Therapeutic Reviews

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Acetaminophen (Paracetamol) AHFS 28:08:92

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There are increasing reports of unintentional overdose of acetaminophen (paracetamol, rINN) resulting in hepatotoxicity. To reduce this risk, the dose of acetaminophen should never exceed the maximum recommended dose, be appropriate for the weight of the patient, and reduced when risk factors for hepatotoxicity exist, e.g., old age, poor nutritional status, fasting/anorexia, concurrent use of drugs that interact with acetaminophen metabolism, and chronic alcohol use.

For international educational and comparative purposes, this article also refers to formulations not available in the USA, e.g., propacetamol.

Class: Non-opioid analgesic.

Indications: ***PO*** mild–moderate pain, migraine and tension headache, fever.
IV *short-term treatment* of mild–moderate pain, moderate–severe pain (in combination with an opioid) and fever when PO or PR routes not possible.

Contraindications: ***IV*** severe hepatic impairment or severe active liver disease.

Pharmacology

Acetaminophen is a synthetic non-opioid analgesic and antipyretic.[1,2] It acts mainly in the CNS, where it has several effects. It is a weak inhibitor of cyclo-oxygenase (COX)-2, an effect that lasts a short time (≤2 h) after a dose,[3,4] but can also be anti-inflammatory through inhibition of peroxidase regeneration. The latter action, which prevents the oxidation of inactive COX to active COX, can be significant when peroxidase levels are low, e.g., in intact cells in the CNS, but not when peroxidase levels are

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much higher, e.g., with tissue damage and/or inflammation in the periphery.[5] In addition, acetaminophen has been shown to:

- interact with L-arginine-nitric oxide, opioid and cannabinoid systems[6,7]
- activate descending serotoninergic inhibitory pain pathways.[8,9]

It is possible that the analgesic effect of acetaminophen is dependent on synergy between some or all these mechanisms.[10] Evidence of synergy between acetaminophen and NSAIDs suggests differing analgesic mechanisms.[11,12]

Acetaminophen is widely used for acute musculoskeletal pains and acute headache. When used in combination with an opioid to treat *postoperative pain*, IV acetaminophen has an "opioid-sparing" effect and improves overall analgesia.[13] Postoperative nausea and vomiting also is reduced, but only when the acetaminophen is administered before, during or immediately after surgery. The improvement correlated with the degree of pain relief (but not opioid use), suggesting a possible indirect or direct antiemetic effect of acetaminophen.[14]

Evidence of the efficacy of acetaminophen in combination with an opioid in the treatment of *cancer pain* is mixed. However, the RCTs that suggested no benefit[15,16] were underpowered,[17] and another RCT showed a small but clinically important additive effect in about one-third of patients despite the fact that half were already taking an NSAID or a corticosteroid.[18] Given that an acetaminophen regimen of 650 mg–1 g q.i.d. may pose a considerable pill burden to some patients with cancer, a pragmatic solution might be:

- to limit the long-term use of acetaminophen to patients in whom definite benefit is seen within 2 days of starting it
- if already taking acetaminophen with definite past benefit and increasing pain necessitates the *addition* of an opioid, the ongoing need for acetaminophen should be determined by stopping it after 3–4 days of satisfactory pain relief with both drugs; the acetaminophen is restarted only if the pain returns.

Single doses of IV acetaminophen provide dose-dependent analgesia in doses up to 2 g.[19] Increased peak plasma concentrations lead to earlier and higher concentrations of acetaminophen in the CSF, which in turn lead to an earlier onset of action, a longer duration of action, and a greater overall analgesic effect.[20] In patients undergoing molar dental extraction, compared with 1 g, 2 g of acetaminophen gave 50% more relief for 50% more time (5 h vs. 3.2 h).[21] Thus, there may be a place for an initial loading dose when prescribing acetaminophen.

Parenteral propacetamol, an inactive pro-drug of acetaminophen, is available in some countries (not USA or UK), and is used particularly for orthopedic postoperative pain management.[22] Propacetamol 2 g yields acetaminophen 1 g.[23] Because of a significant risk of sensitization, the manufacturer's protocol must be adhered to.

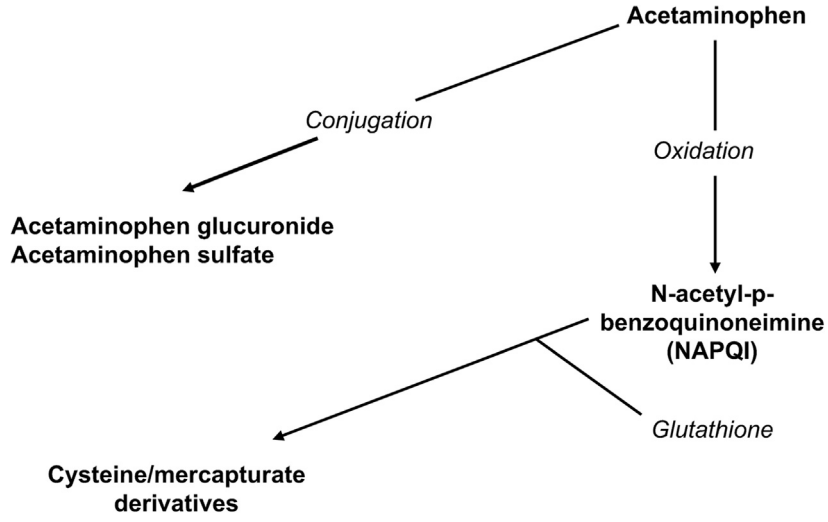

Fig. 1. Metabolism of acetaminophen.

Only 2–5% of a therapeutic dose of acetaminophen is excreted unchanged in the urine; the remainder is metabolized mainly by the liver. At therapeutic doses, >80% of acetaminophen is metabolized to glucuronide and sulfate conjugates. About 5–10% is converted by hepatic CYP450 enzymes (mainly CYP2E1 and CYP3A4) to a highly reactive metabolite, N-acetyl-p-benzoquinoneimine (NAPQI; Fig. 1), which is hepatotoxic. With normal therapeutic doses (i.e., ≤1 g q.i.d.), NAPQI is generally inactivated sufficiently rapidly so as not to cause liver damage.

In addition to dose, there are other determinants of exposure to NAPQI. For example, metabolism of acetaminophen is gender-dependent (women eliminate the drug more slowly[24]) and age-dependent (increased risk of hepatotoxicity in the elderly[25]). An 80-year-old may be exposed to 1.5 times the NAPQI concentration as a 20-year-old when given the same dose of IV acetaminophen.[25] There are also genetic variations in acetaminophen metabolism.[26] Those with CYP2D6 gene duplication (ultra-rapid metabolizers), have a greater susceptibility to hepatotoxicity because of an increased production of NAPQI.[27] Specific drugs also may inhibit glucuronidation or induce the oxidation of acetaminophen to NAPQI (see Box A).

Unintentional and deliberate overdose and NAPQI-induced hepatotoxicity

An overdose of acetaminophen overwhelms its normal metabolism, shifting more acetaminophen into the NAPQI pathway. NAPQI is normally inactivated by conjugation with glutathione but, in overdose, the body's glutathione store becomes exhausted and the accumulation of NAPQI leads to liver parenchymal cell death.

Although overdose is traditionally associated with ingestion of a large single dose of acetaminophen as a deliberate suicide attempt, reports of unintentional overdose from its analgesic use are increasing.[28,29] A man aged 43 with Crohn's colitis and weighing 30 kg died of hepatic failure after taking 4 g/24 h for only 4 days.[30] Indeed, there are numerous reports of hepatotoxicity associated with chronic use of 5–7.5 g/24 h.[31] Thus, the dose of acetaminophen must always be appropriate for the weight and circumstances of the patient, and the maximum recommended dose not exceeded.

Repeated suprathreshold ingestion over a time period of >8 h ("staggered overdose") produces a higher risk of liver and multi-organ failure, and a lower unassisted survival rate, than single time point overdose. About two-thirds of staggered overdoses relate to medicinal use rather than attempted suicide.[32] The likelihood of an unintentional/staggered overdose is greater in patients with one or more risk factors for acetaminophen hepatotoxicity (Box A).

Box A Risk factors for acetaminophen hepatotoxicity[33,34]

Old age
Poor nutritional status
Fasting/anorexia
} lower glutathione stores

Concurrent use of glucuronidation inhibitors and/or CYP2E1-inducing drugs, e.g., phenobarbital, primidone, probably isoniazid, and possibly St. John's wort
Chronic alcohol use

A single time point overdose of acetaminophen below 125 mg/kg (7.5 g or 15 tablets in a 60 kg person) is unlikely to result in liver damage. At twice this dose, the probability of liver damage is around 50%, but the individual may remain well. A dose of 500 mg/kg (30 g or 60 tablets in a 60 kg person) is almost certain to produce life-threatening liver damage. Acetaminophen overdose also can lead to acute renal failure, although this is often reversible without the need for dialysis.[35]

Overdose, whether deliberate or unintentional, can be treated with a glutathione precursor, e.g., IVI acetylcysteine (Box B)[36,37] or PO methionine.[38,39] If given within 15 h of the overdose, acetylcysteine prevents NAPQI from reacting with liver cell proteins. Further, because it has a protective effect against apoptosis (programmed cell death), acetylcysteine can help to a lesser extent if given for ≤3 days after the overdose.

Box B Use of acetylcysteine

A total dose of 300 mg/kg is given by three separate IVI over a total of 21 h. The recommended volume of diluent varies according to the weight of the patient. For those weighing 41–100 kg:
- *loading dose:* 150 mg/kg diluted in 200 mL, given over 1 h
- *second dose:* 50 mg/kg diluted in 500 mL, given over 4 h
- *third dose:* 100 mg/kg diluted in 1000 mL, given over 16 h.

For those weighing 21–40 kg, use half the volume of diluent. For patients whose weight falls outside of these ranges, see Prescribing Information.
5% dextrose in water, 0.45% sodium chloride or WFI can be used as diluent.

Acute alcohol intake does *not* increase the risk of hepatotoxicity. Indeed, because alcohol and acetaminophen compete for the same oxidative enzymes, acute alcohol consumption at the time of an acetaminophen overdose may be protective. However, because alcohol consumption induces the production of the relevant enzymes, if *chronic* alcohol use suddenly stops, acetaminophen will be metabolized more rapidly, and could lead to hepatotoxicity.[40] In any case, some alcoholics are more susceptible to acetaminophen toxicity, possibly because of their poor nutritional status.[41]

To reduce the chance of unintentional overdose, the United States Food and Drug Administration has recommended that:[42,43]
- the amount of acetaminophen in a prescription tablet, capsule, or other dosage unit is limited to a maximum of 325 mg by the end of 2013
- the maximum single dose is lowered to 650 mg
- a boxed warning is added highlighting the potential for severe liver injury
- patients should not exceed a total daily dose of 4 g.

Implementation is in process and "extra strength" products containing 500 mg/dose unit remain available. However, over-the-counter products now recommend a maximum dose of 2.6–3 g/24 h, which patients should not exceed unless directed by a doctor.
Bioavailability 60% after 500 mg PO, 90% after 1 g PO; PR is about two-thirds of PO, but is higher with two 500 mg suppositories than with one 1 g suppository.
Onset of action 15–30 min PO; 5–10 min IV (pain relief), 30 min IV (antipyretic effect).
Time to peak plasma concentration widely variable PO, e.g., 20 min in fasting state but 1–2 h if delayed gastric emptying;[44] 15 min IVI (this is synchronous with the end of a 15 min infusion).
Plasma half-life 1.25–3 h PO;[44] 2–3 h IV.
Duration of action 4–6 h PO and IV.

Cautions
Severe hepatic impairment or severe active liver disease (IV use contraindicated in this setting), particularly if associated with alcohol dependence and malnutrition. In severe renal impairment (creatinine clearance <30 mL/min), the dose interval should ≥6 h.

Most dispersible or effervescent acetaminophen-containing tablets (alone or combined with an opioid) have a Na^+ content of ≥14 mmol/tablet. Thus, a dose of 8 tablets/24 h would exceed the recommended maximum daily dietary Na^+ intake of 100 mmol (6 g of sodium chloride). Dispersible or effervescent formulations should thus be avoided in patients with hypertension or renal impairment, particularly if already on a salt-restricted diet. In contrast, non-soluble formulations contain negligible Na^+.[45]

Acetaminophen can be taken by at least two-thirds of patients who are hypersensitive to aspirin or other NSAID.[46,47] In people with a history of aspirin/NSAID-induced asthma, give a test dose of 250 mg (half a tablet) and observe for 2–3 h. If no undesirable effects occur, acetaminophen can safely be used in standard doses.[48]

Drug Interactions

Concurrent use of glucuronidation inhibitors and/or CYP2E1-inducing drugs, e.g., phenobarbital, primidone, probably isoniazid, and possibly St. John's wort may increase the risk of acetaminophen toxicity (Box A).

Concurrent use of the $5HT_3$-receptor antagonists tropisetron and granisetron can completely block the analgesic effect of acetaminophen,[10] but ondansetron may be safe in this respect.[49]

Concurrent use with warfarin: a regular *daily* intake of acetaminophen ≥1300 mg for one week may increase the INR to >6,[50,51] but a total *weekly* dose of acetaminophen of ≤2 g has no effect. The underlying mechanism is not clear, but may relate to interference with the hepatic synthesis of factors II, VII, IX and X. A recent post-mortem series found that concurrent acetaminophen increases the risk of a bleed with warfarin 2.7 times.[52]

Undesirable Effects

Very common (>10%): dyspepsia, elevated liver enzymes (Box C).
Rare (<0.1%, >0.01%): PO cholestatic jaundice,[53,54] acute pancreatitis, thrombocytopenia, agranulocytosis, anaphylaxis.[55-57]
IV malaise, hypotension.

Box C Acetaminophen and elevated liver enzymes[58,59]

The plasma levels of various liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase, γ-glutamyl transferase) can increase with normal doses of acetaminophen.

For example, ALT increased >3 times the upper limit of normal in 40% of young healthy volunteers receiving 4 g/day, with the highest increase 14–16 times greater. The rise was evident after 72 h, and persisted for a median of one week after discontinuation.

These changes are probably unimportant in the absence of functional or synthetic liver impairment (e.g., indicated by an increase in plasma bilirubin or a reduction in clotting factors, respectively) and possibly improve with ongoing use, although this is poorly documented.

Awareness of this phenomenon may aid interpretation of abnormal LFTs, and help avoid the erroneous assumption that rapidly worsening LFTs must indicate rapidly worsening disease within the liver, e.g., from liver metastases.

Chronic acetaminophen use increases the risk of renal impairment 2.5 times; and the risk is related to dose and cumulative exposure over a lifetime.[60,61] The risk is higher in diabetics, and when renal impairment is associated with systemic vasculitis.

The use of acetaminophen in pregnancy and early childhood increases the risk of a child developing asthma.[62] However, there is no hard evidence that acetaminophen precipitates asthma in established asthmatics.[48,63]

Dose and Use

In palliative care, typical PO doses for adults generally range from 500 mg–1 g q.i.d.[18] However, in patients with risk factors for acetaminophen hepatotoxicity (Box A), it is safer to opt for a submaximal dose. Further, despite the lower PR bioavailability, in practice the rectal dose is generally the same as the PO dose.

IV

IV acetaminophen (1 g in 100 mL) is given by infusion over 15 min. There have been case reports of massive inadvertent iatrogenic IV overdose leading to hepatic failure, sometimes fatal, particularly in children.[64] The available IV solution contains *10 mg/mL*. When written up just as mg, it has occasionally

been misread and given as mL, with the result that the patient has received *10 times* the prescribed dose. To minimize the chance of this happening, a prescription for IV acetaminophen should be written in terms of *both* mg *and* mL, not just as mg.

IV acetaminophen can be used when administration PO or PR is not possible. The dose depends on body weight and the presence/absence of risk factors for acetaminophen hepatotoxicity:
- adults and children >50 kg, 1 g up to q4 h, maximum recommended dose 4 g/24 h
- adults and children >50 kg *plus any risk factors*, restrict maximum dose to 3 g/24 h
- adults and children 10–50 kg, 15 mg/kg up to q4 h, maximum recommended dose 60 mg/kg/24 h.[65]

Supply

Acetaminophen (generic)
Tablets 325 mg, 28 days @ 650 mg q.i.d. = $15.
Tablets 500 mg, 28 days @ 1 g q.i.d. = $15.
Caplets (capsule-shaped tablets) and ***Geltabs*** 500 mg are available OTC; many patients find these easier to swallow.
Oral suspension 160 mg/5 mL, 1 g/30 mL, 28 days @ 1 g q.i.d. = $168.

Tylenol® (McNeil)
Tablets 325 mg, 28 days @ 650 mg q.i.d. = $21.
Tablets (Caplets) 500 mg, 28 days @ 1 g q.i.d. = $22.
Oral suspension 160 mg/5 mL, 28 days @ 1 g q.i.d. = $178; cherry, grape or bubble gum flavor; available OTC.

Sustained-release
Tablets ER (Caplets) 650 mg, 28 days @ 650 mg q.i.d. = $19.

Tylenol® Arthritis Relief (McNeil)
Tablets ER (Caplets) 650 mg, 28 days @ 650 mg q.i.d. = $19.

Rectal Preparations
Suppositories 120 mg, 325 mg, 650 mg, 28 days @ 1 q.i.d. = $66, $74 and $79, respectively.

Ofimev® (Cadence)
Injection (for IV infusion) 10 mg/mL, 100 mL vial (1 g) = $15.

This is not a complete list; oral acetaminophen is also available in several combination products with weak opioids or oxycodone.

Abbreviations

CNS	Central nervous system
COX	Cyclo-oxygenase
CSF	Cerebrospinal fluid
CYP450	Cytochrome P450
INR	International normalized ratio
IV	Intravenous
IVI	Intravenous infusion
LFT	Liver function test
NAPQI	N-acetyl-p-benzoquinoneimine
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over the counter (i.e., can be obtained without a prescription)
PO	Per os, by mouth
PR	Per rectum
q4h	Every 4 hours
q.i.d.	quarta in die, four times daily
RCT	Randomized controlled trial
rINN	Recommended International Non-proprietary Name
WFI	Water for injection

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