Over-the-counter Analgesic Toxicity: Exploring the FDA's Safe Use Initiative

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Learning Objectives

- Evaluate the risks, benefits, and safe use of common analgesics
- Understand the burden and reasons for patient-related medication errors and identify strategies to prevent overdose
- Discuss Advisory Committee recommendations meant to deter overdose and hepatic toxicity
- Recognize the signs and symptoms of overdose from commonly used analgesics and strategies to treat acute toxicity

Scope of the Problem: Acetaminophen

- Acetaminophen is the most widely used antipyretic/ analgesic in the United States
  - 8 billion purchased doses of OTC single-ingredient products containing APAP
  - 9.7 billion purchased doses of combination OTC products containing APAP
- Fatal medication errors occurring at home have increased by 564% (1983-2004)

Phillips DP, et al. *Arch Intern Med*. 2008;168:1561-1566.
Bronstein AC, et al. *Clin Toxicol.* 2007;45(8):815-917.
Clark J. *Air Med J*. 2001;20:16-17.
US Food and Drug Administration. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164898.pdf.

Scope of the Problem: NSAIDs

- >30 million people worldwide consume prescription nonsteroidal anti-inflammatory drugs (NSAIDs) daily
- >100,000 yearly hospitalizations in the US due to NSAID-related complications
- >21,000 salicylate exposures reported to poison centers (2004)

Singh G. *Am J Ther*. 2000;7(2):115-121.
Wolfe MM, et al. *N Engl J Med.* 1999;340:1888-1899.
Watson WA, et al. *Am J Emerg Med*. 2005;23(5):589-666.

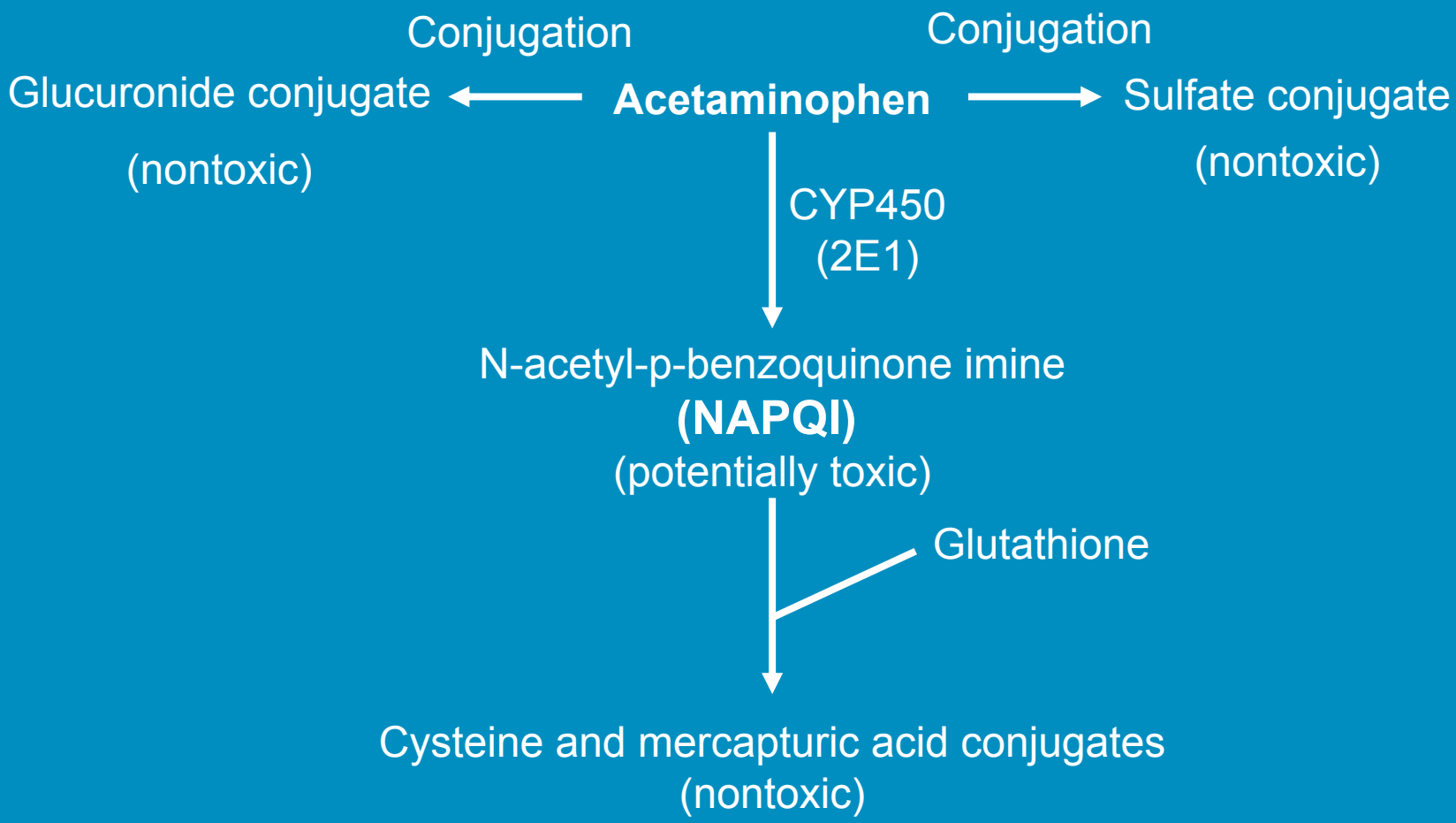
Acetaminophen

Acetaminophen

- ≈80% of people used acetaminophen in last 6 months but only ≈40% knew the liver can be affected
- Far fewer (15%) correctly identified acetaminophen as a component of some Rx opioid analgesics
- Acetaminophen-containing Rx analgesics
  - 11 billion doses
  - 2001—2005: combination Rx use ↑ 38%
  - >182 million prescriptions for combination Rx products
  - Hydrocodone/acetaminophen most frequent

Ganley C, et al. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. A scientific review paper and recommendation statement from the Acetaminophen Hepatotoxicity Working Group; 2009.
Stumpf JL, et al. *J Am Pharm Assoc* (2003). 2007;47:35-41.

Hepatic Metabolism of Acetaminophen



Routes of Unintentional Adult & Pediatric Overdose

ADULT	PEDIATRIC
• Unknowingly ingesting acetaminophen (APAP) from combination products	• Administering wrong pediatric formulation (ie. using infant drops [80 mg/0.8 mL] for children's suspension [160 mg/5 mL])
• Unknowingly ingesting APAP from widely used single-ingredient products	• Using multiple products or strengths that cause consumer confusion
	• Incorrect calculation for weight-appropriate dose
	• Incorrect dosing device (i.e., tablespoon instead of teaspoon, dropper versus syringe)

US Food and Drug Administration. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM175767.pdf.

Acetaminophen: Dosing Definitions

- Therapeutic dose defined as ≤4 g in adults and ≤75 mg/kg in children per 24-hr period
- Acute overdose defined as a toxic amount (>4 g) ingested in ≤8 hrs
- Repeated supratherapeutic ingestion (RSTI or chronic overdose) refers to multiple ingestions over a period >8 hrs totaling >4 g per 24-hr period

Guidelines for the management of acetaminophen overdose. McNeil Consumer & Specialty Pharmaceuticals, 2005.
Daly FF, et al. *Ann Emerg Med*. 2004;44(4):393-398.

Treatment of Acute Overdose

Case Study

Case Study: Acetaminophen Overdose Patient History

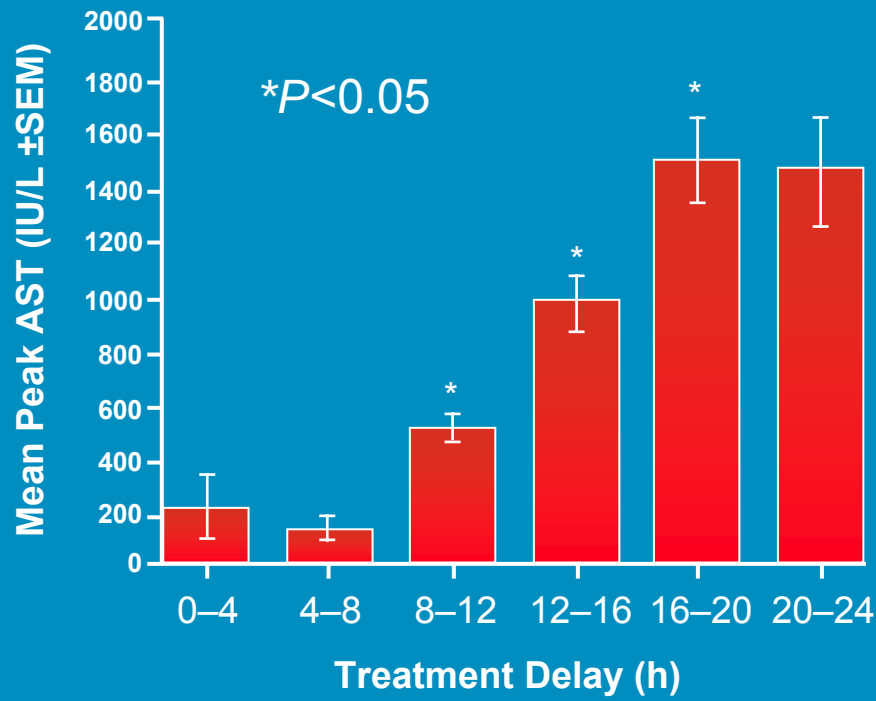
- 32-year-old female
- Arrives in emergency department at 9:48 AM
- Complains of bilateral headache, nausea, dizziness, insomnia
- Gets depressed
- Occasional social alcohol use
- No other remarkable past medical history
- Family member reports she ingested 50 x 325 mg acetaminophen early this morning at 12:30 AM

Question

- When NAC is delayed, after what time is increased injury to the liver noted?
  A. 8 to 10 hours
  B. 10 to 18 hours
  C. 18 to 24 hours
  D. 24 to 48 hours
  E. >48 hours

Time Is Liver

- Prompt recognition and treatment of APAP toxicity is essential to prevent morbidity and mortality
- 11/2023 (0.54%) fatalities in those with values above nomogram line and increases in higher-risk patients
- 0 fatalities if NAC started within 16 hrs postingestion



NAC = N-acetylcysteine; AST = aspartate aminotransferase; SEM = standard error of the mean.
Smilkstein MJ. *N Engl J Med*. 1988;24:1557-1562.

Case Study: Physical Examination

- Pulse rate: 74/minute
- Regular heart beats, no murmurs
- Blood pressure: 119/74 mm Hg
- Conscious, but lethargic
- Normoactive bowel
- No tenderness or rebounding pain in abdomen
- Extremities freely movable, no pitting edema

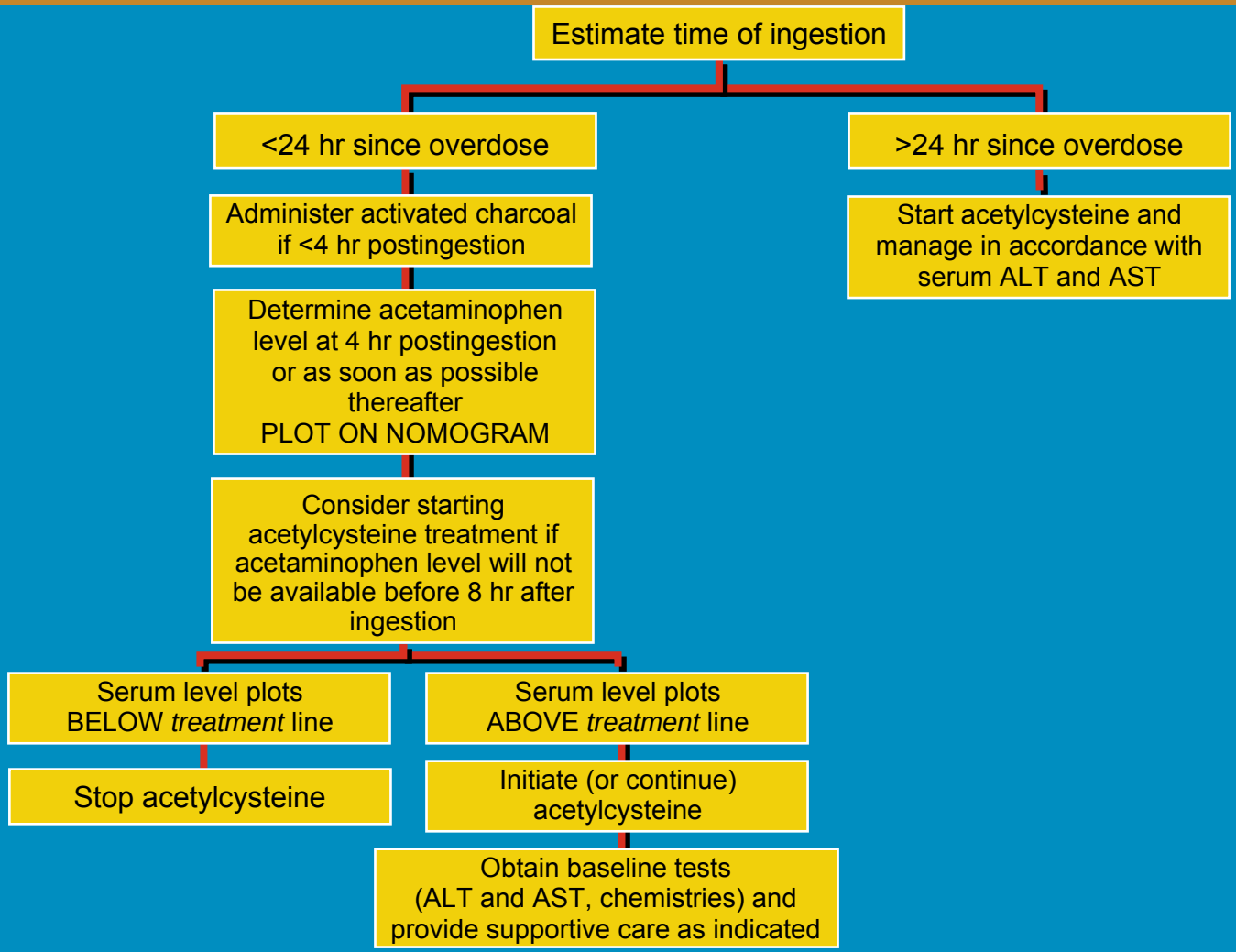
Presentation: Acute Overdose

Stage	Approximate Time Postingestion	Symptoms
I	0 to 24 hours	Anorexia, nausea, and vomiting
II	24 to 72 hours	Right upper quadrant abdominal pain (common); AST, ALT, and, if poisoning is severe, bilirubin and PT (usually reported as the INR) sometimes elevated
III	72 to 96 hours	Vomiting and symptoms of liver failure; peaking of AST, ALT, bilirubin, and INR; sometimes renal failure and pancreatitis
IV	>5 days	Resolution of hepatotoxicity or progression to multisystem organ failure (sometimes fatal)

ALT = alanine aminotransferase; PT = prothrombin time; INR = international normalized ratio.

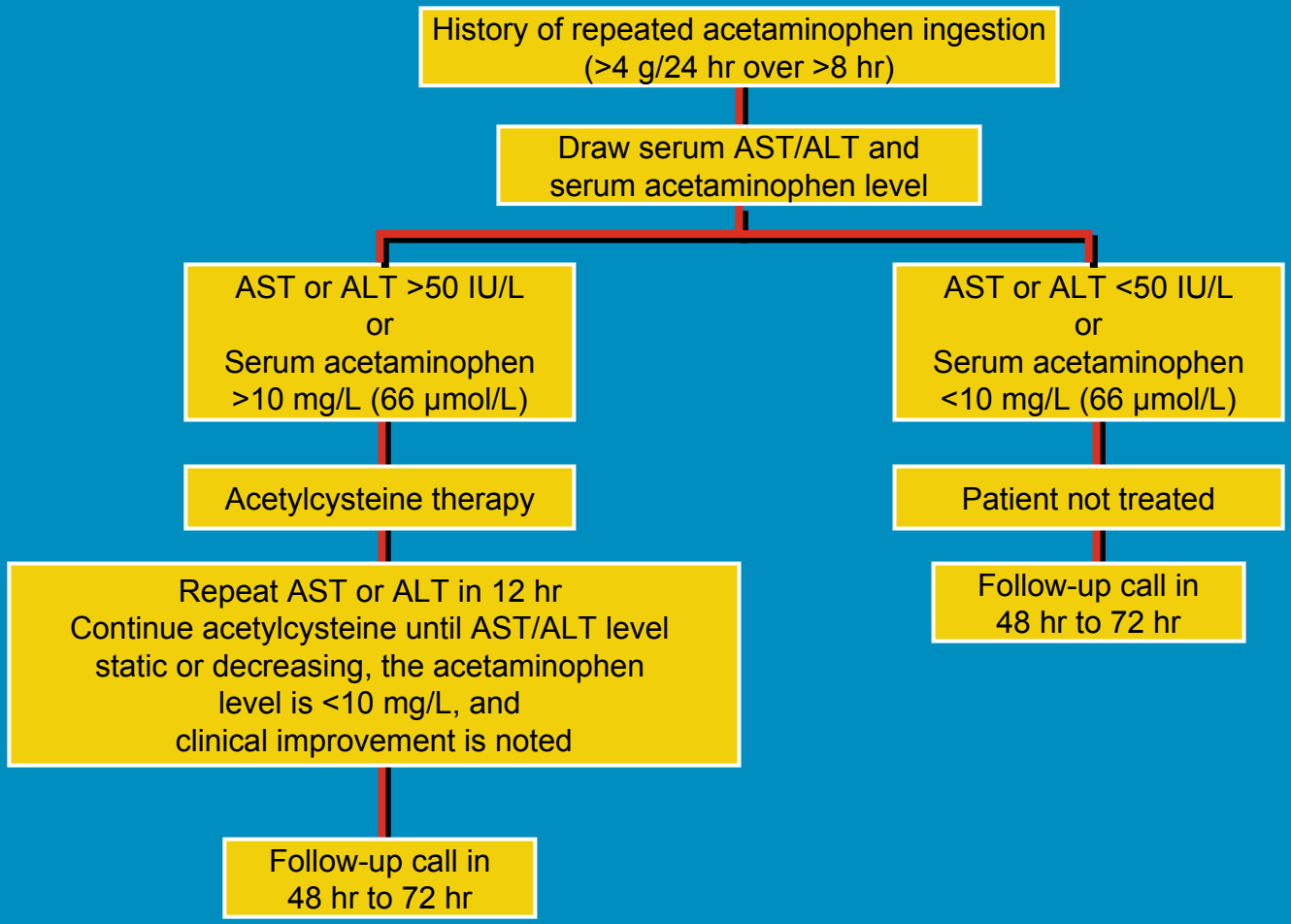
The Merck Manual. 18th edition. http://155.91.16.2/mmpe/sec21/ch326/ch326c.html#BGBHJFCE. Accessed March 18, 2010.

Management of Acute Acetaminophen Overdose



Guidelines for the management of acetaminophen overdose. McNeil Consumer & Specialty Pharmaceuticals; 2005.

Management of RSTI

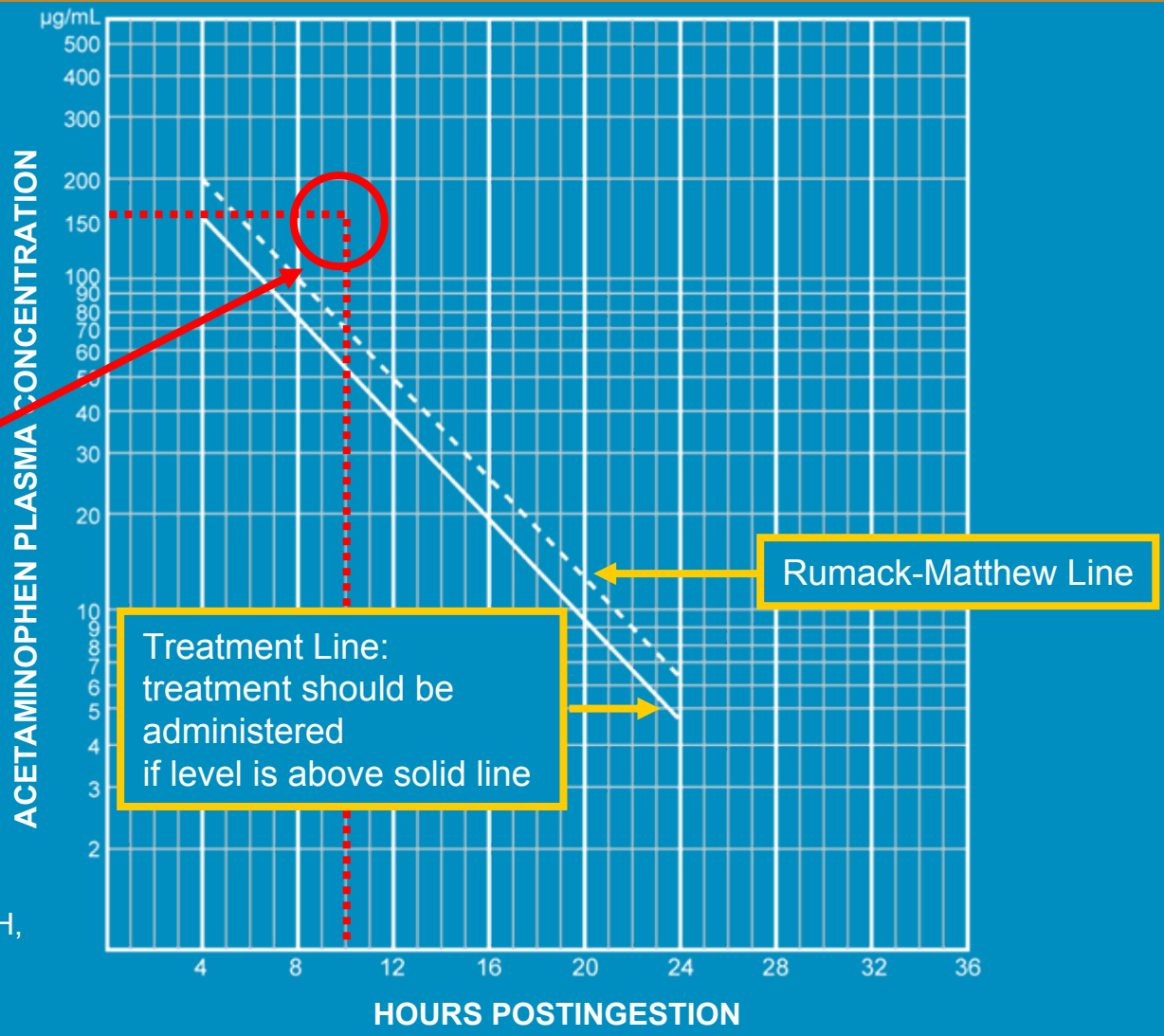


Daly FF, et al. *Ann Emerg Med*. 2004;44(4):393-398.

Case Study: Chemistries

- Hemoglobin = 13.8 g/dL
- White blood cells = 5990/µL
- Platelets = 220 x 1000/µL
- AST/ALT: 52/47 IU/L
- Benzodiazepine (urine): negative
- Acetaminophen (blood): 151.33 µg/mL (10 hr postingestion)

Case Study:
Rumack-Matthew Nomogram Check



Adapted from Rumack BH, Matthews H. *Pediatrics*. 1975;55:873.

Case Study: Treatment

- Patient weighs 50 kg
- IV NAC
  - 150 mg/kg (7500 mg) IV + 200 mL diluent over 60 minutes
  - 50 mg/kg (2500 mg) IV + 500 mL diluent IV for 4 hours
  - 100 mg/kg (5000 mg) IV + 1000 mL diluent IV for 16 hours

-OR-

- Oral NAC
  - 140 mg/kg (7000) loading dose
  - 70 mg/kg (3500) every 4 hours for 17 doses starting 4 hours after the loading dose

NAC Administration

- In 2004, the US approved NAC treatment over 20 to 21 hr
- If body weight is >40 kg:
  - Loading dose: 150 mg/kg over 60 min in 200 mL 5% dextrose
  - Second dose: 50 mg/kg infused over 4 hr in 500 mL 5% dextrose
  - Third dose: 100 mg/kg infused over 16 hr in 1 L 5% dextrose
- If body weight is <40 kg:
  - Acetylcysteine solution should be diluted per prescribing information

Guidelines for the management of acetaminophen overdose. McNeil Consumer & Specialty Pharmaceuticals; 2005.
Rowden AK, et al. *Clin Lab Med*. 2006;26:49-65.

Treatment Pitfalls and Other Issues

- Not checking acetaminophen and liver enzymes at the end of therapy
- Not checking PT/INR and creatinine if liver enzyme level persists over time
- Other issues
  - Using gastric lavage, activated charcoal; clinical benefit is unclear
  - Acetaminophen levels from extended-relief formulations not as predictable as with immediate-release formulations

Rowden AK, et al. *Clin Lab Med*. 2006;26:49-65.
Brok J, et al. *Cochrane Database Syst Rev*. 2006;(2):CD003328.

Case Study: 2-week Follow-up

- Follow-up at 2 weeks:
  - AST: 25 IU/L
  - ALT: 26 IU/L
  - Creatinine: 0.7 mg/dL
  - INR: 2.0

Summary

- Acetaminophen is the most widely used antipyretic and analgesic, combined with ~125 medications
- Determine when and amount of acetaminophen ingested
- Use the nomogram for single acute exposures
- Early treatment is key, NAC is the antidote
- Hepatotoxicity can occur in acute overdose, but rarely leads to need for transplantation or death

Advisory Committee to the FDA

Acetaminophen
Recommendations

FDA Statement Prior to 2009 Advisory Committee Meeting

- To date, the agency has considered acetaminophen safe when used according to the directions on its OTC and Rx labeling
- Taking more than the recommended dose of 4 g/d, however, can cause liver damage
- Many cases of acetaminophen overdose are caused by consumers inadvertently taking more than the recommended dose
- FDA is not looking to remove acetaminophen from market

Audience Polling Questions

- Do you think the maximum daily dose should be limited?
  A. Yes
  B. No
  C. I have not decided

- Do you think the single adult dose should be limited?
  A. Yes
  B. No
  C. I have not decided

Advisory Committee to FDA Recommendations: Pros vs Cons

Item	Yes (High/Low priority)	No	Pros	Cons
Maximum daily dose <4 g/d	21 (11/10)	16	• ↑ margin of safety between labeled dose and suggested threshold dose to injury (suggested as low as 7.5 g) • Single tab/gelcap limited to 325 mg so more tabs/gelcaps would have to be consumed to become toxic	• Lower total and single dose will be less effective and potentially prompt ↑ dose, or switching to opioids, or less safe OTC alternatives such as NSAIDs • Reduces options for minor pain
Maximum single adult dose of 650 mg	24 (12/12)	13		

Audience Polling Questions

- Do you think the 2 x 500 mg dose should be prescription?
  A. Yes
  B. No
  C. I have not decided

- Do you think Rx combination (opioid/acetaminophen) products should be eliminated?
  A. Yes
  B. No
  C. I have not decided

Advisory Committee to FDA Recommendations: Pros vs Cons (cont'd)

Item	Yes (High/Low priority)	No	Pros	Cons
If single dose lowered, 2 x 500 mg dose to be Rx	26 (8/18)	11	• Potentially decrease unintentional acetaminophen overdoses associated with chronic misuse/abuse of these drugs • Control dosing of each drug separately	• Decoupling makes what was a Schedule III drug now a Schedule II drug – Must be written Rx, no call ins. No refills, need follow-up visit. ↑ abuse potential. APAP tox limits use. ↑ diversion • Switching to NSAID or opioid combination • Higher costs • Reduces options for pain management
Recommend pack size limits	17 (2/15)	20		
Eliminate non-Rx combination products	13 (2/11)	24		
Eliminate Rx combination products	20 (10/10)	17		

FDA Reported Hepatotoxicity for Acetaminophen

- FDA Advisory Committee recognizes APAP hepatoxicity “rarely occurs from appropriate use”
  - Most hepatoxicity result of unintended or deliberate overdose
- Postmarketing case reports by FDA Adverse Event Reporting System (AERS)
  - 307 reported* cases of acetaminophen-related hepatotoxicity in adults and children (January 1998 to July 2001)

*Not all cases are reported to AERS.

US Food and Drug Administration. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM171901.pdf.

Acetaminophen Is Safe at Therapeutic Doses in Patients With Comorbidities

- 30,865 adults enrolled in prospective trials treated with multiple-dose acetaminophen (1966-2003)
  - 4,263/30,865 patients received 4 g/d for a mean 5.5 days
- Of 129 (0.4%) of subjects with reported ALT above the ULN, no cases of hepatic failure or clinically significant liver injury reported
- Comorbid conditions included:
  - Acute stroke, CABG
  - Diabetes
  - Multiple sclerosis
  - Advanced cancers
  - Total hip arthroplasty, abdominal surgery

ULN = upper limit of normal; CABG = coronary artery bypass graft.

Dart RC, et al. *Pharmacotherapy*. 2007;27:1219-1230.

Hepatotoxicity in Children Is Rare With Therapeutic Dosing of Acetaminophen

- 32,307 children received acetaminophen for a median of 3 days
  - Therapeutic dosing (≤75 mg/kg/d, up to 4 g/d)
- No cases of liver disease or patients requiring liver transplant
- 4 children with ↑ LFTs (highest AST was 375 IU/L and ALT 362 IU/L)
- LFTs normalized quickly and completely without therapy
- All elevations judged to be "possibly" related to acetaminophen exposure (Naranjo score = 3)
- Asymptomatic increases in LFTs happen with therapeutic dosing of acetaminophen

LFT = liver function test.

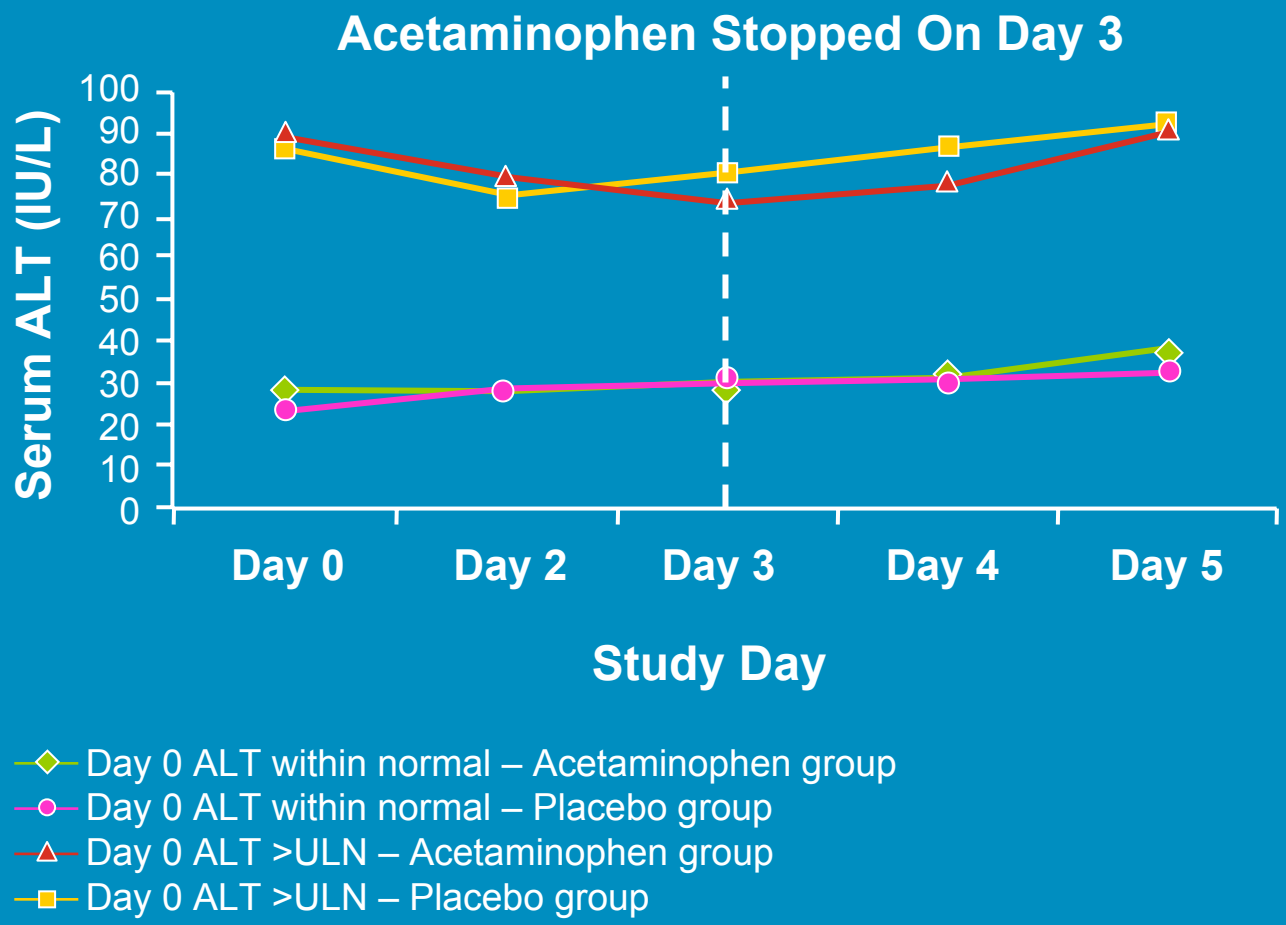
Lavonas EJ, et al. *Hepatology*. 2008;48(suppl):506A. Abstract 444.

Special Concerns for Acetaminophen-related Hepatoxicity Following Overdose

- Alcoholic patients
  - Depletion of glutathione stores due to chronic alcohol ingestion
  - Induces P450 2E1
- Unintentional overdose
- Patients with preexisting liver disease
- Dehydration, fasting, or malnutrition

Myers RP, et al. *Clin Gastroenterol Hepatol*. 2008;6(8):918-925.
Rowden AK, et al. *Clin Lab Med*. 2006,26:49-65.

No Change in ALT With Acetaminophen 4 g/d x 3 d in Newly Abstinent Alcoholics



Kuffner EK, et al. *BMC Med*. 2007;5:13.

Summary: No Acute Liver Injury With Acetaminophen 3-4 g/d in Patients With Liver Disease

	Andreasen 1979	Benson 1983	Dargère 2000	McNeil 2007
Population				
Alcoholic cirrhosis	4	2	–	2
Alcoholic/Hep C	–	–	–	6
Hep C cirrhosis	–	3	–	4
Hepatitis C	–	7	17	–
Other diseases[a]	–	14	–	–
Dosing Regimen	3 g x 5 d	4 g x 5-13 d	3 g x 7 d	4 g x 4 d[b]
Number Exposed	4	26	17	12
Clinical Safety				
Change in ALT	NC	NC	NC	NC
Change in other[c]	NC	NC	NR	NC
Acute liver failure	None	None	None	None

a = Other includes Laennec's cirrhosis, unspecified cirrhosis, and primary biliary cirrhosis. b = One additional dose given the morning of the fifth day. c = Clinical laboratory tests associated with liver function. NC = no change, NR = not reported.

Audience Polling Questions

- Are these data enough to provide clinicians with an evidenced-based argument for the continued use of acetaminophen at currently labeled doses?
- What additional data would you need to support current doses used in practice?

Position Statements and Recommendations

Position Statements Cite Concerns

- American Pain Foundation
  - Many will be driven to take medicines with potentially even greater risks
  - Petition site sponsored by the APF to “Educate, Do Not Regulate”
    - http://www.thepetitionsite.com/1/Acetaminophen-Educate-Do-Not-Regulate
- American Academy of Pain Medicine
  - Recognizes risks of products containing acetaminophen and those combining acetaminophen with other therapies
  - Supports safe and responsible use of acetaminophen

American Pain Foundation. http://www.painfoundation.org/newsroom/position-statements/fda-acetaminophen-recommendations.html. Accessed January 26, 2010.
American Academy of Pain Medicine. http://www.painmed.org/pdf/acetaminophen_statement.pdf. Accessed January 26, 2010.

Recommendations for Acetaminophen Use in Guidelines/Position Statements

Organization	Recommendation/Comment
2009 American Geriatrics Society *Recommendation for persistent pain*	325–500 mg every 4 hr or 500–1000 mg every 6 hr. Reduce maximum dose 50%-75% in patients with hepatic insufficiency or history of alcohol abuse.
2009 National Pain Foundation *Position statement*	Do not exceed the recommended single dose and total daily dose of acetaminophen.
2009 American Pain Society *Recommendation for chronic pain*	Asymptomatic elevations of aminotransferase levels at dosages of 4 g/d.
2000 American College of Rheumatology *Recommendation for osteoarthritis*	Hepatic toxicity with acetaminophen is rare with doses of <4 g/d. Careful monitoring of PT is recommended for patients taking warfarin who subsequently begin high-dose acetaminophen treatment.
1996 National Kidney Foundation *Science Advisory Committee Recommendation*	Drug of choice in patients with impaired renal function.

Summary

- Advisory Committee recommends limiting the OTC single adult dose to 650 mg and the total daily dose to <4 g/d
- However, therapeutic dosing of acetaminophen ≤75 mg/kg/d or ≤4 g/d is safe in most patients
- At therapeutic doses, transient asymptomatic elevations occur but are unlikely to cause hepatic injury
- Medical societies, physicians, and the public may be hesitant to accept recommendations to limit acetaminophen products

NSAIDs

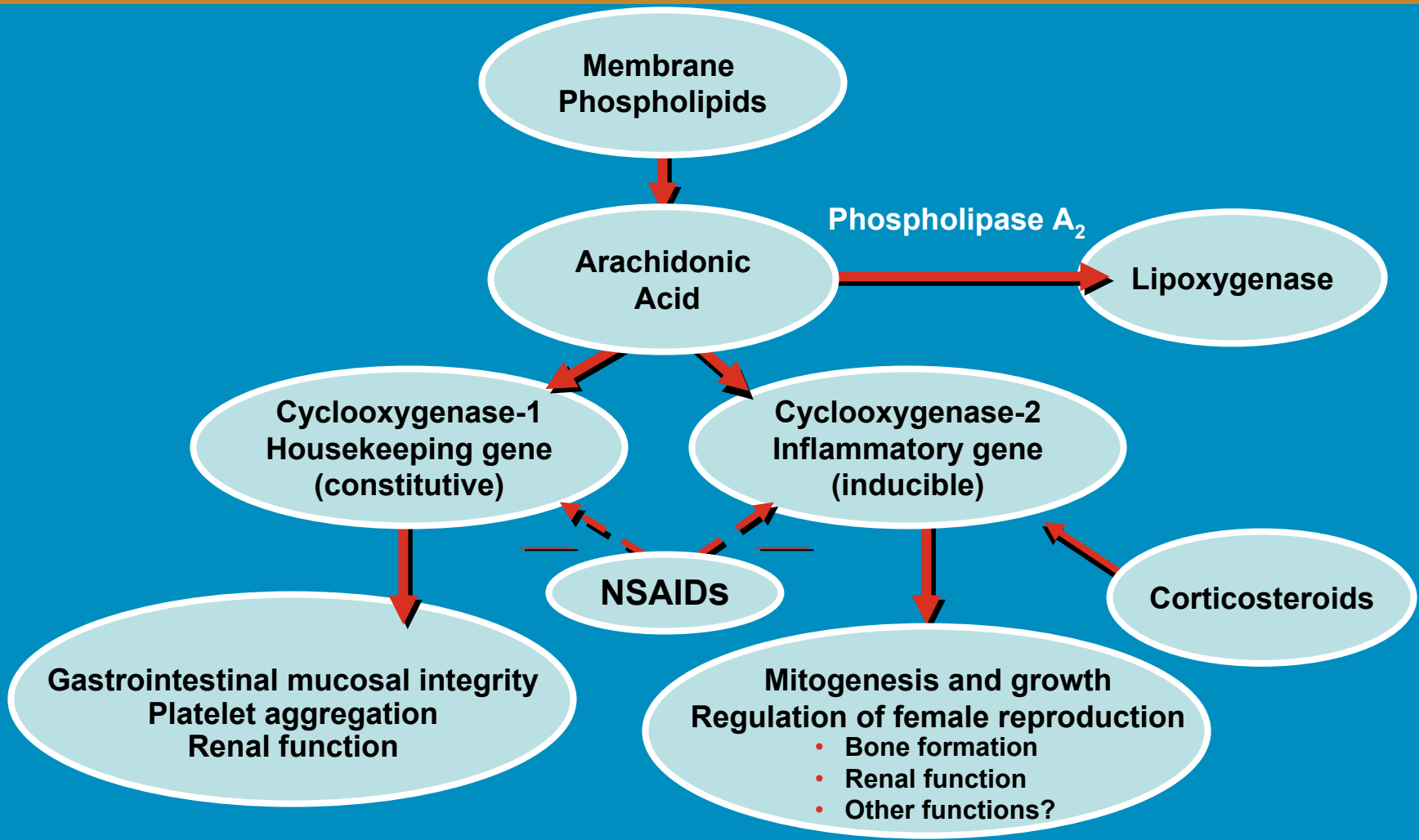
NSAID Activity

ASA	• Inhibits COX-1 and modifies COX-2 – COX-1 enables basal cellular homeostasis (platelet function, gastric mucosal integrity, renal blood flow regulation) – COX-2 increases inflammation and pain states • Low-dose, long-term use blocks the formation of thromboxane A_2 in platelets
NSAID	• Nonselective for COX enzymes • Prevents COX-mediated production of prostaglandin and thromboxanes, but not leukotrienes and other eicosanoids
COX-2	• Selective inhibition of COX-2

ASA = acetylsalicylic acid; COX = cyclooxygenase.

Parente L. *Biochem Pharmacol*. 2003;65(2):153-159.
Hawkey CJ. *Best Pract Res Clin Gastroenterol*. 2001;15(5):801-820.
Patrono C. *N Engl J Med.* 1994;330:1287-1294.

Cyclooxygenase Pathways



Adapted from: Wolfe MM, et al. *N Engl J Med*. 1999;340(24):1888-1899.

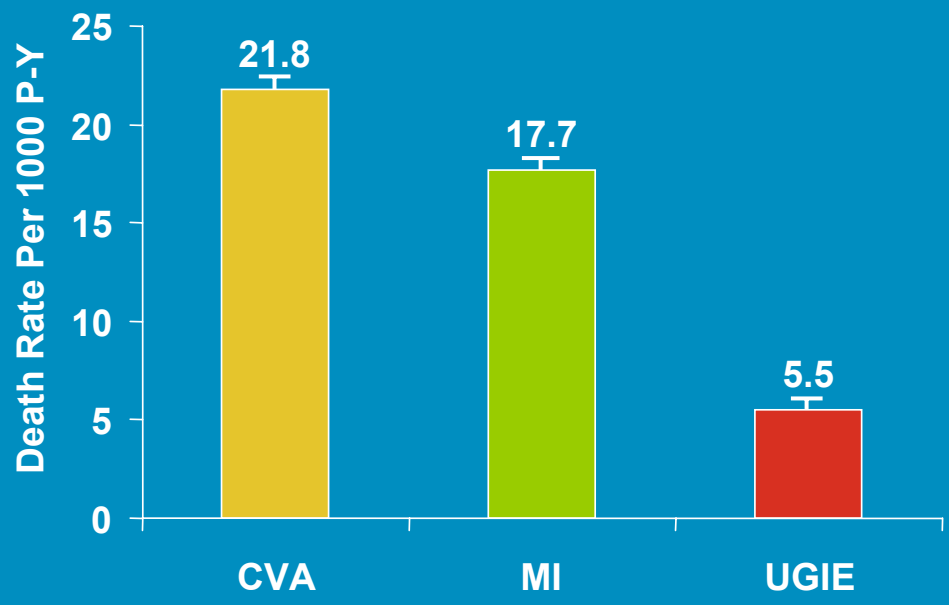
Burden of NSAID-related Complications

- ~111.4 million NSAID prescriptions in 2000
- Annual US hospitalizations for serious gastrointestinal (GI) complications is estimated to be ~103,000
- At an estimated cost of $15,000 to $20,000 per hospitalization, the annual direct costs of such complications exceed $2 billion
- Acute overdose fatality is rare
  - 55 NSAID-associated (not including aspirin) fatalities in 2006

Laine L. *Gastroenterology*. 2001;120(3):594-606.
Singh G, et al. *Arthritis Rheum*. 1997;40(suppl):S93. Abstract.
Bronstein AC, et al. *Clin Toxicol (Phila)*. 2008;46:927-1057.

Death Rate Following UGIE, MI, or CVA With Recent NSAID Use

- 2008 VA study (N=474,495)
- First report showing absolute risk of death following recent NSAID use
- Significant predictors of mortality:
  - Time spent on a traditional NSAID or COX-2
  - Advancing age
  - Failure to ensure adequate gastroprotection
  - Multiple comorbidities

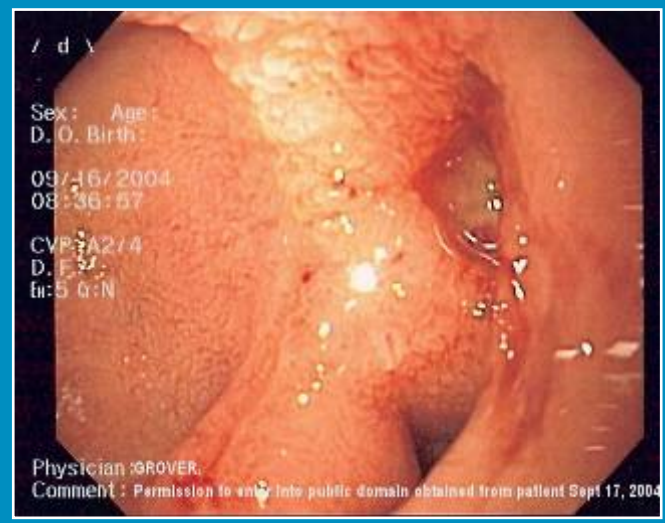


UGIE = upper gastrointestinal events; MI = myocardial infarction; CVA = cerebrovascular accident; VA = Veterans Affairs; P-Y = person years.

Abraham NS, et al. *Aliment Pharmacol Ther*. 2008;28(1):97-106.

NSAID-associated Toxicity at Therapeutic Dosing

- Dyspepsia: pain, reflux, bloating, diarrhea
- ~1% of patients treated for 3-6 months and 2%-4% of patients treated for 1 yr will develop ulcers, bleeding, or GI perforation
- The risk is approximately 3.1-4.5 times that of patients not using NSAIDs



- Rates of peptic ulcer and upper GI hemorrhage are similar for diclofenac, naproxen, piroxicam, and sulindac (1989-1991)

García Rodríguez LA, et al. *Epidemiology.* 2001;12:570-576.
Indocin [package insert]. Whitehouse Station, NJ: Merck and Company, Inc; March 2007.
Lanza LL, et al. *Arch Intern Med.* 1995;155:1371-1377.

FDA Reported GI Toxicity Data for NSAIDs

- Postmarketing case reports by FDA Adverse Event Reporting System
  - 279 cases of GI bleeding associated with the OTC use of NSAIDs between 1998 and 2001
    - 197 cases for ibuprofen, ketoprofen, and naproxen
    - 82 cases for aspirin
    - Data supports nephrotoxic risk with NSAID use
    - Acute renal failure appears to be rare

US Food and Drug Administration. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM171901.pdf.

Management of Acute NSAID Ingestion

- No specific antidote
- Gastric emptying (<1 hr following ingestion)
- Gastric decontamination with activated charcoal 1 g/kg
- Proton pump inhibitor for gastroprotection
- Administer supportive care if needed
  - Airway control with assisted ventilation
  - Arterial blood gases if hypoventilation or acidosis suspected
  - Treat metabolic acidosis with sodium bicarbonate
  - Monitor serum electrolytes and fluids
  - Monitor for renal or hepatic injury
  - Hemodialysis if renal failure develops

Smolinske SC, et al. *Drug Saf*. 1990;5(4):252-274.
O'Malley GF. *Emerg Med Clin North Am*. 2007;25(2):333-346.

Salicylate Toxicity

- >21,000 salicylate (ASA and non-ASA) exposures in poison centers in 2004
  - 2,968 hospitalizations
- ASA alone: 61 deaths in 2006
  - ~50% categorized as intentional overdose
- Incidence of unintentional poisoning is not known, but may be underdiagnosed

Bronstein AC, et al. *Clin Toxicol*. 2007;45(8):815-917.
Watson WA, et al. *Am J Emerg Med*. 2005;23(5):589-666.
Anderson RJ, et al. *Ann Intern Med*. 1976;85(6):745-748.

Signs and Symptoms of Acute Salicylate Overdose

- Vomiting
- Hyperventilation (~30 minutes)
- Metabolic acidosis (~12-24 hours)
- Dehydration
- Electrolyte imbalance
- Hyperthermia
- Pulmonary and cerebral edema
- Convulsions
- Tinnitus

O'Malley GF. *Emerg Med Clin North Am.* 2007;25:333-346.

Salicylate Toxicity Pitfalls

- Failure to recognize salicylate toxicity
- Failure to appreciate continued absorption of salicylate
- Misinterpreting clinical significance of serum salicylate level
- Reliance on 1 or 2 salicylate levels only, unless level is 0
- Misinterpretation of low serum salicylate levels as nontoxic
- Waiting until serum salicylate levels are determined before beginning urinary alkalinization
- Accidentally adding bicarbonate to isotonic saline
- Forgetting to add potassium to the urinary alkalinization infusion
- Failure to recognize emergent need for hemodialysis
- Initiating intubation and mechanical ventilation without hyperventilation and without simultaneous hemodialysis
- Premature discharge without demonstrating metabolic stability

O'Malley GF. *Emerg Med Clin North Am.* 2007;25:333-346.

Diagnostic Studies for Acute Ingestion

- Basic electrolytes to assess levels and acid-base status; baseline renal function
- Arterial blood gas in severe overdose or altered mental status
- Acetaminophen and salicylate levels to rule out concurrent pain medication ingestion
- Fingerstick glucose to rule out hypoglycemia as an etiology of any alteration in mental status
- Screening electrocardiogram to assess for toxin-induced prolongation of the QRS or QTc

O'Malley GF. *Emerg Med Clin North Am*. 2007;25:333-346.
Dargan PI, et al. *Emerg Med J.* 2002;19:206-209.
Ford et al. *Textbook of Clinical Toxicology.* W.B. Saunders; 2001.

Treatment of Acute Toxicity

- Give GI decontamination with activated charcoal 1 g/kg
  - Weigh risk of aspiration vs possible benefits
- Serum and urine alkalinization with bicarbonate and potassium chloride
- Supportive care
  - Secure airway breathing and circulation (rarely an issue with NSAID poisoning)
  - IV crystalloid to replace volume losses
  - Monitor for need for hemodialysis

Smolinske SC, et al. *Drug Saf*. 1990;5(4):252-274.
O'Malley GF. *Emerg Med Clin North Am*. 2007;25(2):333-346.

Indication for Hemodialysis in Acute Salicylate Poisoning

- Severe acidosis or hypotension refractory to optimal supportive care (regardless of absolute serum aspirin concentration)
- Evidence of end-organ injury (ie. seizures, rhabdomyolysis, pulmonary edema)
- Renal failure
- High serum aspirin concentration (>100 mg/dL) despite relatively stable metabolic picture
- Consider for patients who require endotracheal intubation unless that indication for mechanical ventilation is respiratory depression secondary to a coingestant

O'Malley GF. *Emerg Med Clin North Am.* 2007;25:333-346.

Summary

- NSAIDs are common therapies that account for toxicity by unintentional overexposure and gastric or renal injury
- Chronic exposure, even at recommended doses, may result in emergency situations due to GI and CV toxicity
- No antidote available
- Prevention is by education and cautious NSAID use

Conclusions

- OTC analgesic overexposure is common in the US due to ease of availability and lack of physician oversight
- Prompt recognition and treatment may prevent morbidity and mortality associated with analgesic overdose
- Advisory committee to FDA recommends more stringent labeling and lower doses to prevent overexposure and hepatotoxicity
- Subacute toxicity due to chronic NSAID exposure may result in GI or CV AEs
- Patient education and careful use is required for prevention

Thank you!