Introduction

Paracetamol (N-acetyl-p-aminophenol) is a safe and effective agent that is widely used for its analgesic and antipyretic properties. It was first used in medicine in 1893 but only became popular in the second half of the last century. It is one of the successors in the same therapeutic class, acetanilide and phenacetin, as the analgesic-antipyretic of choice for patients in whom salicylates and other nonsteroidal anti-inflammatory drugs are contraindicated. Due to its weak inhibition of cyclo-oxygenase, paracetamol is not indicated as an anti-inflammatory drug.

The conventional adult oral dose of paracetamol is 0.5g to 1g every 4 to 6 hours with a maximum daily dose of 4g. Rectal doses for persons over 12 years of age are 0.5g to 1g administered up to four times daily. In children, oral and rectal doses depend on age and body weight, with a maximum of four doses in a 24-hour period.

Absorption of paracetamol from the gastro-intestinal tract is rapid. The peak plasma concentration is attained within 30 to 60 minutes and the elimination half-life in plasma is about 2 hours following administration of a therapeutic dose. Paracetamol is distributed into most body tissues and plasma protein binding is negligible at therapeutic doses, but increases with increasing plasma concentrations. The drug readily crosses the placenta although there is no published evidence of teratogenic effects.

Paracetamol: Safety versus Toxicity

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Paracetamol is an effective analgesic-antipyretic that can be administered safely to children and adults at the appropriate therapeutic doses. The drug is readily metabolised by the liver and toxic metabolites are removed by conjugation with endogenous glutathione. Accidental or deliberate overdosage can lead to hepatic toxicity that can be fatal if not treated urgently with antidotes that replenish depleted glutathione. Pharmacists have an important role to play in patient education to help reduce the incidence of paracetamol poisoning.

Keywords: paracetamol, metabolism, toxicity, poisoning

The metabolic reactions by which drugs are biotransformed in the body are divided into two phases. Phase I reactions prepare a drug for the subsequent phase II reactions. The latter are the true detoxification pathways which result in products that are generally water-soluble and easily excreted in urine or bile.

The metabolic biotransformation of paracetamol predominantly proceeds through phase II pathways in the liver (Figure 1). The main reaction is hepatic conjugation with glucuronic acid, which accounts for about 60% of renally excreted metabolites. Conjugation with sulphate contributes a further 35% to urinary metabolites. A small amount, about 3%, is excreted as mercapturic acid, the N-acetylcysteine conjugate. Less than 5% of paracetamol is excreted unchanged in urine.

The conjugates are not chemically reactive and therefore not likely to cause any organ damage. However mercapturic acid is formed via the conjugation reaction between a potentially hepatotoxic reactive intermediate and sulphhydryl groups in glutathione. This reactive intermediate is probably N-acetyl-p-benzoquinoneimine (NAPQI), a cytotoxic electrophile that binds to cellular proteins. Compared with...
Table I: Factors influencing the metabolism and toxicity of paracetamol

**Drug interactions**
- Exposure to drugs that are inducers of hepatic drug-metabolising enzymes, e.g. phenobarbital, increases susceptibility to hepatotoxic effects of paracetamol. A
- Inhibition of glucuronidation of both paracetamol and zidovudine may occur when the drugs are administered concurrently resulting in increased toxicity of both drugs.
- Resistance to the hepatotoxic effects of paracetamol is seen in the presence of drugs that are inhibitors of microsomal enzymes. Cimetidine, an inhibitor of cytochrome P-450, decreases the toxicity of paracetamol by preventing formation of hepatotoxic metabolites while having no effect on conjugation reactions that yield non-toxic metabolites.

**Alcohol**
- Acute exposure to alcohol (ethanol) decreases metabolism of paracetamol by Phase II pathways so that the drug exhibits a longer elimination half-life.
- Chronic exposure to alcohol with no hepatocellular changes leads to induction of Phase I and Phase II metabolism. Induction of cytochrome P450 2E1 increases Phase I metabolic oxidation of paracetamol with enhanced toxicity due to increased formation of toxic metabolite.
- When the extent of alcoholic liver disease becomes extensive there is a reduction in the metabolism of paracetamol as seen in cirrhosis.

**Diet**
- Animal studies have shown that hepatotoxicity of paracetamol increases after a low-protein diet. This may be due to reduced levels of intracellular glutathione that offsets the reduced amount of cytochrome P450 caused by protein deficiency.
- An increase in hepatotoxicity of paracetamol has also been seen in animals after overnight fasting due to depletion of glutathione levels.

**Genetics**
- Genetic control of drug metabolism is exemplified by the appearance of racial differences in glucuronidation of paracetamol between Caucasians and Chinese.
- Variability in rates of metabolic oxidation of paracetamol by cytochrome P450 in human populations has been identified. Where the rate of oxidation is highest there is increased susceptibility to hepatotoxicity of paracetamol. At the lowest rate, about 25% of the highest, there is relative resistance to hepatotoxicity.
- CYP2D6, one of the pharmacogenetically important cytochrome P450 isoforms that exhibits polymorphism, may contribute significantly to the formation of the toxic metabolite at toxic doses of paracetamol especially in CYP2D6 ultra-rapid and extensive metabolisers.

Glutathione is a tripeptide consisting of the amino acids cysteine, glutamic acid and glycine. Thus the formation of mercapturic acid involves the sequential cleavage of glutamic acid and glycine from the glutathione moiety in the conjugate to give the cysteine conjugate which is, in turn, N-acetylated to the mercapturic acid.

Besides hepatic damage, paracetamol can also induce damage to the kidney medulla. Prostaglandin synthetase, which is more predominant than cytochrome P450 in the kidneys, is involved in the formation of NAPQI via an intermediate free radical, N-acetylbenszenosiquinoneimine, that can bind to renal proteins. This free radical may undergo reduction with glutathione to reform paracetamol. Therefore the biotransformation of the free radical is adversely affected by depletion of glutathione.

**Paracetamol toxicity and treatment**

When administered in the recommended therapeutic doses, paracetamol is usually well tolerated. Hypersensitivity reactions including skin and other allergic reactions may occur occasionally. Haematological reactions have also been reported. Prolonged use of the drug may cause nephropathy and animal studies have indicated the possibility of tumour-inducing effects.

The major toxic effects of paracetamol are by far associated with acute overdosage, which is primarily manifested as a dose-dependent hepatocellular necrosis unless treated promptly. Renal tubular necrosis occurs less commonly and may be seen in the absence of liver damage. Myocardial abnormalities and pancreatitis are also non-hepatic symptoms of overdosage.

The early symptoms of overdosage are not alarming and in the first 12 hours could include nausea, vomiting, lethargy and sweating. While damage to the liver starts to take place within hours of ingestion, clinical manifestations such as abdominal pain and tenderness followed by jaundice may only be apparent after 24 to 48 hours and may be delayed by 4 to 6 days after ingestion. Abnormal liver function tests with increases in
Figure 1: Pathways of paracetamol metabolism and toxicity

Metabolic enzymes:
1. Cytochrome P450 (CYP1A2, CYP2E1, CYP3A4, CYP2D6)
2. Prostaglandin synthetase
3. Glutathione transferase
4. UDP-Glucuronyltransferase
5. Phenolsulphotransferase
6. Gamma-Glutamyltranspeptidase
7. Aminopeptidase M
8. N-Acetyltransferase

Symbols: → = urinary excretion
seen as early as 8 hours from ingestion although they may result later within the first 24 hours. Liver damage reaches a maximum in 72 to 96 hours after ingestion and may progress to hepatic failure with ensuing complications. Acute renal tubular damage may occur concurrently with liver damage. The metabolism and consequently the toxicity of paracetamol are influenced by a number of factors (Table I). The adult minimum toxic dose of about 12 g may be lowered to 6 g in high-risk patients because of increased susceptibility. Thus there may be a relatively narrow margin between the recommended adult daily dose of 4 g and the minimum toxic dose. Paracetamol doses of 20 to 25 g are potentially fatal. The relatively mild symptoms that are seen in the first hours after ingestion and the delay in clinical manifestations of hepatic damage may deter patients from seeking prompt treatment at a hospital even in the absence of symptoms. Gastric lavage is usually performed if ingestion was within 2 to 4 hours of admission and full supportive measures are instituted. Although peak plasma paracetamol concentration is best measured at least 4 hours after ingestion and not later than 16 hours from ingestion, therapy should not be delayed if significant overdosage is suspected. Plasma paracetamol concentrations are compared against a standard nomogram reference line that relates plasma concentration to time after ingestion. When the plasma concentration of the patient is above the normal reference line treatment must be instituted. For patients who are at increased risk of toxicity a lower high-risk treatment line is employed. Methionine and N-acetylcysteine are the two antidotes that are used to treat paracetamol toxicity. The former is available as an oral preparation and the latter as oral and intravenous formulations. Oral administration is the preferred treatment route in the United States. However, in the United Kingdom, intravenous N-acetylcysteine is preferred because the unpleasant taste and odour of the oral form of the antidote may exacerbate the early symptoms of nausea and vomiting.

N-Acetylcysteine is a well-tolerated source of intracellular cysteine, the rate-limiting amino acid in glutathione synthesis. There are four mechanisms by which the antidote may act:

- promotion of the synthesis of glutathione which is necessary for the detoxication of the reactive metabolite, NAPQI, by conjugation;
- stimulation of the synthesis of glutathione used in the protection of protein thiols;
- relief of the saturation of sulphate conjugation which occurs during paracetamol overdose; and
- direct involvement in the reduction of NAPQI.

N-Acetylcysteine may be effective when administered 15 hours or more after an overdose and may even be of benefit 24 hours after paracetamol ingestion. Since by this time most of the metabolite NAPQI would have reacted with cellular proteins, the antidote may, at a late stage, afford protection against subsequent cellular changes. Methionine is not as effective when administration is delayed. This may possibly be due to inhibition of glutathione synthesis by thiol-containing enzymes involved in the synthetic pathway.

**Pharmacy practice points**

The relative ease with which paracetamol can be obtained as a non-prescription medicine is believed to be a major factor that accounts for the relatively high incidence of accidental and deliberate overdosage in the United Kingdom and the United States.

Several measures have been taken to reduce incidents of paracetamol poisoning. In the United States, standards for product labelling were revised to clarify dosing instructions and introduce a more specific warning.
The regulatory authorities in the United Kingdom subjected some oral paracetamol dosage forms to prescription control with exemptions based on restricted pack sizes, number of packs that could be supplied, and requirements for warning statements. The regulatory authorities are known to have difficulty measuring and administering a correct dose of a medicine. Of more concern is the fact that many adults fail to associate brand names with the active ingredient in the product, leading to excessive cumulative doses when multiple sources of paracetamol are administered. Notwithstanding the fact that intentional paracetamol poisoning cannot be prevented without direct intervention, the pharmacist has an important role to play in reducing the incidence of accidental poisoning.

Table II lists several practice points that could contribute to improved patient education on the use of paracetamol.

## References


## Conclusion

At therapeutic doses, paracetamol exhibits a good safety profile that makes it a popular drug found in most households. However, the ease with which it may be obtained should not be interpreted as a guarantee of absolute safety. Some patients are at an increased risk of poisoning at lower doses than are normal for the rest of the population. In any case, the consequences of overdosage are severe and can lead to death. Thus early and prompt treatment of poisoning is imperative even in the absence of symptoms. Pharmacists advising patients on caution in the use of paracetamol can reassure them that, in using the drug correctly, they can benefit from its therapeutic efficacy in the treatment of mild and moderate symptoms.