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Potassium Channel Openers in Myocardial Ischaemia

Therapeutic Potential of Nicorandil

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Abstract

Potassium channel openers or agonists represent a novel new class of compounds in the treatment of a range of cardiovascular disorders, particularly angina pectoris and hypertension. Nicorandil is the only clinically available potassium channel opener with antianginal effects, and with comparable efficacy and tolerability to existing antianginal therapy. It confers benefits through a dual action: opening the mitochondrial K_{ATP} channels leading to preconditioning of the myocardium and a nitrate-like effect. Myocardial preconditioning is important in reducing infarct size, severity of stunning and cardiac arrhythmias. These effects make nicorandil a unique antianginal compound that reduces both pre- and afterload and improves coronary blood flow. Comparative and noncomparative studies support the use of nicorandil as monotherapy or in combination with other antianginal therapy for stable angina pectoris. However, large studies are required to confirm its role in the treatment of acute coronary syndromes despite the favourable results from small studies.

1. K_{ATP} Channels and Ischaemic Preconditioning

Noma[1] originally described adenosine triphosphate (ATP)-sensitive potassium channels (K_{ATP}) in guinea pig cardiac myocytes in 1983. He proposed that these channels couple myocardial metabolism to membrane electrical activity and that this may provide a cardioprotective mechanism. This was subsequently proven the case and 2 types of K_{ATP} channels were identified: sarcolemmal (sarc K_{ATP} channels) and mitochondrial (mito K_{ATP} channels). Each of these channels has a different mode of action in myocardial preconditioning and protection.

Opening of the sarc K_{ATP} channels has been proposed to produce cardioprotection via a shortening of phase 3 repolarisation of the action potential and membrane hyperpolarisation, which leads to reduction in calcium overload and preservation of ATP. On the other hand, activation of mito K_{ATP} channels may lead to intramitochondrial depolarisation, and a reduction in mitochondrial calcium overload and matrix swelling which enhances ATP production. This in turn reduces cardiac workload and enhances myocardial viability. K_{ATP} channels are composed of 2 types of proteins: an inwardly rectifying K^+ channel (kir6.x) and sulfonylurea receptor (SUR) subunit. At least 2 inwardly rectifying subunits: kir6.1 & kir6.2 and 3 sulfonylurea subunits, SUR1, 2A & 2B have been identified. Each K_{ATP} channel pore is surrounded by 4 kir6.x subunits and requires a SUR protein to function.

The combinations of these subunits vary according to the tissue type, e.g. vascular smooth muscles and cardiac myocytes.[2] Recent studies provided evidence that mito K_{ATP} channels rather than sarc K_{ATP} channels are the dominant players in the process of ischaemic preconditioning (IPC) and myocardial protection.[3-5]

IPC was demonstrated first by Murry et al.[6] in a canine model in 1986 by preceding short cycles of sublethal ischaemia and intermittent reperfusion, resulting in a 75% reduction in infarct size. The study concluded that the multiple anginal episodes that often precede myocardial infarction might delay cell death during subsequent coronary occlusion. Therefore, IPC is a phenomenon where single or multiple brief periods of ischaemia and reperfusion have a cardioprotective effect which in turn results in a marked reduction in myocardial infarct size, severity of stunning or cardiac arrhythmias. IPC occurs in all animal species (including species which lack significant collateral circulation) and in human beings, and has been demonstrated using several methods including: inducing ischaemia in adjacent myocardium,[7] myocardial stretch,[8] rapid ventricular pacing,[9] heat stress,[10] ischaemia in remote organs[11] and pharmacologically by using K_{ATP} channels openers.[12] Furthermore, observational studies on warm-up angina, preinfarction angina and coronary angioplasty demonstrate IPC in humans.[13-16]

The exact molecular mechanism of IPC and myocardial protection is unclear and several mechanisms are proposed. IPC may involve the stimulation of adenosine receptors;[17,18] the release of endogenous mediators from vascular endothelium and myocytes such as bradykinin,[19] noradrenaline[20] and free radicals;[21] the activation of protein kinase C (PKC)[22] and the opening of K_{ATP} channels.[23] Recently, it has been reported that PKC opens K_{ATP} channels[24] and it is the opening of mito K_{ATP} channels, which are thought to be the end effectors of many signal transduction systems.[4,5]

Several studies in animal species and with human atrial muscle preparations demonstrate that blocking K_{ATP} channels with agents such as glibenclamide and tolbutamide abolishes the cardioprotective mechanism, whereas activating these channels using pharmacological agents such as cromokalim, bimakalim, pinacidil and nicorandil provides protection.[25] We discuss nicorandil in more detail as it is the only established potassium channel opener (agonist) with antianginal properties in the treatment of both exertional and vasospastic angina pectoris.

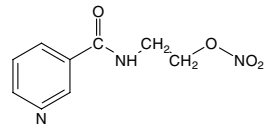

Fig. 1. Chemical structure of nicorandil.

2. Nicorandil

Nicorandil is a hybrid compound that consists of N-[2-hydroxyethyl] nicotinamide vitamin group and an organic nitrate (fig. 1.). It is the first clinically available K_{ATP} channel opener with a nitrate-like effect. Like nitrates, nicorandil activates cytoplasmic guanylate cyclase leading to an increase in cellular levels of cyclic guanosine monophosphate and a reduction in cytosolic calcium and thus, to a relaxation of vascular smooth muscles.[26] As a K_{ATP} channel opener, nicorandil increases efflux of potassium ions from the cell, leading to a more negative resting membrane potential (hyperpolarisation), and also shortens the action potential duration. This inhibits calcium influx, causing a reduction in intracellular calcium leading to relaxation of vascular smooth muscle and vasodilatation (indirect calcium channel blocking effect).[27,28]

In a recent study, Sato et al.[29] found that nicorandil exerts a direct potent cardioprotective effect on heart muscle cells by opening of mitochondrial K_{ATP} channels.

Through its dual action, nicorandil reduces both pre-load (nitrate-like effect) and after-load (potassium channel opener effect), and improves coronary blood flow without changing cardiac stroke volume indices or causing significant hypotension (in therapeutic doses), and without causing reflex

tachycardia or an increase in oxygen consumption. Angiographic studies have shown that nicorandil dilates both stenotic and nonstenotic coronary arteries.[30] It is not negatively inotropic and it may, therefore, be used with relative safety in patients with nonsevere left ventricular dysfunction.

Nicorandil can be used safely in combination with other cardiovascular agents and tolerance does not appear to develop with long term therapy. There is no evidence that nicorandil induces proarrhythmia or exacerbates myocardial ischaemia. Nicorandil does not adversely affect the lipid profile or blood glucose levels. Its main adverse effect is headache, which is usually transient, occurs on initiating therapy and invariably resolves.[31]

2.1 Pharmacokinetics

Oral nicorandil is rapidly absorbed. Bioavailability is 75% ± 23% (mean ± standard deviation), and unlike organic nitrate, there is little hepatic first-pass effect. Maximal plasma concentrations are achieved within 1 hour after oral administration and plasma half-life is approximately 1 hour while the duration of its effect extends to approximately 12 hours.

Nicorandil is metabolised and de-nitrated by the liver to an inactive alcohol metabolite, followed by urinary excretion. Nicorandil appears to be well tolerated in the elderly and no special dose adjustment is required in this group or in patients with chronic hepatic or renal impairment. It is contraindicated in patients with cardiogenic shock, left ventricular failure with low filling pressures, hypotension and in idiosyncrasy.[32,33]

2.2 Clinical Trials and Therapeutic Potential

2.2.1 Stable Angina Pectoris

Several trials have demonstrated that oral nicorandil is effective and well tolerated in the treatment of stable angina pectoris.[31,34,35] Comparative studies suggest that nicorandil has equivalent antiischaemic and antianginal efficacy to nitrate,[36] β-blockers (metoprolol, atenolol and propranolol),[37-39] and calcium channel antagonists (nifedipine, diltiazem and amlodipine).[34,35,40]

Nicorandil has been shown to be effective as monotherapy in the treatment of chronic stable angina pectoris when compared with placebo in several double-blind trials and an increase in exercise tolerance was experienced by patients in 1 study.[41]

The Impact of Nicorandil in Angina (IONA) study is a multicentre, double-blind controlled study with patients with stable angina pectoris randomised to either placebo or nicorandil 20mg twice daily, which will report soon.[42] The primary study endpoint is the combined endpoint of coronary heart disease death, nonfatal myocardial infarction or unplanned cardiac hospitalisation. Patients continue on their usual standard antianginal therapy. The study has recruited over 5000 patients from the UK (men over 45 and women over 55 years) with evidence of angina pectoris and documentation of coronary artery disease with at least 1 of: previous myocardial infarction; previous coronary artery bypass graft surgery (CABG); coronary artery disease proven by angiography or a positive exercise test (≥1mm ST depression) in the 2 years prior to randomisation. The follow-up period is for 1 to 3 years.

The SNAPE study[43] is a multicentre, randomised, double-blind, double-dummy study designed to assess the efficacy and safety of nicorandil compared with isosorbide mononitrate (ISMN) for the treatment of angina pectoris in elderly patients with stable coronary heart disease. 194 elderly patients (≥65 years) with stable angina pectoris and a positive exercise test result (≥0.1 mV ST segment depression) were randomly assigned to nicorandil 10mg twice daily or ISMN 20mg twice daily. The study concluded that although nicorandil seems to be as safe and effective as ISMN for the treatment of elderly patients with stable angina pectoris, ISMN may be superior to nicorandil for the symptomatic treatment of angina pectoris in this population.[43] The study was for a short period of time and in a specific population group. The study was also underpowered to detect a significant difference between the 2 treatment groups in the primary end-point, a decrease in ischaemia during exercise.

2.2.2 Vasospastic Angina Pectoris

Nicorandil has demonstrated efficacy in the prevention and relief of spontaneous or ergometrine-induced episodes of coronary vasospasm. This efficacy is comparable to that of nifedipine. In 32 patients who had documented episodes of ST segment elevation during angina pectoris, Kishida[44] found that oral nicorandil was associated with a significant reduction in the frequency of episodes of anginal pain and the frequency of ST segment elevation during Holter monitoring.[44,45]

2.2.3 Unstable Angina Pectoris

Patients with unstable angina pectoris are at high risk of progression to complete coronary occlusion and acute myocardial infarction. Preconditioning the myocardium, through recurrent ischaemia or pharmacologically using K_{ATP} channel openers such as nicorandil, helps to limit infarct size and improves myocardial functional recovery. Furthermore, nicorandil has marked anti-ischaemic effects when used prior to coronary angioplasty.[46]

Our group recently reported on cardioprotection by opening K_{ATP} channels in 188 patients with unstable angina pectoris in a randomised, double-blind, placebo-controlled study, using oral nicorandil 20mg twice daily for a minimum of 48 hours. Patients with myocardial infarction identified retrospectively from troponin-T analysis were excluded. We found that nicorandil, added to aggressive antianginal treatment, significantly reduces episodes of both silent and painful transient myocardial ischaemia, nonsustained ventricular and supraventricular arrhythmia compared with placebo. The observed antiarrhythmic effect is probably secondary to its anti-ischaemic action and/or IPC.[47]

Similarly, in a smaller double blind study of 74 patients with unstable angina pectoris, therapy with intravenous nicorandil was more effective in reducing angina attacks than isosorbide dinitrate.[48]

2.2.4 Acute Myocardial Infarction

Oral nicorandil was administered after routine therapy for acute myocardial infarction in a placebo-controlled, double-blind pilot safety study of 45 patients. It was well tolerated with good safety. There was a trend towards a reduction in development of Q-waves in patients who presented with subendocardial infarction and also a reduction in the incidence of arrhythmias in the nicorandil group.[49]

2.2.5 Patients undergoing Coronary Artery Bypass Graft

Severe peripheral vasodilatation and hypotension were noted to develop immediately after CABG in patients who continued to take nicorandil until the time of surgery. This required vasopressor support with norepinephrine (noradrenaline) for periods ranging from 15 to 48 hours postoperatively. The severe vasodilatation could be caused by the loss of vasomotor tone and the effects of re-warming after surgery. When nicorandil was stopped a few days before surgery in such patients, the vasodilatation effect was no longer observed.[50-51] Recently, Hayashi et al. have shown that administration of nicorandil during CABG enhanced the myocardial protective effects against ischaemia-reperfusion.[52] No patients required assistance in weaning off bypass.

3. Conclusion

Potassium channel openers, such as nicorandil, offer a novel approach to the treatment of symptomatic myocardial ischaemia. The efficacy of nicorandil is well established in chronic stable angina pectoris, where it may be used as monotherapy (in 'mild' disease) and in combination with conventional antianginal therapy, and also in those who may not tolerate β-blockade. Small studies suggest that nicorandil may have a role in acute ischaemic syndromes, although such findings need to be confirmed in larger trials. Nicorandil does not appear to be proarrhythmic when used in clinical doses, and there are theoretical reasons why potassium channel activation may be 'cardioprotective'. Findings from the major outcome study, IONA, are keenly awaited and will clarify further the role of nicorandil in chronic occlusive coronary artery disease.

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