NEW USES FOR OLD DRUGS

ASPIRIN — THE FIRST MIRACLE DRUG

By Peter Elwood, MD, FRCP, and Michael Stillings, DPhil

Over 100 years ago, aspirin became the first drug to be made synthetically, and its marketing laid the foundation of the modern pharmaceutical industry. It is still the benchmark against which other analgesics are measured. In the mid-1970s, aspirin use entered a new phase when it was shown to reduce substantially the risk of coronary thrombosis. Overviews of more than 145 randomised, controlled trials have confirmed its value in the reduction of risk of vascular thrombosis.

The aspirin story is not over, and possible new uses to reduce cognitive decline and dementia, Alzheimer’s disease, cataract and intestinal cancer are currently under investigation.

CARDIOVASCULAR DISEASE

Aspirin has a remarkable feature that the other non-steroidal anti-inflammatory drugs (NSAIDs) do not have — by virtue of its labile acetyl group, it irreversibly inhibits cyclo-oxygenase (COX), the main mediating enzyme in the synthesis of prostaglandins. It is this feature which explains aspirin’s action on platelets and, ultimately, its cardiovascular protection. Other NSAIDs also inhibit COX, but the effect declines as the drug is metabolised and excreted.

Platelet activity Al Donné, a French physiologist, seems to have been the first researcher to describe platelets, in 1842. However, they were largely ignored until the late 1950s when there was general agreement about their role in coronary and other thrombotic processes.

Once the relevance of platelets to thrombosis came to be generally accepted, the search for drugs that affected platelet aggregation began. Numerous drugs were tested and, in 1967, the effect of aspirin on platelet aggregation was first shown.

Once the anti-aggregant effect of aspirin on platelets had been described, the need for trials of its efficacy in myocardial infarction and other thrombotic conditions became obvious. Platelet activity is substantially reduced by a small dose of aspirin — 10mg or even less — and larger doses have no increased effect. The effect of a single dose is detectable for up to 10 days, by which time, all the platelets affected by the drug have been replaced by new, unacetylated platelets.

The smallness of the doses of aspirin that affect platelets demonstrates the potency of the drug in inhibiting COX in this specific blood fragment. Within platelets, COX is responsible for the synthesis of a prostaglandin-like substance called thromboxane — a potent platelet aggregant. Excessive aggregation of platelets within blood vessels is responsible for the clots that cause heart attacks and ischaemic strokes. The inhibition of thromboxane production by aspirin, is the basis for the drug’s protective action in coronary thrombosis and ischaemic stroke.

Aspirin has justifiably been called the first miracle drug. In this article, a summary is given of the history of aspirin and its use in cardiovascular disease. A brief account of possible new uses is also included.

Potential uses for aspirin include prevention of pre-eclampsia, dementia, cataracts and colorectal cancer.
Salicylates have been used medicinally for over 2,000 years

About 400 BC, Hippocrates recommended a brew of leaves from the willow tree (Cortex salicis) to ease pain in childbirth. This is the first recorded mention of the use of salicylates for pain relief.

Salicylates are widely distributed in plants, and many herbal remedies probably depend on them for their effect. In 1763, the Reverend Edward Stone wrote to the President of the Royal Society in London reporting that he had successfully used a powder prepared from the bark of the common white willow to treat fever in “over 50 patients suffering from various aches”. The Reverend Stone’s letter brought salicylates to the attention of chemists and, in 1859, salicylic acid was first synthesised from carbolic acid. It was used for the relief of pain and fever, although it proved to be irritant to the stomach. Over 145 trials of aspirin’s use in vascular disease have now been published, and overviews of these show remarkable consistency in the results. All vascular events (MI, stroke and deep vein thromboses) are reduced by about one-third, and all deaths by about one-fifth by a small daily dose of aspirin. These estimates apply to males and females, hypertensive and non-hypertensive patients, diabetic and non-diabetic subjects. The previous history of the patient appears to be of little relevance to the benefit received from aspirin. However, vascular events still occur among patients on aspirin. Some failures are undoubtedly due to poor compliance with tablet taking. In one trial it was found that the subjects who took aspirin regularly experienced a 51 per cent reduction in vascular events, whereas those who took aspirin on less than half the days recommended showed only a 17 per cent reduction. An MI which occurs in a patient taking aspirin is likely to be of reduced severity. Low-dose daily aspirin has the same beneficial effect in patients who have had a stroke or a transient ischaemic attack.

Strokes can be ischaemic (blocked blood vessel), haemorrhagic (bleeding from a blood vessel), or embolic (a clot which has been displaced from within the heart). Aspirin should only be given after an ischaemic stroke, and not if haemorrhage has occurred. Embolic strokes are likely to occur in patients with atrial fibrillation and, although aspirin is beneficial in such cases, anticoagulants are the drug of choice in embolic stroke.

Another thrombotic condition in which aspirin has been shown to be of benefit is deep vein thrombosis. Patients recovering from surgery are at risk of deep vein thrombosis and, recently, its occasional occurrence, possibly as a result of long-distance flights, has received much media attention. Low-dose aspirin gives the same relative protection against deep vein thrombosis as it does in other conditions of vascular risk.

Primary prevention When assessing the risks and benefits of primary prevention, it is important to distinguish between “relative” reduction and “absolute” reduction in risk.

The relative reduction in vascular risk achieved by aspirin is around one-third. A risk reduction of one-third indicates that about 30 patients have to be treated for one year to prevent one event. Men who have recently had a stroke or an MI are at high risk, and about 10 per cent will have a further event within the following year.

The absolute reduction depends on how “at risk” the subjects under consideration are. Trials in healthy British doctors and US physicians have confirmed that taking aspirin reduces the relative risk of suffering a vascular event in healthy subjects to the same degree as in post-MI patients. However, the absolute saving in terms of the number of events is trivial because healthy subjects are at low risk of a vascular event. The absolute risk reduction calculated in these trials showed that 500 to 1,000 healthy subjects have to be given aspirin for one year, for one event to be prevented. Although the cost of treatment would be low, the number of subjects within that group of 500 who would experience side effects is relatively large, and one or two might have a serious bleed.

For most people, the risk of suffering a heart attack or stroke lies between these extremes. The subject who smokes, who is overweight and takes little exercise, who has raised blood pressure, or raised cholesterol is at increased risk. For any patient, the risk of suffering a vascular event must be balanced against the risk of a bleed or other undesirable effect of long-term aspirin (see Figure 1).

Emergency use There are two situations in which aspirin can be life-saving. The first is “early” aspirin, when the drug is given on first contact with a patient with chest pain, who may be having a coronary thrombosis.

An extension of this is “immediate” aspirin, ie, the drug is taken by subjects themselves as soon as they experience the sudden onset of severe chest pain. Patients who are judged, for any reason, to be at high risk of experiencing a thrombotic event should be instructed to...
NEVER USES FOR ASPIRIN

The story of aspirin is far from over and a number of new uses of the drug are being investigated. Some of these arise from its antithrombotic effects but others appear to arise from other actions of the drug. That aspirin has other actions should not be surprising, because salicylates have many functions in plants that have nothing to do with platelets or thrombosis.

Pre-eclampsia A possible reduction in pre-eclampsia and in retarded foetal growth have been reported in a number of small trials where subjects were given aspirin, but these results are controversial. If aspirin is beneficial, this is likely to be because it reduces the risk of placental infarction. A major trial was set up in an attempt to settle the controversy, but, although it gave no convincing evidence of benefit from aspirin, uncertainty persists, particularly concerning benefit on retarded foetal growth.

Dementia A reduction in cognitive decline and dementia in patients who take aspirin has been suggested. If confirmed, this will be of enormous importance to public health. It seems likely that aspirin might have some effect, because a high proportion of cases of dementia are caused either by damage following a stroke, or repeated, small, sub-clinical cerebral infarcts — multi-infarct dementia. Lesser degrees of damage from vascular lesions may also be prevented by low-dose aspirin. Evidence from a number of trials is urgently needed but results from one trial have already suggested benefit.

Another form of dementia is Alzheimer’s disease. The causes of this disease are not thoroughly understood but it is thought that some of the damage occurs through inflammatory processes around the so-called tangles that develop within the substance of the brain.

Recommendations for aspirin use

- Patients who have had an MI, stroke or transient ischaemic attack — give 75–100mg aspirin daily, indefinitely
- Patients with unstable angina — give 75–100mg aspirin daily, indefinitely
- Patients with stable angina (these patients are at high risk of a thrombotic event) — give 75–100mg aspirin daily, indefinitely
- Patients with intermittent claudication (these patients are at high risk of a thrombotic event) — give 75–100mg aspirin daily, indefinitely
- Patients with deep vein thrombosis — give 75–100mg aspirin daily until the condition is well stabilised. (Subjects likely to expose themselves to a situation where risk of DVT is high should be advised to take a single dose of 300mg)
- Patients at high-risk of a cardiovascular event — low-dose aspirin should be considered in addition to whatever other drugs are judged appropriate. In addition, patients at risk of a thrombotic event should be advised to carry a tablet of soluble aspirin to be taken if sudden chest pain occurs
- Patients with diabetes — although these patients are at increased risk of a cardiovascular event, there is probably no additional indication for aspirin prophylaxis, unless they have the above indications, in which case, treat as above
- Patients with cognitive decline and/or dementia — low-dose aspirin might be helpful
- Patients with colon polyps or other bowel conditions giving a high risk of cancer — watch the journals for reports of the results of trials being conducted

Figure 1: The risk:benefit profile of aspirin in patients at low and high risk of a cardiovascular event

<table>
<thead>
<tr>
<th>Risk of heart attack</th>
<th>Undesirable side effects</th>
</tr>
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<tbody>
<tr>
<td>Low risk</td>
<td>Patients judged to be at increased risk because of age, smoking, raised blood pressure, etc. (eg, soluble, effervescent and enteric-coated). Whether all of these preparations are suitable for cardiovascular use is questionable. There appears to be no convincing evidence that they have a greater benefit than ordinary aspirin in terms of the incidence of serious bleeding. There is evidence that absorption of aspirin from enteric-coated tablets is erratic in some individuals, although it is questionable as to whether this is significant at platelet level, given the low dose of aspirin needed to reduce the risk of a vascular event.</td>
</tr>
<tr>
<td>High risk</td>
<td>Patients with a recent vascular event</td>
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</tbody>
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Aspirin, even at low doses, has an anti-inflammatory action. It is not surprising, therefore, that a large number of observational studies have shown a reduced incidence of Alzheimer's disease in patients taking aspirin or other anti-inflammatory drugs.21,22

**Cataracts**

An association between regular aspirin taking and reduced development of cataract has been reported. If real, this may be due to the inhibition of an enzyme within the lens tissues. Although the benefit from regular aspirin is likely to be modest, there seems to be a potentially important reduction in posterior subcapsular cataract, a particularly disabling subtype.23

**Colorectal cancer**

Of great interest is a marked reduction in colorectal cancer in habitual aspirin takers. This has been reported in a number of studies.24,25 When diseased, a number of plants secrete salicylates in order to kill the affected parts and to limit the spread of the disease. This may give a clue as to the mechanism of aspirin in cancer and it has, therefore, been suggested that within human subjects the drug may enhance apoptosis of the cells involved in early cancer.

A number of trials have been set up in patients with familial polyposis and in other high-risk groups to find out whether this is the case.

**CONCLUSIONS**

Numerous trials have established that a small daily dose of aspirin (75 to 150mg) reduces the risk of a vascular event by about one-third. If a patient is on any treatment for cardiovascular disease (eg, a cholesterol-lowering or antihypertensive drug), then it could be judged clinically irresponsible if a patient at increased risk of thrombosis is not receiving aspirin.

Aspirin, used in cardiovascular prophylaxis, is undoubtedly the most thoroughly tested and the most highly cost-effective drug available in clinical practice today.

Information about aspirin may be found on the web site for the European Aspirin Foundation (www.aspirin-foundation.com).

### REFERENCES


### LOW-DOSE ASPIRIN IN CARDIOVASCULAR DISEASE

Aspirin reduces the risk of a cardiovascular event, such as heart attack, stroke or deep vein thrombosis, by about 30 per cent if a thrombosis does occur in patients on low-dose aspirin the infarct is likely to be less serious.

The absolute reduction in risk is dependent on the patient group:

- Three events per hundred per year in patients at high risk
- Three events per thousand per year in healthy subjects at low risk

The reduction in risk is dependent upon compliance. Benefit obtained from erratic doses is substantially less than that from a regular daily dose.
Correction

Reference 20 is from J Neurol Neurosurg Psychiatry not BMJ.