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REVIEW

Cilostazol: an antiplatelet agent for the neurointerventionist?

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ABSTRACT

Antiplatelet agents are essential for the successful management of patients undergoing a variety of neurointerventional procedures. The most commonly used anti-platelet agents are aspirin, clopidogrel and prasugrel. However, there exist an alternative class of anti-platelet agent that may prove useful for neurointerventionists. In particular a drug called cilostazol may have numerous added advantages above and beyond its antiplatelet effect that may be valuable for our patients. In this short review we aim to highlight some of these potential advantages.

INTRODUCTION

Antiplatelet agents are essential tools in the armory of all neurointerventionists. In recent years the need for them has grown as neurointerventional procedures have become more complex. The success of any intervention involving stents is heavily reliant upon the adequate control of the clotting system. The standard antiplatelet regimen for most neurointerventional procedures involves aspirin and clopidogrel with prasugrel as a backup in cases of resistance. The mechanism of action, dosing, and side effects of these drugs is well documented and they represent the preferred choice for many of us. However, there exists an alternative class of antiplatelet agents that is less well known but may have additional effects above and beyond those on platelet aggregation. This class of drug is the phosphodiesterase (PDE) inhibitors and, in particular, cilostazol.

Preventing platelet aggregation can be achieved either via inhibition of membrane receptors or by affecting the intracellular signaling pathways and, while the former may provide high specificity, the latter may have broader effects with suppression of platelet activation irrespective of the initial stimulus. PDEs are important in the intracellular signaling pathway which, among other actions, is involved in platelet aggregation. Cilostazol is a strong and specific reversible inhibitor of PDE3 in platelets and smooth muscle cells where it inhibits platelet activation and causes muscle relaxation, respectively. In addition to these actions, it has several other effects that we believe are potentially of benefit to interventional neuroradiologists.

ANTIPLATELET EFFECT

Cilostazol is a potent PDE3 inhibitor that results in an increase in intracellular cAMP. Raised levels of cAMP result in inhibition of the normal platelet activation and aggregation pathway. This inhibition of platelet aggregation has been shown to occur in a

dose-dependent manner.¹ Studies in both healthy adults² and patients with peripheral arterial disease³ comparing aspirin, ticlopidine, clopidogrel, cilostazol or combinations of these agents have shown that cilostazol does not significantly prolong the bleeding time either alone or in combination with the other drugs. It therefore appears that cilostazol can be added to other antiplatelet inhibitors without increasing the risk of bleeding. In addition, cilostazol is active in sheer stress-induced platelet aggregation, an effect not seen with aspirin. Interestingly, patients with type 2 diabetes have reduced platelet inhibition compared with non-diabetics following blockade of the P2Y₁₂ receptor. A small pilot study recently showed that the addition of cilostazol to standard dual antiplatelet treatment with aspirin and clopidogrel enhances the effect of the P2Y₁₂ receptor pathway and hence may explain why cilostazol is particularly efficacious in diabetic patients.⁴⁻⁶

Cilostazol has a half-life of approximately 10 h and reaches peak plasma concentration in just under 3 h after oral administration. It is mainly metabolized via the cytochrome p450 pathway⁷ and therefore potential drug interactions with, for example, erythromycin are possible.

ANTI-ATHEROSCLEROTIC EFFECT

Cilostazol is also known to have anti-atherosclerotic effects. The exact mechanism of this effect is not known, but it has been shown that cilostazol can alter the lipid profile of patients with increases in high-density lipoprotein and lowered triglyceride.⁸ In addition, it is known to alter monocyte chemo-attractant protein-1 which recruits monocytes to atherosclerotic lesions.⁹ It is perhaps no surprise then that cilostazol has shown a benefit in patients with both intracranial and extracranial atherosclerotic disease. Kwon *et al* reported that, with aspirin monotherapy (100 mg per day), 28.8% of patients with symptomatic intracranial arterial stenosis progressed and 15.4% regressed. Dual therapy with aspirin (100 mg per day) and cilostazol (200 mg per day) resulted in progression in 6.7% of patients and regression in 24.4%.¹⁰ A small study that used cilostazol alone reported similar results, with 50% of patients showing regression of intracranial stenosis as demonstrated by both MR angiography and digital subtraction angiography at 12 months. Furthermore, this improvement was seen in symptomatic lesions and in severe lesions (>50% stenosis). Similar findings of a benefit of cilostazol compared with aspirin were found in a recent meta-analysis of patients with ischemic stroke,¹¹ with an associated decreased risk of intracranial



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hemorrhage with cilostazol. This lower risk of hemorrhage was confirmed for those patients at high risk in a subgroup analysis of data from the Cilostazol Stroke Prevention Study 2.¹² Cilostazol has also been shown to have an effect on extracranial carotid plaque, with a recent study demonstrating MRI signal change within plaques that indicates an increase in the fibrous components and a concomitant decrease of lipid/necrotic components during treatment with cilostazol.¹³ Additionally, with the growing acceptance of mechanical thrombectomy, there is an emerging need for acute carotid stenting and cilostazol is well suited to this situation, given its favorable actions on plaque stabilization and documented lower risk of hemorrhage compared with other antiplatelets.¹²

IN-STENT STENOSIS EFFECT

Cilostazol has been extensively studied in the setting of cardiology and coronary stenting. The Coronary Stent Restenosis in Patients Treated with Cilostazol (CREST) trial demonstrated a significantly lower rate of restenosis in the cilostazol group.⁴ This effect is not limited to the coronary vascular system and similar results are now being reported in patients undergoing carotid artery stenting. Takigawa *et al* showed a significant reduction in the rate of in-stent restenosis for patients treated with cilostazol (0% vs 15.7%) compared with other antiplatelets.¹⁴ Similar results have been seen in the ReSISter-CAS study conducted by Yamagami *et al*¹⁵ where the use of cilostazol was associated with a lower rate of in-stent restenosis, and also by Takayama *et al*.¹⁶ Given this effect on restenosis, the use of cilostazol at least warrants consideration when intracranial stenting is considered, especially if this is done for atherosclerotic disease where restenosis has been seen in up to 33% of patients,¹⁷ albeit mostly asymptomatic.

These improvements in outcome are also associated with a good safety profile. Data from the prospective registry on carotid stenting in Japan showed a statistically significant lower incidence of the primary end point (including myocardial infarction, transient ischemic attack, ischemic or hemorrhagic stroke) in the combined aspirin plus cilostazol group.¹⁸

ANTI-VASOSPASTIC EFFECT

The treatment of subarachnoid hemorrhage has evolved rapidly over the last decade. While the use of stent-assisted coiling or flow diversion in the setting of acute subarachnoid hemorrhage is best avoided, it may still be necessary. In this scenario the use of antiplatelet agents cannot be avoided, so the correct choice of antiplatelet agent is essential. Aside from its action on platelet aggregation and smooth muscle cells, cilostazol is also a potent vasodilator. This vasodilatory effect has been seen in the prevention of delayed cerebral vasospasm following subarachnoid hemorrhage. A recent meta-analysis reviewed the effect of cilostazol on the development of cerebral vasospasm and the clinical outcomes. The findings of the meta-analysis showed a significant reduction in the incidence of symptomatic vasospasm, severe vasospasm, vasospasm-related new cerebral infarctions, and poor outcome in patients treated with cilostazol. There was no significant effect on mortality.¹⁹ These findings suggest that cilostazol is potentially useful for patients with subarachnoid hemorrhage and, if stenting is required in the setting of subarachnoid hemorrhage, then the use of cilostazol should be given serious consideration.

CONCLUSION

Ultimately, only well-designed and carefully conducted randomized clinical trials will provide us with the evidence we require for the use of cilostazol, or any drug. Given the current available evidence, in our opinion cilostazol at least warrants further investigation to determine its potential use in the realm of neurointervention.

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