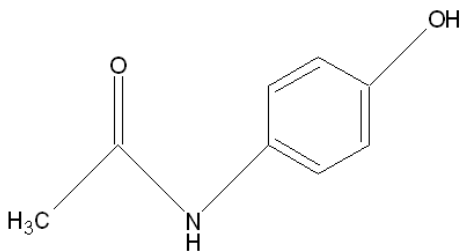


Acetaminophen for the elderly

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Acetaminophen is an analgesic and an antipyretic with a weak anti-inflammatory property. The chemical name is N-acetyl-*p*-aminophenol (APAP). The drug is known as paracetamol outside the USA. Acetaminophen is the active metabolite of phenacetin, which is a member of the aniline derivatives or also known as the coal tar analgesics. It is a white crystalline powder with a molecular weight of 151.16 and a pKa of 9.51 at 25°C.

CLINICAL PHARMACOLOGY



Acetaminophen's mechanism of action is not well understood. There is significant data to suggest a central mechanism of action. Because of its high lipid solubility and its weak plasma protein binding it can cross the blood brain barrier easily. Various theories have been put forward to explain the mechanism of action of acetaminophen. Acetaminophen diminishes the thalamic evoked potentials elicited by nociceptive electrical stimulation.

There maybe some peripheral effect of acetaminophen by reducing prostacyclin synthesis.

At the spinal level, acetaminophen may have a direct action on a COX-2 variant or a COX-3 type of isoenzyme and inhibit release prostaglandin E₂ release. It may act spinally to inhibit the nitric oxide generation which may impair the nociceptive potential of N-Methyl-D-Aspartate (NMDA) or NK-1 activation.

At the supraspinal level, it may inhibit the descending inhibitory pathways via indirect effects on serotonergic pathways. It may also affect the opioid systems predominantly by modulating dynorphin release and κ receptor function.

ADVERSE EFFECTS

Acetaminophen is considered one of the safer analgesics. It should be used with caution in patients with preexisting hepatic damage and history of chronic alcohol abuse (more than three alcoholic drinks per day). Acetaminophen is metabolized by the glutathione pathway. These patients have a potential for glutathione storage depletion. However, there is no absolute contraindication to use a short course of acetaminophen under medical supervision in patients with mild preexisting liver disease.

Some of the rare adverse effects of acetaminophen are: Agranulocytosis, anemia, dermatitis, allergic, thrombocytopenia, hepatitis, sterile pyuria and renal failure (with prolonged use of high doses in patients with preexisting renal impairment). Mild bronchospasm has been reported in less than 5% of patients who aspirin sensitive asthma.

Acetaminophen has very few drug interactions. Caution is advised when used with the following drugs:

- Zidovudine - this drug is used in patients in patients with human immunodeficiency virus infection. As reported by Richman et al concurrent administration of acetaminophen and zidovudine may lead to increased incidence of bone marrow suppression.

- Hepatotoxic and hepatic enzyme inducer drugs - there is an increased risk of hepatotoxicity with prolonged use of high doses of acetaminophen in patients taking these drugs.
- Coumadin - Acetaminophen used in doses greater than 2 grams per day chronically may increase the anticoagulant effect. Prothrombin time is not affected by short term use of acetaminophen.
- Salicylates and aspirin - Controversy surrounds the issue of increased risk of analgesic nephropathy when taken chronically in a high dose in a preparation with combined analgesics. Some would consider high dose of acetaminophen as 1.35 grams per day or a total ingestion of 1 kilogram per year for 3 years (when using a combined analgesic preparation).
- Difunisal - when taken concurrently with acetaminophen, the plasma concentration of acetaminophen is increased by 50%

Although acute nephrotoxicity has been reported after massive overdose of acetaminophen, there is very little clinical evidence to suggest that habitual appropriate use of acetaminophen causes nephropathy. The National Kidney Foundation's position has been to recommend the use of acetaminophen in patients with renal failure and also the non-narcotic of choice for patients with preexisting kidney disease.

LABORATORY VALUES AFFECTED

Patients taking acetaminophen may have the following laboratory values altered:

- *Blood Glucose levels:* Acetaminophen may cause falsely lowered values when blood glucose is determined using the oxidase method but not when the glucose-6-phosphate dehydrogenase method is used.

- Pancreatic function: Acetaminophen taken prior to the bentiromide test will invalidate the results. It should be discontinued 3 days prior to the test.
- 5-Hydroxyindoleacetic acid (5-HIAA) determination: Acetaminophen may cause false positive results if the reagent nitrosonaphthol is used.

OVERDOSAGE

Acetaminophen toxicity may result from a single dose of 150 mg to 250 mg/Kg or greater than 7.5 grams to 10 grams within 8 hours.

A minor portion of acetaminophen metabolism is by the cytochrome P-450 dependent N-hydroxylation to form N-acetyl-*p*-benzoquinone imine (NAPQI). This metabolite without adequate levels of reduced glutathione available directly arylates and oxidizes cellular proteins, leading to inhibition of enzyme activities. High doses of acetaminophen overwhelm the glucuronidation and sulfation pathways and deplete the glutathione pool.

Management of acetaminophen toxicity consists of vigorous supportive therapy and gastric lavage. The drug of choice is N-acetylcysteine. It is a glutathione precursor that replenishes the glutathione store in the liver. The earliest manifestation of acetaminophen hepatotoxicity is malaise, nausea, vomiting and diaphoresis. It takes 48 hours to 72 hours for hepatic toxicity to develop. Liver damage from acetaminophen toxicity results in centrilobular hepatic necrosis.

N-acetylcysteine is available for oral use in the USA, whereas it is available in the intravenous form in Europe. It is ideally given within 8 hours or less of ingestion but should be given if less than 36 hours have elapsed since ingestion of acetaminophen. Treatment should be started immediately without waiting for acetaminophen levels, if the history is suggestive of acetaminophen toxicity. When administered orally it is diluted to a 5% solution by mixing in water and should be given within 1 hour of preparing it.

The loading dose of oral N-acetylcysteine is 140 mg/Kg followed by 70 mg/Kg every 4 hours for 17 doses. Treatment is stopped if plasma acetaminophen levels indicate that the risk of hepatotoxicity is low.

Adverse effects of N-acetylcysteine are nausea, vomiting, diarrhea, skin rash, urticaria and anaphylactoid reaction. Further information on acetaminophen overdose can be obtained from:

Rocky Mountain Poison Center, Denver, CO
Telephone number: 800-525-6115

DOSAGE AND ADMINISTRATION

The oral doses of acetaminophen are 325 mg to 1000 mg. Doses can be given every 4 hours to 6 hours. The maximum dose should not exceed 4000 mg per day.

The rectal dose is 650 mg. Rectal administration is suboptimal because its absorption may be affected by stool present in the rectum.

The extended release acetaminophen formulation Tylenol Arthritis Extended Relief Caplets contains 650mg of acetaminophen in a unique, patented bilayer. The first layer dissolves quickly (roughly about 325 mg), whereas the second layer is time released to provide 8 hours of relief.

Acetaminophen is used mainly as an analgesic and antipyretic. It is a good alternative to patients in whom aspirin is contraindicated. There is no dose alteration when taken by the elderly. The American College of Rheumatology in their updated guidelines has recommended acetaminophen as the first line pharmacologic therapy because of its cost, efficacy and safety profile.

Acetaminophen in the elderly has proven to have broad tolerability, reasonable efficacy and a low side effect profile. It has very few drug interactions, an important consideration in the elderly who are usually on several medications. The use of acetaminophen in the elderly is considered safe and without significant side effects when used appropriately.

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