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# Comparative Study of the Effects of the Commonly Used Antidepressants on the Cardiovascular System

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## ABSTRACT

**This study included 120 patients with major depressive disorder, divided into three groups. Group I: 60 patients received tricyclic antidepressants (half of them were put on amitriptyline and the other half on imipramine). Group II: 30 patients received tetracyclic antidepressant maprotiline. Group III: 30 patients received monoamine oxidase inhibitor tranylcypromine.**

**Before and after 6 weeks of treatment, all patients were submitted to (a) Measurement of blood pressure (both supine and standing) and (b) ECG.**

**The results revealed: 1- Tricyclic antidepressants (amitriptyline and imipramine) have significant effects on ECG (increase in heart rate, prolongation of P-R interval and QTc time). 2- Imipramine has significant increasing effect on the degree of orthostatic hypotension while the other 3 drugs have non-significant increase. 3- The only significant cardiovascular effect of maprotiline was decreased amplitude of T-wave. 4- Tranylcypromine was the least cardiotoxic (except significant lowering of supine blood pressure).**


## INTRODUCTION

The major area of concern to develop regarding the tricyclic compounds since their introduction has been their toxic effects on the cadiovascular system (Blackwell, 1981). Tricyclic antidepressants may produce significant disturbances of cardiac rhythm, conduction and orthostatic hypotension (Fowler *et al.* 1976).

Reed *et al.* (1980) stated that tricyclic antidepressants can usually be used safely without major cardiovascular complications in patients with heart disease. Glassman *et al.* (1983) emphasized that this group of drugs may even suppress ventricular arrhythmia.

Raeder *et al.* (1978) mentioned that maprotiline has a lower incidence of cardiovascular reactions than the TCAs. Daly and Connolly (1981) reported that the cardiotoxicity of the this tetracyclic is similar to tricyclics.

For patients with certain cardiac problems, MAOIs may have an advantage over TCAs (Coldman *et al.* 1986). The main side effects are orthostatic hypotension (Kendell and Zealley, 1983).

### Aim of the Work

The aim of this work is to study and compare the effects of antidepressants which are in common use in Egypt, on the cardiovascular system.

## SUBJECTS AND METHODS

The study included 120 patients with major depressive disorder. The age ranged between 18-45 years with a mean of 35.12 ± 6.89 years. They were 76 females and 44 males. They were divided into three main groups:

Group I: 60 patients received tricyclic antidepressants. This group is subdivided into 2 subgroups.

Group I A: 30 patients were put on amitriptyline (100 mg/day).

Group I B: 30 patients received imipramine (100 mg/day).

Group II: 30 patients were put on tetracyclic antidepressant maprotiline (100 mg/day).

Group III: 30 patients were treated by monoamine oxidase inhibitor tranylcypromine (30 mg/day).

Patients with cardiovascular disease were excluded (e.g. myocardial infarction, arrhythmia .....). The patients were drug-free for at least one month before being involved in this study. Actually, 100 patients had never received antidepressant before, 20 patients were asked to discontinue their antidepressant for one month. Only one antidepressant was used for each patient.

Before and after treatment, all patients were submitted to:

A- Measurement of blood pressure (both supine and standing).

B- ECG (heart rate, T-wave amplitude, P-R interval, QTc time and QRS complex).

According to Goldman *et al.* (1986) and Kutcher*et al.* (1986), examination of the cardiovascular system after treatment was carried out after 6 weeks. During this period, patients were prevented to take medications other than the prescribed antidepressant.

QTc(QT corrected)= Measured QT

Length of the cardiac cycle (i.e. R-R interval)

## RESULTS

**1- Blood Pressure :**

- Table (1) Shows that:

- Tricyclics (amitriptyline and imipramine) tend to decrease systolic blood pressure and increase diastolic blood pressure, but the differences are non significant (P>0.05).

- Maprotiline has no effect on supine blood pressure,

TABLE I

*Effect of Antidepressants on Supine Blood Pressure*

| Supine blood pressure (difference between before and after treatment) | Amitriptyline | Imipramine | Maprotiline | Tranylcypromine |
|---|---|---|---|---|
| Systolic | | | | |
| - Mean (diff.) | 0.33 | 1 | 0 | 4.67 |
| -S.D. | 8.60 | 7 | 8.45 | 9.55 |
| - t (diff.) | 0.21 | 0.78 | 0 | 2.68 |
| - P | >0.05 | > 0.0. | - | < 0.05 |
| | (n.s.) | (n.s.) | no change | (sig.) |
| Diastolic | | | | |
| - Mean (dif.) | - 0.33 | - 0.33 | 0 | 2.67 |
| - S.D. | 1.27 | 3.92 | 4.23 | 5.21 |
| - t (diff.) | 1.45 | 0.46 | 0 | 2.81 |
| - P | > 0.05 | > 0.05 | - | < 0.05 |
| | (n.s.) | (n.s.) | no change | (sig.) |

n. s. = Non Significant sig. = Significant

**TABLE II**

*Effect of Antidepressants on the Degree of Orthostatic Hypotension*

| Orthostatic hypotension (difference between before and after treatment) | Amitriptyline | Imipramine | Maprotiline | Tranylcypromine |
|---|---|---|---|---|
| Systolic | | | | |
| - Mean (diff.) | 2 | 4.33 | 2 | 1.67 |
| -S.D. | 6.64 | 7.85 | 5.85 | 5.14 |
| -t (diff.) | 1.65 | 3.03 | 1.89 | 1.78 |
| - P | >0.05 | < 0.01 | > 0.05 | > 0.05 |
| | (n.s.) | (sig.) | (n.s.) | (n.s.) |
| Diastolic | | | | |
| - Mean (dif.) | 1.67 | 3.67 | 2 | 1 |
| - S.D. | 5.47 | 8.19 | 8.05 | 4.814 |
| - t (diff.) | 1.67 | 2.45 | 1.36 | 1.14 |
| - P | >0.05 | < 0.05 | > 0.05 | > 0.05 |
| | (n.s.) | (sig.) | (n.s.) | (n.s.) |

n. s. = Non Significant sig. = Significant

**TABLE III**

*Effect of Antidepressants on Heart Rate (assessed by ECG)*

| Heart rate (beat / min.) (difference between before and after treatment) | Amitriptyline | Imipramine | Maprotiline | Tranylcypromine |
|---|---|---|---|---|
| - Mean (diff.) | 75.87 | 6.7 | 2.5 | 0.87 |
| -S.D. | 9.26 | 10.27 | 6.97 | 4.1 |
| t (diff.) | 3.47 | 3.56 | 1.27 | 1.16 |
| - P | < 0.01 | < 0.01 | > 0.05 | > 0.1 |
| | (sig.) | (n.s.) | (n.s.) | (n.s.) |

n. s. = Non Significant sig. = Significant

**TABLE IV**

*Effect of Antidepressants on T-wave Amplitude*

| T-wave Amplitude (mm) (difference between before and after treatment) | Amitriptyline | Imipramine | Maprotiline | Tranylcypromine |
|---|---|---|---|---|
| Mean (diff.) | 0.2 | 0.13 | 0.4 | 0 |
| S.D. | 0.55 | 0.51 | 0.62 | 0 |
| t (diff.) | 1.99 | 1.44 | 3.54 | 0 |
| P | > 0.05 | > 0.05 | < 0.05 | - |
| | n.s. | n.s. | sig. | no change |

n. s. = Non Significant sig. = Significant

**TABLE V**

*Effect of Antidepressants on P-R Interval*

| P-R Interval (Second) (difference between before and after treatment) | Amitriptyline | Imipramine | Maprotiline | Tranylcypromine |
|---|---|---|---|---|
| Mean (diff.) | 0.013 | 0.011 | 0.005 | 0 |
| S.D. | 0.02 | 0.018 | 0.014 | 0 |
| t (diff.) | 3.56 | 3.34 | 1.95 | 0 |
| P | < 0.01 | < 0.01 | >0.05 | - |
| | sig. | sig | n.s. | no change |

n. s. = Non Significant sig. = Significant

**TABLE VI**

*Effect of Antidepressants on QTc Time*

| QTc time (Second) (difference between before and after treatment) | Amitriptyline | Imipramine | Maprotiline | Tranylcypromine |
|---|---|---|---|---|
| Mean (diff.) | 0.019 | 0.021 | 0 | 0.005 |
| S.D. | 0028 | 0.032 | 0.027 | 0.018 |
| t (diff.) | 3.72 | 3.59 | 0 | 1.52 |
| P | < 0.001 | < 0.01 | - | > 0.05 |
| | h.s. | sig | no change | n.s |

n.s. = Non Significant
sig = Significant
h.s = Highly Significant

**TABLE VII**

*Effect of Antidepressants on QRS complex.*

| QRS complex (Second) (difference between before and after treatment) | Amitriptyline | Imipramine | Maprotiline | Tranylcypromine |
|---|---|---|---|---|
| Mean (diff.) | 0.006 | 0.008 | 0.003 | 0 |
| S.D. | 0.0-17 | 0.024 | 0.010 | 0 |
| t (diff.) | 1.93 | 1.83 | 1.67 | 0 |
| P | > 0.05 | > 0.05 | > 0.05 | - |
| | n.s. | n.s. | n.s. | no change |

n. s. = Non Significant

- Tranylcypromine tends to decrease both systolic and diastolic blood pressure significantly (P< 0.05).

Table (2) reveals:

- Imipramine increases the degree of orthostatic hypotension (both systolic P < 0.01 and diastolic (P>0.05) to a significant degree.
- Although the other 3 drugs tend to increase the degree of orthostatic hypotension, the differences are non significant (P>0.05).

**II- ECG :**

Table (3) shows:

Tricyclics (amitriptyline and imipramine) increase heart rate to significant degrees (P< 0.01).

- Maprotiline (P>0.05) and tranylcypromine (P>0.1) tend to increase heart rate but to non significant degrees.

Table (4) shows:

- Maprotiline decreases the amplitude of T-wave to a significant degree (P<0.05).
- Tricyclics decrease the amplitude of T-wave, but to non-significant degrees (p>0.05).
- Tranylcypromine has no effect on T-wave amplitude.

Table (5) shows:

- Tricyclics (amitriptyline and imipramine) prolong the P-R interval to significant values (p<0.01).
- Maprotiline prolongs the P-R interval to a non significant degree (P>0.05).
- Tranylcypromine has no effect on P-R interval

Table (6) shows:

- Tricyclics increase QTc time, being highly significant with amitriptyline (P<0.001) and significant with imipramine (P<0.01).
- Maprotiline has no effect on QTc time
- Tranylcypromine tends to increase QTc time but to a non-significant value (P>0.05).

Table (7) shows:

- Tricyclics (amitriptyline and imipramine) and maprotiline increase the duration of QRs complex but to a non-significant degree ( P > 0.05 ), while tranylcypromine has no effect in this respect.

## DISCUSSION

Amitriptyline and imipramine have no significant effect on supine blood pressure. Imipramine showed significant increase in the degree of orthostatic hypotension, while the effect of amitriptyline was insignificant.

Glassman and Bigger (1981) emphasized that orthostatic hypotension is common with tricyclics. Luchins (1983) attributed such effects to the adrenergic blocking action of this group of drugs.

Amitriptyline and imipramine significantly increased heart rate. This is in agreement with Ziegler and Bigger (1977). The increased heart rate noted with tricyclic antidepressants is believed to be due to the anticholinergic action of these drugs (Luchins, 1983).

Tricyclics insignificantly flattened T-wave. They significantly prolonged P-R interval and QTc time, but insignificantly prolonged QRS complex.

These findings are in agreement with Raisfeld (1972) and Petit *et al.* (1977). These effects are attributed to their quinidine-like action (White *et al.* 1982). TCAs have a direct effect on the myocardium and a high affinity for cardiac muscle in the form of a depressant effect on contractibility and conduction velocity (Montgomery, 1982). However, Luchins (1983) reported that TACs at therapeutic doses do not impair cardiac mechanical functioning.

The effect of maprotiline was insignificant on supine blood pressure, orthostatic hypotension, heart rate, P-R interval, QRS and QTc time. Maprotiline significantly flattened T-wave.

The effects of maprotiline on the cardiovascular system were less significant on supine blood pressure, compared to TCAs. These findings are compatible with Robinson (1984).

Maprotiline has a cardiovascular profile essentially similar to TCAs, however, it is still less cardiotoxic than them. It has quinidine-like effects on ECG. (Butckhardt *et al.* 1978).

The effects of tranylcypromine on ECG were insignificant, but it produced significant lowering of supine blood pressure.

Razani *et al.* (1983) emphasized that tranylcypromine produced a significant decrease in standing blood pressure compared with the level before therapy. However, the degree of orthostatic hypotension did not show significant increase compared with the pretreatment levels. This was in part due to decrease in supine blood pressure. This is in agreement with our study. Rifkin *et al.* (1985) found that tranylcypromine can cause severe orthostatic hypotension in 17 % of cases.

Halper and Mann (1988) reported that quinidine-like effects are not exhibited by MAOIs and these agents may actually speed conduction. Their use has been associated with cardiac slowing, which is of modest proportions and has not been associated with clinical complications.

## RECOMMENDATION

I- An association between an abnormal QTc interval and sudden cardiac death has been found in various diseases (Bexton *et al.* 1986). Prolongation of QT interval have been linked with development of ventricular arrhythmia (Ward, 1964) and after myocardial infarction (Schwartz and Wolf, 1978). Diabetic patients with diabetic neuropathy also have prolongation of QTc interval (Bellavere *et al.* 1987).

So, in such patients, we recommend avoiding antidepressants which cause prolongation of QTc interval (amitriptyline and imipramine) as their use in such circumstances may carry the risk of sudden death.

II- Prolongation of P.R. interval (first grade heart block) paves the way for advanced grades of heart block with all its hazards. Antidepressants which possess this property (e.g. tricyclic) should be better avoided in cardiac patients because they are more vulnerable to such effect.

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## ABSTRAIT

### Une Étude Comparative des Effets des Antidepressants Communément Utilisés sur le Systéme Cardiovasculaire

Cette étude comprend 120 patients souffrant de désordre dépressif majeur qui est distribués en 3 groupes:

1- Le premier groupe: est formé de 60 patients qui reçoivent des antidepressants tricycliques, la moitié a reçue amitriptyline, et l'autre moitié imipramine.

2- Deuxième groupe: est formé de 30 patients qui reçoivent d'antidepressant tetracyclique maprotiline.

3- Troisième groupe: est formé de 30 patients qui reçoivent monoamine oxidase inhibitor, tranylcypromine.

Six semaines avant et aprés le traitement, tous les patients ont participés à :

a) des mésures pour la pression du sang (couché et debout)

B) E C G

Les resultats ont demontrés que:

1- Antidepressants tricycliques (Amitriptyline et imipramine) avaient des effets significatifs sur L'ECG (augmentation du taux de coeur, prolongation de l'interval P - R et le temps de QT).

2- Imipramine provoque une augmentation significative sur le degré de l'hypoension orthostatique, tandis que les 3 autres, ne cause aucune augmentation significative.

Le seul effect cardiovasculaire significatif de maprotiline est, la diminution de l'amplitude de l'onde T.

4- Tranylcypromine était le moins cardiotoxique (sauf la diminution significative de la pression sanguaine (couché).

## الموجز

### دراسة مقارنة لأثار مضادات الإكتئاب الشائع استخدامها على الجهاز الدورى

إشتملت هذه الدراسة على ١٢٠ مريض يعانون من نوبة اكتئابية عظمى مقسمين إلى ثلاث مجموعات، المجموعة الأولى ٦٠ مريض عولجوا بمضادات الإكتئاب الثلاثية (ترايسيكليك)، ثلاثون تلقوا عقار الأميتريبتيلين وثلاثون عقار الإيميبرامين. والمجموعة الثانية ٣٠ مريض تلقوا عقار المابروتيلين (تتراسيكليك). المجموعة الثالثة ٣٠ مريض تلقوا عقار مثبطات أكسيد أحادى الأمين ترانيلسيبرومين.

وتم قياس كل من: ١- ضغط الدم (من وضعى الرقود والوقوف).

٢- رسم القلب الكهربائى، قبل بداية العلاج وبعد ستة أسابيع من تعاطى العقاقير.

وقد أظهرت النتائج مايلى:

١- زيادة سرعة القلب ومسافة "ب-ر" وزمن ك ت س فى مرض المجموعة الأولى.

٢- إن عقار الايميبرامين قد زاد من هبوط ضغط الدم الوضعى فى حين لم يثب وجود أثر للعقاقير الأخرى.

٣- أن عقار المابروتيلين قل أنقص من سعه موجة "ت".

٤- أن عقار الترانيلسيبرومين كان أقل عقار مؤثر على الجهاز الدورى (فيما عدا إقلال ضغط الدم فى وضع الرقود).