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Potassium channel openers in myocardial ischaemia – clinical experience with nicorandil

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Studies of contemporary populations show that patients with Angina pectoris have significantly impaired quality of life [1, 2]. Despite taking one or more conventional antianginal drugs, patients frequently experience three or more anginal episodes each week, and increased angina frequency, which is associated with decreased overall feeling of well-being. Ideally, antianginals should not only relieve symptoms with little or no side-effects, but they should also improve patient outcome [3]. The deficiencies of current medical therapy for angina are well recognised [4] and with the exception of aspirin, beta blockers and statins, it makes little or no impact on disease progression. In order to favourably improve outcome, aggressive cardiovascular risk factor management should be undertaken in parallel with stringent efforts to optimise and tailor medical treatment to the individual patient.

This review looks at a novel agent, the potassium adenosine triphosphate-(K_{ATP})-sensitive channel opener, nicorandil and its role in the treatment of myocardial ischaemia.

Background

Potassium channels, particularly those regulated by intracellular ATP are ubiquitous in the heart and blood vessels and are important modulators of cardiovascular function. Opening potassium channels, there is an increased efflux of potassium ions from the cell and the resting membrane potential is shifted towards more negative values (hyperpolarisation); this leads to an inhibition of calcium influx or indirect calcium antagonism, causing a fall in intracellular calcium concentration, relaxation of vascular smooth muscle cells and vasodilatation.

Nicorandil was developed as the first oral K_{ATP} channel opener in Japan where it became available in the early 1980s, since when it has been widely used in that country. It was introduced in the UK in 1994, and became available in Austria in 1997. Nicorandil is described as a hybrid compound, consisting of a nicotinamide vitamin group and an organic nitrate. Similarly to nitrates, nicorandil also leads to activation of the enzyme guanylate cyclase which in turn induces an increase in intracellular cyclic guanosine monophosphate (cGMP) and a decrease in intracellular calcium ions. Ultimately this results in reduction in vascular tone, predominantly in the venous vascular bed, so that mainly the venous capacitance vessels are dilated. Because of this dual mechanism of action, both preload and afterload are reduced producing a dose-related improvement in haemodynamics (Figure 1).

Nicorandil causes reduction in total peripheral resistance and blood pressure, at therapeutic concentrations this effect is small [5] and transient, and does not normally lead to first-dose hypotension. It improves resting coronary blood flow without changing cardiac or stroke volume indices and without causing reflex tachycardia or an increase in oxygen consumption. Nicorandil is not negatively inotropic at therapeutic doses and contractility is largely unchanged, it may therefore be used with relative safety in patients with left ventricular dysfunction, but it does not have a licence for the treatment of heart failure. Angiographic studies have shown that the drug dilates both stenotic and non-stenotic coronary arteries.

Unlike classical nitrates there appears to be an absence of haemodynamic tolerance to nicorandil. This was demonstrated in a study [6] of 25 patients with congestive heart failure who were infused with either glyceryl trinitrate (GTN) or nico-

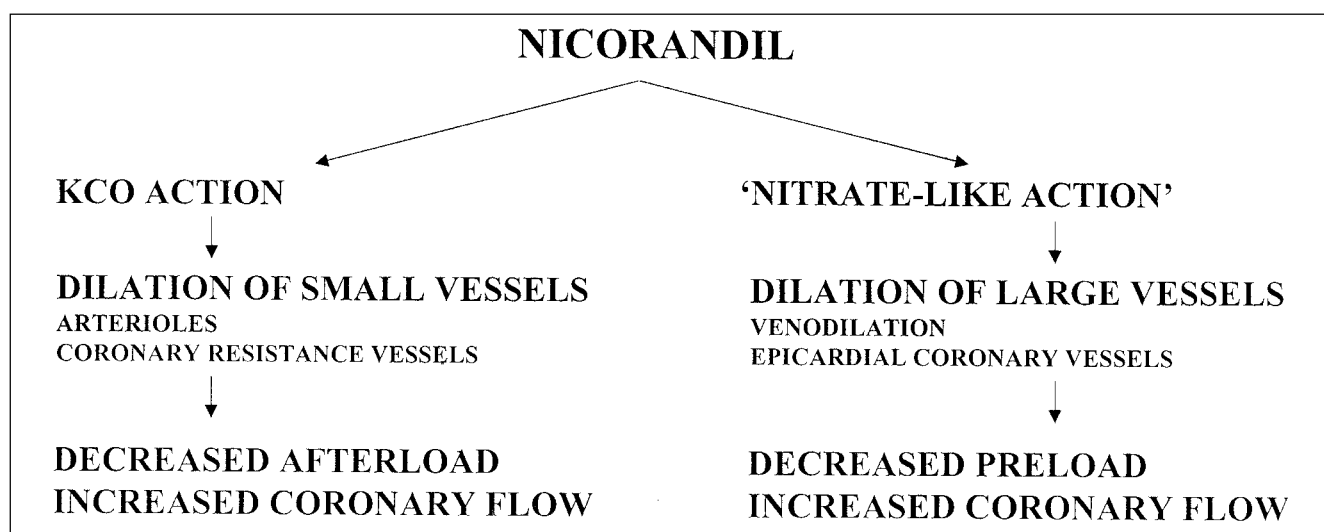


Figure 1. Mechanism of action of nicorandil (KCO, Potassium channel opener)

randil. While both groups of patients demonstrated reductions in pulmonary capillary wedge pressure, after 1 hour, the difference between the minimal PCWP value and the 24-hour PCWP value for GTN was 5.1 mmHg versus 1.4 mmHg for nicorandil ($p < 0.005$). Tachyphylaxis developed in 12 (60 %) patients during GTN infusion versus 3 (15 %) patients during nicorandil infusion. It is unclear how nicorandil circumvents the problem of tolerance and further larger studies are required to confirm this finding and to establish the mechanisms involved, but it appears that unlike GTN, nicorandil is not totally dependent on its activation of cGMP to be effective.

Clinical experience

Nicorandil is indicated for the prevention and long-term treatment of angina, and is available (in the UK) as 10 and 20 mg tablets; the recommended starting dose is 10 mg twice daily which can be titrated upwards to a maximum of 30 mg twice daily, although the usual therapeutic range is 10–20 mg twice daily. It may be appropriate when starting therapy to advise patients who are susceptible to nitrate-induced or non-specific headache to divide the 10 mg scored tablet in two and to give 5 mg twice daily.

Clinical trials

Nicorandil has been extensively studied in Europe in more than 1500 patients with angina, both in placebo-controlled studies and in comparative studies with other antianginals. The majority of studies show that nicorandil is superior to placebo in reducing angina episodes and increasing exercise duration [7]. While one placebo-controlled study [8] did not show any significant improvement in angina frequency, total exercise duration, or time to ischaemia with nicorandil, another placebo-controlled study of 46 patients, two hours post-dosing, showed nicorandil improved time to onset of angina by 38 %, without significant alteration in heart rate or blood pressure [9]. Nicorandil also appears to have comparable efficacy to nitrates, beta blockers and calcium antagonists.

In a comparative study of oral doses of nicorandil 20 mg twice daily and isosorbide-5-mononitrate 20 mg twice daily, both drugs showed comparable improvement in exercise duration and time to onset of angina [10]. In a comparative study with atenolol 50–100 mg twice daily, propranolol 40–50 mg twice daily and metoprolol 100 mg twice daily, nicorandil in doses 10 and 20 mg twice daily produced equivalent improvement in angina attack rate and exercise tolerance with chronic dosing [11], whereas atenolol significantly reduced heart rate, this did not change significantly in patients receiving nicorandil.

Nicorandil has also been compared to a number of calcium antagonists. In a randomized study of nicorandil 10 mg twice daily, increasing to 20 mg twice daily versus nifedipine 20 mg twice daily, both agents showed equal efficacy in terms of increased exercise duration and time to onset of angina, but, unlike nicorandil, nifedipine significantly increased resting heart rate [12].

Is nicorandil cardioprotective?

The term cardioprotection, although ill-defined, is now widely used. It has been proposed that nicorandil may possess cardioprotective properties in a number of models of ischaemia/reperfusion, myocardial stunning, and in canine models of coronary ligation it may cause limitation of infarct size. It has also been shown to prevent platelet aggregation. It has been suggested that nicorandil may mimic ischaemic preconditioning [13], a condition which offers powerful protection against

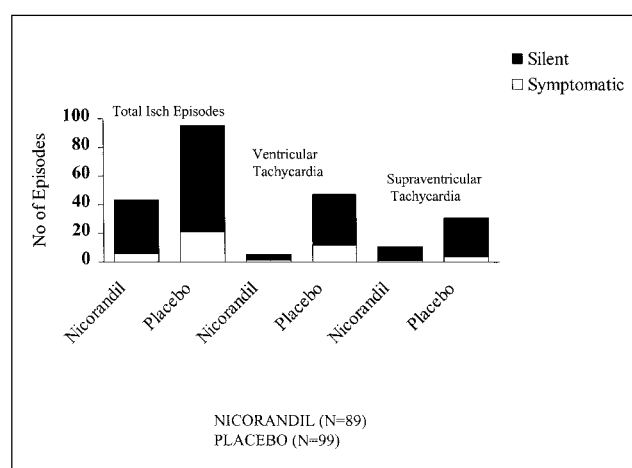


Figure 2. Nicorandil in unstable angina (adapted from Patel DJ et al. [14])

ischaemic necrosis (see Yellon review in this issue, p: 8–11). The clinical value of these apparent properties of nicorandil remains to be established, however, by attenuation of ischaemia, nicorandil may play an important role in bypass surgery and confer protection in patients undergoing percutaneous transluminal coronary angioplasty (PTCA).

Findings from two recent studies in unstable angina [14] and acute myocardial infarction [15] support the view that nicorandil is safe and may have a protective role in acute ischaemic syndromes. A randomised, double-blind, placebo-controlled trial was conducted to assess the safety and efficacy of oral nicorandil in unstable angina. The study in 200 patients with unstable angina [14] showed that nicorandil, when added to aspirin, unfractionated heparin, nitrates, atenolol and diltiazem, significantly further reduced the numbers of episodes of transient myocardial ischaemia, supraventricular tachycardia and ventricular tachycardia, compared to placebo (Figure 2).

Beneficial effects of nicorandil were also seen in a small, placebo-controlled, double-blind safety study in 45 patients with acute myocardial infarction [15]. This showed a reduction in the incidence of arrhythmic events and the overall incidence of adverse events was lower in patients with acute myocardial infarction who received nicorandil orally. The drug also appeared to attenuate the progression of infarction in patients without Q-wave abnormalities at the time of inclusion. But nicorandil did not appear to attenuate infarct progression in those with Q-wave changes on entry to the study. While it is difficult to make firm conclusions on the cardioprotective effects of nicorandil, further studies to evaluate the safety and efficacy of nicorandil as an adjunctive therapy in acute ischaemic syndromes are justified.

Outcome study

The first major outcome study, Impact of Nicorandil in Angina (IONA) is currently underway in the UK. The primary aim of the study is to show that treatment with nicorandil can reduce cardiovascular events in patients with stable angina. IONA is planned to recruit 5000 patients, men and women, and is being co-ordinated by the University of Glasgow. Patients will consist of existing or newly diagnosed angina pectoris, and will include those who have had a myocardial infarction or coronary artery bypass graft surgery. Patients will receive either nicorandil 20 mg twice daily or placebo, in ad-

dition to their standard antianginal therapy. Minimum patient follow-up will be 12 months and maximum 3 years and the study will continue until the target for follow-up is achieved, ie, 8750 patient years or until May 2001. The primary composite end-point will be death from coronary heart disease, non-fatal myocardial infarction or unplanned hospitalisation from chest pain.

Tolerability and safety

Long-term safety of nicorandil has been extensively assessed [16, 17]. In 1680 subjects treated with nicorandil, headache was the problem most commonly encountered and this usually occurs early on commencement of treatment and disappears with chronic dosing. The problem can be minimised by reducing the initial dose to 5 mg twice daily (see above). Adverse events usually occurred early in the course of treatment and after 30 days fewer than 10 % of patients reported adverse events. Nicorandil is generally well tolerated and dizziness, flushing and oedema are rarely observed. It has no significant effect on heart rate or on the electrocardiogram, when used in therapeutic doses, similarly it does not cause hypotension or have clinically relevant adverse effects on laboratory parameters such as lipids, glucose metabolism etc.

Nicorandil also 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 dysfunction. The drug is not recommended for use in children and should not be used in pregnancy.

Nicorandil is contraindicated in cardiogenic shock, left ventricular failure with low filling pressures and in hypotension, as well as in patients who demonstrate an idiosyncratic response or hypersensitivity to the drug.

Combination treatment

Angina patients are frequently elderly and may suffer from concomitant diseases requiring polypharmacy. Studies show that nicorandil does not interact with inhibitors or inducers of hepatic drug metabolism such as cimetidine and rifampicin respectively, or with the anticoagulant, acenocoumarol and cardiovascular agents such as frusemide and digoxin. Because sulphonylureas, such as glibenclamide and the vasodilator diazoxide act as potassium channel blockers, these are best avoided in patients taking nicorandil. Equally importantly, nicorandil can be combined safely with other antianginals such as nitrates, beta blockers, and calcium antagonists, and studies demonstrate that the incidence of adverse events does not increase when it is combined with these agents.

Nicorandil – current use

Nicorandil may be effective as monotherapy in some, perhaps more mildly symptomatic, patients. It may be less useful for those who are headache-prone. It can be used safely as an 'add-on' to beta blockers and calcium antagonists. It may be beneficial in patients who cannot tolerate either of these other agents, particularly those who feel lethargic on beta blockade, or have profound ankle oedema with a calcium antagonist. Nicorandil may also have a role in individuals with obstructive

airways disease, dyslipidaemia or diabetes, where a beta blocker is inappropriate. Similarly it may prove useful in patients who are difficult to manage with drugs which increase heart rate or, we can speculate, where nitrate tolerance is a problem.

Conclusion

K_{ATP} channel openers in the cardiovascular system appear to exploit natural endogenous protective mechanisms which come into play during ischaemia [18]. Nicorandil is an effective agent with comparable efficacy and tolerability to existing antianginals. Nicorandil may be particularly useful where some of these antianginals are contraindicated or ineffective. While the role of nicorandil in acute ischaemic syndromes remains to be defined, the results of small recently conducted studies give cause for optimism.

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