Chronic oral dipyridamole as a ‘novel’ antianginal drug: the collateral hypothesis

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Abstract

Dipyridamole is an adenosine transport blocker that produces elevation of tissue adenosine levels. The oral formulation has long been used as a ‘coronary vasodilator’, but inappropriate vasodilation can lead to a pro-ischemic effect. However, available evidence linking adenosine to angiogenesis raises the possibility of a therapeutically relevant anti-ischemic effect of the drug. Molecular biology data show that in a hypoxic milieu, increased interstitial adenosine increases proliferation of endothelial cells in culture by stimulating A₁ and A₂ adenosine receptors and induces vascular endothelial growth factor which leads to angiogenesis. Morphologic data indicate that chronic, intermittent dipyridamole administration increased endomyocardial capillary length density by 33% in hypertensive and 11% in normotensive rabbits. Experimental data suggest that chronic treatment with dipyridamole increases collateral flow and decreases exercise-induced left ventricular dysfunction in the territory dependent upon a critical coronary stenosis. Clinical data indicate that the meta-analysis of all published double-blind, placebo-controlled, randomized trials assessing the effect of dipyridamole as an antianginal agent showed a highly significant drug benefit (odds ratio = 0.299, confidence intervals = 0.202–0.443). Treatment duration (log time in days) was significantly correlated to the observed benefit (log odds) ($r = -0.75, P = 0.0031$), consistently with a structural change in the collateral coronary circulation requiring time to emerge. The available data support the ‘adenosine collateral hypothesis’ (i.e., a beneficial angiogenetic effect of chronic endogenous adenosine accumulation). The angiogenetic effect would be different from the coronary vasodilator effect in several respects: coronary anatomical target (mainly capillaries instead of arterioles); cellular target (mainly endothelium rather than smooth muscle cell); receptor target (A₁ and A₂ rather than A₀ adenosine receptors); time required for effect (weeks or months rather than minutes or hours); clinical use (possibly therapeutic for angiogenesis; mainly diagnostic for vasodilator stress testing). Prospective, properly designed trials are needed to assess convincingly the efficacy of a drug used for 40 years and yet possibly prematurely discarded as an effective antianginal treatment.

Keywords: Adenosine; Collateral vessels; Dipyridamole; Myocardial ischemia

1. Introduction

Dipyridamole is an adenosine transport blocker that produces elevation of tissue adenosine levels [1]. It has been approved for decades as a ‘coronary vasodilator’ and is still being used as an anti-platelet agent [2]. A 1988 meta-analysis of published trials on dipyridamole as an antianginal drug demonstrated consistently a beneficial effect of long-term treatment with oral dipyridamole [3]. In spite of this, its use as an antianginal drug has been diminishing. In fact, clinical observations without physiologic support are mere statistical epiphenomenology, and the two widely known effects of dipyridamole as a coronary vasodilator and as an anti-platelet agent make it an unlikely candidate for anti-ischemic action. Acute coronary vasodilation can indeed be responsible for the pro-ischemic effect [4,5], which is defined by Waters as “the potential of an antianginal drug to occasionally worsen ischemia in an unpredictable and dangerous manner” [6]. Coronary arteriolar vasodilation due to stimulation of A₀ adenosine receptors can induce vasodilation leading to flow maldistribution and to true ischemia, which is the basis of the widespread use of intravenous dipyridamole as a stress test.
to diagnose coronary artery disease, detected as a flow heterogeneity (by myocardial scintigraphy) or as an ischemic regional dysfunction (by stress echocardiography) [7]. The anti-platelet effect is also unlikely to play a role in the prevention of anginal attacks since very effective anti-platelet agents do not have any anti-ischemic efficacy [1]. Coronary vasodilation will not make any good, and can possibly be harmful, whereas an anti-platelet effect should be completely neutral in the prevention of myocardial ischemia.

Any beneficial effect of dipyridamole on myocardial ischemia should recognize an entirely different mechanism—which we hypothesize might be its coronary pro-angiogenic mechanism, according to molecular biology, morphologic, experimental and clinical data. The ‘adenosine collateral hypothesis’ presented here attempts to fit the updated results of the meta-analysis of clinical trials into the physiological framework of a possible coronary angiogenic effect of chronic endogenous adenosine accumulation.

2. The coronary angiogenic effect of adenosine: the experimental evidence

Chronic myocardial ischemia such as occurs with coronary artery stenosis leads to the development of a collateral circulation [8]. This type of growth of new blood vessels has been demonstrated in heart and skeletal muscle and results from a reduction in the oxygen supply/demand ratio [9]. Angiogenesis—the formation of new blood vessels—involves the activation, migration, and proliferation of endothelial cells and is regulated by several molecules [8,9]. It has been shown that adenosine is involved in this angiogenic effect of the reduced oxygen supply [10]. In support of this concept, low oxygen concentrations (2%) have been demonstrated to increase the proliferation of endothelial cells in culture [11] by stimulating A₁ and A₂ adenosine receptors present on the endothelial cell surface [11]. Addition of an adenosine receptor antagonist to the hypoxic conditioned media prevented this increase in endothelial cell proliferation [11]. Endogenous adenosine produced by ischemia induces vascular endothelial growth factor mRNA in the heart [12], and also increases its stability so that new peptide can be synthesized without new transcription [13].

Dipyridamole increased the formation of capillaries in rat and rabbit hearts [14–16]. Two months of chronic, intermittent dipyridamole administration (4.0 mg/kg s.c. twice daily) increased endomyocardial capillary length density by 33% in hypertensive rabbits and 11% in the normotensive rabbits compared with the respective vehicle-treated animals [16]. According to Schaper, a relatively strong case can be made for purine nucleosides as ischemia-related mitogen activators in small coronary blood vessels [8]. In the presence of a critical coronary stenosis, adenosine acts as a regulator of endogenous growth factors triggered by repeated episodes of ischemia.

It has been experimentally shown that chronic long-term treatment with dipyridamole increased collateral flow and improved transmural blood flow and systolic wall thickening during exercise-induced ischemia, with a beneficial protective anti-ischemic effect more marked than that exerted by diltiazem [17]. These data were obtained in miniswine, which were selected as an experimental model because the anatomy and physiology of their coronary collateral circulation is similar to that of humans [17]. When near-maximal physiological capacity of the collateral vessels was assessed during exercise, collateral dependent blood flow was found to be greater in dipyridamole-treated than in diltiazem-treated and vehicle-treated animals. This 30% increased blood flow to the collateralized myocardium was physiologically meaningful since exercise-induced mechanical dysfunction was reduced by almost 30% in comparison with diltiazem. The beneficial effect of the drug was observed after chronic stimulation with relatively low doses (28 μg/kg/min, producing only a 50% acute increase in transmural coronary flow), intermittently administered (90 min per day, 5 days a week) for 8 weeks. Therefore, a relatively weak and intermittent pharmacological stimulation can produce physiologically relevant benefit if adequately prolonged over time, since development of a collateral circulation requires several weeks [17].

If the collateral circulation pathway is indeed activated, one should expect that clinical studies with longer duration of treatment show the greatest benefit, and studies with no crossover design should have better results, since the improvement in collateral circulation is not expected to regress immediately at interruption of treatment, and some long ‘carry-over’ effect on placebo therapy should take place. In dogs, collaterals often reach their full development and remain available for at least 4 months after the obstruction has been relieved; these vessels may adequately protect the myocardium in the event of subsequent occlusion [18].

3. The coronary angiogenic effect of endogenous adenosine: the clinical evidence

A meta-analysis of dipyridamole in the treatment of angina pectoris was presented by Sacks et al. in 1988 [3], which included 11 trials [19–28]. As detailed by Sacks et al. [3], all studies selected for analysis met the following inclusion criteria: (1) dipyridamole was used for treatment or prophylaxis of angina, and the results were assigned to ‘improvement’ or ‘no improvement’ on the basis of frequency of anginal attacks; (2) treatment and control were randomly allocated; (3) all trials were double-blinded and placebo-controlled. Dosages employed ranged from 37.5 to 225 mg/day and duration of treatment from 2 weeks to 6 months. The combined odds ratio for the pooled published
results was 0.29, with a 95% confidence interval of 0.19–0.43, which is a highly statistically significant benefit \((P < 0.01)\). The summary estimate, however, fails to draw attention to two important biological sources of heterogeneity in the results—i.e., the drug dose and the duration of treatment. Although there was no significant relationship between drug dose and benefit over a relatively wide range of 37.5–225 mg/day, higher doses were more likely to be associated with benefit, with the two perfectly neutral studies using the lowest dosage (37.5 mg/day). Larger benefits were observed with studies of longer duration. The 4 studies with the longer duration of treatment all shared a non-crossover study design and showed a clearly positive effect of treatment. The conclusions of the study by Sacks et al. remain unchanged if the two studies published afterwards are included in the analysis [29,30]. The updated analysis confirms the presence of a significant fit between entity of benefit (log odds) and duration of treatment (log time in days): \(r = -0.75; P = 0.0031\). This possible beneficial effect of dipyridamole as a function of the duration of the treatment agrees with the concept that coronary anastomoses can provide a considerable amount of blood flow. In dogs, they are maximal 3–6 months after a gradual coronary occlusion developing over a few days [18]. The protection provided by collaterals is ‘a race against time’ [31], which cannot be won by the drug if the period of observation is too short. Once the benefit of a collateral circulation has developed, weeks and months of therapy withdrawal are not enough to lose it. Other non-pharmacological treatments, such as enhanced external counterpulsation, thought to act by improving the collateral circulation, are characterized by a beneficial effect emerging over several weeks [32] but long-lasting after discontinuation of treatment.

4. The pro-ischemic effect of dipyridamole-induced vasodilation: much adenosine about something?

Coronary vasodilation induced by dipyridamole might theoretically concur with the angiogenetic potential of the drug, by adding a mechanical stimulus to angiogenesis [33]. In fact, there is potential for mechanical forces to contribute to vascular growth. In vitro studies indicate that physical forces such as repetitive mechanical stretching can modulate cellular function and induce proliferation [34,35]. Increased collateral-dependent blood flow found experimentally can result from a direct chemical effect of adenosine and/or from an adenosine potentiated vascular response to repeated mechanical stress, since changes in shear forces are important in remodeling muscular arteries to which epicardial collateral vessels belong [36]. However, coronary vasodilation induced by dipyridamole can also possibly be harmful and pro-ischemic, as shown by theoretical [37], experimental [38] and clinical [39] evidence, as well as by extensive clinical experience with cardiac imaging during acute dipyridamole administration [7,40]. Test positivity is based on flow heterogeneity with myocardial perfusion imaging, but requires absolute subendocardial hypoperfusion and true myocardial ischemia with two-dimensional echocardiography [40]. In spite of the well-established fact that dipyridamole infusion can provoke, at appropriately high doses, ischemia with a frequency comparable to maximal exercise testing in patients with coronary artery disease [8], the pro-ischemic effect should play a very minor role in a regimen of chronic oral therapy for several reasons. First, ischemia is consistently evoked by dipyridamole only when high doses of the drug are acutely given by the intravenous route. In patients with angiographically assessed coronary artery disease, the frequency of echocardiographically detected transient regional dysfunction (a highly sensitive and specific marker of myocardial ischemia) decreases sharply with declining doses of intravenous dipyridamole, being about 75% with high dose of 0.84 mg/kg [41], only about 50% with a dose of 0.56 mg/kg [41], and virtually absent with a dose of 0.28 mg/kg, which is used as a selective test for identifying myocardial viability as an inotropic response in regions with baseline dyssynergy [42]. A single oral administration of 150 mg dipyridamole did not affect the threshold of ischemia in an atrial pacing study [43]. These data on the negligible pro-ischemic effect of the drug administered orally for therapeutic purposes are consistent with pharmacokinetic data, indicating that the blood concentration of dipyridamole after oral administration of 150 mg/day (0.8–1.4 \(\mu\)g/ml) is about one-fourth of that after intravenous administration of 0.56 mg/kg (4.6 ± 1.3 \(\mu\)g/ml) [44,45]. Second, angina-like chest pain can be evoked by adenosine accumulation independently of ischemia production [46], and this may lead to an overrating of a ‘steal phenomenon’ identified only on the basis of clinical symptoms. Third, the ischemic effect of intravenous dipyridamole is antagonized by antianginal therapy with calcium antagonists, beta-blockers and/or nitrates [47]. Since dipyridamole should probably be tested in future clinical trials as an add-on therapy associated with standard treatment, the pro-ischemic potential of oral formulations should be further lowered.

From the conceptual point of view, the angiogenetic effect would be different from the coronary vasodilator effect in several respects, summarized in Table 1. The pro-ischemic effect of the drug is dose-dependent, emerging in minutes or hours, is linked to stimulation of \(A_2\) adenosine receptors present on the smooth muscle cell of the coronary arteriole, and is currently exploited for diagnostic purposes with vasodilator stress testing with cardiac imaging techniques [42]. By contrast, the possible angiogenetic effect would require weeks or months of therapy to be detectable, is achieved through the stimulation of \(A_1\) and \(A_2\) adenosine receptors present on endothelial cells, and is of obvious potential therapeutic interest.

It is possible that the two effects cross-talk, with vasodi-
Table 1

The effects of adenosine accumulation on the coronary circulation

<table>
<thead>
<tr>
<th>Effect</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing</td>
<td>minutes or hours</td>
<td>weeks or months</td>
</tr>
<tr>
<td>Dose, route of administration</td>
<td>high, intravenous</td>
<td>low, oral</td>
</tr>
<tr>
<td>Coronary target</td>
<td>arterioles</td>
<td>capillaries</td>
</tr>
<tr>
<td>Cellular target</td>
<td>smooth muscle cell</td>
<td>endothelial cell</td>
</tr>
<tr>
<td>Receptor target</td>
<td>A₂</td>
<td>A₁ and A₂</td>
</tr>
<tr>
<td>Main clinical interest</td>
<td>diagnostic</td>
<td>therapeutic (?)</td>
</tr>
</tbody>
</table>

Collateral vessel growth in the human heart may be considered a very complex equation with a two-digit number of variables, including various types of growth factors (vascular endothelial, fibroblast, insulin growth factors) and their receptors [48]. Adenosine may change the end-result of this equation, by potentiating endogenous growth factors such as vascular endothelial growth factor. The self-adaptation of the heart to coronary occlusion is not perfectly developed, and collateral vessel growth may be largely defective. As stated by Schaper, “this defective adaptation should lead the way to the development of therapeutic strategies that use pathways that are already outlined by nature” [48]. Accumulation of endogenously produced adenosine is certainly one of these pathways, and it is now time for the clinician to begin the quest for better angiogenesis in the human heart.

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References


