A REPORT ON THE EFFECTS OF PHENELZINE (NARDIL), A MONOAMINE OXIDASE INHIBITOR, IN DEPRESSED PATIENTS

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INTRODUCTION

PHENELZINE, β-phenylethylhydrazine, of structural formula, is regarded as a

$CH_2 - CH_2 - NH - NH_2$

potent, rapidly acting, long-lasting monoamine oxidase (M.A.O.) inhibitor. The administration of such compounds protects 5-hydroxytryptamine (serotonin) which is destroyed by M.A.O. 5-hydroxytryptamine is believed to act in the brain as a chemical mediator, the function of which is to control the pulsating action of oligodendroglial cells which supply the other brain tissues with nutrient. It has been suggested that a relative 5-hydroxytryptamine deficiency is the fundamental biochemical disorder of severe depressive states and that M.A.O. inhibitors such as phenelzine tend to promote restoration to more normal concentration and activity.

However, a recent leading article (1) comments on observations which make it difficult to relate the central action of M.A.O. inhibitors to an effect on the rate of inactivation of the catechol amines.

Phenelzine is said to exhibit adequate anti-depressant activity at dosage levels that are without serious toxicity. Claims are made for an effect comparable in scope, speed and safety to that produced by electro-convulsive therapy.

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All published reports of clinical trials known to the authors have come from the United States in the last year or so and in the treatment of endogenous depression they generally accept that phenelzine is active.

For example Thal (2) in comparing the usefulness of eleven anti-depressant drugs found phenelzine to be the most valuable tested. He noted that relief in some patients commenced within 4–8 hours. Recovery was usually noted in 2 or 3 weeks and was maintained after discontinuation of the medication. Haematological, blood chemistry and liver function tests carried out at weekly intervals before, during and after treatment were found to be normal.

Furst (3) treated a group of 50 out-patients from private practice with severe depressive illness. Dosage varied from 60–90 mg. daily in divided doses. If response occurred within one week or less, the dosage was gradually reduced. A maintenance level was eventually achieved in about 4 weeks and was continued for a further 2–3 months. Side-effects were minimal. Complete remissions were observed in 69 per cent. of the patients.

Arnow (4) analysed 580 case records from 16 investigations and reported that the great majority of patients with endogenous depressions respond favourably to phenelzine and only a small minority need E.C.T. He comments that freedom from clinically important side-effects and the specificity of the drug allow its use as a diagnostic measure.

In this country Hutchinson and Smedberg (7) have reported the results of a double-blind crossover trial as follows: "34 depressed female in-patients who had failed to respond to other treatment. Nine (26 per cent.) patients were discharged, 13 (30 per cent.) showed great improvement and 14 (41 per cent.) were regarded as moderately or slightly improved. Five patients (14 per cent.) were made worse." He considers that phenelzine has a place in the treatment of depression and comments on the absence of side-effects.

Method

A pilot double-blind study preceded an ordinary clinical trial.

Subjects totalling 68 men and 64 women (of whom 14 per cent. were aged 18 to 30, 66 per cent. 31 to 60, and 20 per cent. 61 or over) were either in-patients or attending at a Day Hospital. The majority were suffering from obvious endogenous depression of a moderate to severe degree. The preliminary and subsequent weekly assessments were made on the basis of the following symptom rating scale:

I. Morbid thoughts and feelings; e.g. ideas of reference, suicidal ideas, ideas of unworthiness, somatic delusions, obsessions, etc.

II. Feelings of depression.

III. Loss of interest, fatigue, lack of energy.

IV. Agitation (including restlessness, irritability and tension).

V. Sleep disturbance.

VI. Disturbance of appetite and loss of weight.

Scoring: 0=not present; A=mild; B=moderate; C=severe.

The double-blind trial, in which placebo and active agent were each given for a fortnight, conformed to an accepted pattern in which the order of administration was only known to the dispenser.

The maker's recommended dosage of three 15 mg. tablets daily was used throughout in this part of the study.

For the rest there was some variation according to accumulating clinical experience. The commencing dose of 3 or 4 tablets daily was increased if necessary by 1 tablet daily at weekly intervals. No patient received more than 6 tablets daily.

Final results of treatment were rated as follows: fully recovered, much improved, improved, no change or worse.

Results

I. Double Blind Trial

(a) *Placebo 1st fortnight* (17 patients)

Statistical comparisons

Pre-treatment rating with 2nd placebo week no significant difference.

Pre-treatment rating with last week (2nd week on active agent) significant at $< \cdot 01$ level of confidence.

Second placebo week with 2nd week on active agent significant at $< \cdot 01$ level.

(b) *Active agent 1st fortnight* (8 patients)

Comparisons of weekly ratings did not show any significant degree of difference. However, this small group of patients had a proportionately greater share of the failures (5 out of 8).

It seemed reasonable to assume that beneficial effects of the active agent accounted for the results in (*a*) above thus justifying the commencement of an ordinary more extensive clinical trial of the drug.

Below is an analysis of the results in a group of 132 patients (68 male and 64 female) who had the drug for 2 weeks or more.

II. Ordinary Clinical Trial

(a) *Males* (68)

Recovered	29·4%	52·9%	63·2%
Much improved	23·5%		
Improved	10·3%		
No change or worse ..	36·5%		

χ^2 not significant at ·05/·01 unless "recovered" and "much improved" groups are taken together.

(b) *Females* (64)

Recovered	47·0%	59·5%	70·4%
Much improved	12·5%		
Improved	10·9%		
No change or worse ..	29·6%		
χ^2 highly significant ..	$< \cdot 01$		

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DIAGNOSTIC CATEGORIES

Males:

First depression (significant at ·01 level)	(33)	$\chi^2=19\cdot6$
Recurrent depression (not significant)	(12)	$\chi^2=1\cdot97$
Involutional depression (not significant)	(4)	$\chi^2=0$
Senile (not significant)	(8)	$\chi^2=1\cdot0$
Reactive Psychoneurotic states Schizo-affective states	(11)	(too small for χ^2)

Females:

First depression (nearly significant at ·05 level (·05=5·99))	(11)	$\chi^2=5\cdot08$
Recurrent depression (significant at ·01 level)	(22)	$\chi^2=14\cdot6$
Involutional/menopausal depression (significant at ·01 level)	(15)	$\chi^2=12\cdot9$
Senile (not significant)	(6)	$\chi^2=\cdot16$
Reactive depression (not significant)	(7)	$\chi^2=2\cdot83$
Schizo-affective states	(3)	(too small for χ^2)

Note i: The group of first depressions excluded those patients falling ill for the first time in the involutional or senile periods.

Note ii: The numbers of "recovered" and "much improved" patients were taken together in this analysis of diagnostic categories.

SIDE-EFFECTS

In at least one-third of the women but in only a small number of the men there were complaints of dizziness, unsteadiness and drunken feelings, particularly in the first few days, and more so in those patients, mainly women, receiving higher dosage. One patient receiving 6 tablets daily was confined to bed for several days with marked postural hypotension (B.P. supine 140/95 to 110/80 compared with 75/45 to 65/35 after 5 minutes standing). Tolerance quickly developed, and if not, beneficial effects of the drug were compensatory. Some distinguished between active agent and placebo because of the absence of dizziness with the latter tablets, thus confirming a genuine side-effect.

In 15 women and one man oedema of the feet, ankles and legs of varying degrees of severity occurred usually after no less than 2 weeks at high dosages (4–6 tablets a day). However, 2 patients on the recommended dosage of 3 tablets a day are included. In 3 women the oedema seemed more generalized involving the hands and face. It is of interest that 13 out of 16 patients with oedema responded well to treatment as regards their psychiatric symptoms. Without exception oedema cleared up when medication ceased or dosage was reduced to a minimum.

Difficulty in starting micturition was noted in the cases of 2 men and 3 women when dosages were increased. A critical level between 3 and 4 tablets a day was demonstrated for one patient. Once again tolerance developed quite quickly.

Two men and 3 women became mildly hypomanic on phenelzine. In only 2 was there definite evidence of previous mood swings in this direction.

Several women developed a craving for chocolates and sweets which seemed related to effects of the drug. There was quite a dramatic increase in weight in two of these patients (2 stones in 2–3 months).

One patient on 6 tablets a day for many weeks who showed generalized oedema, developed a vertigo which has remitted since treatment ceased.

The significance of complaints about constipation is not easy to assess.

Our experience does not support claims for minimal or complete freedom from side-effects. However, whilst the incidence is relatively high these are not severe and can be easily reversed. There has been no clinical evidence of toxic damage such as disorder of the haemapocitic system, kidneys or liver function, although Kathari (5) reports that 7 out of 13 cases showed some abnormality in liver function tests on 15 mg. of phenelzine t.i.d. Findings which contrast with those of Furst (3). His pre-test analysis, C.B.C., alkaline phosphatase, thymol turbidity and cephalin flocculation tests on 30 cases did not differ significantly with those taken after the second month of ingestion.

Our routine investigation in cases with oedema has not provided any data pointing to its cause.

Five patients have had EEG recordings before and after treatment. No significant changes have been observed such as are comparable with those due to E.C.T.

We have commented (6) previously on the absence of side-effects when E.C.T. is given with or immediately following a course of phenelzine.

Because of a tendency to relapse on withdrawal of the drug it was found possible to keep several women in the involutional group on high dosage, e.g. 4–5 tablets a day for as much as 3–5 months followed in a few cases by a maintenance dose of 1–2 tablets a day.

Discussion and Conclusions

Our findings support the claims for the usefulness of phenelzine in typical endogenous depressions.

In the 6 schizo-affective states characterized by depressive feelings and relatively milder forms of thought disorders (e.g. only one patient had hallucinations) there were no beneficial effects at all.

Only one out of 6 patients who seemed to have depression secondary to a psychoneurosis showed any benefit.

The better results on the female side may well represent a true sex difference but further confirmation is needed, paying particular regard to the involutional/menopausal category which showed the best response of all.

We were not clinically impressed by the effects in the senile and reactive groups although numbers involved are too small for a firm appraisal.

Patients with marked agitation did not benefit and in some cases were thought to be made worse.

Of 21 patients who failed to respond to phenelzine and subsequently had E.C.T., 10 did well. Only 3 patients with recurrent depressions, who had previously benefited from E.C.T., did not improve on phenelzine. We feel

that had all patients been given E.C.T. the initial results would have been better by between 5 and 10 per cent.

No follow up study of the relapse rates has yet been attempted. However, our experience to date leads us to assume that the relapse rate in the first few weeks after the drug is discontinued is perhaps less than we would have anticipated had E.C.T. been the treatment. Duration of treatment in patients who have responded has varied from 1 to more than 6 months (including maintenance dosage).

Relapses whilst on maintenance dosage have again responded to increased dosage. In a group of 20 females given placebo at the third week those responding, but still with symptoms, showed mild to quite marked relapses after the first few days with a quick reversal on returning to active agent.

Ten patients who failed to respond to phenelzine were then given Tofranil and only 2 seemed to benefit.

Earlier observations in the fairly rapid action of phenelzine are confirmed. Significant responses have been seen within 24 hours and for the majority before the second week. Such features are of considerable importance if this drug is going to be used at large, where perhaps morbidity risks will not be so carefully assessed. Suicidal thoughts need not by any means always call for hospitalization and E.C.T. However, in treating such patients with the newer anti-depressants the general practitioner should consider daily assessments until he is certain of a response of failure.

Summary

A controlled trial was carried out to evaluate the effects of phenelzine on mainly endogenous types of depressive illness. The results are regarded as largely validating the claims for the drug's therapeutic value, and that it has an effect comparable in scope, speed and safety to that produced by E.C.T.

In a preliminary double-blind study a comparison of symptom rating when 2 weeks of placebo were followed by 2 weeks of active agent showed a significant difference at the ·01 level of confidence.

In the routine clinical trial which followed the results with female patients were highly significant ($< \cdot 01$).

The males did less well in this study and results in terms of χ^2 achieve the ·05/·01 level of confidence only when the totals of recovered and much improved patients are taken together.

70·1 per cent. of the females and 63·2 per cent. of the males showed some response to treatment.

True but easily reversible side-effects have been noted including dizziness, oedema—mainly of the lower limbs, difficulty of micturition and hypomania.

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