JAMC Vol. 5, No. 1, 1992

REVIEW ARTICLE

DIPYRIDAMOLE (PERSANTIN)

Mohammad Tahir Khattak

INTRODUCTION :

It has been shown that platelet aggregation and the formation of thrombi are pathophysiologically important in various forms of coronary artery disease and cerebrovascular disease. Platelet function modifying drugs have been used in patients with a wide variety of cardiovascular and cerebrovascular conditions. These disorders include patients with stable and unstable angina, acute myocardial infarction, coronary artery bypass grafts, prosthetic cardiac valves, transient cerebral ischemic attacks and strokes. the ideal antiplatelet drug should have potent antithrombotic activity, be clinically effective and have a low risk of causing bleeding and significant side effects.

As a result over the years various antiplatelet agents were developed, including aspirin, dipyridamole, sulphinpyrazone and ticlodipine which have been used singly or in combination in patients with cardiovascular and cerebrovascular disorders.

Dipyridamole (Persantin) was introduced in 1959. It is a pyridopyrimidine derivative and is still a widely prescribed drug. It has been the centre of a lot of controversy especially regarding its antiplatelet and antithrombotic actions. This review will look at the mechanism of action of dipyridamole and the evidence available from clinical trails regarding its use as an antithrombotic drug.

MECHANISM OF ACTION

The mechanism by which dipyridamole exerts its antithrombotic effects in vitro and in vivo has been the subject of controversy. The main modes by which dipyridamole has been suggested to inhibit platelet function are through :

1. Inhibition of the enzyme cyclic nucleotide phospho-diesterase in platelets.[1] This leads to an increase in the cellular concentration of cyclic AMP and the subsequent potentiation of the platelet inhibiting actions of prostacyclin.

2. Blockade of cellular uptake and metabolism of adenosine, which acts at A2 receptors for adenosine to stimulate platelet adenylyl cyclase.[2] I increased concentrations of adenosine leads to platelet inhibition and prevents platelet aggregation.

3. Direct stimulation of the release of the platelet inhibitors prostacyclin and prostagland in D2 from vascular endothelium and thereby augmenting the action of

From Ayub Medical College, Abbottabad.
MOHAMMAD TAHIR KHATTAK, MBBS, MRCP, D-CARD, Assistant Professor of Cardiology.

circulating prostacyclins.[3] Such compounds directly inhibit platelet function.

4. Augmentation of the platelet inhibiting action of dispirin.

5. Prolongation of platelet survival.[4]

Some authors have, however, found it difficult o demonstrate the platelet inhibiting pharmacological effects of dipyridamole in human beings.

There is conflicting evidence as regards interactions, in humans, with aspirin and whether such pharmacokinetic interaction leads to a synergistic antiplatelet effect. The effects of dipyridamole on the duration of platelet survival do not, however, establish its role as an anti-platelet drug in human beings.

CLINICAL TRIALS OF DIPYRIDAMOLE :

1). CHRONIC STABLE ANGINA :

There is evidence that dipyridamole can exacerbate angina pectoris in a significant number of patients given 150 mg per day.[5] This is not surprising since one of the most useful effects of dipyridamole is its ability o dilate coronary resistance vessels rather than conductance vessels and thereby induce myocardial ischemia. Chesebro et al, however, have shown that aspirin and dipyridamole in patients with stable angina pectoris reduced the incidence of myocardial infarction and the appearance of new atherosclerotic lesions.[6] It is difficult to be sure as to how much dipyridamole contributed to the antithromobotic effects of aspirin and to the observed result of the study. There is little evidence for thrombosis and platelet activation in stable angina pectoris.

2). UNSTABLE ANGINA :

Because of its vasodilator effects on coronary resistance vessels and the risk of precipitating myocardial ischemia the use of dipyridamole is contraindicated in patients with unstable angina.[7]

3. PRIMARY PREVENTION OF ACUTE MYOCARDIAL INFARCTION :

To date there have been no clinical trials of dipyridamole in the primary prevention of myocardial infarction and as such there is no available data.

4. SECONDARY PREVENTION OF ACUTE MYOCARDIAL INFARCTION :

Two large clinical trial have addressed the question of the use of dipyridamole alone or in combination with aspirin in the secondary prevention of myocardial infarction.

In the PARIS I Study (Persantine — Aspirin Reinfarction Study) patients who had an acute myocardial infarction received one of the following : aspirin alone, aspirin plus

dipyridamole or matching placebos.[8] The results of the study showed that there was a statistically non-significant trend towards a reduction in overall mortality, cardiac mortality and in the frequency of non-fatal myocardial infarction.

In the PARIS II Study (Persantine-Aspirin Reinfarction Study) patients who had survived an acute myocardial infarction received aspirin plus dipyridamole or placebo.[9] Again here was a statistically non-significant reduction in coronary mortality and overall mortality.

In the PARIS I study aspirin alone was compared with aspirin plus dipyridamol and the two regimes did not differ significantly as regards end-points In the PARIS-II study a group receiving aspirin alone was not included. Is is therefore difficult to be sure whether aspirin, dipyridamole or both accounted for the observed reduction in the incidence of coronary events in the PARIS II study.

The only controlled trial of dipyridamole alone in the secondary prevention of myocardial infarction failed to show any effect on overall mortality and cardiac complications.[10]

5. SECONDARY PREVENTION OF TIA AND CVA

Two important clinical trials have assessed the benefit of dipyridamole in the secondary prevention of transient cerebral ischemic attacks and strokes.

In the AICLA Study patients who had had a TIA or CVA received aspirin or aspirin plus dipyridamol.[11] Both treatment regimes led to a significant reduction in the incidence of cerebral infarction and myocardial infarction. There was, however, no statistically significant difference between the two treatment groups.

In the other, PARIS Trial in Cerebral Ischemia, patients who had had TIA's received aspirin or aspirin plus dipyridamole. The observed results were similar in both treatment groups.

From these clinical studies it is clear that dipyridamole adds nothing significant to the efficacy of aspirin in the secondary prevention of cerebral infarction.

6. CORONARY ARTERY BY-PASS GRAFTING :

Several studies have shown that aspirin alone or in combination with dipyridarmole reduce the incidence of saphenous vein graft thrombosis postoperatively.[13] However the overall impression is that dipyridamole is unlikely to contribute significantly to the beneficial effect of aspirin in maintaining graft patency. Aspirin alone is more likely to have substantial efficacy in this setting.[14]

7. MECHANICAL VALVE PROSTHESES :

Patients with mechanical cardiac prosthetic valves remain on life long anticoagulant therapy to reduce the frequency of thromboembolic episodes. There appears to be some benefit of dipyridamole inpatiens with artificial heart valves who have had thromboembolic episodes despite anticoagulation.[15] The study which suggested this is relatively old and the effects of combining dipyridamole with modern valve prosthesis is unknown.

CONCLUSIONS :

Dipyridamole is still a widely prescribed drug usually in combination with aspirin. It is used by general practitioners, physicians and cardiologists alike. Most of the clinical trials to assess the efficacy of dipyridamole have been in combination with aspirin. Where dipyridamole alone was used the results have been conflicting. Where aspirin alone has been compared with aspirin and dipyridamole the results suggest that dipyridamole contributed little if anything to the antithrombotic action of aspirin. [16] Reviews of dipyridamole have not established any additional benefit over aspirin alone. [17]

In the United Kingdom as of 1980 dipyridamole has only been licensed as an adjunct to oral anti-coagulation for prophylaxis of thromboembolism associated with prosthetic cardiac valves. [18] Dipyridamole may be useful in the occasional patient with a contraindication to aspirin i.e. hypersensitivity or active peptic ulceration.[19] It may yet become established as a useful antithrombotic agent. Dipyridamole can lead to unpleasant side effects like headache, flushing, hypotension and gastrointestinal disturbance. It is contraindicated in unstable angina and aortic stenosis and may exacerbate migraine.[20] It should not be routinely used after coronary artery bypass surgery or valve replacement. The present evidence and consensus does not support its use as an antiplatelet and antithrombotic drug.

REFERENCES :

1. Goodman and Gillman. the Pharmacological Basis of Therapeutics. 8th Edition, 1991.
2. Goodman and Gillman. The Pharmacological basis of Therapeutics. 8th, Edition, 1991.
3. Moncada S, Korbut R. Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiatingendogenous prostacyclin. Lancet 1978; 1286-9.
4. Fitzgerald GA. Dipyridamole. N. Eng J Med, 1987; 316:1247-57.
5. Tsuya T, Okeda M, torie H, Ishikawa K. Effect of dipyridamole at the usual oral dose on exercise — induced myocardial ischemia and stable angina pectoris. Am J Cardiol 1990; 66 275-78.
6. Chesebro JH, Webster MWI, Smith HC, et. al. Antiplatelet therapy in coronary disease progression. Reduced infarction and new vessel formation. Circulation 19890; 80; Supplement II.
7. In Braunwald E. Heart Disease. A Textbook of Cardiovascular Medicine. 3rd Edition 1988. W.B. Saunders Company.
8. Persantine-Aspirin Reinfarction Study Research Group. Persantine and aspirin in coronary heart disease. Circulation 1980; 62: 449-61.
9. Klimt CR, Knatterud GL, Stamler J, Meier P. Persantine-Aspirin. Reinfarction Study Part II. Secondary coronary prevention with perseantine and aspirin. J Am Coll Cardiol 1986; 7: 251-69.
10. Gent AE, Brook CGD, Folley TH, Miller TN, Dipyridamole : A controlled trial of its effects in acute myocardial infarction. Mr Med J. 1968; 4:366-8.
11. Bousser MG, Eschwege E, Haguenau M. et al. AICLA Controlled trial of Aspirin and Dipyridamole in the secondary prevention of atherosclerotic cerebral ischemia. Stroke 1983; 14:5-14.

12. American — Canadian Co-operative Study Group. Persantine-Aspirin trial in cerebral ischemia. Part II. Endpoint results. Stroke 1985; 16: 406-15.
13. Chesebro JH, Fuster V. Elveback CR, et al. Effect of dipyridamole and aspirin on late vein graft patency after coronary bypass operations. N. Eng J Med 1979; 301-962-6.
14. Lorenz RL, Von Schacky C, Weber M, et al. Improved aortocoronary bypass patency by low-dose aspirin (100 mg daily): effects on platelet aggregation and thrombaxane formation. Lancet 1984; 1:1261-4.
15. Sullivan JM, Harken DE, Gorlin R. Effect of dipyridamole on the incidence of arterial embolic after cardiac valve replacement. N Eng J Med. 1971: 284:1391-94.
16. Andiplatelets trials collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. Br Med J 1988; 296, 320-331.
17. Fitzgerald GA. Dipyridamole. N. Eng J Med. 1987; 316: 1247-57.
18. Metcalfe MJ, Lip G, Dunn FG. Dipyridamole. Letter. N. Eng J. Med. 1992; 339: 1229.
19. Willard JE, Lange RA, Hillis LD. The use of aspirin in ischemic heart disease. N. Eng J Med. 192; 327: 175-181.
20. British National Formulary. Number 19, 1990.