



# Aspirin: reinventing itself

Professor Desmond Fitzgerald

**L**ike a successful artist, aspirin keeps reinventing itself. It has managed to keep age at bay by serious and frequent makeovers, so that each new crop of physicians sees a new side of an old drug. And yet the largest market for aspirin remains its initial indication – pain.

## Effective painkiller

Aspirin was the first synthesised drug, generated to reduce the toxic effects of salicylic acid. The new compound was an acetylated derivative of salicylic acid (hence the name, acetylsalicylic acid), a modification that was to extend its life well beyond any drug manufactured since. Aspirin was a highly effective painkiller that was sold worldwide, often from the back of small vans. It has antipyretic, analgesic and anti-inflammatory properties that insured a broad range of uses.

In the 1970s, a well-known side effect of aspirin, inhibition of thrombosis, was successfully applied to cardiovascular disease. Recently, the story has gone full circle with many commentators suggesting that the beneficial effect of aspirin in cardiovascular disease arises from its anti-inflammatory effects.

## Cyclooxygenase and prostaglandins

For most of its life, aspirin was a drug without a known mechanism of action. The discovery of prostaglandins and the enzyme responsible for their generation, cyclooxygenase, ultimately explained its activity. Or so it seemed. Prostaglandins are generated from arachidonic acid, a lipid in all cell membranes. Cyclooxygenase introduces molecular oxygen into arachidonic acid forming a precursor for a

wide range of prostaglandins. These, in turn, have a broad spectrum of biological activity, including inflammation (prostaglandin  $E_2$ ), pain (prostaglandin  $E_2$  and prostacyclin), temperature control (prostaglandin  $D_2$ ) and platelet activation (thromboxane). Aspirin delivers its acetyl group (from acetylsalicylic acid) to a serine in cyclooxygenase, an irreversible reaction that kills the enzyme. In the process, aspirin is converted to salicylic acid. Therefore, how aspirin influences so many processes became evident once this mechanism was elucidated.

## Two cyclooxygenases

Phillip Needleman and his colleagues at the University of Washington had shown for some years that the activity of cyclooxygenase (and therefore the ability of cells to make prostaglandins) could be induced by growth factors and cytokines. The increased activity required the synthesis of a new protein, ultimately called COX-2 to distinguish it from the previously identified COX-1.

COX-1 and COX-2 are the products of distinct genes and so are differentially regulated. COX-1 is in platelets and is responsible for the generation of prostaglandins in the stomach which protect against mucosal injury. COX-2 is largely absent from cells, but is expressed at sites of inflammation. Although similar in structure, they can be distinguished pharmacologically.

Aspirin inhibits both isoforms, although it is more potent against COX-1. By inhibiting COX-1, aspirin inhibits platelet activation and this explains its antithrombotic properties. On the other hand, inhibition of COX-1 in the stomach places some patients at risk of peptic ulceration and, more rarely, gastrointestinal bleeding and perforation.



## Dosing of aspirin

Platelet COX-1 is particularly sensitive to aspirin as platelets turn over slowly and the protein is irreversibly inactivated by acetylation. It is possible to achieve cumulative inhibition of platelet COX-1 using very small doses of aspirin, even as low as 30mg daily. In contrast, at least 30 times more aspirin is required for pain relief or an anti-inflammatory effect.

For this reason, small doses of aspirin are sufficient if the indication is to prevent thrombosis. Moreover, there is no advantage to controlled release or coated aspirins, as they do not abolish the very low rate of gastrointestinal side effects seen with regular aspirin. The dose of aspirin that gives maximal platelet inhibition at minimal cost is 75mg daily. There is additional benefit at higher doses. On the contrary, the risk of gastrointestinal side effects continues to rise with increasing dosage.

## Indications for low dose aspirin

Aspirin is indicated in patients with unstable angina or a prior transient ischaemic attack. Aspirin is also of value in patients with coronary artery or peripheral vascular disease. However, it is unlikely to be of benefit as primary preventative therapy in a healthy population, as the potential benefit (preventing one major cardiovascular event per thousand individuals treated in a year) is offset by the risk of a serious gastrointestinal side effect.

## New uses for an old drug

Epidemiological evidence suggests that aspirin reduces the risk of colon cancer, where COX-2 is expressed and may play a role in protecting the cancer cells from dying. COX-2 has also been implicated in angiogenesis, the formation of new blood vessels surrounding tumours. Another important (re)discovery is that salicylic acid has anti-inflammatory activity, by interfering with proteins that act as inducers of inflammatory genes. Salicylic acid also prevents the proliferation of vascular smooth muscle cells by blocking the effects of growth factors. This activity may explain why aspirin is more effective in vascular disease than would have been predicted from its antiplatelet activity alone.

## Conclusion

In an era of new drugs requiring complex clinical assessment prior to being released on the market, the pharmaceutical industry must look upon aspirin with awe. And it's still going strong.

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