RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Toxicology

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Faculty Disclosure

- Amit Kapadia, PharmD
  - No conflicts to disclose

- Andrew Nunes, PharmD
  - No conflicts to disclose

Learning Objectives

- Identify the role of Poison Control Centers in managing patients with medication overdoses
- List three medications that may lead to hospitalization following overdose
- Distinguish potential toxic outcomes of medications commonly encountered in rheumatology
- Determine the likely need for emergency room evaluation depending on the medication involved

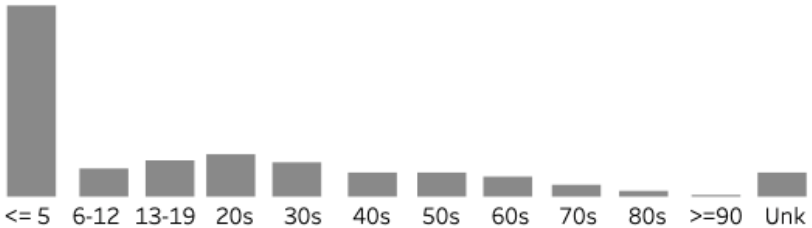
U.S. Poison Control Centers

- National Poison Data System 2019 Data
  - Responded to 2,148,141 human exposure cases
  - One exposure case every 15 seconds (on average)
- Top 3 medication exposures
  - Pain relievers, antidepressants, sedatives
- Drugs used in Rheumatology
  - Less common, potentially serious consequences

U.S. Poison Control Centers

DISTRIBUTION OF HUMAN EXPOSURE CASES

WHO WAS EXPOSED ?



AGE GROUPS OF CASES

43%

OF CASES WERE FOR CHILDREN AGES <= 5

Case #1

- 76 y/o F with Rheumatoid Arthritis, renal impairment
  - Nausea, vomiting
  - Inflammation of mouth and lips
  - Elevated transaminases
  - Pancytopenia

Name The Drug

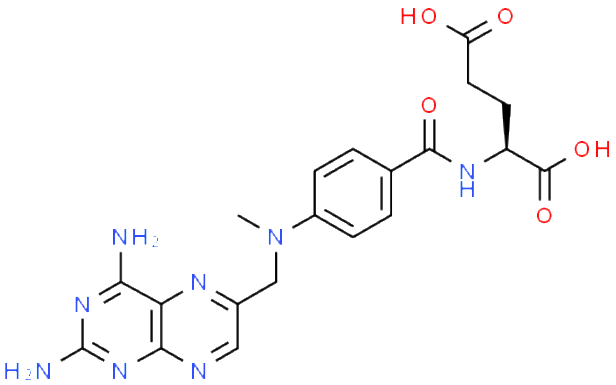
- A) abatacept
- B) methotrexate
- C) rituximab
- D) acetaminophen

Drug Profile

<u>Mechanism of toxicity:</u>

Folic acid antagonist

- Interferes with DNA synthesis/repair
- Tissues with active proliferation are more sensitive to this effect



Immunosuppressive and/or anti-inflammatory effects

- mechanism unknown

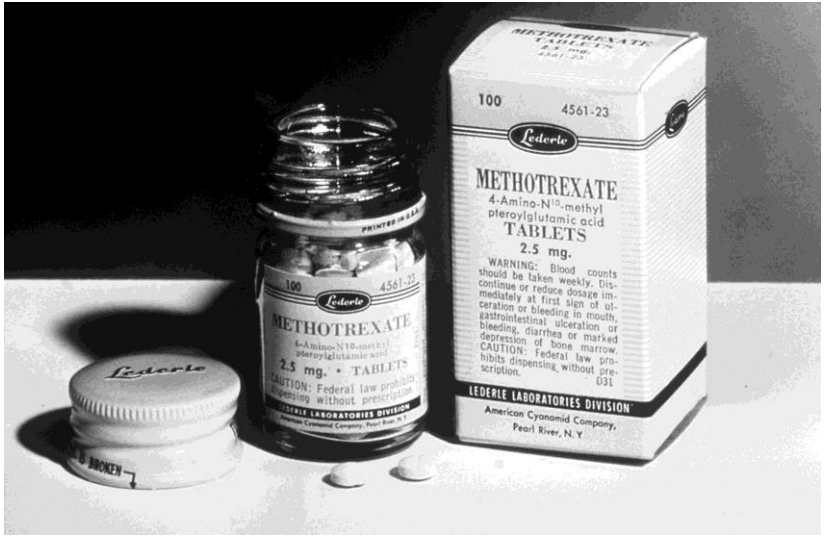
It’s definitely:

- A) abatacept
- B) methotrexate
- C) rituximab
- D) acetaminophen

Methotrexate

- First made in 1948, leukemia treatment

- Acute overdose
  - Incomplete absorption w/ large oral
  - Injectables more severe
- Chronic overdose
  - Renal impairment, diabetes, age
  - Accumulates in third space fluid
- Leucovorin / Glucarpidase treatments



Case #2

- 67 y/o F presents to ER after large ingestion of her medication. Presents alert and awake about 45 min after ingestion.
  - Initial VS: 96/60 hr 58 rr20 97% on ra t98.5
  - Quickly becomes unresponsive and unable to protect airway. Intubated and develops VT cardiac arrest. EKG QRS 125/QTC 533. ROSC after CPR.
  - Chem with notable K of 2.2
  - Upon contacting PCC initiated high dose diazepam and epinephrine. Pt started on norepinephrine and vasopressin, given Mg and K for QT>>.
  - Coded again and passed away within 3 hr of arrival.

It must have been:

- A) etanercept
- B) rituximab
- C) abatacept
- D) hydroxychloroquine

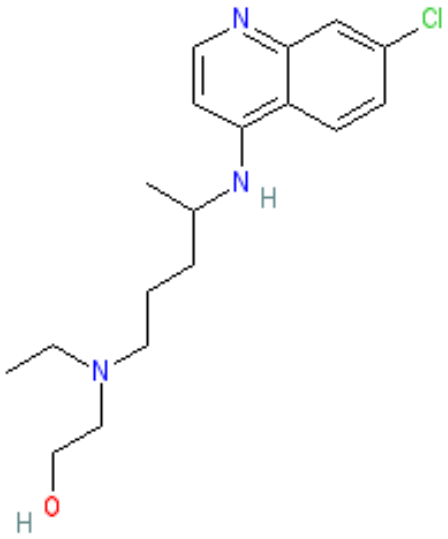
Drug Profile

Mechanism of action: unknown, mild immunosuppressant?

Mechanism of toxicity: negative inotropic action, depresses contractility.

Key Pharmacokinetics: $T_{1/2}$: 40 days,

Toxidrome: within first 2 hr triad: hypokalemia, QRS>>, Hotn



What Could Have Caused This?

- A) etanercept
- B) rituximab
- C) abatacept
- D) hydroxychloroquine

Hydroxychloroquine

Brand: Plaquenil ®

Analog of quinine, extracted from tree bark in 1820s to treat malaria

Doses >8g cause life threatening toxicity

Tox triad: hypokalemia, hotn, QRS>>

Serious tox effects in first 2 hr

Case #3

- 68 y/o M with history of osteoarthritis, gastric ulcer
  - Abdominal pain
  - Jaundice

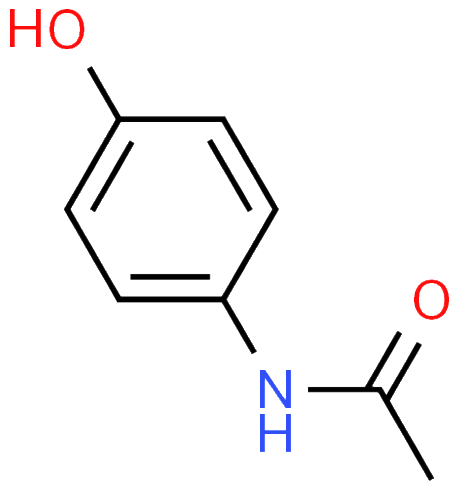
Find The Culprit

- A) leflunomide
- B) sulfasalazine
- C) ibuprofen
- D) acetaminophen

Drug Profile

<u>Mechanism of toxicity:</u>
Production of NAPQI (via cytochrome P450 2E1)

- Detoxified by glutathione in liver cells
- Glutathione capacity exceeded in large overdose
  - Hepatotoxicity → liver failure



Increased risk

- Alcoholism, Isoniazid use
- Fasting/malnutrition

Now I Know For Sure:

- A) leflunomide
- B) sulfasalazine
- C) ibuprofen
- D) acetaminophen

Acetaminophen

- An added ingredient in many combination products
  - Most commonly used medication for pain and fever in the U.S. and Europe
- Acute/Chronic overdose
  - Inadvertent double/triple doses are generally benign
  - Usually, no early symptoms
- Treatment
  - N-acetylcysteine
  - Liver transplant

Case #4

- 42 y/o F referred to clinic by pharmacy
  - Headache and stomach pains
  - BP: 166/100 hr 99 100% on ra 98 rr20
  - Cbc: plt 150 (previously 166), otherwise wnl

Who done it?

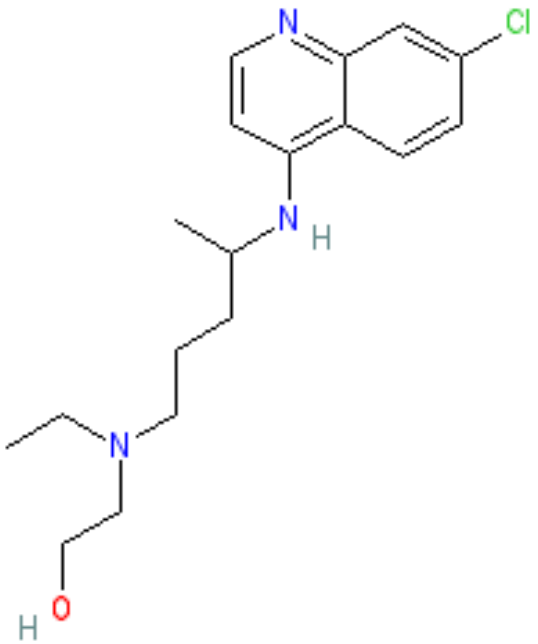
- A) leflunomide
- B) naproxen
- C) rituximab
- D) adalimumab

Drug Profile

Mechanism of action/tox: anti-inflammatory and immunomodulatory activity

Key Pharmacokinetics:
Peak level: 6-12 hr,
$T_{1/2}$ of active metabolite: 7-8 days

Toxidrome: extension of adverse effects: htn, pancytopenia.
*In chronic overdose one case of interstitial nephritis



Leflunomide

Brand: Arava ®

-generally, well tolerated in overdose

-CBC/CMP if symptomatic

-dialysis will not clear the metabolite, but cholestyramine may increase clearance

Case #5

- 40 y/o M with history of undifferentiated spondyloarthropathy, limited drug insurance
  - Oligozoospermia (low sperm count)
  - Reddish-orange urine color

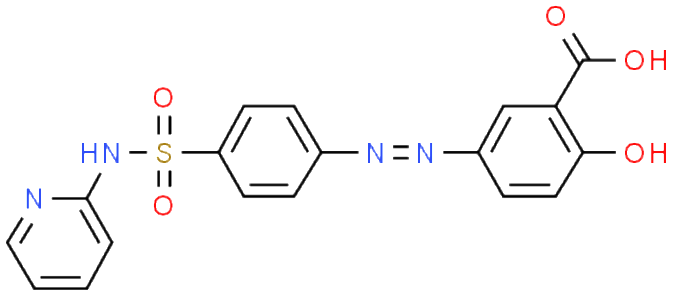
For sure it’s:

- A) sulfasalazine
- B) naproxen
- C) hydroxychloroquine
- D) tofacitinib

Drug Profile

Mechanism of toxicity:
Unclear

- Prodrug
  - 5-aminosalicylic acid linked to sulfapyridine
  - Azo bond broken by gut bacteria



- May inhibit prostaglandins
  - local anti-inflammatory, immunosuppressive
  - Affinity for connective tissue, colon

I Knew It Was:

- A) sulfasalazine
- B) naproxen
- C) hydroxychloroquine
- D) tofacitinib

Sulfasalazine

- Brand: Azulfidine®, Sulfazine®
  - Multiple indications, differing dosing ranges
- Acute/chronic overdose
  - Extension of adverse effects observed with therapeutic use
  - GI effects, headache, dizziness, drowsiness
- Rare severe effects
  - Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Hepatitis, hemolytic anemia, methemoglobinemia
- Genetic polymorphism variations

Case # 6

- 37 y/o F with presents to ER for uncontrolled RA joint pain, severe abdominal pain, nausea and vomiting.
  - hypertensive, acidemia, acute renal failure
  - Received 2 L of IVF fluids, anti-emetic
    - ➢ acidosis resolves and renal function improves

It’s Probably:

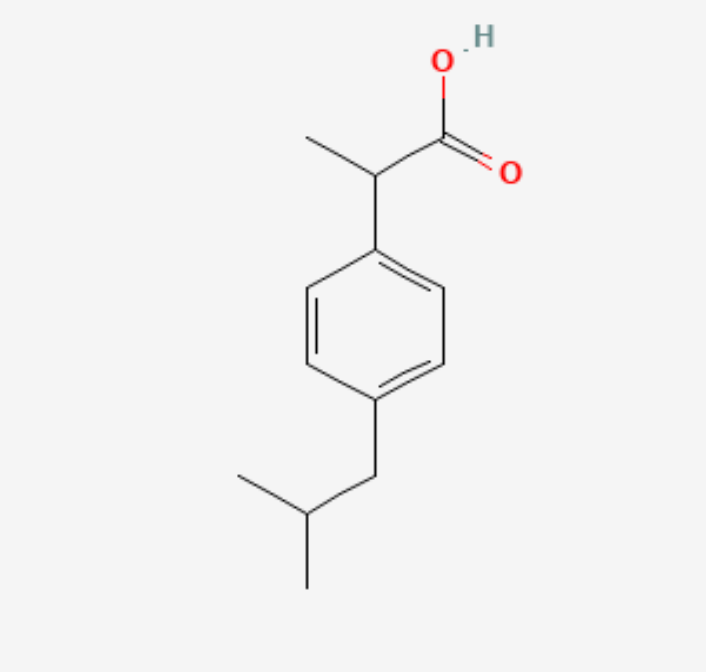
- A) leflunomide
- B) methotrexate
- C) ibuprofen
- D) acetaminophen

Drug Profile

Mechanism of action: nonsteroidal anti-inflammatory with analgesic and antipyretic activity via prostaglandin synthesis inhibition. Thromboxane inhibition.

Toxidrome: GI symptoms, Acute renal failure, metabolic acidosis and bleeding risk.

Key Pharmacokinetics:
Peak 1-2 hr and $T_{1/2}$ 1.8 to 2 hr.



No doubt, This Time I’m Positive It’s:

- A) leflunomide
- B) methotrexate
- C) ibuprofen
- D) acetaminophen

Ibuprofen

Brands: Advil ®, Motrin IB ®

-High threshold for toxicity

-CBC/BMP, IV fluids

-available in multiple combination products

Biologic and Targeted Synthetic DMARDS

No established toxic dose. Generally well tolerated in accidental extra dose

TNF-alpha inhibitors: Certolizumab pegol (Cimzia ®), Etanercept (Enbrel ®), Adalimumab (Humira®, Hyrimoz™, Cyltezo ®, Cyltezo ®, Abrilada™, Hadlima™, Hulio ®, Amjevita™, Infliximab (Remicade ®) Golimumab Simponi ®

IL-6 receptor antagonists: Tocilizumab (Actemra ®): *dose limiting neutropenia, Sarilumab (Kevzar ®)

T-cell costimulation blocker: no specific tox dose established
Abatacept (Orencia ®), Rituximab (Rituxan ®, Truxima ®, Riabni™)

JAK inhibitors: Tofacitinib (Xeljanz ®), Baricitinib (Olumiant ®), Upadacitinib (Rinvoq™)

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Questions?