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Comparison of a New Antidepressive, Lofepramine, with Imipramine in a Double-Blind Multicentre Trial

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SUMMARY. Lofepramine, an imipramine derivative, shows lower acute toxicity in animals when compared with desipramine and imipramine. Its anticholinergic effect is less pronounced than that of desipramine. In an open clinical trial lofepramine showed a marked antidepressive action. A double-blind multicenter trial of lofepramine v. imipramine, evaluated by means of the AMP system, showed a remarkable degree of concurrence with regards to the effects of those two products.

KEY WORDS: Lofepramine - Imipramine - Double-Blind Multicentre Trial - AMP System.

1. PHARMACOLOGY

Lofepramine (clofepramine) is an imipramine derivative, N-methyl-N-4-chlorobenzoylmethyl-3- (10, 11 dihydro-5-dibenz-(b, f)-azepine-5-yl-propylamidohydrochloride, a tertiary amine in which the amino groups in the side chain are substituted with a 4' -chlorophenyl-acyl group (Fig. 1).

Pharmacological investigations by Eriksoo & Rothe (5) have shown that lofepramine possesses a very low acute toxicity viz. an LD_{50} of > 2.5 g/kg mouse. It is markedly lower than for imipramine or desipramine. Experiments with lofepramine tagged with ^{14}C revealed a good absorption. In animals lofepramine showed a less pronounced peripheral anticholinergic effect than desipramine. For further details concerning the pharmacological similarities and differences between lofepramine and conventional tricyclic antidepressants we refer to the extensive investigation by Eriksoo & Rothe (5).

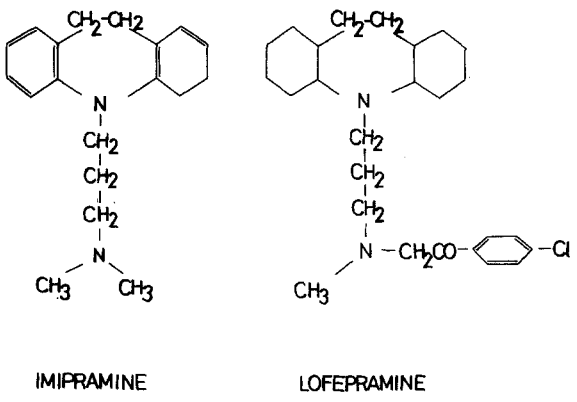

Fig. 1. Chemical compound of imipramine and lofepramine

2. OPEN CLINICAL TRIAL

Siwers et al. (6, 7) treated 15 patients with various types of depression with lofepramine. Lofepramine was administered orally in ever increasing doses (up to 100 mg t. d. s.) during three to four weeks. Seven patients showed a marked improvement. This gains in importance by the fact that some of the patients had previously been resistant against antidepressants and/or E. C. T.

3. DOUBLE-BLIND CLINICAL TRIAL

3. 1. Aim of Trial and Methodology

At the psychiatric university clinics of Munich and Zürich, as well as at the psychiatric clinic of the Palatinate at Landeck identical methodology was employed in a double-blind study on lofepramine vs. imipramine, in order to compare the spectrum of activity and the side effects of those two antidepressants (3). Patients were allocated to the two trial groups in a randomized way. On the day 0, 5, 10, 20 and 30 the patients were examined and the findings were recorded according to the AMP system (1). In Zürich the Hamilton scale for depression was used additionally.

3. 2. Selection of Patients

Only newly admitted depressive patients were incorporated into the trial. Altogether 49 patients were treated with lofepramine and 52 with imipramine. The mean age of the patients on lofepramine was 49. 4 $\pm$ 12. 9 years, those on imipramine had a mean age of 47. 4 $\pm$ 13. 5 years. The age range of the groups were 25 to 78 and 16 to 78 years, respectively. Most patients had been diagnosed as suffering from endogenous depression. Table 1 shows that the patient material treated with lofepramine was somewhat more homogenous than that of the imipramine group.

3. 3. Duration of Treatment and Dosage

In 48 out of the 49 lofepramine patients the planned minimal duration of treatment of 20 days could be achieved. In 45 out of 52 imipramine patients this was possible, too. 38 patients were treated with lofepramine for 30 days and 37 patients received imipramine for such a period. A fixed oral dosage schedule was used: The lofepramine patients were given 35 mg t. d. s. for 3 days and from the 4th day onwards 210 mg/day. The imipramine patients were started on 25 mg t. d. s. for three days and thereafter they received 150 mg daily.

Table 1. Diagnoses

Diagnoses		Number of patients lofepramine	imipramine
295. 0	Schizophrenia, simple	-	1
295. 7	Schizoaffective psychosis	-	1
296. 0	Involutional melancholia	14	13
296. 2	Endogenous depression	28	29
296. 3	Circular depression	-	1
298. 0	Reactive depressive psychosis	-	2
300. 0	Neurosis	1	-
300. 2	Phobic neurosis	1	-
300. 4	Depressive neurosis	4	1
300. 6	Depersonalization syndrome	-	1
300. 7	Hypochondriacal neurosis	1	1
305. 9	Headaches	-	1
309. 6	Psychic disturbances with senile or pre-senile brain disease	-	1
		49	52

3. 4. Hamilton Scale

The Hamilton scale was used in Zürich only. The ECDEU version of 1966 (24 items) was applied. The total Hamilton scores show a better course of treatment for the 15 lofepramine patients, compared with an equal number of imipramine patients (see Fig. 2). However, a two-way analysis of variance for repeated measurements does not show any significant differences (Table 2).

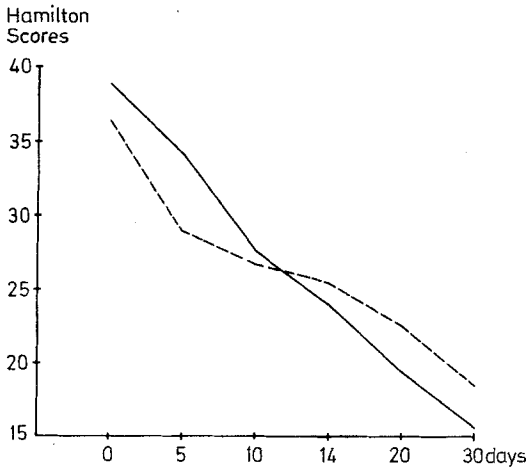

Fig. 2. Hamilton-Scale. Hamilton scores on day 0-30. ——— lofepramine; ------ imipramine

Table 2. Hamilton scores (mean values)

product	days					
	0	15	10	15	20	30
lofepramine	38.93	34.10	27.60	24.07	20.23	16.43
imipramine	36.37	28.93	26.77	25.20	22.50	18.57

F-value: A 0.019 n. s. between the groups
B 35.384 $p \leq 0.001$
AB 1.469 n. s. interaction

A covariance analysis too, did not yield significant differences between lofepramine and imipramine with regard to their influence on the Hamilton scores.

3.5. AMP System, Evaluation of Symptoms

The frequency, coefficients of severity and significant changes were calculated for the 123 psychic and 58 somatic symptoms of the AMP system. For further details concerning the statistical methods we refer to Angst & Baumann (2) as well as to Baumann et al. (4).

Calculation of frequency and coefficient of severity show that with both drugs all characteristic depressive symptoms are reduced in the course of treatment. As expected, neither lofepramine nor imipramine resulted in complete resolution of all symptoms.

By means of the chi-square test it was evaluated which symptoms changed significantly in the course of treatment. On the 5th day of treatment already, a great number of depressive symptoms were reduced under lofepramine as well as under imipramine. Up to the termination of treatment the number of improved symptoms increased further.

Lofepramine and imipramine have little effect upon the symptoms "tension" and "motor unrest", whereas the symptom "inner unrest" yields well to both products.

The evaluation by AMP for symptoms shows only unsignificant differences between lofepramine and imipramine.

3. 6. AMP System, Evaluation at Syndrome Level

The symptoms of the AMP system can be attributed to 12 syndromes. Their mean values for the control days are summarized in Table 3. Those mean values are not original scale values but "T-transformed" figures which lie between 33 and 80 (m=50, s=10).

Table 3. Mean values of AMP syndromes (T-transformed values)

syndrome	lofepramine					imipramine				
	0	5	10	20	30	0	5	10	20	30
1. apathic syndrome	61	57	55	51	49	59	55	55	50	48
2. hallucinatory-desintegrative syndrome	42	42	41	41	41	42	42	42	42	42
3. hostility syndrome	44	44	42	42	42	44	42	43	42	42
4. manic syndrome	45	44	43	43	44	44	43	43	43	44
5. somatic-depressive s.	59	56	53	50	48	58	54	52	49	46
6. paranoid syndrome	42	41	40	38	38	41	40	40	39	38
7. catatonic syndrome	54	48	46	44	42	52	50	48	46	43
8. retarded-depressive s.	60	54	53	51	46	59	54	53	50	47
9. hypochondriacal s.	61	57	54	52	49	60	55	54	50	47
10. psychoorganic syndrome	56	53	51	50	48	56	52	51	47	45
11. autonomic syndrome	63	58	57	56	54	61	58	57	57	54
12. neurological syndrome	51	51	51	53	52	53	52	53	53	52

Comparison of lofepramine and imipramine by means of covariance analysis with respect to their effect on the 12 AMP syndromes shows no significant

differences between the two products. The course of the apathic and of the somatic depressive syndromes (Fig. 3) as well as those of the inhibited depressive and hypochondriacal syndromes emphasize the great similarity of the antidepressant effect of the two products.

The syndrome profiles for all 12 AMP syndromes are shown before and after treatment with lofepramine (Fig. 6) and imipramine (Fig. 5).

The almost identical curves for the two products demonstrate the high degree of similarity between the effects of those two antidepressants.

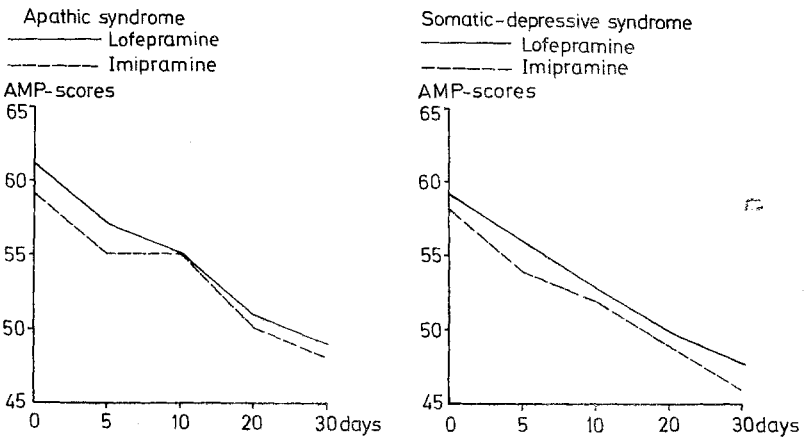

Fig. 3. Course of the apathic and of the somatic-depressive syndrome under lofepramine and imipramine

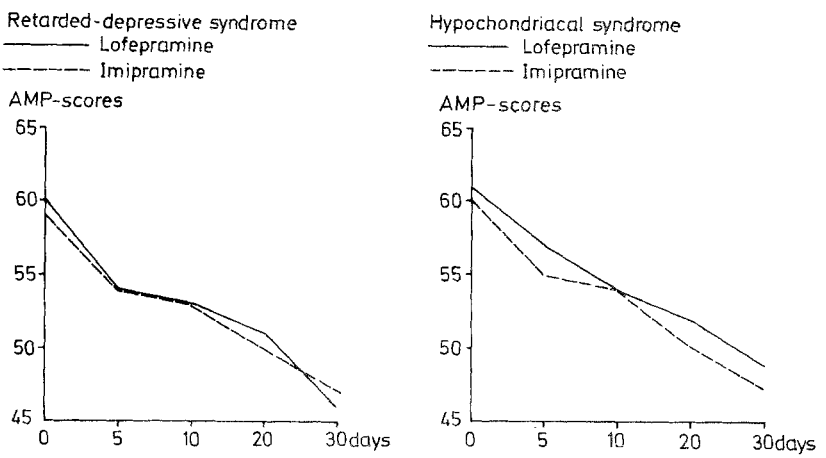

Fig. 4. Course of the retarded-depressive and the hypochondriacal syndrome under lofepramine and imipramine

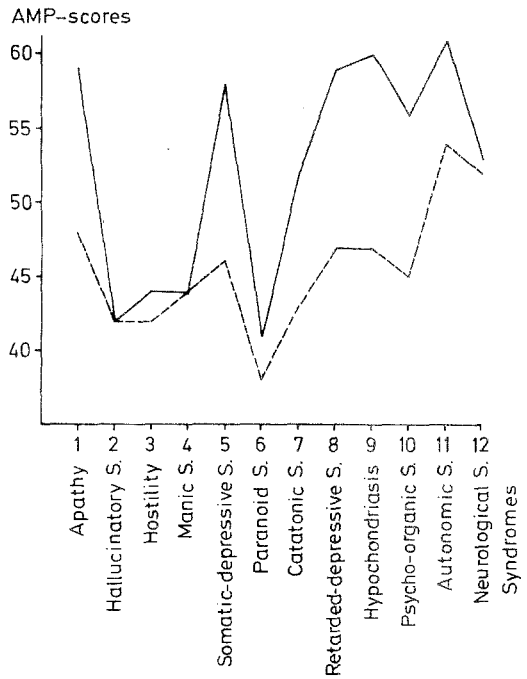

Fig. 5. Imipramine: profile of the AMP syndromes on day 0 (———) and 30 (----)

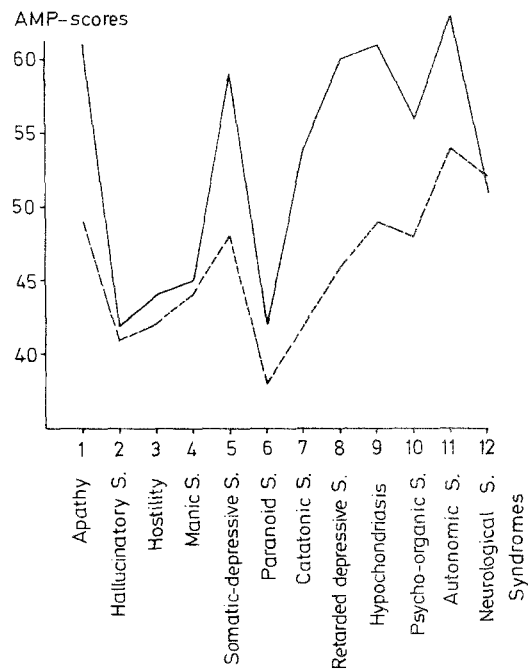

Fig. 6. Lofepramine: profile of the AMP syndrome on day 0 (———) and 30 (-------)

3.7. Side Effects

The evaluation of the AMP system for symptoms shows that for both products the frequency of occurrence of a fine hand tremor increased. With lofepramine this increase is somewhat more pronounced than with imipramine (on day 20 $p \leq 0.1$). Increased thirst and dryness of the mouth are transitory only with lofepramine, however, with imipramine those symptoms are of a more permanent nature. With both products constipation, pressure within the head, cardiac sensations, vertigo and perspiration decrease.

3.8. Laboratory Findings

In Zürich the findings on day 10 and 20 were compared by means of a t-test with pre-treatment levels (day 0). The following significant differences were noted: Under lofepramine blood urea decreases by 12.14 mg% ($p \leq 0.01$). Further, bilirubin diminished by 0.15 mg% ($p \leq 0.02$). A non-significant reduction at 10% level is found for haemoglobin and erythrocytes, as well as a tendency towards eosinophilia ($p \leq 0.1$).

With imipramine changes on the 10% level are found for a tendency towards weight gain and a reduction of band neutrophiles. For the time being, findings on the 10% level must be considered as non significant.

In the psychiatric university clinic of Munich, laboratory tests (haematological parameter, liver and kidney function) were carried out at the start and at the end of the trial. The evaluation of the collected data shows that lofepramine as well as imipramine do not cause any changes which suggest toxic effects.

REFERENCES

1. Angst, J., Battegay, R., Bente, D., Berner, P., Broeren, W., Cornu, F., Dick, P., Engelmeier, M.-P., Heimann, H., Heinrich, K., Helmchen, H., Hippius, H., Poeldinger, W., Schmidlin, P., Schmitt, W., Weis, P.: Das Dokumentations-System der Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie (AMP). Arzneimittel-Forsch. (Drug Res.) 19, 399-405 (1969)
2. Angst, J., Baumann, U.: Zur Methodik klinischer Prüfungen von Antipsychotika. Vortrag in Wroclaw (Polen) 1973. Tagungsbericht (im Druck)
3. Angst, J., Dittmer, Th. L. J., Heinrich, K., Hippius, H., Seibel, I.: A double-blind study comparing Clofepramin and Imipramin. Int. Pharmakopsychiat. (in press)
4. Baumann, U., Rothweiler, R., Scheidegger, P.: Methodische Probleme bei Psychopharmakaprüfungen unter besonderer Berücksichtigung des AMP-Systems. Arzneimittel-Forsch. (Drug Res.) (1974)
5. Eriksoo, E., Rothe, O.: Chemistry and Pharmacology of a new potential Antidepressant. (N-Methyl-N- 4-chlorobenzoyl-methyl-3- (10,11-dihydro-5H-dibenz (b,f) azepin-5 yl -propylamine hydrochloride) (Leo 640, lopraminehydrochloride). Arzneimittel-Forsch. (Drug Res.) 20 1561-1569 (1970)

6. Siwers, B., Freyschuss, U., Hamberger, B., Tuck, D., Malmfors, T., Sjoerquist, F.: A quantitative approach to the initial clinical trial of tricyclic antidepressants: a comparison of Leo 640 and Nortriptyline. Europ. J. clin. Pharmacol. 3, 12-17 (1970)
7. Tuck, R. J., Kahan, E., Siwers, B.: Biological and pharmacokinetic evidence for generic equivalence of three imipramine preparations: comparison with a new imipramine analogue. Acta pharmacol. (Kbh.) 304-313 (1973)