ANTIDEPRESSANT EFFICACY AND SAFETY OF MIANSERIN : A DOUBLE-BLIND, PLACEBO AND AMITRIPTYLINE CONTROLLED COMPARISON STUDY IN DEPRESSION

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ÖZET

DEPRESYONDA MİANSERİN'İN ANTİDEPRESAN ETKİNLİĞİ VE GÜVENİRLİĞİ: BİR ÇİFT-KÖR PLASEBO VE AMİTRİPTİLİN KONTROLLU KARŞILAŞTIRMA ÇALIŞMASI

Mianserin'in antidepresan etkinliği ve güvenirliğini değerlendirmek amacıyla bir çift-kör ,plasebo ve amitriptilin kontrollu karşılaştırma çalışması yapıldı.

Hastalar DSM-III-R tanı kriterlerine göre major depresyon (n=60) ve distimik bozukluk (n=40) olarak belirlendi.Sekiz haftalık çalışma boyunca hastalar randomize yöntemle mianserin (n=40),amitriptilin (n=40) ve placebo (n=40) gruplarına ayrıldı Son ilaç dozları ortalamaları günlük mianserin grubu için 56 mg ve amitriptilin grubu için 126mg idi.Değerlendirmeler 0,7,14,28,56'na günlerde Hamilton Depresyon Ölçeği (HAM-D),klinik Global İzlenim Skalası, Asberg'in yan etki skorlarına ve bazı biyokimyasal parametrelerle yapıldı.

Hem mianserin ve hem de amitriptilin'in antidepresan etkinliğinin plasebo grubundan anlamlı olarak (P<0.001) yüksek olduğu görüldü.Amitriptilin grubunda mianserin ve placebo grubuna göre daha fazla antikolinerjik ve sedatif yan etkilerle başdönmesi göründü.

Anahtar Kelimeler : Mianserin , Amitriptilin,Antidepresan Tedavi,Yan Etki,Çift-kör Çalışma,Plasebo.

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SUMMARY

A double-blind,placebo and amitriptyline-controlled comparison study was performed to evaluate the antidepressant efficacy and safety of mianserin. Patients with DSM-III-R defined major depression (N=60) and dysthymic disorder (n=60) randomly received either mianserin (N=40),or amitriptyline (N=40), or placebo (N=40) twice daily for the 8 week study period.The mean final daily medication dose was 56 mg and 126 mg for the mianserin and amitriptyline treatment groups,respectively. Assesments were made on days:0,7,14,28,56 by the Hamilton Rating Scale for Depression (HAM-D),the Clinical Global Impression Scale(CGI), the Rating Scale for Side-Effects (Asberg) (RSSE), and some biochemical parameters .

Both the mianserin and amitriptyline treatment groups showed a significantly greater improvement from baseline (P<.001) than placebo group.The amitriptyline group showed a higher proportion of anticholinergic and sedative side effects and dizziness compared with patients who received either mianserin or placebo.

Key Words: Mianserin, Amitriptyline,Antidepressant Therapy, Side-Effect,Double-Blind Study, Placebo.

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INTRODUCTION

It is now well known that depression is the fourth most frequent disease;and that the most satisfying results from pharmacological therapy in psychiatry are obtained in this disease.Although there is a high success in the therapy of this group,about 20% of the patients can not be treated or their treatment has to be stopped due to one of several reasons(e.g. the fact that every antidepressant is not effective in every patient,the presence of serious organic disorder other than depression "cardiovascular disease,prosthatic hypertrophy,glaucoma etc." and the serious side effects of some of these drugs (especially MAO inhibitors and tricyclic antidepressants)).For these reasons,every effort is being made to manufacture new antidepressants without these drawbacks.The last product of these efforts is mianserin (1-30).

Like the therapies with other drugs,the effects of antidepressants are greatly influenced with racial and national factors (6).

Mianserin has been used during the last decade in Turkey.It has been synthesized in 1966 as a piperazino-azepine group tetracyclic antidepressant, and is different in many ways from tricyclics.Especially the fact that its antiserotonin (11,30), antihistaminic effects and its cardiotoxic side effects are much less (8.19,22,24,30) than the other tricyclic antidepressants .It has been suggested that the antidepressant activity of mianserin is through the blocking of presynaptic alpha-2 adrenoceptors and thus reducing the presynaptic adrenoceptor number and sensitivity which is claimed to increase in depression (27,29).

This research was designed to compare the antidepressant effects and haematological,hepatic,renal,cardiovascular,systemic and subjective side-effects of mianserin,which is a relatively novel antidepressant for the Turkish population and a standard and reference antidepressant amitriptyline which is older and more established in relation to the above mentioned effects and side-effects.

MATERIALS AND METHOD

A. The Choice of Patients : 120 male inpatients were included in this study. These were diagnosed as major depression in the case of 60 patients, and dysthimia in the case of 60 patients,according to the DSM-III-R criteria.

The criteria for being included in this study are listed in table-I.The criteria for being excluded can be seen in table-II

Table-I :Criteria for Inclusion in the Study

1.To fit in DSM-III-R Major Depression and Dysthymic disorder criteria

2. Acceptance of hospitalization

3. Hamilton Rating Scale for Depression (17 items) score being a minimum of 16p.

4. 18-70 age group

Table-II Criteria for Exclusion from the Study

1.Hungtington's Chorea,epilepsy,organic brain disease,

2.Narrow-angle glaucoma,

3.Prostate hypertrophy,

4.Severe,uncontrolled diabetes,

5.Serious liver,kidney,heart and respiratory system diseases,

6.Severe asthma and other allergic conditions,

7.Malignancy,

8.The use of lithium,reserpin,alpha methyl dopa,

9.Alcoholism ,substance abuse,

10.The use of MAOI's at least 2 weeks ago,

11.Liver enzyme inducers (e,g,barbiturates),antihistaminics, fenfluramine,

12.Therapy with other antidepressants, at least one week ago,

13.Drug dependence,

14.The use of ECT,fluoxethine in the last six weeks or a more recent time,

15.Anorexia nervosa,bulimia,schizophrenia or psychotic disorders in patient's history,

16.Severe allergy or multiple adverse drug reactions in patient's history,

17.Severe suicidal risk.

The patients were divided into three groups randomly (Table-V).The groups were given amitriptyline,placebo or mianserin in special capsules,in a double blind fashion.In the beginning,patients in the amitryptiline group were given50 mg daily amitryptiline in the evening and at noon while being given placebo in the morning. The patients in the mianserin group were given placebo in the morning and at noon,while being given 30 mg of mianserin in the evening.The dosage of the drugs were increased starting from the third day of the therapy, and a maximum of two times the original dosage for both drugs were reached and the therapy was continued in this dosage.

Two patients from the major depression group and one patient from the dysthymia group could not continue with the amitriptyline therapy.

The therapeutic groups,sex,age,HAM-D mean scores (D-0) and mean duration of disease of the patients completing the study are shown in table-III.

Table-III :The distribution of patients according to drug,sex,age,pre-treatment mean HAM-D and mean duration of disease (n=120)

	Amitriptyline Group	Mianserin Group	Placebo Group
	n = 40	n = 40	(n = 40)
Age (mean year)	21.4	21.4	21.5
HAM-D mean scores	28.1	27.9	27.9

	Major depression	Dysthymia Group	Major depression	Dysthymia Group
Mean duration of disease (year)	1.2	2.9	1.0	2.8

B.The Assessment of Antidepressant Effect : In the individual interviews at D-0,D-7,D-14,D-28 and D-56'th days,the general clinical assessment of the patients were made and clinical improvements were noted.At the same time, the 17-item Hamilton Rating Scale for Depression (HAM-D),the clinical global Impression scale (CGI) scores of the patients,were also assessed without the patient's knowledge (Table-IV).

Table-IV :The HAM-D scores of the patients for days D-0,D-7,D-14,D-28 and D-56
Comparison of two drug Groups.

DURUG TAKEN	D-0	D-7	D-14	D-28	D-56	Significance
Amitriptyline 126 mg/day n=4	28.1	22.1*	18.2*	14.1*	12.2*	
Mianserin 56 mg/day n=40	27.9	20.2*	18.1*	10.9*	9.5*	(P=0.269)
Placebo (n = 40)	27.9	24.3	20.4	18.2	18.5	(P=0.01)

C.The Designation of Criteria for Side-Effects :

find out about the side effects appearing as subjective complaints,each week the patients were questioned with the Rating Scale for Side-Effects (Asberg) (RSSE) and the side effects were recorded (Table-V).

2.Each week,the patients' pulse rates and arterial blood pressures (supine and on foot) were recorded.

3.On D-0 and D-56'th day the following investigations were conducted.

a-ECG and body weight measurement

b-After a fasting starting from the previous night,blood was taken from the arm veins and the following laboratory investigations were conducted in the biochemistry laboratory: complete blood count, hemoglobin, haematocrit, leukocyte formula,platelet count,fasting blood glucose,serum uric acid,blood urea,serum creatinine,serum alkaline phosphateses,blood sodium, potassium, alcium, transaminases, total protein,albumine, globuline, cholesterol, total lipid and triglyceride.

D. Statistical Analysis

Analysis of variance was made for HAM-D,CGI,RSSE scores,body weight,pulse rate and blood pressure.For the biological parameters,student's paired "t" test, and chi-square test were used for statistical analysis.

RESULTS

There were no substantial differences between the two drug groups,in relation to mean age,severity of disease, duration of disease,body weight and HAM-D scores.In other words, the groups were more or less homogenous and had similar characteristics.

A-COMPARISON OF ANTIDEPRESSANT EFFECT

a.Statistical Comparison of the Mean HAM-D Scores:

As shown in Table III, both drugs started to lower HAM-D scores significantly, starting from the first week ($P<0.001$). Thus,both drugs have antidepressant effect and when compared,this effect is not significantly different between these two drugs ($P>0.001$). But,both drugs are significantly more effective than the placebo.($P<0.001$).

b.The Assessment of Patients According to Clinical General Opinion: On the 56'th day of the study, the patients were assessed table-V shows the patients according to therapeutic efficiency, drug group and disease group in relation to this assessment.

B-SIDE-EFFECTS

a.The Results of Using Standard Side Effect Check-List for Subjective Complaints:

No major subjective sign,forcing us to discontinue therapy, was found in either group.But in the beginning,one patient from the major depressive group,taking amitriptyline complained from sleeping during the day and dropped out in the first week.Also one patient from the dysthymic group complained from excessive fatigue the morning after taking the drug,and had to discontinue treatment.

When the three groups are compared for dizziness,sexual dysfunction and anticholinergic side effects such as dry mouth,blurred vision, constipation, complaints are significantly ($p<0.05$) more frequent in amitriptyline group than other groups.Also fatigue and somnolence are significantly ($p<0.05$) more frequent in amitriptyline and mianserin groups than the placebo group (see table-VI).

Table -VI:Percentage of Patients with Treatment-Related Side Effects During Double-Blind Therapy.

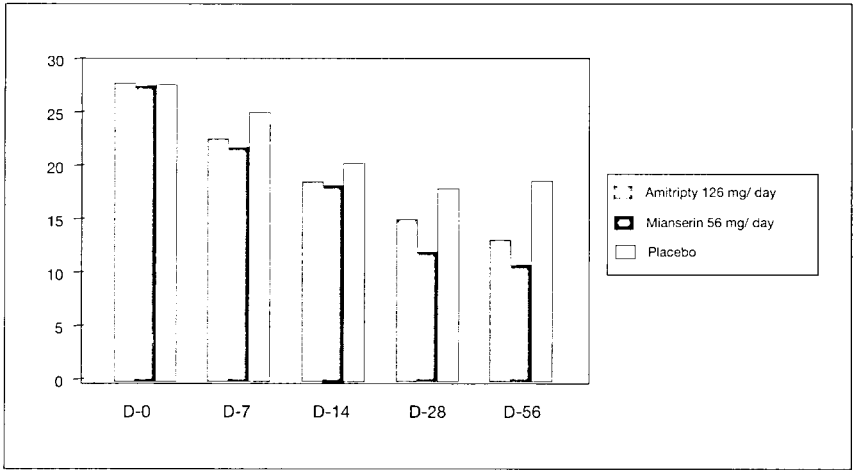
Organ System Side Effect	TREATMENT GROUPS Amitriptyline (n=20)	Mianserin (n=20)	Placebo (n=20)
Psychiatric Disorders			
Somnolence	40 a.b.	26a	12
Insomnia	8	4	9.6
Agitation	15 b	4	12
Sexual dysfunction	20 a.b.	4	2.6
Amnesia	4	0.4	0.8
Central and Peripheralnervous system			
Headache	10	4	12
Tremor	11.6 a.b.	2	2
Dizziness	30 a.b.	2	8
Autonomic nervous system			
Dry mouth	80 a.b.	16	18
Increased sweating	4	2	4
Gastrointestinal system			
Nausea	10	4	9.6
Diarrhea	2	0	10.0
Constipation	20 a.b.	5.6	4
Dyspepsia	4	4	2
Anorexia	0.8	0.8	3.2
Vomiting	1.2	0.8	0.8
Urinary system			
Micturination disorder	8	4	0.8
Special Senses			
Vision abnormalities	16 a.b.	4	4.8
Taste perversion	4	2	0.8
Cardiovascular system			
Palpitations	6	2	1.2
General Fatigue	24 a	16 a.	10

a - P<0.05 Compared with placebo
b- P<0.5 Compared with mianserin.

b.The patients' pulse rate,blood pressure while sitting and blood pressure on foot were measured .No significant difference was observed between the three groups.

c.The ECG's,biochemical investigations and body weight measurements, all taken in day D-O and D-56 were reviewed and no statistically significant differences.

Figure-1: Time Course of the Diagram of HAM-D mean total scores for the treatment days at D-0,D-7,D-14,D-28 and D-56.



(*)Significant (P< 0.01) (Compared with D-O).

DISCUSSION

In this study ,aimed to determine and compare the antidepressant effects and various side effects of amitriptyline and mianserin,60 inpatients with major depression diagnosis and 60 inpatients with dysthymia diagnosis were included,making a total of 120 inpatients.When the pretreatment and posttreatment clinical assessments and HAM-D scores were compared, it was observed that both drugs had statistically significant ($p<0.01$) antidepressant effect than the placebo, starting at the first week of treatment.The antidepressant effect of the two drugs, and their effect on different patient groups were compared and no significant ($p>0.01$) differences were noted.These findings are in accordance with the literature (8,14,18,21,29).

The side effects (dizziness,sexual dysfunction,anticholinergic side effects) were more frequent ($p<0.05$) in the amitriptyline group,than other groups.Also somnolence and fatigue are significantly more frequent in both drug groups than the placebo group.All these results are in accordance with the literature (8,13,14,18,24).

In the biochemical and other laboratory investigations including many biological parameters,conducted to find out the side effects of the two drugs,no significant differences were observed between the pre-treatment and post-treatment values.

Disturbance of cardiac conduction and arrhythmia (13,19,24), hepatic side effects including jaundice and increased levels of transaminases,convulsions (28), blood dyscrasias (like granulocytopaenia, agranulocytosis, pancytopaenia,

aplastic anemia) that start at the 4-6'th week of therapy and which are thought to be due to racial hypersensitivity (1,6,15,16,20), have been reported for mianserin.The fact that these side effects did not occur in our group suggests that either the aforementioned side effects are due to national/racial hypersensitivity, or/and these side effects are very rare (1,15,16).

Tricyclic antidepressants have been used extensively and with satisfying results on depression for many years.Yet while this disease group has a high suicide risk,those drugs are being used more and more frequently for committing suicide.In other words,the psychiatrist is giving the patients a death weapon with his own hands.In fact,some statistics show that for every one million recipes including tricyclic antidepressants, a mean of 38.5 suicides with those drugs occur.Also these drugs have a high cardiotoxic,hepatotoxic, anticholinergic side effect incidence.For these reasons,it is necessary to manufacture new antidepressants free from these side effects, that have fewer side effects,allowing the person to continue his daily life normally, likemianserin (3,4,6,8,9,10,18,20,22,23).

Since our hospital is a military hospital , a great percentage of the patients are from the 20-22 age group males.For this reason,although depression is two times more frequent among women but, there is not woman in our study.Although this may seem to be a disadvantage at first sight but,we believe that since it produces homogeneity (which is a important drug studies), it turns out to be an advantage.

In conclusion, we have shown that while both amitriptyline and mianserin start their effect during the first week of treatment with approximately equal pharmacological effects,mianserin has less side effects than amitriptyline and mianserin has little or no cardiac,hepatic,haematological,renal,neurological and anticholinergic side effects in the Turkish population.These characteristics make mianserin superior to classical tricyclic antidepressants,such as amitriptyline in our community.

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