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Different Profile of Propranolol and Amitriptyline Effects on Migraine Prophylaxis

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Abstract: This study was conducted to compare the prophylactic activity of propranolol and amitriptyline on frequency, duration and severity of migraine attacks. The rebound effects of these drugs were also evaluated. In a clinical study 105 patients were randomly allocated to one of three groups. The study was divided into three phases, each phase 45 days. In the first phase all patients received two tablet/day, placebo. In the second phase, group one received propranolol (40 mg, twice per day), group two amitriptyline (25 mg, twice per day) and group three continued to receive placebo. In the third phase of the study, all patients received placebo. Patients were free to have acetaminophen-codeine on migraine attacks. All patients were given diagnostic headache diaries in which to record frequency, duration and intensity of attacks. Propranolol and amitriptyline significantly reduced the frequency, duration and intensity of attacks. In contrast to propranolol group, there was a rebound effect following discontinuation of amitriptyline. It seems that propranolol has a therapeutic activity (other then a prophylactic effect) on migraine attacks, however, amitriptyline has only a prophylactic effect.

Key words: Headache, migraine, propranolol, amitriptyline, betablocker

INTRODUCTION

Migraine is a chronic and intermittent disorder, often incapacitates its sufferers, therefore demands effective therapy. The attacks may be from 4 to 72 h in duration and can be classified according to the presence or absence of preceding transient focal neurological manifestations (visual, sensory, speech, or motor symptoms) into two distinct categories, migraine without aura (common migraine) and migraine with aura (classic migraine). More than 18% of women and 6% of men in the United States, have at least one migraine attack per year[1]. Epidemiological studies revealed a clear racial difference in genetic vulnerability to migraine[2,3]. Prevalence is also age dependent (most common between 25 and 55 years of age) and income dependent, affecting lower socioeconomic group more than those in higher income. This disease results in limitations in daily function, reduced quality of life and loss of productivity is considerable and makes treatment of migraine very important in general practice[4].

The pharmacological treatment of migraine may be acute (abortive, symptomatic) or preventive (prophylactic)[5] and patients who are experiencing frequent severe headaches often require both approaches. Preventive therapy is given to reduce the frequency and severity of anticipated attacks and improve the quality of life of migraine sufferers[6].

The major drug groups for preventive migraine treatment include β-adrenergic blockers, antidepressants, calcium channel antagonists, serotonin antagonists, anticonvulsants and non-steroidal anti-inflammatory drugs (NSAIDs)[7].

Numerous trials have documented the effects of these drugs on prevention of migraine attacks[8]. The purpose of this study was to compare the preventive effects of amitriptyline and propranol for prophylaxis of migraine using a randomized single blind placebo-controlled design.

MATERIALS AND METHODS

A clinical study was performed on 105 patients with migraine headaches. Patients aged 15 to 45 years old were randomly selected from the out patient clinic of the neurologist author.

To be eligible, patients had to meet diagnostic criteria for migraine as defined by the International Headache Society (HIS), i.e. at least 5 headache attacks lasting for 2 to 48 h with at least two of following symptoms: lateralized headache, pulsing pain of moderate to high intensity, exacerbation by effortful physical activity, nausea or vomiting in addition to photo and phonophobia[9].

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Patients with secondary headache and also those with a neurological disorder were excluded. The minimal duration of the disorder had to be one year with at least two attacks having taken place during the last month. Proper information regarding the use of medications was provided to patients and informed consent was obtained before entry. Exclusion criteria included last two months trials of medication for prophylaxy of migraine, sever medical or psychiatric illness, use of contraceptive pills, analgesic usage for other illnesses and presence of alcohol or drug abuse. Patients unable to complete a headache diary or differentiate various headache types were also excluded.

Patients allocated randomly to one of three groups. The study was divided into three phases, each phase 45 days. In the first phase (baseline) all patients received two tablets/day placebo (an inert compound).

In the second phase (days 46 to 90) group one received propranolol (40 mg, twice per day), group two, amitriptyline (25 mg twice per day) and group three continued to receive placebo. In the third phase of the study (days 91 to 135) patients were free from prophylactic medication, however, they received placebo. All patients were free to have acetaminophen-codeine on migraine attacks.

All patients were given diagnostic headache diaries in which to record all headaches during the entire study period. Headache type, frequency, duration and intensity were all to be described each period. Headache intensity was scored on a 1-10 point scale, with 1 reflecting the less intensity (absence of effect on daily activity) and 10 reflecting the most intensity (prohibition of daily activity). Patients were blinded to the use of placebo. The investigator was blinded to patients and the agents during review of diary entries and for outcomes assessment.

RESULTS

Out of 105 patients who enrolled in the trials, 95 patients (90%) completed the study. At baseline, patients averaged 4.02 migraine attacks per month (range, 2-8) with SD of 2.03. The average duration of migraine attacks during baseline phase was 25.12 (range 6 to 48) with SD of 11.98 h.

The frequency, duration and intensity of migraine attacks were significantly different in phase one (baseline), in comparison to the results of phase two or three, in propranolol group (Table 1).

There were significant reductions in frequency ($p<0.01$), duration ($p<0.05$) and severity ($p<0.05$) of attacks in phase two as compared with the results of phase one. However, there were no significant differences between the results of phase 2 and phase 3, in this group (Table 2).

Table 1: Effect of propranolol on migraine attacks

	Frequency (attacks/month)	Duration (h)	Intensity (1 to 10)
Phase 1 (baseline)	3.83±2.2	25.00±12.5	7.36±2.02
Phase 2 (propranolol)	1.90±1.86	13.46±13.8	4.63±3.92
Phase 3 (Placebo)	2.66±2.26	17.40±13.3	5.70±3.58

There are significant differences between the results of phase one (baseline) and phase two (Propranolol use) for frequency ($p<0.001$) duration (0.01) and intensity (0.01) of migraine attacks. There are also significant differences between the results of phase two (Propranolol use) and phase 3 (Placebo) for frequency, duration and intensity (0.05) (n=32)

Table 2: Effect of amitriptyline on migraine attacks

	Frequency (attacks/month)	Duration (h)	Intensity (1 to 10)
Phase 1 (baseline)	4.6±1.71	26.6±12.37	7.33±2.27
Phase 2 (amitriptyline)	3.1±2.15	16.6±10.54	5.23±3.46
Phase 3 (Placebo)	4.3±2.02	26.0±10.4	6.60±3.39

There are significant differences between the results of phase one (baseline) and phase two (amitriptyline use) for frequency ($p<0.01$), duration (0.005) and intensity (0.05). There are no significant differences between the results of phase two and phase three for frequently, duration and intensity (n=30)

There were no significant differences among phases 1, 2 and 3 in control group, for the above mentioned parameters. Mann-Whitney test demonstrated a more reduction in frequency of attacks in phase two of propranolol group compared to amitriptyline group (0.05).

Following discontinuation of amitriptyline usage, more attacks occurred in this group, compared to propranolol group ($p<0.05$). Ten patients in propranolol group, 20 patients in amitriptyline group and 6 patients in placebo group had complaint from the side effects of drugs. Hypotension, weakness and vomiting were the most frequent side effects of propranolol and anticholinergic effects, the most side effects of amitriptyline.

DISCUSSION

This study was conducted to compare the prophylactic effect of propranolol and amitriptyline. Both drugs were effective in reducing intensity, duration and frequency of migraine attacks. Results are comparable with previous reports[10,11]. However, Holdroff[12] claimed that propranlol had no beneficial effect, compared to placebo. He employed a 20 mg dose two times per day, which is half dose employed in our study. It has been suggested that prescribing inadequate doses of preventive medications is a major cause of therapeutic failure. Therefore, 40 mg day^{-1} of propranolol might be inadequate in that study. After discontinuation of drug the rebound effect of propranolol was less than amitriptyline, so that there were significant differences between phase three and phase one in propranolol group. It means propranolol may have therapeutic effect on migraine attacks. However, amitriptyline reduced the frequency of migraine attacks as far as it was used.

The mechanism involved in antimigraine prophylactic effects of amitriptyline and propranolol is unknown. Several lines of evidence indicated a relationship between serotoninergic or adrenergic system and migraine[8]. A preventive migraine drug could raise the threshold to the activation of the migraine process either centrally or peripherally. Drug could decrease activation of the migraine generator, enhance central antinociception, rise the threshold for spreading depression, or stabilize sensitive migrainous nervous system by changing serotonergic or sympathetic tone[8]. Some have suggested that down-regulating the 5HT2 receptor or modulating the discharge of serotonergic neurons may be involved in migraine prevention[13,14].

Amitriptyline down-regulates both the 5HT2 and β-adrenergic receptors[8]. Propranolol can also bind to 5HT2 receptors and so exert site-selective vasoconstrictive effects via serotonergic blockade[15]. This drug is also believed to reduce stress-induced release of serotonin from platelets[16].

It should be considered that undoubtedly there are more than one mechanism involved in migraine attacks and preventive drug also most likely work by more than one mechanism of action. Different profile of results in phase three of prepranolol and amitriptyline, might be related to different mechanisms of actions of these two drugs.

It has been claimed that prevention of migraine attacks by early treatment of acute migraine headaches or prophylactic management of headaches might minimize headache recurrence[7]. This hypothesis is strengthened by the results of propranolol. However, the frequency, duration and intensity of migraine attacks in phase three in amitriptyline group were not significant, compared to the results in phase one of this group or placebo group. These results disprove the hypotheses that prevention of migraine attacks reduces headache recurrence.

Less frequency of migraine attacks in phase three of propranolol group and fewer side effects may consider this drug as a preferred drug for migraine treatment. However, other than these, the design of an effective treatment program begins with profiling both the headache condition and patient variables. Important patient variables include age, sex, childbearing status and medical conditions such as hypertension and vascular diseases. Depression, anxiety disorders, irritable bowel syndrome and epilepsy are comorbidities of migraine, which should be considered in the design of a treatment program[7]. Taking advantage of the side effect profile of drug is also important. An underweight patient, or a depressed patient might be candidate for amitriptyline. When migraine and hypertension and/or angina occur together, propranolol might be drug of choice.

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