A Practitioner Based Evaluation of Nicorandil on Symptoms and Quality of Life in Patients with Chronic Stable Angina Pectoris

Kiowski W, Riebenfeld D

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A Practitioner Based Evaluation of Nicorandil on Symptoms and Quality of Life in Patients with Chronic Stable Angina Pectoris

W. Kiowski¹, D. Riebenfeld²

Nicorandil is an antianginal agent with unique pharmacological properties combining a nitrate-like action with vasodilatation through opening of ATP-potassium channels. The antianginal effects of nicorandil have been carefully studied in mostly small, comparative trials but its usefulness outside of the setting of clinical trials is less well studied. We investigated the antianginal effects (patient diary for angina episodes and nitroglycerin consumption for immediate pain relief) of nicorandil in 200 patients (46% females, 71.4 ± 9.9 years) followed by 56 primary care physicians in general practice. Nicorandil was started at 2 × 10 mg and, increased after 3 weeks to 2 × 20 mg, if tolerated and judged necessary, for a total of 12 weeks. Nicorandil was given as monotherapy in 22% and in combination with beta-blockers, calcium antagonists or long-acting nitrates in 78% of patients. An assessment of quality of life was performed at baseline and at week 12.

Nicorandil was withdrawn in 14 patients (7%) because of headache and/or flushing and in 10 patients because of acute illnesses unrelated to therapy or administrative reasons. After 12 weeks, nicorandil resulted in small but statistically significant (p < 0.05) decreases of systolic (−5.0 ± 14.3 mmHg) and diastolic (−2.4 ± 8.6 mmHg) blood pressure and heart rate (−1.9 ± 9.0 bts/min). Weekly anginal episodes and nitroglycerin consumption decreased markedly by −5 ± 6.3 and −5.6 ± 8.5 (p < 0.001) and ratings of quality of life improved for all aspects (p < 0.001). Both patients and physicians rated efficacy and tolerability in 80 to 90% as excellent or good and 169 out of 174 patients opted for long-term nicorandil therapy after 12 weeks.

Thus, nicorandil given alone or in combination proved to be highly efficacious and well tolerated in patients with chronic stable angina pectoris followed by their private physicians in general practice. J Clin Basic Cardiol 2001; 4: 149–152.

Key words: nicorandil, angina pectoris, quality of life

**Patients and Methods**

The study was conducted in the offices of 56 general practitioners and internists in Switzerland. Two hundred patients with chronic stable angina pectoris agreed to participate in this open label, 12 weeks trial that was approved by the local ethics committees. Exclusion criteria were a recent (< 3 months) myocardial infarction and known intolerance to nicorandil.

After obtaining written informed consent patients were instructed in the use of diaries to record the frequency of angina pectoris episodes and the number of acutely acting nitroglycerin preparations required for pain relief. In addition, an attempt was made to assess patients’ quality of life using a scale of 1 (best) to 5 (worst) for the following questions: “How is your general well being?”, “How is your physical capacity?”, “How is your endurance during strenuous physical work?”, and “How much are you bothered by angina pectoris in daily life?”. Patients were asked to fill out the questionnaire at the end of each week. Moreover, at the end of the study, patients were asked to judge the efficacy and tolerability of nicorandil as excellent, good, moderate, or poor and physicians were asked to perform the same rating.

Following the baseline visit, patients were started on open label nicorandil 2×10 mg daily and were scheduled for a further visit three weeks later. Concomitant therapy was continued. If tolerated and/or judged clinically necessary, nicorandil was increased after three weeks to 2×20 mg daily. Down titration to 2×5 mg daily was allowed in case of adverse effects. Patients were scheduled for a final visit after 12 weeks when they were given the option to continue nicorandil.

At each visit, seated casual blood pressure (sphygmomanometer), heart rate (radial pulse) and body weight were measured.

**Statistics**

Paired t-test was used to analyse changes as compared to baseline. Results are presented as means ± standard deviation and proportions as percentages.
Results

Patient characteristics
Baseline patient characteristics are given in Table 1. Patients were elderly and mildly to moderately symptomatic with a history of prior myocardial infarction on average 7.85 ± 7.9 years earlier in approximately 30 %, coronary artery bypass grafting 7.2 ± 4.4 years earlier in 13.5 %, and percutaneous coronary intervention 3.8 ± 3.4 years earlier in 12.5 % of the patients. Only 14 % of patients were current smokers and antihypertensive drugs other than beta-blockers and calcium antagonists were used in approximately one fourth. Diabetes mellitus was infrequent with 6.3 % of patients using oral hypoglycaemic drugs and only one patient using insulin. Beta-blockers were used most frequently, followed by long-acting nitrates in 20 patients, mostly because of adverse effects of these therapies.

Patient disposition during study
During the 12 weeks of follow up, 24 patients discontinued nicorandil. In 14 of them (7 %), adverse effects (headaches and/or flush in 10 patients, gastrointestinal disturbances in 1 patient(s)) led to withdrawal of nicorandil within the first three weeks. Lack of compliance (3), administrative reasons (2) and acute illness (1 death from cerebral haemorrhage, 1 heart failure non-cardiac hospitalization) accounted for the other withdrawals from the trial. None of the acute illnesses was considered to be related to study medication by the treating physicians. Thus, 176 patients (88 %) completed the 12 week treatment period as planned. Of these, 121 completed the weekly quality of life questionnaire. The final nicorandil dose was 2 × 5 mg in 3.5 %, 2 × 10 mg in 70.8 %, 2 × 15 mg in 2.9 %, and 2 × 20 mg in 22.8 %.

Clinical effects of nicorandil
Haemodynamic and antiangial effects of nicorandil are summarized in Table 2. On average, nicorandil caused small but significant decreases of systolic (−5.0 ± 14.3 mmHg) and diastolic (−2.4 ± 8.6 mmHg) blood pressure at week 12. Heart rate decreased slightly but significantly (−1.9 ± 9.0 bts/ min) while weight was unchanged. Weekly anginal episodes and nitroglycerin consumption decreased markedly by −5 ± 6.3 and −5.6 ± 8.5. Although most of these effects were present at week 3, additional effects were seen at week 12.

Figure 1 shows the average weekly scores for the four questions relating to patients’ quality of life. As shown, all scores for the 4 questions improved markedly over time, again with the greater portion of the effect being present after 3 weeks already.

After 12 weeks, physicians rated efficacy and tolerability of nicorandil as excellent or good in 85.4 % and 89.3 % of patients, respectively (Table 3). Likewise, 84.7 % and 89.3 % of patients rated efficacy and tolerability as excellent or good, respectively. Consistently, tolerability was judged as poor in approximately 7 % by patients and physicians, reflecting the number of patients who discontinued the trial because of adverse effects. Finally, 169 patients opted for continuation of nicorandil after 12 weeks.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Nicorandil 3 weeks</th>
<th>Nicorandil 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.4 ± 9.9</td>
<td>74.4 ± 13.4</td>
<td>74.0 ± 13.7</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>54 / 46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/previous smoker (%)</td>
<td>14 / 19.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris NYHA class</td>
<td>74.5 / 25.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of angina pectoris (years)</td>
<td>4.29 ± 5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>29.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention (%)</td>
<td>12.5</td>
<td></td>
<td></td>
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<tr>
<td>Coronary artery bypass grafting (%)</td>
<td>13.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers (%)</td>
<td>44.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists (%)</td>
<td>26.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long acting nitroglycerin preparations (%)</td>
<td>29.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molsidomine (%)</td>
<td>9.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet inhibitors (%)</td>
<td>3.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (%)</td>
<td>9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitors, angiotensin receptor antagonists, diuretics (%)</td>
<td>26.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral hypoglycaemic drugs (%)</td>
<td>6.0</td>
<td></td>
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</tbody>
</table>

### Table 2. Haemodynamic and antianginal effects of nicorandil

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Nicorandil 3 weeks</th>
<th>Nicorandil 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>141.8 ± 18.5</td>
<td>137.4 ± 17.9</td>
<td>136.5 ± 16.4**</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82.3 ± 9.1</td>
<td>80.3 ± 9.7</td>
<td>79.9 ± 8.7</td>
</tr>
<tr>
<td>Heart rate (bts/min)</td>
<td>72.8 ± 9.9</td>
<td>72.0 ± 9.7</td>
<td>71.2 ± 8.6*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.5 ± 13.4</td>
<td>74.4 ± 13.4</td>
<td>74.0 ± 13.7</td>
</tr>
<tr>
<td>Angina pectoris episodes (per week)</td>
<td>6.3 ± 6.4</td>
<td>2.6 ± 3.3**</td>
<td>1.3 ± 2.1**</td>
</tr>
<tr>
<td>Nitroglycerin consumption (per week)</td>
<td>6.6 ± 8.9</td>
<td>2.5 ± 3.9**</td>
<td>1.0 ± 1.7**</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.001

### Table 3. Rating of nicorandil by physicians and patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Physicians</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– excellent</td>
<td>44.8</td>
<td>42.1</td>
</tr>
<tr>
<td>– good</td>
<td>40.6</td>
<td>42.6</td>
</tr>
<tr>
<td>– moderate</td>
<td>13.5</td>
<td>13.2</td>
</tr>
<tr>
<td>– poor</td>
<td>1.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Tolerability (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– excellent</td>
<td>54.8</td>
<td>50.8</td>
</tr>
<tr>
<td>– good</td>
<td>34.5</td>
<td>38.5</td>
</tr>
<tr>
<td>– moderate</td>
<td>3.6</td>
<td>4.1</td>
</tr>
<tr>
<td>– poor</td>
<td>7.1</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Rating of efficacy was based on 179 patients and of tolerability on 197 patients.
No formal dose comparison was performed but it was interesting to see that the efficacy of the lower dose of $2 \times 10$ mg/d, which was used in the majority of patients, was similar to that of the highest dose of $2 \times 20$ mg. Thus, the number of weekly anginal episodes decreased from $5.8 \pm 6.2$ to $1.3 \pm 2.3$ ($p < 0.01$) in patients taking $2 \times 10$ mg/d and from $6.1 \pm 7.1$ to $1.0 \pm 1.8$ in patients taking $2 \times 20$ mg/d. Similarly, weekly nitroglycerin consumption decreased by $5.1 \pm 6.2$ and $7.1 \pm 13.5$ in patients taking $2 \times 10$ and $2 \times 20$ mg/d nicorandil, respectively.

Discussion

The present study confirms in a large population with chronic stable angina pectoris, that nicorandil is a highly effective antiangiinal agent [9–16, 19], reducing the number of anginal episodes and use of nitrates for immediate pain relief by approximately 80%. Expectedly, improved control of anginal pain caused a profound improvement of quality of life, as assessed by a previously used simple questionnaire [16]. These effects were equally found in the 22% of patients who received nicorandil as monotherapy and the remainder of patients in whom it was added to other antiangiinal therapy. The starting dose of $2 \times 10$ mg per day proved to be effective in the majority of patients but antiangiinal effects were similar after 12 weeks in patients who required the higher dose of $2 \times 20$ mg. This long-term antiangiinal efficacy provides further evidence that antiangiinal and haemodynamic tolerance to nicorandil does not develop to a significant degree [10, 17, 18]. Also, cross-tolerance between nicorandil and nitroglycerin does not seem to occur [20]. Although cross-tolerance was not examined in this study, the finding that the decrease in nitroglycerin consumption paralleled closely that of the reduction in anginal episodes is consistent with this contention. Expectedly, the main adverse effect was headache and/or flushing, which accounted for 13 out of a total of 14 adverse event related treatment discontinuations. Although this incidence (7%) is somewhat higher than that reported in the prescription-event monitoring study of nicorandil, eg 3.5% [21], it is still low given the good overall clinical efficacy. Taken together, therefore, nicorandil appears to be an effective and safe drug for the management of these patients in the setting of general practitioners and internists.

Interestingly, these pronounced antiangiinal effects were achieved with only a small fall of blood pressure, confirming previous results [22, 23]. This finding supports the notion that not only reductions of blood pressure and afterload [24] but also coronary vasodilatation with increased oxygen delivery [6, 25] as well as reduced oxygen demand through a reduction in preload [4, 6] are important determinants of nicorandil’s antiangiinal effects. Obviously, it is impossible to determine the relative importance of activating KATP channels as compared to the nitrate-like effect for the antiangiinal effects of nicorandil.

Likewise, one could only speculate about the importance of opening KATP channels for the induction of ischaemic preconditioning. It is of interest, though, that nicorandil, when added to aggressive antiangiinal treatment for unstable angina, reduced transient myocardial ischaemia compared to placebo suggesting that pharmacological preconditioning through its effect on KATP might be clinically relevant [26]. However, data in patients with chronic stable angina pectoris is missing in that regard. Results from the large (5000 patients) investigation of Nicorandil in Angina (IONA) study [27] should clarify whether this unique pharmacological effect of nicorandil not only improves symptoms but also reduces ischaemia related cardiac events, eg death, non-fatal myocardial infarction and hospitalization for angina pectoris. Clearly, demonstration of such an effect would place nicorandil at the front of the therapeutic armamentarium for angina pectoris since neither nitrates nor calcium channel or beta-blockers, with the exception of post-infarction patients [28, 29], have a protective effect in chronic stable angina pectoris.

Blood pressure decreased somewhat during nicorandil therapy. Interestingly, heart rate did not increase but decreased also slightly. However, almost half the patients in this trial were taking a beta-blocker, rendering conclusions regarding effects of nicorandil on heart rate difficult. Nevertheless, unchanged heart rate was also found in almost all studies of patients receiving nicorandil [22, 23].

A number of interesting aspects were revealed in this study. Thus, a surprisingly low fraction of patients received antiplatelet agents or HMG-CoA reductase inhibitors even though the value of these agents is established, at least in secondary coronary prevention [30–32]. As 55.5% of patients either had a previous myocardial infarction or had undergone coronary revascularisation, a much wider or, in the case of platelet inhibitors, a general use would have been expected. This finding clearly shows that further educational efforts are needed to optimize medical therapy of these patients.

There are a number of limitations of this trial. Thus, it was neither randomised nor placebo controlled. Obviously, results from such trials might be biased by patients’ as well as physicians’ preferences. Also, exercise testing was not performed rendering the evaluation of the antiangiinal effects of nicorandil purely subjective. However, the efficacy in this trial is not far from what has been found in smaller, placebo controlled or comparative trials of nicorandil [9–16, 19]. Also, 80% out of a total of 8713 patients in the prescription-event monitoring study of nicorandil [21] reported good efficacy.

Formal dose comparison was not performed making it impossible to draw conclusions regarding the efficacy of $2 \times 10$ vs $2 \times 20$ mg doses. However, it appears that a dose of $2 \times 10$ mg/d is sufficient for the majority of patients while only approximately one fourth of patients requires a dose of $2 \times 20$ mg/d to achieve a similar clinical effect. Finally, concomitant therapy was not standardised, making conclusions about the antiangiinal efficacy in combination with other drugs difficult.

In conclusion, nicorandil given alone or in combination with other antiischaemic drugs proved to be highly efficacious and well tolerated in patients with chronic stable angina pectoris followed by their private physician in general practice. The improvement in quality of life suggests that it should be considered as a therapeutic option for the long-term management of angina pectoris. Whether the effects of nicorandil on KATP channels will be associated with additional benefit awaits further study.

References:

Appendix

List of Investigators:
Dr. med. Battaglia Enrico, Via Stefano Franchini 1, 6000 Lugano
Dr. med. Bieler Magnus, Rorschacherstrasse 19, 9000 St. Gallen
Dr. med. Blanc Jac.-Phil., via alle Scuole, 6946 Ponte Capaciosa
Dr. med. Blickenstorfer Heinz, Marktgasse 3, 9600 Dübendorf
Dr. méd. Bourgeois Jean, Chemin du Mont-Blanc 28, 1700 Aubeonne
Dr. méd. Bruchez Bernard, Av. de la Gare 17, 1520 Martigny
Dr. med. Brunner Harald, Kornmattstrasse 8b, 4102 Binningen
Dr. med. Bugiani Giorgio, Ackerstrasse 6, 5432 Neuenhof
Dr. med. Cadablt Andrea, In der E 39, 8047 Zürich
Dr. med. Coço Giuseppe, Marktgasse 1a, 4310 Rheinfelden
Dr. med. Fiori Gabriele, Via Vallemaggia 10, 6900 Locarno
Dr. med. Flieg Stephan, Rosenstegstrasse 30, 8280 Kreuzlingen
Dr. méd. Frantzen André, rte du Collège 13, 1912 Leytron
Dr. med. Frei Alfred, Wilenstrasse 126, 8832 Wilen b. Wollerau
Dr. med. Gerber Andreas, Basseltweg 26, 2542 Pieterlen
Dr. med. Grenier Philippe, St. Jakobstrasse 87, 9950 St. Gallen
Dr. med. Hadinia-Gitat Mahmoud, Jakob Eglistrasse 3, 4132 Muttenz
Dr. med. Hagemann Oscar, Fasaneistraße 11, 4515 Oberdorf
Dr. med. Hilfiker Max, Mühllegasse 22, 3400 Burgdorf
Dr. med. Hüsli Friedrich, Olmstrasse 500, 6652 Winznau
Dr. méd. Inesch Alain, 28, chemin du Mont Blanc, 1170 Aubeonne
Dr. méd. Jeker Bernard, Place du Midi 40, 1950 Neuch\"altern\"e
Dr. med. Klein Gerhard, Dorfstrasse 18, 6242 Wuwil
Dr. med. Kleiney-Bühler Milan, Huebweisenstrasse 3, 8954 Gerdowidow
Dr. med. Kozak Josef, Herrnackerstrasse 28, 8730 Uznach
Dr. med. Kull Hans Ulrich, Oberl Heslibachstr. 42, 4515 Oberdorf
Dr. méd. Laurent Antoine, rue de la Gare 6C, 1860 Aigle
Dr. med. Leemann Arnold, Alte Bahnhofstrasse 3, 5610 Wohlen
Dr. med. Lüttold Benno E., Dorfstrasse 29/31, 4222 Zwingen
Dr. med. Maurer Hermann, Blumenaustrasse 20, 9000 St Gallen
Dr. med. Mayer Rames, Via Mordasini 12, 6800 Bellinzona
Dr. méd. Meile Jean Oscar, Via Pocobelli 15, 6815 Melide
Dr. méd. Métrailler Alain, 3971 Cheminong
Dr. med. Müller Robert Alfred, Talützentrum, 9000 St. Gallen
Dr. med. Nagel Gideon, Burgfelderstrasse 20, 4058 Basel
Dr. med. Nager Gabriella, Freiestrasse 211, 8032 Zürich
Dr. méd. Nguyen Thi, Av. de Chaully 25, 1012 Lausanne
Dr. med. Oswald Norbert, Bahnhofstrasse 14, 7130 Ilanz
Dr. méd. Parate Jacques, av. du Simplon 21, 1890 St. Maurice
Dr. méd. Piccinn Pascal, av. de la Gare 9, 1890 St. Maurice
Dr. méd. Polètais Alois, Paradisgärtli, 7130 Ilanz
Dr. méd. Provodlo Romeo, Av. Mericier-de-Molin 2, 3960 Sierre
Dr. méd. Reynod Frédéric, rue du Midi 2, 1033 Lutassane
Dr. méd. Riek Markus, Schmiedgasse 7, 6430 Schwyz
Dr. med. Sabert Mosar, Binzenstrasse 3, 8733 Eschenbach
Dr. méd. Sala Gamarroco, Bahnhofstrasse 35, 6460 Alzendorf
Dr. méd. Sandell David, rue des Dents-du-Midi 34, 1868 Collombey
Dr. med. Schneider Thomas A., Rue Hennestadt 17, 4058 Basel
Dr. med. Tschurr Enrico, Via Nürtal 1, 7402 Bonaduz
Dr. méd. Valenti Paolo, Av. du Cort 7E, 1260 Nyon
Dr. méd. Vourtsis Konstantin, Seetalstrasse 21, 9000 St. Gallen
Dr. med. Weissenberger Benno, Hardstrasse 111, 4052 Basel
Dr. med. Wimmersberger Walter, Steinmühlestrasse 21, 8953 Dietikon
Dr. med. Zubr Michel, Bahnhofstrasse 8, 5504 Othmarsingen

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