



Clinical Pharmacology & Toxicology Pearl of the Week

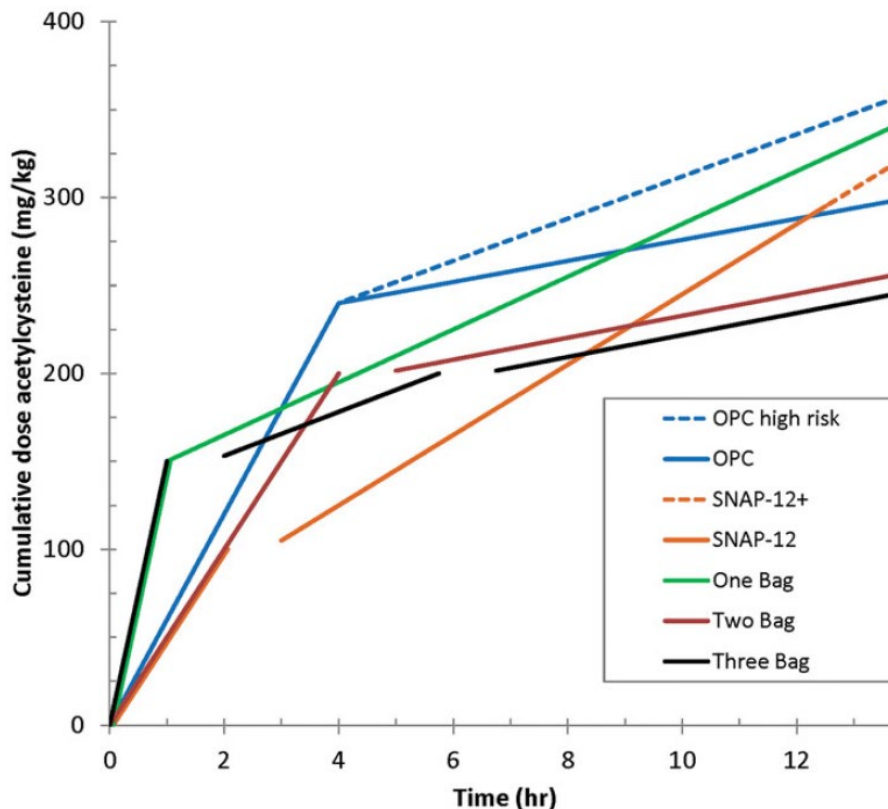
~ Newer IV NAC regimens, Part 2 ~

Case:

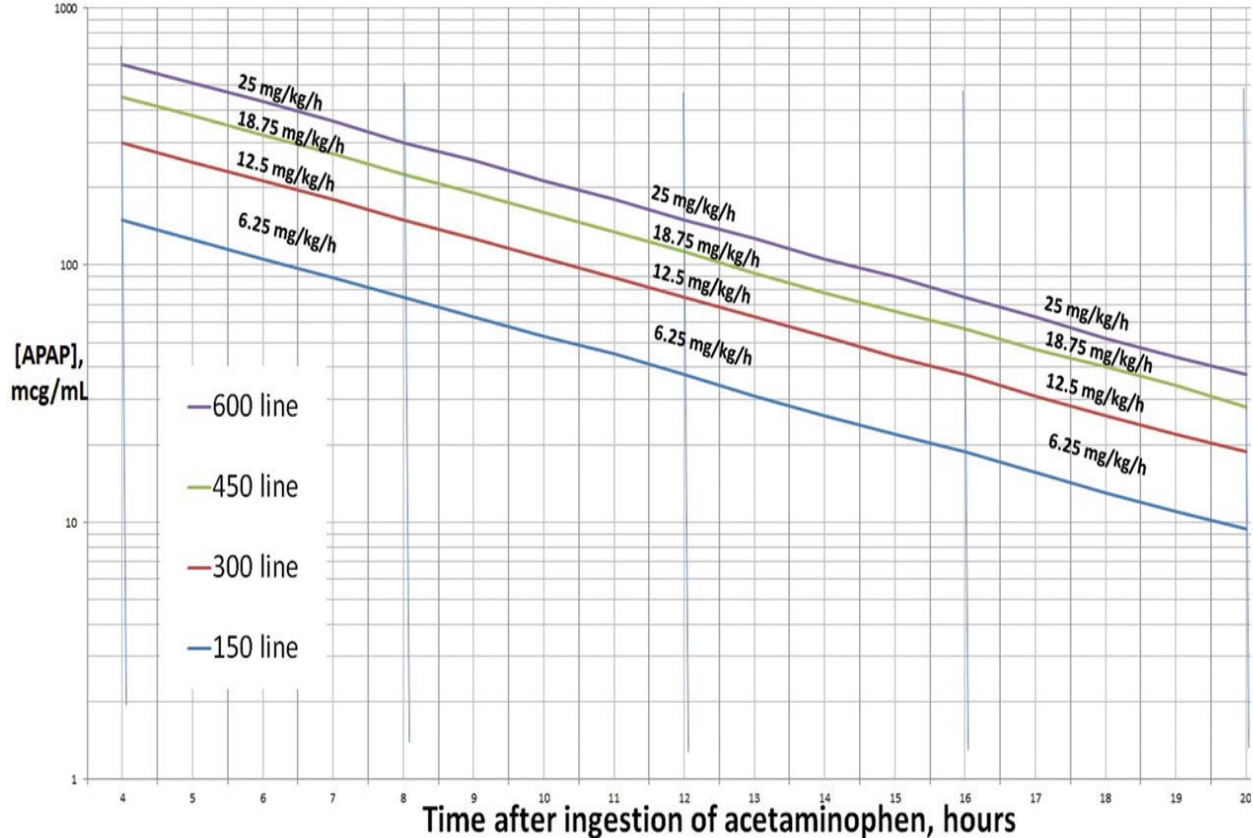
- ✓ A 25-year-old female ingested a supratherapeutic amount of acetaminophen (APAP) at 10am.
- ✓ The 4-hour APAP concentration was 1200 $\mu\text{mol/L}$, indicating that hepatotoxicity (serum AST or ALT > 1000 IU/L) was likely.
- ✓ The patient was started on IV N-acetylcysteine (NAC) and made a full recovery. No evidence of hepatotoxicity occurred during her hospital stay.

IV NAC regimens:

- ✓ The graph below shows the differences in IV NAC infusion rates when comparing rate and duration of loading and maintenance dose (Mullins et al, 2019)
- ✓ Breaks in the black (3-bag), red (Australia/New Zealand 2 bag), and orange (SNAP) regimens are to account for the delays in stopping one bag and switching to the next bag. Ontario Poison Centre (OPC) and 2-step regimens do not have any delay between loading dose and maintenance infusion
- ✓ While the optimal dose and duration of IV NAC varies depending on patient risk, most infusions provide at least 300 mg/kg of NAC over a 12-21 hour time period for patients with an average risk of hepatotoxicity



What about massive APAP ingestions?



- ✓ Varying definitions of massive ingestion include: an ingestion > 30 grams, an ingestion > 500-600 mg/kg, or a 4-hour [APAP] > 300 ug/ml (1986 umol/L).
- ✓ The above graph shows the suggested rate of IV NAC maintenance infusion based upon the patient's equivalent 4-hour [APAP] (Hendrickson, 2019).
- ✓ With the traditional 3-bag regimen, this is accomplished by doubling or tripling the rate of the 3rd bag from 6.25 mg/kg/hr to 12.5 or 18.75 mg/kg/hr.
- ✓ With newer regimens, the maintenance infusion can also be increased as needed. Given the higher maintenance dose of the two-step IV NAC regimen, adjustment for higher risk patients is less likely to be necessary.
- ✓ With massive ingestions, other therapies such as fomepizole and dialysis are often recommended in addition to IV NAC. This is especially if the 4-hour [APAP] is close to 6000 umol/L, the patient is comatose, and if metabolic acidosis and elevated lactate are present.
- ✓ It is also important to ensure that GI decontamination is performed if there are no contraindications. 1 g/kg of activated charcoal can be given up to 4 hours post-ingestion.

- ✓ Consultation with a poison centre / medical toxicologist physician is recommended for current advice on management of the massive APAP ingestion.

Side by side comparison of the different IV NAC regimens:

Variable	Traditional '3 bag'	SNAP	Australia '2 bag'	Two-step (PADIS)	Ontario
Loading dose	150 mg/kg over 1 hour	100 mg/kg over 2 hours	200 mg/kg over 4 hours	150 mg/kg over 1 hour	240 mg/kg over 4 hours
Maintenance	50 mg/kg X 4h then 100 mg/kg X 16h	200 mg/kg over 10 hours	100 mg/kg over 16 hours	15 mg/kg/hr for 20 hours	6 mg/kg/hr for at least 8 hours
Duration	≥ 21 hours	≥ 12 hours	≥ 12 hours	≥ 21 hours	≥ 12 hours
Dose at 12 hours	244 mg/kg	300 mg/kg	250 mg/kg	315 mg/kg	288 mg/kg
Dose at 21 hours	300 mg/kg	300 mg/kg	300 mg/kg	450 mg/kg	342 mg/kg
Stopping rules at 12 hours?	No	Yes	Yes	No	Yes
Dose adjustment in HT or dialysis?	Yes	Yes	Yes	No	Yes

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultations are also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click [HERE](#) for more details.

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).

References:

1. Mullins et al. Comment on "transition to two-bag intravenous acetylcysteine for acetaminophen overdose", Clinical Toxicology 2019, DOI: 10.1080/15563650.2019.1649418
2. Hendrickson R. What is the most appropriate dose of N-acetylcysteine after massive acetaminophen overdose? Clin Tox 2019.