Nadolol Compared to Propranolol for Treating Chronic Stable Angina Pectoris*

Lawrence A. Miller, M.D.; Michael H. Crawford, M.D.; and Robert A. O'Rourke, M.D.

In order to determine the relative efficacy and dose equivalency of propranolol four times a day and nadolol once daily for the treatment of stable angina pectoris, ten patients were studied in a double blind randomized placebo controlled crossover study. Total daily doses of propranolol and nadolol were determined by titrating until an equivalent degree of reduction in the heart rate response to exercise was achieved. At these doses, the treadmill exercise time to 0.1 mV of electrocardiographic ST-segment depression was increased from 248 ± 75 seconds on placebo to 405 ± 56 seconds on propranolol (p < 0.05) and 471 ± 46 seconds on nadolol (p < 0.01). Also, the mean frequency of angina decreased from eight attacks per week on placebo to three on propranolol and nadolol (both p < 0.05). In six of the ten patients, the effective total daily dose of propranolol and nadolol was identical, and the dose ratio for all ten patients was 1.17 ± 1, propranolol to nadolol. However, individual dose titration is recommended when switching from propranolol four times a day to nadolol once daily because of the dosage variability noted in 40 percent of the patients.

Nadolol, a nonselective beta-adrenergic receptor blocking agent without intrinsic sympathomimetic or membrane stabilizing activity has recently become available for the treatment of stable angina pectoris. In multiple controlled trials, propranolol has been found to be effective in the treatment of stable exertional angina. However, the use of propranolol is limited by central nervous system side effects because of its liposolubility, and therefore, its ability to cross the blood-brain barrier. Nadolol is a hydrophilic beta-blocking agent which markedly limits its ability to cross the blood-brain barrier and thus, central nervous system side effects are comparatively minimal. Also, nadolol has a half-life of 12 to 17 hours and has the potential advantage of single daily dosing which improves patient compliance. Therefore, patients frequently are switched from propranolol to nadolol because of these advantages. However, the differences in absorption and metabolism of propranolol and nadolol potentially place the patient with angina at risk of inadequate beta blockade when switching from one medication to the other. In some studies where two different populations were treated with propranolol and nadolol and then compared, the effective equivalent daily dose was reported to be similar. In a more recent study where the same patients were treated with both agents, it was recommended that the nadolol dose be less, possibly one-half the propranolol dose. Accordingly, we devised this double-blinded randomized crossover study to determine the relative effectiveness and dose equivalency of nadolol and propranolol in patients with chronic stable exertional angina.

Materials and Methods

Patient Population

Ten male patients with chronic stable exertional angina were selected from our outpatient population and studied. Patients were chosen if they had (1) fixed coronary artery disease by coronary angiography or a documented myocardial infarction in the past, (2) exertional angina occurring in a stable pattern for the past three months relieved by sublingual nitroglycerin, and (3) an exercise tolerance test demonstrating at least 0.1 mV ST-segment depression. Patients were excluded from the study if they had a history of congestive heart failure, bronchospastic or obstructive lung disease, hepatic or renal dysfunction, myocardial infarction within the past six months, required digitalis, had exercise limitations, or required the use of psychotropic adrenergic drugs. The protocol was approved by the institutional review board of the University of Texas Health Science Center, and informed consent was obtained from each patient. Patients were withdrawn from all antiangina medications except sublingual nitroglycerin.

All ten patients entered into the study were able to be withdrawn from their prior antiangina medications without the development of unstable angina. The patients were all men with an age range of 38 to 70 years and a mean age of 56.8 years. Five patients had coronary artery disease documented by cardiac catheterization: two patients with three-vessel disease, two patients with two-vessel disease, and one patient with one-vessel disease. Five patients had a prior myocardial infarction: four inferior and one subendocardial in location. Two patients had previous coronary artery bypass grafting. Three patients had a history of hypertension, one patient had diabetes mellitus. No patient had symptomatic peripheral vascular disease.

Procedures

Placebo was given four times daily (QID) for a period of one to three weeks to obtain a baseline level of angina frequency. Nitroglycerin dosage was standardized at 0.3 mg per tablet, and fresh tablets were given each week to assure potency. Patients were
Angina/Week

**Figure 1.** Angina frequency for each patient during the three treatment periods. The order of propranolol and nadolol therapy was randomized (see text).

Instructed to take nitroglycerin only for chest discomfort and not prophylactically. Each patient underwent an exercise treadmill test prior to entry into the study to assure the absence of physical limitations to exercise testing as well as to familiarize them with the procedures to minimize potential training effects. Patients kept a weekly diary indicating the number of episodes of angina and the number of tablets of nitroglycerin consumed. At the end of each week, patients were asked to compare average severity and duration of angina to the prior one-week period and note any side effects. A resting sitting blood pressure and heart rate were obtained, and a pill count performed. Patients then underwent an exercise treadmill test utilizing a Bruce protocol which included a warm-up stage of one mile per hour and a 5 degree grade. A lead V5 was continuously monitored during exercise with a 12-lead ECG obtained every minute of exercise and at the onset of angina. Patients were exercised until disabling angina, fatigue, or dizziness caused them to stop. No patient experienced an arrhythmia that prematurely terminated the test.

Following the placebo lead-in period, a double-blind randomization to propranolol QID or nadolol once daily (QD) was performed. Placebo was provided for the additional three doses in the patients assigned to nadolol so that they took pills QID at all times. Patients were initially started on 80 mg total daily dose of beta-blocker. Each week patients returned for evaluation. If the resting heart rate was 60 beats per minute or less, and the peak exercise heart rate was F110 beats per minute, this was considered adequate beta-adrenergic receptor blockade. If this criteria were not met, the total daily dosage was increased by 30 mg each week up to a maximum daily dosage of 240 mg. After optimal dosage was achieved, patients had an exercise treadmill test. They were then tapered off their medication and placed on placebo QID for one week. At the end of that week, they had repeat exercise treadmill testing to confirm that no changes had occurred since entry into the study.

Following this second placebo period, patients were crossed over to the other beta-blocker. Optimal dosage was determined in a manner similar to the first drug period and repeat exercise testing was performed. Exercise testing was performed approximately nine hours after the last propranolol dose and 24 hours after the last nadolol dose.

**Data Analysis**

The measurements made during propranolol and nadolol therapy were compared to those on placebo therapy by paired Student's t-testing, where each patient serves as his own control. All measurements are expressed as the mean ±1 SEM and p<0.05 was considered statistically significant.

**Results**

**Effects on Angina Pectoris**

Ten patients completed this part of the study. The effects of placebo, propranolol, and nadolol on the frequency of angina per week are shown in Figure 1. Both drugs were equally effective in reducing the angina attack rate. The mean level of 8±10 attacks per week on placebo decreased to 3±4 for propranolol and 3±3 for nadolol (both p<0.05). The effect was similar for nitroglycerin consumption with a mean consumption of 10±4 tablets per week on placebo, 4±1 tablets per week on propranolol, and 4±2 tablets per week on nadolol (both p<0.05). Evidence for beta blockade was
Dose Equivalency

In all ten patients, the dose required to achieve equivalent beta-blockade was compared (Fig 6). In six of the ten patients, the same total daily dose of propranolol and nadolol were required to achieve maximum therapeutic effect. Four patients required differing dosages, three lower doses of nadolol and one a higher dose of nadolol. Thus, the average ratio of propranolol to nadolol was 1.17:1.

Discussion

Previous studies have been performed comparing nadolol and propranolol to placebo in the treatment of angina. Shapiro et al. using a double-blinded protocol, compared a single daily dose of nadolol to placebo in patients with stable exertional angina. They found a significant reduction in frequency of anginal episodes, and nitroglycerin consumption, as well as an increase in exercise time. Jones et al. compared a 160 mg morning dose of a long-acting propranolol prepara-

**Figure 3.** Mean values for peak exercise heart rate during the three treatment periods.

*Effects on Exercise Performance*

Two of the ten patients initially entered into the study could not be exercised because of adverse symptoms. One patient complained of dizziness while taking propranolol which was not noted on an equivalent dose of nadolol. One patient developed an upper respiratory infection which precluded exercise testing during propranolol therapy. Therefore, the response to exercise was completely evaluated for both drugs in eight patients. Peak exercise heart rate decreased from 137 ± 11 beats/min on placebo to 106 ± 11 on propranolol and to 97 ± 11 on nadolol (both p<0.01, Fig 3). As an objective measurement of the improvement in exercise tolerance, the exercise time to 0.1 mV of ST-segment depression was increased from 248 ± 75 seconds on placebo to 405 ± 56 seconds on propranolol (p<0.05) and 417 ± 46 seconds on nadolol (p<0.01, Fig 4). Additionally, the double product at onset of angina decreased from 19.9 ± 5.4 beats mm Hg/min × 10⁵ for placebo to 13.6 ± 3.3 × 10⁵ for propranolol (p<0.01) and to 12.1 ± 2.6 × 10⁵ with nadolol (p<0.001, Fig 5).

**Figure 4.** Mean values for exercise duration to 0.1 mV of ST-segment depression during the three treatment periods.
tion, slow release oxprenolol, and nadolol. Nadolol was found to result in decreased nitroglycerin consumption and a reduced number of angina attacks when compared with other single daily dose medications. At 24 hours post-dose, exercise performance was increased with nadolol compared to the other beta-blockers. Ling et al. and Furberg et al. evaluated the effects of nadolol and propranolol, each comparing two similar patient populations rather than utilizing a drug crossover protocol. Nadolol QD and propranolol QD were equally effective in increasing exercise tolerance and decreasing the frequency of angina attacks and nitroglycerin consumption. Prager et al. compared nadolol QD to propranolol QD, also in two similar patient populations. Nadolol and propranolol were equally effective in decreasing the angina attack rate, but nadolol appeared more effective in increasing exercise duration. However, in all three studies, the endpoint of dose titration was a 50 percent reduction in the frequency of angina attacks and consumption of nitroglycerin rather than equivalent beta-blockade. It is unclear whether equivalent full beta-blockade would have produced the same result. In a noncrossover study where equivalent beta-blockade was achieved by titration to a resting heart rate of <60 beats per minute, Hill and Fand demonstrated an equivalent increase in exercise duration, decrease in angina frequency, and decrease in exercise double-product. This present study, using equivalent beta-blockade as the endpoint of dose titration in a blinded crossover study, showed that propranolol QID and nadolol QD are equally effective in decreasing angina frequency, nitroglycerin consumption, and improving exercise performance in any individual patient.

In evaluating equivalent beta-blocking activity of propranolol and nadolol given intravenously by comparing dose-responses to an infusion of isoproterenol, nadolol was found to be six times more potent than propranolol on a milligram for milligram basis. However, the pharmacokinetics of the chronic oral administration of nadolol and propranolol differ significantly, so that these results are not applicable when considering switching from one oral preparation to the other. The oral administration of nadolol results in approximately 30 percent absorption. Studies of hydrophilic beta-blocking drugs show peak blood levels to be relatively constant and predictable. This is in comparison with propranolol where there is excellent absorption, but up to 20-fold variation in peak blood levels due to first pass hepatic metabolism. Nadolol is 30 percent bound to plasma proteins and is excreted unchanged in the urine and feces. Propranolol is highly bound to plasma proteins and is subject to extensive hepatic degradation with production of active metabolites. The half-life of nadolol has been reported to be between 12 to 16 hours, whereas that of

![Exercise Double Product](image)

**Figure 5.** Mean values for the peak exercise heart rate-systolic blood pressure product during the three treatment periods.

![Daily Dose](image)

**Figure 6.** Total daily dose of the two drugs at an equivalent degree of beta-blockade.
propranolol is 3.5 to 6 hours. However, as with all beta-blockers, the duration of effect of beta-adrenoceptor blockade may exceed that of the measured half-life. As a result, choosing an equivalent dosage of beta-blocker when switching from one drug to another is dependent on individual patient variables that alter gastrointestinal absorption, hepatic function, and protein binding.

In our attempt to assess dose equivalency, we chose a patient population similar to that encountered by the practicing clinician. Mean age was that usually seen in patients with angina, and the patients did not have overt hepatic or renal dysfunction. Equivalent beta-blockade was determined by a reduction in resting and peak exercise heart rate. We chose this rather than an isoproterenol infusion since the results of the latter might not have any clinical significance. Our observations of equivalent beta-blockade at a ratio of 1.17:1 propranolol: nadolol, would support previous observations that propranolol QID and nadolol QD provide comparable beta-blockade, decrease in frequency of angina, decrease in nitroglycerin consumption, and increase in exercise tolerance at nearly equal doses in patients with coronary artery disease. However, 40 percent of our patients demonstrated differences in the total daily dose of each agent to achieve equivalent beta-blockade. Therefore, individual dosage titration with each agent is necessary when switching from one to the other.

Acknowledgments: The coordination of this study by Gemma T. Kennedy, RN, MSN, and the technical assistance of K. Wray Amon, BS, and Rita Garcia are greatly appreciated.

References
22 Cruikshank JM. The clinical importance of cardioselectivity and lipophilicly in beta-blockers. Am Heart J 1980; 100:161-78