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An introduction to paracetamol

By the perioperativeCPD team

Introduction

Paracetamol is a commonly used medicine that can help treat pain and reduce a high temperature. It's typically used to relieve mild or moderate pain, such as headaches, toothache or sprains, and reduce fevers caused by illnesses such as colds and flu. In normal doses it is considered safer than many analgesics as it has no effect on the cardiovascular and respiratory systems and unlike Non-steroidal anti-inflammatory drugs (NSAIDs) it does not cause gastric irritation or bleeding.

It is widely available, from pharmacies to corner-shops, in a host of preparations, on its own and in combination with other analgesics and decongestants. However, the accessibility of paracetamol might detract from its effectiveness as an analgesic. In particular, paracetamol should be regarded as a baseline medication for painful conditions, i.e. the first medicine to take, and to continue with while other analgesics are added or taken away from a regimen.

One caution, especially for the perioperative environment, is that as IV paracetamol has close to 100% bioavailability and IV doses must be adjusted in low weight individuals to prevent overdose.

Mechanism of Action

Although paracetamol was discovered nearly 150 years ago and has been used for more than 50 years, the exact way it works is still not fully understood by scientists or doctors. Any Google search will bring up a confusing mix of competing theories, none which have been conclusively proved. What is agreed is that paracetamol has a different and very complicated mode of action compared to other analgesics.

Paracetamol is historically miscategorised along with NSAIDs, maybe because like NSAIDs it has an effect on the cyclooxygenase (COX) pathways. While paracetamol has analgesic and antipyretic properties it lacks the peripheral anti-inflammatory properties that all NSAIDs must have.

Note: for a better understanding of prostaglandins and the cyclooxygenase (COX) pathways see our NSAIDs module.

The inhibition of COX enzymes can provide relief from the symptoms of inflammation and pain (see Fig. 1). Paracetamol may inhibit the COX pathway in the central nervous system but it does not in peripheral tissues. Paracetamol does not appear to bind to the active site of either the COX-1 or COX-2 enzyme used by NSAIDs; instead, it reduces the activity of COX by a different mechanism. It has been theorised that paracetamol inhibits a variant of COX-1, also called COX-3, but this has not been confirmed.

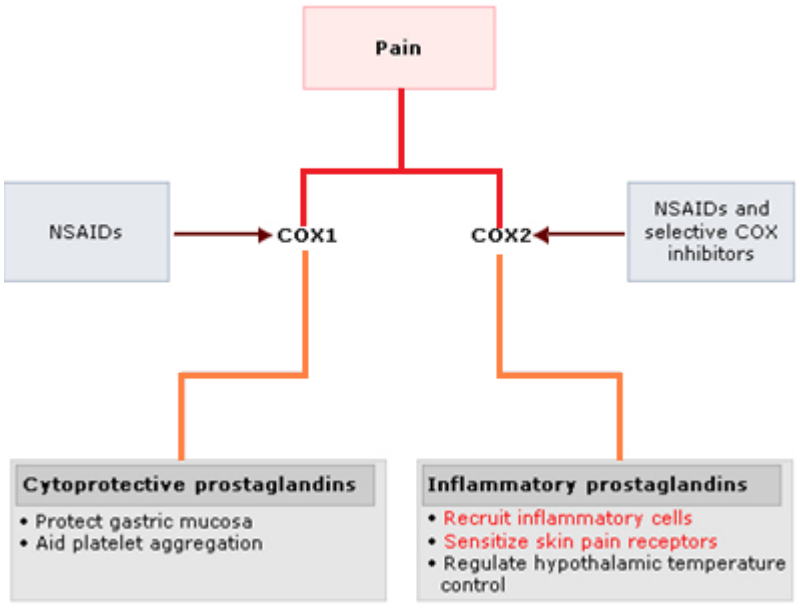

Fig 1 Mechanism of action of NSAIDs (not paracetamol)

Other studies have suggested that paracetamol or one of its metabolites, e.g. AM 404, also can activate the cannabinoid system contributing to its analgesic action. The body's cannabinoid system is a key endogenous system for regulating pain sensation, with modulatory actions at all stages of pain processing pathways.

The antipyretic action of paracetamol is probably produced a by a central effect on the hypothalamic heat-regulating centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. In reality, no one knows exactly how paracetamol works.

Routes of Administration

Solid tablets

Solid tablets of paracetamol are the most familiar formulation for the majority of people.

The peak level is reached in the blood between 30 minutes to 2 hours. This results in the greatest effects of paracetamol occurring after 1-3 hours and those effects last for around 6 hours, depending on individual factors in any particular person.

After taking paracetamol orally, up to 80% of the dose is 'available' for action, so, if a person takes 1 gram of paracetamol (1000 mg), about 800 mg takes effect in their body.

Soluble tablets

Soluble tablets are often provided to elderly patients who may have difficulty swallowing solid tablets, some of which can be quite large.

Soluble tablets, however, contain sodium bicarbonate, which provides the 'fizz' that helps the tablets dissolve easily in water. The downside is that sodium bicarbonate quite dramatically increases the amount of sodium that a person might ingest. If a person took the maximum four doses of soluble paracetamol each day, this would increase their total intake of 'salt' by up to 6 g, and 6 g of salt is the recommended daily intake for an adult.

Therefore, people who have high blood pressure, heart failure or kidney failure should be encouraged not to take soluble paracetamol products because it could have a detrimental effect on other aspects of their health.

Liquid

The liquid forms of paracetamol are generally used for children and in adults with swallowing difficulties.

Adult-strength formulations are available, which partly avoids the need to administer large volumes of the liquid. However, these preparations are generally more expensive than tablets, so tend to be reserved, in adults, for those who are genuinely unable to take the medicine by any other route.

Intravenous

Intravenous (IV) infusions of paracetamol are used quite extensively in hospitals after surgery and where people are unable to take oral preparations.

Like most drugs given directly into a vein, nearly all of it takes effect within the body. IV drugs can take effect quickly and IV paracetamol can be shown to have a high concentration in the blood within 15 minutes, resulting in its effects being seen after 20-30 minutes.

Suppositories

Suppositories of paracetamol are available, although they are used less often due to the availability of IV preparations. Paracetamol is slowly absorbed from the rectum and its bioavailability is variable.

Oral Dosage

Oral tablets and capsules are generally available as 500 mg of paracetamol per tablet. This has resulted in paracetamol dosing being easily remembered as 1 or 2 tablets taken up to 4 times a day. The maximum recommended oral dose of paracetamol in the UK is 4g per day or 8 tablets.

Oral solutions of paracetamol are made primarily with children in mind and this is reflected in the three most commonly available strengths:

120 mg/5 ml and 250 mg/5 ml are classed as paediatric preparations

500 mg/5 ml is an adult-strength formulation

Metabolism – Normal Liver

Paracetamol is metabolised in the liver and primarily produces two inactive products, a glucuronide and a sulphate metabolite, both of which are non-toxic and normally excreted unchanged by the kidneys in urine (Fig 2). A small amount (5-10%) of a toxic product called NAPQI is also produced via an alternative pathway.

In normal liver function, however, this toxic metabolite is inactivated by glutathione, a chemical known as an antioxidant, into a harmless molecule that is then also excreted in urine.

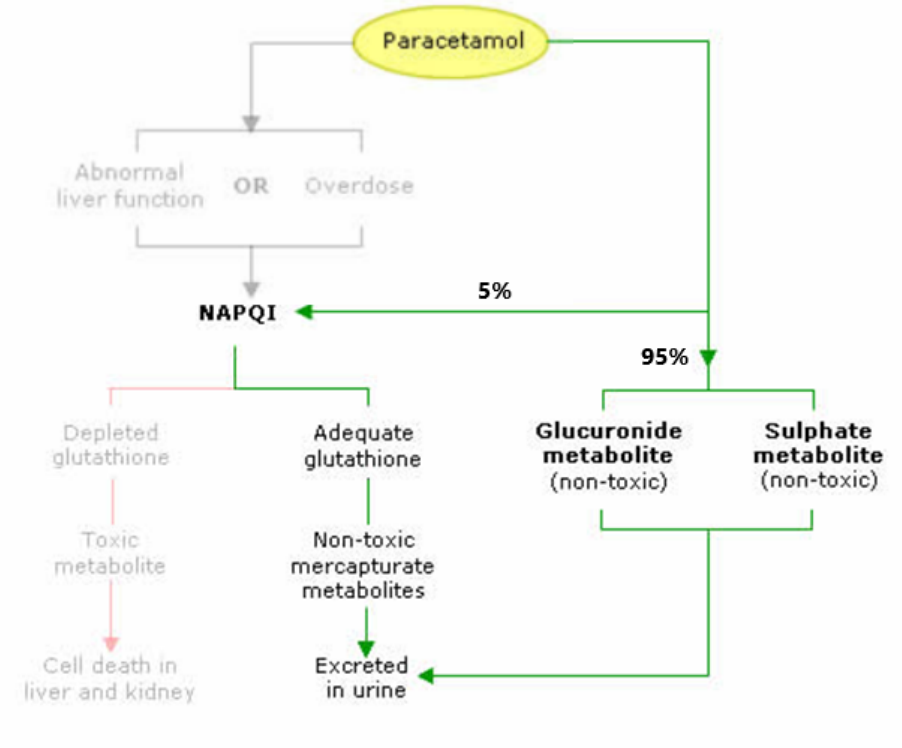

Fig 2 Metabolism of paracetamol when liver function is normal and therapeutic dose given

Metabolism – Abnormal liver or overdose

In people whose liver is not functioning properly, or where large doses of paracetamol are taken, such as in a deliberate overdose or where a patient is given too much paracetamol for their weight or liver function, the liver becomes overloaded and is unable to process paracetamol in the normal way. When this happens, more of the toxic metabolite NAPQI is produced.

Even under these circumstances, provided the person has good stores of glutathione in the liver, they may not come to harm (Fig 3).

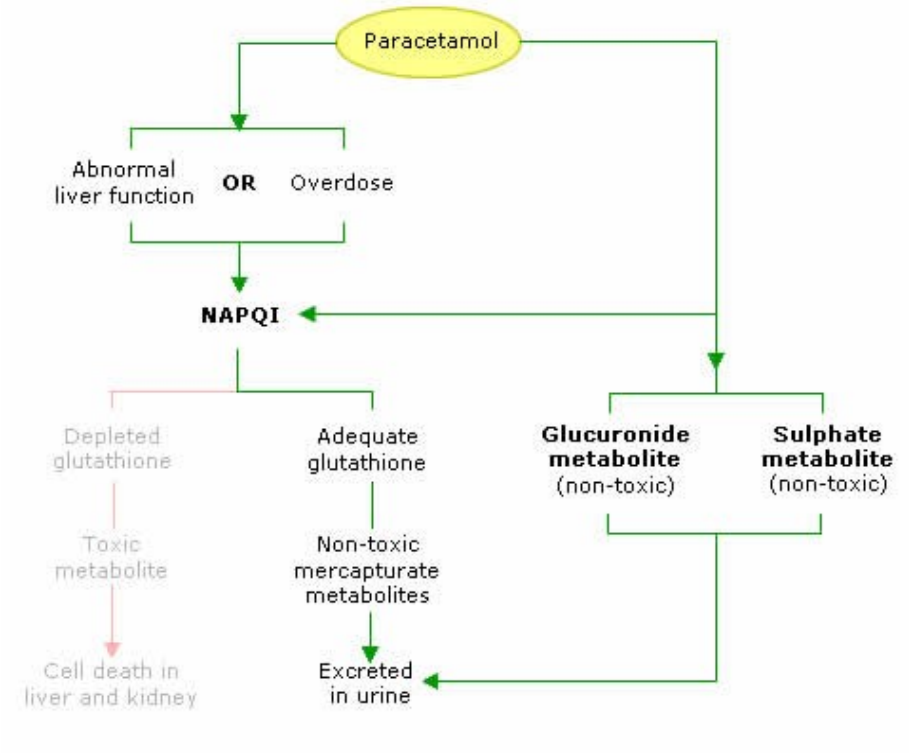

Fig 3 Metabolism of paracetamol when liver function is not normal or overdose taken and patient has adequate glutathione

However, where they have insufficient glutathione, perhaps due to existing liver disease, high alcohol intake, malnutrition, the use of other drugs such as some older anti-epileptic medications (carbamazepine or phenytoin) or simply because they have taken such a large dose of paracetamol, then even this secondary pathway fails to work. In that situation, the toxic metabolite of paracetamol causes damage directly to the liver and even the kidneys, known as necrosis or 'cell death' (Fig 4).

The damage to the liver and kidneys may become irreversible and potentially lead to the death of the patient. A lethal dose in a normal weight healthy person is considered around 10-15 grams in 24 hours.

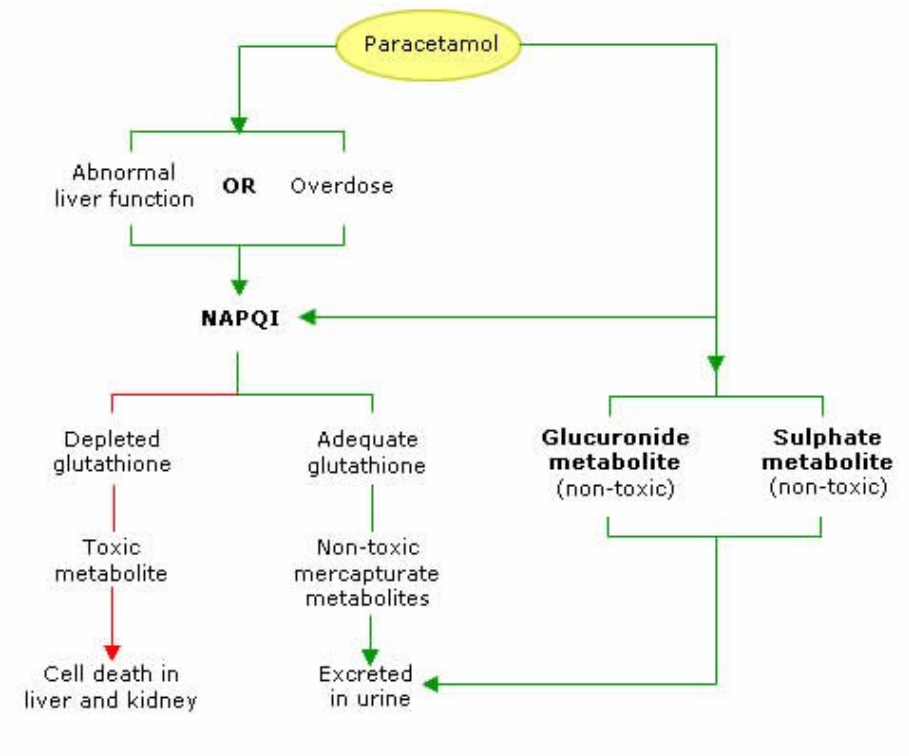

Fig 4 Metabolism of paracetamol when liver function is not normal or overdose taken and patient has insufficient glutathione

Overdose and treatment – Antidote

The antidote to acute paracetamol overdose is IV NAC (N-acetylcysteine). Like glutathione, NAC binds to the toxic metabolite of paracetamol and effectively neutralises it, so it can be excreted by the kidneys and prevent damage to the cells of the liver and kidneys. If given within 8 hours of the overdose, NAC is virtually 100% effective.

Risk Factors for Toxicity

For many patients, paracetamol is seen as a reasonably harmless medication. However, the increasing use of the IV formulation has revealed another, more potentially harmful side to it, even at therapeutic doses.

There is now an increased awareness of the risks of paracetamol in susceptible patients, including the elderly, children and people with other risk factors.

The most important risk factors to consider when prescribing paracetamol are:

- Liver failure or deranged liver function tests
- Renal failure
- Chronic alcoholism
- Acute or chronic malnutrition
- Dehydration

Liver failure or deranged liver function tests

If the liver is less able to process the paracetamol effectively, this may potentially lead to increased levels of toxic metabolites.

Liver failure is not a complete contraindication to the use of paracetamol, but dose reduction and increased duration between doses should be considered to optimise the safety of the medication.

Renal failure

Creatinine clearance <30 ml/min increases the risk of accumulation of paracetamol and its metabolites because the paracetamol is not effectively excreted.

Whilst not a contraindication to the use of paracetamol in any form, a dose reduction should be considered to ensure safety.

Chronic alcoholism

Chronic alcoholism causes depletion of liver enzymes, direct damage to liver cells and consequent reduction of liver function.

Therefore, as for other forms of liver disorders, paracetamol may cause toxic levels of metabolites to accumulate.

Acute or chronic malnutrition

Malnutrition results in depletion of liver enzymes, which forces the metabolism of paracetamol towards the toxic route, thus increasing overdose risk.

Dehydration

Dehydration can increase the risk of both liver and renal dysfunction and reduces circulating volume, effectively increasing the levels of paracetamol and its consequent metabolites.

The consequence of excessive paracetamol use in any of these conditions is likely to be an overdose.

Common Side-effects

Most side-effects from paracetamol are rare with normal therapeutic doses and, if they occur, are usually mild.

Organ System	Common (>1/100, <1,10)	Rare (>1/10000, <1/1000)	Very rare (<1/10000)
General			Hypersensitivity reaction
Cardiovascular		Hypotension (with intravenous infusion)	
Gastrointestinal	Redness of rectal mucous membranes		
Liver		Increased levels of hepatic transaminase enzymes	

Side-effects - Dosing in Low Body Weight

In 2010, there was significant publicity about the role of IV paracetamol in the tragic death of a 19-year-old girl in Scotland.

Her low body weight had not been taken into account when IV paracetamol was prescribed, leading to an inadvertent but significant overdose of the drug. As a result, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued a Drug Safety update at the time, to remind prescribers of the need to adjust dosing of IV paracetamol in individuals with low weight.

Table 1 shows the dosing of standard strength IV paracetamol (10mg/ml).

Patient weight	Dose per administration	Maximum daily dose of paracetamol via any route
≤ 10 kg	7.5 mg/kg	30 mg/kg
> 10 kg to ≤ 33 kg	15 mg/kg	60 mg/kg not exceeding 2 g
> 33 kg to ≤ 50 kg	15 mg/kg	60 mg/kg not exceeding 3 g
> 50 kg with additional risk factors for hepatotoxicity	1 g	3 g
> 50 kg and no additional risk factors for hepatotoxicity	1 g	4 g

Table 1 Dosing of standard strength IV paracetamol (10mg/ml)

Key Points

- Paracetamol is a safe and effective medication for baseline analgesia in all painful conditions, despite its exact mechanism of action remaining unknown
- Paracetamol has a low incidence of side-effects and is generally well tolerated
- Reductions in paracetamol doses should be considered for certain patient groups, including the frail and elderly
- All patients with a weight under 50 kg need weight adjusted doses
- Overdose can cause permanent kidney and liver damage and even death

References

Major source of information:

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