

Rediscovering Aspirin

By PAMELA MASON, PHD, MRPHARMS

New potential uses for the “old” medicine, aspirin, are increasingly being found. This article sets out the evidence for aspirin preventing cataract formation, Alzheimer’s disease, eclampsia and hypertension in pregnancy and cancer. Recent research on the potential of aspirin to treat bacterial infections is also mentioned.

Aspirin tablets have been available for over a hundred years, but research continues to find new indications

Salicylates, in the form of willow bark, have been used as an analgesic since the time of Hippocrates. Their antipyretic effects have been recognised for over 200 years. Acetylsalicylic acid, or aspirin, was introduced in the late 1890s and has been used since then to treat a variety of painful or inflammatory conditions, such as headache, migraine, dysmenorrhoea, dental pain, rheumatic disorders and febrile conditions, including colds and influenza. The analgesic and anti-inflammatory effects of aspirin occur through inhibition of the enzyme cyclo-oxygenase (COX), which is involved in prostaglandin production. Aspirin inhibits both isoforms of cyclo-oxygenase — COX 1 and COX 2.

The antiplatelet activity of aspirin was recognised during the late 1960s, and today the drug has an established role in the management of cardiovascular disorders. Again, inhibition of COX is responsible for aspirin’s beneficial effects.

In blood platelets, inhibition of COX prevents the production of thromboxane A₂, a vasoconstrictor that would otherwise cause platelet aggregation and is potentially thrombotic. In the blood vessel walls, how-

ever, COX inhibition prevents the synthesis of prostacyclin, a vasodilator that has anti-aggregating properties and is potentially anti-thrombotic. The net benefit of aspirin is believed to arise because the effects of the drug on vascular tissue are generally shorter-lived than those on platelets. Vascular tissue regains its ability to regenerate prostacyclin within a few hours, but platelets affected by aspirin are unable to synthesise COX and therefore thromboxane A₂ again, and so the effects of aspirin here lasts for up to 24 hours, until more platelets are released by the bone marrow.

Aspirin improves survival when given in the early stages of myocardial infarction¹ and has a beneficial role in the treatment of unstable angina, reducing mortality and the incidence of non-fatal myocardial infarction.² At a dose of 75–150mg daily it is effective for the secondary prevention of myocardial infarction and stroke.^{3–6} Aspirin is also of value in the primary prevention of cardiovascular events, but the benefits only outweigh the possible harm (eg, gastrointestinal bleeds and haemorrhagic stroke) in patients at high risk of heart problems.⁷ In low risk individuals, aspirin appears to be of no benefit.⁸ However, this does not mean that aspirin definitely has no benefit — just that there is currently insufficient evidence available.

Research is now beginning to reveal that aspirin may have benefits other than in pain, inflammation and cardiovascular disease. There is increasing interest in the potential for aspirin to prevent cancer, cataract, Alzheimer’s disease, and eclampsia and hypertension in pregnancy. Recent research also indicates a potential role for aspirin in fighting infections.

CANCER

During the past decade, there has been a growing body of evidence suggesting that aspirin may lower the risk of certain cancers including colorectal, oesophageal, stomach, breast, ovarian and prostate cancer. The strongest evidence to date relates to colorectal cancer.

Colon cancer One of the first studies linking aspirin with reduced colon cancer risk was published in 1988. From studying a population-based register of patients with tumours in Melbourne, Australia, researchers reported a 40 per cent lower risk of colon cancer among individuals who had used aspirin compared with individuals who had not.⁹

Results of trials since that time have been mixed, but this is partly due to differences in methodology. A California-based cohort

Dr Mason is a freelance journalist

study in 13,987 men and women of over 73 years found that those who had used aspirin at least daily had a 50 per cent higher incidence of colon cancer than those who used aspirin less than monthly.¹⁰ The risk of ischaemic heart disease was also increased in individuals who had taken aspirin. However, two years later a hospital based case-control study reported an approximately 50 per cent lower incidence of colorectal cancer among individuals who regularly used aspirin compared with those who did not use it at all.¹¹

Another study involving 662,424 individuals over a six-year period found that the use of aspirin 16 or more times a month was associated with a 42 per cent reduction in the risk of fatal colon cancer and a 34 per cent reduction in the risk of fatal rectal cancer.¹² Compared with non-aspirin users, people who used aspirin for 10 or more years had a 64 per cent reduced risk for colon cancer. However, a randomised trial among male physicians did not demonstrate a protective effect of aspirin in reducing the risk of colorectal cancer at a dose of 325mg every day.¹³

The idea that the overall relative risk of colorectal cancer is reduced in people taking long-term aspirin has been supported by a more recent study.¹⁴ However, there is also evidence that any benefit may not be evident until aspirin has been taken for several years. For example, in another study, women who consistently took two or more aspirin tablets per week for four years, or for five to nine years, had no appreciable reduction in the risk of colon cancer as compared with non-users.¹⁵ There was a slight reduction in risk among women who took aspirin for 10-19 years, but it was not statistically significant. However, there was a statistically significant reduction in risk after 20 years of consistent use of aspirin, with the maximal reduction in risk being observed in women who took four to six tablets a week.

The relationship between aspirin use and colorectal cancer in patients with a history of the condition has been investigated in two recent placebo-controlled studies.^{16,17} Both studies found aspirin to be beneficial in reducing the frequency of new colorectal polyps.

In the first study,¹⁶ 517 patients with previous malignant disease were divided into a placebo group and an intervention group given 325mg aspirin daily for one year. Compared with the placebo group, those taking aspirin had a significantly lower risk of developing new colorectal adenomas and had a longer time to diagnosis of the first polyp. The second study¹⁷ reported a more modest benefit in 1,084 patients with a history of recent colorectal adenoma randomised to placebo or aspirin, 81 or 325mg daily. Most of the benefit was in the low dose group. Compared with placebo, the unadjusted relative risk of any adenoma was significantly reduced in the lower aspirin dose, but not the higher dose. Similarly,

advanced neoplasms were significantly less likely in those taking aspirin at the lower, but not the higher, dose.

One potential mechanism for a beneficial effect of aspirin in colorectal cancer is the inhibition of prostaglandin E2 production, through COX 2 inhibition. Both human and experimental colorectal cancer cells produce increased amounts of prostaglandin E2.¹⁸ The precise role of prostaglandin E2 in colorectal carcinogenesis is unclear but it does appear to be involved early in the process. There is also some evidence that COX enzymes are involved in both the production and metabolic activation of carcinogens in the colon, events potentially inhibited by aspirin.

Oesophageal cancer Aspirin has also been linked to a reduced risk of oesophageal cancer, although the evidence is not as strong as it is for colorectal cancer. For example, in an epidemiological study of 14,407 US residents, occasional aspirin use was associated with a 90 per cent reduction in the risk of developing oesophageal cancer and no regular users of aspirin developed the condition. However, only 15 cases of oesophageal cancer¹⁹ were seen in the study group as a whole, making reliance on the study findings premature.

In a large case-control study people who reported having previously used at least one aspirin tablet per week for a period of six weeks or more had a 52 per cent reduction in the risk of developing oesophageal adenocarcinoma and a 48 per cent reduction in the risk of developing squamous cell carcinoma.²⁰ Current aspirin use was even more strongly associated with a lower risk of developing both types of cancer.

A recent meta-analysis of data from nine observational studies confirmed a positive effect of aspirin in oesophageal cancer.²¹ Patients with any exposure to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) had a 43 per cent reduction in the odds of developing oesophageal cancer. There was evidence of a dose-response effect, with a greater reduction in risk associated with frequent use of aspirin or NSAIDs.

An Italian study found that long-term use of aspirin dramatically reduced the incidence of tumours of the oesophagus, mouth and throat.²² This research pooled data from three smaller studies, and after controlling for factors such as smoking and diet, showed that the incidence of the three types of cancer in people who had taken aspirin regularly for at least five years was a third that in people who had not taken aspirin.

Other cancers The evidence for an effect of aspirin in the development of cancers in other organs is weaker than for colorectal and oesophageal cancer. However, recent studies have suggested that aspirin could

have a beneficial effect in cancers of the ovary, prostate and lung. Studies looking at the effect of aspirin on cancers of the breast, endometrium and pancreas have yielded conflicting results. In addition, a recent study that examined the incidence of leukaemia between 1993 and 2000 among 28,224 women suggests that taking aspirin (but not other NSAIDs) at least twice weekly reduces the risk of developing leukaemia.²³

ALZHEIMER'S DISEASE

Studies involving long-term users of NSAIDs have provided evidence that these drugs may reduce the risk of Alzheimer's disease.²⁴ More recent data have also shown an inverse relationship between aspirin (as well as other NSAIDs) and Alzheimer's disease, but not other forms of dementia.²⁵ The mechanism is unclear, but there is an inflammatory component to Alzheimer's disease, so inhibition of COX 2 may be responsible.

CATARACT

Aspirin has been linked with the prevention of cataracts, but randomised intervention trials of five to six years' duration (using 160-325mg daily) suggest no effect.^{26,27} Moreover, a longer term analysis in male doctors found that cataract development was significantly higher in doctors using aspirin for more than 180 days a year than in those who seldom or never used aspirin.²⁸ This latter study is a preliminary finding but, on the evidence to date, it appears that aspirin has no useful effect in preventing cataracts.

INFECTION

Recent *in vitro* studies suggest that salicylic acid (the active metabolite of aspirin) reduces the ability of *Staphylococcus aureus* to initiate and spread infection by reducing the production of virulence factors and inhibiting gene activity.²⁹ The researchers suggest that aspirin might have a potential role in treating staphylococcal infections. Clinical studies will clearly need to be carried out, however, before a place in therapy can be recommended.

ECLAMPSIA

A relative excess of thromboxane A2 over prostacyclin has been implicated in the development of eclampsia and hypertension induced by pregnancy. Several studies to date have shown a protective effect of low-dose aspirin in women with risk factors for eclampsia.

A recent meta-analysis of data from four studies³⁰ in women at high-risk of developing eclampsia found a significant benefit of low-dose aspirin therapy in reducing peri-

natal death and eclampsia. Aspirin was also associated with an increase of 215g in mean birth weight and a reduction in the rates of spontaneous preterm birth. However, it has been suggested that this evidence is preliminary and should not be used as a basis for treatment until further work has been carried out. Indeed, a recent trial in pregnancies with impaired placentation showed that daily administration of 150mg aspirin did not prevent subsequent development of pre-eclampsia.³¹

CONCLUSION

All pharmacists know that aspirin has beneficial effects on pain, inflammation and fever and in the management of cardiovascular disorders. However, there is increasing evidence that aspirin use may also be associated with reduced risk of cancer, particularly colon cancer, and Alzheimer's disease. This represents another strand in the fascinating story of aspirin, although it is too soon to recommend the drug for cancer prophylaxis.

REFERENCES

1. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349-60.
2. Wallentin LC and the Research Group on Instability in Coronary Artery Disease in Southeast Sweden. Aspirin (75mg/day) after an episode of unstable coronary artery disease: long-term effects on the risk for myocardial infarction, occurrence of severe angina and the need for revascularization. *Journal of the American College of Cardiology* 1991;18:1587-93.
3. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, 1: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
4. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ* 2002;324:71-86.
5. Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. *Archives of Internal Medicine* 2002;162:2197-202.
6. Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS et al. Indications for early aspirin use in acute ischaemic stroke. A combined analysis of 40,000 randomised patients from the Chinese acute stroke trial and the international stroke trial. *Stroke* 2000;31:1240-9.
7. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the US preventive services task force. *Annals of Internal Medicine* 2002;136:161-72.
8. Boltri JM, Akerson MR, Vogel RL. Aspirin prophylaxis in patients at low risk for cardiovascular disease: a systematic review of all-cause mortality. *Journal of Family Practice* 2002;51:700-4.
9. Kune AS, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations and medications. Case control results from the Melbourne colorectal cancer study. *Cancer Research* 1988;48:4399-404.
10. Panganini-Hill A, Chao A, Ross RK, Henderson BE. Aspirin use and risk of chronic disease: a cohort study in the elderly. *BMJ* 1989;299:1247-50.
11. Rosenberg L, Palmer JR, Zaubler AG, Warshauer ME, Stolley PD, Shapiro S. A hypothesis - non-steroidal anti-inflammatory drugs reduce the risk of large bowel cancer. *Journal of the National Cancer Institute* 1991;83:355-8.
12. Thun MJ, Calle EE, Namboodri MM, Flanders WD, Heath CW Jr. Aspirin use and the risk of fatal cancer. *Cancer Research* 1993;53:1322-7.
13. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. *Journal of the National Cancer Institute* 1993;85:1220-4.
14. Bosetti C, Gallus S, La Vecchia C. Aspirin and cancer risk: an update for 2001. *European Journal of Cancer Prevention* 2002;11:535-42.
15. Giovannucci E, Egan KM, Hunter DJ, Stampfer MJ, Colditz GA, Willett W, Speizer FE. Aspirin and the risk of colorectal cancer in women. *New England Journal of Medicine* 1995;333:609-14.
16. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Kereszies R et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *New England Journal of Medicine* 2003;348:883-90.
17. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R et al. A randomized trial of aspirin to prevent colorectal adenomas. *New England Journal of Medicine* 2003;348:891-9.
18. Pugh S, Thomas GAO. Patients with adenomatous polyps and carcinomas have increased colonic mucosal prostaglandin E2. *Gut* 1994;35:675-8.
19. Funkhouser EM, Sharp GB. Aspirin and the reduced risk of esophageal cancer. *Cancer* 1995;76:1116-9.
20. Farrow DC, Vaughan TL, Hansten PD, Stanford JL, Risch HA, Gammon MD et al. Use of aspirin and other non-steroidal anti-inflammatory drugs and the risk of esophageal and gastric cancer. *Cancer Epidemiology and Biology Prevention* 1998;7:97-102.
21. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer. *Gastroenterology* 2003;124:47-56.
22. Bosetti C, Talamini R, Franceschi S, Negri E, Garavello W, La Vecchia C. Aspirin use and cancers of the upper aerodigestive tract. *British Journal of Cancer* 2003;88:672-4.
23. Kasum Cm, Blair CK, Folsom AR, Ross JA. Non-steroidal anti-inflammatory drug use and risk of adult leukemia. *Cancer Epidemiology Biomarkers Prevention* 2003;12:534-7.
24. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 1997;48:626-32.
25. Broe GA, Grayson DA, Creasey HM, Waite LM, Casey BJ, Bennett HP et al. Anti-inflammatory drugs protect against Alzheimer's disease at low doses. *Archives of Neurology* 2000;57:1586-91.
26. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K et al. Randomised trial of prophylactic daily aspirin in British male doctors. *BMJ* 1988;296:313-6.
27. Chew EY, Williams GA, Burton TC, Barton FB, Remaley NA, Ferris FL 3rd. Aspirin effects on the development of cataract in patients with diabetes mellitus: early treatment diabetic neuropathy study report 16. *Archives of Ophthalmology* 1992;110:339-42.
28. Christen WG, Ajani UA, Schaumberg DA, Glynn RJ, Manson JE, Hennekens CH. Aspirin use and risk of cataract in posttrial follow-up of physicians health study I. *Archives of Ophthalmology* 2001;119:405-12.
29. Kupferwasser LI, Yeaman MR, Nast CC, Kupferwasser D, Xiong YQ, Palma M et al. Salicylic acid attenuates virulence in endovascular infections by targeting global regulatory pathways in staphylococcus aureus. *Journal of Clinical Investigation* 2003;112:149-51.
30. Coomarasamy A, Honest H, Papaioannou S, Gee H, Khan KS. Aspirin for prevention of pre-eclampsia in women with historical risk factors: a systematic review. *Obstetrics and Gynecology* 2003;101:1319-32.
31. Yu CK, Papageorghiou AT, Parra M, Palma Dias R, Nicolaidis KH. Fetal medicine foundation second trimester screening group. Randomised controlled trial using low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine artery doppler at 23 weeks gestation. *Ultrasound Obstetrics and Gynecology* 2003;22:233-9.