Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study

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The objective of the present study was to assess the efficacy of bisoprolol in migraine prophylaxis. A double-blind placebo-controlled study was conducted in 226 patients with migraine with or without aura, a migraine history of at least 2 years and at least 3 documented attacks during the 28 days run-in period. The duration of treatment was 12 weeks following an initial 28 days' run-in period. Patients reported the number of attacks and their severity in a diary. Treatment with bisoprolol 5 mg resulted in a significant reduction in the frequency of migraine attacks (39% vs 22%) compared to placebo treatment (p<0.05). Treatment had no effect on the duration and severity of the attacks. Bisoprolol was well tolerated. ð *Beta-blockade, bisoprolol, migraine, prophylaxis*

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The goals of migraine therapy are amelioration of the symptoms associated with the acute attack and reduction of the number of attacks (1). Prophylactic treatment should be considered if the patient has two or more migraine attacks per month or if the severity of the attacks is debilitating for a period of 24 h or longer despite acute treatment. Clinical trials have shown that some beta-blockers are effective in the prevention of migraine (for review, see ref. 1). There is no correlation between the efficacy of these drugs and their potential to pass the blood-brain barrier, membrane-stabilizing properties, ability to block 5HT receptors or beta-receptor selectivity. Beta-blockers with intrinsic sympathetic activity are ineffective in migraine treatment (1).

In the present study, we compared the efficacy of 5 mg and 10 mg bisoprolol, a beta-1-selective-blocker, and placebo in reducing the frequency of attacks of migraine with or without aura. We also evaluated the effect of bisoprolol on the duration and severity of the migraine attacks.

Patients and methods

Patients of either sex, 18 and 75 years old, were included if (i) they suffered from migraine with or without aura (2); (ii) had a migraine history of a least 2 years' duration; and (iii) developed at least three documented migraine attacks during the 28 day run-in period. Patients who were already using drugs for the prevention of migraine or who were being treated with cardiovascular drugs were excluded from the study. Other exclusion criteria were the usual contraindications for beta-blocker use or hypersensitivity to these agents. During the study period (including the placebo run-in period) the patients were not allowed to use any other drugs for migraine prophylaxis. Patients should have had not less than 3 and not more than 10 migraine attacks during the run-in period. They were asked to take the trial medication and needed to complete Headache Report Forms on a regular basis. All patients gave their prior written or verbal informed consent, in accordance with the local requirements. The protocol was approved by the local ethics committees.

The study was performed in accordance with the World Medical Association Declarations of Helsinki (1964) and Tokyo (1975). It was carried out in 14 centres in France, The Netherlands, Belgium and Spain, and was a randomized double-blind placebo-controlled study. The study duration was 16 weeks: a single blind placebo run-in period of 4 weeks was followed by a treatment period of 12 weeks. The patients were seen at 4-week intervals at the out-patient clinic. Patients who met the inclusion criteria were instructed to take one tablet every day in the morning, of the identical tablets of bisoprolol 5 mg, bisoprolol 10 mg or placebo.

Efficacy was assessed both subjectively and objectively: patients were asked to keep a diagnostic headache diary recording all periods of headache during the entire study period. Attacks had to be recorded in detail as regards duration, intensity, unilateral and/or

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Table 1. Patient characteristics.

	Bisoprolol 5 mg	Bisoprolol 10 mg	Placebo	Total
Number	74	77	75	226
Male/female	16/58	13/64	11/64	40/186
Mean age (years)	38.3	38.9	38.9	38.7
Height (cm)	165.8	166.6	163.6	165.4
Weight (kg)	62.5	65.5	62.7	63.6
Family history of migraine	28	27	26	81
Age at onset (years)	18.1	20.1	22.7	20.3
Migraine with aura (N)	17	22	12	51
Migraine without aura	57	55	63	175
Mean duration of attacks (h)	20.6±18.8	25.8±21.5	23.4±17.5	23.3±19.4
Severity: (N)				
mild (with aura)	4	2	1	7

moderate	24	30	32	86
severe	46	45	42	133

pulsating pain, nausea, vomiting, photophobia, phonophobia. They were allowed to use their usual acute medication for relief of pain and vomiting during each attack, but had to keep a detailed account of the drug consumption in their diaries. In addition, physicians recorded these data in the case record forms for the run-in period as well as for the treatment period. The headache data were recorded at baseline and during control visits after 4, 8 and 12 weeks in the treatment period. Baseline examinations included physical examination, general clinical status report on concomitant disease(s), concomitant medication(s), cardiovascular findings (blood pressure, heart rate, ECG), as well as on biochemical and haematological findings. At control visits, cardiovascular findings were recorded, compliance, efficacy and tolerability were rated, and questions were asked about the patients' evaluation of their well-being, adverse effects, and changes as to concomitant medication.

Statistical analysis

Data are reported as means±l standard deviation of the mean, unless noted otherwise. For the main target variables no statistically significant differences were found between the intention-to-treat and per protocol populations. The results of the intention-to-treat analysis are therefore reported. The comparability of treatment groups was analysed for demographic and other baseline data using Chi-square tests, two-tailed Fisher Exact tests, analyses of variance and Kruskal-Wallis tests as appropriate. The efficacy was analysed with covariance analysis, with the run-in period as a covariant; the frequency of migraine attacks and the duration of attacks were analysed using two-sided t-tests for pairwise comparison of adjusted means. All data presented here were compiled using the Statistical Analysis System (SAS Institute, Cary, NC).

Results

The total number of patients randomized was 226 (men 18% and women 82%, mean age 38.7 years, sanging from 14 to 68 years) (Table 1). Migraine with aura was diagnosed in 23% of patients (mean age 20 wears) and migraine without aura in 175 (77%). The mean frequency of migraine attacks per month in the 2 years prior to the study was reported to be 5.5±2.8. The attacks were rated moderate to severe by almost dl patients; in 7 patients with aura the attacks were rated as mild. The mean duration of attacks (23.3±19.4 h) did not differ significantly between the treatment groups.

Evaluation of efficacy

Endpoint analysis (i.e. analysis of the data in the period from randomization to the last observation) shows that the frequency of migraine attacks is significantly reduced in patients using bisoprolol. The frequency of migraine attacks during the 12 week double-blind treatment period was 2.6±1.7 and 2.6±1.9 (4-week average) on bisoprolol 5 mg and 10 mg respectively, and 3.2±1.8 (4-week average) on placebo. The differences in the reduction of the frequency of migraine attacks (39% vs 22%) were statistically significant for both active treatment groups compared to placebo ($p<0.05$). The duration of attacks was generally shorter during treatment with

bisoprolol 5 mg (9.5±6.5 h) compared to bisoprolol 10 mg (14.3±21.5 h) and placebo (13.2±11.9 h). There was no statistical difference between the intention-to-treat and per protocol analysis. The duration of the attack with 5 mg bisoprolol was significantly reduced compared to placebo (p<0.05) (CI -8.3, -0.2), but not significant for bisoprolol 10 mg (p=0.63) (CI -5.0, -3.0). There was no statistically significant reduction in the severity of headaches.

Table 2. Frequency of migraine attacks per month.

Period	Bisoprolol 5 mg	Bisoprolol 10 mg	Placebo
Last 2 years	5.6±2.8	5.6±2.9	5.2±2.4
Run-in	4.4±1.6	4.2±1.9	4.0±1.8
1–4 weeks	3.1 ±2.0	3.1 ±2.3	3.5±2.0
5–8 weeks	2.5±2.2*	2.3±1.7*	3.0±2.1
9–12 weeks	2.3±l.8*	2.3±2.1*	3.2±1.7
End-point	2.7±1.7*	2.6± 1.9*	3.2±1.8
End-point (adj.)	2.6*	2.6*	3.2

*p<0.05. Adjusted means comparisons endpoint versus paseline: Bisoprolol 5 mg versus placebo (p=0.029). Bisoprolol 10 mg versus placebo (p=0,032). 95% confidence intervals for treatment differences: Bisoprolol 5 mg versus placebo (-1.05, -0.05). Bisoprolol 10 mg versus placebo (-1.06, -0.06).

Safety and tolerance

Thirty-one patients dropped out of the study, 11 from the bisoprolol 5 mg group patients, 9 from the bisoprolol 10 mg and 11 from the placebo group. From these drop-outs, 4, 7 and 4 patients had adverse events, respectively. In the placebo group, 4 patients discontinued the trial because of inefficacy. One or more adverse events were reported by 84 patients (37%). Of those patients there were 26 (35%) on bisoprolol 5 mg, 33 (43%) on bisoprolol 10 mg, and 25 (33%) on placebo. The tolerability of study medication was rated "very good" by 81–82% of the patients on bisoprolol, and by 84% of the patients using placebo.

The most frequent adverse events were fatigue and dizziness. Fatigue did not occur more frequently in the bisoprolol groups than in the placebo group, with (bisoprolol 5 mg: n=7; bisoprolol 10 mg: n=9; placebo n=7). Dizziness was reported by 6, 5 and 4 patients, respectively. Statistically significant difference (p<0.05). Heart rate, systolic and diastolic blood pressure were significantly lower (p<0.05) after bisoprolol (either dose) than after placebo (Table 3).

Discussion

The results of this study indicate a prophylactic effect of a once daily dose of bisoprolol 5 mg and bisoprolol l0 mg. The frequency of migraine attacks wait reduced. This finding is consistent with the result of other studies of beta-adrenergic blockers used for migraine prophylaxis. The primary purpose of prophylactic migraine therapy is reduction of the frequency of attacks. The response rate to placebo, 22% is consistent with that reported in the literature (3). The response to

bisoprolol (5 mg and 10 mg) is 38–39%, similar to the efficacy of other beta-blockers (1).

The mechanism of actions of beta-blockers in migraine prophylaxis is unknown, although several modes of action have been proposed (4, 5). Vascular and central effects on cortical and subcortical pathways are suggested (6, 7).

Bisoprolol is a beta-1-selective beta-blocker without intrinsic sympathico-mimetic activity (ISA). Owing to its high beta-1-selectivity, an influence on periphery arteries is unlikely, as no significant effects of bisoprolol on peripheral blood flow has been demonstrated previously (8, 9). On the other hand, the significance of beta-1-selectivity in migraine prophylaxis is not clear, as the non-selective beta-blockers propranolol and timolol have been shown to be equally effective in migraine prophylaxis (10). It seems unlikely that migraine prophylaxis with beta-blockers depends on a peripheral effect on arteries.

It remains undetermined what is the dominant mechanism responsible for the effects of beta-blockers. Feelings of stress are frequently reported as a provoking factor for a migraine attack. As stress leads to an increase in catecholamine and all beta-blockers have in common their ability to block the effects of catecholamines, this very basic mechanism of action of beta-blockers might be the most dominant mechanism in this indication. The not very impressive response rate may reflect that only subgroups profit from prophylactic treatment with beta-blockers.

We did not demonstrate that bisoprolol 10 mg is superior to 5 mg bisoprolol. At a 5 mg dose, the maximal benefit in reducing attack frequency was achieved. Interestingly, we found that bisoprolol 5 mg was superior to the 10 mg dose in reducing the attack duration. We suspect that difference at base-line as well as the large standard deviation in the 10 mg groups (attack duration=14.3±21.5 h) may have contributed to the apparent superiority of the 5 mg dose in reducing attack duration.

Table 3. Changes in heart rate and blood pressure.

	Baseline	Bisoprolol 5mg	Baseline	Bisoprolol 10mg	Baseline	Placebo
Heart rate (bpm±sd)	76.2±10.9	67.4±10.3*	73.4±8.7	64.0±9.5*	76.4±10.6	73.9±11.9
SBP (mmHg±sd)	122.6±14.3	113±12.9*	122.9±13.9	111.8±13.9*	125.8+15.9	122.1±13.8
DBP (mmHg±sd)	77.6±10.6	71.8±10.6*	77.3±7.5	71.0±10.3*	78,8±9.4	77.1±10.5

*$P<0.05$. SBP=Systolic Blood Pressure. DBP=Diastolic Blood Pressure.

This study confirms previous findings that 5 mg bisoprolol is effective in migraine prophylaxis, and is comparable to 100 mg metoprolol (10). This dose is also used for anxiety (11), suggesting that 5 mg bisoprolol is an optimal dose for the treatment of central nervous system conditions.

Drugs used in disease prevention should be safe and well tolerated. The present

study demonstrates that bisoprolol 5 mg is safe and well tolerated. Also, it is superior to placebo in reducing migraine attack frequency.

We conclude that bisoprolol is an effective drug for the prophylactic treatment of migraine attacks.

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