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% (1993-2004)

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)
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


Hepatic Metabolism of Acetaminophen

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugation</td>
<td>Glucuronide conjugate (nontoxic)</td>
</tr>
<tr>
<td>Conjugation</td>
<td>Sulfate conjugate (nontoxic)</td>
</tr>
<tr>
<td>Oxidation</td>
<td>N-acetyl-p-benzoquinone imine (NAPQI) (potentially toxic)</td>
</tr>
<tr>
<td>Reduction</td>
<td>Glutathione</td>
</tr>
<tr>
<td>Formation</td>
<td>Cysteine and mercapturic acid conjugates (nontoxic)</td>
</tr>
</tbody>
</table>

Routes of Unintentional Adult & Pediatric Overdose

<table>
<thead>
<tr>
<th>ADULT</th>
<th>PEDIATRIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>错误地摄入阿司匹林（APAP）来自组合产品</td>
<td>错误地摄入APAP来自广泛使用的单成分产品</td>
</tr>
<tr>
<td>错误地使用多种产品或不同浓度的APAP</td>
<td>错误地计算体重适宜剂量</td>
</tr>
<tr>
<td>错误地使用制备工具（例如：茶匙而不是茶匙）</td>
<td></td>
</tr>
</tbody>
</table>


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


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

Treatment of Acute Overdose

Case Study
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.

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

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

Management of Acute Acetaminophen Overdose

1. Estimate time of ingestion
2. Administer activated charcoal if <4 hr postingestion
3. Start acetylcysteine and manage in accordance with serum ALT and AST
4. Determine acetaminophen level at 4 hr postingestion

Management of RSTI

1. History of repeated acetaminophen ingestion (>4 g/24 hr over >8 hr)
2. Draw serum AST/ALT and serum acetaminophen level
3. AST or ALT >50 IU/L or serum acetaminophen >10 mg/L (66 µmol/L)
4. Follow-up call in 48 hr to 72 hr
5. Repeat AST or ALT at 12 hr
6. Follow-up call in 48 hr to 72 hr
7. Follow-up visit in 48 to 120 hr

Case Study: Chemistries

- Hemoglobin = 13.8 gr/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: 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

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

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

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

Advisory Committee to FDA Recommendations: Pros vs Cons

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes (90%)/No (10%)</th>
<th>No</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum daily dose &lt;4 g/d</td>
<td>21 (11/10)</td>
<td>16</td>
<td>! margin of safety between labeled dose and suggested threshold dose to injury (suggested as low as 7.5 g)</td>
<td>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</td>
</tr>
<tr>
<td>Maximum single adult dose of 650 mg</td>
<td>24 (12/12)</td>
<td>13</td>
<td>Single tab/gelcap limited to 325 mg so more tablets/caps would have to be consumed to become toxic</td>
<td>REDuces options for minor pain</td>
</tr>
</tbody>
</table>

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

- 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)

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes (High/Low priority)</th>
<th>No</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>If single dose lowered, 2 x 500 mg dose to be Rx</td>
<td>17 (2/15)</td>
<td>17</td>
<td>Potentially decrease unintentional acetaminophen overdoses associated with chronic misuse/abuse of these drugs.</td>
<td>Control dosing of each drug separately.</td>
</tr>
<tr>
<td>Recommend pack size limits</td>
<td>21</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eliminate non-Rx combination products</td>
<td>13 (2011)</td>
<td>13</td>
<td>Switching to NSAID or opioid combination potential. APAP tox limits use.</td>
<td></td>
</tr>
<tr>
<td>Eliminate Rx combination products</td>
<td>20 (10/10)</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA Reported Hepatotoxicity for Acetaminophen

- FDA Advisory Committee recognizes APAP hepatotoxicity “rarely occurs from appropriate use”
  - Most hepatotoxicity 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.

Acetaminophen Is Safe at Therapeutic Doses in Patients With Comorbidities

  - 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

Acetaminophen Stopped On Day 3

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Serum ALT (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>100</td>
</tr>
<tr>
<td>Day 1</td>
<td>50</td>
</tr>
<tr>
<td>Day 2</td>
<td>20</td>
</tr>
<tr>
<td>Day 3</td>
<td>10</td>
</tr>
<tr>
<td>Day 4</td>
<td>5</td>
</tr>
<tr>
<td>Day 5</td>
<td>0</td>
</tr>
</tbody>
</table>

Special Concerns for Acetaminophen-related Hepatotoxicity 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

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.

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

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol cirrhosis</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol/Her C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hep C cirrhosis</td>
<td>3</td>
<td>4</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>7</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other diseases</td>
<td>14</td>
<td>17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>3 g x 5 d</th>
<th>4 g x 7 d</th>
<th>3 g x 7 d</th>
<th>4 g x 6 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Exposed</td>
<td>4</td>
<td>26</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

| Change in ALT                | NC            | NC          | NC           | NC          |
| Change in otherc             | NC            | NC          | NR           | NC          |
| Acute liver failure          | No            | Yes         | None         | Yes         |

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

Position Statements and Recommendations

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](http://www.thepetitionsite.com/1/Acetaminophen-Educate-Do-Not-Regulate)

American College of Rheumatology
- 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.

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

**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.


**Cyclooxygenase Pathways**

**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


**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


**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)


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

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 hyperventilation 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

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

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

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 toxic-induced prolongation of the QRS or QTc
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

Supportive care

- Secure airway breathing and circulation (rarely an issue with NSAID poisoning)
- IV crystalloid to replace volume losses
- Monitor for need for hemodialysis

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

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!