Clinical Pharmacology & Toxicology Pearl of the Week

~ Neurotoxicity after IV Acetylcysteine (NAC) overdose ~

Case:

- ✓ A 21-year-old female presented following a reported ingestion of 15 – 20 X 500 mg of acetaminophen tablets over 8 h to treat a headache. A serum acetaminophen concentration was 847 umolL/L 6 h after the final ingestion, and serum AST was 60 IU/L and serum ALT was 47 IU/L (upper limit of normal 41 and 54 IU/L, respectively). The patient was started on the traditional 3 bag regimen of IV NAC and the MD wrote the order for same.

- ✓ 12 hours later, the patient was reported to be increasingly agitated, somnolent, with intermittent headache and vomiting. A CT scan showed cerebral edema. The patient developed status epilepticus requiring intubation and sedation for control.

- ✓ An IV NAC dosing error was discovered when the orders were reviewed and the infusion pump was interrogated.

Background:

- ✓ IV NAC mixing and dosing errors do occur, especially with the traditional 3 bag IV NAC infusion.

- ✓ Cases of IV NAC neurotoxicity in the literature report between 1242 – 4500 mg/kg of IV NAC given.

- ✓ One theory is that acetylcysteine increases glutamateric signaling within the CNS. This increase in neuroexcitation may be responsible for the toxic effects observed in association with acetylcysteine overdose. IV NAC is also a hyperosmolar solution.

Clinical features:

- ✓ The clinical features are consistent with increased intracranial pressure, intracranial hypertension and cerebral edema and usually occur several hours after the IV NAC therapy has been initiated.

- ✓ Intractable vomiting, altered mental status, myoclonus and seizures are some of the most common symptoms. Acute renal failure and hemolysis may also be present.

- ✓ These features are separate from anaphylactoid reactions, which typically occur during the first (loading) dose of IV NAC.

Management:

- ✓ Stop the infusion as soon as the dosing error is discovered.
- ✓ Seizures respond to benzos, barbiturates, propofol, and attention to the ABCs.
- ✓ NAC is dialyzable. Hemodialysis may play a role once the dosing error is discovered, and particularly if the patient is symptomatic.
- ✓ Prevention involves a combination of standardized orders, dose calculators, smart pump programming, computerized order entry with validation, education, and changing to a NAC protocol with fewer bags (i.e., one or two bag protocols).

Case resolution:

- ✓ The patient received the 3rd bag of IV NAC at 100 mg/kg/hr instead of 100 mg/kg over 16 hours.
- ✓ The patient was eventually discharged with profound neurological injury and required continuous nursing care.

References:

1. Heard et al. Massive acetylcysteine overdose associated with cerebral edema and seizures, Clinical Toxicology 2011, 49:5, 423-425.
2. Bailey et al. Status Epilepticus after a Massive Intravenous N-Acetylcysteine Overdose Leading to Intracranial Hypertension and Death. Ann Emerg Med. 2004; 44:401-406.
3. Ali Mahmoudi et al. N-acetylcysteine overdose after acetaminophen poisoning. International Medical Case Reports Journal 2015:8 65–69.
4. Ogilvie et al. Acetaminophen overdose in children. CMAJ 2012 184 (13) 1492-1496.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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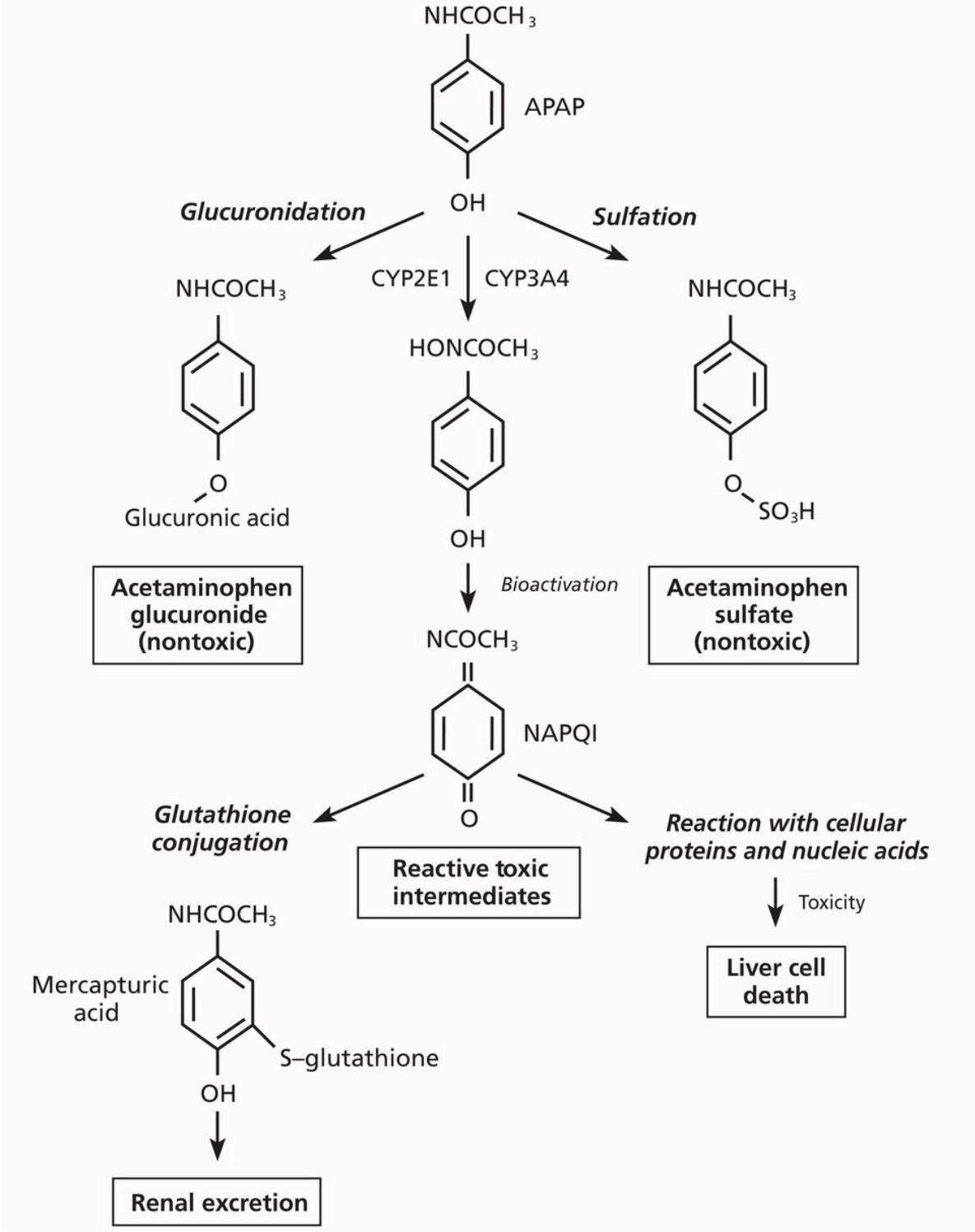
Created: May 4, 2022

Reviewed: July 21, 2025



Metabolism of acetaminophen. From Ogilvie et al. CMAJ 2012.