Headache
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Journal compilation © 2008 American Headache Society

ISSN 0017-8748
doi: 10.1111/j.1526-4610.2007.00785.x
Published by Blackwell Publishing

Research Submission

Nebivolol and Metoprolol for Treating Migraine: An Advance on β-Blocker Treatment?

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Objective.—To evaluate the efficacy of oral treatment with nebivolol and metoprolol in the prophylaxis of migraine attacks.

Background.—β-Blockers such as propranolol and metoprolol are known to be effective in preventing migraine attacks. Following earlier observations of successful use of nebivolol in a few hypertensive patients with concomitant migraine, we conducted a prospective study to ascertain whether nebivolol would be effective and better tolerated, in a methodologically strict, randomized and double-blind setting.

Design and Methods.—Randomized, double-blind study in 30 patients with confirmed migraine diagnosis, a minimum 1-year history, onset prior to 50 years of age, written records of attacks for the previous 3 months, and minimum 2 attacks per month. Primary endpoint was frequency of attacks (prevention of migraine attacks) in the final 4 weeks of a 14-week treatment on full dose of metoprolol and nebivolol. Secondary endpoints were time to therapeutic effect, duration of attacks, intensity of headache, consumption of analgesics, evaluation of accompanying symptoms, migraine disability assessment, clinical global impression, quality of life, and responder rates. The statistical analysis was prospectively planned and conducted for all randomized patients.

Results.—Both metoprolol and nebivolol where similarly effective regarding the main endpoint (prevention of migraine attacks) as well as the secondary ones, and both had a fast onset of action, typically within 4 weeks from starting therapy, with responder rates increasing relatively little over time after the first 4 weeks. Use of acute pain medication decreased on both drugs, as well as accompanying symptoms. Both patients' and physicians' evaluations of disability and disease status were similarly favorable to the 2 treatments. Regarding safety, nebivolol was considerably better tolerated than metoprolol in terms of all reported events, treatment-related events, and event severity.

Conclusions.—Our results suggest that nebivolol is as effective as metoprolol in the prophylaxis of migraine attacks, with the advantages of being better tolerated and not requiring up-titration to achieve therapeutic levels. Further and larger trials should be conducted on nebivolol in the prevention of migraine attacks as it may provide an improvement in current migraine prophylaxis with β-blockers.

Key words: migraine, prophylaxis, nebivolol, metoprolol, randomized trial

(*Headache* 2008;48:118-125)

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Accepted for publication December 28, 2006.

Migraine is generally an episodic headache with certain associated features, such as sensitivity to light, sound, or movement, and often with nausea or vomiting accompanying the headache. None of the features are obligatory, and indeed given that the migraine aura is reported regularly in only about 15% of patients, the use of a migraine diary is often required for conclusive diagnosis.[1] Yet, the condition can be very disabling and has high socioeconomic and personal impacts, ranking among the 20 most disabling diseases worldwide, according to the World Health Organization.[2]

β-Blockers have been established as effective treatments for prophylaxis of migraine, with most evidence being available on propranolol, timolol, metoprolol, and nadolol, while acebutolol and pindolol have been shown to be ineffective.[3-8] Thus, some but not all β-blockers are effective in migraine prophylaxis and there is considerable variability in effectiveness across all prophylactic treatments.[9]

Nebivolol is a third-generation cardioselective β-1 blocker used in hypertension. It lacks intrinsic sympathomimetic activity and has little or no membrane-stabilizing activity, while its pharmacological profile[10,11] would suggest potential effectiveness and good tolerability in migraine prophylaxis. Compared to metoprolol and propranolol, nebivolol is a more selective β-1 blocker, with higher lipid solubility to enhance blood-brain-barrier penetration, as well as good endothelial-activated relaxation via the NO-system[12-17] unusual for this drug class, in addition to a highly favorable safety profile compared with other β-blockers.[18,19]

We have observed in our department over recent years that the use of nebivolol in hypertensive patients with concomitant migraine is invariably associated with improvement in migraine attacks. As this effect had not been reported previously, we decided to follow our observations with a prospective study of this drug.

MATERIALS, DESIGN, AND METHODS

Patient Selection and Blinding.—We enrolled patients referred to our outpatient department from primary care physicians in Central Western Germany from November 2003 to October 2004, following approval by the health authorities and the ethics committee of state chamber. External monitoring of our study conduct was performed by MedPharmTec-Services (Munich), with independent audit byGQS(Society for Quality Assurance in Clinical Research, Dortmund) and statistical analysis by Dr Heike Wöhling (Dabio GmbH, Höhenkirchen).

A total of 38 patients were screened, of whom 30 were eligible, randomized, and included in the intention-to-treat (ITT) analysis. Diagnosis was according to established criteria for migraine with/without aura (ICHD-II, codes 1.1-1.2),[2] with a minimum 1-year history, onset prior to 50 years of age, written record of attacks for the previous 3 months, and a minimum 2 attacks per month during screening. The full protocol selection criteria are displayed in Table 1. The total duration of the study was 30 weeks, with 12 weeks for collection of disease parameters for eligibility, of which the last 4 weeks were used as baseline for the study. After baseline, there followed a 2-week up-titration period for metoprolol (not required for nebivolol) and 14 weeks on full-dose of metoprolol or nebivolol and another 2 weeks at the end for down-titration of both drugs. To ensure blinding procedures were maintained, all medication was encapsulated and dispensed in identical blister-packs, with the addition of encapsulated double-placebos as required. The medication packs were appropriately labeled according to visit and week number to allow blinded up- and down-titration as follows:

Week 1: metoprolol 47.5 mg; OR nebivolol 5 mg

Week 2: metoprolol 95 mg; OR nebivolol 5 mg

Weeks 3–16: metoprolol 142.5 mg; OR nebivolol 5 mg

Week 17: metoprolol 95 mg; OR nebivolol 5 mg alternate days

Week 18: metoprolol 47.5 mg: OR nebivolol 5 mg every 2 days

Both drugs were obtained from their respective manufacturers (metoprolol: Beloc-Zoc®/Betaloc®, Astra-Zeneca; nebivolol: Nebilet®, Menarini). All treatment packs contained a sufficient overage to allow for missed/delayed visits and to aid in compliance checking, the latter prospectively set at 80%–120% of the prescribed dose. To optimize migraine diary completion and encourage treatment compliance, a short message system (SMS: cell-phone alert) was used to

Table 1.—Criteria for Patient Selection

Inclusion
Patients of either gender
Age between 18 and 65 years, inclusive
Confirmed migraine diagnosis (according to ICHD-II: 1.1 and 1.2)
Onset of migraine history <50 years of age
History of migraine >12 months
Documented records (number, duration, and severity of attacks) in previous 3 months
At least 2 migraine attacks/month in previous 3 months
2-6 migraine attacks in the 4 weeks prebaseline (screening period)
Adequate acute, symptomatic treatment of attacks (to remain unchanged)
Current contraception accepted if >3 months and unchanged during trial
Able and willing to provide written informed consent
Exclusion
Prophylactic migraine treatments in the previous 3 months
Concomitant β-blocker, calcium antagonist
Concomitant nondrug migraine treatment (p. ex. biofeedback, acupuncture, herbals)
Use of symptomatic treatment for more than 10 days per month
Change of current symptomatic treatment for migraine
History of hypersensitivity to metoprolol or nebivolol
History of alcohol or controlled substance abuse
Pregnancy or breast feeding
Fecund females without contraception
Congestive heart failure (NYHA class III-IV) or any serious cardiologic condition
Heart rate <50 bpm
Systolic blood pressure <100 mmHg
Peripheral arterial occlusive disease (PAOD Fontaine stage >IIa)
Uncontrolled diabetes mellitus
History of bronchospasm
Clinically relevant abnormal laboratory values (hematology, biochemistry, urinalysis)
Participation in another trial in previous 30 days
Any other severe condition (including cancer), according to clinician's opinion

remind patients to complete the diaries and to take the medication at appropriate times, throughout the study.

All patients were fully medically evaluated during the required 7 study visits, from baseline to the end of study, including laboratory assessments and electrocardiogram (ECG).

Statistics.—The aim of the study was to evaluate treatment effect on the number of migraine attacks as reported on patients' migraine diaries. The endpoint was the last 4 weeks of the 14-week treatment on full-dose medication (weeks 12–16). Secondary endpoints were time to therapeutic effect (evaluated 4-weekly), duration of attacks, intensity of headache, consumption of analgesics, evaluation of accompanying symptoms, migraine disability assessment (MIDAS),[20] clinical global impression (CGI: change/improvement of condition) and patients' global impression (PGI: impairment of condition),[21] quality of life,[22] and responder rates, defined as a decrease of at least 50% in number of attacks from baseline to endpoint.

The statistical analysis was prospectively planned and conducted on an ITT basis, in all randomized patients. As this was the first ever study of nebivolol in migraine, no previous data existed on expected treatment effect. Our intention was to test whether the nebivolol effects would be different from those of an established β-blocker, and thus provide information for subsequent large pivotal trials, if warranted by the results. Therefore, a formal sample size calculation was not possible, but we felt sure that a total of 30 patients would yield clinically meaningful differences, should these exist, between the 2 groups over a 14-week full-dose treatment period. Frequency tables were compared between the 2 groups by Fisher test. Mean values were compared between groups using the Wilcoxon Mann-Whitney *U* test. All tests were planned as 2-sided with only the primary efficacy variable (frequency of attacks) meriting a formal *P* value, all other variables serving as estimates of plausibility of the main variable. Randomization was computer-generated in blocks of 4 and patients were assigned random treatment sequentially.

All data were obtained from standardized diary cards, except the SF-36 questionnaire, the global impressions (patient and doctor), and the adverse events reporting, which were completed during the clinic visits. Other than the standard instruments of assessment, attack severity was recorded on a 100-mm visual analogue scale (VAS). Safety was evaluated by adverse event monitoring and frequency tables. All key instruments of assessment have been validated and all materials provided to patients were written in lay language.

RESULTS

On entry, the groups were comparable regarding demographic, general clinical, and migraine

Table 2.—Disposition, Demographics, and Status of Patients at Baseline

Screened (n)		38	
Screen failures (n)		8	
	ALL	Metoprolol	Nebivolol
Randomized (ITT population); n (%)	30 (100)	14 (47)	16 (53)
Failed to complete 12-week treatment	2 (7)	1 (7)	1 (6)
Completed treatment	28 (93)	13 (93)	15 (94)
Age: mean years (SD)	39 (10)	41(7)	38 (13)
Females: n (%)	26 (87)	13 (100)	12 (75)
Height: mean cm (SD)	169 (8)	165 (8)	172 (8)
Weight: mean kg (SD)	65 (12)	64 (10)	65 (14)
Heart rate: mean bpm (SD)	67 (7)	65 (5)	68 (8)
Systolic blood pressure: mean mmHg (SD)	119 (12)	118 (11)	120 (13)
Diastolic blood pressure: mean mmHg (SD)	75 (7)	74 (6)	75 (8)
History of migraine: mean years (SD)	17 (10)	19 (10)	15 (11)
Headache with aura/other symptoms: n (%)	29 (97)	14 (100)	15 (94)
Migraine attacks 1 month preentry: mean (SD)	3.4 (1)	3.4 (1)	3.3 (1)
MIDAS at baseline[#]: n (%) No impairment	–	–	–
Mild impairment	2 (7)	–	2 (13)
Moderate impairment	6 (20)	4 (29)	2 (13)
Severe impairment	22 (73)	10 (71)	12 (75)
Days with headache (previous 3 months): mean (SD)	18 (11)	18 (10)	18 (11)
Pain intensity (previous 3 months): mean (SD)	8 (1)	8 (1)	8 (1)
Baseline quality of life (SF-36): mean (SD) physical	38 (19)	37 (8)	39 (11)
Mental	38 (11)	39 (11)	37 (11)

ITT = intention-to-treat; bpm = beats per minute; MIDAS = migraine disability assessment; SF-36 = 36-item short form health survey.
[#]5-item questionnaire with scores 0-5 (Grade I), 6-10 (Grade II), 11-20 (Grade III), and 21+ (Grade IV), plus 2 questions on number of days with headache and pain intensity (1–10 score).
No statistical difference between groups in any demographic or disease status parameters at baseline.

parameters (Table 2), except that there were no males in the metoprolol group (4 males on nebivolol), and the population characteristics reflected those attending primary care centers for treatment of migraine. There were no statistically significant differences between groups at entry.

All but 4 patients were female, the mean age being 39 years with a mean 17-year migraine history, most patients (97%) presenting with migraine with aura (ICHD-II code 1.2)2 and other accompanying symptoms, with a mean 18 days of headache per month in the previous 3 months.

At endpoint (14 weeks' treatment on full dose), migraine attacks decreased similarly in the 2 treatment groups relative to baseline (Table 3), from a mean 3.4 to 1.3 attacks (metoprolol) and from 3.3 to 1.6 attacks (nebivolol). Most of the improvement was recorded during the first 4 weeks of treatment. The disability scores (MIDAS) also showed similar improvement results for both groups, as did the SF-36 questionnaire results. On the whole, evaluations tended to favor only slightly one or the other treatment, none of the differences reaching formal statistical significance. For instance, slightly fewer patients on nebivolol (67%) than on metoprolol (77%) were taking any pain medication during the last 4 weeks of the study, which result is corroborated by the slightly lower recorded attack severity (VAS: mean 54 mm for metoprolol and 50 for nebivolol), yet responder rates were slightly higher for metoprolol (57%) than for nebivolol (50%). Both the PGI (general impairment; Fig. 1) and the CGI (change or improvement; Fig. 2) confirmed the effects of the 2 treatments, with the CGI suggesting that there is a slight penalty on improvement for metoprolol-treated

Table 3.—Results

	Metoprolol (n = 14)	Nebivolol (n = 16)
Primary endpoint		
Frequency of migraine attacks: mean (SD)*	1.3 (1.0)	1.6 (1.5)
Secondary endpoints		
Onset of action (attacks during weeks 0–4): mean (SD)	1.9 (1.2)	2.2 (1.3)
Responder rate at endpoint: %	57	50
Duration of migraine attacks at endpoint: mean hours (SD)	26 (55)	15 (14)
Severity at endpoint[#]: mean (SD)	54 (16)	50 (24)
Patients using pain medication at endpoint: n (%)	10 (77)	10 (67)
Migraine Disability Assessment (MIDAS)		
No impairment: n (%)	2 (15)	2 (13)
Mild impairment: n (%)	5 (39)	2 (13)
Moderate impairment: n (%)	4 (31)	6 (40)
Severe impairment: n (%)	2 (15)	5 (33)
Days with headache: mean (SD)	13 (18)	14 (14)
Pain intensity: mean (SD)	6 (2)	6 (3)
Quality of life (SF-36): mean (SD)		
Physical	46 (7)	50 (10)
Mental	48 (8)	45 (13)

*Difference between the 2 groups: not statistically significant (Wilcoxon Mann-Whitney *U* test).
All endpoints measured at 12–16 weeks.
[#]Measured on 100-mm visual analogue scale.

patients, possibly due to lack of tolerability, which results on the metoprolol group displaying smaller changes at the beginning of treatment (weeks 0-4), whereas the nebivolol group showed a more even distribution across the improvement range.

Although most patients completed the treatment and good compliance was achieved for all patients, there was a noticeable difference with regard to general tolerability in favor of nebivolol (Table 4). One patient in each group was withdrawn from treatment due to an adverse event, 1 due to deterioration of migraine (metoprolol group) and 1 due to sleep disturbance (nebivolol group). The incidence of treatment-related events was almost double on metoprolol (30 events/13 patients) relative to nebivolol (15 events/11 patients) and there was a clear excess reporting of moderate or severe events on metoprolol (86% and 43%, respectively) compared with nebivolol (38% and 13%, respectively). As expected, the cardiovascular system was the main target for those events reported by multiple patients, all other events being reported by only 1 individual in either group. The most common event in both groups was fatigue (metoprolol: 79%; nebivolol: 44%) and bradycardia (35% metoprolol; 6% nebivolol). Only fatigue was reported by more than 1 patient on nebivolol. Most events, regardless of relationship to treatment, occurred during the first 4 weeks of treatment for nebivolol-treated patients and remained relatively low thereafter, while despite the gradual up-titration of metoprolol,

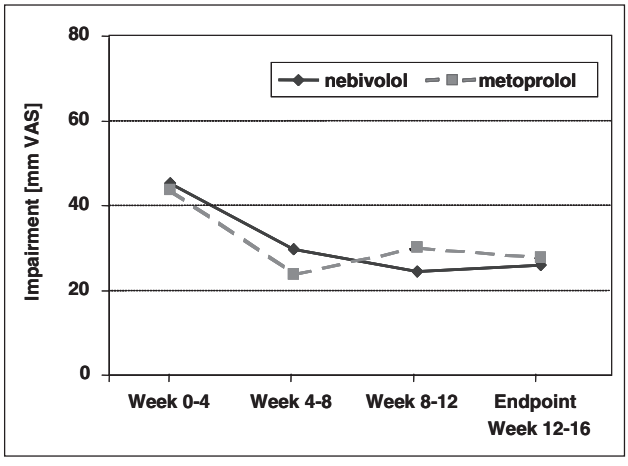

Fig 1.—Patients' global impression (PGI: impairment of the general condition).

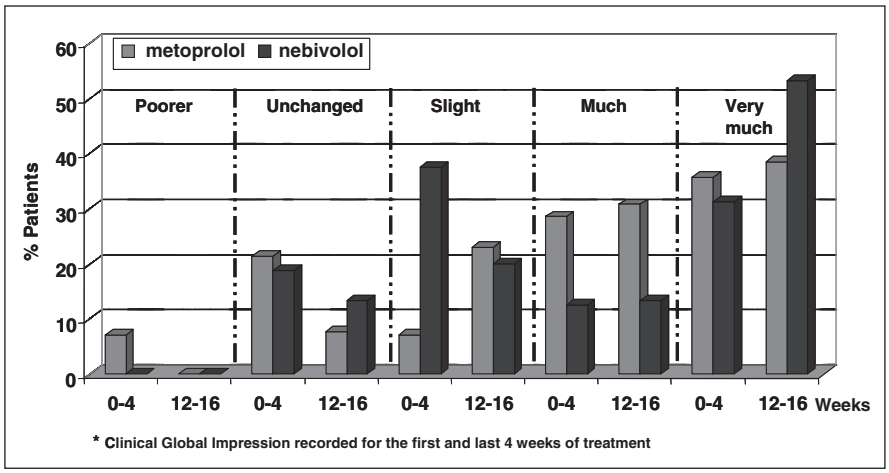

Fig 2.—Doctor's evaluation (CGI: change/improvement in condition).

occurrence of events remained relatively high for the first 2 months after starting treatment, gradually decreasing thereafter (Fig. 3). Regarding changes in laboratory parameters and ECG, there were no clinically relevant or statistically significant changes for either treatment group.

COMMENTS

To date, there is no published evidence on the effect of nebivolol for the prophylaxis of migraine attacks, although there is ample evidence that some, albeit not all β-blockers are effective prophylactic treatments, as reflected in recent evidence-based advice to family doctors by the American College of Physicians and American Society of Internal Medicine.[3] Although nebivolol is a relatively newer, third-generation β-1 selective blocker approved, as all others, for the treatment of hypertension, we were interested in its characteristics of high blood-brain-barrier penetration, good endothelial-activated relaxation and low risk of orthostatic hypotension.[18] Our theory was that, if these characteristics had a

Table 4.—Adverse Events

	Metoprolol (n = 14) N (%)	Nebivolol (n = 16) N (%)
Total number of reported events	44	32
Total number of treatment-related events*	30	15
Patients with treatment-related events*	13 (93)	11 (69)
Patients reporting mild events*	1 (7)	4 (25)
Patients reporting moderate events*	12 (86)	6 (38)
Patients reporting severe events*	6 (43)	2 (13)
Patient withdrawal due to events#	1 (7)	1 (6)
Most common reported events§*		
Fatigue	11 (79)	7 (44)
Bradycardia	5 (35)	1 (6)
Hypotension	2 (14)	1 (6)
Supraventricular extrasystoles	2 (14)	–

*Possibly, probably, or definitely related to treatment.
#1 deterioration of migraine (metoprolol); 1 sleep disturbance (nebivolol).
§Reported by more than 1 patient in either treatment group.

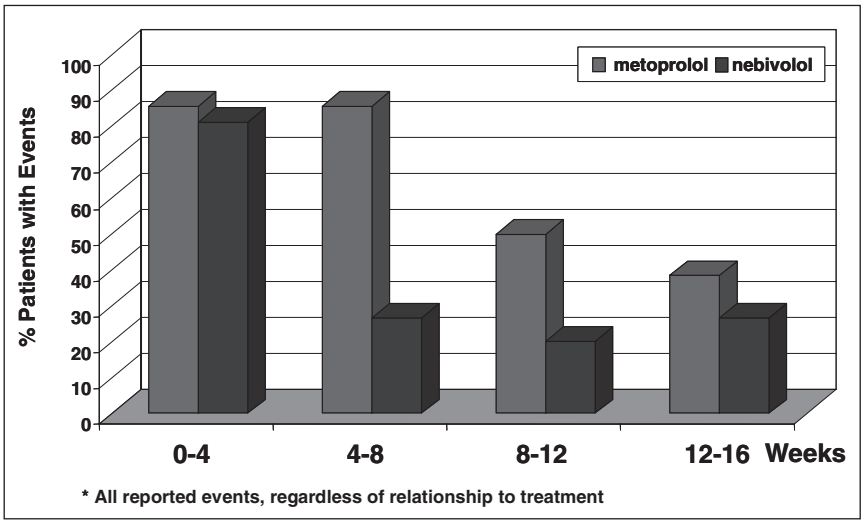

Fig 3.—Temporal occurrence of events.

practical effect in the clinic, they would confer near-ideal conditions to prevent migraine attacks with a better safety profile than we see with current β-blockade. Our experience in using this drug in a few hypertensive patients with migraine gave us the impetus to conduct the current early trial. Yet, we were cautious about pharmacological properties not bearing fruits in therapeutic trials, in which case there was a risk of one—previously untested—treatment (nebivolol) not having an effect, which would result in a large number of treatment withdrawals over the 18-week total treatment period (including up- and down-titration). We therefore included a sufficient number of patients that would allow us to detect only major, clinically meaningful differences in terms of migraine prophylaxis. Thus, we are unable to interpret the nuances of the therapeutic profile of nebivolol with greater precision, other than report a robust suggestion that nebivolol is a β-blocker with, previously not reported, prophylactic effects in migraine sufferers. Importantly, the milder effects of nebivolol on the usual cardiovascular targets of β-blockade, expressed as adverse events in these patients, together with the possibility of starting treatment without the need to up-titrate the dose to achieve therapeutic levels would make a major impact on our current strategies for migraine prevention, if its efficacy can be confirmed in a wider population of migraineurs.

This study strongly suggests that, regarding prevention of migraine attacks, nebivolol is similar to metoprolol. Our data also strongly suggest that nebivolol is considerably more tolerable than metoprolol, while not requiring any up-titration of dose, both of which would facilitate the management of migraine patients who can be sensitive to the introduction and maintenance of β-blockade. What with oral analgesics accounting for the bulk of oral medications in migraine attacks (all our patients were taking analgesics at baseline, data not shown), only 60% of patients on nebivolol (86% on metoprolol) were taking any analgesics at the end of the study, which is a considerable improvement for this condition.

We selected our patients carefully and undertook evaluations for 3 months before considering them eligible, to reduce the disease variability that can be high in this setting, and we further tried to enhance the quality of the data by using easy-to-follow diaries with a cell-phone alerting system and regular clinic visits to ensure correct completion of the diaries and full datasets. Only 2 patients did not yield complete information (withdrawals due to events, 1 from each group) and their last evaluations were carried forward for the ITT analysis, thus the final database is not biased in favor of either treatment group due to incomplete datasets.

CONCLUSIONS

Nebivolol is a selective β-blocker with prophylactic effects on migraine, similar to those of metoprolol, in terms of attack prevention. The tolerability of

nebivolol in migraine prophylaxis will be an advance in current therapy, if its efficacy can be confirmed in larger pivotal trials, which must now be performed, to ascertain the nuances of its efficacy profile in wider populations with migraine, relative to other current treatments and placebo.

Acknowledgment: Dr. Schellenberg is supported by a research grant from Berlin-Chemie AG.
Conflict of Interest: None

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