

## Clinical trial with a beta-receptor antagonist (propranolol) in Parkinsonism

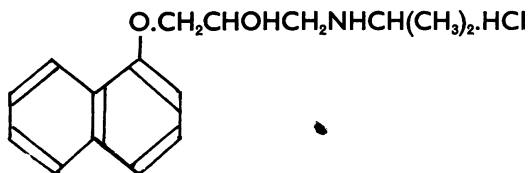
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Pronethalol (Alderlin), an adrenergic beta-blocking agent introduced in 1963, was successfully tested in the management of various cardiac arrhythmias, phaeochromocytoma, angina pectoris, and hypertension. Herring (1964) administered the drug to 10 patients with Parkinsonism, in view of the well known 'tremor-potentiating effect' of adrenaline, and observed a diminution of tremor following an intravenous dose of 50 mg.

Due to the subsequent detection of carcinogenic changes in mice, although not in rats, Alderlin was withdrawn and replaced by the chemically similar, but non-toxic preparation propranolol, which was the drug employed in the present trial.

Propranolol (Inderal), 1-isopropylamino-3-(1-naphthylxy)-2-propanol-hydrochloride, is an adrenergic, beta-receptor antagonist, having 10-20 times the therapeutic ratio of Alderlin. It is available as 10 mg. scored tablets and in 5 mg. ampoules for intravenous injection and possesses the following structural formula:



### CLINICAL MATERIAL AND METHOD

Seventeen patients (nine males, eight females) between 32 and 50 years of age, and 13 (seven males, six females) between 52 and 66 participated in the trial.

No patient was proved to have arteriosclerotic cerebrovascular disease at the time of onset of Parkinsonism but three had a conclusive history of encephalitis. No case of chemical Parkinsonism was included.

Twelve patients were in hospital during the first two weeks of the trial, and 18 during the entire observation period, which varied from one to eight weeks.

Twenty patients who were taking anti-Parkinson drugs when first examined maintained the same dose throughout the trial.

Inderal, 5 mg. ( $\frac{1}{2}$  tablet), was given three times a day for two days, followed by daily increments of 15 mg., until a

satisfactory clinical response was obtained or the daily total reached 60 mg., which was the optimal dose observed in a preliminary pilot study. If no effect was produced by 60 mg. a day for three days, the drug was discontinued.

Five patients, with moderate to severe tremor, were given 20-30 mg. of Inderal intravenously during a period of two to four minutes. Tremor was recorded with the aid of an E.E.G. apparatus, and the pulse, blood pressure, and dynamometer recordings were taken before, during, and three minutes after the end of the injection. Similar recordings were also made before and 30 minutes following oral medication.

All examinations were performed by the author alone and the symptoms and signs were evaluated clinically and/or mechanically, and graded in units of 10 from 0 (normal) to 100% (maximum severity). A number of timed performance tests were used as a measure of the patient's functional capacity. For the purpose of assessment an improvement of less than 10% was not considered significant.

All patients were normotensive and free from any symptom or sign of cardiac disease.

Routine blood, urine, and liver function studies were carried out on seven patients.

### CLINICAL RESULTS

As measured by the timed performance tests, eight patients (27%) obtained a significant degree of clinical improvement from oral therapy with Inderal (10% or more). The improvement recorded was 30% in two patients, 20% in three, and 10% in three.

Rigidity, present in 24 patients, was significantly improved in seven (30% in two, 20% in two, and 10% in three). Bradykinesia, present in 12 patients, was significantly improved in five (20% in two and 10% in three). An additional seven patients reported an improvement of rigidity and/or bradykinesia which could not be measured objectively in three, and was, as recorded by the timed performance tests, less than 10% in four. The increased strength of the 'hard-grips' was confirmed by the dynamometer in 12 patients. In no case did it exceed 30% and was usually between 15 and 25%.

Tremor, present in 26 patients, was significantly

improved in only three (20% in one, 10% in two). Subjective improvement, or a reduction of less than 10%, occurred in an additional six patients.

The drug was discontinued in 14 patients, because a daily dose of 60 mg. failed to produce any effect after three days. Several of these patients received 90 mg. daily for two to three days without significant change.

Two patients discontinued the drug due to restlessness and insomnia and one because of dizziness. Mild degrees of headache, nausea, and dizziness in four patients disappeared spontaneously after two to three days at an unchanged dosage level.

No direct psychostimulating or antidepressive effects were observed. A slight sedative or tranquillizing action was described by seven patients, including two of the three in whom tremor was significantly improved.

Thirty minutes after an oral dose of 20 mg. the systolic blood pressure was reduced from 10 to 20 mm. Hg in eight patients, was not significantly changed in 20, and was elevated from 10 to 20 mm. Hg in two. The pulse rate was decreased by 10 to 20 beats per minute in 14 patients, not significantly changed in 15, and increased by 15 beats per minute in one.

In none of the five patients receiving an intravenous dose of 20 to 30 mg. was any appreciable effect

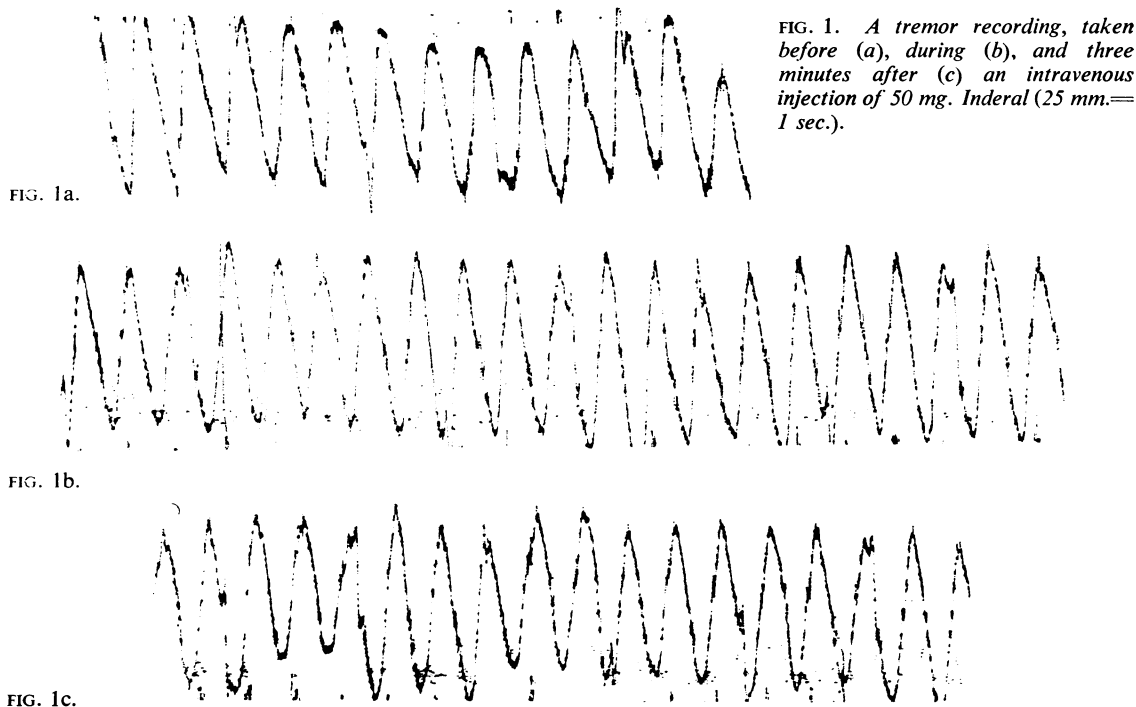
observed on the amplitude or rate of tremor. A slight reduction of both blood pressure and pulse rate occurred in three of these cases. The tracing of a patient who received 50 mg. intravenously, during a period of five minutes, is shown in Figure 1.

The control laboratory examinations were within normal limits.

#### DISCUSSION

Herring (1964) was undecided as to whether the slight reduction of tremor, following an intravenous dose of 50 mg. of Alderlin, was due to a block of the beta adrenergic receptors or to a mild sedative effect of the drug.

The results of the present study indicate that the improvement of tremor is secondary. No significant change, in either amplitude or rate, was observed during or within three minutes of concluding an intravenous injection. In addition, oral therapy produced a significant but very slight degree of improvement in only three patients. An improvement of less than 10% is not uncommonly seen as the result of hospitalization. The improvement of tremor was mainly observed in periodicity, and to a less extent in amplitude and ease of elicitation. The rate, as measured by an electronic recorder, remained unchanged. It was also observed that the reduction



of tremor varied inversely as to its severity. No patient having a moderately severe to severe tremor, showed any significant response to the drug, even to doses of 90 mg. a day.

The significantly increased functional capacity, as demonstrated objectively in eight patients, was due to the improvement of rigidity and bradykinesia. The improved muscular performance resulted in a better gait, and foot drop disappeared in one patient. The increased 'grip strength' was also demonstrated by the dynamometer following intravenous injection.

Although three patients who were unable to tolerate clinically effective doses of other specific preparations have been satisfactorily maintained on Inderal for periods of up to eight weeks, the results of the present study do not indicate that the drug is a particularly effective anti-Parkinsonism agent. It does not possess the efficacy of currently available anti-cholinergic and/or antihistaminic compounds.

#### SUMMARY

Eight of 30 patients with non-chemical Parkinsonism were significantly improved by the oral administration of Inderal, an adrenergic, beta-receptor blocking agent.

The drug was most effective in ameliorating rigidity and bradykinesia, producing a significant improvement of tremor in only three of 26 patients. The 'anti-tremor' action of Inderal was considered to be a secondary one. No significant reduction in the amplitude or rate of tremor was observed following doses of 20 to 50 mg. intravenously in six patients.

The results of the trial do not indicate that Inderal in the doses used is a particularly efficacious, anti-Parkinsonism drug.

#### REFERENCE

- Herring, A. B. (1964). Action of pronethalol on Parkinsonian tremor. *Lancet*, 2, 892.