Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 1999; 2 (2), 213-217

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Indexed in
Chemical Abstracts
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Comparison of the antiischaemic and antianginal effects of nicorandil and amlodipine in patients with symptomatic stable angina pectoris: the SWAN study

The SWAN Study Group[1]

This multicentre, double-blind, randomised study compared the antiischaemic and antianginal effects of nicorandil and amlodipine in patients with symptomatic stable angina pectoris. Nicorandil is a new coronary and balanced peripheral vasodilating agent that operates through two mechanisms of action: activation of ATP-dependent K-channels and stimulation of guanylate cyclase.

A total of 121 patients with symptomatic stable angina pectoris were randomised to receive nicorandil 10 mg twice daily (bd) or amlodipine 5 mg once daily (od) for 8 weeks (optional dosage increase after 2-4 weeks to 20 mg bd and 10 mg od, respectively). Symptom-limited exercise tolerance tests were performed at baseline, and after 2 and 8 weeks treatment, respectively. In addition, the number of anginal attacks, nitroglycerin (NTG) usage, blood pressure (BP), heart rate (HR) and adverse events were recorded, and a subjective assessment of quality of life performed. 118 patients (nicorandil, n=56; amlodipine, n=62) were evaluable for efficacy. Time to onset of ST-segment depression increased only in the amlodipine-group whereas time to anginal pain along with total exercise duration increased in both treatment groups. Both nicorandil and amlodipine reduced the magnitude of ST-segment depression at maximal identical workload, while the sum of weekly anginal attacks and the number of NTG units required for pain relief decreased. No differences were apparent between treatment groups for any of these target variables. HR remained unchanged in both groups. Resting BP decreased in the amlodipine group, but not among nicorandil recipients. In both treatment groups, ratings for quality of life variables improved over the course of the study. Compared with amlodipine, nicorandil was associated with a more favourable tolerability profile.

The antiischaemic and antianginal effects of nicorandil were comparable to amlodipine in patients with symptomatic stable angina pectoris. In addition, both drugs were generally well tolerated and had a positive effect on quality of life in this patient population. *J Clin Basic Cardiol 1999; 2: 213–7.*

Key words: coronary heart disease, potassium channel activator – nicorandil, calcium channel blocker – amlodipine, exercise tolerance test

Nicorandil is a new drug for the treatment of coronary heart disease (CHD) that has well-described pharmacological properties [1]. It induces vascular smooth muscle relaxation by a dual mechanism of action: stimulation of guanylate cyclase leading to increased cellular levels of cyclic guanosine monophosphate [2, 3], and hyperpolarisation of the vascular smooth muscle cell membrane by the opening of ATP-sensitive potassium (K_{ATP}) channels and a closing of calcium (Ca^{2+}) channels resulting in a reduction in intracellular Ca^{2+} concentration [4–6]. The dose-response relationship for vascular relaxation with nicorandil differs from that of other nitrovasodilators, suggesting that the opening of K_{ATP} channels makes a significant contribution to its vasodilatory properties [2].

In patients with CHD, nicorandil increases blood flow, and hence oxygen delivery to the ischaemic myocardium via vasodilatation of the coronary vasculature [7–9], and reduces myocardial oxygen consumption by decreasing preload (increased systemic venodilatation) and afterload (decreased systemic vascular resistance) [10, 11]. Moreover, the antiischaemic effects of nicorandil in patients with CHD are apparent at dosages that do not evoke pronounced decreases in systemic blood pressure (BP) [12].

Previous trials have demonstrated that oral nicorandil, 10–20 mg twice daily (bd), is effective and well tolerated in the treatment of stable angina pectoris [13–15]. Comparative studies suggest that nicorandil has equivalent efficacy to nitrates [14], β-adrenoreceptor antagonists [16–18] and certain Ca^{2+} channel blockers [13, 19] for reducing both ischaemic and anginal symptoms. To date, however, trials comparing nicorandil with newer Ca^{2+} channel blockers such as amlodipine have not been conducted.

Thus, the objective of this multicentre, double-blind, randomised study was to compare the antiischaemic and antianginal efficacy and tolerability of nicorandil with that of amlodipine in patients with symptomatic stable exercise-induced angina pectoris.

Methods

Patients

Patients aged 18–80 years with symptomatic stable angina pectoris were screened for enrolment in the study. Eligible patients had a history of stable angina pectoris for ≥ 3 months and CHD confirmed by a history of myocardial infarction or a positive angiogram (> 50 % stenosis of a main coronary artery). Exclusion criteria included: myocardial infarction, invasive coronary intervention, unstable angina, angina at rest or vasospastic angina within the last 3 months; hypertension with supine diastolic blood pressure (DBP) > 105 mmHg; electrocardiogram (ECG) recordings not allowing evaluation of the ST-segment; manifest congestive heart failure (New York Heart Association class III–IV); peripheral arterial obstructive disease or any other exercise test limiting disease; cardiac valvular disease with haemodynamic or clinical consequences; supine systolic blood pressure (SBP) < 100 mmHg or DBP < 70 mmHg; postural hypotension (> 20 % decrease in SBP after 1 min standing); and severe concomitant disease. Female patients were to be postmenopausal or surgically sterile.

Received May 18th, 1999; accepted June 16th, 1999.

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All patients gave informed consent. The study was performed in accordance with the Declaration of Helsinki (revised version, Hong Kong 1989) and was approved by the respective local Ethics Committees.

Study design

The study had a randomised, double-blind, parallel-group design and was performed at 25 centres in Austria (n = 11) and Switzerland (n = 14).

Following an initial screening visit, all patients deemed suitable for enrolment received isosorbide dinitrate (ISDN) controlled-release tablets (20 mg once daily [od]) for 2 weeks. After 1 week, patients returned and resting BP, heart rate (HR) and a standard 12-lead ECG were recorded, following which an exercise tolerance test (ETT) was performed. If a positive ETT was obtained (ie, occurrence of anginal symptoms and ST-segment depression of ≥ 0.1 mV), patients returned again 1 week later and a second ETT was performed after recording resting BP and HR. Patients who met the study inclusion criteria were subsequently randomised to receive either nicorandil 10 mg bd orally or amlodipine 5 mg od orally, blinding being achieved by the double-dummy technique. After 2 weeks' treatment, BP and HR were recorded and an ETT performed. Depending on the patient's clinical condition, study medication was either maintained at the same dosage for the remainder of the study or increased to nicorandil 20 mg bd or amlodipine 10 mg od (in exceptional cases, an increase in dosage was also permitted after a further 2 weeks of receiving the lower dosage regimen; patients switched to the higher dosage could also revert to the lower dosage regimen after 2 weeks, if necessary). Patients returned at 2-week intervals for a further 6 weeks, BP and HR being recorded at each visit. After 8 weeks of treatment, a 12-lead resting ECG was recorded and a final ETT performed. Patient diaries were assessed and compliance and adverse events were recorded at each visit. All adverse events spontaneously reported by the patient or observed by the investigator during the study were recorded, regardless of whether or not they were considered to be drug-related.

Exercise tolerance tests

All ETTs were performed using an upright bicycle (initial workload 50 W, increasing by 25 W at 2-min intervals) and were symptom limited. ST-segment depression was measured before and after exercise. During ETTs, the ECG was continuously monitored in chest leads V_{1-6} at 1-min intervals. The lead showing the largest ST-segment depression during ETTs at baseline was used for ST-segment evaluation in subsequent ETTs.

ETTs were performed ≥ 24 hours after taking ISDN controlled-release tablets or 12 or 24 hours after taking nicorandil or amlodipine, respectively. Patients were instructed not to take short-acting nitrates before visits when ETTs were planned. ETTs were postponed if nitroglycerin (NTG) had been taken in the last 2 hours.

Patient diaries and quality-of-life assessment

All patients received a diary in which the number of anginal attacks/day and the number of NTG tablets or spray puffs required for pain relief were recorded. Patients also completed a 4-variable quality-of-life questionnaire (general feeling; ease of physical activity; physical endurance; strain of angina) scored on a 5-point scale at 2-week intervals during the study.

Statistical analysis

A total of 50 patients per treatment group was required to detect a difference between the medications of $\Delta = 0.65$ SD (standard deviation) of the difference, with a probability of 90 % (power) at the $\alpha = 5$ % level of significance (two-tailed, two-sample problem, normally distributed). Statistical analysis was performed on an intention-to-treat basis using endpoint data, ie, for those patients withdrawing early, the last value for each parameter was carried forward. Differences between treatment groups were assessed using analysis of variance with respect to the parallel-group design for the target variables at study end. Mean changes from baseline within treatment groups were calculated as 95 % confidence intervals.

Results

Patients

A total of 143 patients were recruited for this study, of whom 121 were randomised (Table 1). Reasons for non-randomisation included inclusion criteria not being met (n = 9), sudden death (n = 1), increased angina (n = 2), other adverse events (n = 8) and withdrawal of consent (n = 2). Six patients dropped out during treatment with randomised study medication, 5 because of adverse events (nicorandil, n = 3; amlodipine, n = 2) and one due to compliance problems (amlodipine). Antianginal pre-treatment was similar in the two treatment groups, with acetylsalicylic acid, nitrates, β-adrenoreceptor antagonists and Ca^{2+} channel blockers being the most commonly prescribed agents. In total, 37 % of patients (nicorandil, n = 21; amlodipine, n = 24) had concomitant essential hypertension while 21 % (nicorandil, n = 16; amlodipine, n = 10) had hypercholesterolaemia.

A total of 118 patients (nicorandil, n = 56; amlodipine, n = 62) were evaluable for efficacy on an intention-to-treat basis. Of these, 59 were enrolled in Switzerland (nicorandil, n = 30; amlodipine, n = 29) and 59 in Austria (nicorandil, n = 26; amlodipine, n = 33). The treatment groups were comparable for demographic and clinical characteristics within and be-

Table 1. Mean (± SD) demographic and clinical characteristics at the start of the study (safety patient population)

Characteristic	Treatment group	
	Nicorandil (n = 57)	Amlodipine (n = 64)
Gender (male : female)	44 : 13	53 : 11
Age (years)	62 ± 9	62 ± 9
Bodyweight (kg)	76 ± 12	76 ± 10
No. of anginal attacks/week	4.3 ± 4.1	4.4 ± 5.5
Duration of history of angina pectoris (months)	51 ± 69	57 ± 64
No. of patients with previous history of MI	14	26
No of units of NTG required for immediate relief	1.9 ± 2.9	1.6 ± 2.4
ETT parameters*		
Time to onset of 0.1 mV ST-depression (min)	4.7 ± 0.3	5.1 ± 0.3
Time to onset of anginal pain (min)	5.2 ± 0.3	5.6 ± 0.3
Total exercise duration (min)	6.7 ± 0.3	7.3 ± 0.4
ST-segment depression (mV)	-0.17 ± 0.01	-0.17 ± 0.01

* Mean ± SEM of 56 evaluable patients in the nicorandil group and 62 evaluable patients in the amlodipine group.
Abbreviations: ETT = exercise tolerance test; MI = myocardial infarction; NTG = nitroglycerin

tween the two countries, with the exception of history of previous myocardial infarction among patients recruited in Austria (nicorandil, n = 2; amlodipine, n = 14). The mean (± SD) number of anginal attacks/week was similar in both nicorandil and amlodipine groups at baseline (3.4 ± 3.7 and 3.3 ± 3.6, respectively). However, the mean number of NTG units required for pain relief was significantly higher (p = 0.04) in the nicorandil group (2.3 vs 1.0 units/week). Baseline BP, HR and ETT variables were similar in the two treatment groups.

Dose titration

The percentage of patients following the high dosage regimen was similar in the nicorandil and amlodipine groups at 2, 4, 6 and 8 weeks (50 % and 43.5 %, respectively, at the end of the study).

Exercise tolerance tests

ETTs were to be performed at 12 hours after drug administration (24 hours after active drug in the amlodipine group). However, in the nicorandil group, the mean (range) time to ETT at week 2 was 16 (9–27) hours and at endpoint was 16 (10–28) hours. Corresponding values at week 2 and endpoint for the amlodipine group were 17 (11–31) and 16 (12–32), respectively. Overall, around 70 % of patients in both treatment groups performed ETTs at >14 hours after study drug administration.

Time to onset of ST-segment depression increased in both treatment groups during the study (Table 2). However, the difference compared to baseline was only statistically significant in the amlodipine group. Time to onset of angina pain and total exercise duration were significantly higher in all patients at 2 and 8 weeks compared to baseline, while the magnitude of ST-segment depression at maximal identical workload was significantly decreased. There were no significant differences between the two treatment groups and no significant medication and country interactions for any of the ETT target variables.

In the nicorandil group, anginal pain was the most common reason for discontinuing the ETT at baseline, at 2 and 8 weeks and at endpoint. However, while anginal pain was the most common reason for discontinuing ETT at baseline among amlodipine-treated patients, at 2 and 8 weeks and at endpoint the primary cause of discontinuation of ETT was muscle fatigue. In addition to the decrease in the proportion of patients experiencing anginal pain during ETTs, the intensity of pain experienced was also decreased. Thus, 38 and 36 patients in the nicorandil and amlodipine groups, respectively, experienced pain of at least AP^{3+} intensity during baseline ETTs (defined as anginal pain causing moderately severe discomfort and requiring NTG for symptom relief), compared with 20 and 15 patients, respectively, at endpoint.

Anginal attacks, NTG consumption and quality of life

The sum of weekly anginal attacks decreased progressively in both treatment groups during the 8-week treatment period (Table 3), becoming statistically significant compared to baseline after 4 weeks. There was no significant difference between the two treatment groups in terms of antianginal efficacy. The number of NTG units required for immediate relief similarly decreased in both groups. The decrease was significant at 4, 6 and 8 weeks in patients receiving nicorandil, and at weeks 4 and 6 in the amlodipine group. No significant between-group differences were apparent. Overall, the ratings for all 4 quality-of-life variables improved during the study in both treatment groups (data not shown).

Blood pressure and heart rate

In both treatment groups, BP measured immediately prior to ETTs was generally significantly lower ($p < 0.05$) after 2 and 8 weeks of treatment than at baseline, although no clinically significant changes in HR were apparent. With respect to BP and HR at peak exercise and during recovery, there were no significant differences to baseline among nicorandil recipients. In contrast, BP at these time points during ETTs after 8 weeks' treatment was significantly lower ($p < 0.05$) compared with baseline among amlodipine-treated patients, while a small increase in HR was noted during recovery.

Standing and supine BP – when measured in two week intervals during the course of the study – decreased slightly in the nicorandil group but was not statistically different to baseline at any visit. Among amlodipine-treated patients, BP decreased significantly compared to baseline at all visits with the exception of standing DBP at 2 weeks. All differences between

Table 2. Mean (± SEM) target efficacy variables in patients receiving nicorandil 10–20 mg twice daily or amlodipine 5–10 mg once daily for 8 weeks

Parameter	Nicorandil (n = 56)			Amlodipine (n = 62)		
	Baseline	2 weeks	Endpoint	Baseline	2 weeks	Endpoint
Time to onset of 0.1 mV ST-segment depression (min)	4.7 ± 0.3	5.0 ± 0.3	5.1 ± 0.3	5.1 ± 0.3	6.0 ± 0.4*	5.7 ± 0.3*
Time to onset of anginal pain (min)	5.2 ± 0.3	6.1 ± 0.3*	6.1 ± 0.4*	5.6 ± 0.3	6.6 ± 0.3*	7.0 ± 0.4*
Total exercise duration (min)	6.7 ± 0.3	7.2 ± 0.3*	7.2 ± 0.4*	7.3 ± 0.4	7.9 ± 0.4*	7.9 ± 0.3*
ST-segment depression at maximal identical workload (mV)	-0.17 ± 0.01	-0.14 ± 0.01*	-0.13 ± 0.01†*	-0.17 ± 0.01	-0.12 ± 0.01*	-0.12 ± 0.01†*

* Indicates that the difference to baseline was statistically significant.
† Values shown are for the 8-week time point (endpoint analysis not performed).

Table 3. Sum of weekly anginal attacks and nitroglycerin (NTG) consumption in patients receiving nicorandil 10–20 mg twice daily or amlodipine 5–10 mg once daily for 8 weeks

Parameter	Nicorandil (n = 56)			Amlodipine (n = 62)		
	Baseline	2 weeks	Endpoint	Baseline	2 weeks	Endpoint
Sum of weekly anginal attacks	3.4 ± 0.5	2.9 ± 0.6	2.1 ± 0.4*	3.3 ± 0.5	2.5 ± 0.5	0.9 ± 0.2*
No. of NTG units for immediate pain relief	2.3 ± 0.6	1.9 ± 0.6	1.5 ± 0.5*	1.0 ± 0.2	0.8 ± 0.2	0.6 ± 0.3

* Indicates that the difference to baseline was statistically significant.

Table 4. Summary of adverse events reported during treatment with nicorandil 10–20 mg twice daily or amlodipine 5–10 mg once daily for 8 weeks that were considered at least probably related to study medication

Adverse event	Nicorandil (n = 57)	Amlodipine (n = 64)
Peripheral oedema	0	7
Headache	3	1
Vertigo	2	0
Flushing/burning face	0	2
Nausea	0	1
Abdominal pain	0	1
Tachycardia	0	1
Itching	0	1
Trembling	0	1

the two groups at the end of the study were significant (supine SBP, p = 0.0002; supine DBP, p = 0.02; standing SBP, p = 0.001, standing DBP, p = 0.01). HR in the supine position remained almost unchanged in both treatment groups during the trial and there were no significant differences between groups. Standing HR also remained fairly constant in both groups. Although there was a statistically significant difference (p = 0.05) between the two treatment groups after 8 weeks' treatment, this was not considered clinically significant.

Tolerability

All 121 patients who were randomised to receive study medication were included in the safety analysis. A total of 29 adverse events were reported by 20/57 (35.1 %) patients in the nicorandil group, while 20/64 (31.3 %) patients in the amlodipine group reported 34 adverse events. The most common adverse events that were considered at least probably related to treatment included mild or moderate headache and vertigo in the nicorandil group, and peripheral oedema in the amlodipine group (Table 4). These adverse events have previously been associated with nicorandil and amlodipine, respectively, and were therefore not unexpected. No deaths occurred during treatment with either nicorandil or amlodipine. Among five patients withdrawn because of adverse events, one nicorandil-treated patient experienced severe, long-lasting vertigo judged to be causally related to the study medication. Two other patients in each treatment group experienced adverse events necessitating treatment withdrawal (nicorandil: severe angina pectoris and tachycardia, one patient each; amlodipine: severe angina pectoris and myocardial infarction, one patient each). In each case, however, causal relationship with the study medication was considered remote.

No clinically relevant changes in laboratory parameters were apparent in either treatment group during the study.

Discussion

In recent years, improved understanding of the pathogenesis of angina pectoris in patients with CHD has led to significant advances in the prevention and treatment of this condition. Despite such advances, however, angina pectoris continues to have a profound effect on the quality of life of those individuals affected, and currently available antianginal agents (eg, nitrates, β-adrenoreceptor antagonists, Ca^{2+} channel blockers), while clinically effective, all have limitations. For example, there is no doubt that Ca^{2+} channel blockers such as amlodipine are effective in reducing both subjective and objective symptoms of angina pectoris [20]. However, the utility of this agent is often limited by its propensity to cause low BP and troublesome adverse events, principally peripheral oedema and other vasodilatory effects (flushing, headache and dizziness). A need, therefore, exists for new antianginal agents with improved efficacy, safety and tolerability.

Nicorandil, which belongs to the class of compounds known as K_{ATP} channel activators, is an innovative new agent for the treatment of angina pectoris. Clinically, nicorandil fulfils many of the goals of drug therapy in patients with angina pectoris: subjective and objective symptoms of myocardial ischaemia are relieved, while the drug appears to be well tolerated [21–24]. Moreover, comparative studies in patients with chronic stable angina pectoris have established that nicorandil has equivalent efficacy to nitrates [14], β-adrenoreceptor antagonists [16–18] and certain Ca^{2+} channel blockers [13, 19]. In this study we chose to compare the antianginal and antiischaemic efficacy of nicorandil with that of amlodipine, a highly effective, established therapeutic agent for the treatment of angina pectoris.

In the present study, both nicorandil and amlodipine demonstrated objective and subjective efficacy in patients with angina pectoris. Amlodipine was associated with increases in the time to onset of ST-segment depression, whereas time to anginal pain compared with baseline and total exercise duration were increased in both treatment groups. While amlodipine appeared to be more effective than nicorandil in terms of antiischaemic efficacy, it is important to consider that several parameters may have favoured amlodipine in this study. For example, ETTs were scheduled to be performed at 12 and 24 hours, respectively, after the administration of nicorandil and amlodipine. In reality, however, this time interval was rarely adhered to, and in some cases patients performed ETTs at up to 32 hours post-dose. Given that amlodipine has a longer elimination half-life compared with nicorandil, plasma levels of the latter would have been expected to be subtherapeutic at this time. Moreover, only around 50 % of patients were titrated to a nicorandil dosage of 20 mg bd, the optimal dosage for the management of angina pectoris. Taken together, it is not surprising that the results for some ETT parameters appeared to favour amlodipine. However, no statistically significant between-group differences were apparent for all ETT parameters assessed, indicating that nicorandil is as effective as amlodipine in terms of objective efficacy.

Another important finding in this study was the effect of amlodipine on BP. In contrast to nicorandil, for which no consistent changes in BP were apparent, amlodipine evoked pronounced decreases in BP. These effects were apparent even at the lowest dosage investigated (5 mg od). In addition to the pharmacokinetic differences between nicorandil and amlodipine, the difference between these two agents in terms of their haemodynamic profile may have also contributed to the more favourable effect of amlodipine during ETTs. Although nicorandil had no apparent effect on BP in this study, either at rest or during ETTs, it is important to consider that many ETTs were performed when drug plasma levels were expected to be subtherapeutic and that most patients were maintained on the low-dose regimen. Thus, it would be interesting to determine the potential haemodynamic effects of nicorandil at the higher dosage of 20 mg bd, which may contribute to increased therapeutic efficacy.

Assessment of various aspects of quality of life demonstrated that angina pectoris has a significant effect on the quality of life of these patients. Overall, there was a trend towards an improvement in quality of life during the study, the magnitude of which was comparable in the two treatment groups. In addition to an improvement in quality of life, the frequency of angina pectoris and NTG usage decreased in parallel in both nicorandil- and amlodipine-treated patients. Taken to-

gether, these results confirm that both agents are clinically effective for the management of angina pectoris, and that nicorandil is as effective as amlodipine.

While a decrease in BP may have contributed to the therapeutic efficacy of amlodipine in this study, this was not without limitation. Indeed, peripheral oedema, a well-known adverse effect of amlodipine that is related to the pronounced haemodynamic effects of this agent, was commonly reported (9 patients at least one record) and frequently deemed to be drug-related. Overall, the incidence of peripheral oedema in this study was comparable to that in previously published studies [20], and given that the incidence of this adverse event is dose-related, it is likely that a greater proportion of patients would have been affected had the dose-titration been more widespread. In contrast, fewer drug-related adverse events were reported among nicorandil recipients, the most common of which was headache (3 patients). This adverse event has been previously reported for nicorandil, and was therefore not unexpected. While the incidence of drug-related adverse events was higher among amlodipine recipients, the rate of patient withdrawal as a result of poor tolerability was similar in the two treatment groups. However, it is important to consider that the duration of the present study was relatively short (8 weeks), and for the long-term patient the acceptability of drug-related adverse effects becomes crucial in the management of chronic disease states such as angina pectoris. For nicorandil, the most frequent adverse event was headache, which frequently resolves with long-term therapy [23]. Such findings indicate that nicorandil may be a favourable therapeutic option for the long-term management of angina pectoris.

In conclusion, this study demonstrates that nicorandil is as effective as amlodipine for attenuating anginal symptoms, increasing exercise capacity and improving quality of life in patients with symptomatic stable angina pectoris. However, nicorandil appears to have a more favourable tolerability profile, which indicates that this agent may be particularly advantageous for the long-term management of angina pectoris.

A significant advantage of nicorandil is the lack of effects on BP, making the drug especially suitable for patients with a tendency to hypotension.

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