APAP & NAC UPDATES

Natalie I. Rine, PharmD, BCPS, BCCCP
Director – Central Ohio Poison Center, Nationwide Children's Hospital
February 18th, 2023

OBJECTIVES

- Review the pharmacokinetics and metabolism of acetaminophen
- Describe the standard workup for an acetaminophen exposure
- Explain the appropriate use of the Rumack-Matthew Nomogram
- Discuss standard treatment protocols for acetylcysteine
- Discuss alternative treatment options for the management of massive acetaminophen overdose

ACETAMINOPHEN (APAP) OVERVIEW

- Acetaminophen is one of the most widely used medications worldwide for its analgesic and antipyretic properties
- Widespread availability over-the-counter and inclusion in numerous combination products makes it a commonly observed agent in cases of overdose and toxicity
- Remains the most common cause of acute liver failure in the US in patients 15 years and older

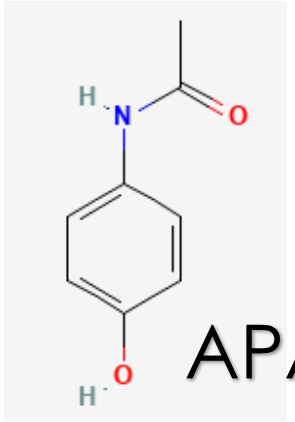
Schult, RF, Acquisto NM. Acetaminophen and salicylates. Toxicology/Practice Issues. ACCP. 2018: 7-30.

APAP: PHARMACODYNAMICS / KINETICS

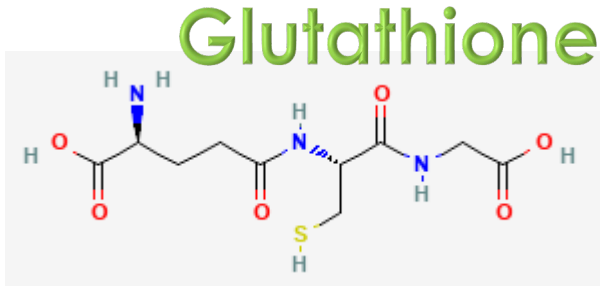
- Therapeutic serum level: 5-20 mCg/mL
- Peak effect: 10-60 minutes (delayed in acute overdose)
- Half-life elimination: prolonged following toxic doses
  - Neonates: ~7 hours
  - Infants: ~4 hours
  - Adolescents: ~3 hours
  - Adults: ~2 hours
- Metabolism: primarily hepatic

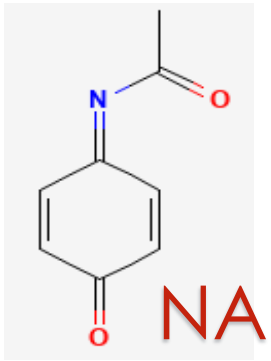
Acetaminophen. Lexi-Drugs. Lexicomp.

APAP: METABOLISM

APAP Sulfate ← Sulfation 20-40% —  APAP — Glucuronidation 40-60% → APAP glucuronide

CYP2E1 | 5%



→  NAPQI →

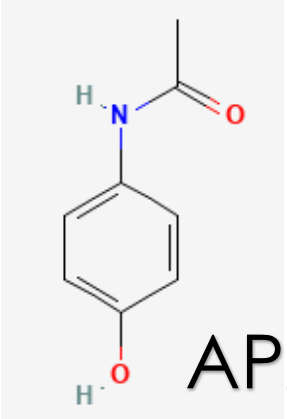
APAP glutathione
APAP-cysteine
APAP mercapturate

https://pubchem.ncbi.nlm.nih.gov/

Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.

APAP: TOXICITY

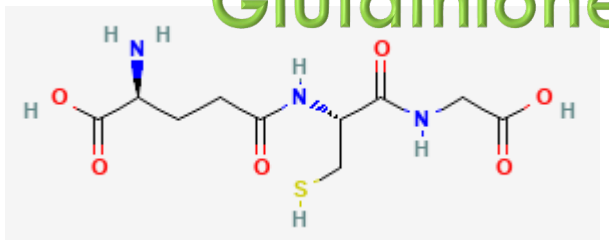
APAP Sulfate ← [X] on



APAP

Glucuronidation (40-60%) → APAP Glucuronide

CYP2E1 | 5%



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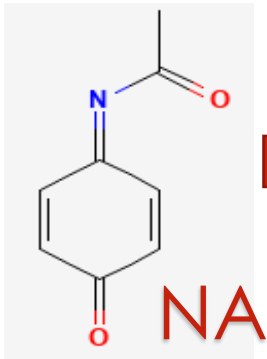
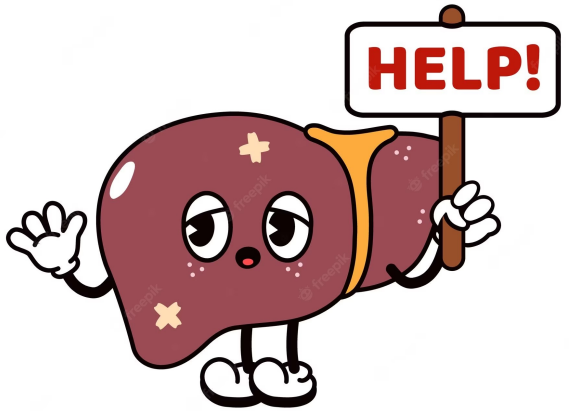


NAPQI →



https://pubchem.ncbi.nlm.nih.gov/

Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.

PHASES OF TOXICITY

- Phase I (12-24 hours post exposure)
  - Generally asymptomatic presentation
  - If symptomatic: nausea, vomiting, malaise
- Phase II (24-36 hours post exposure)
  - Onset of hepatotoxicity (transaminase concentration > 1000 IU/L)
- Phase III (72-96 hours post exposure)
  - Fulminant hepatic failure
  - Hepatic encephalopathy, coma, possibly hemorrhage, acute renal failure
  - Lab abnormalities: hypoglycemia, lactic acidosis, prolonged PT
- Phase IV (7 days post exposure)
  - Resolution of most lab abnormalities within a week of exposure
  - ALT and serum creatinine may take several weeks to normalize

Schult, RF, Acquisto NM. Acetaminophen and salicylates. Toxicology/Practice Issues. ACCP. 2018: 7-30.

ACUTE INGESTION VS RSI

- Single acute ingestion
  - All APAP ingested in < 8 hours
    - Adult: > 150 mg/kg
    - Pediatrics (≤ 7 years old): > 200 mg/kg
- Repeated supratherapeutic ingestion (RSI)
  - Adults:
    - ≥ 10g or 200 mg/kg over 24 hours or
    - ≥ 6g or 150 mg/kg/day for ≥ 48 hours
  - Pediatrics:
    - ≥ 200 mg/kg over 8-24 hours or
    - ≥ 150 mg/kg/day for 2 days or
    - ≥ 100 mg/kg/day for 3 or more days

Alhelail MA, et al. Clin Tox. 2011(49): 1-18.

INITIAL WORKUP & TREATMENT

- Single acute ingestion
  - APAP lvl **at least** 4 hours post ingestion & plot on nomogram
    - Initiate NAC if above treatment line
  - Consider charcoal if < 4 hours post ingestion

- Repeated supratherapeutic ingestion
  - Does patient meet dosing criteria or any of the following:
    - Amount unknown
    - Signs / symptoms of hepatoxicity
    - Suicidality / intent for self-harm
  - If elevated serum AST / ALT or APAP ≥ 10 mCg/mL → initiate NAC

Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.
Spiller HA, et al. J Emerg Med. 2006:30(1):1-5.

KING'S COLLEGE CRITERIA

- If patient critically ill / rapidly deteriorating – consider the following to assess need for liver transplant:
  - Arterial pH < 7.3
  - INR > 6.5 (PT > 100 sec)
  - Creatinine > 3.4 mg/ dL
  - Grade III or IV hepatic encephalopathy
- Other predictors of poor prognosis w/o transplant:
  - Lactate > 3.5 mmol/L after fluid resuscitation (< 4 hours) OR lactate > 3 mmol/L after full fluid resuscitation (12 hours)
  - Phosphate > 3.75 mg/dL (at 48-96 hours)

O'Grady JG, et al. Gastroenterology. 1989. 97(2):439-445.

TWO GUYS WALK INTO A PUB…

- Barry Rumack & Henry Matthew

NOMOGRAM USE RULES

- Single ingestion
- Single (known) time
- Single drug
- Immediate release

- USA: middle line
- Check units
- Check time

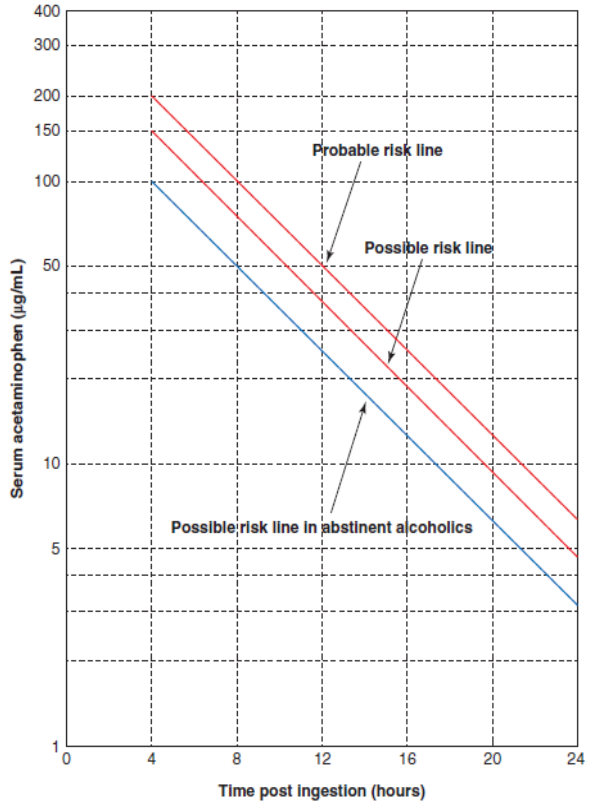


Figure 1. Rumack-Matthew nomogram including a line of 100 mcg/mL at 4 hours line and 25 mcg/mL at 12 hours, for abstinent alcoholic patients after an acute acetaminophen overdose.

Reprinted with permission from: Ali FM, Boyer EW, Bird SB. Estimated risk of hepatotoxicity after an acute acetaminophen overdose in alcoholics. Alcohol 2008;42:213-8.

Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.

N-ACETYLCYSTEINE (NAC)

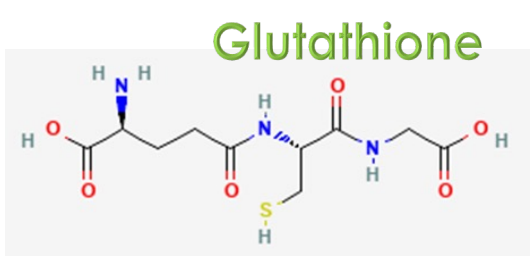
- Initiate therapy within 8-10 hours of ingestion

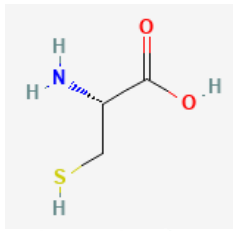
Standard Regimens

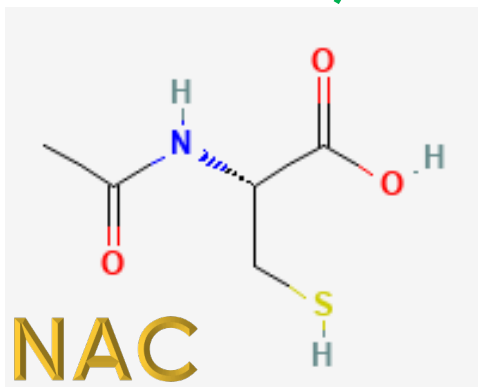
- 21 hour **IV** regimen: (300mg/kg total dose)
  - Loading dose: 150mg/kg infused over 1 hour (max dose 15g)
  - Second dose: 50mg/kg infused over 4 hours (max dose 5g)
  - Third dose: 100mg/kg infused over 16 hours (max dose 10g)
- 72 hour **oral** regimen: (1330mg/kg total dose)
  - Loading dose: 140mg/kg
  - Subsequent dosing: 70mg/kg every 4 hours

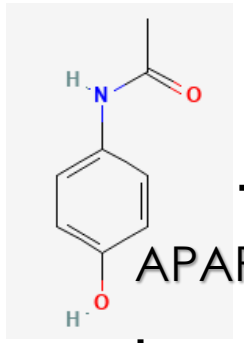
Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.

NAC: MECHANISM OF ACTION









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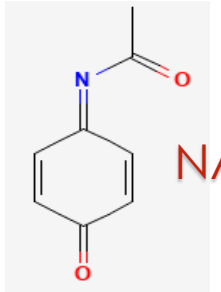
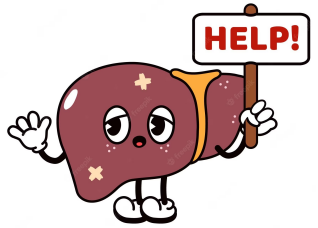


2

1

3

4



- 1) Enhance sulfation
- 2) Glutathione precursor
- 3) Substitute for glutathione
- 4) Improves multiorgan function during hepatic failure

https://pubchem.ncbi.nlm.nih.gov/

Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.

NAC: NON-ALLERGIC ANAPHYLACTOID REACTIONS (NAARS)

- Most associated with IV administration
  - Highest incidence during first hour of therapy
- Mild to severe
  - Rashes, flushing / erythema, hives
  - Angioedema, bronchospasm, hypotension
- Patients presenting with higher serum acetaminophen levels at lower risk of developing anaphylactoid reactions

Acetylcysteine. Lexi-Drugs. Lexicomp.
Schult, RF, Acquisto NM. Acetaminophen and salicylates. Toxicology/Practice Issues. ACCP. 2018: 7-30.

ALTERNATE NAC ADMINISTRATION PROTOCOLS

WONG ET AL, 2016

RESEARCH ARTICLE

Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions

Anselm Wong[a,b,c,d] and Andis Graudins[a,b,d]

[a]Emergency Physician and Clinical Toxicologist, Monash Health Toxicology Service, Monash Health, Victoria, Australia; [b]School of Clinical Sciences, Faculty of Medicine, Nursing and Health Sciences, Monash University, Victoria, Australia; [c]Austin Toxicology Service, Austin Hospital, Victoria, Australia; [d]Victorian Poisons Information Centre, Austin Hospital, Victoria, Australia

CLINICAL TOXICOLOGY, 2016
VOL. 54, NO. 2, 115–119
http://dx.doi.org/10.3109/15563650.2015.1115055

Study Design	Pre-post data analysis
Methods	• Prospectively identified patients administered 20 hour two-bag regimen from February 2014 - June 2015 • Compared to historical cohort of patients treated with 21 hour three-bag regimen from October 2009 - October 2013
Patients	N = 599; three-bag (389) vs two-bag (210)

Results	Primary Endpoints
	• Incidence of non-allergic anaphylactoid reactions
	  • 10% vs 4.3%; p=0.02
	• Incidence of GI reactions:
	  • 39% vs 41%; p=0.38

SCHMIDT ET AL, 2018

CLINICAL RESEARCH

Fewer adverse effects associated with a modified two-bag intravenous acetylcysteine protocol compared to traditional three-bag regimen in paracetamol overdose

Lars E. Schmidt[a], Ditlev N. Rasmussen[b], Tonny S. Petersen[c], Ines M. Macias-Perez[d], Leo Pavliv[d], Byron Kaelin[d], Richard C. Dart[e] and Kim Dalhoff[c]

[a]Rigshospitalet and Glostrup University Hospital, Copenhagen, Denmark; [b]Hvidovre and Amager University Hospital, Copenhagen, Denmark; [c]Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark; [d]Cumberland Pharmaceuticals Inc., Nashville, Tennessee; [e]Rocky Mountain Poison and Drug Center, Denver, CO, USA

CLINICAL TOXICOLOGY
2018, VOL. 56, NO. 11, 1128–1134
https://doi.org/10.1080/15563650.2018.1475672

Study Design	Retrospective chart review
Methods	Conducted chart review in three Danish medical centers from January 2012 – December 2014 comparing safety and efficacy data
Patients	N = 767; three-bag (274), two-bag (493)
Results	• Overall incidence non-allergic anaphylactoid reactions: 9% • 17% vs 4%, $p < 0.001$ • No difference in hepatotoxicity rates (4% incidence overall) • Interruptions or delays: 12% vs 5%

WONG ET AL, 2020

EClinicalMedicine. 2020 Mar; 20: 100288.
Published online 2020 Mar 19. doi: 10.1016/j.eclinm.2020.100288
PMCID: PMC7082646
PMID: 32211597

Efficacy of a two bag acetylcysteine regimen to treat paracetamol overdose (2NAC study)

Anselm Wong,[a,b,c,*] Geoff Isbister,[d,e] Richard McNulty,[f,g] Katherine Isoardi,[h,i] Keith Harris,[j,k] Angela Chiew,[l,m] Shaun Greene,[a,b,n,o] Naren Gunja,[g,p,q] Nicholas Buckley,[r,s] Colin Page,[j,k] and Andis Graudins[c,t]

Study Design	Multi-center observational study with non-inferiority analysis
Methods	• Reviewed patients presenting with paracetamol overdose from 2009 – 2019 who were referred to inpatient toxicology units from ED • Primary non-inferiority analysis: • Included single, acute ingestions with serum paracetamol concentration performed at four to eight hours post ingestion
Patients	Reviewed 6419 paracetamol overdose cases • N = 2763 received acetylcysteine; 783 (three-bag) vs 1003 (two-bag)
Results	Primary Outcome: development of acute liver injury • 4-8hr APAP lvls: 16 (2.9%) vs 21 (3.1%) • 8-24hr APAP lvls: 46 (23%) vs 70 (21%) Secondary Outcome: incidence of adverse reactions • 65 (7.1%) vs 17 (1.3%); $p < 0.0001$

2-BAG METHOD: ADVANTAGES

- Non-inferior efficacy when compared to 3-bag method
- Less incidence of NAARs
- Less incidence of gastrointestinal reactions
- Reduced infusion administration errors
- Reduced burden on central pharmacy / IV room compounding time

MANAGEMENT OF MASSIVE APAP OVERDOSE

MASSIVE OVERDOSE – DEFINITION

- No single definition

- Ingestion of > 50g APAP, > 40g APAP
- Ingestion of > 30g APAP with co-ingested opioid or antimuscarinic agent
- Extremely high serum concentrations: > 300 mCg/mL, > 500 mCg/mL

Hendrickson RG, et al. J Med Toxicol. 2010;6:337-344.
Chiew AL, et al. Clin Toxicol. 2017;55:1055-1065.
Marks DJB, et al. Br J Clin Pharmacol. 2017;83:1263-1272.

HENDRICKSON 2019

CLINICAL TOXICOLOGY
2019, VOL. 57, NO. 8, 686–691
https://doi.org/10.1080/15563650.2019.1579914

REVIEW

What is the most appropriate dose of *N*-acetylcysteine after massive acetaminophen overdose?

Robert G. Hendrickson

Department of Emergency Medicine, Oregon Health and Science University, Portland, OR, USA

RISK OF HEPATOTOXICITY

- Dose-dependent relationship with initial APAP level and hepatotoxicity *despite prompt administration of NAC*

Table 2. The risk of hepatotoxicity by initial acetaminophen concentration in patients treated with an IV NAC 6.25 mg/kg/h final infusion and with NAC started within 8 h of their ingestion [4,6].

Acetaminophen concentration range	Risk of hepatotoxicity (ALT > 1000 IU/L)
<150-line	<1%
150–300 line	1–4%
301–500 line	7–13%
>500 line	31–33%

Hendrickson RG. Clin Toxicol (Phila). 2019;57(8):686-691.

NAC DOSING COMPARISON

Table 1. Comparison of NAC infusion rate and total dose per day for traditional IV NAC, PO NAC and potential altered IV NAC protocols.

Protocol	Initial infusion	"Second bag"	Total NAC in first 5h	NAC continuous infusion rate	Total NAC in first 24h	Total NAC per day all additional days
FDA IV NAC (Prescott protocol)	150 mg/kg IV	12.5 mg/kg/h IV over 4 h	200 mg/kg	6.25 mg/kg IV	300 mg/kg (319 mg/kg if continued at 6.25 mg/kg/h)	150 mg/kg
Oral NAC	140 mg/kg PO	70 mg/kg every 4 h	210 mg/kg	17.5 mg/kg PO*	560 mg/kg	420 mg/kg
SNAP protocol	100 mg/kg IV over 2 h	20 mg/kg/h IV over 10 h	160 mg/kg	20 mg/kg/h (×10h)	300 mg/kg (540 mg/kg if continued at 20 mg/kg/h rate)	N/A
IV NAC with "double dose" continuous infusion	150 mg/kg IV	12.5 mg/kg/h IV over 4 h	200 mg/kg	12.5 mg/kg IV	438 mg/kg	300 mg/kg
IV NAC with "triple dose" continuous infusion	150 mg/kg IV	12.5 mg/kg/h IV over 4 h	200 mg/kg	18.75 mg/kg IV	556 mg/kg	450 mg/kg
IV NAC with "quadruple dose" continuous infusion	150 mg/kg IV	12.5 mg/kg/h IV over 4 h	200 mg/kg	25 mg/kg IV	675 mg/kg	600 mg/kg

*PO NAC is dosed at 70 mg/kg every 4 h. The reference to 17.5 mg/kg/h "continuous infusion" is not meant to suggest that PO NAC be given as a continual infusion, but as a way to compare the dose per hour of IV and PO NAC. Additional differences in bioavailability, etc, exist between PO and IV NAC and should not be considered an exact comparison.

Hendrickson RG. Clin Toxicol (Phila). 2019;57(8):686-691.

300/450/600 TREATMENT LINES

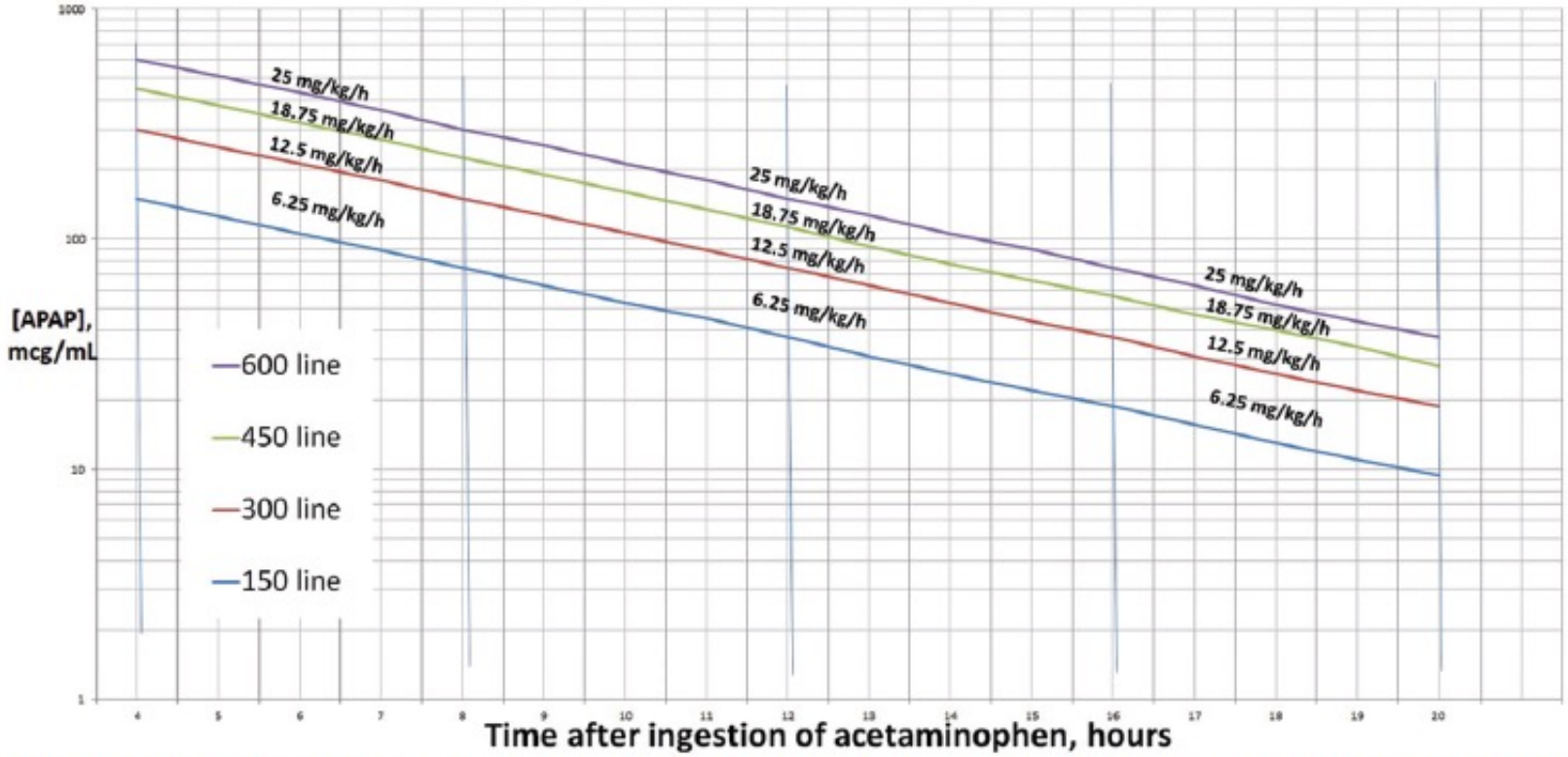


Figure 1. NAC dose adjustment for massive acetaminophen overdoses. Plot the time and concentration of acetaminophen after massive overdose to determine the continuous NAC infusion rate.

Hendrickson RG. Clin Toxicol (Phila). 2019;57(8):686-691.

DOSING RATIONALE

Table 3. Correlation of ingested dose of acetaminophen with the predicted 4-hour [APAP] [16], the approximate "Treatment line", and predicted dose of NAC [15].

Ingested dose	Predicted $[APAP]_{4h}$	Approximate APAP "line"	Predicted dose of NAC
16g	157 mcg/mL	~150-line	6.25 mg/kg/h
32g	314 mcg/mL	~300-line	12.5 mg/kg/h
48g	472 mcg/mL	~450-line	18.75 mg/kg/h
64g	629 mcg/mL	~600-line	25 mg/kg/h

Column 2 (Predicted $[APAP]_{4h}$) is the predicted 4 h acetaminophen concentration that is produced from the ingested dose in column 1. Column 3 (APAP "line") is the treatment line that correlates most closely with the value in column 2 – note that these are not exact matches, simply approximations. Column 4 is the predicted dose of NAC needed with an acetaminophen concentration above the treatment line in column 3 – details of this approximation are in the text.

Hendrickson RG. Clin Toxicol (Phila). 2019;57(8):686-691.

HENDRICKSON PROTOCOL - SAFETY

Table 4. NAC concentration and osmolarity of alternative dosing strategies for NAC in massive overdoses.

Dosing formulation	Dose of NAC	Min-Max dose of NAC	Diluent/solution	Max concentration	Max osmolarity
"1st bag"	150 mg/kg	6–15 g	200 mL D5W	75 mg/mL	603–890 mOsm/L
"2nd bag"	50 mg/kg	2–5 g	500 mL D5W	10 mg/mL	297–368 mOsm/L
"3rd bag"	100 mg/kg	4–10 g	1000 mL D5W	10 mg/mL	297–368 mOsm/L
Double 3rd bag	200 mg/kg	8–20 g	1000 mL D5W	20 mg/mL	344–485 mOsm/L
Triple 3rd bag	300 mg/kg	12–30 g	1000 mL D5W or sterile H_20	30 mg/mL	156–390 mOsm/L (sterile H_20) 391–603 mOsm/L (D5W)
Quadruple 3rd bag	400 mg/kg	16–40 g	1000 mL D5W or sterile H_20	40 mg/mL	208–520 mOsm/L (sterile H_20) 438–720 mOsm/L (D5W)

All formulations are for patients between 40 and 100 kg.
Calculations assume the following: 20% NAC = 2.6 mOsm/mL, D5W = 0.25 mOsm/mL, 1/2NS = 0.154 mOsm/mL. Solutions are reduced by the amount of NAC volume added. For example, if 150 mL of NAC is in 1000 mL D5W, calculations are based on 150 mL of NAC and 850 mL of D5W, since 150 mL of D5W would be removed prior to mixing. All calculations are for patients 40–100 kg.

Hendrickson RG. Clin Toxicol (Phila). 2019;57(8):686-691.

HEMODIALYSIS

Blood Purification in Toxicology: *Reviewing the Evidence and Providing Recommendations*

- Perform systematic reviews on the use of extracorporeal treatments (ECTRs)
- Provide clinical recommendations on the use of ECTRs in poisoning, including criteria for indication / cessation / modality of ECTR
- Publish guidelines for prospective data collection, calculations, and data reporting to assist clinicians, authors and reviewers
- Offer tools and collaboration for multicenter research opportunities

HEMODIALYSIS - APAP

- Consider ECTR when:
  - APAP level > 1000 mCg/mL and NAC is NOT administered
  - Patient with AMS, metabolic acidosis, elevated lactate and APAP level > 700 mCg/mL and NAC is NOT administered
  - Patient with AMS, metabolic acidosis, elevated lactate and APAP level > 900 mCg/mL despite NAC administration

- ECTR Modality
  - Intermittent hemodialysis preferred
    - Can consider CRRT, intermittent HP, exchange transfusion (neonates)
  - Continue NAC therapy at increased rate

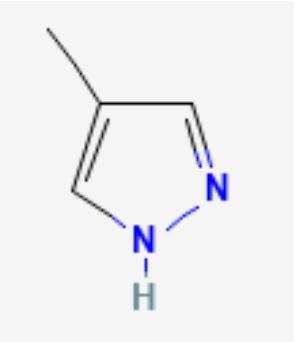
Gosselin S, et al. Clin Toxicol (Phila). 2014;52:856-867.

FOMEPIZOLE

- 4-methylpyrazole

- Antidote: ethylene glycol and methanol toxicity
- Competitive inhibitor of alcohol dehydrogenase
  - Prevents formation of toxic metabolites

- Inducer & inhibitor of cytochrome P450 enzymes
  - Use in APAP toxicity?
  - CYP 2E1 inhibition



Howland MA. Goldfrank's Toxicologic Emergencies. 2019: 1435-1439.

FOMEPIZOLE

Hum Exp Toxicol. 2018 December ; 37(12): 1310–1322. doi:10.1177/0960327118774902.

4-Methylpyrazole Protects against Acetaminophen Hepatotoxicity in Mice and in Primary Human Hepatocytes

Jephte Y. Akakpo[1], **Anup Ramachandran**[1], **Sylvie E. Kandel**[1], **Hongmin Ni**[1], **Sean C. Kumer**[2], **Barry H. Rumack**[3], and **Hartmut Jaeschke**[1]

[1]Department of Pharmacology, Toxicology & Therapeutics, University of Kansas Medical Center, Kansas City, KS, USA.

[2]Department of Surgery,University of Kansas Medical Center, Kansas City, KS, USA.

[3]Department of Emergency Medicine and Pediatrics, University of Colorado School of Medicine, Denver, CO, USA

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Fomepizole as an Adjunctive Treatment in Severe Acetaminophen Toxicity

Kartik R. Shah [a,*], Michael C. Beuhler [b]

[a] *Division of Medical Toxicology, Department of Emergency Medicine, Atrium Health's Carolinas Medical Center, Medical Education Building, 3rd Floor, 1000 Blythe Blvd, Charlotte, NC, 28203, USA*

[b] *Division of Medical Toxicology, Department of Emergency Medicine, Atrium Health's Carolinas Medical Center, North Carolina Poison Control, 4400 Golf Acres Drive, Suite B-2, Charlotte, NC, 28203, USA*

FOMEPIZOLE

Journal of Medical Toxicology (2020) 16:169–176
https://doi.org/10.1007/s13181-019-00740-z

ORIGINAL ARTICLE

The Effect of 4-Methylpyrazole on Oxidative Metabolism of Acetaminophen in Human Volunteers

A. Min Kang[1,2] · Angela Padilla-Jones[2] · Erik S. Fisher[2] · Jephte Y. Akakpo[3] · Hartmut Jaeschke[3] · Barry H. Rumack[4] · Richard D. Gerkin[2] · Steven C. Curry[1,2]

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SUMMARY

- Acetylcysteine has nearly 100% prevention of hepatotoxicity and death when initiated in 8-10hrs
  - Best to wait for 4 hour levels
- Many regimens of acetylcysteine used: 1 bag / 2 bag / 3 bag methods
  - Aim to decrease medication errors and adverse events
- Massive overdoses have increased risk of bad outcome despite early intervention with antidote
  - Consider: activated charcoal, increased doses of NAC, hemodialysis, fomepizole

POISON CONTROL

CENTRAL OHIO POISON CENTER

- Specially trained nurses & pharmacists
- Staffed 24/7/365
- Professional callers: consultation with board-certified medical toxicologist
- National phone number – routed by caller's location

POISON HELP™
1-800-222-1222
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QUESTIONS

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