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Paracetamol (Acetaminophen): Clinical Applications, Safety Profile and Toxicity

Sangram Vijay Bagal[1], Suraj Ratilal Gavade[2], Sarang Shankar Virkar[3], Nilesh Patole[4]
[1, 2, 3]*B. Pharm Final Year,* [4]*Guide, Pharmacology Department, Mandesh Institute of Pharmaceutical Science and Research Centre, Mhaswad*

Abstract: ***Paracetamol (acetaminophen; N-acetyl-p-aminophenol) is one of the most frequently consumed pain and fever medicines in the world. Sold without prescription in most countries and listed as an essential medicine by the WHO, it is the usual first choice for mild to moderate pain and for febrile illness across all age groups, including pregnancy. When taken within recommended limits it is much gentler on the stomach, kidneys and cardiovascular system than NSAIDs. Its weakness is a small gap between a safe dose and a liver-damaging one. Combined with easy access and its inclusion in a great many multi-ingredient products, this has made paracetamol a leading cause of drug-induced acute liver failure in numerous regions. This article reviews how the drug works and is handled by the body, what it is used for, its adverse effects, the biochemistry of its toxicity, the presentation of overdose, and present-day treatment centred on N-acetylcysteine (NAC).***
Keywords: paracetamol, acetaminophen, analgesic, antipyretic, hepatotoxicity, NAPQI, N-acetylcysteine, overdose.

I. INTRODUCTION

Paracetamol emerged from nineteenth-century chemistry, but its clinical story began in the late 1940s, when it was recognised as the active breakdown product of two older drugs, acetanilide and phenacetin. Those precursors had been linked to methaemoglobinaemia and kidney damage, whereas paracetamol itself avoided these problems. By the 1950s it was on the market, and it has remained a mainstay of pain relief ever since. Its appeal lies in low cost, good tolerability, a wide choice of dosage forms (tablets, liquids, suppositories, effervescent preparations and intravenous solution), and the absence of the platelet and gastric effects that limit NSAIDs and aspirin.This reputation for safety can be misleading. Overdose, whether deliberate or unintended, is a significant public-health burden and accounts for a large proportion of poisoning admissions and acute liver failure cases in the United Kingdom, the United States, Europe and parts of Asia.

II. CHEMISTRY AND PHARMACOLOGY

A. Mechanism of Action

Despite decades of use, how paracetamol relieves pain and lowers temperature is not completely understood. Several explanations are currently favoured:

- Inhibition of COX in the central nervous system. Paracetamol appears to suppress cyclooxygenase activity where the local concentration of peroxides is low, as in the brain. This reduces hypothalamic prostaglandin E2 and accounts for the fever-lowering effect, while the lack of action in inflamed peripheral tissue explains why it has little anti-inflammatory benefit.
- Formation of AM404. In the brain, paracetamol is deacetylated to p-aminophenol and then joined with arachidonic acid to produce AM404, a compound that acts on TRPV1 and cannabinoid CB1 receptors and blocks anandamide reuptake.
- Descending serotonin pathways. The drug seems to strengthen serotonergic pain-inhibiting signals running down to the spinal cord, with 5-HT3 receptors implicated.

B. Pharmacokinetics

Parameter	Typical value
Oral bioavailability	Roughly 63–89%, depending on dose
Time to onset (oral)	30–60 minutes
Time to peak level	0.5–2 hours for immediate-release forms
Protein binding	Low (approximately 10–25%)
Volume of distribution	About 0.9 L/kg
Half-life	1.5–3 hours in healthy adults; longer in overdose or hepatic disease
Elimination	Chiefly via the kidneys as conjugated metabolites

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C. Biotransformation

The liver handles most of the drug through three routes:

- Glucuronidation (UGT1A1, 1A6, 1A9) takes up around half to three-fifths of the dose.
- Sulfation by SULT enzymes accounts for roughly 20–30%. This route becomes saturated readily and is underdeveloped in newborns.
- Oxidation by cytochrome P450, mainly CYP2E1 with minor input from CYP1A2 and CYP3A4, converts 5–10% of the dose into the reactive intermediate N-acetyl-p-benzoquinone imine (NAPQI).
- A small portion leaves the body unchanged.

With ordinary doses, glutathione (GSH) quickly neutralises NAPQI, and the products are excreted in urine as cysteine and mercapturic acid conjugates.

III. THERAPEUTIC APPLICATIONS

A. Pain relief

Paracetamol is advised as the first drug to try for mild to moderate acute pain such as headache, toothache, muscle and joint pain, period pain, sore throat and pain after surgery. In hospital it forms part of multimodal analgesia, lowering the amount of opioid patients need. The intravenous preparation is used around the time of surgery and for those unable to swallow.

The case for its use in persistent pain is weaker than once believed. Pooled analyses indicate that it offers no meaningful relief for acute low back pain and only a small, borderline-significant benefit in osteoarthritis (Machado et al., 2015). Consequently, many current guidelines treat it as a short-term or supporting option rather than a foundation of chronic pain treatment.

B. Fever

The drug is extensively used to bring down temperature in children and adults. Its purpose is comfort; it does not cure the cause of the fever, and there is no solid evidence that it prevents febrile convulsions or shortens infections. Because it is not linked to Reye syndrome, it is favoured over aspirin when children have viral illnesses.

C. Additional indications

- Patent ductus arteriosus (PDA): an alternative to indomethacin or ibuprofen in premature babies, especially if NSAIDs cannot be given.
- Fixed-dose combinations: paracetamol is paired with codeine, tramadol, dihydrocodeine, caffeine, NSAIDs, antihistamines and decongestants, the latter in many cold and flu remedies.
- Migraine: used alone or with caffeine or an antiemetic during acute attacks.
- Pregnancy and breastfeeding: generally the preferred pain and fever medicine, though questions remain (see Section 4.5).

D. Standard adult dosing

Adults typically take 500 mg to 1 g by mouth every 4 to 6 hours, up to a ceiling of 4 g per 24 hours. A lower daily limit, often 2–3 g, is recommended for people weighing under about 50 kg, those who are chronically undernourished or drink heavily, and anyone with liver disease. Doses for children depend on body weight and must be taken from the product label or a clinician’s advice. Intravenous doses are also weight-adjusted and capped per day.

IV. SAFETY AND ADVERSE EFFECTS AT THERAPEUTIC DOSES

A. Overall tolerability

Within the recommended range, side effects are infrequent and usually minor. Paracetamol does not meaningfully affect platelets, seldom irritates the stomach lining, and rarely triggers bronchospasm in people with aspirin-sensitive asthma, although a few such individuals may react at high doses.

B. Liver

For healthy adults, therapeutic doses are safe. Small, temporary rises in liver enzymes can appear with sustained intake of 4 g daily; in one trial of healthy volunteers taking this amount for two weeks, some developed raised ALT (Watkins et al., 2006). Genuine liver injury at true therapeutic doses is uncommon and usually involves unnoticed overuse, fasting or other predisposing factors.

C. Allergy and skin reactions

Uncommon reactions include rashes, hives, angioedema and anaphylaxis. Very rarely, severe skin disorders occur, namely Stevens–Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis. Regulators advise stopping the drug immediately if a skin reaction develops.

D. Other effects

- Blood: thrombocytopenia, neutropenia and agranulocytosis are extremely rare, as is methaemoglobinaemia.
- Heart and kidney: regular high doses have been associated with modest rises in blood pressure, and observational studies hint at cardiovascular, kidney and gastrointestinal risks, though a causal link has not been proven (Roberts et al., 2016).
- Lungs: several observational studies connect frequent use with asthma, but confounding by indication is likely.
- Intravenous use: pain at the infusion site, low blood pressure, and dosing mistakes, particularly in children and light adults, where mg/mL confusion has caused overdoses.
- High anion gap metabolic acidosis: prolonged therapeutic use can lead to 5-oxoproline (pyroglutamic) acidosis through glutathione depletion, especially in malnourished, septic or renally impaired patients and those also receiving flucloxacillin.

E. Particular patient groups

1) Pregnancy. Paracetamol is commonly used and long considered safe in pregnancy. Some observational studies have reported links between extended prenatal exposure and neurodevelopmental, urogenital or respiratory outcomes, but confounding limits their reliability. An international consensus statement (Bauer et al., 2021) advises using it only when clinically needed, at the smallest effective dose and for the shortest time, while emphasising that untreated pain or fever also poses risks. The evidence remains disputed, and women should be encouraged to discuss use with their healthcare provider.

2) Newborns and children. Neonates conjugate the drug less efficiently, but they also produce less NAPQI, so their overall risk is lower than previously feared. Accurate weight-based dosing is still essential, and repeated excess doses given to feverish children are a well-recognised cause of accidental poisoning.

3) Older adults. The drug is usually chosen in preference to NSAIDs, but frailty, low weight and poor nutrition justify a reduced daily ceiling.

4) Liver disease. Stable chronic liver disease or cirrhosis is not an absolute bar; many hepatologists accept up to 2 g/day. Caution is needed in decompensated disease, active alcoholic hepatitis and severe malnutrition.

5) Chronic alcohol use. Long-term drinking induces CYP2E1 and lowers glutathione, which should in theory increase NAPQI production. Clinical proof of harm at therapeutic doses in drinkers is limited and contested (Dart and Bailey, 2007), but lower maximum doses are prudent, especially during fasting or acute intoxication.

6) G6PD deficiency. Paracetamol is generally regarded as safe.

F. Drug interactions

Interacting drug	Consequence
Warfarin	Regular use (around 2 g/day or more for several days) can raise the INR
Enzyme inducers (carbamazepine, phenytoin, rifampicin, phenobarbital, isoniazid, chronic alcohol)	May increase NAPQI generation and, in theory, hepatotoxicity risk
Flucloxacillin	Greater likelihood of high anion gap metabolic acidosis
Metoclopramide, domperidone	Hasten absorption
Colestyramine	Absorption falls if taken within an hour
Zidovudine	Possible added neutropenia

V. TOXICITY

A. *Epidemiology*

In the UK, paracetamol is the drug most often implicated in overdose presentations, and in the USA and Europe it is among the foremost causes of acute liver failure (Larson et al., 2005). Overdoses may be intentional (self-harm) or unintentional, the latter arising from taking too much for symptom relief or from not realising that several products contain the drug. Policy responses include limiting pack sizes (UK, 1998) and capping the paracetamol content of prescription combination tablets (USA, 2011).

B. *How it damages the liver*

After an overdose, the glucuronidation and sulfation routes become saturated and a larger share of the drug is oxidised by CYP2E1 (plus CYP1A2 and CYP3A4) to NAPQI. Liver glutathione falls to about a third of normal or lower, and unneutralised NAPQI attaches covalently to cysteine groups on cellular proteins, particularly in mitochondria (Mitchell et al., 1973; Jaeschke et al., 2012). The injury unfolds as follows:

1) Protein adducts form and mitochondria begin to malfunction.
2) Oxidative and nitrosative stress builds, through reactive oxygen species and peroxynitrite.
3) JNK is activated and moves to the mitochondria, intensifying oxidative damage.
4) The mitochondrial permeability transition occurs, ATP is lost and nucleases are released.
5) Hepatocytes die by necrosis, mainly in the centrilobular (zone 3) region, where CYP2E1 is most abundant.

Sterile inflammation driven by damage-associated molecular patterns adds to the injury, and the liver's capacity to regenerate then determines recovery. The kidney can also be hurt, with acute tubular necrosis resulting partly from local CYP activation; this may happen even when liver tests are only mildly abnormal.

C. *Risk factors*

1) A large single dose, or repeated excessive doses over hours or days (staggered overdose).
2) Fasting, malnutrition and low body weight, which reduce glutathione.
3) Chronic alcohol use and enzyme-inducing drugs, which raise CYP activity.
4) Existing liver disease.
5) Genetic variation in CYP and UGT enzymes (a minor contribution).
6) Late presentation or late antidote administration.
7) Modified-release products, whose absorption is slow and prolonged.

In otherwise healthy people, one acute ingestion of **150 mg/kg or more**, or over roughly 12 g in an adult, is considered potentially toxic. People with risk factors can be harmed by less. Any suspected overdose should be assessed by a clinician or poison information service, whatever amount is reported.

D. *Clinical course*

Phase	Time from ingestion	Features
I	0–24 hours	Often no symptoms, or nausea, vomiting, malaise, pallor and sweating. Liver tests normal.
II	24–72 hours	Right upper abdominal pain and tenderness; ALT/AST, bilirubin and INR begin to climb; urine output may fall and renal function worsen.
III	72–96 hours	Liver injury at its worst: jaundice, clotting abnormalities, low blood sugar, encephalopathy, lactic acidosis, brain swelling and multi-organ failure; death is possible.
IV	4 days to 2 weeks	Survivors recover with full restoration of liver tissue; others progress to death or need transplantation.

A symptom-free first day can be falsely reassuring and does not rule out serious poisoning.

E. *Investigations*

1) A serum paracetamol level, ideally at least 4 hours after ingestion for a single acute overdose, interpreted against a treatment nomogram (Rumack–Matthew; Rumack and Matthew, 1975).
2) Liver function tests (ALT/AST, bilirubin), INR/prothrombin time, urea, creatinine, electrolytes, bicarbonate, glucose, blood gas, lactate and a full blood count.

3) Repeat levels and blood tests when the time of ingestion is uncertain, the overdose was staggered, or a modified-release product was taken.
4) Screening for other ingested substances such as salicylate, and a psychiatric and risk assessment for every deliberate overdose.

The nomogram is valid only for a single acute ingestion with a known time. Treatment thresholds differ among countries and have changed over time (for instance, the 150 mg/L at 4 hours line versus lower lines for higher-risk patients in some places), so local guidance should be followed.

VI. TREATMENT OF OVERDOSE

A. *Initial Measures*

1) Stabilise the patient, give standard supportive care and involve a toxicology service or poisons centre.
2) Activated charcoal may be given if the patient arrives within about 1–2 hours of a potentially toxic dose (longer for modified-release products or co-ingestants), provided the airway is protected.
3) Gastric lavage and induced vomiting are not routinely advised.

B. *N-acetylcysteine (NAC)*

NAC is the specific antidote. It restores glutathione, may bind NAPQI directly, boosts sulfation, and has antioxidant and circulatory effects that help even after liver failure has set in (Prescott et al., 1979; Smilkstein et al., 1988). It works best when started **within 8** hours of ingestion, at which point it prevents nearly all serious liver damage; but it should be given at any time if toxicity is evident or if timing or levels are uncertain.

Commonly used regimens:

1) Standard three-bag intravenous regimen (about 21 hours): a one-hour loading infusion followed by infusions over 4 and 16 hours, dosed by weight.
2) Modified or shorter regimens (for example two-bag or 12-hour protocols), adopted in some settings to lessen side effects.
3) Oral regimen (about 72 hours): used in certain countries, notably the USA, where IV supply has been limited.

Treatment continues beyond the standard course if paracetamol is still detectable, ALT is raised or rising, or INR is abnormal, until recovery is clear.

Side effects of IV NAC include nausea, vomiting, flushing, itching, hives and angioedema. These anaphylactoid reactions depend on infusion rate and are generally mild; they are handled by pausing or slowing the infusion and giving antihistamines rather than stopping the antidote. Serious reactions such as bronchospasm or hypotension are unusual. Dosing errors, particularly in children and light patients, can cause hyponatraemia and fluid overload.

C. *Acute liver failure*

Patients whose injury is worsening need intensive-care monitoring and early contact with a transplant centre. Care includes continued NAC, correction of low glucose, clotting problems and brain swelling, renal support if needed, and avoidance of nephrotoxic drugs. Indicators of poor prognosis (modified King's College criteria) are:

1) Arterial pH below 7.30 after fluid resuscitation, or
2) INR above 6.5 together with creatinine above 300 µmol/L **and** grade III–IV encephalopathy.

Lactate, phosphate and other markers further inform prognosis. Emergency liver transplantation can save carefully selected patients. Haemodialysis and similar techniques rarely help remove paracetamol but may be used for severe acidosis or kidney failure.

D. *Special situations*

1) Staggered or repeated excess dosing: the nomogram does not apply; decisions rest on total dose, timing, paracetamol level, ALT and INR, with a low threshold to give NAC.
2) Unintentional chronic overdosing: liver injury can occur at lower doses, especially with risk factors; manage according to blood results and local protocols.
3) Children: accidental ingestion is frequent but usually involves small quantities, and severe toxicity is less common than in adults. Use weight-based thresholds and consult poison services.
4) Pregnancy: manage as in non-pregnant patients, since NAC is effective and crosses the placenta; involve obstetric teams.
5) Mental health: every deliberate overdose requires a risk assessment and suitable follow-up before discharge.

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VII. PREVENTION AND PUBLIC HEALTH STRATEGIES

1) Clear labels stating the maximum daily dose and warning of paracetamol hidden in combination products.
2) Limits on pack size and quantity sold.
3) Child-resistant containers.
4) Standard measuring devices and dosing charts for children.
5) Education on safe dosing for patients, parents and health professionals.
6) Prescriber awareness of cumulative dose from combination products, and avoidance of duplicate paracetamol prescribing.
7) Safeguards against intravenous dosing errors, such as weight-based prescribing and clear infusion protocols.
8) Timely access to medical care and poisons information.

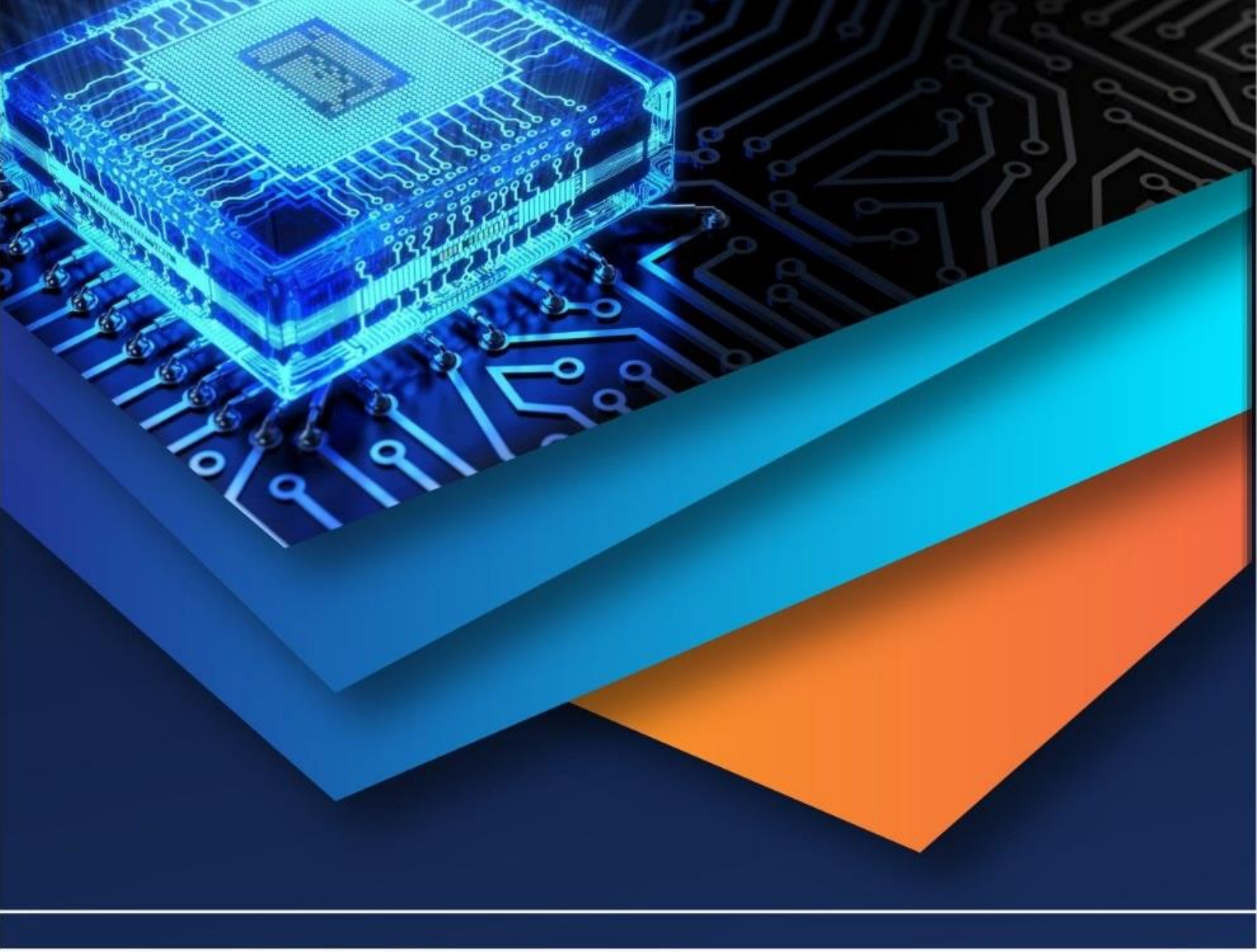
VIII. CONCLUSION

When used as directed, paracetamol is an effective and well-tolerated medicine with an excellent safety record. Its value is best proven in acute mild to moderate pain and fever, and its place in chronic pain is narrower than long assumed. The main danger is dose-dependent liver injury caused by NAPQI, which is largely avoidable and very treatable when identified early, with NAC as the central therapy. Public education, careful prescribing, sensible regulation and prompt toxicological assessment remain vital to reducing harm. Unresolved questions include the drug's exact mode of action, long-term safety in pregnancy, risks of prolonged high-dose use, and the best NAC regimens.

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