The prevention of migraine: a critical review with special emphasis on β-adrenoceptor blockers

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Migraine is one of the most frequent neurological disorders affecting up to 15% of the general population. Many patients require not only management of individual migraine episodes but also prophylactic treatment. β-adrenoceptor blockers, flunarizine and valproic acid have been established as first-line agents for the prophylaxis of migraine attacks. Among the β-adrenoceptor blockers propranolol and metoprolol are best documented and hence deserve preferential use. On the other hand, it appears that other β-adrenoceptor blockers, perhaps with the exception of those with intrinsic sympathomimetic activity, can be equally effective. Uncertainties regarding the relative merits of various treatment modalities are largely caused by lack of adherence to specific requirements for clinical trials on migraine prophylaxis. Therefore, this article reviews internationally recommended conditions for reliable studies on migraine prophylaxis and appraises individual agents in the light of these criteria.

Keywords: metoprolol, migraine prophylaxis, propranolol, trial design

Introduction

The International Headache Society (IHS) defines migraine as a disorder characterized by intermittent attacks of headache combined with nausea, photophobia and/or phonophobia [1]. Some rare forms of migraine have been associated with specific alterations of genes encoding P/Q calcium channels [2]. The more common forms of migraine are those with or without an aura; these have not been linked to specific genes, and it is still under discussion whether they might represent multiple disease entities [3].

Several options exist for the medical treatment of acute migraine attacks, which include acetylsalicylic acid, acetaminophen (also known as paracetamol), ergot alkaloids and, more recently, 5-$HT_{1B/D}$ receptor agonists such as sumatriptan [4]. Some patients, however, require some form of prophylactic treatment. Although the need for prophylactic treatment in certain patients is undisputed, there is considerable discussion about optimal prophylactic treatment modalities, partly because no reliable animal models exist to study prophylactic treatment. Therefore, identification of adequate prophylactic treatment relies entirely on clinical studies. The nature of migraine, however, mandates specific considerations in the design of clinical studies. Thus, this manuscript will initially discuss criteria for valid studies on prophylactic treatment based on the recommendations of the IHS [5]. Thereafter, we will summarize current knowledge on therapeutic options with these methodological criteria in mind with a special emphasis on β-adrenoceptor antagonists, since they are the best studied and most frequently used form of prophylactic treatment.

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Trial design

The diagnosis of migraine must be carefully distinguished from other forms of headache including tension type headache, cluster headache or paroxysmal hemicrania, which are likely to have a different pathophysiology and may require different forms of treatment. However, several studies, particularly from the older literature, have not consistently differentiated between migraine and other headache forms. Hence, the interpretation of their results may be confounded by patient heterogeneity. This is important since β-adrenoceptor blockers have not been proven to be effective in the prophylaxis of nonmigraine

primary headaches [6]. Newer studies on migraine treatment, i.e. those appearing after publication of the headache classification by the IHS in 1988, have routinely included only patients with clearly identified migraine.

In many patients, including those with migraine, chronic headache and/or an increase in migraine frequency can also occur secondary to inappropriate use of headache medication such as analgesics, ergot alkaloids and 5-$HT_{1B/D}$ receptor agonists. Several studies indicate that migraine patients who developed drug-induced headache do not respond to prophylactic treatment but rather require complete withdrawal from their headache medication [for a review see 7]. Therefore, strict exclusion of patients with drug-induced headache or medication misuse is mandatory for reliable studies on prophylactic migraine treatment, but this has not routinely been done in earlier studies.

Since frequency of migraine attacks is the most common reason to initiate prophylactic treatment, it is impossible to precisely determine prophylactic effects without a sufficiently long run-in-phase. Based on the possible fluctuation of attack frequency, reliable studies require a run-in-phase of at least 4 weeks following the discontinuation of all drugs which might influence the frequency of migraine attacks. Furthermore, if trials are conducted using a cross-over-design a wash-out-period of at least 4 weeks is required in order to avoid carry-over-effects. Even longer washout periods may be necessary if flunarizine is involved, since this drug has a very long half-life [8]. Unfortunately, several studies appearing prior 1995 have not routinely included a sufficiently long run-in-phase or wash-out-periods.

The necessary duration of a reliable study on prophylactic migraine treatment is determined by three factors, i.e. the minimal frequency of attacks justifying prophylactic treatment (i.e. three per month) and their possible fluctuation, the required time for titration to effective dosages (see below), and finally the time required to reach full prophylactic efficacy (6–8 weeks). Based on these considerations, the study duration for drugs in the prevention of migraine should be at least 3 months. Shorter studies may overemphasize placebo effects, as indicated by a relatively high placebo responder rate in short studies [9]. Due to these considerations shorter studies are likely to yield falsely negative results.

Following the initiation of prophylactic treatment, many patients experience adverse events in the first days of treatment but the desired prophylactic effects require several weeks to develop. This dissociation may impair patient compliance and favour high drop-out rates. Thus, comparison of placebo and active treatment on an intention-to-treat basis may underestimate the benefit of active treatment if target dosages are approached too fast.

Unfortunately, only a minority of studies on prophylactic migraine treatment have adhered to all of the above criteria. Moreover, the number of patients in several studies apparently has not been based on proper power calculations, which further complicates appreciation of their value. The combination of these factors may explain, why even drugs such as propranolol and metoprolol, which are of clearly proven prophylactic value, have not demonstrated superiority over placebo in a few small studies [10–13].

Therapeutic options for prophylactic migraine treatment

Although prophylactic treatment is beneficial to most patients, a sizeable fraction does not experience sufficient efficacy of prophylactic agents and/or the prophylactic efficacy wanes with time. This has led to the investigation of numerous prophylactic treatment modalities. Such studies have failed to demonstrate therapeutic effects beyond placebo, e.g. for selective 5-HT reuptake inhibitors [14], MAO-B inhibitors [15], antiepileptic drugs such as carbamazepine [16] and lamotrigine [17], or calcium entry blockers such as nimodipine [18], nifedipine [19], and most recently cyclandelate [20]. Although the ergot alkaloid dihydroergotamine has been used for prophylactic treatment, there is no good evidence for its efficacy in this indication. On the other hand, the calcium entry blocker verapamil was more effective than placebo in two small trials [21, 22]. Most recently, it has been reported that the converting enzyme inhibitor lisinopril can be used as a prophylactic treatment for migraine [23]. While the results from that study look promising, they should be interpreted with caution until they are confirmed by other data, particularly since this study included only 47 patients.

Among drugs which have demonstrated value in the prophylactic treatment of migraine, treatment recommendations can vary markedly between countries. These differences, however, do not appear to be based on than scientific arguments. For example, flunarizine has been unequivocally demonstrated to be effective and well tolerated in more than 10 open and almost 20 placebo controlled trials [for reviews see 24, 25], and hence is considered a drug of first choice in most European countries but currently is not available in the US. Based on the currently available evidence, β-adrenoceptor blockers, the calcium entry blocker flunarizine and, more recently, the antiepileptic drug valproic acid [6, 26–28] can be considered as first-line prophylactic agents. Other agents including nonsteroidal anti-inflammatory drugs (NSAID) such as acetylsalicylic acid [29–31], naproxen [32] or tolfenamic acid [33] and 5-HT_2 receptor antagonists such as pizotifen [34] and methysergide

[35] are considered as second-line agents only. This is based on direct comparative studies to some of the above first-line agents, a less favourable risk/benefit ratio and/or because their beneficial effects are less well documented than those of the first-line agents. The place of verapamil cannot be determined as yet due to the lack of direct comparative studies with established first line drugs.

β-adrenoceptor blockers in the prophylactic treatment of migraine

The efficacy of β-adrenoceptor blockers for the prophylaxis of migraine was discovered by chance when patients with migraine, who received β-adrenoceptor blockers for cardiac disorders, observed a significant reduction of migraine frequency [36]. Among all agents for prophylactic migraine treatment, β-adrenoceptor blockers have been studied most intensively and are being used the most frequently (for reviews see [37–40]). Among the β-adrenoceptor blockers, propranolol and metoprolol have been characterized most extensively in the prophylaxis of migraine, and are generally recognized to be effective [38]. While different doses of these two agents have been used in the various trials, their meta-analysis suggests that 160 mg day^{-1} of propranolol and 200 mg day^{-1} of metoprolol can be considered as effective prophylactic doses. These doses have also been used most frequently in comparative studies with other agents (see below), but clinical experience suggests that lower doses may also be effective in many patients. On the other hand, it remains controversial whether prophylactic efficacy in migraine is a property of all β-adrenoceptor blockers or limited to individual members of this drug class with specific properties. β-adrenoceptor blockers are typically classified according to factors such as selectivity for the β_1-adrenoceptor subtype, lipophilicity (and hence penetration into the central nervous system), membrane-stabilizing effects and intrinsic sympathomimetic activity; moreover, some β-adrenoceptor blockers have high affinity for certain 5-HT receptor subtypes [41].

β_1-adrenoceptor selectivity does not appear to play a major role in determining prophylactic efficacy since nonselective agents such as propranolol, moderately β_1-selective agents such as metoprolol and highly β_1-selective drugs such as bisoprolol [42, 43] all are effective prophylactics. Thus, concomitant blockade of β_2-adrenoceptors does not appear to be required for effective migraine prophylaxis.

Due to the lack of validated animal models, the site of action for prophylactic β-adrenoceptor blocker effects has not been defined. While propranolol, metoprolol, oxprenolol and alprenolol are very lipophilic and hence penetrate well into the central nervous system, atenolol, nadolol, and practolol are only slightly or not at all lipophilic [41]. Since several members of the latter group including atenolol [44, 45] and nadolol [46–50] have demonstrated their efficacy in the prophylaxis of migraine attacks, high lipophilicity and hence penetration into the central nervous system does not appear required for prophylactic efficacy. The prophylactic efficacy of atenolol [44, 45], nadolol [46–50] and timolol [51, 52] demonstrates that membrane-stabilizing effects are also not required to reduce the frequency of migraine attacks.

Four β-adrenoceptor blockers with intrinsic sympathomimetic activity, i.e. acebutolol [53], alprenolol [54], oxprenolol [55] and pindolol [56–58], have been studied for prophylactic efficacy but did not demonstrate superiority relative to placebo. However, the absence of proof should not be mistaken as proof of absence for a prophylactic effect for several reasons: Firstly, only two studies were performed with pindolol and only one each for the other agents. Second, all of these studies have apparently been underpowered since they included only 26–33 patients, i.e. less than 20 per treatment arm. Third, the headache type was not clearly defined in some studies. Finally, the evaluation time was very short in most of these trials and sometimes lasted only 4 weeks. Given the fact that even clearly effective agents such as propranolol or metoprolol failed to demonstrate efficacy in small isolated trials [10–13], the present data are insufficient to define a role for intrinsic sympathomimetic activity in the prophylaxis of migraine due to poor trial design.

Several β-adrenoceptor blockers including propranolol and pindolol exhibit a high affinity for 5-HT receptors including 5-HT_{1A} as well as 5-$HT_{1B/D}$ and 5-HT_2 receptors which are either targets for acute migraine therapy or other prophylactic acting agents, respectively [58–60]. While propranolol is clearly effective in migraine prophylaxis, pindolol is of questionable efficacy (see above). Therefore, the role of 5-HT receptor affinities still needs to be determined.

Taken together, these data demonstrate that the hypothesis that only certain β-adrenoceptor blockers are effective prophylactic agents is not supported by the available evidence. While the role of intrinsic sympathomimetic activity cannot be determined at present, it is evident that concomitant blockade of β_2-adrenoceptors, lipophilicity or membrane-stabilizing effects are not required. Hence, with the possible exception of drugs with intrinsic sympathomimetic activity, prophylactic efficacy seems to be a class effect of all β-adrenoceptor blockers. From a practical point of view, these data suggest that β-adrenoceptor blockers with intrinsic sympathomimetic activity should not be used for the prophylaxis of migraine attacks, whereas propranolol and metoprolol appear to deserve preferential use. However, this preference is not based on superior efficacy or tolerability relative to other β-adrenoceptor blockers but merely

reflects the fact that these two have been investigated more extensively than the other drugs.

Clinical trials on β-adrenoceptor blockers in the prophylaxis of migraine

Among all β-adrenoceptor blockers propranolol, and to a lesser extent metoprolol, underwent the most extensive clinical testing and served in many clinical trials as reference drugs when β-adrenoceptor blockers were compared with nonadrenergic drugs. Holroyd *et al.* [38] performed a meta-analysis for propranolol in the prophylaxis of migraine. The 53 studies included in the meta-analysis involved 2403 patients who were treated with either propranolol (modal treatment 160 mg), a reference substance and/or placebo. On average, propranolol yielded a 44% reduction in migraine activity when daily headache recordings were used to assess treatment outcome, and a 65% reduction of migraine activity when clinical ratings of improvement and global patient reports were used. The drop-out rate due to side-effects was 5.3%. The fact that propranolol in three clinical trials [10–12] and metoprolol in one clinical trial [13] did not perform better than placebo again emphasizes that the efficacy of a drug cannot be judged by a single trial and more important, that the trial design is crucial to prove the efficacy of a drug. If efficacy is shown, the overall performance among the group of β-adrenoceptor blockers is very similar with regard to the reduction of migraine attacks. Again, following a run-in-phase an evaluation time of at least 3 months is necessary to receive reliable data on the potential efficacy in migraine prophylaxis. For further details of any specific drug the reader is referred to previous reviews [24, 25, 37–40].

Other prophylactic antimigraine drugs in comparison with β-adrenoceptor blockers

Various drugs have been compared with β-adrenoceptor blockers in the prophylaxis of migraine. Meanwhile eight clinical trials [61–68] compared the calcium channel blocker flunarizine with β-adrenoceptor blockers (six trials with propranolol, two with metoprolol). In all trials flunarizine was equally effective with the β-adrenoceptor blockers, but had a qualitatively different adverse event profile. Based on these comparative studies as well as the placebo-controlled trials (for reviews see [24, 25]), flunarizine is considered a drug of first choice in migraine prophylaxis. In the light of the negative results with other calcium entry blockers [19, 20], it remains to be determined whether the prophylactic efficacy of flunarizine is related to its calcium entry blocking properties.

In two small clinical trials [69, 70] valproic acid (up to 2000 mg day^{-1}) has been compared with propranolol (up to 240 mg day^{-1}). In both trials the efficacy (reduction of attack frequency) of both drugs was identical, which is in line with the documented efficacy of valproic acid relative to placebo [26–28]. Although the profiles of adverse effects were different, a comparable low rate of adverse events was reported in both trials.

Based on the proven efficacy of NSAID against acute migraine attacks, their prophylactic values have also been tested relative to placebo [71] and relative to β-adrenoceptor blockers. As early as 1983 Baldretti *et al.* [29] compared in a small trial including 18 patients the efficacy of propranolol (1.8 mg kg^{-1}) with that of acetylsalicylic acid (13.5 mg kg^{-1}). In this trial, both drugs were equally effective and reduced frequency, duration, and intensity of the attacks to the same extent. Other studies, however, were not able to confirm these results. In a small double-blind cross-over trial, 200 mg day^{-1} metoprolol were significantly more effective than 500 mg day^{-1} acetylsalicylic acid [30]. In a double-blind multicentre trial including 243 patients Diener *et al.* compared low dose acetylsalicylic acid (300 mg day^{-1}) *vs* metoprolol (200 mg day^{-1}) and placebo [31]. Both drugs were superior to placebo, but metoprolol reduced frequency of migraine attacks significantly better than acetylsalicylic acid (reduction of monthly attacks from 3.55 to 1.82 *vs* 3.38–2.27). Acetylsalicylic acid, however, caused significantly less adverse events and showed a lower rate of drop outs. Kjaersgard Rasmussen *et al.* [33] compared propranolol (40 mg three times daily) with tolfenamic acid (100 mg three times daily) in 76 patients and found both drugs to be equally effective in the reduction of headache time (migraine days and hours) as well in pain intensity; moreover, tolfenamic acid caused less adverse events and less drop outs. Taken together with the data from the placebo-controlled NSAID trials [71], these controversial reports have resulted in the classification of NSAID as second line prophylactic agents in migraine treatment.

Calcium entry blockers such as nimodipine or nifidipine have not demonstrated superiority relative to placebo [18] and accordingly were also found to be less effective than propranolol [19]. On the other hand, verapamil is frequently used as a migraine prophylactic in the US. While two studies dating from the early 1980s have reported verapamil to be superior to placebo [21, 22], both did not adhere to the above-mentioned criteria for valid studies and have included too few patients to allow reliable conclusions. Moreover, verapamil has never been tested in comparison with established prophylaxis drugs. Therefore, the scientific basis of its frequent use in the US remains weak, and calcium entry blockers other than

flunarizine cannot be considered suitable for migraine prophylaxis.

Conclusions and treatment recommendations

Within the last 30 years more than 100 clinical trials have been conducted to investigate β-adrenoceptor blockers in migraine prophylaxis. While the beneficial effect of propranolol and metoprolol is clearly established, the value of other β-adrenoceptor blockers remains to be determined, since only a minority of trials was carried out with a suitable trial design and enough patients to run reliable statistics. Nevertheless the available data suggest that β_1-selectivity, penetration into the central nervous system, membrane-stabilizing effects and 5-HT receptor affinity do not play a major role for prophylactic efficacy; in contrast, consistently negative results with β-adrenoceptor blockers with intrinsic sympathomimetic activity suggest that this property may be undesirable for migraine patients. While agents such as flunarizine or valproic acid are now also considered as drugs of first choice for prophylactic migraine treatment, they remain less well established than the β-adrenoceptor blockers. Apart from aspects of regulatory approval, the differential use of β-adrenoceptor blockers relative to other first line agents should largely be determined by the differential adverse event profiles of the various agents relative to concomitant conditions of an individual patient to maximize compliance.

In general, prophylactic treatment will be successful when certain aspects are considered: Prior to the start of migraine prophylaxis the patient should note frequency, duration and severity of migraine attacks in a diary. This diary may help to verify effects of therapy. The initial drug dosage should be low (e.g. propranolol 20 mg day^{-1}) and must be increased slowly since adverse effects can occur prior the prophylactic effects and impair patient compliance. The prophylaxis should be maintained for a minimum of 3 months to allow efficacy evaluation in a specific patient. When successful prophylactic treatment should be continued for 12 months. Thereafter, discontinuation can be attempted but drug doses should be decreased slowly, particularly with β-adrenoceptor blockers in order to avoid tachycardia or hypertension. The natural history of migraine should then be assessed for 2–3 months.

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