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Aspirin: old and new

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ABSTRACT Aspirin (acetylsalicylic acid) is one of the most commonly used drugs today. Initially used as a potent analgesic, anti-inflammatory and antipyretic agent, its uses have expanded considerably over the years, and new therapeutic indications are still being researched. This review looks briefly at the established uses and outlines some of the developing areas.

KEYWORDS Adverse effects, aspirin, cyclo-oxygenase, therapeutic uses

LIST OF ABBREVIATIONS Antiphospholipid syndrome (APS), confidence interval (CI), central nervous system (CNS), cyclo-oxygenase (COX), cardiovascular disease (CVD), *in vitro* fertilisation (IVF), gastrointestinal (GI), myocardial infarction (MI), nonsteroidal anti-inflammatory drugs (NSAIDS), prostaglandin H_2 (PGH), relative risk (RR), thromboxane (TX)

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MECHANISM OF ACTION

The principal mechanism of action of aspirin is that it permanently inactivates the COX activity of the COX enzymes, COX-1 and COX-2. COX-1 is expressed constitutively in many tissues and seems to be relevant to the tissue homeostatic functions of prostaglandins, and COX-2, an inducible form produced in response to external stimuli, has a role in many inflammatory and proliferative reactions. These isoenzymes catalyse the first step in prostanoid biosynthesis, the conversion of arachidonic acid to PGH_2 which is the immediate precursor to $PGE_{2'}$ $PGF_{2\acute{a}'}$ $PGI_{2'}$ and TX $A_{2'}$. The irreversible nature of the inhibition produced by aspirin (in contrast to most NSAIDs which are reversible inhibitors) means that it requires generation of new enzyme to restore function, which can only be achieved in nucleated cells.

Aspirin, therefore, acts as an analgesic by peripheral inhibition of COX-2 formation at the site of tissue injury, and centrally within the CNS. Its antipyretic effects are also central. Its cardiovascular effects are exerted in the platelet (where aggregation is an important part of platelet function) and the vessel wall. In the endothelium, it reduces production of the antiaggregatory prostacyclin (largely a COX-2 effect). In the platelet, it inhibits the formation of the proaggregatory thromboxane (largely a COX-1 effect) which lasts for the ten-day lifetime of the platelets. The overall balance is to reduce platelet adhesiveness to cells such as endothelial cells.

USES

Aspirin as an analgesic, antipyretic and anti-inflammatory agent

Aspirin is a highly effective analgesic and is widely prescribed in general practice or bought over the counter in the community. It is used in treating mild to moderate pain, especially headaches, but can also be used in some forms of severe chronic pain. Despite the introduction of many new NSAIDs, aspirin still has a significant role in the treatment of diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis and spondyloarthropathies, due to its better tolerability. Aspirin is also effective in relieving the symptoms of fever, but should not be given to children or adolescents where it may cause Reye's Syndrome.

Aspirin as an antithrombotic agent

Use as prophylaxis for cardiovascular events (see Table 2). One of aspirin's major uses today is in the primary and secondary prevention of cardiovascular diseases. Aspirin is an effective antithrombotic agent in doses of 50–100 mg, and even doses as low as 30 mg may be effective (see Table 1).[1] Aspirin at a dose of 75 mg daily in people with occlusive vascular disease (secondary prophylaxis) reduces the risk of non-fatal MI by a third; non-fatal stroke by a quarter; and vascular mortality by a sixth. In people without pre-existing occlusive vascular disease, use of low dose aspirin (primary prophylaxis) depends critically on the balance between the absolute thrombotic risk of developing cardiovascular disease (defined as non-fatal MI, stroke, coronary and stroke death, and new angina) and the haemorrhagic risk to the patient.[2–4] In patients with antiphospholipid syndrome who have already had a

TABLE 1 Vascular disorders for which aspirin has been shown to be effective and minimum effective doses.[1]

Disorder	Minimum effective daily dose, mg
Men at high cardiovascular risk	75
Hypertension	75
Stable angina	75
Unstable angina	75
Acute MI	160
Transient ischaemic attack & ischaemic stroke	50
Severe carotid artery stenosis	75
Acute ischaemic stroke	160

TABLE 2 Indications for considering low-dose aspirin to prevent CVD events.

Indications for primary prevention

- 50 years with a total CVD risk of ≥20%
- End organ damage from hypertension
- Type II diabetes who are over 50 years
- Selectively in diabetes <50 years with one of the following:
  1. disease for more than 10 years
  2. already treated for hypertension
  3. retinopathy or nephropathy, and blood pressure controlled to ≤150/90

Indications for secondary prevention

- Coronary heart disease (MI, stable and unstable angina)
- Stroke
- Transient ischaemic attack
- Peripheral vascular disease

TABLE 3 Risk of stroke in atrial fibrillation if taking antithrombotic therapy.

Risk Group	Risk of stroke if untreated	Risk of stroke if on aspirin	Risk of stroke if on warfarin	NNT
Very high Previous ischaemic stroke or TIA	12%	10%	5%	13
High > 65 years and one other risk factor from: hypertension, diabetes, heart failure or left ventricular dysfunction	5–8%	4–6%	2–3%	22–47
Moderate > 65 years and no other risk factors < 65 years and other risk factors	3–5%	2–4%	1–2%	47–83
Low < 65 years and no other risk factors	1–2%	1%	0·5%	200

stroke, aspirin seems as effective as warfarin in preventing recurrence of the stroke.

Other cardiovascular uses

Aspirin is also used in the treatment of acute coronary syndromes, including MI, and acute stroke (once haemorrhage has been excluded).

Atrial fibrillation, even in the absence of valvular heart disease, increases the risk of thromboembolism six-fold. Aspirin can reduce the risk of thromboembolic stroke by about a fifth, but is less effective than warfarin, where the risk reduction is about two thirds. Aspirin, however, is associated with fewer serious adverse effects than warfarin. Treatment with warfarin is therefore preferred in people at high risk of stroke, unless contraindicated. But in people at moderate risk, practice is more variable, though most still use warfarin in this situation. The decision on which to use for moderate risk should ultimately be made after carefully weighing the overall risk of stroke compared to bleeding and taking into account the individual's personal preference. People under 65 years with no other risk factors are at low risk and should not be given antithrombotic prophylaxis, unless aspirin is given for other indications. Table 3 stratifies the risk of stroke and the degree of benefit from treatment with either aspirin or warfarin.[2]

Finally, aspirin can be used in patients who have had certain revascularisation procedures, such as angioplasty and coronary bypass operations, if they have a vascular condition for which aspirin is already indicated. It has no effect on graft survival following femoral-popliteal bypass with native veins, but is beneficial, alone or with dipyridamole, where a prosthetic bypass has been used.

Aspirin and cancer prevention

Several retrospective studies have shown that prophylactic long-term use of aspirin daily, and to a lesser extent NSAIDs, is associated with a halving in the risk of developing colorectal cancer.

Prospective research on the prevention of colorectal cancer has often focused on colorectal adenomas,

assuming that the effects of chemopreventive agents on adenomas will reflect their effects on cancer. This avoids the size and duration required for trials using colorectal cancer itself as the outcome. Two large randomised prospective trials looking at adenomas in high risk patients have now provided further supportive evidence. In the first study, in patients with a previous colorectal cancer, aspirin (325 mg) had a moderate effect in preventing recurrent adenomas at twelve months (17% in aspirin group vs 27% on placebo, RR 0·65, CI 95% 0·46–0·91). In the second study, patients with colonic adenomas receiving 81 mg aspirin daily showed a 19% reduction in the risk of recurrent adenomas (CI 95% 0·69 0·96). However, this beneficial effect was not seen at a higher dose of 325 mg daily and it is unclear why this was so. A third, smaller, study also showed a reduction in the recurrence of larger adenomas. Overall, the evidence is encouraging but not conclusive. Other studies show that aspirin or NSAIDs may be protective against gastric cancer, and possibly against cancers of the oesophagus, prostate, ovary, breast and lung.[5]

Several mechanisms by which aspirin and NSAIDs might prevent carcinogenesis have been postulated. The main mechanism is thought to be by inhibiting synthesis of prostaglandins (especially PGE_2) which are potent signalling molecules and have a key role in carcinogenesis. Lipoxygenase-mediated apotosis induced by NSAIDs in colon cancer cells has also recently been reported. Another hypothesis is that these drugs induce the expression of a protein, p21, that is involved in regulation of normal cell growth. There is also genetic variability in the response of individuals to the protective effects of NSAIDs based on polymorphisms leading to variable activity of their metabolising COX isoenzymes.

Cancer chemoprevention using aspirin and NSAIDs offers tantalising prospects for the future. However, detailed considerations of the total benefit in relation to toxicity, as well as the most appropriate dose, are needed before aspirin can be recommended routinely for this use.[6]

Aspirin, cognitive decline and dementia

Several observational studies have reported that low dose aspirin and other NSAIDs may protect against dementia of vascular and/or Alzheimer's type. Protection against cerebral vascular disease is not surprising perhaps, but protection against Alzheimer's disease is less obvious. Cerebrovascular disease has also been implicated in the clinical manifestations of Alzheimer's. Alzheimer's disease may also, at least partially, be due to inflammatory processes in cognitive brain centres, the microglia being of central importance. Aspirin and NSAIDs might attenuate the inflammation (in which case low-dose aspirin may be insufficient treatment). More likely is the hypothesis that any anti-dementia effect is independent of changes in cyclo-oxygenase activity and occurs by influencing processing of beta amyloid-42 peptide, the principal component of amyloid plaques, an effect that has been shown to occur at clinically low doses of aspirin. The jury is still out on the use of aspirin as a simple intervention against cognitive decline, and randomised prospective trials are needed to confirm this. Although there are as yet no such trials, most UK and Canadian specialists consider aspirin should be prescribed in patients with cognitive impairment and vascular risk factors.[7]

Aspirin in pregnancy complications

Antiphospholipid syndrome

Combined treatment with aspirin (75 mg) and unfractionated heparin in pregnant women with a history of recurrent miscarriages and antiphospholipid antibodies is standard care.

Pre-eclampsia

Low-dose aspirin (75 mg) reduces the risk of pre-eclampsia by around 15% for women at both low and high risk, with a similar reduction in the risk of perinatal death. Aspirin should therefore be considered, particularly in women at high risk. More widespread use may be appropriate in countries with a high prevalence of pre-eclampsia.[8]

Other possible uses

Research is still ongoing but results from some studies done so far show promise in the use of aspirin for the following indications:

- Migraine treatment;
- Prevention of cataracts;
- Improving circulation in gums;
- Prevention of adult leukaemia;
- Prevention of HIV replication;
- Increasing success rates in IVF programmes.

GASTROINTESTINAL SIDE EFFECTS AND TOLERABILITY OF ASPIRIN

Aspirin, regardless of dose or formulation, can cause gastric irritation, increased occult blood loss and sometimes serious GI bleeding. The risk is about 1 in 200 patient years overall, about twice the background risk, and lower with lower doses though never entirely disappearing. Aspirin is safer compared to other NSAIDs, which cause a five-fold increased risk of GI bleeding. Serious adverse GI effects are more likely in patients with underlying risk factors, such as previous GI bleeding, previous peptic ulcer disease, taking concomitant drugs that increase the likelihood of GI bleeding (such as corticosteroids, other NSAIDs) and advanced age. Overall, the benefits of prophylactic low-dose aspirin in prevention of cardiovascular events far outweigh the risks in all but low-risk patients. Studies also show no significant excess risk of intracerebral haemorrhage on aspirin.

OTHER ADVERSE EFFECTS

Other adverse effects of aspirin include pseudoallergy (potentially life threatening in some), nasal polyps, Reye's syndrome in children and adolescents where aspirin is no longer recommended, chronic nephritis, and, in high doses, tinnitus. Deliberate aspirin overdose is less common than paracetamol in the UK, while the reverse is the case in the US.

ASPIRIN RESISTANCE

Aspirin resistance is the inability of aspirin to inhibit platelet activation and aggregation, seen in up to 35% of individuals. The causative mechanisms are multifactorial, including non-compliance with aspirin therapy, inadequate dose, genetic polymorphisms of COX-1 and other genes involved in thromboxane biosynthesis, drug interactions, upregulation of non-platelet sources of thromboxane biosynthesis and increased platelet turnover. Individuals at high risk of aspirin resistance may be treated best with an additional antiplatelet agent, eg clopidogrel. Research is ongoing into defining aspirin resistance, developing reliable tests for it, and establishing the risk of associated cardiovascular events.[9]

ASPIRIN – A DRUG FOR ALL SEASONS?

Aspirin is a valuable drug for many conditions, a fact not appreciated until long after its development. Indeed it could be argued that were a drug with so many mechanisms, and potential benefits and harms put forward for licensing today with the typical data presented for a new drug, it might well be rejected with the manufacturers told to go away until they could define its role better and until they had better evidence!

KEYPOINTS

- Aspirin is one of the most commonly used drugs worldwide.
- Its main mechanism of action is by reducing prostaglandin biosynthesis through inhibition of the cyclooxygenase enzymes.
- Aspirin still plays an important role as an anti-inflammatory agent mainly in rheumatological conditions due to its good tolerability.
- One of the major uses of aspirin is in the primary and secondary prophylaxis of cardiovascular events.
- There is growing evidence that aspirin protects against colorectal carcinoma and probably cancers of the stomach, oesophagus, breast, prostate, and lung, but more robust randomised clinical trials are needed before it can be recommended for this.
- Aspirin and NSAIDs show promise in preventing cognitive decline in vascular and/or Alzheimer's dementia, but further randomised trials are still needed to confirm this.
- Aspirin reduces pregnancy loss in women with antiphospholid syndrome and decreases the risk of pre-eclampsia in women at risk.
- Research is still ongoing into other novel uses of aspirin.

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