Novel uses and potential for calcium antagonists in revascularization

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Calcium antagonists affect the arterial wall and blood components in many ways: these include their classical vasomotor functions, as well as newly-documented effects on platelet aggregation, rheology, the platelet membrane receptor glycoprotein IIb/IIIa complex and on tissue factor, a glycoprotein that initiates the clotting cascade. Calcium antagonists slow atherogenesis in animals, perhaps through inhibiting calcium incorporation, lowering heart rate or reducing thrombus formation, although no benefits were shown in prospective clinical studies of stenosis progression. However, it has been possible to attenuate proliferation in in vitro and in vivo experimental models.

These discoveries are leading to novel calcium antagonist applications in revascularization. They have the potential to act synergistically in thrombolysis, but so far there has been very little evaluation of this. During coronary intervention, the myocardial protective action of calcium antagonists could be of benefit against stunning and in the no-reflow phenomenon. Their action on vasomotor tone and thrombus formation might affect acute closure or restenosis, although clinical studies have not yet shown this, perhaps because systemic administration of calcium antagonists does not achieve a high enough local concentration. Local drug delivery into the arterial wall may have potential. Calcium antagonists could be of use in cardiac surgery by preventing spasm or providing myocardial protection.

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Introduction

Calcium antagonists are commonly used to prevent ischaemia and treat hypertension. They have wide-ranging effects on the arterial wall and blood components. Discoveries in vascular biology and platelet function, are leading to novel application of these drugs in revascularization. Some effects are caused by all calcium antagonists; some only apply to those within a particular category. This must be taken into account before clinical use. The three categories are dihydropyridines (e.g. amlodipine, nifedipine), papaverine derivatives (e.g. verapamil) and benzothiazepines (e.g. diltiazem). Other drugs, for example carvedilol, may also have calcium antagonist properties.

Calcium antagonists may be particularly useful in vascular disease when given locally, achieving high concentrations where needed, whilst minimizing systemic side effects. This should be considered when planning future use. This article summarizes the effects of calcium antagonists in vascular applications and then discusses their clinical use in revascularization, in association with thrombolysis, angioplasty or bypass surgery.

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Relevant effects of calcium antagonists

Vasomotor

Because of their action on calcium flux across plasma membranes, calcium antagonists have long been recognized as important in arterial wall haemodynamics. Their effects on endothelins also contribute to this; nisoldipine, isradipine, nitrendipine and nifedipine counteract the vasoconstriction of endothelin-1[1]. The action on vasoconstriction may be therapeutic in vessel pathology related to spasm, especially where thrombus formation is a possibility. The drug may also aid those with predominantly microcirculatory disturbances, for example systemic sclerosis or even Syndrome X. It is significant that the anti-spasmodic effect on coronary arteries of some calcium antagonists can be achieved without impairing myocardial contractility[2].

Thrombus formation

Several aspects of thrombus formation appear to be related to calcium flux. Certain platelet functions are, for example, dependent on intracellular calcium for optimal activation. Platelet aggregation in vivo can be rapidly...
inhibited by calcium antagonists, although there is evidence to suggest that a rebound phenomenon may occur in some cases, as documented several hours after a single oral dose of nitrendipine. This calcium antagonist also alters platelet reactivity by acting on platelet membrane glycoprotein, IIb/IIIa, forms a complex with binding sites for fibrinogen; this is a calcium-dependent function. As predicted, several compounds that recognise the complex, and can inhibit platelet aggregation, act by steric hindrance of calcium influx at the platelet membrane level and verapamil has also been shown to interfere with the platelet receptor complex. The anti-platelet action of calcium antagonists could be synergistic to the action of aspirin on platelet activation. Tissue factor, a glycoprotein that initiates the clotting cascade, is induced in vitro by several growth factors and other vasoactive substances. The induction is dependent on intracellular calcium mobilization and can potentially be blocked by calcium antagonists, which would attenuate local vessel thrombus. The various thrombus-minimizing effects of calcium antagonists could be clinically helpful in combination with thrombolysis and after angioplasty, as well as in certain surgical cardiac procedures, as discussed below.

**Atherosclerosis**

Calcium ions are thought to be atherogenic; they interfere with the release of platelet-derived growth factor, mediating cell migration, proliferation and matrix production, intracellular calcium overload of smooth muscle cells and lipoprotein storage. The traffic of low density lipoprotein appears to be improved by verapamil and diltiazem in particular. Uptake of calcium into the arterial wall is necessary for the formation of calcium-dominated atherosclerotic plaque. Under experimental conditions in vitro and in vivo in a rat model, all classes of calcium antagonists inhibited progressive mural calcium incorporation and thus atherogenesis. Through reducing blood pressure, calcium blockers reduce wall shear stress and thus potentially minimize atherosclerosis development. Lowering heart rate by antagonists with this property can also affect atherosclerosis development in animal models. Calcium antagonists attenuate endothelium dysfunction and, as mentioned above, affect thrombus formation, further emphasizing their beneficial effects on atherosclerosis progression in animals. A retrospective analysis after bypass surgery in patients taking verapamil suggested that progression of coronary disease was slower. However, prospective clinical studies with 2–3 years’ use of verapamil, nicardipine or nifedipine have not recorded a beneficial effect on pre-existing coronary stenosis progression.

**Smooth muscle cells**

Intracellular calcium is an important part of the intracellular signalling pathway, leading to cell proliferation. Calcium influx after growth factor stimulation contributes to proliferation of vascular smooth muscle cells. In experimental animal cell culture studies, proliferation is inhibited by several classes of calcium antagonists. The proliferation of human vascular smooth muscle cells grown from veins, vein graft stenoses and arterial stenoses can be inhibited by all three categories of calcium inhibitors. Carvedilol, a calcium channel blocker with beta-blocker and antioxidant properties, also inhibits human vascular smooth muscle cell proliferation in vitro. A large number of studies have been carried out in vivo, and the cell proliferation showing inhibition with calcium antagonists. Detailed investigation into the time course of administration of nifedipine showed that it was only effective at preventing cell proliferation when given during critical time points after injury. This confirms its involvement in cell cycle activation at an early stage.

**Fibroblasts**

Adventitial fibroblasts may be potentially important cells in both hypertension and restenosis development. Cell culture studies with these fibroblasts have shown that nifedipine delays the transition from the G0/G1 to the S phase in vitro, thus preventing proliferation. Within the dihydropyridines, there appears to be a rank order of effect on cell proliferation. Nifedipine has a larger effect than nisoldipine, followed by nitrendipine and nimodipine.

**Myocardial stunning**

Myocardial stunning is characterized by reversible post-ischaemic contractile dysfunction despite full restoration of blood flow. The underlying mechanisms are not clearly understood, although stunning may be related to an increase in free cytosolic calcium during ischaemia and reperfusion, and a lower myofibril calcium sensitivity. Abnormalities in calcium homeostasis may be implicated in myocardial stunning after thrombolysis, coronary angioplasty or bypass surgery. It appears that low calcium levels during reperfusion protect against stunning; thus calcium antagonists given at the critical time may attenuate post-ischaemic dysfunction of theoretically still viable myocardium. When given at the time of reperfusion, calcium antagonists limit the entry of calcium ions via calcium channels and will therefore diminish any pathogenic calcium movement in the cell. Clinically, both nisoldipine and nifedipine, given before or during prolonged ischaemia at coronary angioplasty seem to prevent myocardial stunning, with a greater effect observed with nisoldipine. Improvement in systolic function may be related to redistribution.
of coronary blood flow and to slight reduction in afterload induced by the calcium antagonist. Alternatively, nisoldipine may improve diastolic function by a further intrinsic mechanism. This may involve reducing intracellular calcium overload or balancing intracellular calcium homeostasis in ischaemic regions of the myocardium. These clinical data may provide new insights into the role of calcium homeostasis during reperfusion and the myocardial stunning process.

**Calcium antagonists and thrombolysis**

Most studies on the benefits of calcium antagonists after myocardial infarction were carried out before the era of thrombolysis, or this variable was not considered separately. In various studies, verapamil has been shown to reduce infarct size and ischaemic injury, preventing re-infarction and some of the benefit may be related to the anti-thrombotic effects exerted at clinically relevant doses. Other calcium antagonists, notably nifedipine, appear to have an adverse effect on survival. Intermittent occlusion in association with thrombolytic-mediated reperfusion has been observed to improve with intracoronary vasodilating agents. The use of such therapeutic agents may be synergistic to thrombolysis in acute infarction, although few investigations have been published. A placebo-controlled clinical trial of long-acting diltiazem and aspirin versus aspirin alone in patients receiving thrombolysis with a first acute myocardial infarction is currently in progress.

**Calcium antagonists and coronary angioplasty**

**Myocardial protection**

Calcium antagonists may have a role in minimizing ischaemia during coronary intervention, possibly by reducing myocardial oxygen demand and lactate production. This is important, as the repeated short bursts of ischaemia that occur during angioplasty may lead to persistent disorders of myocardial function and delayed muscle recovery. Myocardial stunning after angioplasty can be prevented by pre-treatment with nisoldipine or nifedipine. The ischaemic tolerance of the myocardium is similarly improved by administering intracoronary verapamil to the post-stenotic area between inflations. The vasomotor properties of verapamil and nisoldipine also increase blood flow and may thus be used to improve early diastolic filling after intervention.

**No-reflow phenomenon**

The no-reflow phenomenon describes a situation when, after opening an occluded coronary artery, poor distal blood flow is persistently recorded despite apparent removal of the obstructive lesion. It is associated with poor prognosis after intervention. Whereas intracoronary nitrates are often used to manage the no-reflow phenomenon, this is not always successful. Intracoronary verapamil is more likely to treat this promptly.

Although the exact cause is not known, the success of calcium antagonists in managing the no-reflow phenomenon clinically confirms previous suppositions that the problem may be related to a combination of local platelet thrombi plugging, myocardial contraction resulting in arterial narrowing, and distal microvascular spasm, all of which may be altered by calcium antagonists.

**Acute closure**

The newly discovered effects of calcium on thrombus formation may lead to wider usage during intervention. In this context, increased vasomotor tone may precipitate thrombus after prolonged arterial spasm at angioplasty; this may be influenced by verapamil administration. Activation of platelets is also relevant in this setting. Oral administration of verapamil for one month reduced platelet aggregability, as measured by ex vivo testing, in patients with stable angina. Although the clinical significance of this is unknown, the effect may be of benefit when such patients undergo intervention.

Passivation of platelets describes the process whereby platelets are rendered less active at the arterial wall after intervention. The action of calcium antagonists on the platelet IIb/IIIa receptor may be particularly relevant. A large clinical study has shown that inhibition of this receptor using a monoclonal antibody resulted in a reduction in acute closure rates.

**Restenosis**

The pathology of restenosis includes thrombotic factors, inflammation, cell proliferation and migration, matrix formation and remodelling. As discussed above, calcium antagonists can have significant consequences for several of these components. It is presumed that early prevention of platelet aggregation influences the cascade of events leading to the intimal proliferative component of restenosis. This was confirmed when inhibition of the IIb/IIIa platelet receptor with a monoclonal antibody was shown to affect clinical restenosis rates in patients at 6 months, although this was not a primary endpoint of the study. Calcium antagonists may also act similarly at the correct local dose, sufficient to affect passing platelets. As calcium antagonists are also known to have an inhibitory effect on cell proliferation itself, early clinical studies investigated their consequences on restenosis rates after coronary angioplasty when given at conventional systemic doses. The results are somewhat controversial, because of differences in endpoints or small sample sizes, but a meta-analysis of...
five of the most controlled studies using diltiazem or nifedipine indicated that there was a 30% reduction in the likelihood of angiographic or stress test-defined restenosis\[41]. However, the relevance of such a definition of restenosis is disputed and it has been suggested that a still larger clinical trial is required to settle the issue. Other important pathological steps in the development of restenosis appear to be recoil and subsequent remodelling. Calcium antagonists influence recoil and may thus also play a role in remodelling, although this topic has undergone little investigation.

**Local drug delivery**

Local drug delivery is especially useful and practical after intervention to achieve high functional doses of agents where they are needed. To undertake this, site-specific catheter technology is under development\[42]. Although systemic administration of calcium antagonists has not shown convincing beneficial effects on restenosis, there may still be scope for such local drug delivery. This may be to the adventitia, where it can potentially influence both proliferative and remodelling reactions\[43], or loaded on to stents to provide a prolonged effect through the entire wall. Local calcium antagonist delivery ensures that enough drug reaches the wall where the effect is needed. Concentrations are potentially higher than those achieved by systemic delivery, without an increase in side effects. Further local delivery studies are required to see which calcium antagonist, which dose, which device and which time course of administration might be best for this purpose.

**Calcium antagonists and cardiac surgery**

**Prevention of spasm**

Myocardial infarction after coronary artery bypass surgery is a significant cause of morbidity, although the exact pathology has not yet been completely elucidated. As spasm may play a relevant role in the induction of ischaemia, the effect of calcium antagonists on vaso-motor tone in this situation may be beneficial. High-pressure distention of veins using saline, as used to achieve a large enough size for grafting, carries the risk of damaging the intima and may predispose to later occlusion and spasm of the graft.

There is a case for the use of relaxing agents such as calcium antagonists instead of saline. Organ bath studies indicate that complete relaxation of grafts can be achieved with verapamil\[44,45] and other calcium antagonists\[45]. This is similar to that achieved with glyceryl trinitrate or papaverine\[44,45]. Advantages of verapamil would be its longer duration of action when transplanted at bypass grafting compared with glyceryl trinitrate and its lack of toxicity and adverse platelet effects with the previously used papaverine. In patients, a combination of glyceryl trinitrate and verapamil, a preferable therapy to papaverine, was found to achieve a good time course of action and increase blood flow in grafted internal mammary arteries\[45]. The addition of verapamil to the priming solution in cardiopulmonary bypass can also be of value in preventing peri-operative coronary vasospasm in patients with variant angina\[46] and in aiding local delivery to grafts\[47] or native coronary arteries\[48].

**Myocardial protection**

Significant myocardial injury may occur during aortic cross-clamping; intravenous administration of verapamil a few minutes before clamping reduces myocardial injury when assessed by creatine kinase\[49].

**Conclusions**

The uses of calcium antagonists at revascularization, whether by thrombolysis, angioplasty or bypass surgery are expanding as new discoveries about their functions emerge, and delivery techniques improve. Many of the potential uses discussed here probably require higher doses than conventionally given, but the exact dose required locally remains to be determined. In particular, the concentrations at which the antiplatelet and anti-proliferative actions of calcium antagonists might be expected to be effective may not be attainable with therapeutic dosing regimens currently used and local drug delivery may be necessary to achieve this. It is thus clear that many potential uses of calcium antagonists remain relatively unexplored in this field.

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