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## A LONG-TERM EVALUATION OF PARGYLINE HYDROCHLORIDE IN HYPERTENSION\*

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PARGYLINE hydrochloride is a non-hydrazine monoamine oxidase inhibitor which, although originally developed for its euphoric properties, has had wide use as an antihypertensive agent. A number of papers have appeared describing the effectiveness of this drug in lowering the blood pressure in ambulatory and hospitalized hypertensive patients, especially in the erect position (Bryant *et al.*<sup>3</sup>, Ford<sup>4</sup>, Maronde *et al.*<sup>11</sup>, Sutnick *et al.*<sup>13,14,15</sup>). We have been evaluating pargyline since 1962, and an earlier communication (Sutnick *et al.*<sup>14</sup>) reported that 84% of patients receiving the drug over a period of 3 months had an orthostatic drop in blood

pressure. Side effects were seen in over one-half the patients studied and necessitated discontinuance of the drug in 8% of the total. The most common side effect was postural hypotension and in the majority of cases this was corrected by adjustments in dosage. Other side effects included fluid retention, increased appetite, urinary frequency, mild constipation, nervousness, dryness of the mouth, and elevated blood urea nitrogen (transient). There were no significant changes in the hematologic studies or urinary findings related to drug administration, nor were there any liver function abnormalities, as have been noted with

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the hydrazine types of monoamine oxidase inhibitors (Sutnick *et al.*<sup>14</sup>).

From these studies, it became apparent that pargyline was a potent antihypertensive agent, at least during short-term therapy. We, therefore, decided to continue administering the drug to those patients who initially demonstrated a satisfactory lowering of blood pressure with no significant intolerance in an attempt to evaluate its long-term antihypertensive effect.

**Material and Methods.** A group of 18 patients from the Hypertension Clinic of the Temple University Hospital and one private patient were included in the study. There were 14 females and 5 males ranging in age from 36 to 69 years.

Based on laboratory studies and clinical evaluation, all patients had been previously classified as having moderate to severe hypertension considered to be either essential or of proven renal etiology.

Controlled blood pressure measurements were obtained after all antihypertensive medications had been withdrawn or a placebo alone given for a period of at least 2 weeks. All blood pressures were recorded in both supine and erect positions.

The initial dose of pargyline was 12.5 to 25 mg. daily which was then increased by increments of 25 to 50 mg. daily at intervals of one to 2 weeks with the ultimate and arbitrary goal of decreasing the orthostatic blood pressure by at least 30 mm. of Hg systolic or 20 mm. of Hg diastolic, or both. An arbitrary maximum dose of 200 mg. was set for every patient unless intolerable side effects ensued or an optimal fall in blood pressure could be achieved at lower dosage.

The following laboratory determinations were made before the administration of the drug and at varying intervals during the study: hemoglobin, hematocrit, white blood cell count and differential count, urinalysis, blood urea nitrogen, serum glutamic oxaloacetic transaminase, and serum alkaline phosphatase. Sixteen of the 19 were part of a previous study of pargyline. Three patients were added to the study without benefit of all of these extensive laboratory procedures; however, necessary laboratory studies were performed as indicated for each individual.

**Results.** Only 8 patients (42.1%) maintained an adequate blood pressure response to pargyline when it was given for a period of 6 months to 2

years. Eleven patients (57.9%) became refractory to the drug even when the dosage was increased to the arbitrary level of 200 mg. per day.

Of the 8 patients that maintained a satisfactory response, the drug had to be discontinued in two. One patient developed congestive heart failure, and the drug was discontinued. Pargyline therapy was subsequently resumed and he has continued to demonstrate satisfactory decrease in blood pressure. The other patient developed symptoms of cerebrovascular insufficiency which were initially thought to be due to postural hypotension. He continued to have symptoms when the drug dosage was decreased and was eventually removed from the study.

Of the 11 patients who became refractory, 5 developed side effects. Four patients had fluid retention of 15 to 20 pounds. Two of these had to discontinue the drug before they reached the maximum arbitrary dosage of 200 mg. a day. Upon cessation of the drug the fluid retention disappeared. One patient developed a psychotic episode characterized by hallucinations.

**Discussion.** Previous studies have shown monoamine oxidase inhibitors to be potent antihypertensive agents. Pargyline is no exception (Sutnick *et al.*<sup>13,14,15</sup>). The effect is seen most frequently in the erect position, although some patients do obtain a moderately good response in the supine position.

There were rather frequent side effects noted in our original studies<sup>13,14,15</sup>. Early in this study all 19 patients demonstrated an optimal fall in blood pressure with few side effects. However, 7 (36.8%) of them developed side effects severe enough to cause the drug to be discontinued as the dosage was increased over an extended period of time in order to maintain an adequate lowering of blood pressure. Other patients complained of dryness of the mouth, increased appetite, in-

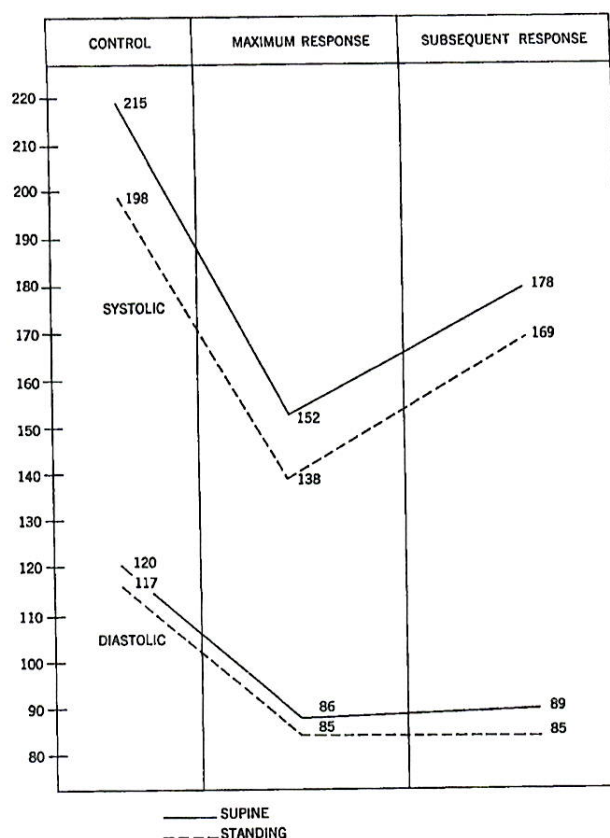


Fig. 1.—Composite of 8 patients who had an adequate response to long-term pargyline administration.

ability to sleep, and minor weight gains. We did not decrease drug dosage in those patients with mild side effects as long as the side effects were tolerable.

A large percentage of the patients experienced a feeling of well-being during their pargyline therapy. This feeling of well-being did not depend on whether the patient continued to respond to the drug or whether he became refractory.

The maximum hypotensive response was orthostatic in 11 (57.8%) of 19 patients. The remaining 8 patients (42.1%) had a supine and orthostatic

response. These figures correlate well with our previous findings (Sutnick *et al.*<sup>14</sup>).

The mode of action of pargyline is still open to question. Brest and co-workers<sup>12,16</sup> have reported the hypotensive effect to be due to a decrease in total peripheral resistance, but there is some question whether this is true in all patients. It has been suggested that this effect is obtained by virtue of accumulation of norepinephrine and epinephrine in bound form in blood vessels, thus rendering them less sensitive to circulating catecholamines (Gertner<sup>5</sup>).



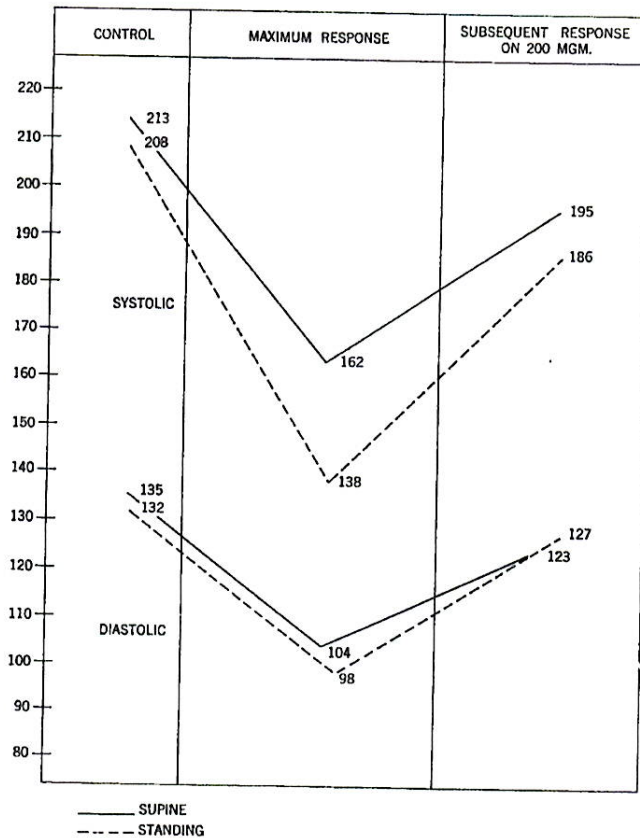


Fig. 2.—Composite of 11 patients who became refractory to long-term pargyline administration.

It is the present consensus that the inhibition by pargyline of the enzyme monoamine oxidase has little if any effect on the lowering of blood pressure in the dosage usually employed in man. It has recently been shown that various monoamine oxidase inhibitors, including pargyline, share the ability to prevent the physiologic release of norepinephrine onto the receptor sites adjacent to the terminal end of the postganglionic fiber (Brodie<sup>1</sup>, Gessa, Cuenca and Costa<sup>7,8</sup>). This action resembles the effect of bretylium. Like bretylium, pargyline and other monoamine oxidase inhibitors block the pharmacologic action of guanethidine and inhibit the response to low fre-

quency electrical sympathetic nerve stimulation but do not block the responses to higher frequency stimulation (Brodie<sup>1</sup>, Gessa, Cuenca and Costa<sup>7,8</sup>).

It has been suggested that the accumulation of norepinephrine in the sympathetic ganglia opposes acetylcholine action and this depresses ganglionic transmission (Gertner<sup>6</sup>, Gillespie, Terry and Sjoerdsma<sup>9</sup>). Brodie and Costa<sup>2</sup> however, were able to demonstrate only very minimal and transient ganglionic blockade by pargyline and other monoamine oxidase inhibitors.

**Summary.** Nineteen patients who previously were noted to have significant hypotensive response to pargyline

hydrochloride in a short-term study were followed from 6 months to 2 years.

1. Only 8 patients (42.1%) continued to maintain an adequate lowering of blood pressure.

2. Eleven patients (57.9%) became

refractory to the drug at the arbitrary dosage of 200 mg. per day.

3. Seven patients (36.8%), whether refractory or responding, had side effects severe enough to cause the drug to be discontinued.

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#### SUMMARIO IN INTERLINGUA

##### Un Evalutation Perdurative del Effectos de Hydrochloruro de Pargylina in Hypertension

Dece-novem patientes in qui previemente significative responsas hypotensive a hydrochloruro de pargylina habeva essite constatate in un studio de breve duration esseva tenite sub observation durante periodos de inter 6 menses e 2 annos.

1. Solmente 8 patientes (42,1 pro cento) continuava manifestar un adequate reduction del tension de sanguine.

2. Dece-un patientes (57,9 pro cento) disveloppava refractorietate contra le pharmaco a un dosage arbitrari de 200 mg per die.

3. Septe patientes (36,8 pro cento), incluse certes con refractorietate e alteres qui respondeva positivemente, manifestava adverse effectos secundari sufficientemente sever pro requirer le suspension del medication.