AMERICAN COLLEGE OF EMERGENCY PHYSICIANS
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Analgesic Overdoses: Not Such a Pain

Pain medications account for some of the most common overdoses, both acute and chronic, that emergency department personnel must manage. New sustained-release formulations of acetaminophen are available. New data on the mechanisms and indications for N-acetylcysteine are available. The lecturer will review the management of such overdoses, including indications for blood levels and antidotal therapy.

- Develop an approach for acetaminophen overdoses, including chronic or delayed presentations, that do not fit the nomogram.
- Review the basics of salicylate toxicity and its management.
- Discuss unusual systemic complications of analgesic overdoses and their treatment.
- Describe the management of overdose with new analgesics, including the cyclooxygenase inhibitors.

MO-24
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Room # N219
Las Vegas Convention Center

**Consultant – McNeil, Inc.*

FACULTY

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ANALGESIC OVERDOSES: NOT SUCH A PAIN

Marsha Ford, MD, FACEP, FACMT

I. SALICYLATES

A. Compounds:

--acetylsalicylic acid
--salicylic acid
--sodium salicylate
--methyl salicylate (5cc of 100% contains 7 g salicylate)
--diflunasil (derivative of salicylic acid)
--salsalate

In many OTC and pharmaceutical preparations

B. Types of Poisoning

1) Acute--accidental, non-accidental (child abuse), deliberate, congenital
2) Chronic--often a problem in the elderly

C. Pharmacokinetics

1. Absorbed primarily in small bowel, some gastric absorption
   Reasons for delayed absorption:
   --large amount --bezoar formation
   --food in stomach --coingestants which decrease gut motility
   --pyloric spasm
   --product variability in rates of disintegration/dissolution (e.g. enteric-coated)
2. Metabolism via hydrolysis and conjugation
   T 1/2e prolonged in elderly and neonates
3. Can remove via hemodialysis
   a) Vd 0.2 – 0.3 L/kg
   b) Low molecular weight
   c) Protein binding decreases with increasing levels
   d) Renal elimination <u>more</u> important at higher serum concentrations as metabolic pathways become saturated

Pitfall # 1 – Failure to realize that time to peak absorption can be delayed
Exception: liquid preparations, e.g. methyl salicylate

D. Toxicopathology

Inhibits cyclooxygenase-1 enzyme in prostaglandin synthetase complex.
Through this and other poorly understood mechanisms, the following occur:

1. Direct CNS stimulation
2. Uncouples oxidative phosphorylation
3. Interferes with glycolysis and Krebs cycle function
4. Decreases platelet function, inhibits activation of vitamin K dependent factors II, VII,IX,X
5. Gastric irritant

E. Clinical Effects

Early Signs/Symptoms

Hyperventilation--- respiratory alkalosis
Nausea/vomiting
Tinnitus/decreased hearing
Diaphoresis

Other

* Acid-base disturbances
--respiratory alkalosis
--metabolic acidosis
--respiratory acidosis

* CNS disturbances
--agitation, confusion, coma, seizures

An important indicator of severe poisoning
Worsened by CNS depressant drugs

* Pulmonary
--noncardiogenic pulmonary edema
Increased with age > 30, smoking, chronic ingestion,, metabolic acidosis or CNS disturbances

* Renal
--oliguria secondary to dehydration, ATN

* Other
--hypokalemia secondary to vomiting, renal loss and/or intracellular shift; hematological effects including petechiae, purpura; hyperpyrexia (uncommon)

F. Differential Diagnosis

Pitfall # 2 – Failure to consider in patients with metabolic acidosis ± altered mental status ± pulmonary edema

M ethanol, metformin
U remia
D KA, AKA
P araldehyde, phenformin
I ron, ischemia, inhalants (CO, CN, HS)
L actate
E thylene glycol, ethanol
S alicylates, solvents, sympathomimetics

G. Lab

1. Bedside screening
Add 1-2 drops 10% $FeCl_3$ to 1-2 ml urine, look for purple color
False positives--acetoacetate, phenothiazines, phenylpyruvic acids
2. Plasma salicylate level
--measures parent drug + metabolites
--toxic level ≥ 30 mg/dL
--falling levels represent tissue distribution and/or excretion

Pitfall #3 – Failure to monitor serum salicylate levels frequently in acute ODs

- ♦Q 1-2 hours: Very symptomatic, levels rapidly climbing > 50 mg/dL
- ♦Q 3-4 hours: Mild-moderate toxicity or levels declining < 50 mg/dL

3. Glucose levels
   --hypoglycemia or hyperglycemia
   --CSF glucose can be low with normal serum glucose

4. Ketosis

H. Management

1. Airway management critical

Pitfall #4 – Failure to prevent respiratory acidosis

- ♦hyperventilate intubated patients initially, use ABGs to guide
- ♦do not administer banzodiazepines, other drugs that blunt respiratory drive

2. Decontamination
   --AC + cathartic
   --MDAC in cases of massive ingestions, severe poisoning
   --AC 1 g adsorbs 550 mg salicylate; maximum adsorption seen with AC given in 10:1 ratio to salicylate; some desorption from AC occurs

3. Enhanced elimination

a) Urinary and blood alkalinization
--By ion trapping, decreases salicylate entry into CSF and increases renal excretion

--Indications for use: salicylate level $\geq$ 40 mg/dL and/or patient with hyperventilation, tinnitus/deafness and/or diaphoresis
--increasing urine pH from 5 to 8 increases salicylate excretion 10-20 times

--Technique:

If patient hydrated, give 1-2 mEq $NaHCO_3$ IV bolus followed by continuous infusion to maintain urine pH >7.5 and blood pH 7.45-7.5

Continuous infusion: Adult--mix 150 mEq $NaHCO_3$ in 850 ml D_5W;
Initial IV rate at 1.5 -2 times normal maintenance infusion rate

If patient dehydrated, coadminister 0.9% NS at 20 ml/kg over 30 minutes, then begin normal continuous infusion rate

REMEMBER, YOU MUST AVOID HYPOKALEMIA IN ORDER TO ADEQUATELY ALKALINIZE URINE

Pitfall #5 – Failure to alkalinize urine

--Complications: Fluid overload, pulmonary edema, hypocalcemia
--Contraindicated: oral bicarbonate--increases GI absorption of salicylates
acetazolamide--produces systemic metabolic acidosis, which would facilitate salicylate entry into the CSF

b) Hemodialysis
--efficient salicylate removal
--affords control of fluid and electrolyte balance

Indications: --serum level ≥100 mg/dL (acute)
--severe acidemia uncontrolled with $NaHCO_3$
--pulmonary edema
--CNS manifestations other than hyperventilation, tinnitus/deafness
--renal failure

Pitfall #6 – Failure to hemodialyze appropriately, including getting nephrology involved early

4. Other
--FFP, vitamin K, ? platelets
--supportive therapy

SHOULD I USE THE DONE NOMOGRAM TO MAKE CLINICAL DECISIONS?

No!! There are many problems with this nomogram:
--single dose, acute OD only
--not for enteric-coated or methyl salicylate
--the slope of the regression curve was calculated assuming salicylates followed first-order kinetics
--calculated to demonstrate that a theoretical value, S_0 [plasma salicylate concentration at time zero of overdose] correlates with the severity of the salicylate overdose. However, due to concerns regarding continued GI absorption, the graph was drawn to begin at 6 hours post-ingestion. At 6 hours post-ingestion, your patient can be DEAD!

BOTTOM LINE: Use your clinical judgement. Don't wait to draw levels.

II. ACETOMINOPHEN (APAP)

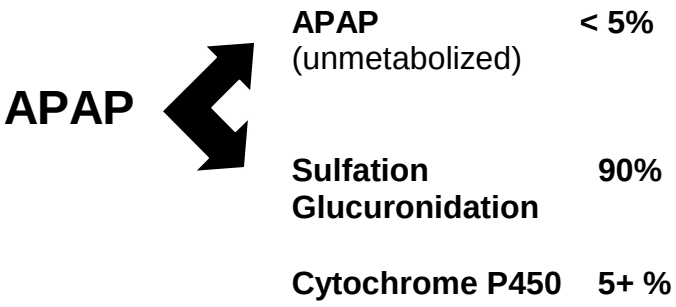
--major metabolite of phenacetin

A. Compounds
--Tylenol, Tempra, Datril, Anacin 3, Panadol, many OTC and pharmaceutical preparations

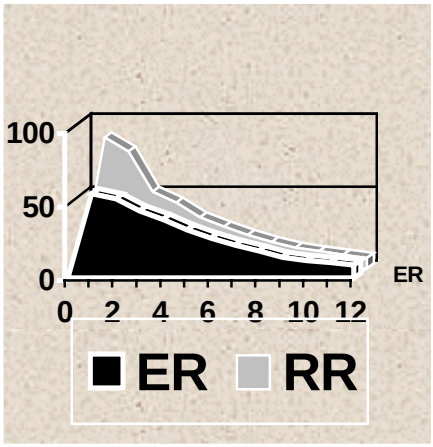
Pitfall # 1 – Failure to get a history of chronic overingestion, especially in patients with underlying risk factors

B. Pharmacokinetics
1. Absorption--within 1 H in therapeutic doses, within 2-4 H in OD

2. Metabolism



3. Extended release APAP



Max [APAP]
ER 62.6 mcg/ml
RR 94.3 mcg/ml
p <0.001
AUC
ER 426 mg h/L
RR 432 mg h/L
p = 0.77

Enhanced toxicity can be seen with:
a) MFO inducers--barbiturates, , INH, ethanol
b) glutathione depletion--alcoholism, poor PO intake

C. Toxicopathology
Minimum acute toxic ingestion--140 mg/kg

D. Clinical Effects
Hepatic
Initial--nausea,vomiting, diaphoresis
Next (24-48 H)--apparent clinical improvement, but LFTs begin to rise
Followed by (72-96 H)--peak hepatoxicity
Recovery--occurs in 7-8 days

Renal
Dysfunction and ARF can occur with severe, mild or no hepatoxicity. Occurs 3-4 days after ingestion, peaks at 5-10 days, heralded by proteinuria, hematuria

Other
Coma, metabolic acidosis

E. Diagnosis

1. Suspect in all OD cases. APAP is a "time bomb".
2. Draw one (and one only!!) APAP level at least 4 H post-ingestion. Plot on nomogram to make decision regarding treatment. No further levels are needed.
   --colorometric assays unreliable in face of increased bilirubin, renal failure, salicylism.

Pitfall #2 – Using the nomogram for chronic ingestions or when the ingestion occurred more than 24 hours earlier.

F. Treatment

1. AC + cathartic
   --can give with NAC. Do not need interval between NAC and AC.
   --adsorbs APAP, can convert toxic OD to nontoxic
2. N-acetylcysteine
   a) Mechanisms of action
      1) glutathione precursor
      2) glutathione substitute
      3) increases sulfation metabolism
      4) Some conversion of NAPQI back to APAP

   b) Oral Dose: INITIAL: 140 mg/kg initial
      MAINTENANCE: Traditional has been 70 mg/kg Q 4 H for additional 17 doses

      : Some toxicological experts now recommending shorter maintenance regimens (usually 6 to 10 doses), with careful retesting of AST and INR (some recheck APAP level to make sure it is undetectable).

      If AST or INR are abnormal, or if APAP still measurable, continue for traditional 17 doses.

Pitfall #3 –With shortened regimens, failure to adhere **RIGIDLY** to regimen with respect to elevated AST/INR or measurable APAP.
A "little abnormal" is not acceptable.

   c) Comes in 10% (10 g/100 ml) or 20% (20 g/100 ml) solutions. Dilute 2-4x with juice, cola

If emesis a problem, try:
   --antiemetics---metoclopramide, ondansetron, granisetron
   --drip through a tube, e.g. NG, Miller-Abbot

   d) Administer within first 8 hours after ingestion. Efficacy in preventing hepatoxicity rapidly declines after 16 hours post-ingestion.

Pitfall #4 – Failure to administer within 8 hours postingestion in acute OD, or as soon as chronic toxicity is suspected.

--investigational; associated with anaphylactoid reactions
--useful if PO NAC not tolerated (maximize antiemetics)
--may play role in delayed treatment of NAC-induced hepatic failure

DO NOT USE WITHOUT CONSULTING REGIONAL POISON CENTER

Pitfalls 5 & 6 – #5 Failure to maximize antiemetic therapy.

#6 Failure to dilute NAC and administer slowly.

f) Pregnant patients--treat the same as non-pregnant patients

4. Labs
   a) Baseline AST, INR if toxic level on nomogram in acute ODs, chronic ingestions
   b) Lytes, creatinine/BUN, glucose if ill
   c) To monitor:
      1) daily INR
      2) If INR starts to rise, add daily lytes, creatinine
      3) For severe hepatotoxicity, check INR, ABG, creatinine q 12 hours

Be aware that elevated AST establishes hepatotoxicity but levels have no predictive value.

G. Benefits of NAC after hepatotoxicity has developed
   1) Mechnisms: Free radical scavenger, improves hepatic oxygen delivery (blood flow) and uptake
   2) Improves survival, decreases cerebral edema

H. Guidelines for liver transplant

PH < 7.3 after 4.5% albumin infusion

Or in patients with pH > 7.3

PT > 100 secs
Creatinine > 300 micromole/L (>3.4 mg/dL) > all 3 must coexist within a 24 hour period
Grade III/IV hepatic encephalopathy

I. Strategies for chronic ingestions

A. > 7.5 grams per 24 hours, or history of ethanol abuse or other risk factors
B. Check AST and APAP level. If AST normal and APAP not detected, no further therapy needed
C. If AST or INR elevated or APAP measured, treat with NAC loading + 6 maintenance doses. IF AST and INR normal and APAP non-detectable, no further therapy.
D. IF AST or INR still elevated, continue for minimum 72 hours.

J. NAC Endpoints of Therapy

A. Acute ODs and Chronic Ingestions
   After 24 hours of NAC, if AST/INR normal and APAP not detected, STOP

B. Any hepatotoxicity
    NAC for 72 hours
    At 72 hours, if INR < 2.0, STOP
C. If INR > 2.0 or if fulminant hepatic failure
    Continue NAC until INR < 2.0 or death

K. Followup
    Fatalities are rare. Be aggressive, even with severe hepatoxicity. Recovery is complete--no residual hepatic damage

III. NSAIDS

A. Substances
    1. Pyrazolones – phenylbutazone
    2. Fenamates (anthranilic acids) – meclofenamate, mefenamic acid
    3. Acetic acids – diclofenac, etodolac, indomethacin, ketoralac, nabumetone, sulindac, tolmetin
    4. Propionic acids – carprofen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin
    5. Oxicams – piroxicam, meloxicam

B. Pharmacology/Toxicopathology
    1. NSAIDS reversibly block COX-1 and COX-2
    2. Prevent formation of prostaglandins, prostacyclins, and thromboxane

C. Clinical Effects -- Ibuprofen
    1. Hall – Retrospective study n = 126
        19% symptomatic within 4 hours of ingestion
        CNS depression, GI upset
    2. Hall – Prospective study n = 45 adults, 39 peds
        Symptoms always occurred within 4 hours of ingestion
        9% adults, 5% peds with coma, metabolic acidosis, apnea
        Ingestion of > 400 mg/kg ibuprofen also at risk for bradycardia, hypotension, seizures, renal/hepatic toxicity

D. Clinical Effects – Other
    1. Fenamates – muscle twitching, seizures
    2. Pyrazalones – GIs, pulmonary edema, seizures, coma, acid-base and electrolyte abnormalities, respiratory and cardiac arrest
    3. Other Propionic Acids – GIs, CNS depression, metabolic acidosis, seizures, coma
    4. Acetic acids – CNS depression, tinnitus, headache, renal toxicity (sulindac)
    5. Oxicams – mild CNS

E. Treatment
    1. No specific labs
    2. Decontamination with AC
    3. Supportive therapy

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