

The treatment of migraine with propranolol

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■ Within recent years a variety of agents have been employed for the symptomatic and prophylactic treatment of the migraine syndrome. The responses to two such agents, ergot derivatives and methysergide, have often been so striking as to have achieved the stature of diagnostic criteria. Despite this fact, a number of migraine sufferers remain without effective therapy because either they are not benefited by these drugs or they cannot risk or tolerate the side effects produced by them.

Recently, Rabkin et al.,¹ Wykes,² and Bekes et al.³ independently noted seemingly fortuitous headache improvement in three patients with migraine treated for cardiovascular disease with propranolol, a beta-adrenergic receptor blocker. These observations coupled with our experimental results of propranolol's effects on cerebral blood flow and metabolism⁴ prompted a controlled study on the efficacy of this substance as a modifier of the migraine syndrome.

Method

The study group consisted of 25 patients, 13 of whom were women. The mean age was 40.6 years, with a range of 19 to 61 years. In every instance these patients were recognized therapeutic management problems, and all met the established criteria for diagnosis of migraine.⁵ Six patients failed to complete the study for reasons unrelated to the trial drug per se, so that 19 patients comprised the final study group. Thirteen of these patients had headache with no focal neurological distur-

bance, and 6 suffered from headache preceded or accompanied by neurological phenomena.

All patients had normal neurological examinations and were free of disorders that could be aggravated by beta-adrenergic receptor blockade, namely, cardiac disease, asthma, and diabetes mellitus.

A randomized double-blind study technique with a single crossover of propranolol (Inderal®), 20-mg. tablets, and placebo (manitol)* was employed. The patients were instructed to take a single tablet four times a day. They were not told that they would receive a placebo for one-half of the study period. The duration of the study was six months per patient. Each patient was seen at four-week intervals to assess the frequency and severity of headaches and drug side effects. Blood pressure and heart rate were also recorded at these visits. No restriction was placed on the use of symptomatic medication (salicylates, ergotamine, etc.) for headache during the study. Prophylactic use of ergotamine compounds and methysergide was prohibited, however.

Results

Table 1 defines the symptomatic response to Inderal. The criteria for improvement of symptoms were based upon frequency and

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* Both drugs were provided by Ayerst Laboratories.

TABLE 1
DEFINITIONS OF SYMPTOMATIC RESPONSES TO
PROPRANOLOL AND PLACEBO

EXCELLENT	ALL OR NEARLY ALL SYMPTOMS OF MIGRAINE ABSENT AFTER FIRST WEEK OF STUDY
GOOD	MORE THAN 50% REDUCTION IN FREQUENCY OR SEVERITY OF HEADACHES
FAIR	MINIMAL SYMPTOMATIC IMPROVEMENT
NO EFFECT	

duration of headaches, type and amount of symptomatic medication required for relief, and subjective description of headaches. Analyzing each three-month time period individually in response to Inderal is conspicuous.

First three months. Eight patients received Inderal and 11, placebo. Five of the 8 (63%) patients receiving Inderal had a good or excellent response, 2 had minimal improvement, and 1 was unaffected. Ten of the 11 (91%) of those receiving placebo had no effect. One patient had a fair response. This comparative effect is significant ($p < 0.002$).

Second three months. In the group of 8 patients who received Inderal first, 6, or 75%, had no effect from placebo, whereas 2 who had done well on Inderal continued to do as well on placebo. In the group receiving Inderal in the second half of the study, 10 of the 11, or 91%, had excellent or good responses. One patient had no effect from either drug.

During this second three-month period the response to Inderal again was significantly better than that to placebo ($p < 0.02$).

Analyzing all patients irrespective of sequence of drug administration, 15 of 19 (79%) responded better to Inderal than to placebo. Four of the 19 (21%) responded similarly to Inderal and placebo. Two of these patients had no effect from either substance. One patient had a good and 1 had an excellent response to placebo (Table 2). Both of these beneficial reactions to placebo followed favorable responses to Inderal. This could represent placebo effect or a carry-over effect of Inderal.

Classic vs. common migraine. Good or excellent responses to Inderal were obtained in 77% of patients with common migraine and

in 83% of those with classic migraine. It is noteworthy that in 2 patients with classic migraine, Inderal completely eliminated headache while neurological prodromes continued in an attenuated form.

Male vs. female response. Seven of 9 men, or 77%, had good or excellent response to Inderal, while 8 of 10 women similarly benefited.

Side effects

A single patient complained of abdominal cramps and diarrhea, which were easily controlled by anticholinergics.

Side effects are variable but rare. In Steven's series of 1,500 cardiac patients treated with oral propranolol, light-headedness, drowsiness, nausea, and diarrhea were the most frequently encountered side effects.⁹ However, no side effects occurred in 98.5% of his patients.

Discussion

The pathogenesis of migraine remains enigmatic. The roles of vasoactive amines and their metabolism, imbalance of vasoconstrictor-vasodilation mechanisms, and precapillary shunting have not been satisfactorily explained. Thus, any explanation of the efficacy of propranolol in the prophylactic treatment of migraine would at best be speculative.

The pharmacology of propranolol deserves

TABLE 2
RELATIVE RESPONSES OF 19 PATIENTS TO
PROPRANOLOL AND PLACEBO

		PROPRANOLOL RESPONSE				
		NO EFFECT	FAIR	GOOD	EXCELLENT	TOTAL
PLACEBO RESPONSE	NO EFFECT	2	2	8	4	16
	FAIR				1	1
	GOOD			1		1
	EXCELLENT				1	1
	TOTAL	2	2	9	6	19

TABLE 3
SUMMARY OF SALIENT PHARMACOLOGIC
PROPERTIES OF PROPRANOLOL

DECREASES VASODILATOR RECEPTIVITY \longrightarrow
INCREASED VASCULAR RESISTANCE
DECREASES CEREBRAL O ₂ UTILIZATION
DECREASES CARDIAC OUTPUT AND BLOOD PRESSURE BY DECREASING VENTRICULAR CONTRACTILITY
INCREASES GLYCOGEN IN BRAIN AND MUSCLE BY REDUCING PHOSPHORYLASE ACTIVITY
REDUCES HEART RATE
a. DECREASED ACTIVITY OF S-A NODE
b. DECREASED CONDUCTION THROUGH A-V NODE
LOCAL ANESTHETIC (potency of Lidocaine)
INHIBITS PARKINSONIAN TREMOR
± ANTICONVULSANT

comment. The major sites of beta-adrenergic activity are the conducting system of the heart and the smooth muscle of the arteries, veins, and bronchioles.^{7,8} Catecholamine-mediated phosphorylase activation also enhances glycogenolysis.⁹⁻¹² Hence, the potential complications of beta blockade are precipitation or potentiation of heart failure, asthma, and hypoglycemia. Fortunately, these hazards are confined to patients with these special proclivities and can be obviated by careful patient selection. Table 3 summarizes the major pharmacologic effects of propranolol.

Various mechanisms may be important in explaining the beneficial influence of propranolol upon migraine. The most evident is blockade of vasodilator receptors in adrenergically innervated vessels.¹³⁻¹⁷ This putatively would influence the extracranial vessels' contribution to the headache phase^{18,19} by creating a vasoconstrictor bias and preventing reactive vasodilation.

Our unpublished observations of reduced cerebral oxygen consumption in dogs after propranolol administration suggest an effect on intracranial vessels secondary to alteration of cerebral metabolism.⁴ Others^{20,21} have demonstrated that this independent effect of propranolol is probably due to inhibition of beta-adrenergically controlled cerebral glyco-

genolysis and glycolysis.²² The resultant effect would be removal of a metabolic vasodilator influence on the smallest vessels at the tissue level. This net vasoconstrictor effect should be maximal on the tissue vessels that probably do not serve as a source of pain. Theoretically we might predict that the neurological prodromes of migraine would be made *worse*, but this was not true in our patients. Equally vexing is the ability of propranolol to block the vasoconstrictive effects of barium chloride topically applied to pial vessels.²³ This paradoxical antispasmodic effect further reflects lack of beta-adrenergic specificity of propranolol as recognized in other systems.²⁴⁻²⁷

We conclude that propranolol is an effective and safe agent for prophylaxis in complicated and repetitive migraine. Further experience will determine whether propranolol should assume a position of first-choice therapy.

Summary

Nineteen patients with refractory migraine were treated with prophylactic propranolol, 80 mg. per day, and placebo in a six-month double-blind study. Fifteen of 19 patients responded better to propranolol than to placebo, 2 (10.5%) were improved by active drug and placebo, and the remaining 2 were unresponsive to both substances.

The authors conclude that propranolol prophylaxis is a safe and effective therapy for migraine. Familiarity with the pharmacologic effects of propranolol and careful selection of patients are essential.

The exact mechanisms of action of propranolol in migraine are unknown. However, the authors speculate on the possible modes of action in view of the current understanding of the properties of propranolol.

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