Chapter 54

β-Adrenoceptor Blocking Drugs in Migraine Prophylaxis

Peer Tfelt-Hansen and Paul Rolan

β-Blockers (β-adrenoceptor antagonists) were introduced into medicine for the treatment of angina pectoris and cardiac arrhythmias, but they have subsequently proved valuable in many other conditions, including hypertension and migraine. The hypotensive action of these drugs was not predicted from their pharmacologic properties and was observed initially in patients receiving treatment for angina (43). Similarly, the value of propranolol in migraine was discovered in 1966 by Rabkin (45), who reported that migraine improved in a patient receiving propranolol for angina pectoris. Many controlled trials have since confirmed that propranolol is effective in the prophylaxis of migraine, and other β-blocking drugs—namely nadolol, metoprolol, atenolol, timolol, and bisoprolol—also have been demonstrated to be effective in the prophylaxis of migraine. In contrast, several β-blocking drugs with partial agonist activity—alprenolol, oxprenolol, pindolol, and acebutolol—have not been demonstrated to be effective in migraine prophylaxis. Several reviews of the prophylactic use of β-blocking drugs in the treatment of migraine have been published (3,31,32,51,58, 60,64).

The mode of action of β-blocking drugs in migraine remains to be elucidated, but the effective drugs are at present the drugs of first choice in migraine prophylaxis.

PHARMACOLOGIC BACKGROUND

The adrenergic receptors on which noradrenaline, the principal neurotransmitter at the peripheral sympathetic synapses, evokes responses have been classified as α and β types (1). α-Receptors are abundant in the resistance vessels of the skin, mucosa, and kidney and result in vasoconstriction when stimulated. β-Receptors have been subdivided into β_1-receptors, which predominate in the heart subserving myocardial excitation, and β_2-receptors in the arteries of the skeletal muscle and bronchi, subserving vasodilatation and bronchodilatation (30).

A β-blocking drug, for example, propranolol, which has equal affinity for β_1- and β_2-receptors, is described as being a nonselective drug, whereas agents such as metoprolol and atenolol have greater affinity for β_1- than for β_2-receptors and are examples of β_1-selective blocking drugs, even though the selectivity is not absolute. Propranolol is a pure antagonist and has no capacity to activate β-adrenoceptors. Several β-blocking drugs, for example, pindolol and acebutolol, activate β-receptors, but the intrinsic activities of these drugs are less than the full agonist, such as isoprenaline. These partial agonists are said to have intrinsic sympathomimetic activity (34). Some β-blocking drugs possess properties in addition to their effect in blocking β-receptors. Membrane-stabilizing activity has a direct effect on nervous tissue in the heart and is similar to the effect of local anesthetics. Membrane-stabilizing activity is present for some of these agents (Table 54-1).

There are considerable differences in the pharmacokinetics of the β-blocking drugs. The difference that could be important in the treatment of migraine might be expected to relate to the penetration of the drugs into the central nervous system. The entry of β-blocking drugs into the central nervous system depends on protein binding, ionization, and lipid solubility. Of these, the most important factor determining entry into the brain is lipid solubility, for which there are great differences in β-blocking drugs. Propranolol, alprenolol, oxprenolol, and metoprolol are extremely lipophilic and readily pass into the central nervous system. In contrast, atenolol is much more hydrophilic and passes into the central nervous system poorly (11).

For many years it has been suggested that 5-hydroxytryptamine (5-HT) may be involved in the development of a migraine attack, and several β-blocking drugs have substantial affinity for the 5-HT binding site in the

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TABLE 54-1 Efficacy of β-Adrenoceptor Blockers in Migraine Prophylaxis and Their Properties

	Efficacy in Migraine	*Penetration into CNS*	*MSA*	*Cardioselective*	*PAA*	*Affinity for 5-HT in CNS*[a]
Alprenolol	No	Yes	Yes	No	Yes	High
Oxprenolol	No	Yes	Yes	No	Yes	High
Propranolol	Yes	Yes	Yes	No	No	High
Pindolol	No	Yes	Yes	No	Yes	High
Nadolol	Yes	—	No	No	No	—
Timolol	Yes	Yes	No	No	No	—
Acebutolol	No	Yes	Yes	Yes	Yes	—
Atenolol	Yes	Poorly	No	Yes	No	Low
Metoprolol	Yes	Yes	No	Yes	No	—
Practolol	?[b]	Poorly	No	Yes	Yes	—
Bisoprolol	Yes	—	—	Yes	No	—

[a] As judged from inhibition of specific ^{3}H-5-HT binding to crude synaptic membrane from rats (35).
[b] Only an open trial reported efficacy of practolol before it was withdrawn due to side effects.
Abbreviations: MSA, membrane-stabilizing activity; PAA, partial agonist activity.

brain (see Table 54-1). Thus, alprenolol, oxprenolol, propranolol, and pindolol have high affinity for these binding sites, whereas atenolol has low affinity.

As clearly illustrated in Table 54-1 the fact that a β-blocking drug is effective in migraine prophylaxis does not depend on whether it penetrates easily into the central nervous system, is cardioselective, has membrane-stabilizing activity or binds to 5-HT sites in the brain. The only common property that the active β-blocking drugs have in common is the lack of partial agonist activity. It does seem that partial agonist activity prevents β-blocking drugs from exerting a beneficial effect in migraine prophylaxis, but the mechanism behind this remains obscure.

On the basis of one trial, it has even been questioned whether the efficacy of β-blocking drugs in migraine is related to blockade of β-adrenoceptors (55). It was reported that propranolol, in the clinically used racemic form *d*,*l*-propranolol, and *d*-propranolol, which has only a slight β-blocking effect, were significantly superior to placebo with no differences between the two forms of propranolol, indicating that an effect not related to β-blockade was an important factor in the action of propranolol in the prophylaxis of migraine. However, when the results were reanalyzed using conventional statistical methods, there was a significant effect for *d*,*l*-propranolol on the headache index, but no significant effect for *d*-propranolol compared with placebo (58). For headache days there were no difference between the three treatments. The trial thus did indicate that the β-blocking effect per se is important in migraine prophylaxis.

WHAT IS THE MODE OF ACTION OF β-BLOCKING DRUGS IN MIGRAINE?

It was originally hypothesized that β-blocking drugs were effective in migraine prophylaxis because they inhibit the vasodilatory phase of migraine. How this should be reconciled with the effectiveness of β-blocking drugs in migraine with aura, where a decrease in cerebral blood flow is present, is not clear. In a study on migraine with aura there was no increase in aura without headache (27), and one might presume that the preventive effect of β-blocking drugs must occur on the first phase of the attack, which clearly is initiated in the central nervous system.

There are some indications that β-blocking drugs exert their effect on the central catecholaminergic system. The contingent negative variation (CNV)—an event-related, slow, negative cerebral potential recorded over the scalp in simple reaction time tasks with warning stimulants—is significantly increased and its habituation reduced in untreated migraine patients in comparison with controls and tension-type headache sufferers. The CNV returned to normal values after migraine prophylaxis with β-blocking drugs (50). Furthermore, after 3 months of treatment with metoprolol or propranolol, it was shown that there was a significant correlation between CNV before treatment and the clinical response of β-blocking drugs: patients with higher CNVs tended to respond better to therapy. This indicates that in patients with central catecholaminergic hyperactivity, the chance of a positive response to β-blocking drugs in migraine prophylaxis is better and indirectly points to an effect in the central nervous system being responsible for the migraine prophylactic effect. In a recent study similar effects of β-blockers was found on intensity dependence of auditory evoked cortical potentials in migraine patients (49).

PHARMACOKINETICS OF β-BLOCKING DRUGS EFFECTIVE IN MIGRAINE

Propranolol is highly lipophilic and is well absorbed. Much of the drug is metabolized by the liver during its first

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passage through the portal circulation, resulting in 25% bioavailability. There is great interindividual variation in the presystemic clearance of propranolol, resulting in enormous variability in plasma concentration after oral administration of the drug (approximately 20-fold). Propranolol is extensively metabolized, and one of the products of hepatic metabolism is 4-hydroxypropranolol, which possess some β-blocking effect. The half-life in plasma is about 4 hours but, as in hypertension, the drug is effective when administered twice daily. A sustained-release formulation of propranolol has been developed to maintain the concentration of propranolol in plasma over a 24-hour period (21).

Nadolol is hydrophilic and incompletely absorbed. The bioavailability is 35%, and interindividual variability in bioavailability is less than with propranolol. Nadolol is not extensively metabolized and is largely excreted intact in the urine. The half-life of nadolol in plasma is in the range of 12 to 20 hours, and it can consequently be administered once daily. Nadolol may accumulate in patients with renal failure.

Timolol is well absorbed and is subject to moderate first-pass metabolism, resulting in a bioavailability of 50%. It is metabolized by the liver, and the half-life in plasma is about 4 hours. It can be administered twice daily.

Metoprolol is well absorbed, but there is considerable first-pass metabolism, resulting in about 40% bioavailability. Its metabolism is subject to a genetic polymorphism with about 6% of the Caucasian population being poor metabolizers (26). As a result, plasma concentrations of the drug vary widely (up to 17-fold) and there is recent retrospective evidence that poor metabolizers may have a significantly higher adverse effect rate (67). The plasma half-life of metoprolol is 3 to 4 hours. In standard formulation it can be given twice daily. A sustained-released formulation of metoprolol has been developed to maintain the concentration in plasma over a 24-hour period; this formulation can be given once daily.

Atenolol is incompletely absorbed, but most of the absorbed drug reaches the systemic circulation, resulting in a bioavailability of 50%. There is relatively little variation in the plasma concentration of atenolol, with a fourfold range between patients. The drug is excreted largely unchanged in the urine, and the half-life in plasma is 5 to 8 hours. It can be given once daily and may accumulate in patients with renal failure.

Bisoprolol is 90% bioavailable and is eliminated by both renal and hepatic mechanisms. Its long half-life makes it suitable for administration once daily.

RESULTS OF CLINICAL TRIALS WITH β-BLOCKING DRUGS IN MIGRAINE

On the basis of controlled clinical trials in which a β-blocking drug was compared with a placebo, it can be concluded that propranolol, metoprolol, timolol, nadolol, atenolol, and bisoprolol have documented efficacy in migraine prophylaxis (3).

The main effect has been to reduce the frequency of attacks in patients with migraine with aura and without aura. In most trials, a mixed population of patients with migraine with aura and without aura have been included, but some trials (27,42,59) have studied these two forms of migraine separately and found similar results, as in the mixed patient populations. There is thus no reason to believe that the two forms of migraine respond differently to prophylaxis with β-blocking drugs.

In this chapter, only trials in which β-blocking drugs have been compared with placebo or in which two β-blocking drugs have been compared with each other are reviewed. In addition, for many years, propranolol has been the standard comparative drug for migraine prophylaxis and has been compared with several agents that are not β-blocking drugs. These trials are mentioned in the chapters concerning these agents, but generally the results have shown similar efficacy for the new drug and propranolol.

The crossover design comparing active drug against placebo has been used in most trials (Table 54-2). The blinding of the patients in these trials may be open to question because patients can often determine that they are on a β-blocking drug because of the pulse-slowing effect, particularly during effort. There are also negative trials with β-blocking drugs, however, suggesting that the blinding problem is not that great. In addition, it is reassuring that β-blocking drugs also have been found effective in the parallel group design, where the problem with blinding is less important.

β-Blocking Drugs Compared With Placebo

A number of double-blind controlled clinical trials comparing one β-blocking drug against placebo are summarized in Table 54-2. A total of 1,535 patients were recruited for the trials, and 83% of the patients completing the treatments were evaluable. By modern standards, many of the early studies can be criticized from a methodologic point of view. In many studies there are too few patients and the treatment periods are short (e.g., 4 to 6 weeks). However, the conclusion that propranolol is effective in migraine prophylaxis has been confirmed in more recent trials with better methodology. In addition, nadolol, timolol, metoprolol, atenolol, and bisoprolol have shown better efficacy than placebo in double-blind controlled clinical trials (see Table 54-2). However, in some trials propranolol failed to show a significant difference from placebo (2,22,56). It is most likely that the apparent lack of effect in these trials may be a statistical type 2 error (lack of power to detect the difference).

β-Blocking drugs possessing partial agonist activity, pindolol, alprenolol, oxprenolol, and acebutolol showed

TABLE 54-2 Controlled Double-Blind Clinical Trials Comparing β-Blocking Drugs With Placebo in the Prophylaxis of Migraine

Trial (Ref)	*Drug, Dosage (mg)*	*Study Design*	*No. of Patients (No. Evaluated), Type of Migraine*	*Run in*	*Duration of Treatment*	*Factors Evaluated*	*Investigators' Conclusion*
Weber and Reinmuth (63)	Prop 20 qid	CO	25 (19) MO, MA		3 mo × 2	"Symptomatic response"	Prop > Pl
Malvea et al. (35)	Prop ? mg	CO	31 (29) MO	30 days open	6 wk × 2	Preference, headache units per day, relief medication	Prop very effective in some patients
Widerø and Vigander (65)	Prop 40 qid	CO	45 (30) MO, MA (responders in pilot)	Open pilot study of Prop for 2–11 mo	3 mo × 2	Attack rate, preference	Prop > Pl
Børgesen et al. (7)	Prop 40 qid	CO	45 (30) MO, MA	2 wk no drug	12 wk × 2	Frequency, preference	Prop > Pl
Ludvigsson (33)	Prop 20/40 tid	CO	32 (28) children MO, MA		13 wk × 2	Frequency	Prop > Pl
Forssman et al. (16)	Prop 80 tid	CO	40 (32) MO, MA	10 wk no drug	12 wk × 2	Attack rate, headache days, "integrated headache," relief medication	Prop > Pl
Diamond and Medina (12)	Prop 80–160/day	CO	83 (62) MO, MA		4–8 wk × 2	Preference, headache index, relief medication index	Prop > Pl
Holdorff et al. (22)	Prop 40 bid–tid	Pa	56 (36) MO, MA		12 wk	Migraine index, subjective rating	Prop = Pl
Nadelmann et al. (38)	Prop 20–80 qid	CO	64 (41) MO, MA	6 wk dose-finding	12 wk × 2	Headache unit, relief medication index	Prop > Pl
McDevitt (34)	Prop LA 160?	CO	38 (31) MO, MA		8 wk × 2	Frequency, severity, duration	PropLA > Pl
Pradalier et al. (44)	Prop LA 160	Pa	55 (41) MO	4 wk Pl	12 wk	Frequency	Prop LA > Pl
Al-Qassab and Findley (2)	Prop LA 80 Prop LA 160	CO	45 (30)	4 wk Pl	8 wk (1 wk wash-out)	Frequency, duration, severity	Prop LA 80 and Prop LA 160 vs. Pl NS
Sjaastad and Stenrud (52)	Pind 7.5–15 per day	CO	28 (24) MO, MA	3 wk no drug	3 wk × 2 (3 wk wash-out)	Headache index, headache days	Pind vs. Pl NS

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Ekbom (13)	Alpren 200 bid	CO	33 (28) MO, MA		6 wk × 2 (1 wk wash-out)	Frequency, preference, headache index	Alpren vs. Pl NS
Ekbom and Zetterman (15)	Oxpren 80 tid	CO	34 (30) MO, MA		8 wk × 2 (1 wk wash-out)	Frequency, preference	Oxpren vs Pl NS
Nanda et al. (39)	Acebut	CO	43 (33) "migraine"	4 wk no drug	12 wk × 2 (4 wk wash-out)	Frequency	Acebut vs. Pl NS
Briggs and Millac (8)	Tim 10 bid	CO	14 MO, MA	4 wk no drug	6 wk × 4[a]	Frequency, preference	Tim > Pl
Steiner et al. (53)	Tim 10 bid	CO	107 (94) MO, MA	4 wk Pl	8 wk × 2	Frequency, global preference	Tim > Pl
Ryan et al. (47)	Nad 80 od Nad 80 bid Nad 80 tid	Pa	80 (79) MO, MA	2 mo Pl	3 mo	Frequency, severity	Nad in all group > Pl
Andersson et al. (4)	Met LA 200 od	Pa	71 (62) MO, MA	4 wk no drug	8 wk	Frequency, migraine days, severity score, relief medication	Met LA > Pl
Kangasneimi et al. (27)	Met LA 200 od	CO	77 (74) MA?	4 wk no drug	8 wk × 2 (4 wk wash-out)	Frequency, migraine days, global duration, relief medication	Met LA > Pl
Steiner et al. (53)	Met 50–100 bid	Pa	59 (54) MO, MA	4 wk Pl	8 wk	Frequency, severity score, relief medication	Met vs Pl NS[b]
Forssman et al. (17)	Aten 100 od	CO	24 (20) MO, MA	60 days no drug	90 days × 2 (2 wk wash-out)	Frequency, integrated headache, relief medication	Aten > Pl
Johannson et al. (25)	Aten 100 od	CO	72 (63) MO, MA	8 wk	12 wk × 2 (3 wk wash-out)	Integrated headache, migraine days	Aten > Pl
van de Ven et al. (61)	Bis 5 od Bis 10 od	Pa	226 (195) MO, MA	4 wk	12 wk	Frequency, attack duration	Bis 5 = Bis 10 > Pl

[a] Patients crossed over twice, receiving timolol during two periods and placebo during two.
[b] In the initial double-blind 12-week treatment there was no difference between metoprolol and placebo; but in a further follow-up of 12 weeks, nonresponders to placebo or metoprolol switching to metoprolol 50 bid or metoprolol 100 mg bid, respectively, resulted in significant improvement.
Abbreviations: Acebut, acebutol; Alpren, alprenolol; Aten, atenolol; Met, metoprolol; Nad, nadolol; Oxpren, oxprenolol; Pind, pindolol; Prop, propranolol; Tim, timolol; Bis, bisoprolol; LA, long-acting, slow-release formulation; Pl, placebo; od, once daily; bid, twice daily; tid, three times daily; qid, four times daily; CO, crossover; Pa, parallel groups; MO, migraine without aura; MA, migraine with aura; NS, no statistically significant difference; >, more effective than.
Modified and extended from Andersson and Vinge (3).

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no significant difference from placebo in several early trials (see Table 54-2). It was suggested by an open study with practolol that partial agonist activity does not exclude efficacy in migraine prophylaxis because good results were obtained in 39 and 43 patients treated (48), but this result has never been confirmed in a double-blind trial. The fact that the β-blocking drugs with partial agonist activity were only studied in relatively small trials some time ago has led reviewers to state that the beneficial effect may have escaped detection (3). Because propranolol was found to be effective in similar small trials, the β-blocking drugs with partial agonist activity probably are not effective in migraine.

In contrast to the demonstration of the prophylactic effect of β-blocking drugs in migraine, two double-blind placebo-controlled trials (6,18) have not shown any effect of propranolol in the acute treatment of the migraine attack.

Clinical Trials Comparing Two β-Blocking Drugs or Two Doses of the Same β-Blocking Drug

Controlled double-blind clinical trials comparing the effect of two different β-blocking drugs or two doses of one drug are summarized in Table 54-3. The general results are that when two β-blocking drugs are used in equipotent doses, determined by their effect on heart rate and blood pressure, they are equally effective in migraine prophylaxis. The exception is one study in which nadolol 160 mg per day was significantly more effective than propranolol 160 mg per day (57).

These comparative clinical trials are in most cases probably too small to demonstrate any differences between two active treatments. Comparability should be evidenced by giving narrow confidence intervals. As illustrated in Figure 54-1, even when metoprolol and propranolol resulted in similar responses (28), wide confidence intervals showed that considerable differences in efficacy between the two drugs could have remained undetected. In a much larger crossover study ($N = 80$) (59), no difference between timolol and propranolol was found, although the study had a power of 0.88 to detect a difference of less than 25% between the two treatments. Thus, in this clinical trial, the two drugs were equipotent in their clinical effects. Another problem with most of the comparative trials is the lack of inclusion of placebo. Strictly speaking, a placebo also should be included in comparative trials to demonstrate that the active drugs had a significant effect (24). If two β-blocking drugs are given, and there is a decrease compared with run-in, it could be caused by the time effect (a decrease in frequency with time regardless of treatment) (24).

Generally, attempts to correlate plasma concentrations of β-blocking drugs and their effect in migraine prophylaxis have failed (5,10,68), even when active metabolites of propranolol were taken into account (10). This does not exclude a dose–response relationship in individual patients, and in some studies (9,53) higher doses seem to be more effective than the lower doses of a β-blocker investigated. In contrast, a large parallel-groups study comparing 5 and 10 mg of bisoprolol with placebo showed the same efficacy for both active doses and a trend for shorter attacks with 5 mg compared to 10 mg or placebo (61).

The Efficacy of β-Blocking Drugs in Clinical Trials

As demonstrated in Tables 54-2 and 54-3, the different designs and ways of reporting the results, sometimes with complicated headache indices, make it difficult to judge the percentage of patients benefiting from β-blocker treatment in these trials. In a review (25) of results of both controlled trials and published open studies, with 2,403 patients treated with a modal dose of 160 mg propranolol, it was reported that based on a headache index, the improvements were 44% compared with pretreatment and 33% compared with placebo. However, the composite nature of the headache index, taking both severity and duration of attacks into account, makes it difficult to extrapolate these results to clinical practice.

Side Effects in Clinical Trials of β-Blocking Drugs in Migraine Prophylaxis

The tolerability of β-blocking drugs in migraine prophylaxis is an important issue because clinical experience has shown that some patients stop treatment because of the side effects produced by the drugs. In many of the mentioned controlled, clinical trials there were not significantly more side effects with active drug than with placebo. This may because the trials included too few patients, had an inadequate side effects reporting system, or there was an actual effect in which the drug did not produce side effects. In one relatively large crossover trial (59), two β-blocking drugs, timolol and propranolol, resulted in significantly more side effects than placebo (Table 54-4). Timolol and propranolol induced side effects in 46% and 42%, respectively, whereas 28% experienced side effects from placebo, and 11 of 96 patients withdrew from the trial because of side effects (9 patients on β-blockers and 2 patients on placebo). Thus, in a well-designed trial there are more side effects on active drug than on placebo.

THERAPEUTIC USE OF β-BLOCKING DRUGS IN MIGRAINE PROPHYLAXIS

The doses and pharmacokinetic properties of β-blocking drugs effective in migraine are summarized in Table 54-5.

TABLE 54-3 Controlled Double-Blind Clinical Trials Comparing Two β-Blocking Drugs or Two Doses of a β-Blocking Drug in Migraine Prophylaxis

Trial (Ref)	*Drug, Dosage (mg)*	*Study Design*	*No. of Patients (No. Evaluated)*	*Run-in*	*Duration of Treatment*	*Factors Evaluated*	*Investigators' Conclusion*
Ekbom (14)	Pind 2.5 tid Pind 5 tid	Pa	30 (26) MO, MA	4 wk no drug	4 wk	Frequency, headache index, duration	Pind vs. Pl NS[a]
Stensrud and Sjaastad (55)	*d,l*-Prop 40 qid *d*-prop 40 qid	CO	20 (19) MO, MA		4 wk × 3 (1 wk wash-out)	Headache days, headache index	*d,l*-Prop > Pl *d*-prop vs. Pl NS[b]
Stensrud and Sjaastad (56)	Aten 50 bid Prop 80 bid	CO?	35 (28) MO, MA		6 wk × 2	Headache index, migraine days	Aten vs. Prop NS, Aten > Pl, Prop vs. Pl NS
Tfelt-Hansen et al. (59)	Tim 10 bid Prop 80 bid	CO	96 (80) MO		12 wk × 3	Frequency, headache index	Tim vs. Prop NS, Tim > Pl, Prop > Pl
Ryan (46)	Nad 80/day Nad 160/day Prop 160/day	Pa	48 (45) MO, MA	4 wk Pl	12 wk	Frequency, headache index	"Suggest that both Nad and Prop reduce frequency and severity"
Olerud et al. (41)	Nad 80–160/day Prop 80–160/day	Pa	28 (27) MO, MA	4 wk	24 wk 120 days PL?	Frequency, relief medication, duration	Nad vs. Prop NS[a]
Sudilovsky et al. (57)	Nad 80/day Nad 160/day Prop 160/day	Pa	140 (98) MO, MA	4–8 wk	12 wk	Several headache indices	Nad 160 > Prop 160, Nad 160 vs. Nad 80 NS
Kangasneimi and Hedman (28)	Met LA 200 od Prop 80 bid	CO	36 (35) MO, MA	4 wk Pl	8 wk × 2 (4 wk wash-out)	Frequency, severity, migraine days, relief medication	Met LA vs Prop NS, both > Pl run-in
Olsson et al. (42)	Met 50 bid Prop 80 bid	CO	56 (56) MO, MA	4 wk pl	8 wk (4 wk wash-out)	Frequency, migraine days, severity, relief medication	Met vs. Prop NS, both > Pl run-in
Havanka-Kannianinen et al. (20)	Prop LA 80 od Prop LA od	CO	48 (42) MO, MA	4 wk Pl	12 wk × 2 (4 wk wash-out)	Frequency, migraine days, severity	Prop LA 80 vs. Prop LA 160 NS
Carroll et al. (9)	Prop LA 80 od Prop LA 160 od	CO	51 (37) MO, MA	4 wk Pl	12 wk × 2	Frequency, duration, severity	Prop LA 160 > Prop LA 80
Worz et al. (66)	Met 50 bid Bis 5 od	CO	125 (78)	4 wk	12 wk × 2	Frequency	Met vs Bis NS; both reduced frequency by 50% vs run-in

[a]Too small a parallel trial to demonstrate a difference in our opinion.
[b]Not the author conclusion, but the conclusion after reanalysis with conventional statistical methods (56).
Abbreviations: Acebut, acebutol; Alpren, alprenolol; Aten, atenolol; Met, metoprolol; Nad, nadolol; Oxpren, oxprenolol; Pind, pindolol; Prop, propranolol; Tim, timolol; Bis, bisoprolol; LA, long-acting, slow-release formulation; Pl, placebo; od, once daily; bid, twice daily; tid, three times daily; qid, four times daily; CO, crossover; Pa, parallel groups; MO, migraine without aura; MA, migraine with aura; NS, no statistically significant difference; >, more effective than.
Modified and extended from Andersson and Vinge (3).

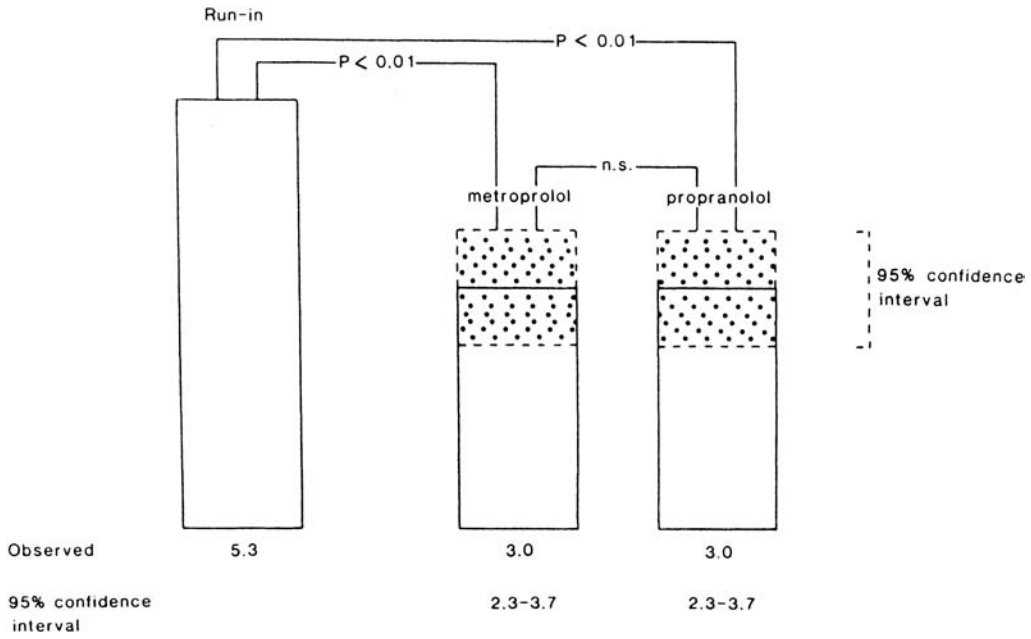

FIGURE 54-1. Mean number of migraine attacks per 4 weeks during run-in, metoprolol, propranolol periods (*bars with unbroken lines*) (27). The dotted areas represent the 95% confidence intervals for the difference between the two drugs. Note that for both β-blocking drugs the real mean frequency of attacks could be in the range of 2.3 to 3.7 per 4 weeks instead of the measured 3.0. The trial is thus too small to demonstrate comparability. From Tfelt-Hansen (58).

The effective therapeutic dosage range is wide probably caused by significant pharmacokinetic and pharmacodynamic variability. Consequently, the dose of a β-blocking drug should be titrated for each individual patient especially with metoprolol because of the possibility of a patient being a poor metabolizer. The patients should start with the lowest dose indicated in Table 54-5; then, depending on efficacy and side effects, the dose can be increased gradually with 4 to 8 weeks between increases in doses. Until the patient has reached the final dose, pulse and blood pressure should be controlled at each visit. The patients should try the highest dose they can tolerate without side effects for 2 months before the β-blocking drug is deemed to be ineffective, and if there is no effect, another avenue of therapy should be explored.

To ensure a high level of compliance, it is recommended that patients take β-blocking drugs either once or twice a day, a frequency of dosing that has been found to be effective in controlled trials. It appears that compliance is much better with once a day dosing (37). Nadolol, atenolol, and bisoprolol, which have long half-lives, can be administered once a day. The same is the case for the long-acting preparations of propranolol and metoprolol, which can be substituted for the short-acting forms in the same dosage once the effective dosage has been found.

Withdrawal symptoms can occur occasionally after a sudden cessation of propranolol therapy, but this is rare among migrainous patients. However, to avoid this potential but rare hazard, treatment with a β-blocking drug should not be stopped abruptly, but the dose reduced gradually over a period of about 2 weeks. A few patients may note a worsening of their migraine when propranolol is begun. If this occurs, the dosage should be reduced. Patients should be warned in advance about this problem.

TABLE 54-4 Side Effects in 83 Migraine Patients in a Double-Blind Three-Way Crossover Trial Comparing Timolol (10 mg twice daily) and Propranolol (80 mg twice daily) With Placebo

	Timolol	*Propranolol*	*Placebo*
With side effects	38	35	23
Without side effects	45	48	60
Most commonly reported side effects			
Fatigue/tiredness	18 (22%)	11 (13%)	15 (18%)
Dizziness	5 (6%)	4 (5%)	2 (2%)
Nausea	2 (2%)	5 (6%)	2 (2%)
Sleep disturbances	4 (5%)	3 (4%)	2 (2%)
Depression	2 (2%)	3 (4%)	0
Abnormal dreaming	2 (2%)	0	0

From Tfelt-Hansen et al. (59).

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TABLE 54-5 Doses and Pharmacokinetic Properties of β-Blocking Drugs Effective in Migraine

	Tablets Size (mg)	*Daily Dosage, Range (mg)*	*Dosing (Frequency per Day)*	*Bioavailability*	*Half-Life (h)*	*Primary Metabolic Route*
Propranolol						
Regular	10, 20, 40, 80, 90	40–320	Twice	25%	3–5	Hepatic
Long-acting	60, 80, 120, 160	60–320	Once			
Metoprolol						
Regular	50, 100	50–200	Twice	40%	3–4	Hepatic
Long-acting	50, 100, 200	50–200	Once			
Nadolol	40, 80, 120, 160	40–240	Once	35%	12–20	Renal
Atenolol	50, 100	50–200	Once	50%	5–8	Renal
Timolol	10, 20	10–20	Twice	50%	3–5	Hepatic
Bisoprolol	1.25, 2.5, 3.75, 5, 7.5, 10	5–10	Once	90%	10–12	Hepatic and renal

Which β-Blocking Drug Should Be Used in the Prophylactic Treatment of Migraine?

In our opinion, there is no evidence for one drug being more effective in migraine prophylaxis than another among those with proven efficacy. One should choose one of the effective β-blocking drugs and make oneself familiar with that drug. However, if adverse effects of a central nervous system origin occur with, for example, propranolol, a change to atenolol could be made. The failure to respond to one β-blocking drug does not generally predict the failure to respond to another; if available, several β-blocking drugs could be used consecutively in the same patient.

Side Effects

Side effects to β-blocking drugs generally occur in 10 to 15% of patients. The most common side effects are fatigue, cold extremities, gastrointestinal symptoms (flatulence, diarrhea, constipation), and dizziness. Side effects of central nervous system origin (19,21) include vivid dreams, nightmares, insomnia, depression, and memory disturbances. Impotence is a relatively rare side effect.

Contraindications

Contraindications to the use of β-blocking drugs include asthma and chronic obstructive lung disease, congestive heart failure, partial or complete atrioventricular conduction defects, Raynaud's disease, peripheral vascular disease, and brittle diabetes.

Cautions

β-Blocking drugs should not be used during actual abuse of ergotamine because it may precipitate overt ergotism (62).

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