

What's New with Acetaminophen?

Laurie Seidel Halmo, MD, FAAP
Assistant Professor of Pediatrics and Medical Toxicologist
Section of Hospital Medicine
University of Colorado School of Medicine



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Disclosures

I will be discussing off-label use of medications in this presentation.

No financial disclosures.



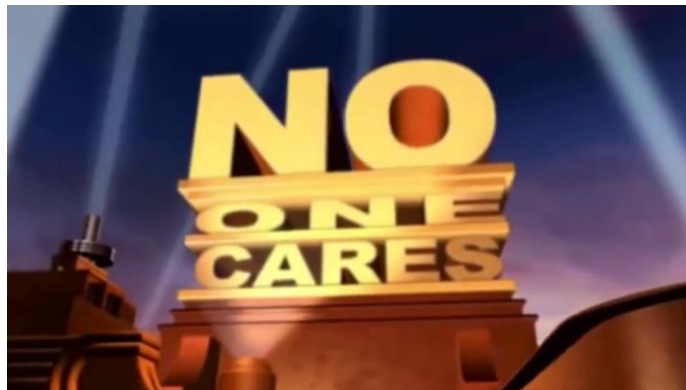
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Learning Objectives

1. Recognize clinical scenarios in which standard N-acetylcysteine dosing may be insufficient.
2. Describe two possible mechanisms by which fomepizole may help mitigate acetaminophen toxicity.



2020 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 38th Annual Report

David D. Gummin MD^a, James B. Mowry PharmD^b, Michael C. Beuhler MD^c, Daniel A. Spyker PhD, MD^d, Alvin C. Bronstein MD^e, Laura J. Rivers BS^f, Nathaniel P. T. Pham MS^g and Julie Weber RPh^h CLINICAL TOXICOLOGY 2021, VOL. 59, NO. 12, 1282-1501

Table 17A. Substance Categories Most Frequently Involved in Human Exposures (Top 25).

Substance (Major Generic Category)	All substances	% ^a	Single substance exposures	% ^b
Analgesics	265,479	10.32	166,482	8.92
Cleaning Substances (Household)	215,338	8.37	186,618	10.00
Cosmetics/Personal Care Products	168,025	6.53	158,756	8.51
Antidepressants	136,266	5.30	61,294	3.28
Sedative/Hypnotics/Antipsychotics	126,448	4.92	47,042	2.52



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Table 18. Categories Associated with Largest Number of Fatalities (Top 25)^g.

Substance (Minor Generic Category)	All substances	% ^b	Single substance exposures	% ^c
Miscellaneous	334	10.27	13	2.03
Sedative/Hypnotics/Antipsychotics				
Pharmaceutical and Illegal	263	8.09	42	6.55
Opioid Preparations				
Acetaminophen Alone	242	7.44	107	16.69
Miscellaneous Alcohols	223	6.86	28	4.37
Miscellaneous Stimulants and Street Drugs	199	6.12	43	6.71



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Table 17C. Substance Categories Most Frequently Involved in Pediatric (<5 years) Exposures (Top 25)^a.

Substance (Major Generic Category)	All substances	% ^b	Single substance exposures	% ^c
Cosmetics/Personal Care Products	109,327	11.82	105,877	12.33
Cleaning Substances (Household)	104,459	11.30	99,991	11.64
Analgesics	69,955	7.57	63,669	7.41
Foreign Bodies/Toys/Miscellaneous	62,004	6.71	60,448	7.04
Dietary Supplements/Herbals/Homeopathic	59,575	6.44	56,727	6.60



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A real case

8 yo F: "My favorite things are Frozen, Elsa, and children's Tylenol. It's so good!!"



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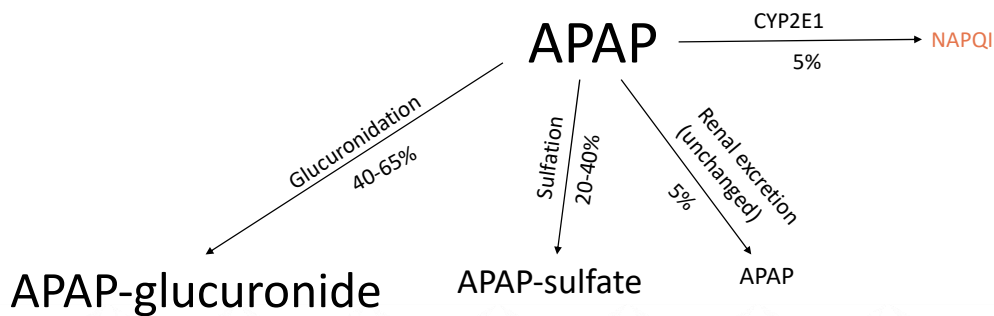
A real case

8 yo F: “My favorite things are Frozen, Elsa, and children’s Tylenol. It’s so good!!”

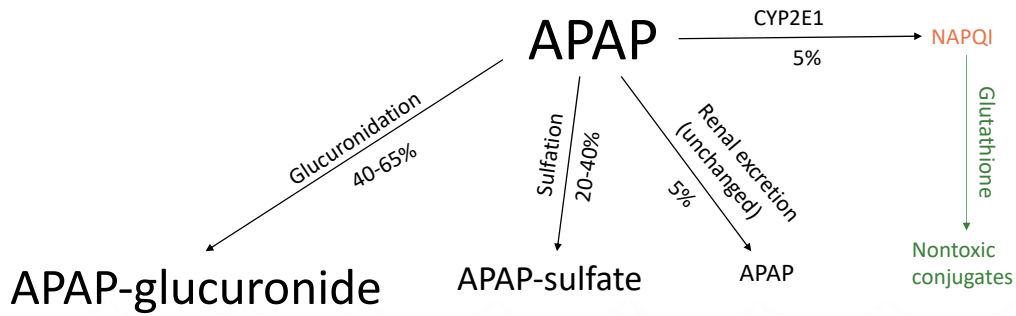
12hr acetaminophen concentration: 84 mcg/mL

LFTs: WNL

APAP Metabolism: Therapeutic dose

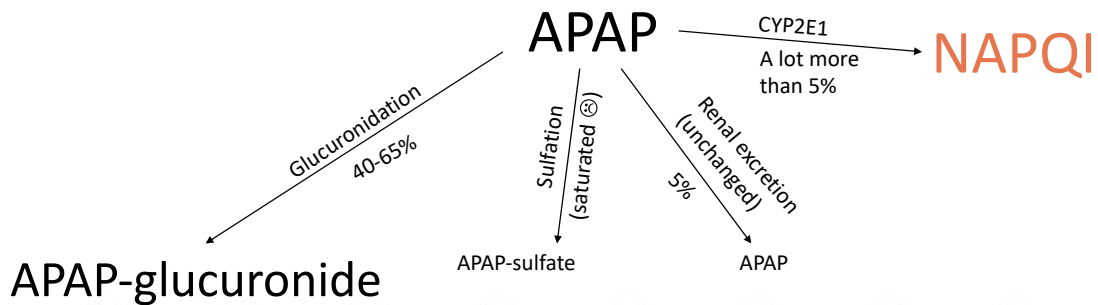


APAP Metabolism: Therapeutic dose



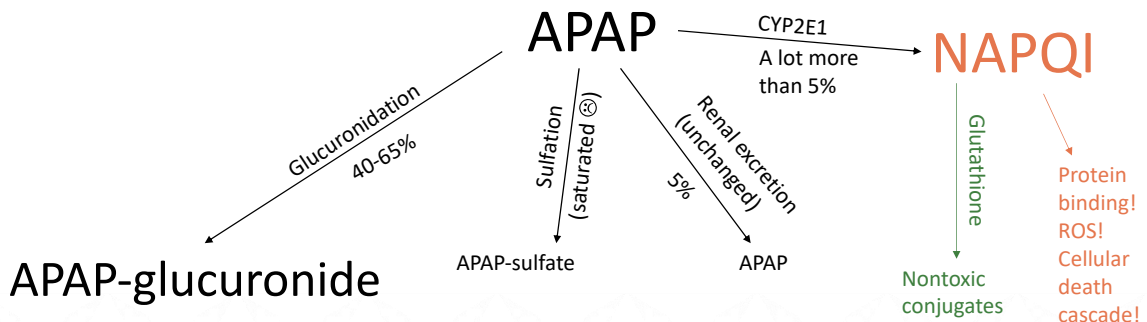
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APAP Metabolism: Supratherapeutic dose

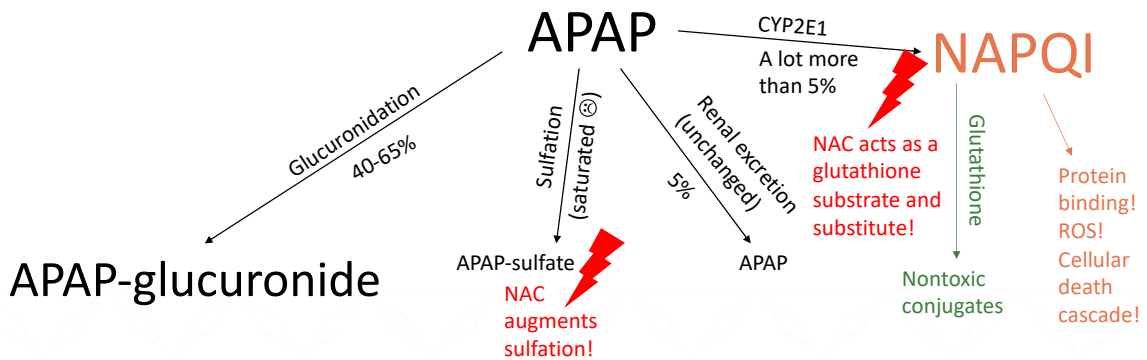


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APAP Metabolism: Supratherapeutic dose



NAC to the rescue!



How much NAC is the right amount of NAC?

Protocol	Loading dose	Second bag	Continuous rate	Total NAC in first 24hrs	Daily NAC dose after
FDA IV	150mg/kg	50mg/kg	6.25mg/kg/hr x16 hrs	319 mg/kg in 24 hrs	150 mg/kg
Oral NAC	140mg/kg	N/A	70mg/kg q4hr	560 mg/kg in 24 hrs	420 mg/kg
"2-bag"	200mg/kg	N/A	6.25mg/kg/hr x16hrs	319 mg/kg in 24 hrs	150 mg/kg
SNAP	100mg/kg	N/A	20mg/kg/hr x10hrs	540 mg/kg in 24 hrs	480 mg/kg

How much NAC is the right amount of NAC?

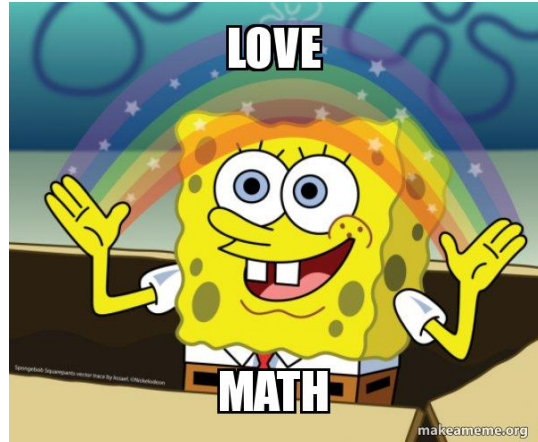
Acetaminophen and acetylcysteine dose and duration: Past, present and future

BARRY H RUMACK, and D NICHOLAS BATEMAN
Clinical Toxicology (2012), **50**, 91–98

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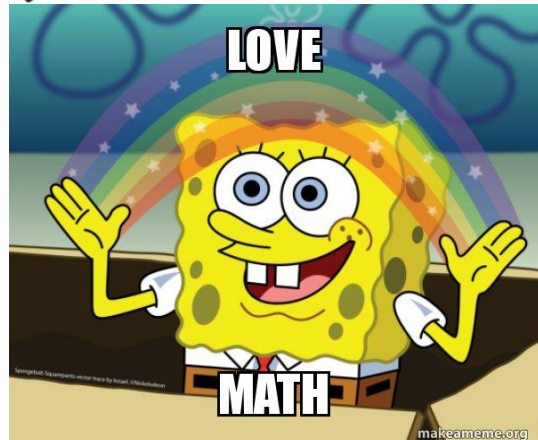
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FDA IV protocol: designed for
15.9g APAP ingestion

= 32 pills of 500mg each



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

Robert G. Hendrickson

CLINICAL TOXICOLOGY

<https://doi.org/10.1080/15563650.2019.1579914>

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%
>500line	31–33%



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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



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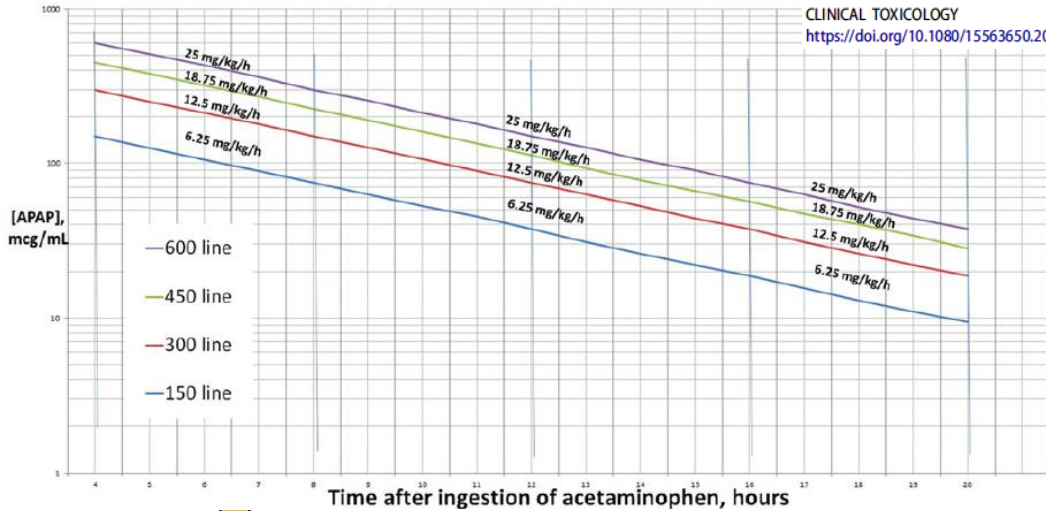
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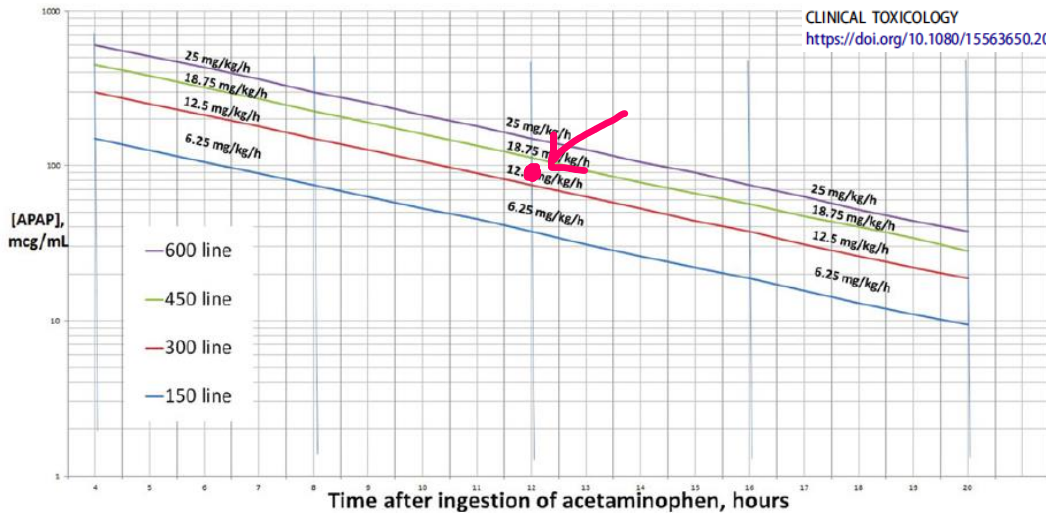
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Case resolution

Got the “2-bag” protocol with “double dose” terminal rate
200mg/kg over 4 hrs followed by **12.5mg/kg/hr** x16 hrs
LFTs remained WNL
Discharged home with poison prevention education



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Some other (real) cases

16 yo M presents with somnolence and vomiting. Found with multiple large, empty bottles of acetaminophen nearby. Unknown time of ingestion.
Acetaminophen concentration upon arrival: 821 mcg/mL



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16 yo M presents with somnolence and vomiting. Found with multiple large, empty bottles of acetaminophen nearby. Unknown time of ingestion.

Acetaminophen concentration upon arrival: 821 mcg/mL

15 yo F presents with somnolence. A subsequent search of her room yields a large bag of tablets identified as acetaminophen.

Acetaminophen concentration ~18hrs after ingestion: 89 mcg/mL

AST: 18 ALT: 12



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25

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AST: 18 ALT: 12

16 yo F presents with abdominal pain and vomiting. States she took "15 tabs of Tylenol yesterday."

Acetaminophen concentration ~24 hrs after ingestion: 24 mcg/mL

AST: 4062 ALT: 2314

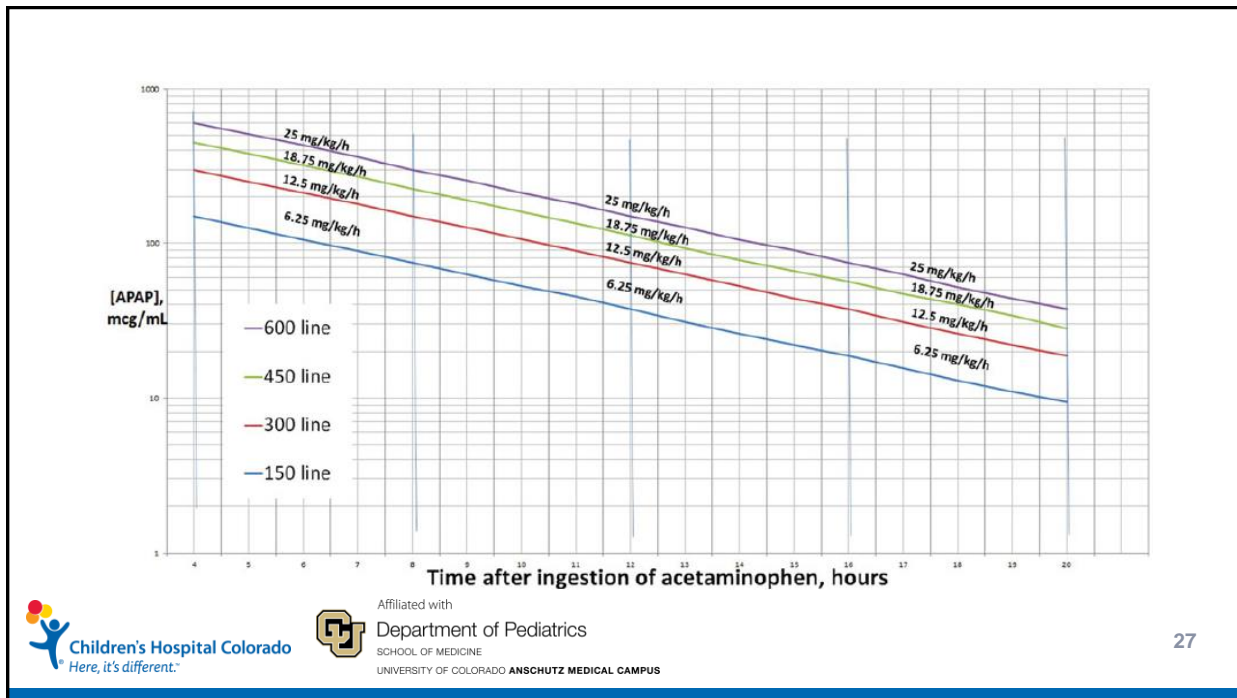


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Cases 2 and 3: PMID 34709101

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What else can we do?

IF NICOLAS CAGE CAN STILL GET WORK

THEN YOU CAN DO ANYTHING

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A Gargantuan Acetaminophen Level in an Acidemic Patient Treated Solely With Intravenous N-Acetylcysteine

Michele Zell-Kanter, PharmD,¹ Patrick Coleman, MD,²
Patrick M. Whiteley, MD,³ and Jerrold B. Leikin, MD^{4*}
American Journal of Therapeutics 20, 104–106 (2013)

59F found unconscious in a pool of blood

Superficial cuts to neck and forearms

VS: T <88F, HR 81, R 12, BP 93/53 sats 100% on FiO2 100% (intubated immediately)

ABG pH 6.9 lactate 22 HCO3 <5 -> started on bicarb drip

AST 103 ALT 74

IV naloxone given: no response

IV fomepizole given

Later, initial acetaminophen concentration results: **1141 mcg/mL -> started on NAC**



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Next day: pH up to 7.45, bicarb stopped

Transaminases peak: AST 3150 ALT 2780

Transaminases decline following day, normal by day 4

INR, bilirubin remained WNL



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Potential adjunct treatment for high-risk acetaminophen overdose

Luke Yip

Rocky Mountain Poison and Drug Center, Denver, CO, USA

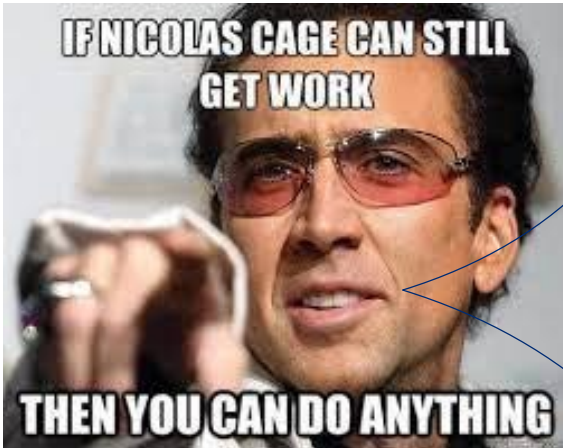
✉ luke.yip@rmpdc.org

Kennon Heard

Department of Emergency Medicine, University of Colorado

School of Medicine, Aurora, CO, USA

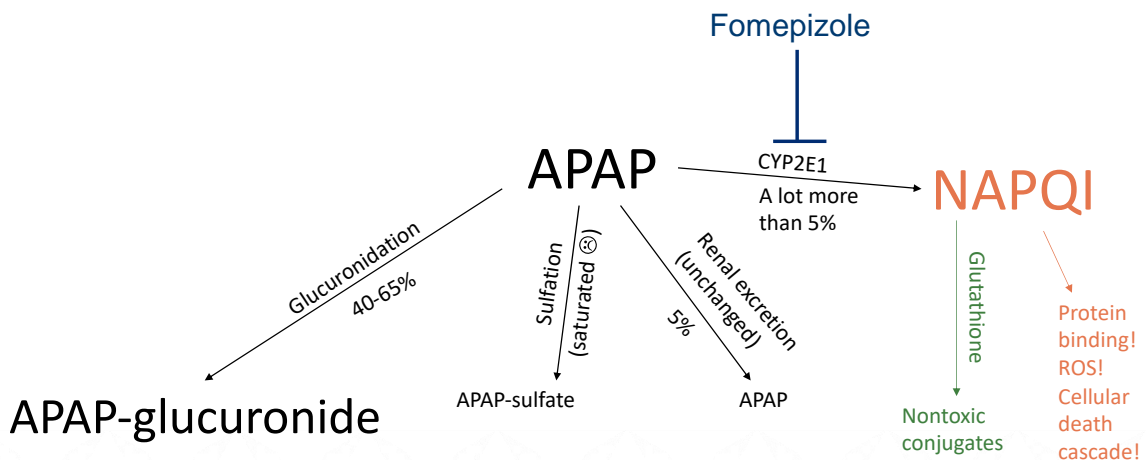
CLINICAL TOXICOLOGY, 2016
VOL. 54, NO. 5, 459



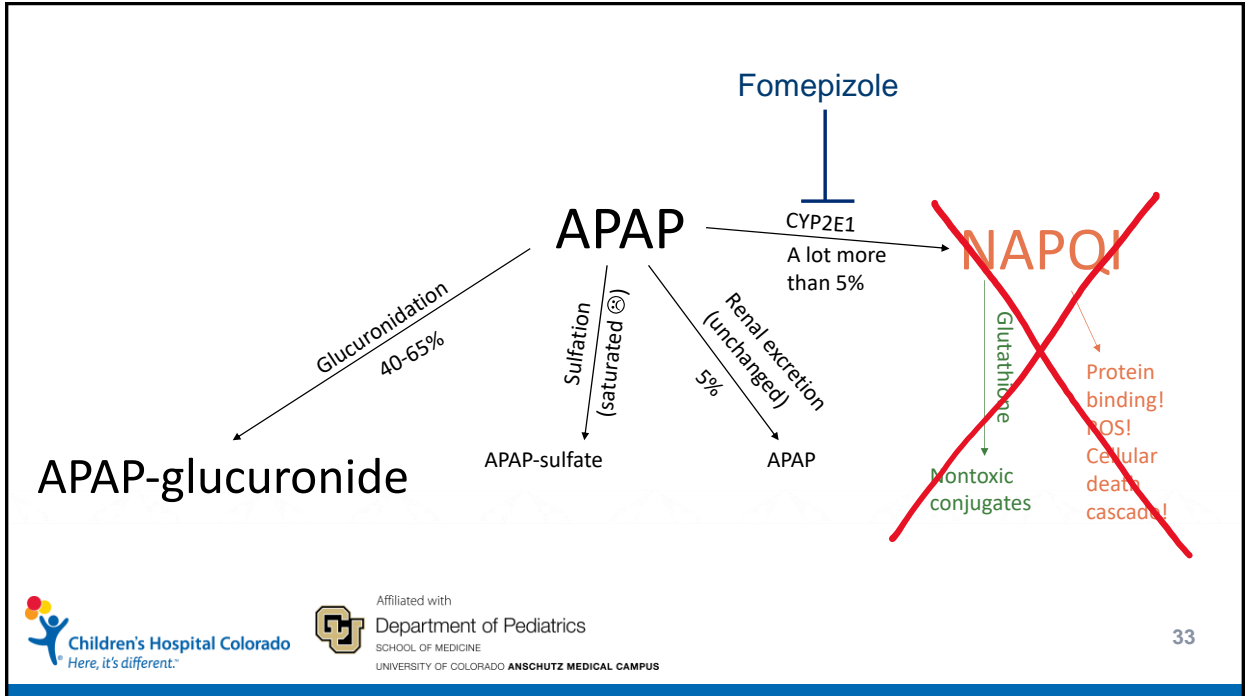
Like give fomepizole for acetaminophen toxicity!



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↙ 4MP = fomepizole

Human and Experimental Toxicology
2018, Vol. 37(12) 1310-1322

4-Methylpyrazole protects against acetaminophen hepatotoxicity in mice and in primary human hepatocytes

JY Akakpo¹, A Ramachandran¹, SE Kandel¹, HM Ni¹, SC Kumer², BH Rumack³ and H Jaeschke¹

(a)

Group	ALT (U/L)
APAP (6h)	~3000
APAP+4MP (6h)	~200*

APAP

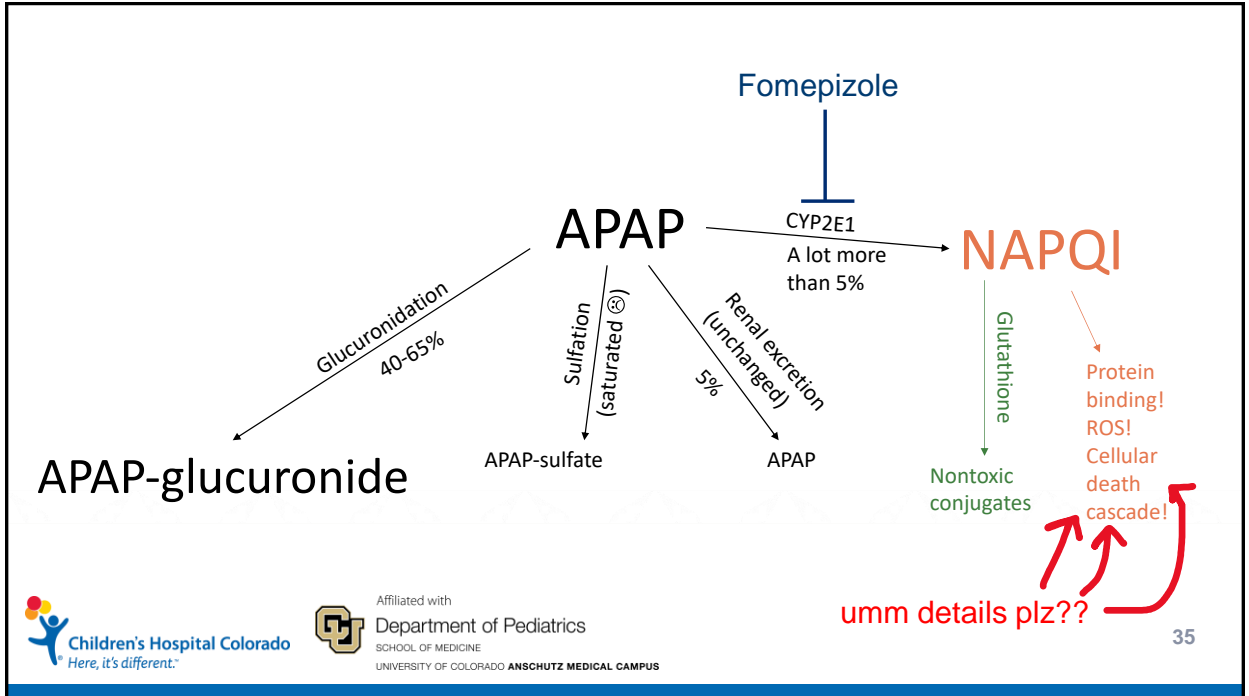
APAP + 4MP

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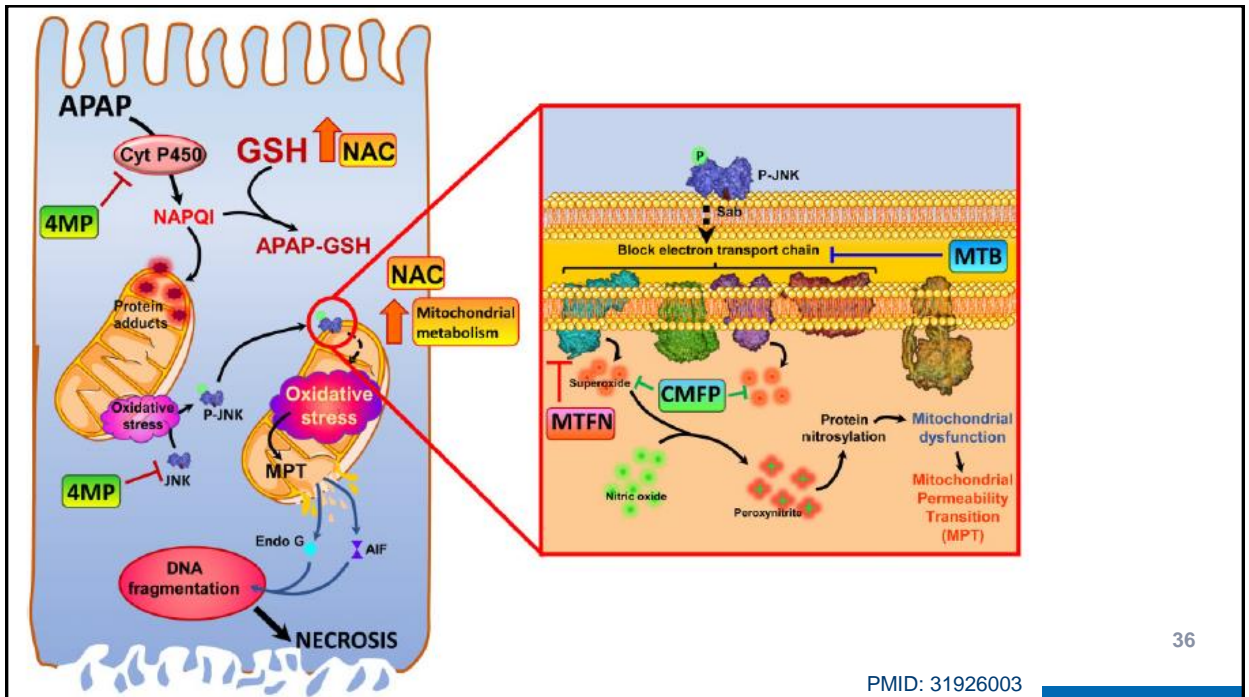
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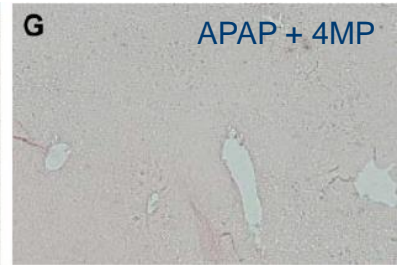
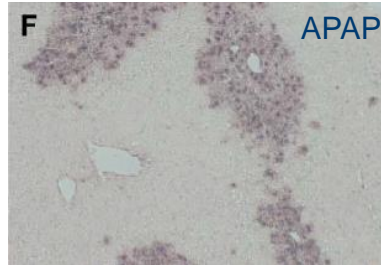
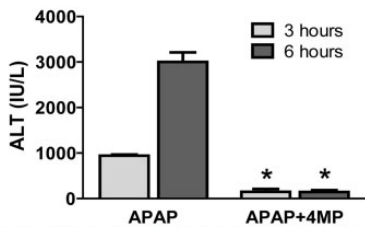


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Delayed Treatment With 4-Methylpyrazole Protects Against Acetaminophen Hepatotoxicity in Mice by Inhibition of c-Jun n-Terminal Kinase

Jephte Y. Akakpo,* Anup Ramachandran,* Luqi Duan,* Matthew A. Schaich,†
Matthew W. Jaeschke,* Bret D. Freudenthal,† Wen-Xing Ding,*
Barry H. Rumack,‡ and Hartmut Jaeschke*¹

TOXICOLOGICAL SCIENCES, 170(1), 2019, 57–68



Case resolutions

16 yo M with somnolence and vomiting. APAP: 821 mcg/mL

Got 15mg/kg fomepizole upon arrival. Started on NAC with double terminal rate. LFTs WNL initially; rose to the 100s, then normalized within a few days. Discharged to psych.

15 yo F with somnolence. APAP ~18hrs after ingestion: 89 mcg/mL AST: 18 ALT: 12

Started on NAC with double terminal rate. Got 15mg/kg fomepizole 26 hrs post ingestion. Peak LFTs: AST 142 ALT 55, quickly normalized. Discharged to psych.

16 yo F with abdominal pain and vomiting. Took “15 tabs of Tylenol yesterday.”

APAP~24 hrs after ingestion: 24 mcg/mL AST: 4062 ALT: 2314

Started on NAC with double terminal rate. 2 hrs later LFTs peak: AST 6222 and ALT 3812. Got 15mg/kg fomepizole 32 hrs post ingestion. Full recovery over the next days.

Summary

Acetaminophen toxicity is still a major cause of pediatric morbidity

One size NAC does not fit all

Some patients seem to benefit from adjunctive therapy such as fomepizole

Thank you!

References included throughout, but I can email you a list if you like

Questions? Comments? Rude remarks? Email me!
Laurie.halmo@childrenscolorado.org

