Treatment of essential tremor with propranolol

T. J. Murray, M.D., F.R.C.P.[C], *Halifax, N.S.*

Essential tremor has been of considerable interest for over 100 years. Although a monosymptomatic and relatively benign disorder, the tremor is disturbing to patients because it is embarrassing and may interfere with motor tasks.

The tremor involves the hands, the arms and often the head. It may also affect the chin, tongue, laryngeal muscles and eyes. The tremor may begin at any age but commonly starts in the second or third decade. When it develops in old age it is usually labelled as "senile tremor".

The tremor often begins on one side but soon becomes bilaterally symmetrical. It is absent at rest and is increased by posturing or movements of the limb. There may be some independence of the tremor in each limb: Barlow and Schwab[1] have noted that the tremor is decreased if one limb supports the other. The initial limb and hand movements are usually tremulous but the final accurate part of the movement may be steady. Therefore despite tremor the individual may thread needles and type without any difficulty. There are many surgeons with essential tremor who retain their technical accuracy and skill in the operating room, although the shaking is disconcerting to the patients at the bedside. Only late, when its amplitude is greater and an intention quality becomes more marked, does the tremor interfere with handwriting.

The tremor is increased by emotional stress, excitement and physical fatigue. Other aggravating factors may be tobacco, coffee, tea, sexual intercourse and local pain in the hand or arm. Almost all patients with essential tremor find it worse in the presence of strangers and they usually feel that people are staring at them. The tremor is often worse in the morning and one of my patients got up at 5 a.m. to hide his marked morning tremor from his family.

Essential tremor is commonly familial and the inheritance is dominant with variable penetrance.[2] Dana[3] studied one family in which 45 members were afflicted. Minor[4] studied some Russian families and found that these were unusually large with many members living to a very old age. He suggested the disorder was characterized by a triad of tremor, fecundity and longevity. Other early studies suggested that the family members tended to be highly intelligent, often professional people, who tended to be "lusty virile personalities who both work and play hard, eat heavily and drink deeply".[2] The neurologist Babinski, Oliver Cromwell and Louis XV have been cited as examples of these personality features in association with essential tremor. Most of these early observations remain unconfirmed.

Present study

It is well known that emotional factors will increase physiological tremor, essential tremor and Parkinsonian tremor. The administration of adrenalin will have the same effect, and the increase in tremor from emotion has been thought to be due to endogenous secretion of adrenalin.[5] Propranolol (Inderal®), a beta-adrenergic blocking agent, has been shown to decrease the tremorogenic effect of emotion and of intravenously administered adrenalin on physiological tremor and Parkinsonian tremor.[5, 6] Because essential tremor is suspected of being an accentuation of physiological tremor[7] it would be logical to try propranolol in an attempt to control it. Winkler and Young[8] in 1971 noted that a patient with cardiac disease had relief from his essential tremor when his cardiac condition was treated with propranolol. Using a double-blind study they noted good to excellent suppression of tremor with propranolol in 20 out of 25 cases of essential tremor. Four had some improvement but not enough to justify long-term therapy, and one patient was unchanged.

We conducted a preliminary study of 12 cases of essential tremor treated with propranolol. Before starting therapy a full history was taken and a complete examination was carried out, noting particularly any evidence of cardiac or respiratory disease. Investigation included an electrocardiogram and hematological and biochemical studies. Three patients were excluded because of a history of significant cardiac disease or asthma. The remaining 12 cases were treated and followed for four to 12 months.

The initial dosage of 20 mg. t.i.d. was increased to 40 mg. t.i.d. after one week. Improvement was noted after seven to 10 days in most cases (Table I). Six patients had dramatic improvement and in four the tremor completely disappeared. Six other patients had appreciable reduction in tremor of their limbs. One patient had persistence of head tremor, and another of chin tremor, despite disappearance of the hand and arm tremor in both patients.

Because the tremor is relatively benign and justifies long-term therapy primarily because it is disturbing and embarrassing, it seemed justified to have these patients grade their own treatment results. There was some variance with the examiner's assessment mostly because some patients were distressed if even minor tremor remained, while others thought any reduction was gratifying. A degree of improvement we considered good was sometimes classified by the patients as excellent, and *vice versa*. The patient we believed had good improvement because of disappearance of his arm and hand tremor classified his improvement as only fair because his head tremor continued.

There were no serious side effects in this limited series. One patient had mild nausea and two had a vague sense of malaise but symptoms were not marked enough to require changing the dose of propranolol or using other medication for their relief.

Propranolol

Although it has been known for almost 70 years that action of the sympathetic nervous system is mediated by two different receptors, it was not until 1948 that Ahlquist[9] classified them into alpha and beta types. Propranolol has been widely

T. J. MURRAY, M.D., F.R.C.P.[C], Victoria General Hospital, Halifax, N.S.
Presented at the Canadian Congress of Neurological Sciences, Banff, Alberta, June 1972.
Reprint requests to: Dr. T. J. Murray, 5849 University Ave., Halifax, N.S.

used since 1965 as an effective and safe selective beta-adrenergic blocking agent, primarily for treating angina, cardiac arrhythmias, idiopathic subaortic stenosis and pheochromocytomas.

Propranolol is contraindicated in bronchial asthma, allergic rhinitis, sinus bradycardia and heart block (total or greater than second degree), cardiogenic shock, heart failure (right ventricular or congestive) and chloroform or ether anesthesia. Caution must be used in pregnant women, children, and patients with myocardial infarction or angina with poor cardiac reserve. In hypoglycemia the adrenergic effects may be masked, thus removing many of the early warning signs and symptoms.

Discussion

Essential tremor is thought to be a central regulatory defect in the reticular activating system-basal ganglia control over the servo mechanism responsible for physiological tremor. Essential tremor may represent a failure in the damping mechanism of this servo system. This central concept of essential tremor was supported by the occasional reports of successful treatment by thalamotomy.[10] Now that propranolol has been found to be an effective form of therapy, we must consider a possible peripheral basis, or perhaps a combined peripheral and central basis for essential tremor. Constas[11] has shown that in Parkinson's disease there are both central and peripheral mechanisms involved in the emotional effects of this type of tremor.

In examining the possible mechanisms operational in essential tremor, it is important to take into consideration the studies on physiological tremor. Marshall[12] showed that essential tremor follows the same frequency curve by age as does physiological tremor, and he considered essential tremor to be physiological tremor with increased amplitude. When essential tremor begins it is superimposed on physiological tremor but later becomes continuous.

Intravenous adrenalin increases physiological tremor but this effect can be blocked by propranolol. Arterial occlusion by means of a sphygmomanometer cuff on one arm decreases spontaneous physiological tremor and abolishes the effect of adrenalin given in the opposite arm. Intra-arterial adrenalin also increases physiological tremor but the vasoconstriction resulting must be blocked with phenoxybenzamine if increasing the dosage is to further exaggerate the tremor. Marsden[13] showed that beta-adrenergic blockade of one arm abolishes the tremorogenic effect of adrenalin on that arm. He concluded that the effect of adrenalin on physiological tremor was peripheral at the beta receptor. Because of the relationship between physiological tremor and essential tremor and the similar effects on them of emotion, adrenalin and propranolol, it seems likely that propranolol reduces essential tremor by its action at a peripheral receptor. The site of action is unclear, however, since propranolol is known to have central effects.[14]

Conclusion

Although the nature and mechanism of essential tremor have been controversial over the years, there has been general agreement that no useful therapy is available. Those who related the disorder to Parkinson's disease found anticholinergic drugs and levodopa to be of no value. Those who noted a striking relationship to anxiety and emotion were disappointed in the lack of response to sedatives, tranquillizers and antidepressants. The only agent to afford relief was alcohol but this effect is short-lasting. Foley[15] summed up the therapeutic situation while commenting on Winkler and Young's paper and I would like to quote his remarks:

"I reflect on the traditional treatment of essential tremor. The physician confronted with it goes through a kind of ritual. First he assures the patient that he does not have Parkinson's disease. Secondly he utters a few homiletic words on the evils of drink, reminding the patient that many alcoholics have started off as essential shakers and discovered relief from the shaking through the transiently salubrious effect of alcohol. Then, if the physician is over 50, he prescribes phenobarbital which does no good. If he is under 50 he prescribes Librium or Valium, which does no good. If the physician is under 30 he wonders if there might be somebody who would like to put a hole some place in the patient's brain. And interestingly enough, that has sometimes done some good. But it is not recommended except in rare instances. Up to now, this has been the routine."

The addition of propranolol to the therapy of essential tremor may be a further step towards a safe and effective treatment where there was none before.

Table I
Results of propranolol (Inderal) therapy

	Excellent	Good	Fair	Unchanged
Clinical	6	6	–	–
Self-assessment	6	5	1	–

Summary

This paper presents a preliminary study of 12 patients with essential tremor, all of whom had good or excellent suppression of tremor on a moderate dose of propranolol. Whether this beta-adrenergic blocking agent acts centrally on the nervous system or peripherally at the beta receptors remains uncertain. If certain respiratory and cardiac contraindications and precautions are observed, propranolol promises to be an effective form of therapy for this disorder, the treatment of which has hitherto been unsuccessful.

Résumé

Le traitement de la trémulation essentielle par le propranolol

Le présent article constitue une étude préliminaire de 12 malades souffrant de tremblement essentiel et signale que tous ont obtenu une suppression du tremblement bonne ou excellente, par une dose moyenne de propranolol. On ignore encore si cet agent de blocage bêta-adrénergique exerce une action centrale sur le système nerveux ou une action périphérique sur les récepteurs bêta-adrénergiques. Si on prend certaines précautions, concernant les contre-indications respiratoires et cardiaques, le propranolol promet d'être un médicament efficace dans cette pathologie dont les divers traitements s'étaient jusqu'ici révélés inefficaces.

References

1. BARLOW JS, SCHWAB RS: Mutual limb stabilization in relation to tremor characteristics in parkinsonian and essential or heredofamilial tremor. *Neurology* 21: 78, 1971
2. CRITCHLEY M: Observations on essential (heredofamilial) tremor. *Brain* 72: 113, 1949
3. DANA CL: Hereditary tremor, a hitherto undescribed form of motor neurosis. *Am J Med Sci* 94: 386, 1887
4. MINOR L: Uber hereditaren Tremor. *Zentralbl Gesamte Neurol Psychiatr* 28: 514, 1922
5. MARSDEN CD, OWEN DAL: Mechanisms underlying emotional variation in parkinsonian tremor. *Neurology (Minneap)* 17: 711, 1967
6. STRANG RR: Clinical trial with a β-receptor antagonist (propranolol) in parkinsonism. *J Neurol Neurosurg Psychiatry* 28: 404, 1965
7. MARSHALL J: Observations on essential tremor. *J Neurol Neurosurg Psychiatry* 25: 122, 1962
8. WINKLER GF, YOUNG RR: The control of essential tremor by propranolol. *Trans Am Neurol Assoc* (1971) 96: 66, 1972
9. AHLQUIST RP: A study of adrenotropic receptors *Am J Physiol* 153: 586, 1948
10. COOPER IS: Heredofamilial tremor. Abolition by chemothalamectomy. *Arch Neurol* 7: 129, 1962
11. CONSTAS C: Effects of adrenaline, noradrenaline and isoprenaline on parkinsonian tremor. *J Neurol Neurosurg Psychiatry* 25: 116, 1962
12. MARSHALL J: The effect of ageing upon physiological tremor. *J Neurol Neurosurg Psychiatry* 24: 14, 1961
13. MARSDEN CD, FOLEY TH, OWEN DA, et al: Peripheral beta-adrenergic receptors concerned with tremor. *Clin Sci* 33: 53, 1967
14. SINGH KP, BHANDARI DS, MAHAWAR MM: Effects of propranolol (a beta-adrenergic blocking agent) on some central nervous system parameters. *Indian J Med Res* 59: 786, 1971
15. FOLEY J: Discussion following Winkler and Young's paper. *Trans Am Neurol Assoc* (1971) 96: 67, 1972

REVIEW ARTICLE

Chemotherapy of gonorrhea: a review of current status

S. K. Sim, PH.D., *Toronto*

Gonorrhea in the United States has been referred to in a 1971 medical editorial[1] as a pandemic disease and in a 1972 paper[2] as a "current epidemic". From 1964 to 1969 there had been an increase of 70% in the number of reported cases in the U.S.[3] In 1970 there were some 600,000 reported cases in the U.S.[4] and an estimated national total of over two million if unreported cases and contacts that required treatment were to be included.[4, 5] This represents an incidence rate of some 1000 new cases per 100,000 population or 2000 cases per 100,000 persons over 15 years of age, which is considered by some as being of epidemic proportions.[5] In Canada there were some 27,000 reported cases in 1969. Assuming this number to be only 10% of all cases, the estimated incidence rate was 1000 per 100,000 population.[6] Large numbers of gonorrhea cases treated by physicians in private practice are not reported to public health authorities.[7] The world prevalence of gonorrhea in 1970 was estimated to be some 16 million cases[5] and there have been sharp rate-increases in many countries during the past five or six years.[5] Catterall[8] quoted a World Health Organization estimate of 100 million infections (including estimated unreported cases) in the world in 1971.

The spread of gonorrhea within each country and between countries has been facilitated by epidemiological, sociological and ecological factors. The public health problem of control of gonococcal infections is further aggravated by several additional factors such as: (1) short incubation period of the gonococcus; (2) a number of female carriers being asymptomatic for long periods; (3) reluctance of many physicians to report the cases treated by them;[7] (4) high rate of re-infections after initial cure; and (5) frequent defaulting by patients in follow-up tests and in multi-dose administration of required drugs.

The chemotherapy of gonorrhea has passed from a brief pre-war era of therapy with sulfonamides (which quickly lost their usefulness because of rapid development of resistance) through two post-war decades of largely one-drug therapy with penicillin G, to the present stage when several clinically effective agents are available as alternatives to penicillin.

The common gonococcal urethritis can sometimes lead to, or is accompanied by certain serious complications including arthritis, endocarditis, ophthalmia, pelvic inflammation, epididymitis and septicemia. Syphilis may be a coexistent infection. Any of these or other complications require adjustment of the drug in kind and/or in dosage schedule from what is used in uncomplicated gonorrhea. This review will summarize and interpret some of the more significant aspects in the chemotherapy of uncomplicated gonorrhea.

Factors affecting selection of drugs

The several factors which, in varying degrees, have significant bearing on the selection and dosage schedule of particular drugs in the treatment of uncomplicated gonorrhea include the following: (1) effectiveness in curing the infection; (2) ease of administration; (3) toxicity and allergenic properties; (4) treponemicidal action and (5) indirect factors.

1. *Effectiveness.* The drug to be used must be capable of achieving an acceptable cure-rate with the use of tolerable doses. The degree of clinical effectiveness is not only a function of the intrinsic activity (*in vitro* potency) of the agent against the *Neisseria gonorrhoeae* organism, but is also governed by the duration and level of the serum concentration of the drug and its ability to reach the infected tissues. Serum concentration of the free drug is in turn affected by the degree of protein binding and excretion kinetics. For example, as will be discussed below, the *in vivo* effectiveness of a given dose of penicillin is considerably increased merely by altering its excretion kinetics by the concurrent administration of probenecid. In another respect, when considering the effectiveness on the basis of published reports of cure-rates obtained, one must bear in mind that the distribution of resistant strains (especially with respect to re-

Reprint requests to: Dr. S. K. Sim, Associate Professor of Pharmacognosy, Faculty of Pharmacy, University of Toronto, Toronto 181, Ontario.