Arch. Psychiat. Nervenkr. 227, 49—58 (1979)

Archiv für Psychiatrie und Nervenkrankheiten
Archives of Psychiatry and Neurological Sciences

DL-Phenylalanine Versus Imipramine: A Double-Blind Controlled Study

Helmut Beckmann*, Dieter Athen, Margit Olteanu, and Reinhild Zimmer

Psychiatric Hospital of the University of Munich, D-8000 München 2, Federal Republic of Germany

Summary. In a double-blind study, DL-phenylalanine (150—200 mg/24 h) or imipramine (150—200 mg/24 h) was administered to 40 depressed patients (20 patients in each group) for 30 days.

Diagnoses were established according to the International Classification of Diseases (ICD). The AMP system, the Hamilton Depression Scale and the Bf-S self rating questionnaire (von Zerssen et al., 1974) were used to document psychopathological, neurologic, and somatic changes.

Twenty-seven patients (14 on imipramine, 13 on phenylalanine) completed the 30-day trial. No statistical difference could be found between these two drug treatment groups (Student's *t*-test) using the Hamilton Depression Scale and the Bf-S self rating questionnaire. Ratings for anxiety were significantly lower in the imipramine group on days 10 and 20, but not on day 30; in addition, sleep disturbances were more influenced by imipramine on days 1, 5, and 10, but not on days 20 and 30.

Separate analysis of psychopathological syndromes as somatic depressive syndrome and retarded depressive syndrome did not show a group difference (0.05 level of significance using a two-way analysis of variance).

It is concluded that DL-phenylalanine might have substantial antidepressant properties. However, certain methodological considerations still warrant a careful interpretation.

Key words: DL-Phenylalanine as antidepressant – Double-blind trial with imipramine.

Zusammenfassung. In einer Doppelblindstudie an 40 depressiven Patienten wurde unter stationären Bedingungen entweder DL-Phenylalanin (150—200 mg/die) oder Imipramin (150—200 mg/die) über einen Zeitraum von 30 Tagen appliziert.

* New address: Zentralinstitut für Seelische Gesundheit, J 5, D-6800 Mannheim, Federal Republic of Germany

0003-9373/79/0227/0049/$ 02.00

Die psychiatrischen Diagnosen wurden gemäß der International Classification of Diseases (ICD) gestellt. Zur Dokumentation der psychopathologischen, neurologischen und somatischen Befunde wurde das AMP-System, die Bf-S-Selbsteinschätzungsskala (v. Zerssen et al., 1974) sowie die Hamilton-Depressionsskala verwendet.

27 Patienten (14 unter Imipramin-, 13 unter Phenylalanintherapie) vollendeten die Studie. Mit der Bf-S-Skala und Hamilton-Skala konnten keine statistisch signifikanten (Students *t*-Test) Unterschiede zwischen den beiden Behandlungsgruppen gefunden werden. Die Angst-Ratings waren auf der Hamilton-Skala in der Imipramin-Gruppe an Tag 10 und 20 niedriger als in der Phenylalanin-Gruppe, jedoch nicht mehr an Tag 30. Überdies wurden in der Imipramin-Gruppe Schlafstörungen an Tag 1, 5 und 10 günstiger beeinflußt, jedoch nicht mehr an Tag 20 und 30.

Die getrennt durchgeführte Analyse psychopathologischer Syndrome, wie z. B. somatisch-depressives Syndrom und gehemmt-depressives Syndrom, zeigten keine Gruppen-Differenz auf dem 5%-Niveau (2-Wege-Varianzanalyse).

Diese Studie gibt einen weiteren Hinweis auf mögliche antidepressive Eigenschaften von DL-Phenylalanin; gewisse methodologische Erwägungen jedoch ermöglichen noch nicht eine eindeutige Beurteilung.

Schlüsselwörter: DL-Phenylalanin als Antidepressivum – Doppelblindstudie gegen Imipramin.

Introduction

Several investigators have reported on the antidepressant efficacy of the aromatic amino acid phenylalanine. Infusing L-phenylalanine to depressed patients with Parkinson's disease, Birkmayer (1966) noticed the euphoric and drive-enhancing effect of this compound. He proposed using it in endogenously depressed patients. Fischer and his associates (Yariyura-Tobias et al., 1974; Fischer et al., 1975; Spatz et al., 1975) administered DL- or D-phenylalanine to depressed patients in open studies and found a response in 60—70% of the patients. One recent open study on 20 depressed patients, using different rating scales and a self-rating questionnaire, confirmed these results (Beckmann et al., 1977).

Interest has been focused on this amino acid since besides its reduction to phenylketonic acids, it is decarboxylated in vivo (Lovenberg et al., 1962) to phenethylamine, an amphetamine-like substance which has been detected by sensitive methods in various tissues (including brain) of untreated animals (Mosnaim and Sabelli, 1971; Sabelli et al., 1973; Saavedra, 1974) and in the brain (Inwang et al., 1973) and urine of humans (Jepson et al., 1960; Fischer et al., 1968; Boulton and Milward, 1971; Mosnaim et al., 1973).

In addition, it has been reported that this amino acid is metabolized to tyrosine and DOPA in catecholaminergic neurons of the brain (Carlsson and Lindquist, 1978). The purpose of this study is to compare the antidepressant imipramine in hospitalized depressed patients using a double-blind procedure.

Methods

Forty consecutively admitted depressed patients (29 females, 11 males) were studied at the Psychiatric Hospital of the University of Munich. All patients had been pretreated by their referring physicians with various antidepressants, mostly in combination with benzodiazepines (23 patients) or phenothiazines and thioxanthenes (18 patients).

The age of the patients ranged from 20 to 68 years, with a mean age of 46.7 years.

Patients were informed that they would be assigned to a trial with a conventional antidepressant or an essential amino acid shown to have clinical efficacy in several uncontrolled studies. Only after they had given oral consent was drug administration initiated. A placebo-washout period of 2—3 days was observed.

Patients were then assigned to coded charges of either imipramine (150—200 mg/24 h) or DL-phenylalanine (150—200 mg/24 h) in an identical confection. Double-blind conditions were maintained until the last patient had passed the trial.

Routine laboratory checks including EEG and ECG were performed prior to drug administration, and only if no other somatic irregularity was obvious was the trial started. All laboratory checks were repeated weekly. Blood pressure, pulse, and body temperature were measured daily throughout the study.

Diagnoses were established by at least two experienced psychiatrists according to the International Classification of Diseases (ICD, 1975):

	ICD	*n*
Endogenous depression (involutional)	296.0	7
Endogenous depression (monopolar)	296.2	18
Endogenous depression (bipolar)	296.3	2
Depressive neurosis	300.4	11
Neurasthenic syndrome	300.5	1
Hypochondric depression	300.7	1
		40

In general, the clinical symptomatology comprised depressed mood, feelings of sadness, retardation and/or agitation, sleep, and suicidal ideation.

For documentation of psychopathological, neurologic, and somatic changes, the AMP system (Angst et al., 1969) was used on the last placebo day (day 0) and then on days 1, 3, 5, 10, 20, and 30 of the active treatment period.

From the psychopathological symptoms rated in the AMP system, different syndromes were established as: retarded depressive syndrome (hopeless/desperate, sensation of guilt, delusion of guilt, depressed/sad, disturbed attention, disturbed memory, helpless, sensation of insufficiency, disturbed comprehension); somatic-depressive syndrome (difficulty in falling asleep, interrupted sleep, reduced duration of sleep, sensation of being ill, reduced appetite, better in the P.M.; suicidal tendencies and actions, reduced sexuality). In addition, influence on different other syndromes was observed, i.e., influence on hostility, apathetic, catatonic, hypochondric, paranoid, and autonomic syndromes (Baumann and Angst, 1975).

Grading the intensity of each symptom as mild (1), moderate (2), and severe (3), the average sum scores of the syndrome for all patients were computed by dividing by the *n* of patients.

The Hamilton Depression Scale (Hamilton, 1960) and the B-S self rating questionnaire (von Zerssen et al., 1974) were used on the same days that the AMP ratings were performed.

No other antidepressant medication was administered except chloralhydrate (1—2 g per day), flunitrazepam (30 mg per day), or clozapine (12.5—25 mg per day) as sleeping medication.

Statistical evaluations were done by a one-way analysis of variance with repeated measures on the same patients, and by Student's *t*-test.

Results

Of the 40 patients initially selected for the study, 36 (18 on imipramine and 18 on phenylalanine) could be studied until day 20. However, only 27 completed the 30-day trial (14 on imipramine and 13 on phenylalanine).

The global scores on the Hamilton Depression Rating Scale for the DL-phenylalanine and the imipramine group are graphically depicted in Figure 1. As can be seen, there is no statistical difference either in the placebo treatment period (day 0) or on days 10, 20, or 30 between these two drug treatment groups (Student's t-test for grouped data).

Analysis of single items on the Hamilton Depression Scale, such as mood and inhibition, did not reveal significant differences between both treatment groups on the days that the ratings took place. However, anxiety ratings were significantly lower in the imipramine as compared to the phenylalanine group on days 10 and 20 ($P < 0.05$, Student's t-test), but not on day 30. In addition, sleep disturbances as measured on the same scale were significantly better influenced by imipramine on days 1, 5, and 10 ($P < 0.05$, Student's t-test), but not on days 20 and 30.

The relatively high dropout rate was caused by the desire of 8 patients (3 on phenylalanine, 5 on imipramine) to quit the study. All of them considered the

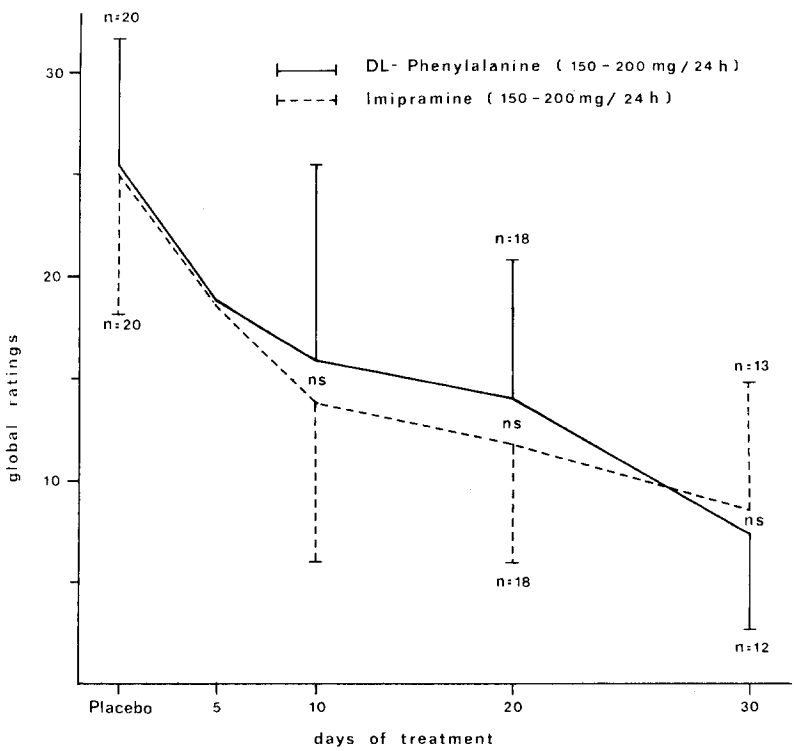

Fig. 1. Scores on the Hamilton Depression Scale for both treatment groups on the last placebo day and days 5, 10, 20, and 30 of the trial. ns: no statistical difference using Student's t-test for grouped data

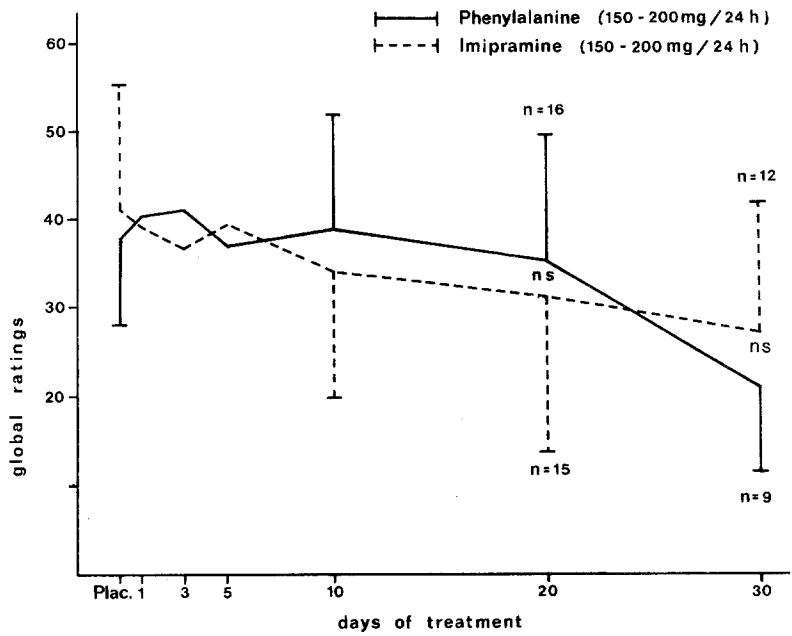

Fig. 2. Scores of the Bf-S self-rating questionnaire (von Zerssen et al., 1974) for both treatment groups on the last placebo day and days 1, 3, 5, 10, 20, and 30. ns: no statistical difference using Student's *t*-test for grouped data

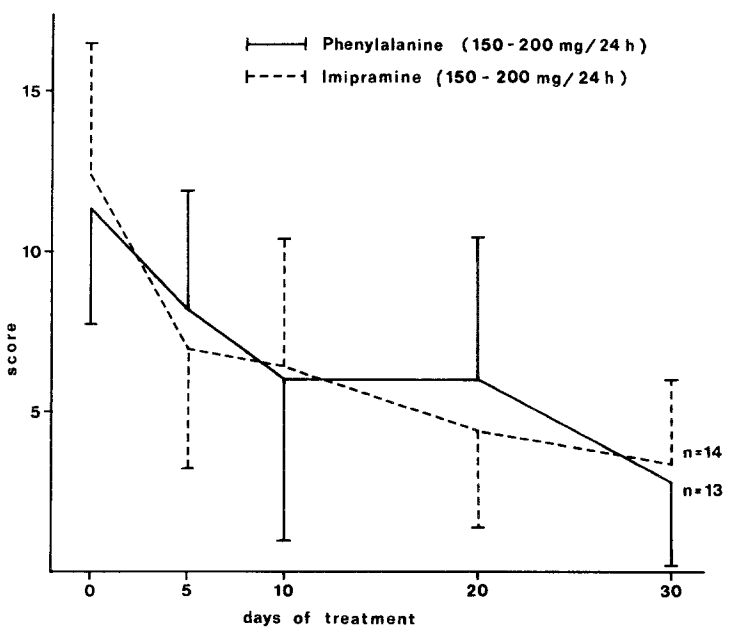

Fig. 3. Scores of the somatic-depressive syndrome as computed from the AMP system on the last placebo day and days 5, 10, 20, and 30. No group difference at the 0.05 level of significance existed. No significant interaction could be found between repeated measures and groups (ANOVA)

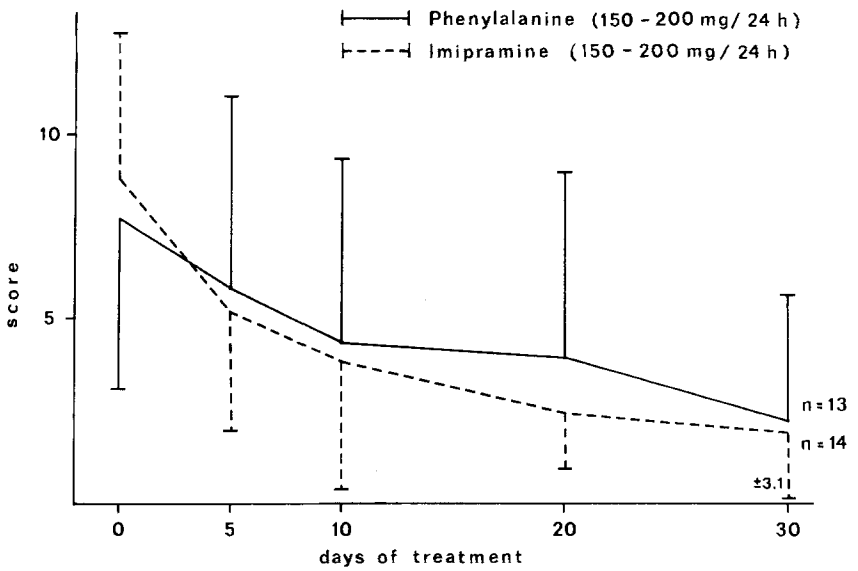

Fig. 4. Scores of the retarded-depressive syndrome as computed from the AMP system on the last placebo day and days 5, 10, 20, and 30. No group difference on the 0.05 level of significance existed. No significant interaction could be found between repeated measures and groups (ANOVA)

treatment ineffective, although this was not always supported by the objective evaluation. Five patients (1 on imipramine, 4 on phenylalanine) were withdrawn for ethical reasons because no substantial relief became apparent during the first 2 weeks of the study. The dropout rate after the third week of treatment was almost identical on both sides and did not seem to explain the nonsignificant clinical outcome.

Figure 2 graphically depicts the global scores on the B-S self-rating questionnaire (von Zerssen) on days 0, 1, 3, 5, 10, 20, and 30 for both treatment groups. Once again it can be seen that there was no statistically significant difference on any day of the drug trial between the DL-phenylalanine and the imipramine group (Student's *t*-test for grouped data). However, on day 30 only 9 patients in the phenylalanine and 12 in the imipramine group had completed their selfrating scales. This was owing to various reasons: (inability to comprehend single items (9 patients, dropping out (8 patients), or refusal (2 patients)).

Analyzing the clinical syndromes as rated by the AMP system and then computing different psychopathological syndromes (as described above) it becomes obvious that on day 0 the global score of the somatic-depressive syndrome was 12.4 ± 4 for the imipramine and 11.3 ± 3 for the phenylalanine group and at the end of the trial, 3.4 ± 2 and 2.8 ± 3, respectively. The two-way analysis of variance for repeated measures does not show a group difference on the 0.05 level of significance. There was a significant change over the time of the trial ($P < 0.001$). No significant interaction could be found between repeated measures and groups (Fig. 3).

Table 1. Global rating scores on day 0, 5, 10, 20, and 30 of the trial as computed from the AMP system ± standard deviation

		Day				
		0	5	10	20	30
Apathetic syndrome	I	4.3 ± 2.7	3.3 ± 2.7	2.6 ± 3.2	1.3 ± 1.0	0.7 ± 0.9***
	P	6.3 ± 3.5	3.8 ± 3.0	3.8 ± 3.1	2.9 ± 2.9	1.8 ± 2.3
Catatonic syndrome	I	5.0 ± 4.4	3.8 ± 3.7	2.4 ± 3.9	0.5 ± 0.6	0.4 ± 0.8***
	P	5.3 ± 3.4	3.8 ± 3.3	2.9 ± 3.0	2.2 ± 2.8	1.3 ± 1.4
Hypochondric syndrome	I	3.9 ± 2.2	2.6 ± 2.3	2.2 ± 2.0	1.0 ± 1.2	1.1 ± 1.9***
	P	4.6 ± 2.5	3.5 ± 2.8	2.9 ± 3.2	2.3 ± 2.7	1.3 ± 1.6
Hostility syndrome	I	0.8 ± 1.3	1.4 ± 3.0	0.4 ± 0.6	0.3 ± 0.6	0.3 ± 0.7**
	P	1.5 ± 1.7	0.6 ± 0.9	0.5 ± 0.7	0.5 ± 0.7	0.2 ± 0.4
Paranoid syndrome	I	0.6 ± 0.8	0.4 ± 0.7	0.6 ± 0.8	0.2 ± 0.4	0.2 ± 0.4 ns
	P	1.2 ± 1.0	0.8 ± 1.0	1.3 ± 2.8	1.4 ± 3.4	0.2 ± 0.3
Vegetative syndrome	I	5.3 ± 3.4	4.9 ± 3.8	5.0 ± 3.7	4.2 ± 3.0	3.0 ± 2.5***
	P	4.0 ± 4.2	2.9 ± 3.6	2.3 ± 2.9	2.0 ± 2.3	1.4 ± 1.9

**: $P < 0.01$; ***: $P < 0.001$, analysis of variance with repeated measures on the same patient
I: imipramine group; P: phenylalanine group

Similar relationships existed for the retarded depressive syndrome (as defined above) where the global scores were initially 8.8 ± 4 for the imipramine, and 7.7 ± 4 for the phenylalanine group. At the end of the study the respective scores were 1.9 ± 3 versus 2.2 ± 3. Again, the two-way analysis of variance does not show a group difference on the 0.05 level of significance. There was a significant change over the time of the trial ($P < 0.001$) and no significant interaction could be found between repeated measures and groups (Fig. 4).

Table 1 shows the scores for the apathetic, catatonic, hypochondriac, hostility, paranoid, and autonomic syndromes. All of these except the paranoid syndrome show a significant decrease during the course of the study (analysis of variance, with repeated measures on the same patient).

Because of difficulties in sleeping, 10 patients (7 on imipramine, 3 on phenylalanine) received choralhydrate. Twenty-two (8 on imipramine, 14 on phenylalanine) received 30 mg flurazepam per night. Eight patients with the most severe sleep difficulties had to be medicated with clozapine (12.5—25 mg per night). All of these (5 on imipramine, 3 on phenylalanine) except one dropped out by day 20 of the trial.

Adverse Reactions. As can be seen from the table, there was a tendency for the autonomic syndrome (dryness of the mouth, accomodation disturbances, constipation, micturation problems, etc.) the show lower ratings for the phenylalanine group as compared to those of the imipramine group, although analysis of variance did not yield significant differences. Diffuse headaches, mainly in the first 10 days of the trial, were complained of by 7 patients (5 on phenylalanine, 2 on imipramine). None of the patients had to be withdrawn from the trial for these reasons. No serious changes were observed in the laboratory values in any of the participating patients.

Discussion

The results of this first double-blind controlled study are in line with former reports obtained in open uncontrolled studies.

It is of interest that depressive 'score symptoms' such as depressed mood, agitation, and/or retardation were influenced equally by both drug regimens, where as anxiety and sleep disturbances were, at least initially, better influenced by imipramine, a finding which agrees with results reported in an earlier study.

Lack of correlation between self-rating and objective rating as evidenced in the present study, where, at the end of the trial, both treatment groups show a rather high score on the Bf-S scale as compared to the score of the Hamilton Scale, is not unusual in our experience, for we have found that self ratings demonstrate clinical response considerably later than objective ratings.

Retrospective inspection of the additional drug administration revealed an equal need for sleeping medication for both groups, although no sedative properties of DL-phenylalanine have ever been noticed.

Relatively high dropout rates exist after the twentieth day of treatment. Most of these patients, who knew that they were participating in a drug trial, wished to be treated with established therapy. However, it is noteworthy that dropout rates

were almost identical on both sides. Of further interest is the fact that it was impossible for the raters or clinical associates to determine from their clinical impression what medication individual patients had received, although rating scores for autonomic side effects tended to be higher for the imipramine patients.

No information exists regarding the mechanism of action of DL-phenylalanine. It has been shown that this compound readily passes the blood-brain barrier (Cramer, 1970), where its decarboxylated product, phenethylamine, which has been shown to possess amphetamine-like properties, might be the active component. In addition, infusion of this amino acid raises growth hormone levels in the plasma of healthy volunteers (Beckmann and Dollhofer, in preparation).

Lowered urinary excretion of phenethylamine has been detected in patients with endogenous depression, whereas manic and schizophrenic patients seem to excrete higher amounts of this compound (Fischer et al., 1968; Boulton and Milward, 1971; Mosnaim et al., 1973). However, data on the exact amount of urinary phenethylamine differ greatly depending on the method of estimation. No differences in urinary phenylethylamine excretion have been found between depressed patients and healthy controls in a preliminary study using a radioenzymatic method (Beckmann and Saavedra, in preparation).

In conclusion, clinical results of this and other studies suggest an antidepressant efficacy of DL-phenylalanine, which, with certain modifications, seems to equal that of the tricyclic antidepressant imipramine.

General methodological considerations, however, dictate that these results be interpreted carefully. As has been shown by Morris and Beck (1974), there exist some 20 controlled studies of imipramine versus placebo which do not show a significant difference in clinical response in depressed patients, and only 30 studies demonstrate the superiority of imipramine over placebo.

In light of this evidence there is a definite need for more controlled studies to prove or disprove the antidepressant efficacy of DL-phenylalanine.

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Received October 26, 1978