A TRIAL ON THERAPEUTIC EFFECTS OF CLOMIPRAMINE IN ENDOGENOUS DEPRESSION - PERSONAL OBSERVATIONS

Leszek Tomasz Ros

REZUMAT

Introducere: Clomipramina este indicată în principal în depresia cu inhibiție psihomotorie, cu nivel redus al anxietății și agresiunii și cu simptome obsesiv-compulsive foarte intense.
Material și Metodă: Clomipramina a fost administrată timp de 6 săptămâni în 50 de pacienți tratați ambulator, diagnosticați cu depresie majoră. La acești pacienți, depresia endogenă a fost la cel puțin al treilea episod și episoadele maniacale nu au apărut niciodată. Toți subiecții studiați au corespuns criteriilor de diagnostic pentru sindromul de depresie endogenă, conform DSM III și DSM IV. Clomipramina a fost administrată oral în doze de la 50 la 150 mg/zi, preparatul folosit fiind Hydiphen, tablete de 25 mg. Autorul nu a utilizat un grup de control, fapt considerat neetic având în vedere riscul suicidar al pacienților. Eficiența tratamentului cu clomipramină în depresia endogenă a fost evaluată utilizând Inventarul Beck pentru depresie înainte și după tratament.
Rezultate: La pacienții cu cea mai mare deprimare a afectului, Hydifen a avut rezultate foarte bune, cu remisiunea completă a simptomelor după tratament. De asemenea, medicamentul a fost eficient la pacienții cu cea mai mare intensitate a simptomelor hipocondriace.
Concluzii: Hydifen este foarte util în cele mai severe forme de depresie. Efecte foarte bune au fost observate în tratamentul depresiilor cu inhibiție psihomotorie, frecvent aproape de stupor.
Cuvinte cheie: clomipramină, depresie endogenă severă, stupor, simptome hipocondriace

ABSTRACT

Background: Clomipramine is indicated mainly in depressions with psychomotor inhibition with low level of anxiety and aggression, and with very intense obsessive-compulsive symptoms.
Material and Method: Clompiramine was administered for six weeks in 50 outpatients diagnosed with major depression. These were patients in whom endogenous depression syndrome occurred at least for the third time and in whom manic episodes were never observed. All studied persons met the criteria of endogenous depression syndrome according to DSM III and DSM IV classifications. The drug was administered orally in doses from 50 to 150 mg daily, in form of 25 mg tablets called Hydiphen®. The author did not compare the results of the drug with a control group as considered that was unethical because of suicidal tendencies of the patients. The effectiveness of clomipramine on endogenous depression was assessed on the basis of results of Becks inventory before and after treatment.
Results: In patients with the greatest mood lowering, Hydiphen® exerted outstandingly good effects with complete remission of symptoms after the treatment. The drug was therapeutically effective in patients with highest intensity of hypochondria.
Conclusions: Hydiphen® is very useful in most severe depressions. Very good effects are observed in the treatment of depressions with psychomotor inhibition, frequently near stupor.
Key Words: clomipramine, severe endogenous depressions, stupor, hypochondriac symptoms

INTRODUCTION

Clomipramine is the drug of choice in the treatment of unipolar affective disorder, that is endogenous depression, also called phasic depression.[1,2] Affective disorders have usually a recurrent course, in form of phases. If the phases include only depressions, this condition is then called unipolar affective disease.[2] Much evidence points to the role of genetic factors in affective diseases.[3]

Clomipramine is an antidepressant drug with tricyclic structure, a dibenzoazepine derivative, and has been introduced to treatment by Kuhn in 1963. It strongly inhibits the intraneuronal uptake of serotonin and, weaker, that of noradrenaline.[4,5] It is indicated mainly in depressions with psychomotor inhibition with low level of anxiety and aggression, with very

Department of Neurosurgery with Outpatient Clinic, Central University Teaching Hospital with Polyclinic, Armed Forces School of Medicine, Warszawa, Poland

Correnspondence to:
Leszek Tomasz Ros, ul. Zablociñska 6 m. 55, 01-697 Warszawa, Poland

Received for publication: Sep. 17, 2003. Revised: Jan. 17, 2004.

intense obsessive-compulsive symptoms.[6,7] The onset of therapeutic action is observed usually after seven days of drug administration.[8] In the so called major depression (endogenous depression), clomipramine significantly increases prolactin level.[9] Clomipramine can rarely cause the increase in anxiety, insomnia, tachycardia, and dryness of the mouth.

Some authors demonstrated dysfunction of serotoninergic and noradrenergic neurotransmission in experimental depression model in rats, where clomipramine proved to be the drug of choice.[10] Other authors studied sexual behaviour of rats treated with clomipramine. They demonstrated that clomipramine therapy in doses higher than 20 mg/kg daily caused significant impairment of sexual behaviour in adult male rats.[11]

In other studies it has been shown that therapeutic effectiveness of clomipramine was very similar to that of moclobemide. Anticholinergic effects, body weight gain and hypotensive effect developed more frequently in the group treated with clomipramine.[12,13] Some authors suggested a high similarity between the effects of clomipramine and imipramine on monoamine levels, mainly noradrenaline and serotonin, in the synaptic cleft. It was shown that in some endogenous depressions, depressions resistant at the pharmacological treatment, amitriptyline, nortriptiline, imipramine and dibenzepin proved slightly more effective than clomipramine.[14] In drug-refractory depressions the administration of clomipramine and maprotiline in intravenous infusions was very effective.[15]

Other authors administered clomipramine to patients with major depression and alcohol-addiction syndrome. A significant improvement of psychic condition was obtained in about 40% of the patients.[16] Adverse effects were observed during administration of thymoleptics, mainly clomipramine. In one study, from 84 patients who received clomipramine, in more than 50 adverse effects developed. The studied thymoleptics exerted no effect on the haemopoietic system, parenchymal organs and on hypothalamic mechanism of baseline thyreotropin, prolactin and cortisol secretion.[17]

In depression treatment, the daily therapeutic dose of clomipramine is between 150-200 mg range, the maximal dose being 300 mg. In the prophylaxis of unipolar affective disease, the dose is up to 150 mg daily. The maximal ambulatory dose should not exceed 150 mg daily.[8]

Preparations: Two clomipramine preparats: Anafranil® 10 mg and 25 mg tablets and Hydiphen® 25 mg coated tablets.

AIM

The aim of the study was to assess the therapeutic effectiveness of clomipramine in endogenous depression, depending on selected demographic factors. The author aimed at answering the question on which specific features of depression the clomipramine is effective.

CLINICAL MATERIAL AND METHODS

Clomipramine was administered in treatment of outpatients in the Health Care Institution, Warszawa-Zoliborz and in patients discharged from the Department of Neurosurgery, Clinical Hospital in Warsaw, 128 Szaserów st. The study group included 50 male and female patients, aged between 18 and 80 years, with the diagnosis of major depression. In these patients endogenous depression syndrome occurred at least for the third time and manic episodes were never observed. All studied persons met the criteria of endogenous depression syndrome according to DSM III and DSM IV classifications. Eventually the author used DSM IV classification, which is more actual. On the basis of clinical observations, CGI scale and DSM IV classification the author concluded that the patients suffered from mild, moderate and severe depressions. The studied subjects were treated with clomipramine and systematically monitored for six weeks. The drug was administered orally in doses from 50 mg to 150 mg daily, in the form of 25 mg tablets called Hydiphen. Additionaly, the patients were treated with diazepam and flunitrazepam to mild the feeling of anxiety and insomnia.

The patients were treated ambulatory, using of pharmacological means and psychotherapy. During successive visits, mental and somatic status of the patients was assessed. Basic laboratory blood tests and chest radiograms were also performed to answer the question of somatic health of the patients. The patients were somatic healthy so there were no contraindications for clomipramine treatment. All patients were treated by the same doctor - the author of the paper. The observations were noted in case records. In the choice of the drug, clinical condition of the patient and most recent reports from international literature were taken into account. The data for the study were collected from case records of the patients. In each case record, the history taken from patient`s family was also presented.

The manuscript is based on Beck`s inventory although each patient underwent also detailed mul-

tiple tests by 24-point Hamilton Depression Assessment Scale and Beck Depression Self-Assessment Inventory and Mongomery-Asberg Scale. The tests that were used had following scales:

- Hamilton scale - scale: 0 - 80,
- Beck Depression Self-Assessment Inventory - scale 0 - 63,
- Montgomery-Asberg scale 0 - 70.

The author evaluated the therapeutic effects on the basis of the above mentioned scales and also on the basis of clinical examination and observation of the patients. Depression intensity was assessed by clinical examination and on the basis of ICD-10 classification. The author used a number of statistical methods: contingency tables, Student`s t-test, Kendall tau correlation coefficient, Pearson correlation coefficients, Cronback alpha coeffcients and chi2 statistical method.[18,19,21,22]

RESULTS AND DISCUSSIONS

Beck Depression Self-Assessment Inventory

The study was based on Beck`s inventory, which consists of questions discussing characteristic symptoms of endogenous depression.

The study was based on parametrical test, which gave results of improvement or possible change for the worse.

In Tables 1 to 20, the percentual distribution of patients depending on symptoms intensity, before and after six week treatment with Hydiphen® and the response achieved by the use of Hydiphen® are presented.

Table 1. Sadness, depression

Symptom intensity	0	1	2	3
% of patients before	0	20	48	32
% of patients after	40	32	20	8

In patients with the greatest mood lowering, Hydiphen® exerted outstandingly good effects with complete remission of symptoms after the treatment, the number of patients with this option decreased fourfold (option B3). In patients with moderately intense mood lowering Hydiphen® produced cure in over half of the subjects.

Table 2. Looking into future

Symptom intensity	0	1	2	3
% of patients before	0	8	48	44
% of patients after	36	32	16	16

The number of patients looking into their future with great or medium pessimism decreased about threefold after treatment with clomipramine. The drug exerted virtually unfavourable effect in patients evaluating their future with pessimism, but not very intense pessimism.

Table 3. Negligence

Symptom intensity	0	1	2	3
% of patients before	8	40	32	20
% of patients after	52	36	8	4

Clomipramine had beneficial effects in patients with very intense belief that they are negligent in their work and they do everything bad (option B2, B3). The drug was less effective in the treatment of patients evaluating their activity not very negatively.

Table 4. Satisfaction with activity

Symptom intensity	0	1	2	3
% of patients before	0	40	24	36
% of patients after	32	40	16	12

The drug exerted very favourable effects in patients completely deprived of satisfaction with their activity (option B3), slightly less favourable effects in patients only partially satisfied with their activities (option B2). Clomipramine proved completely useless in the treatment of patient with the lowest intensity of the symptom (option B1).

Table 5. Feeling of guilt

Symptom intensity	0	1	2	3
% of patients before	8	48	20	24
% of patients after	48	40	12	0

Clomipramine exerted outstanding effects in patients with severe depressive feelings of guilt, taking the form of depressive delusions (option B3). It was therapeutically slightly less effective in feeling of guilt of moderate intensity (option B2) and least effective in patients with low intensity of feeling of guilt (option B1).

Table 6. Deserving punishment

Symptom intensity	0	1	2	3
% of patients before	72	12	0	16
% of patients after	84	12	4	0

Hydiphen® exerted good therapeutic effects in cases of the highest intensity of this symptom, that is in typical depressive delusions of punishment (option B3). The drug was completely useless in patient with milder forms of this symptom.

Table 7. Self-Satisfaction

Symptom intensity	0	1	2	3
% of patients before	0	52	36	12
% of patients after	40	44	12	4

Hydiphen® was fairly effective in the treatment of patients with medium and high intensity of this symptom, i.e. feeling animosity against themselves or hating themselves (option B2, B3). The drug was slightly less effective in the treatment of patients not satisfied with themselves (option B1).

Table 8. Feeling of value

Symptom intensity	0	1	2	3
% of patients before	8	52	36	4
% of patients after	44	44	12	0

The drug was outstandingly effective in patients with the highest intensity of the symptom, that is in developed typical depressive delusions of guilt (option B3), slightly less effective in the treatment of patients with delusions of condemnation (option B2) and least effective in patients regarding themselves only as incompetent (option B1).

Table 9. Suicidal tendencies

Symptom intensity	0	1	2	3
% of patients before	64	0	36	0
% of patients after	72	8	20	0

The drug proved therapeutically effective only in patients with medium intensity of this symptom, that is in such persons who just want to commit suicide (option B2).

Table 10. Weeping

Symptom intensity	0	1	2	3
% of patients before	16	20	52	12
% of patients after	40	44	16	0

The drug proved very useful in the treatment of patients with medium and high intensity of this symptom, that is in such persons who are constantly tearful (option B2) and in those who are completely unable to weep (option B3).

Nervousness

Hydiphen® proved outstandingly good in the treatment of patients with medium and high intensity of this symptom, that is in patients constantly nervous (option B2) and completely not nervous and indifferent (option B3). The drug was particularly uneffective in patients with mild intensity of this symptom, that is slightly more nervous than before (option B1).

Table 11. Interest in people

Symptom intensity	0	1	2	3
% of patients before	4	12	56	28
% of patients after	36	24	32	8

The drug proved most useful in patients with the most severe form of this symptom, that is in those who completely isolated themselves from other people (option B3). The drug was less effective in patients with moderately intense symptom (option B2) and completely ineffective in patients with low intensity of the symptom (option B1).

Table 12. Easiness of decision making

Symptom intensity	0	1	2	3
% of patients before	8	16	52	24
% of patients after	36	40	20	4

The drug proved therapeutically effective in patients with the highest intensity of the symptom, i.e. these who cannot make any decision (option B3). The drug was less effective in patients with less intense symptom, that is having great difficulties in making decisions (option B2). The drug proved completely therapeutically ineffective in patients with mild intensity of the symptom, that is those delaying making decisions more frequently than before depression (option B1).

Table 13. Assessment of own appearance

Symptom intensity	0	1	2	3
% of patients before	56	8	32	4
% of patients after	76	20	4	0

The drug proved superbly effective in patients with medium and high intensity of this symptom, that is in patients feeling that their appearance is ever worse (option B2) and patients convinced that their appearance is awful and odious (option B3), respectively. Unfortunately, the drug was completely ineffective in patients with low intensity of the symptom, that is those worrying that they look old and inattractively (option B1).

Table 14. Ability to work

Symptom intensity	0	1	2	3
% of patients before	12	20	48	20
% of patients after	44	36	16	4

The drug proved highly useful in patients with the highest intensity of the symptom, i.e. those unable to do anything (option B3), slightly less useful in patients with medium intensity of the symptom, that is those forcing themselves with great effort to activity (option B2). The drug was completely ineffective in patients with low intensity of the mentioned symptom, that is patients starting any activity with great difficulty (option B1).

Table 15. Sleep

Symptom intensity	0	1	2	3
% of patients before	16	40	8	36
% of patients after	48	24	12	16

The drug proved quite effective in patients with low grade insomnia (option B1) and with high grade insomnia (option B3). It was completely therapeutically ineffective in patients with medium grade insomnia (option B2).

Table 16. Fatigue

Symptom intensity	0	1	2	3
% of patients before	16	12	48	24
% of patients after	44	32	20	4

The drug proved outstandingly effective in the treatment of patients with the highest intensity of the mentioned symptom, that is patients feeling so intense fatigue that they were unable to do anything (option B3). The drug was relatively effective in patients with moderately intense symptom, i.e. those who were getting tired by all activities performed by them (option B2). The drug was completely ineffective in the treatment of patients with mild intensity of the mentioned symptom, that is those who were getting tired significantly more than before depression (option B1).

Table 17. Appetite

Symptom intensity	0	1	2	3
% of patients before	16	20	44	20
% of patients after	60	20	16	4

The drug was outstandingly effective in patients with the highest grade of appetite loss, that is in patients who completely lost appetite (option B3). It was slightly less effective therapeutically in patients with medium intensity of the mentioned symptom, that is in patients with significantly poorer appetite (option B2). The drug proved completely ineffective in patients with low intensity of the symptom, i.e. those with slightly impaired appetite (option B1).

Table 18. Body weight loss

Symptom intensity	0	1	2	3
% of patients before	88	12	0	0
% of patients after	96	4	0	0

The drug proved relatively therapeutically effective in least emaciated and least cachectic patients (option B1).

Table 19. Concern about own health

Symptom intensity	0	1	2	3
% of patients before	36	12	16	36
% of patients after	56	16	16	12

The drug was therapeutically effective in patients with highest intensity of hypochondria (option B3).

Table 20. Sexual interest

Symptom intensity	0	1	2	3
% of patients before	24	8	32	36
% of patients after	48	16	8	28

The drug proved evidently effective in the treatment of patients with medium intensity of the mentioned symptom, that is in patients whose problems interested them significantly less than before depression (option B2).

CONCLUSIONS

Many authors regard clomipramine as the drug indicated mainly in depressions with psychomotor inhibition with anxiety symptoms.[8,23,24] The results of treatment in depressions with high restlessness, psychomotor agitation, hypochondriac features are less good. The results of this author are partially in agreement with these reports. Hydiphen® is very useful in most severe depressions. Very good effects are observed in the clomipramine treatment of depressions with psychomotor inhibition, frequently near stupor. A moderate improvement is observed in depressions with hypochondriac features. In depressions with manifestations of anxiety, restlessness, motor agitation, the treatment with Hydiphen® produces moderate or weak effects. Clomipramine frequently can be regarded as the drug of choice in the treatment of severe endogenous depressions with very intense obsessive-compulsive manifestations.

REFERENCES

1. Kragh-Sorensen P, Muller B, Andersen JV. Moclobemide versus clomipramine in depressed patients in general practice. A randomized, double-blind, parallel, multicenter study. Journal of Clinical Psychopharmacology 1995;15(Suppl.2):248-303.
2. Vogel B, Hagler M, Hennessey A. Dose dependent decrements in adult male rat sexual behavior after neonatal clomipramine treatment. Pharmacol, Biochemi and Behavi 1996;54(3):605-9.
3. Florkowski A, Gruszczyñski W, Górski H. Treatment of depression in patients with diagnosed alcohol-dependence syndrome. Farmakoter Psychiatr Neurol 1998:3:78-82.
4. Horodnicki JM, Warnecka-Przybylska M, Beoñska J. Evaluation of side reactions during antidepressants treatment of affective psychoses. Psychiat Pol 1991;25(3/4):62-9.
5. Wciórka J. Practical Psychiatry for Family Doctor. Instytut Psychiatrii I Neurologii, Warszawa, 1992.
6. Drapper NR. Applied Analysis of Regression. PWN 1973.
7. Zieliñski R. Tablice statystyczne. PWN, Warszawa, 1972.
8. Kinney GG, Vogel GW, Feng P. Decreased dorsal raphe nucleus neuronal activity in adult chloral hydrate anesthetized rats following neonatal clomipramine treatment: implications for endogenous depression. Brain Res 1997;756(1-2):69-75.
9. Puzyñski S. Depressions. Pañstwowy Zaklad Wydawnictw Lekarskich, Warszawa, 1988.
10. Siek S. Structure of Personality. ATK, Warszawa, 1986.
11. Vijayakumar M, Meti BL. Alterations in the levels of monoamines in discrete brain regions of clomipramine induced animal mode of endogenous depression. Neurochemi Res 1999;24(3):345-9.
12. Kostowski W, Puzyñski S. Experimental and Clinical Psychopharmacology. Pañstwowy Zaklad Wydawnictw Lekarskich, Warszawa.
13. Frazer A. Winokur A. Biological Foundations of Mental Disorders. Pañstwowy Zaklad Wydawnictw Lekarskich, Warszawa, 1982.
14. Bogdanowicz E, Kalinowski A, Swiêcicki L. Management of depression with intravenous infusions of antidepressants (clomipramine and maprotiline). Psychiat Pol 1991; 25(3/4):19-24.
15. Blikiewicz A. Psychiatria, vol II (DSM IV). P.Z.W.L., Warszawa 2003.
16. Fisher RA. Statistical Tables for Biological, Agricultural and Medical Research. Hafner Publishing 1973.
17. Guelfi JD, Payan C, Fermanian J. Moclobemide versus clomipramine in endogenous depression. A double-blind randomised clinical trial. Brit J. Psychiatry 1992;160:519-24.
18. Armitage P. Statistical Methods in Medical Studies. P.Z.W.L. Warszawa 1978.
19. Berêsewicz M, Bidziñska E, Puzyñski S. Effects of management of endogenous depression with tricyclic antidepressive drugs (a comparative analysis of 7 compounds). Psychiatr Pol 1991; 25(3/4):13-8.
20. Caswell F. Success in Statistics. J. Murray Publisher, 1989.
21. Eriksson Elias. Clomipramine and other serotonin reuptake inhibitors in the treatment of depressed mood, anxiety and impaired impulse control. Psychiat Pol 1994;28(5):601-12.
22. Zhu J, Bengtsson BO, Mix E. Clomipramine and imipramine suppress clinical signs and 7 and 8 cell response to myelin proteins in experimental autoimmune neutris in Lewis rats. J. Autoimmuni 1998;11(4):319-27.
23. Shapira B, Vagmur MJ, Grapp C. Effect of clomipramine and lithium on fenfluramine - induced hormone release in major depression. Biological Psychiatry 1992;31(10):975-83.
24. Zebrowska-£upina I, Ossowska G, Klenk-Majewska B. Chronic stress reduces fighting behaviour of rats: the effect of antidepressants. Pharmacol Biochem Behav 1991;39(2):293-6.