Acetaminophen

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Introduction

Acetaminophen is a para aminophenol derivative that has similar analgesic and antipyretic properties to aspirin. Its mechanism of action is not fully understood; its analgesic effects are likely attributed to both inhibition of prostaglandin synthesis in the central nervous system as well as peripheral blockade of pain impulses that increase the pain threshold. Antipyretic effects occur as a result of heat-regulating center inhibition in the hypothalamus. Acetaminophen acts centrally and crosses the blood-brain barrier more than nonsteroidal anti-inflammatories (NSAIDs). Compared to NSAIDs, acetaminophen is not optimal for reducing inflammation due to its lack of prostaglandin synthase inhibition in the periphery. However, preferable to NSAIDs, acetaminophen causes minimal gastric mucosa irritation and platelet inhibition, less drug-interactions, and has a lower risk of nephrotoxicity [1].

Pain-Related Indications

Acetaminophen is available in hundreds of over-the-counter (OTC) products –making it one of the most commonly used non-opioid agents for pain [2]. Over-the-counter acetaminophen accounts for 80% of the acetaminophen drug market [2]. The oral and rectal acetaminophen formulations are indicated for temporary relief of minor aches and pains caused by headache, toothache, muscle and back ache, minor arthritis pain, the common cold, and menstrual cramps, as well as temporary fever reduction [3]. Oral acetaminophen monotherapy relieves mild non-inflammatory pain. The intravenous (IV) formulation is indicated for the treatment of mild to moderate pain in adults and children 2 years or older; however, given its unjustifiably higher cost than the oral and rectal formulations, its place in therapy has been limited [4]. All of the formulations are effective at reducing opioid requirements when used in combination (e.g. hydrocodone-acetaminophen 5/325 [Norco®]). Adding acetaminophen to an opioid is not only advantageous due to its different mechanism of action against pain, but it also has no potential for abuse, dependence, or addiction [1, 2].

Pharmacokinetics

Oral acetaminophen's onset of action is less than 1 h and it achieves peak concentrations within 2 h of administration [1, 3]. The IV onset of action is 5–10 min, reaching its peak effect within 1 h [4]. The oral and IV formulations have almost complete bioavailability while the rectal formulation has 30–70% absolute bioavailability, resulting in less analgesic effects at equivalent doses [3, 4].

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The half-life ranges from 2 to 4 h, and is prolonged in severe renal insufficiency and toxic doses. Hepatic metabolism of acetaminophen mainly occurs as sulfate and glucuronide conjugation; about 5–9% undergoes oxidation by CYP2E1 (with minor contributions from CYP1A2, CYP2A6, CYP2E1, CYP3A4) in the liver to a highly reactive intermediate, *N*-acetyl-*p*-benzoquinone imine (NAPQI). Glutathione inactivates NAPQI in the liver, and when NAPQI concentrations exceed glutathione stores at toxic doses, liver damage can occur [5].

Dosing

Usual oral acetaminophen doses range from 650 to 1300 milligrams (mg) every 4–6 h in adults [3]. An oral acetaminophen dose of 650 mg is more effective than 325 mg; however, a ceiling effect is seen at doses above 1000 mg [1]. Acetaminophen is U.S. Food & Drug Administration (FDA) approved for children two and older, although it is often used off-label in younger children. Pediatric oral dosing is 10–15 mg/kilogram (kg) every 4–6 h as needed, not to exceed 5 doses in 24 h. Many dosing charts include recommendations both by weight and by age; if possible, dosing should be calculated by weight rather than by age. For infants, children, and adolescents, oral doses should be limited to 75 mg/kg. The daily dose cap for children 6–11 years old is 1625 mg per day [3]. Unless otherwise indicated by a medical professional, patients should be counseled to limit acetaminophen doses from all sources, including over-the-counter combination products and prescription products, to less than 4000 mg per day or the product-specific indicated maximum dose.

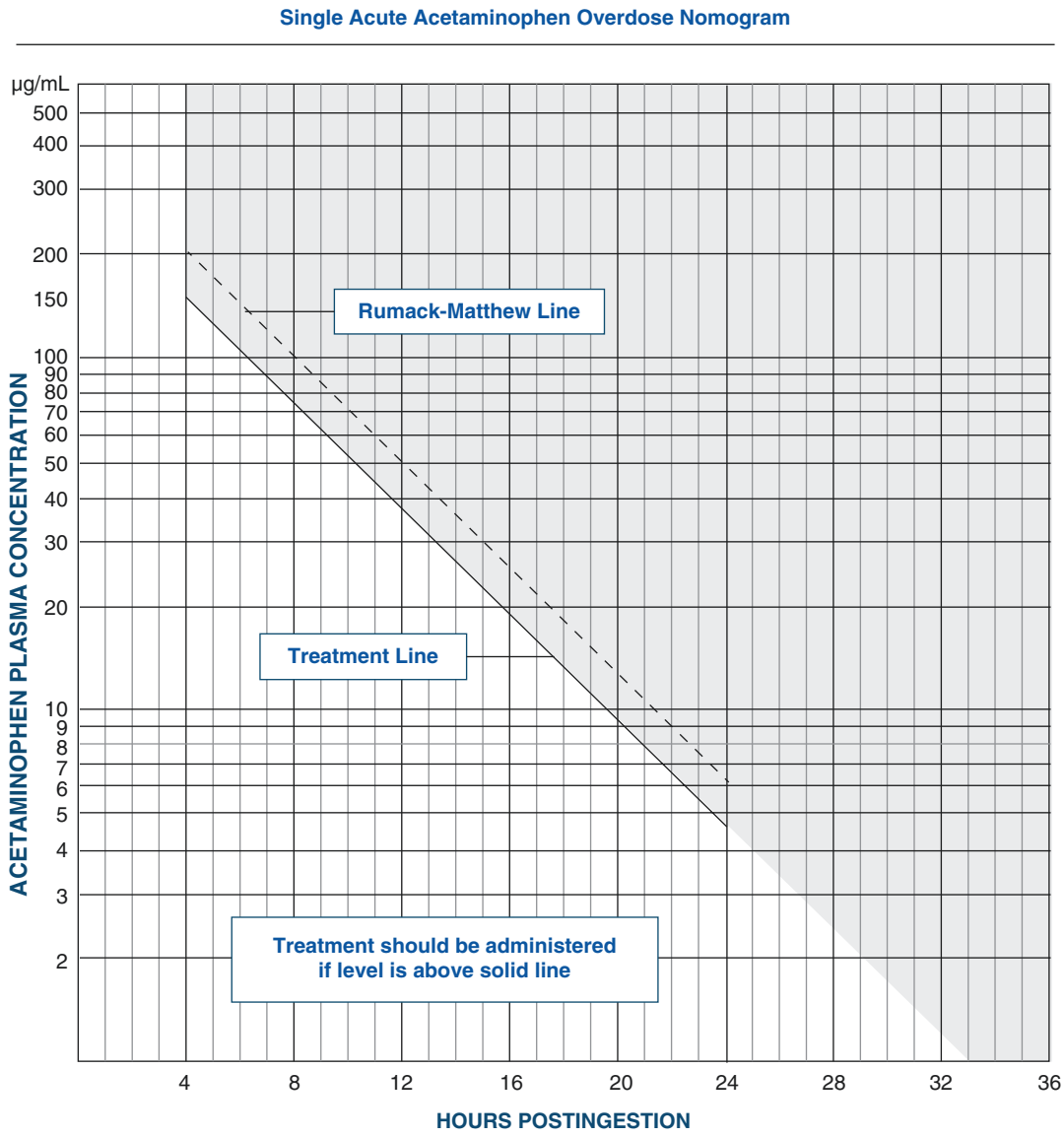
No dose adjustments are required when converting from the oral to the rectal or IV formulations, despite rectal bioavailability being approximately half of the other formulations. For adults and children older than 12 years, rectal dosing is 650 mg every 4–6 h (maximum daily dose 3900 mg) [1]. For infants and children younger than 12 years, rectal dosing is 10–20 mg/kg/dose every 4–6 h, with a maximum daily dose of 75 mg/kg/day. Intravenous dosing in adults greater than 50 kg is similar to oral dosing: 650–1000 mg every 4–6 h (maximum daily dose 4000 mg). For adults less than 50 kg and for children 2–12 years old, dosing is weight based: 15 mg/kg every 6 h with a maximum daily dose of 75 mg/kg/day or 3750 mg [4].

Drug Interactions

Acetaminophen is often preferred over NSAIDs given its minimal drug interactions [1]. However, a notable, yet overlooked, drug-interaction is its antithrombotic effects with warfarin. This effect becomes clinically relevant at acetaminophen doses greater than 1.3–2 grams on two or more consecutive days, which may result in an international normalized ratio (INR) increase as high as 40%; therefore, bleed risk and INR should be monitoring closely if patients significantly change their acetaminophen intake and should be counseled on limiting consumption [4]. Chronic alcohol consumption modifies CYP2E1 activity and depletes glutathione, permitting lower amounts of acetaminophen ingestion to cause liver toxicity. Drugs that induce CYP2E1, such as isoniazid, also increase NAPQI production [4, 5]. Anticonvulsants that induce CYP3A4 (e.g. carbamazepine, phenytoin, phenobarbital) increase metabolism of acetaminophen by up to 40%, leading to increased formation of NAPQI that may exceed glutathione stores [2, 5].

Adverse Effects

The most concerning adverse effect of acetaminophen is hepatotoxicity [1–5]. Potentially fatal liver toxicity can occur when therapeutic doses are exceeded, Fig. 53.1. Once NAPQI formation has depleted glutathione stores by 70%, NAPQI binds to hepatocellular proteins resulting in injury and potentially liver failure [5]. Some patients have genetically low glutathione levels that can predetermine them for hepatotoxicity, and for this reason, daily acetaminophen doses should not surpass 4 grams in any patient [1, 5]. Certain disease states or conditions have glutathione depletion at baseline, such as malnutrition, chronic alcohol abuse, or



Nomogram: acetaminophen plasma concentration vs time after acetaminophen ingestion (adapted with permission from Rumack and Matthew. *Pediatrics*. 1975;55:871-876). The nomogram has been developed to estimate the probability of whether a plasma acetaminophen concentration in relation to the interval postingestion will result in hepatotoxicity and, therefore, whether acetylcysteine therapy should be administered.

CAUTIONS FOR USE OF THIS CHART:

1. Time coordinates refer to time postingestion.
2. Graph relates only to plasma concentrations following a single, acute overdose ingestion.
3. The Treatment Line is plotted 25% below the Rumack-Matthew Line to allow for potential errors in plasma acetaminophen assays and estimated time from ingestion of an overdose (Rumack et al. *Arch intern Med.* 1981;141(suppl):380-385).

Fig. 53.1 Rumack-Matthew Nomogram. "Rumack-Matthew nomogram with treatment (study) line" adapted by Merlin Cyrstal in July 2011 (posted to Wikipedia) is licensed under Creative Commons Attribution-Share Alike 3.0 Unported

impaired liver function. Additionally, age-related decreased metabolism and hepatic flow prolong the clearance of acetaminophen. In these clinical scenarios, hepatotoxicity may occur at repeat doses or slight overdoses, and these patients should have daily doses limited to 2–3 grams [1, 2, 5].

If medical attention is reached within 4 h of acute ingestion, a gastric lavage can decrease pill

load and activated charcoal can decrease acetaminophen absorption by 50–90%. The antidote of choice for acetaminophen poisoning is N-acetylcysteine (NAC), which inactivates NAPQI and restores hepatic glutathione; however, it does not reverse liver damage that has already occurred. NAC is most effective within 8–10 h of ingestion, and has shown some benefit up to 24 h [5]. However, because the symptoms of liver damage may not be noticed for days after ingestion, many patients are not treated within the benefit time window [2].

If the acetaminophen ingestion time is known, the Rumack-Matthew nomogram can be used between 4 and 24 h post-ingestion to determine if NAC should be administered (Fig. 53.1). A level above 150 microgram (mcg)/milliliter (mL) at 4 h, 4.7 mcg/mL at 24 h, or any number within this linear relationship is indicated for treatment with NAC. If the ingestion time is unknown, then NAC should be started if the acetaminophen level is greater than 10 mcg/mL or the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels are elevated beyond the reference range. The risk of hepatotoxicity is less than 5% if NAC is administered to eligible patients within 8 h, but delays beyond 10 h are associated with increased risk of irreversible liver damage [5].

The oral and IV formulations of NAC are equally effective. The standard oral course of NAC is a 140 mg/kg loading dose followed by 70 mg/kg orally every 4 h for a total of 18 doses over 72 h. The IV formulation is administered over 21 h with the following dosing: loading dose of 150 mg/kg IV over 60 min followed by 50 mg/kg over the next 4 h (rate of 12.5 mg/kg/h) and then 100 mg/kg over the next 16 h (rate of 6.25 mg/kg/h). All doses should be capped at 100 kg. NAC may be discontinued when the acetaminophen level is less than 10 mcg/mL and AST/ALT are improving or stable.

Oral NAC should be given with anti-emetics due to its gastrointestinal side effects. Its unpleasant odor can be masked by administering the solution cold and through a straw. If a patient vomits the dose within 1 h of administration, the dose should be re-administered [5]. The IV formulation carries an anaphylaxis risk which is highest during the loading dose [4, 5]. For this reason, the loading dose is recommended to be given over 60 min rather than 15 min. The anaphylaxis risk is greater in patients with asthma or history of bronchospasm, and the oral formulation is preferred in this patient population. If the IV formulation is warranted, these patients should be monitored closely, pre-medicated with antihistamines, and infusions should be interrupted if needed [5].

High Yield Points

- Compared to NSAIDs, acetaminophen is often preferred given its minimal effects on platelet inhibition, minimal gastrointestinal effects, and lower risk of nephrotoxicity.
- Daily acetaminophen doses should be limited to 4000 mg in most patients; elderly patients and patients with certain glutathione-deficient conditions such as malnutrition, chronic alcohol abuse, or impaired liver function should limit their daily intake to 2000–3000 mg.
- *N*-acetyl-*p*-benzoquinone imine (NAPQI) is a toxic minor metabolite that is inactivated by glutathione in the liver; when toxic acetaminophen doses result in excess NAPQI formation that depletes glutathione stores, liver damage can occur.
- Liver damage from acetaminophen overdoses can be irreversible if not treated quickly; the use of oral and intravenous N-acetylcysteine (NAC) within 8–24 h can reduce the risk of hepatotoxicity.

Questions

NC is a 26 year old otherwise healthy female who presented to the emergency department (ED) with presumed acetaminophen overdose. Her husband called 9-1-1 upon finding her

unresponsive after laying down for a nap. A bottle with acetaminophen 500 mg was found next to her, but the ingestion amount and time was unknown. Upon arrival to the ED, she was extremely somnolent but arousable to sternal rub and occasionally to voice. She had no outward evidence of trauma. She was appropriately ventilating and protecting her airway. There was no electrocardiogram (EKG) or laboratory evidence of additional ingestions. Subsequent labs obtained revealed an acetaminophen level of 259 mcg/mL, with normal liver function tests (LFTs).

1. What initial treatment would you consider?
   A. Since ingestion time is unknown, it is not appropriate to give NAC
   B. Give oral NAC: 140 mg/kg loading dose, then 70 mg/kg orally every 4 h for 18 total doses
   C. Give IV NAC: 150 mg/kg loading dose over 1 h, then 50 mg/kg over 4 h, then 100 mg/kg in over 16 h
   D. Since LFTs are not elevated, not necessary to give NAC because no liver damage has occurred
   Answer: C

After completion of her first dose of IV NAC, NC subsequently developed an urticarial rash, predominantly at the lateral neck, cheeks, chest, and abdomen. She became tachycardic and her temperature was noted to be 37.9 degrees Celsius. She responded well to IV diphenhydramine. Her acetaminophen level decreased to 163 mcg/mL after 3 h and LFTs remained within normal limits.

2. Of the options below, which is the most appropriate next course of action?
   A. Place a nasogastric tube and give oral NAC
   B. Give NAC infusion at faster rate to decrease acetaminophen level faster
   C. Give broad spectrum antibiotics since her vital signs are decompensating
   D. NAC can be stopped at this time since her acetaminophen level decreased significantly and LFTs were not elevated
   Answer: A
3. What counseling point about acetaminophen is correct?
   A. Its use should be avoided in patients with a history of gastric ulcers
   B. It is often used for its anti-inflammatory properties
   C. It should be used cautiously due to its potential for abuse
   D. Patients should read all medication labels to ensure the daily acetaminophen limit does not exceed 2000–4000 mg
   Answer: D

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