Dipyridamole

Paldeep Atwal
MRCP(UK), Core Medical Trainee

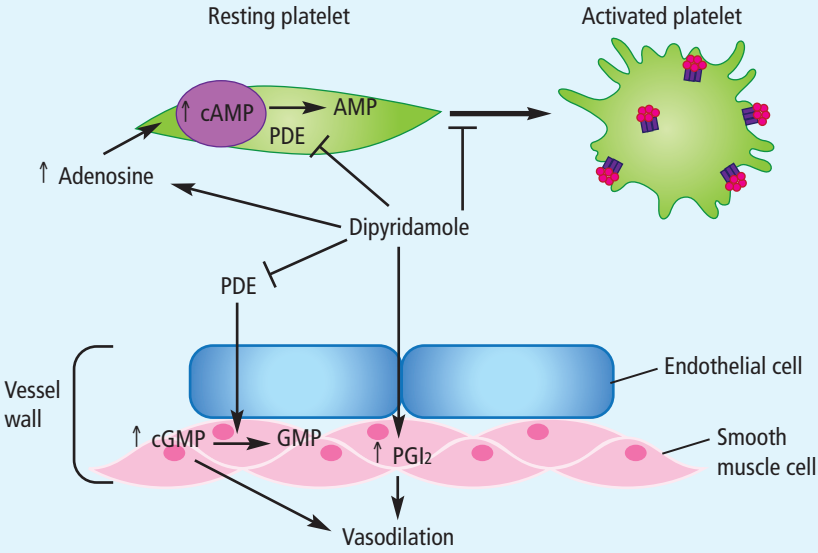
Saira Goheer
MBChB, Foundation Doctor

Gerry McKay
BSc(Hons), FRCP, Consultant Physician

Miles Fisher
MD, FRCP, Consultant Physician

Glasgow Royal Infirmary, Glasgow, UK

Correspondence to:
Professor Miles Fisher, Consultant Physician, Wards 3, 4 & 5, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK;
email: miles.fisher@ggc.scot.nhs.uk



cAMP = cyclic adenosine monophosphate; PDE = phosphodiesterase; AMP = adenosine monophosphate; cGMP = cyclic guanine monophosphate; PGI_2 = prostacyclin.

Figure 1. Mechanism of action of dipyridamole. (Figure redrawn from Kim H-H, Liao JK. Translational therapeutics at the platelet vascular interface; a CME-certified activity. *Arterioscler Thromb Vasc Biol* 2008;28:s39–s42)

Introduction

Without secondary prevention the annual risk of a major vascular event for patients who have had a transient ischaemic attack (TIA) or non-disabling ischaemic stroke is between 4–16%.[1] The risk reduction of subsequent stroke with the combination of low-dose aspirin and modified-release (MR) dipyridamole is well established, and the risk reduction of vascular complications is greater with dual antiplatelet therapy compared to either aspirin or dipyridamole alone. When it was introduced, dipyridamole was used as a coronary vasodilator and only later was it shown to have its antiplatelet properties. Current practice in the UK for the secondary prevention of TIA is to use a combination of MR dipyridamole and aspirin. For secondary prevention of ischaemic stroke, dipyridamole is indicated in combination with aspirin only if clopidogrel is contraindicated or not tolerated.

Pharmacology

Figure 1 outlines the pharmacological action of dipyridamole. It is an inhibitor of cyclic nucleotide phosphodiesterase (PDE) activity which leads to an increased level of intraplatelet cyclic adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP). This causes a reduction in intraplatelet Ca^{2+} due to subsequent increased uptake into the dense tubular system and also increased extracellular secretion. This sequence of events leads to the inhibition of platelet response to adenosine diphosphate, thereby reducing platelet activation and granule excretion. The anti-aggregatory effect of cAMP also potentiates nitric oxide and PGI_2 which both bind to receptors on platelet membranes to stimulate production of cyclic nucleotides thereby inhibiting platelet aggregation and stimulating vasodilation. In addition, dipyridamole inhibits adenosine reuptake by erythrocytes and endothelial cells thereby increasing plasma levels of adenosine. It is known that adenosine is a potent vasodilator and an inhibitor of platelet activation and aggregation by stimulation of adenylate cyclase, thus the efficacy of dipyridamole on inhibition of thrombus formation is increased.

Trials of safety and efficacy

The European Stroke Prevention Study 2 (ESPS-2) was a large randomised control trial involving 6602 patients with a history of recent TIA or ischaemic stroke who were randomised into four treatment arms.[2] These treatment arms were: aspirin 25mg twice a day, MR dipyridamole 200mg twice a day, MR dipyridamole combined with aspirin, and placebo. The follow-up period was two years. The primary endpoints were stroke, death, and stroke or death together. Compared with placebo there was an 18.1% risk reduction of stroke with aspirin alone (p=0.013), a 16.3% reduction with dipyridamole alone (p=0.039) and a 37% reduction with combination therapy (p<0.001). The risk of stroke or death together was reduced by 13.2% with aspirin (p=0.016), by 15.4% with dipyridamole (p=0.015) and by 24.4% with combination therapy (p<0.001). The study also found that headache was the most common adverse effect of dipyridamole. Haemorrhagic complications were significantly more common with aspirin therapy compared to dipyridamole or placebo.

The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) was an open randomised trial involving 2739 patients, comparing combination therapy of aspirin and dipyridamole with aspirin alone.[1] Participants were patients who had suffered a stroke or TIA within the preceding six months. The mean follow up was 3.5 years. The combination of MR dipyridamole and aspirin was more effective than aspirin alone in prevention of the composite primary outcome of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication (absolute risk reduction 1% per year; hazard ratio [HR] 0.80, 95% CI 0.66–0.98). The number needed to treat (NNT) to prevent one primary outcome occurring with combination therapy compared to aspirin alone was 104 (95% CI 55–1006). There was no difference in the incidence of major bleeding complications (HR 0.81, 95% CI 0.65–1.01).

The Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) trial was a large double-blind randomised control trial involving 20 332 patients with a history of ischaemic stroke.[3] PRoFESS compared treatment with combination MR dipyridamole and aspirin with clopidogrel alone. The mean follow up was 2.5 years. The primary outcome was recurrence of stroke. The results showed a recurrence of stroke in 9.0% of people who received combination therapy compared with 8.8% of people who received clopidogrel. The difference was not significant (HR 1.01, 95% CI 0.92–1.11). The increase in major haemorrhagic events in the combination group (4.1%) was significant when compared to the clopidogrel alone group (3.6%) (HR 1.15, 95% CI 1.00–1.32), and this included more incidence of intracranial haemorrhage (HR 1.42, 95% CI 1.11–1.83).

Specific evidence for use in diabetes

Evidence for benefit in people with diabetes comes from examination of subgroups in the above studies. In ESPS-2, 15.3% of patients (1011/6602) had a history of diabetes. Of these, 3.2% (210) were described as 'insulin dependent' and 12.1% (801) were 'non-insulin dependent'. The Cox model for survival data showed that diabetes was a strong predictor of a stroke at 24 months (c=1.22) and that the use of aspirin (c=0.79) or dipyridamole (c=0.77) significantly reduced this risk. When the Cox model was applied to the death endpoint, again diabetes was a strong predictor (c=1.45), and treatment with aspirin (c=0.86) and dipyridamole (c=0.80) significantly reduced this risk.

In the ESPRIT trial, 19% (260/1363) of the patients in the dipyridamole and aspirin combination group and 18% (252/1376) of patients in the aspirin alone group had a history of diabetes mellitus. The combination group had less ischaemic events than the monotherapy group, and death from all vascular causes was reduced (13%) in the combination group compared to the aspirin alone group (16%). The authors found the HR for death from all causes to be 0.88 in the combination group compared to the aspirin alone group.

In PRoFESS, 28.5% of 10 181 patients in the MR dipyridamole and aspirin group and 28% of 10 151 patients in the clopidogrel group had a history of diabetes. In *post-hoc* analysis, 7.3% (213/2903) of patients suffered a recurrence of stroke in the combination group vs 11.8% (334/2840) in the clopidogrel group.

Key points

- MR dipyridamole in combination with aspirin is first line therapy for secondary prevention of TIA
- MR dipyridamole in combination with aspirin is indicated in secondary prevention of ischaemic stroke where clopidogrel is contraindicated or not tolerated
- The risk of major haemorrhagic events is higher with combination therapy of MR dipyridamole and aspirin compared to clopidogrel alone
- Individuals with diabetes are at high risk of macrovascular events including stroke and are likely to benefit from antiplatelet treatment

Discussion

Dipyridamole has a robust evidence base for its efficacy for prevention of secondary strokes and TIAs. Through the ESPS-2 and ESPRIT trials its antiplatelet properties, along with aspirin, showed a significant risk reduction in subsequent strokes. The PRoFESS trial showed no statistical significance in risk reduction of secondary strokes of combination therapy with MR dipyridamole and aspirin compared with clopidogrel alone. MR dipyridamole in combination with aspirin remains first line therapy for secondary prevention of TIA in the UK, and this combination can be used in secondary prevention of ischaemic stroke if clopidogrel is contraindicated or not tolerated. Headache is a common adverse effect of dipyridamole and antiplatelet treatment increases the risk of major haemorrhagic events, a risk that may be greater when using combined antiplatelet therapy. The trial evidence confirms that the benefits and risks of antiplatelet treatment are applicable to individuals with diabetes who have an increased risk of macrovascular complications such as stroke.

Declaration of interests

No conflicts of interest are declared.

References

References are available online at www.practicaldiabetes.com.

References

1. ESPRIT Study Group, Halkes PHA, *et al*. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006;367:1665–73.
2. Diener HC, *et al*. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; 14:1–13.
3. Sacco RL, *et al*. The PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008; 359:1238–51.