How much did you take?

Reviewing acetaminophen toxicity

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Case descriptions

Case 1. A 45-year-old woman presents to your emergency department asking for help. She took 18 extra-strength (500-mg) acetaminophen (APAP) tablets approximately 5 hours ago in an attempt to end her life. She denies taking any other medications and is otherwise healthy. She realizes that she made a mistake and is asking for your help. Her vital signs are stable, examination findings are normal, and she looks well. Her APAP level is 1300 µmol/L (200 mg/L).

Case 2. A 52-year-old man with known depression and a history of suicide attempts was last seen by his friend picking up a bottle of 150 extra-strength APAP tablets for his chronic back pain. Another friend visits approximately 1.5 hours later and finds the man to be somnolent, difficult to rouse, and confused, and the bottle of APAP is empty. He calls 911. The man presents to the hospital with a Glasgow Coma Scale score of 6, a blood pressure of 100/80 mm Hg, and a heart rate of 100 beats/min. Results of preliminary bloodwork, drawn 4 hours after the purchase of the APAP, reveal a pH of 7.0, a lactate level of 15 mmol/L, and an APAP level of 6620 µmol/L (1000 mg/L).

Acetaminophen toxicity is the leading cause of acute liver failure in Canada.[1] When recognized within 8 hours of ingestion and treated with its antidote, *N*-acetylcysteine (NAC), morbidity and mortality are rare.[2] In an effort to promote appropriate risk assessment and avoid overtreatment, we aim to clarify some misconceptions with respect to the identification and treatment of APAP toxicity.

Pathophysiology and mechanisms

Acetaminophen is well absorbed through the gut, with peak serum levels being reached within 2 hours of ingestion; however, this time frame might be prolonged if APAP is taken with other medications that alter gut motility or if it is taken in a delayed-release preparation.[3]

Acetaminophen toxicity stems from saturation of its usual hepatic metabolism mechanisms: sulfation and glucuronidation. When these mechanisms are overrun, the cytochrome P450 system is funnelled more APAP to metabolize. It creates the hepatotoxic metabolite known as *N*-acetyl-p-benzoquinoneimine (NAPQI). Glutathione in the liver helps to reduce NAPQI to a safe renally excretable metabolite. In APAP toxicity, glutathione's reduction capabilities are overwhelmed, leaving NAPQI free in the liver.[3,4]

Presentation

Doses leading to APAP toxicity are described in **Box 1**.[5] Symptoms of toxicity are classically described in 4 phases:

- The first 24 hours are marked by nonspecific symptoms including nausea, vomiting, and malaise.
- Between 24 and 72 hours, hepatotoxicity with right upper-quadrant tenderness develops.
- Starting 3 to 4 days after ingestion, there is a progression to fulminant hepatic failure, including encephalopathy, coagulopathy, and multiorgan failure.
- The fourth phase starts on day 5 and is a turning point—patients either start improving and have complete recovery, or they progress to multiorgan failure and death.[3,6]

This changes in the context of massive ingestion (>500 mg/kg), in which patients present with altered mental status and marked lactic acidosis. These symptoms present within 12 hours of ingestion and are thought to be secondary to mitochondrial dysfunction.[2]

Treatment

All treatment decisions should start with a risk assessment including identifying what agents were ingested, the doses, the time since ingestion, clinical features, and patient factors such as weight and comorbidities. Furthermore, early consultation with your regional poison control centre should always be considered.

Box 1. Therapeutic and toxic doses of acetaminophen

Therapeutic dose
- 60 mg/kg daily, divided into 3 or 4 doses, no greater than 4 g/d

Single-ingestion hepatotoxic dose
- 200 mg/kg or 10 g (whichever is less)

Repeated supratherapeutic ingestion
- Over a 24-h period: 200 mg/kg or 10 g/d (whichever is less)
- Over a 48-h period: 150 mg/kg or 6 g/d (whichever is less)
- If risk factors are present (alcoholism, prolonged fasting, isoniazid use): 100 mg/kg daily or 4 g/d
- For children younger than 6 y, same as above, but if over a 72-h period or longer: 100 mg/kg daily

Data from Dart et al.[5]

While NAC is the antidote to the hepatotoxic effects of APAP metabolites, it does not affect APAP levels.[3] It can be given orally, but it is usually given intravenously in 3 staggered doses: a 150 mg/kg bolus, a 50 mg/kg dose over 4 hours, and a 100 mg/kg dose over 16 hours. The most common reaction is a mild anaphylactoid reaction that results in flushing, rash, and angioedema. It can be treated with antihistamines while continuing the infusion. The infusion should be stopped only if the reaction is deemed severe. It should be restarted once symptoms settle.[3]

Because NAC is so effective in cases in which the patient presents early, the role for activated charcoal is minimal. Nevertheless, it can decrease the need for NAC in fully oriented patients who present within 1 to 2 hours of ingestion. It is also appropriate for massive ingestions in which patients are already intubated. There is no role for ipecac in anyone, and charcoal is not recommended in children younger than 6 years of age regardless of the time of presentation.[7]

Treatment with NAC is initiated based on the Rumack-Matthew nomogram, which delineates treatment thresholds based on APAP levels between 4 and 24 hours after ingestion. It uses 1000 µmol/L (150 mg/L) as the initial "treatment line" at 4 hours.[8]

If the patient presents within 8 hours of ingestion, there are no suspected co-ingestions, and there is no indication of massive overdose, an APAP level measured between 4 and 8 hours after ingestion is all that is needed. Liver function tests do not help risk assessment or prognostication any further. Patients who present within this window and have APAP levels above the threshold can be treated without further testing. In this setting, if NAC is started within this time frame there is universal survival.[7] If levels are not available within the 8 hours, it is prudent to start NAC, as it can always be stopped.

Patients presenting between 8 and 24 hours after ingestion should be immediately started on NAC while awaiting results of APAP measurement. With this delay in treatment, measurement of alanine aminotransferase (ALT) is also recommended. Measurement of APAP and ALT levels should be repeated at the end of NAC treatment. If the APAP level is decreasing and the ALT level is within the normal range, no further treatment is required. If not, continue the NAC and obtain creatinine, glucose, arterial blood gas, and coagulation studies, including international normalized ratio, for hepatic transplant risk stratification.[7]

The nomogram is no longer applicable for patients presenting more than 24 hours after ingestion. Treatment with NAC should be started and APAP, ALT, creatinine, arterial blood gas, glucose, and creatinine levels and international normalized ratio should be measured. If laboratory findings are normal, no further treatment is required; if ALT levels are abnormal, NAC is continued for the full protocol.[7]

With repeated supratherapeutic ingestion, patients with APAP levels below 66 µmol/L (10 mg/L) and ALT or aspartate aminotransferase levels below 0.83 µkat/L (50 U/L) require no further workup or treatment. In all other patients, NAC should be started and the extended workup described above should be conducted for risk stratification. After 8 hours of NAC treatment, measurement of the ALT level should be repeated; if it is stagnant or decreasing, NAC can be discontinued. If it is rising, NAC should be continued and the patient should be assessed for possible admission to intensive care or for appropriateness for hepatic transplant.[7,9]

Appropriateness for hepatic transplant is traditionally based on the King's College Criteria; however, these criteria have been criticized for lacking sensitivity and for missing patients who might benefit from liver transplant. The APACHE II (Acute Physiology and Chronic Health Evaluation II) score has been suggested as an alternative, but it has yet to be evaluated in this context.[10]

While it has not been well studied, hemodialysis has been recommended as the treatment of choice for massive ingestions in which NAC alone might not be enough. An APAP level greater than 6620 µmol/L (1000 mg/L) without symptoms, or signs of mitochondrial dysfunction with an APAP level greater than 4630 µmol/L (700 mg/L) without NAC or greater than 5960 µmol/L (900 mg/L) with NAC are the current indications for this strategy.[2]

Pearls

- If ingestion involves numerous doses within an 8-hour period, total the dose and base the APAP level on the nomogram for the earliest dose taken.
- If capsules are extended release and the dose is 150 mg/kg or more, start NAC and then discontinue it if APAP levels end up being below the 4- and 8-hour thresholds.

Case resolutions

Case 1. The patient is given a 21-hour treatment with NAC, is seen by a psychiatrist, and is discharged home safely with outpatient mental health follow-up.

Case 2. The patient is thought to be experiencing a massive overdose of APAP. Owing to his level of consciousness, he is intubated. Once his airway is secure, he is given activated charcoal and NAC is started immediately. His history, medication record, physical examination and electrocardiogram findings, and bloodwork results are reviewed for other potential causes of his altered mental status. His case is reviewed with the regional toxicologist who recommends a trial

of dialysis. Despite aggressive resuscitation efforts, he does not survive his massive ingestion.

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Competing interests
None declared

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BOTTOM LINE

• When a patient presents with potential acetaminophen (APAP) toxicity, always perform a risk assessment including identifying what agents were ingested, the doses, the time since ingestion, clinical features, and patient factors such as weight and comorbidities.

• If the APAP was ingested within the past 8 hours and there were no co-ingestions, only the initial APAP level is needed to decide whether to initiate treatment with *N*-acetylcysteine (NAC). When the time of ingestion is unclear, or was longer than 8 hours ago, additional workup is required. If it has been longer than 24 hours since ingestion, or if staggered doses were taken over more than 8 hours, the Rumack-Matthew nomogram cannot be used to determine the treatment threshold; treatment must be based on APAP and alanine aminotransferase levels.

• If NAC is started before initial APAP levels are available, it is safe to stop it if results of initial testing subsequently indicate no need for treatment.

• Massive ingestion (> 500 mg/kg) of APAP presents early with altered mental status and lactic acidosis before liver injury; along with NAC treatment, these patients might require dialysis.

POINTS SAILLANTS

• Lorsqu'un patient se présente avec une intoxication potentielle à l'acétaminophène, on doit toujours procéder à une évaluation des risques , y compris la détermination des substances ingérées, des doses, du temps écoulé depuis l'ingestion, des paramètres cliniques et des facteurs inhérents au patient tels que son poids et ses comorbidités.

• Si l'acétaminophène a été ingéré au cours des 8 dernières heures et qu'il n'y a eu aucune autre ingestion simultanée, seul le niveau d'acétaminophène initial est nécessaire pour déterminer si un traitement à la *N*-acétylcystéine(NAC) est requis. Lorsque le moment de l'ingestion est imprécis ou s'est produit plus de 8 heures avant l'intervention, une investigation supplémentaire est nécessaire. S'il s'est écoulé plus de 24 heures depuis l'ingestion ou si des doses ont été prises progressivement dans un intervalle de plus de 8 heures, le nomogramme de Rumack-Matthew ne peut pas être utilisé pour déterminer le seuil thérapeutique; le traitement doit être basé sur les niveaux d'acétaminophène et d'alanine aminotransférase.

• Si le traitement à la NAC a débuté avant que les niveaux d'acétaminophène aient été déterminés, il est sécuritaire de cesser le traitement si les tests initiaux indiquent subséquemment qu'un traitement n'était pas nécessaire.

• Les patients qui font une ingestion massive (> 500 mg/kg) d'acétaminophène présentent rapidement une altération de l'état mental et une acidose lactique avant la survenance d'une lésion hépatique; ils peuvent nécessiter une dialyse en plus d'un traitement à la NAC.