Aspirin Use in the Older Adult

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Introduction

Aspirin is a very commonly used medication with many older adults taking it for a variety of reasons. Deborah Robertson outlines the uses and actions of Aspirin in the elderly.

Main Introduction

Aspirin is a commonly used medication. This familiar drug has been around for over 100 years with its discovery as a medicine first being attributed to the German chemist Felix Hoffmann in 1897 who was working under the direction of Arthur Eichengrün (Sneader 2000). Aspirin belongs to a group of drugs called salicylates and is known as a Non-Steroidal Anti-Inflammatory Drug (NSAID). Although aspirin belongs to the category of medicines known as NSAIDs its mechanism of action differs slightly from other drugs within that class as it has many actions. With increasing knowledge of the effects of this drug, many uses for it have come to light over the last few decades along with our knowledge of side effects, adverse effect and implications for use in vulnerable groups such as the elderly. It is well known to many as an effective analgesic with anti-inflammatory properties and has served this purpose since its discovery at the turn of the 20th century. Modern medicine recognises aspirin's use in many areas of pain management but also utilises its pharmacological properties as an anti-pyretic and as an anticoagulant both in primary/secondary prevention (Bartolucci , Tendera and Howard ; 2011,Lawlor *et al* 2001) and in clot reduction and thrombolysis. More recent research has implicated aspirin in cancer prevention, with a particular focus being on colorectal cancer (Asano and McLeod 2004; Cooper *et al* 2010) but this will not be discussed here.

This article will elucidate the mechanisms of action of aspirin from a basic pharmacological perspective which will illustrate the drugs beneficial effects as well as to explain the chemical basis for some of its common side effects, especially in the elderly population. Further information will provide rationale for dosage, management and monitoring of the patient prescribed aspirin.

Pharmacology of Aspirin

As previously mentioned aspirin belongs to the category of NSAIDs and has a salicylate chemical structure. This salicylate is a pharmacologically active compound in itself and adds to aspirin's mechanism of action.

Mechanism of Action- Pharmacodynamics

So how does the drug aspirin work in the body, and why does it have so many therapeutic indications? We have to look at how aspirin pharmacology works at a cellular level for those answers to become clear. To simplify this as much as possible, the explanations are broken down into aspirin's clear therapeutic areas.

Aspirin as an analgesic and an anti- inflammatory

Aspirin's analgesic activity is largely derived from its action as an anti-inflammatory agent so we will consider these aspects together.

Aspirin's anti-inflammatory activity stems from its action on the cyclooxygenase (COX) enzyme group. The COX enzymes are responsible for the production of prostaglandins, notably the inflammatory prostaglandin H2, within the body (see Figure 1). They are synthesised from the fatty acid arachidonate which is obtained from the diet.

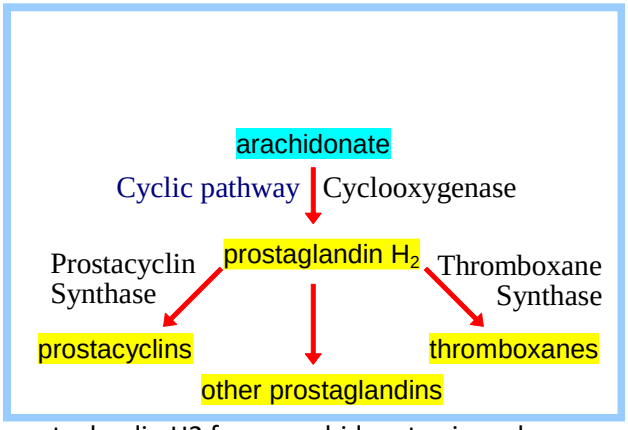

Figure 1. The production of prostaglandin H2 from arachidonate via cyclooxygenase enzyme.

This is a simplistic view of the pathway as there is more than one COX enzyme responsible for the physiological functions, the main two can be seen in figure 2.

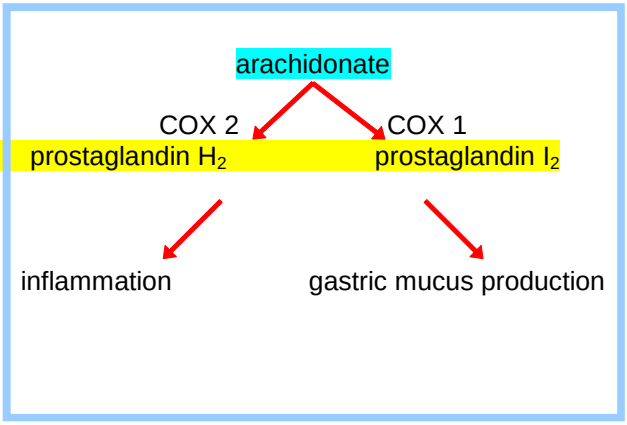

Figure 2. The production of prostaglandins from arachidonate via cyclooxygenase enzymes 1 and 2.

Aspirin, in common with other NSAIDs, is an inhibitor of the COX enzyme therefore blocking the conversion of arachidonate to the subsequent prostaglandins. As you can see form the figures, this can be beneficial in blocking the inflammatory pathway initiated by prostaglandin H_2, but has the detrimental effect of blocking prostaglandin I_2 which produces gastric mucus and has a role in stomach protection as well as other prostaglandins. Different mechanisms stimulate the two types of cyclooxygenase. COX-1 is stimulated continuously by normal body physiology and its concentration in the body remains stable. It is present in most tissues and converts arachidonate into prostaglandins. These prostaglandins in turn stimulate normal body functions, such as stomach mucus production and kidney water excretion, as well as platelet formation. The location of the COX-1 enzyme dictates the function of the prostaglandins it releases, stomach wall, kidney or vasculature. In contrast, the COX-2 enzyme needs to be induced. COX-2's most important role is in inflammation. COX-2 is involved in producing prostaglandins for an inflammatory response (Barber and Robertson 2012).

Another function of some prostaglandins is in the pain pathway. Aspirin can reduce the responsiveness of the C-fibres (polymodal nociceptors) to inflammation, thereby reducing their effectiveness in the transmission of pain (McGavock 2005).

Aspirin as an anti-pyretic

Aspirin's anti-pyretic activity can be linked to its effects as an NSAID (Rang and Dale et al 2011). Its action here is in the hypothalamic region of the brain where its irreversible inactivation of COX enzymes causes a 'reset' of the hypothalamic thermostat, helping to reduce fever (Dale and Haylett 2008). This 'reset' remains in place for the duration of aspirin therapy (Greenstein 2008).

Aspirin as an anti-platelet drug

Aspirin's anti-platelet activity is well understood from a pharmacological perspective. Again the link is through COX enzymes and the thromboxane pathway (see figure 1). The process of platelet adhesion is part of the clotting cascade, the platelets release granules causing white blood cells to stick to the platelets. During this the platelets also release a substance known as thromboxane (TXA_2). This increases the ability of the cells to stick together and form the clot, or thrombus. As aspirin inhibits thromboxane production in the cascade reducing platelet adhesion and aggregation (Barber and Robertson 2012) it is a powerful inhibitor of this aspect of the clotting cascade (Neal 2012). This action helps prevent clot formation and is an important clinical action in the prophylaxis of myocardial infarction and stroke (Rang and Dale et al 2011)

As this effect of aspirin is achieved at a relatively low dose (75-300mg), mostly due to inhibition on COX-1, it often avoids many of the side effects associated with aspirin use.

Pharmacokinetic Effects

Pharmacokinetics can be broken down into the 4 processes seen in Box 1.

Pharmacokinetic Process	
Absorption	from administration site Absorption is generally complete except where enteric coatings are used
Distribution	into blood stream and body systems- There is wide distribution into most body tissues but there is extensive binding to plasma proteins. This is important when considering generation of adverse effects and interactions with other medications.
Metabolism	by the liver- by Hepatic hydrolysis and conjugation
Excretion	by the kidney- 10% salicylic acid, 75% salcycluric acid and 15% glucuronide conjugates, it is dialyzable, useful in overdose

Box 1. Pharmacokinetic Processes

Aspirin is predominantly given as a solid oral medication although other formulations do exist (dispersible oral preparations and suppositories). Oral medications are absorbed from the upper gastrointestinal tract and absorption of aspirin occurs partly in the stomach but mostly in the duodenum. It is rapidly absorbed and is well distributed in the plasma and tissue with some of the drug binding to plasma proteins (Greenstein 2008).

Metabolism occurs in the liver where it is first hydolysed to salicylate (active metabolite) then further metabolised to (inactive metabolites) ready for excretion. Excretion is predominantly renal at the tubular level and aspirin, in common with other NSAIDs can have a detrimental effect on kidney function due to actions on the renal tissues. Active to inactive metabolite excretion occurs in a ratio of 20:80 (McGavock 2005).

The older adult, due to manifestations of normal ageing, may have altered pharmacokinetic parameters, especially decreased liver and kidney function which may have an effect on half-life.

Side Effects, Cautions for Use and Adverse Reactions

Aspirin therapy is often associated with side effects, many of them common to the NSAID class of drugs, some of them tolerable or an inconvenience, but some significant and potentially life threatening. Aspirin must be given with care in many patient groups and a thorough knowledge of the patients medical history and current medications is essential.

Contraindications and Cautions

There are some contraindications to aspirin therapy as well as many areas where aspirin should be prescribed with caution or extreme caution. The British National Formulary [BNF] (Joint Formulary Committee 2012) is an invaluable source of information for anyone involved in the prescribing or administration of aspirin to patients. Some patient groups, especially the elderly, are more vulnerable when it comes to aspirin therapy.

Renal failure

Aspirin use in patients with a degree of renal failure (as many elderly patients do) should be used with caution (Joint Formulary Committee 2012) and avoided in those with severe renal impairment. Renal function should be monitored where needed and patients assessed for risk of bleeding before commencement. Aspirin should be commenced at its lowest therapeutic dose.

Liver disease

Patients with severe liver failure should not be prescribed aspirin as there is a greatly increased risk of bleeding from the gastrointestinal tract (Joint Formulary Committee 2012). In those with mild liver impairment, low starting doses are advised along with regular monitoring.

Elderly

Prescribing of any NSAID drug, including aspirin should be done with caution in the elderly population (Joint Formulary Committee 2012). Bleeding associated with aspirin and other NSAIDs is more common in this sub group of patients and they are more likely to have a fatal or serious outcome. It is due to this increased susceptibility to the effects of aspirin that the BNF (Joint Formulary Committee 2012) recommends the measures seen in Box 2.

Indication	Recommendation
osteoarthritis, soft tissue lesions, back pain	first try weight reduction (if obese) , warmth, exercise, and use of a walking stick
osteoarthritis, soft tissue lesions, back pain and pain in rheumatoid arthritis Use of the drugs opposite should be in a stepwise approach	first try paracetamol
	after paracetamol, try low dose NSAID as an alternative
	if neither drug is adequate full dose paracetamol plus low dose NSAID
	if necessary slowly increase NSAID or add in opioid to paracetamol
	do not give 2 NSAIDs at a time (including aspirin)

Box 2- NSAID use in the elderly-recommendations adapted from BNF (Joint Formulary Committee 2012).

Side Effects and Adverse Reactions

Much of this information can be found in any general pharmacology textbook and the information on side effects and interactions can be found in more detail in the British national Formulary (BNF, Joint Formulary Committee 2012)

Gastrointestinal effects

These are among the most common of the side effects seen with aspirin. They range from simple gastric irritation which manifests as indigestion to the more serious events such as peptic ulceration and gastro intestinal bleeding. These side effects should be monitored for and the patient made aware of the risk of these incidences and symptoms to observe for, such as indigestion or reflux which may be an early warning. As we can see from the pharmacology above, we can link the gastric side effect with the drugs cellular effect on prostaglandin production leading to reduced gastric mucus formation and a small effect of prostaglandins on gastric acid output (Rang and Dale et al 2011; Barber and Robertson 2012).

Other effects

Aspirin can cause confusion, especially in the elderly or susceptible patient. Tinnitus and dizziness are other commonly reported adverse effects and skin reactions can occur. Asthmatic patients who take

aspirin or other NSAIDs may suffer bronchospasm and their use in asthma should be with careful consideration. Leukotriene pathways can be affected by aspirin which can lead to this effect in some patients. Aspirin should not be given to children due to the possibility of Reyes Syndrome (Joint Formulary Committee 2012) unless under specialist supervision for conditions such as Kawasaki syndrome.

Aspirin in overdose

Aspirin overdose can be described as acute or chronic in nature. Acute overdose is an isolated incident of excess ingestion. Chronic overdose can build up over time even at normal doses if the individual becomes sensitive or enters an at risk group. Treatment can consist of gastric lavage and forced alkaline diuresis. This will clear any non absorbed drug from the stomach and the diuresis increases the excretion of the active metabolites (Greenstein 2008).

Dose Schedules

As the drug has many indications, it also has many dose schedules. These depend on the indication for which aspirin is being prescribed.

Analgesic doses

With the advent of many safer simple analgesics, the use of aspirin in this area is limited but for many who chose to take it aspirin remains an effective simple analgesic and is a popular and widely used component of many over the counter analgesic preparations. Available as 300mg tablets, the typical dose for analgesic activity is 300mg-900mg no more than four times per day, in regularly spaced doses. These doses however are at the level which if taken regularly causes many of the common side effects of aspirin.

Anti-platelet doses

For many readers of this article, this will be the most familiar use of the drug aspirin. It has its anti-platelet activity at a dose much lower than those needed for analgesia. A daily dose of 75mg of aspirin is sufficient to have anti-platelet activity of therapeutic benefit. This low dose also helps to avoid many of the side effects associated with aspirin. The dose should be taken at the same time each day to maintain therapeutic plasma levels. In prevention of myocardial infarction, stroke and other embolic events 75mg is the starting dose but may be increased to 300mg daily.

Anti-inflammatory doses

The doses of aspirin used in inflammatory conditions can vary depending on the condition being treated and the age group of the patient. Simple anti-inflammatory uses require doses similar to that used for analgesia, 300-900mg no more than four times daily in regularly spaced doses. More complicated inflammatory conditions requiring NSAID use usually initiated by specialist prescribers.

Interactions

Again in common with other drugs in the NSAID class, aspirin interacts with many other prescribed and over the counter (OTC) medicines. It is vital therefore than careful consideration is given to any other medicines the patient is taking before commencement of aspirin so that a full risk/benefit analysis can be undertaken. Interactions are mostly pharmacodynamic in origin, that is, they occur when one drug has a similar effect to another and the effect can be additive or cumulative.

The commonest of these is the additive anti-coagulant effect when aspirin is taken with other medicines such as warfarin or heparins (Joint Formulary Committee 2012). Giving these medications concurrently greatly increases the risk of unwanted bleeding and should be avoided. Checking with your pharmacist or making use of the BNF or Stockley's Drug Interactions guide is always recommended.

Management and Monitoring

As one can imagine with Aspirin, review and monitoring of patients who take this drug, is an important factor to consider. It is essential that patients and carers are aware of the need for regular review of their medication regimes when aspirin is included. Monitoring should include the effects of the medication, side effects and signs of interaction.

Summary

Aspirin's longevity as a therapeutic medicine can be attributed to its effectiveness and multiplicity of uses. Despite its versatility it is not a drug that can be taken without risk and must be used with caution, especially in the elderly population and people with co-morbid conditions. Interactions and side effects are commonly encountered and these should be outlined to patients on commencement of the medication. Regular monitoring and review of patients on aspirin is recommended as safe and effective practice and should be built into a patient's package of care.

Research continues into aspirin use and benefits in many therapeutic areas and ongoing investment and studies into its actions will ensure that this popular drug will be with us for many years to come.

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