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Extended-Release Dipyridamole/Aspirin

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Contents

Abstract

▲ The fixed-dose combination of extended-release dipyridamole/aspirin (Aggrenox/Asasantin Retard™)[1] combines 2 antiplatelet agents with different mechanisms of action. The combination reduced thrombus formation in human and animal models.

▲ Coadministration of extended-release dipyridamole and aspirin in healthy volunteers had no significant effects on the plasma concentrations of either agent.

▲ Twice-daily oral extended-release dipyridamole/aspirin (400/50 mg/day) was twice as effective as either agent alone in the secondary prevention of stroke in a large clinical trial involving patients with prior stroke or transient ischaemic attack.

▲ The rate of the combined end-point of stroke and death tended to be lower with the combination than with other treatments. The incidence of death was not significantly reduced by any treatment.

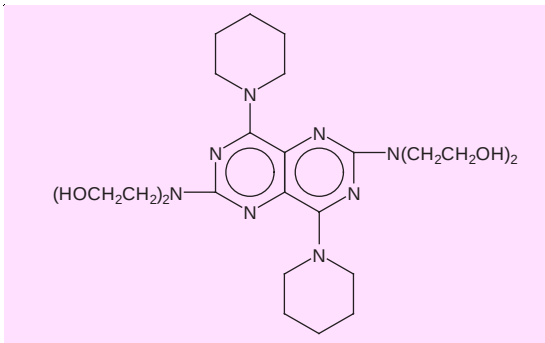
▲ Most adverse events with extended-release dipyridamole/aspirin were mild and similar to those with either agent alone. Bleeding was more common with the combination than with extended-release dipyridamole alone, as was headache when compared with aspirin alone.

▲ Limited pharmacoeconomic analyses suggest that treatment with extended-release dipyridamole/aspirin was cost saving and was cost effective compared with aspirin monotherapy for the secondary prevention of stroke.

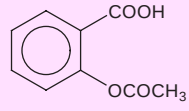
Features and properties of extended-release dipyridamole/aspirin

Indications		
Protection against secondary stroke and transient ischaemic attacks		
Mechanism of action		
Antiplatelet	Fixed-dose combination of 2 platelet antiaggregation agents; an inhibitor of phosphodiesterase and thus adenosine uptake (dipyridamole) and an inhibitor of cyclo-oxygenase (aspirin) in platelets	
Dosage and administration		
Usual daily dosage in clinical trials	400mg extended-release dipyridamole/50mg immediate-release aspirin	
Route of administration	Oral	
Frequency of administration	Twice daily	
Pharmacokinetic profile of the separate drugs		
Drug	Dipyridamole	Aspirin
Time to peak plasma concentration (immediate release)	45-150 min	0.25-2h
Distribution	Wide	Wide
Plasma protein binding	91-99%	Low
Metabolism	Hepatic	Hydrolysed to salicylate in GI system, liver, plasma
Adverse events		
Most common	Typical of aspirin or dipyridamole monotherapy – headache, GI disturbance	
Potentially serious	Bleeding	

1 Use of the trade name is for product identification only and does not imply an endorsement.



Dipyridamole



Aspirin

Dipyridamole/aspirin

For stroke survivors the 5-year risk of suffering another stroke is about 30%.[1] Antiplatelet agents, in particular aspirin (acetylsalicylic acid), have been investigated in large numbers of clinical trials in such patients: the efficacy of aspirin in preventing secondary stroke and transient ischaemic attack (TIA) is generally well accepted. However, its overall efficacy in preventing vascular events is only about 13% relative to placebo,[2] indicating the need for improved treatment options. Combining aspirin with another antiplatelet agent such as extended-release dipyridamole, which inhibits platelet function by an alternative mechanism, has the potential for greater efficacy.

1. Pharmacodynamic Profile

The pharmacodynamic effects of aspirin and dipyridamole monotherapy are well established.[3,4] Very briefly, aspirin inhibits cyclo-oxygenase and limits the production of the potent platelet aggregant thromboxane A_2, thereby inhibiting platelet activation. Dipyridamole reduces platelet aggregation primarily by inhibiting phosphodiesterase, thereby increasing platelet levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) and increasing plasma adenosine levels.[5] This section summarises results of studies which evaluated the pharmacodynamic effects of these 2 agents when coadministered in *ex vivo* and *in vivo* models of thrombosis.

Healthy Volunteers

- The fixed-dose combination of extended-release dipyridamole/immediate release aspirin (Aggrenox/Asasantin Retard™) [400/50 mg/day] was compared with aspirin (50 mg/day) or extended-release dipyridamole (400 mg/day) alone in a double-blind, randomised, placebo-controlled trial in 96 healthy volunteers. Treatment with extended-release dipyridamole/aspirin for 4 days inhibited *ex vivo* platelet aggregation/thrombus formation on a subendothelial matrix to a greater extent than either agent alone ($p < 0.01$).[6]
- In addition, the extended-release dipyridamole/aspirin combination strongly inhibited the formation of very large platelet aggregates. This effect was greater than the added effect of either aspirin and dipyridamole alone ($p < 0.05$ *vs* both treatments and placebo).[6]

Animal Models

- Aspirin (10 to 20 mg/kg/day orally for 7 days) potentiated the antithrombotic effect of a fixed-dose of dipyridamole (2.5 mg/kg/day orally for 7 days) in a dose-dependent fashion in a baboon model of arterial thromboembolism, with the highest dose producing maximal effect. This potentiation effect only occurred when both drugs were administered simultaneously. The combination had a greater effect than dipyridamole alone ($p < 0.001$); aspirin alone (20 mg/kg/day) had no measurable effect.[7]
- Concomitant aspirin and dipyridamole minimised thrombus formation in the highly thrombogenic lesion created by carotid endarectomy in the dog. All of the arteries from 20 dogs treated with dipyridamole/aspirin (50/325 mg/day starting 2 weeks before sacrifice) remained patent. Only one

had significant gross thrombus formation, compared with 6 occlusions and 6 significant gross thrombi in the control group ($p < 0.01$) and 1 occlusion and 6 significant thrombi in dogs given heparin (100 U/kg preoperatively then 10 U/kg/h for 8 hours) [$p < 0.05$].[8]

- Combined administration of dipyridamole/aspirin (14 mg/kg of each drug for 2 doses) to normocoaguable rats reduced the weight of thrombi formed on intravenously inserted platinum wires by 32% ($p < 0.05$ *vs* control). In a separate experiment, dipyridamole/aspirin in the same dosage reduced thrombus weights by 49% ($p < 0.01$ *vs* controls) in rats in whom a hypercoaguable state had been induced by ellagic acid (1.2 mg/100g in barbital saline buffer).[9]

2. Pharmacokinetic Profile

Detailed review is available of the pharmacokinetic properties of immediate-release aspirin.[4] Some data are also available for extended-release dipyridamole.[3] These properties are briefly described below, as are the limited pharmacokinetic data for the extended-release dipyridamole/aspirin combination.

Extended-Release Dipyridamole

- Peak plasma concentrations of dipyridamole (C_{max}) are reached within about 2 to 3 hours after a dose of the extended-release formulation;[3] absorption is incomplete and variable. The drug is widely distributed and is found in the placenta and in breast milk. It is highly bound to plasma proteins (91 to 99%). Dipyridamole is metabolised hepatically and is excreted in the bile as glucuronides.

Aspirin

- Aspirin is partially hydrolysed to the active compound salicylate in the GI mucosa and is then more completely hydrolysed to salicylate on first pass through the liver and systemic circulation. C_{max} of salicylate is achieved within 0.25 to 2 hours of a dose of aspirin. Aspirin is widely distributed, as seen by a volume of distribution of 0.15 to 0.2 L/kg, but is poorly bound to plasma proteins. About 1% of a dose of aspirin is excreted unhydrolysed in the urine with the balance excreted renally as salicylate and its metabolites.[4]

Extended-Release Dipyridamole/Aspirin

- After administration of the last dose of the fixed-dose combination (dipyridamole/aspirin 400/50 mg/day for 4 days) to 24 healthy volunteers, the 2-hour plasma concentrations of dipyridamole and salicylate corresponded to the levels attained in a similar number of individuals who received the drugs singly. Plasma dipyridamole concentrations were 1.77 mg/L in the dipyridamole group and 1.79 mg/L in the dipyridamole/aspirin combination group. Plasma salicylate levels were 1.07 mg/L in the aspirin alone group and 1.22 mg/L in the combination group.[6]

3. Therapeutic Trials

Early investigations of dipyridamole and aspirin given concomitantly at doses ranging from 150/900 to 300/1300 mg/day were inconclusive.[10-12] However, a large double-blind, randomised placebo-controlled trial, the European Stroke Prevention Study (ESPS-1),[13,14] evaluated the combination of dipyridamole and aspirin (225/990 mg/day) in 2500 patients at risk because of prior TIA, neurological deficit or stroke.

At 2 years a significant benefit, relative to placebo, in favour of the dipyridamole/aspirin combination was found for the combined end-point of stroke and death (a 33% decrease, $p < 0.001$), for death alone (30.6%, $p < 0.01$) and fatal or nonfatal stroke (38.1%, $p < 0.001$).[14]

To establish whether this degree of response was due to either dipyridamole or aspirin alone, a second European Stroke Prevention Study (ESPS-2) was initiated.[15,16] This double-blind, randomised placebo-controlled study compared the fixed-dose combination of extended-release dipyridamole/aspirin (400/50 mg/day) with aspirin (50 mg/day) or extended-release dipyridamole (400 mg/day). Treatment in all groups was administered twice daily. A total of 6602 patients with stroke or

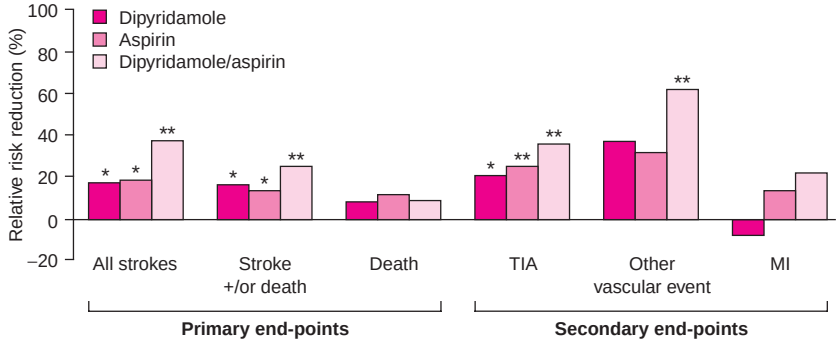


Fig. 1. Risk reduction relative to placebo for primary and secondary end-points at 24 months reported in the second European Stroke Prevention Study (ESPS-2). Patients with prior stroke or transient ischaemic attacks (TIA) received extended-release dipyridamole/aspirin 400/50 mg/day (n = 1650), aspirin 50 mg/day (n = 1649), extended-release dipyridamole 400 mg/day (n = 1654) or placebo (n = 1649).[15,16] **MI** = myocardial infarction; * $p < 0.05$, ** $p < 0.001$ *vs* placebo.

prior TIA were followed up for 24 months. The main efficacy results from this study are reported in this section and are illustrated in figure 1.

Primary End-Points

• Combined treatment with extended-release dipyridamole/aspirin was more effective than either aspirin or extended-release dipyridamole alone in reducing the incidence of stroke and tended to reduce the incidence of the combined end-point of stroke or death compared with the 2 monotherapy regimens.[15,16] In pairwise comparisons, risk of stroke (fatal or nonfatal) versus placebo was decreased by 37% for extended-release dipyridamole/aspirin ($p < 0.001$) and 16.3% and 18.1% for extended-release dipyridamole or aspirin, monotherapy, respectively (both $p < 0.05$).[15]

• Nonfatal strokes occurred less often with the combination (relative risk reduction 39.9% *vs* placebo) than with dipyridamole or aspirin alone (20% and 19.2% risk reduction, respectively; $p < 0.001$ *vs* combination).[15]

• Factorial design analysis showed that the protective effects of extended-release dipyridamole and aspirin in preventing secondary stroke were additive. Each individual drug was less effective than combined treatment with extended-release dipyridamole/aspirin for the end-point of stroke: the relative risk for extended-release dipyridamole/aspirin versus extended-release dipyridamole alone was 24.7% ($p = 0.002$) and versus aspirin alone was 23.1% ($p = 0.006$).[15]

• Risk of the combined end-point stroke or death was reduced by 24% with extended-release dipyridamole/aspirin relative to placebo ($p < 0.001$) and by 15% and 13%, respectively, for extended-release dipyridamole or aspirin alone (both $p < 0.05$ *vs* placebo).[15] The difference in risk reduction with the combination relative to either treatment alone approached, but did not achieve, statistical significance.[15]

• Neither the combination of extended-release dipyridamole/aspirin nor either agent alone significantly reduced death from any cause (fig. 1) or fatal stroke. The relative risk reductions for death compared with placebo were 8.5%, 7.3% and 10.9% for the extended-release dipyridamole/aspirin, extended-release dipyridamole and aspirin groups, respectively.[15]

Secondary End-Points

• Treatment with extended-release dipyridamole/aspirin was more effective than either extended-release dipyridamole or aspirin alone in preventing the occurrence or recurrence of a TIA. Compared with placebo, the relative risks were 35.9% for the

extended-release dipyridamole/aspirin combination ($p < 0.001$), 20.1% ($p = 0.008$) for extended-release dipyridamole and 24.4% ($p < 0.001$) for aspirin monotherapy (fig. 1).[16]

- Extended-release dipyridamole/aspirin showed a greater reduction than either extended-release dipyridamole or aspirin monotherapy in protecting against the incidence of other vascular events (these included deep venous thrombosis, pulmonary embolism, peripheral arterial occlusion and venous retinal vascular events). The relative risk reduction in patients receiving the combination of extended-release dipyridamole/aspirin was 61.7% ($p < 0.001$), whereas for extended-release dipyridamole and aspirin alone the relative risks were 36.7% and 31.6% (borderline significance).[16]

- Treatment with extended-release dipyridamole/aspirin combined or either drug alone did not show any significant effect on the incidence of myocardial infarction, although the trial was not designed to specifically measure this event.[16] The rates of infarction were low (2.1 to 2.9% across all treatment groups).[16]

4. Tolerability

Adverse events following the long term administration of aspirin in controlled trials have been reviewed in detail elsewhere.[17] Growing evidence that lower doses of aspirin are as effective as larger doses in preventing secondary ischaemic events,[2] and a desire to reduce the incidence of possible gastric and bleeding adverse events with aspirin, led to the choice of low dose aspirin in the fixed-dose combination with extended-release dipyridamole. The safety data accumulated with the fixed-dose combination in the second European Stroke Prevention Study (ESPS-2)[16] are summarised below and illustrated in figure 2.

- The incidence of adverse events reported during 24 months' treatment with extended-release dipyridamole/aspirin was greater than with placebo but only slightly greater than with either dipyridamole or aspirin alone. In the extended-release dipyridamole/aspirin group, 64.0% of patients reported an adverse event compared with 56.6% on placebo, 62.5% on extended-release dipyridamole and 60.0% on aspirin. Most of these adverse events were reported to be mild and not specifically related to treatment.

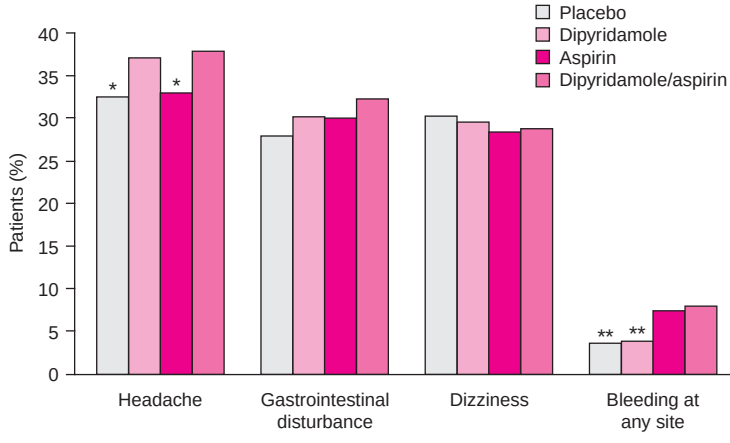


Fig. 2. Commonly reported adverse events during the second European Stroke Prevention Study (ESPS-2). The percentage of patients experiencing each event is shown for 24 months' treatment with extended-release dipyridamole/aspirin 400/50 mg/day (n = 1650), extended-release dipyridamole 400 mg/day (n = 1654), aspirin 50 mg/day (n = 1649) or placebo (n = 1649).* $p < 0.001$ *vs* combination; ** $p < 0.001$ *vs* aspirin or the combination.[16]

• The most frequently reported adverse event with the combination of extended-release dipyridamole/aspirin was headache. 38.2% of patients receiving extended-release dipyridamole/aspirin reported headache, an incidence that was similar to the extended-release dipyridamole monotherapy group (37.2%) but significantly higher than the placebo or aspirin treatment groups (32.4% and 33.1% respectively, $p < 0.001$). This increased incidence of headache was most marked early in treatment and diminished over time. After the first month of treatment the event rate for headache was nearly identical in patients given extended-release dipyridamole/aspirin or placebo.

• Treatment with the extended-release dipyridamole/aspirin combination showed a higher overall incidence of gastrointestinal disturbances (fig. 2), in particular diarrhoea, compared with placebo. The incidence of diarrhoea in the combination group was 12.1%, similar to that seen with extended-release dipyridamole alone (15.4%), whereas it was only 9.3% and 6.6% for the placebo or aspirin monotherapy groups ($p < 0.001$ *vs* dipyridamole regimens). The incidence of this adverse event diminished over time.

• The incidence of the potentially more serious adverse event of bleeding at any site was highest with extended-release dipyridamole/aspirin combination therapy and with aspirin monotherapy. Of a total of 430 such events, 8.7% occurred in combination recipients and 8.2% in aspirin monotherapy recipients, compared with 4.5% and 4.7% of the placebo or extended-release dipyridamole treatment groups, respectively ($p < 0.001$ for both comparisons). Of these, the incidence of severe or fatal bleeding was 1.6% with the extended-release dipyridamole/aspirin combination, 1.2% with aspirin alone and only 0.4% in either the placebo or extended-release dipyridamole monotherapy recipients. The incidence of this adverse event remained stable over time.

• Extended-release dipyridamole/aspirin was associated with mean decreases of erythrocyte counts, haematocrit and blood haemoglobin values after 12 to 24 months of treatment. These differences were also seen in the dipyridamole monotherapy group. The numbers of patients showing clinically abnormal values for these parameters was small; 0.8% of extended-release dipyridamole/aspirin recipients developed abnormally low erythrocyte counts and about 2% developed abnormally low haematocrit or haemoglobin values. For all of these parameters, the incidence appeared to be higher with extended-release dipyridamole/aspirin combination than in the placebo or monotherapy recipients during the first 12 months of treatment only.

5. Pharmacoeconomics

Data from ESPS-2 have been used to analyse the pharmacoeconomics of treatment with the fixed-dose combination of extended-release dipyridamole/aspirin for the secondary prevention of stroke.[18,19]

• In a cost analysis using direct medical costs (drug acquisition, primary care, rehabilitation and hospital costs), the cost in undiscounted New Zealand dollars (1996 currency year) per stroke event was multiplied by the incremental reduction in stroke events relative to placebo in the ESPS-2 trial. Over a 2-year period, the combined formulation of extended-release dipyridamole/aspirin showed savings in direct costs of $NZ905.16 per patient compared with placebo. This was $NZ18 less than the direct savings achieved with aspirin alone ($NZ923.39 per patient).[18]

• When both direct and indirect (lost productivity) costs were considered, incremental cost savings relative to placebo were $NS40.96 larger with the combination ($NZ1023.54 per patient) than aspirin alone ($NZ982.57).[18]

• A cost-effectiveness analysis based on a decision analytic model over 5 years' follow-up suggested that the combination of extended-release dipyridamole/aspirin, compared with aspirin alone, was cost effective, preventing recurrent strokes at an incremental cost of £230 per stroke averted or £75 per stroke-free life-year gained [reported as an abstract]. Sensitivity analysis indicated that the

formulation remained cost effective if the cost of providing long-term care for survivors of stroke was reduced by 50%.[19]

6. Extended-Release Dipyridamole/Aspirin: Current Status

Extended-release dipyridamole/aspirin, a fixed-dose combination of 2 antiplatelet agents, has been approved and launched in the UK. Approvals have also been obtained in France, Finland, New Zealand and South Africa. A US Advisory Committee has supported an indication of prevention of secondary stroke in patients who have had TIA or stroke. The combination has shown clinical efficacy in this indication and is relatively well tolerated; bleeding events appear more common with extended-release dipyridamole/aspirin than with dipyridamole alone but similar in incidence to aspirin monotherapy.

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