Basic pharmacology of non-opioid analgesics

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Summary

Non-opioid analgesics, such as aspirin, non-steroidal anti-inflammatory drugs and paracetamol, are widely used in the treatment of pain, pyrexia and inflammation. Each has therapeutic advantages and potential disadvantages. This article discusses the indications, cautions and contraindications, adverse effects and interactions of these agents.

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NON-OPIOID ANALGESICS such as paracetamol, aspirin and the non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all therapeutic agents (Chowdhury 2006). Their chief use is in the treatment of mild to moderate pain, but they also have anti-pyretic and anti-inflammatory effects (Waterfield 2008). This article aims to give healthcare professionals an insight into the pharmacokinetics and pharmacodynamics of these drugs. Indications for their use, contraindications, adverse effects and drug interactions are also discussed.

Aspirin

Indications Aspirin is indicated for pain associated with headache, musculoskeletal disorders and dysmenorrhoea (Jordan 2008). It also has an antipyretic action and some anti-inflammatory effects. The normal adult dose to treat pain is 300-900mg every four to six hours up to a maximum of 4g daily (British National Formulary (BNF) 2009). Aspirin is an effective analgesic (Chowdhury 2006), but its use is limited by its side effects, and paracetamol is generally preferred because it has similar efficacy and fewer side effects (BNF 2009). In practice, aspirin is prescribed mainly in low doses (75-150mg daily) with the aim of preventing thromboembolic disorders (BNF 2009).

Pharmacodynamics Aspirin achieves its analgesic, anti-inflammatory and antipyretic actions by inhibiting the activity of the enzyme cyclooxygenase 2 (COX-2). This enzyme is generated in acutely inflamed tissues and converts a substance known as arachidonic acid to prostaglandins. Prostaglandins are major contributors to the production of pain, inflammation and increased body temperature. Aspirin inhibits the synthesis of prostaglandins and appears to reduce pain, limit inflammation and reset temperature control to normal levels (Simonsen *et al* 2006, Greener 2009). Aspirin also inhibits the cyclooxygenase enzyme COX-1. This can make the stomach more susceptible to injury in some patients (Wallace 2008).

Pharmacokinetics Aspirin is usually administered orally. Absorption into the blood stream occurs in the stomach and the small intestine. Following absorption, aspirin is widely distributed from the blood throughout the body tissues. Absorption can be delayed by the presence of food in the stomach and is impaired in patients experiencing migraine attacks, because migraines appear to reduce gastric mobility. Aspirin is metabolised in the liver and excreted by the kidney (Chowdhury 2006)

Cautions and contraindications Aspirin is contraindicated in patients with a history of hypersensitivity to the drug. This includes any history of asthma, angioedema, urticaria or rhinitis precipitated by aspirin (Chowdhury 2006, Waterfield 2008). Aspirin can trigger asthma attacks (Simonsen *et al* 2006). The mechanism may be that inhibition of COX-1 results in the formation of the inflammatory mediators responsible for allergy and hypersensitivity (Jordan 2008). It is recommended that aspirin, and products containing aspirin, should not be used in children under the age of 16 years because

of an association with Reye's syndrome, a potentially fatal neurological condition in children (Chowdhury 2006, BNF 2009).

Because aspirin inhibits the synthesis of prostaglandins, which can result in increased stomach acid secretion, it is contraindicated in patients with a history of previous or active peptic ulceration (Waterfield 2008). Aspirin can inhibit the formation of thromboxanes, which promote platelet aggregation and adhesion; therefore it should not be used in patients with haemophilia. It should be used with caution in older adults and in those with hepatic or renal impairment.

Adverse effects The use of aspirin is limited by its side effects, with gastrointestinal irritation and ulceration being the most common. In normal doses, aspirin is associated with slight bleeding from the stomach in about 70% of people (Greenstein and Gould 2009). This can lead to anaemia if the drug is taken continuously over a long period of time. Aspirin can occasionally cause a severe haematemesis and, in larger doses, it can affect the eighth cranial nerve, causing dizziness, tinnitus and temporary deafness (Waterfield 2008). Adverse effects, cautions and contraindications, are summarised in Table 1.

Interactions Almost all drugs bind to plasma proteins when absorbed into the blood stream. If a patient is given two drugs with a high degree of binding to the same plasma protein, one drug can displace the other from its plasma binding site. This increases the concentration of the unbound drug in the blood stream, which can lead to potentially harmful increased effects (Simonsen *et al* 2006).

Aspirin is highly protein bound and can interact with several other protein bound drugs by displacing those drugs from the sites to which they usually bind (Chowdhury 2006). Therefore, it is essential to consider the possibility of drug interactions when prescribing aspirin. For example, aspirin could enhance the effects of anticoagulants, partly by displacing them from their plasma binding sites, which increases the risk of bleeding.

TABLE 1

Cautions, contraindications and adverse effects associated with non-opioid analgesics

	Aspirin	Non-steroidal anti-inflammatory drugs (NSAIDs)	Paracetamol
Cautions and contraindications	Contraindicated in children under the age of 16 years. Contraindicated in patients with a history of hypersensitivity to the drug. Contraindicated in patients with haemophilia. Contraindicated in patients with previous or active peptic ulceration. Use with caution in older adults and patients with renal or hepatic impairment.	Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID. Contraindicated in patients with active peptic ulceration. Contraindicated in pregnancy and breastfeeding. Contraindicated in patients with coagulation defects. COX-2 inhibitors are contraindicated in patients with ischaemic heart disease, cerebrovascular disease, peripheral arterial disease and moderate or severe heart failure. Use with caution in patients with renal, hepatic or cardiac disease.	Caution should be exercised in patients with a history of alcohol dependence or hepatic impairment.
Adverse effects*	Reye's syndrome in children. Gastrointestinal irritation. Gastrointestinal bleeding. Dizziness, tinnitus and temporary deafness. Hypersensitivity responses.	Gastrointestinal effects, nausea, diarrhoea, bleeding and ulceration. Allergic skin reactions. Thromboembolic disease. Renal impairment. Cardiovascular disease. Disruption of natural healing processes. Neurological effects. Hypersensitivity responses.	Skin rashes and blood disorders have been reported.

*Refer to Jordan (2008) for further information on adverse effects

The risk of bleeding also increases when aspirin is given with warfarin because of the enhanced antiplatelet effect (Chowdhury 2006, BNF 2009). Some common interactions are described in Table 2. Strategies to minimise adverse drug interactions are outlined in Box 1.

Non-steroidal anti-inflammatory drugs

Indications NSAIDs form a large group of drugs used to treat pain and inflammation in rheumatic conditions. Other uses include the treatment of back pain and soft tissue disorders such as muscle and ligament strains. NSAIDs are also used to treat dysmenorrhoea, post-operative pain and migraine. Examples include ibuprofen, diclofenac, naproxen and fenoprofen (Waterfield 2008).

TABLE 2

Examples of drug interactions*

Drugs co-administered	Effect
Co-administration of non-steroidal anti-inflammatory drugs (NSAIDs) and calcium channel blockers, nitrates, alcohol, anticoagulants, herbal remedies such as feverfew. Co-administration of intravenous diclofenac and heparins.	Bleeding increased.
Co-administration of more than one NSAID, alcohol, oral anticoagulant, corticosteroids or selective serotonin reuptake inhibitors.	Increased gastrointestinal side effects.
Co-administration of NSAIDs and angiotensin-converting enzyme inhibitors, calcium channel blockers, beta blockers, thiazide diuretics.	Effects of antihypertensive drugs reduced.
Co-administration of NSAIDs and oral hypoglycaemics.	Increased risk of hypoglycaemia.
Co-administration of NSAIDs and morphine.	NSAIDs may increase myoclonus associated with morphine.
Lithium, digoxin, quinolones, methotrexate.	Accumulation can occur when co-administered with NSAIDs. Aspirin does not interact with lithium and digoxin.
Metoclopramide and NSAIDs.	Absorption of NSAIDs increased.
Co-administration of NSAIDs and cholestyramine, opioids, atropine, antipsychotics, tricyclic antidepressants.	Absorption of NSAIDs reduced.
Long-term co-administration of paracetamol and warfarin.	Can enhance the actions of warfarin.

*Refer to Jordan (2008) for further information on interactions

Pharmacodynamics NSAIDs are similar to aspirin in that they act by inhibiting the COX-2 enzyme. This action suppresses the formation of the prostaglandins produced in response to tissue damage, which results in reduced pain and inflammation. The development of newer NSAIDs – such as celecoxib and etoricoxib – which selectively inhibit the COX-2 enzyme (that is, they do not appear to affect COX-1) has been associated with a reduction in gastric adverse effects (National Prescribing Centre (NPC) 2008). These new drugs are known as COX-2 inhibitors to differentiate them from the traditional, non-selective NSAIDs.

Some general principles can be applied to all NSAIDs. There is no preferred drug, because patients vary in their tolerance and response to these drugs. About 60% of patients will respond to any NSAID, but those who do not respond to one may well respond to another (BNF 2009). In single doses, NSAIDs have analgesic activity comparable with that of paracetamol, and in regular full dosage have a lasting analgesic and anti-inflammatory effect (BNF 2009). NSAIDs reduce pain and fever rapidly (within an hour), but take up to three weeks to reduce inflammation (Jordan 2008).

Pharmacokinetics NSAIDs are absorbed rapidly following oral administration and they bind to plasma proteins. NSAIDs are metabolised by liver enzymes with 5-10% excreted unchanged in the urine (Chowdhury 2006).

Cautions and contraindications NSAIDs are contraindicated in patients with active peptic ulceration because these drugs can irritate the lining of the gastrointestinal tract. The most important of the systemic effects of NSAIDs for inducing gastric ulceration is their ability to suppress prostaglandin synthesis (Wallace 2008). Prostaglandins are important in maintaining the integrity and blood supply to the lining of the gut, and they are integral to the natural healing processes (Jordan 2008). NSAIDs should be used with caution in patients with renal, hepatic or cardiac disease. These drugs should also be used with caution in older adults because renal function tends to decline with age and older people are particularly vulnerable to gastric side effects (Chowdhury 2006). Caution is also advised when used in pregnancy and breastfeeding and in patients with coagulation defects (BNF 2009).

Selective COX-2 inhibitors are contraindicated in patients with ischaemic heart disease, cerebrovascular disease, peripheral arterial disease and moderate or severe heart failure. These newer NSAIDs should be used in preference to standard NSAIDs only when specifically indicated – that is, in patients who have a high risk of developing gastroduodenal ulcer, perforation or bleeding – and only after an assessment of the patient's cardiovascular risk (Waterfield 2008, BNF 2009).

In October 2006, the Commission on Human Medicines identified that the non-selective NSAID diclofenac is associated with a similar thrombotic risk profile to the COX-2 inhibitors (Duff 2006).

High-dose ibuprofen is also associated with a small increased risk of thrombosis, while naproxen and low-dose ibuprofen are associated with a lower thrombotic risk. Low-dose naproxen and ibuprofen are considered more appropriate than diclofenac for patients who require an NSAID and where cardiovascular risk is a concern (NPC 2008).

All NSAIDs are contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID. This includes patients in whom asthma, angiodema, urticaria, or rhinitis have been triggered by aspirin or another NSAID (BNF 2009).

Adverse effects All NSAIDs are associated with serious gastrointestinal toxicity (BNF 2009) (Box 2), and are the drugs most commonly reported to the national regulatory agencies for adverse effects (Chowdhury 2006). In addition to adverse gastrointestinal effects such as nausea, diarrhoea, bleeding and ulceration, allergic skin reactions have also been reported (Simonsen *et al* 2006). In clinical practice, ibuprofen at low doses has the lowest incidence of gastrointestinal side effects, but its anti-inflammatory properties are weaker. In higher doses it is associated with similar effects to other NSAIDs (Chowdhury 2006).

Serious adverse effects noted with COX-2 inhibitors, such as thromboembolic disease and serious skin reactions, seem to be dose-dependent. It is recommended that the lowest effective dose is used for as short a time as possible (Simonsen *et al* 2006). Regardless of which NSAID is prescribed, co-prescription of gastroprotective treatment such as a proton pump inhibitor, for example omeprazole, is recommended (NPC 2008). Misoprostol, a prostaglandin analogue, can also be co-prescribed with the NSAIDs to reduce gastric and duodenal ulceration (Jordan 2008). Its use is most appropriate for the frail or very old from whom NSAIDs cannot be withdrawn (BNF 2009).

There is no robust evidence that prescribing a selective COX-2 inhibitor plus gastroprotective treatment offers any significant advantage over the prescription of a traditional NSAID plus gastroprotective treatment in preventing gastrointestinal complications (NPC 2008). It remains essential that patients on long-term NSAIDs are reviewed frequently so that the need for treatment can be evaluated on a regular basis (Chowdhury 2006). The adverse effects of NSAIDs, their cautions and contraindications, are summarised in Table 1.

Interactions NSAIDs can interact with a wide variety of drugs, and many of the interactions are the same as those listed for aspirin. The NSAID drug interactions section in appendix 1 of the BNF (2009) should be consulted for a comprehensive list. Given the large number of interactions between NSAIDs and a variety of drugs, it is important that prescribers ascertain what other medications a patient is taking before this group of drugs is prescribed. Some common interactions are described in Table 2.

BOX 1

Minimising the risk of adverse drug interactions

To minimise the risk of an adverse drug interaction, a prescriber must ascertain every drug a patient is taking. This should include prescribed medications, those bought over the counter, herbal and homeopathic remedies. Adverse drug interactions can occur if herbal medications are taken along with conventional drugs. Prescribers also need to consider the potential for drug-food interactions.

It is impossible to remember every potential drug interaction, but it is useful for prescribers to know where they can access appropriate information (Reddy 2006). The list of drug interactions in the *British National Formulary* is important in helping a prescriber to decide the interactions that could be clinically significant in a patient (Cossey 2004). Further information on drug interactions can be obtained from sources such as *Drug Safety Update*, or specialist textbooks such as *Adverse Drug Interaction: A Handbook for Prescribers* (Karalliedde *et al* 2010).

In primary care, most computer systems will flag up a drug interaction, but prescribers should not be too reliant on these systems as they may not be comprehensive (Reddy 2006).

BOX 2

Risk factors for non-steroidal anti-inflammatory drug (NSAID)-induced adverse effects on the gastrointestinal tract

- Increasing age: 65 years and over.
- Previous history of peptic ulcer or gastrointestinal bleeding.
- Serious comorbidities or disability, such as coronary heart disease, renal or hepatic impairment, diabetes or hypertension.
- Type of NSAID and whether using a combination of NSAIDs.
- Prolonged duration of NSAID use and taking the maximum recommended doses.
- Concomitant use of medications known to increase the risk of upper gastrointestinal adverse events, for example anticoagulants, aspirin and corticosteroids.
- *Helicobacter pylori*.
- Lifestyle factors such as smoking and alcohol consumption.

(Waterfield 2008)

Paracetamol

Indications Paracetamol is a suitable first-choice analgesic for most patients with mild to moderate pain (NPC 2000, BNF 2009). In adults and

children over 12 years of age, it is given in doses of 0.5-1g four to six times daily, up to a maximum of 4g daily (Chowdhury 2006, BNF 2009).

Pharmacodynamics and pharmacokinetics The mechanism of action of paracetamol, which has both analgesic and anti-pyretic properties, is poorly understood (Chowdhury 2006). It is thought the antipyretic action is caused by inhibition of prostaglandin synthesis in the brain and the analgesic effect is the result of the selective inhibition of the COX-3 enzyme in the brain and spinal cord (Waterfield 2008). Paracetamol has no significant effect on COX-1 and COX-2 enzymes, which explains its lack of anti-inflammatory action and lack of unwanted gastrointestinal side effects (Waterfield 2008).

Paracetamol is well absorbed orally, and peak plasma concentrations are usually achieved well within 60 minutes (Greenstein and Gould 2009). The proportion bound to plasma proteins can vary and the drug is almost completely metabolised in the liver (Chowdhury 2006). The main disadvantage of paracetamol is that an overdose of the drug can cause irreversible and life-threatening liver damage. Toxic doses may not be much higher than therapeutic doses and serious paracetamol poisoning causes few symptoms in the first two days following ingestion. This can result in a failure to appreciate the severity of the poisoning.

When the symptoms do appear it can be too late to start treatment (Simonsen *et al* 2006). It is important to ensure that patients are aware of the recommended maximum dosage of paracetamol and are advised to avoid using more than one paracetamol-containing preparation at a time (Chowdhury 2006).

Cautions and contraindications Caution should be exercised in patients with a history of alcohol dependence or hepatic impairment since this may inhibit the metabolism of paracetamol and lead to toxicity even at normal therapeutic doses. Paracetamol is not known to be harmful in pregnancy and at recommended doses the amount transferred in the breast milk is too small to be harmful (BNF 2009).

Adverse effects Paracetamol is well tolerated at normal therapeutic doses and, while adverse effects are uncommon, skin rashes and blood disorders have been reported (BNF 2009). Paracetamol has a major advantage over aspirin and the non-selective NSAIDs in that it does not cause gastric irritation. As a result, paracetamol is preferred, and generally considered a safer alternative, to these drugs, particularly in older adults (Chowdhury 2006). Table 1 summarises cautions, contraindications and adverse effects for paracetamol.

Interactions Paracetamol has no clinically significant interactions with other drugs (Table 2). It can be co-prescribed with warfarin, although prolonged regular use of paracetamol may enhance the anticoagulant effect (BNF 2009).

Conclusion

Aspirin, NSAIDs and paracetamol are therapeutic agents that can be used in the management of pain, pyrexia and inflammatory conditions. Aspirin and NSAIDs are associated with significant side effects, contraindications and interactions, and currently the use of prescribed aspirin is mainly limited to prophylaxis against vascular disease. In contrast to aspirin and NSAIDs, paracetamol is well tolerated, has few side effects and may represent a better option for most patients requiring analgesic therapy. However, the advantages of paracetamol may be overshadowed by the potential risk of overdosage and hepatoxicity.

Before prescribing non-opioid analgesics it is important to take a comprehensive medical history from the patient. This, coupled with the use of information sources such as the BNF to identify contraindications and the potential for adverse effects and interactions, is essential for safe prescribing practice **NS**

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