay or prolong the absorption of APAP and alter the toxicokinetics, we will utilize the following approach to the triage and management of ingestions of extended release acetaminophen:

Procedure

1. We will utilize the same criteria for triage of antimuscarinic or opioid agonist coingestants as for standard acetaminophen, as above.
2. Serum acetaminophen levels be obtained between 4 to 24 hours following ingestion. If the initial level exceeds 150 mcg/mL, we will recommend that N-acetylcysteine therapy be employed either by the standard 21 hour IV regimen or the standard oral NAC dosing strategy for at least 24 hours and continued until the guidelines for stopping NAC above have been met.
3. If the level is undetectable (<10 mcg/dL), do not repeat APAP and NAC is not indicated.
4. If the patient is displaying signs of an antimuscarinic or opioid toxidrome and is OVERTLY symptomatic and the level is detectable (>10 mcg/dL) but below the 150-line, a level should be repeated 4 to 6 hours after the first measurement. If this subsequent level is below the 150-line no NAC is indicated. If it is above the 150-line, administer NAC.

References

Hendrickson RG, McKeown NJ. Acetaminophen. In: Nelson LS et al., editors .Goldfrank's Toxicologic Emergencies, 11e. McGraw-Hill Education: New York,NY; 2019.

Gosselin S, Juurlink DN, Kielstein JT, et al. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. Clin Toxicol. 2014;52:856–867.

Hernandez SH, Howland M, Schiano TD, et al. The pharmacokinetics and extracorporeal removal of N-acetylcysteine during renal replacement therapies. Clin Toxicol (Phila). 2015;53:941–949.

Hendrickson RG. What is the most appropriate dose of N-acetylcysteine after massive acetaminophen overdose. Clin Toxicol 2019; 57: 686-691.

Kiernan EA et al. A case report of massive acetaminophen poisoning treated with a novel ''Triple Therapy": N-acetylcysteine, 4-methylpyrazole, and hemodialysis. Case Rep Emerg Med 2019;9301432.

Zell-Kanter M et al. A gargantuan acetaminophen level in an acidemic patient satreated solely with intravenous N-acetylcysteine. Am J Ther 2013;20(1):104–6

Woolum JA et al. / American Journal of Emergency Medicine 38 (2020) 692.e5–692.e7692.e7

Woolum JA, Hays WB, Patel KH. Use of fomepizole, n-acetylcysteine, and hemodialysis for massive acetaminophen overdose. The American journal of emergency medicine. 2020 Mar 1;38(3):692-e5.

Shah KR, Beuhler MC. Fomepizole as an Adjunctive Treatment in Severe Acetaminophen Toxicity. The American journal of emergency medicine. 2020 Feb 1;38(2):410-e5.

Shah KR, Fox C, Geib AJ, Murphy C, Kopec K, Kerns II W, Dulaney A, Beuhler MC. Fomepizole as an adjunctive treatment in severe acetaminophen ingestions: a case series. Clinical Toxicology. 2020 Jun 12:1-.

Rampon G, Wartman H, Osmon S, Scalzo A. Use of fomepizole as an adjunct in the treatment of acetaminophen overdose: a case series. Toxicology Communications. 2020 Jan 1;4(1):1-4

Akakpo JY, Ramachandran A, Duan L, et al: Delayed treatment with 4-methylpyrazole protects against acetaminophen hepatotoxicity in mice by inhibition of c-Jun n-terminal kinase. Toxicol Sci 2019;170:57-68.

Akakpo JY, Ramachandran A, Kandel SE, et al: 4-methylpyrazole protects against acetaminophen hepatotoxicity in mice and primary human hepatocytes. Hum Exp Toxicol 2018;37:1310-1322.

Min Kang A, Padilla-Jones A, Fisher ES, et al: The effect of 4-methylpyrazole on oxidative metabolism of acetaminophen in human volunteers. J Med Toxicol 2020;16:169-176.

Washington State Poison Center. Using Higher Dose N-acetylcysteine (NAC) for Acetaminophen (APAP) Toxicity. ND, accessed online 1-19-2021.

ACETAMINOPHEN.DOC
RJG and EAK, Last Revised 1/19/2021
Last Revised BWM 1/13/22
BWM, PF, SH 1/27/25