COMBINED THERAPY WITH PERICYAZINE AND TRIMIPRAMINE IN PSYCHOTIC PATIENTS WITH DEPRESSIVE SYMPTOMS: A PILOT STUDY

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The use of a combination of known effective drugs has become more widespread during the past decade. The use of combined neuroleptics appears to be common in treating hard-to-manage hospitalized psychotic patients. These combinations, according to a number of reports, provide better control of symptoms or cause fewer or less intense side-effects than high doses of any separated single drug of the combination. However, some authors have reported undesirable side-effects in using neuroleptics in combination.

Fairly numerous reports have appeared in the past ten years on the use of a combination of antidepressive agents and neuroleptic drugs in the treatment of schizophrenia. Many have described the use of perphenazine-amitriptyline, but other combinations have also been used. Some drug combinations caused toxic side-effects, but many drug combinations yield favorable results.

Because of frequent association of psychotic symptoms and depression in many types of psychiatric diseases, combination of neuroleptics and antidepressants are useful adjuncts to treatment.

A pilot study was conducted with pericyazine and trimipramine to determine therapeutic effect in psychotic patients with depressive symptoms.

Trimipramine (Surmontil) is described as 5- (3-dimethylamino-2-methylpropyl) -10,11-dihydro-5H-dibenz (b, f) azepine with the following constitutional formula.

It occurs in the form of white crystalline powder of bitter taste and without odour.

In 1956 Jacob and Messer synthesized trimipramine with the aim of combining the beneficial effects of imipramine in dysthymic mood change and psychomotor inhibition with therapeutic effects of levomepromazine in state of anxiety and sleep disturbance. The new compound consisted of the iminodibenzyl ring of imipramine to which the dimethylamino-3-methyl-propyl side chain of levomepromazine was attached. The psychotropic properties of the drug were initially screened and evaluated in France.

Trimspramine seems to be indicated as an “inhibitory antidepressive drug”. The preparation should therefore be used more or less alike indications as amitrip-
tyline.\(^{18}\) The sedative component is greater than that of amitriptyline.\(^{18}\) Trimateamine reveals its best effect in depressive states of moderate degree and seems to have quite good antidepressive and anti-anxiety action of rapid onset.\(^{19,20}\) In anti-depressant tests imipramine and trimipramine have similar activity\(^{19,21}\) or in favour of trimipramine for alleviating anxiety and for improvement of insomnia.\(^{22}\) Very few side-effects such as dizziness, unsteadiness, confusion, dry mouth, palpitation, or drowsiness have been reported, which have been described with dosages of 300 to 600 mg. per day of trimipramine\(^{23}\).

Pericyazine was released for clinical study in 1965 in South Africa and became generally available in 1966 as Neulactil. It was first prepared and studied by research workers at Rhone-Poulec Laboratories, and found to have a psychopharmacological profile which suggested therapeutic properties similar to those of chlorpromazine. The antiadrenergic effect of pericyazine is comparable to that of chlorpromazine but its anti-cholinergic effect is almost as that of chlorpromazine. It is reported to be ten times more active than chlorpromazine as a sedative and anti-emetic. Its hypotensive action is minimal. The toxicity, both acute and chronic, in animals, is of the same order as that of chlorpromazine.

Chemically, it is 2-cyano-10-3’-(4-hydroxy-piperidinopropyl) phenothiazine, its structural formula is as follows:

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\[
\begin{align*}
\text{N} & \quad \text{CN} \\
\text{CH}_3 & \quad \text{CH}_2 & \text{CH}_2 & \text{N} & \text{OH}
\end{align*}
\]
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Combined Therapy with Pericyazine
V. Vichaiya

The average daily dosage in adults is about 60 mg. administered in two or four divided doses. It has been used extensively in behaviour disturbances, regardless of their etiology, by reducing or eliminating impulsiveness and aggressiveness.\(^{24,25,26,27,28}\)

In Manic-Depressive psychosis, 64% of cases treated showed substantial improvement; patients in manic phase seem to respond better to pericyazine than those in depressive phase.\(^{29}\)

In schizophrenics, good results are reported between 30-45\%.\(^{29,30}\) In chronic psychotics, 46-73% revealed definite improvement.\(^{29,31}\)

Pericyazine is also of great benefit to the treatment of alcoholic withdrawal symptoms.\(^{32}\)

Best result is obtained by combining pericyazine with metho-trimipramine and its combination with chlorpromazine also seems possible and interesting.\(^{33,34}\) The combination of drugs is well tolerated.\(^{33,34}\)

The chief side-effects are: daytime somnolence which usually diminishes lates but sometimes slowly; very slight lowering of blood-pressure; and the same neurological, gastrointestinal and autonomic disturbances as observed to appear with other neuroleptics. These are usually mild and only occasionally require the use of correctives.\(^{33}\)

**METHODOLOGY**

The present report was carried out in the Female Section of the In-Patient Department of Somdet Chaopraya Hospital. The patients belonged to the following diagnostic categories:

- Manic-Depressive Psychosis, depressive phase 2
- Involutional Melancholia 5
Schizo-affective, depressed 12
Schizophrenia, paranoid type with depressive symptoms 6

The patients were randomly selected. Apart from physical and mental examinations, routine laboratory examination was performed at the beginning and again at the end of the treatment period of six weeks. Blood pressure was recorded every day of the first two weeks.

The patients ranged in age from 19 to 60 years, (average 34.4 years); most of them between 20 to 40 years (17 cases). The duration of onset was between 10 days to 13 years (average 24 years), half of them were below one year. The number of admissions is as follows:—
First 18;
Second 6;
more than second admission 1.

Duration of admission is shown in table 1. Seven cases had a history of suicidal attempt.

Table 1 Duration of admission.

<table>
<thead>
<tr>
<th>Duration of admission</th>
<th>1st week</th>
<th>2nd week</th>
<th>4th week</th>
<th>6th week</th>
<th>more than 6th week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4*</td>
<td>11</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

* Against medical advice.

DOSAGE AND ADMINISTRATION

Taking advantage of the sedative action of pericyazine, the patients were started on a combination of pericyazine 20 to 60 mg. and trimipramine 50 to 100 mg. daily in two or four divided doses. (Average pericyazine 40 mg., trimipramine 75 mg. daily). This dosage was gradually increased until a marked clinical improvement was noted. In the majority of cases, this was achieved around the first two weeks. When symptoms subsided, the dosage was gradually reduced.

The patients were assessed and scored on the Verdun Target Symptoms Rating Scale (Table 2) and Verdun Depression Rating Scale (Table 3) by the author prior to treatment and every fortnightly during the six-week period. The following criteria were used to rate improvement:—
Excellent — if there was complete remission of symptoms or a minimal residue of symptoms, and the patient was being considered for release from hospital;
Good — if the patient was almost asymptomatic with improvement in the majority of symptoms;
Fair — if the patient became adjusted to the hospital environment, but psychotic and depressive symptoms were still present.
Poor — when there was no demonstrable improvement.
Table 2  12 items of the Verdun Target Symptoms Rating Scale.  
(0 = none, 1 = slight, 2 = medium, 3 = severe)

1. Excitement  
2. Suspiciousness  
3. Hostility  
4. Anxiety  
5. Depression  
6. Impairment in Object Relation  
7. Hallucination  
8. Disturbance of thinking  
9. Delusion  
10. Memory Disturbance  
11. Impairment of Consciousness  

Table 3  12 items of the Verdun Depression Rating Scale.  
(0 = none, 1 = slight, 2 = medium, 3 = severe)

1. Mood  
2. Facial Expression  
3. General Appearance  
4. Psychomotor Retardation (observed)  
5. Impairment of Work and Social Interests  
6. Agitation  
7. Depressive Ideation  
8. Suicidal Tendencies  
9. Insomnia  
10. Somatic Complaints  
11. Loss of Appetite  
12. Loss of Weight

RESULTS

During the six-week period of study, 21 cases dropped out, 17 left for favorable reasons, either on discharge or trial visit; 4 cases left the hospital without leave or against medical advice. There was one case which needed E.C.T. for controlling depression.

The mean total target symptoms scores and depression scores are shown in Figure I. Results of improvement are shown in Table 4. Out of 21 cases, 17 were rated as excellent (81.4%), 2 as good (9.5%). The total percentage of significant improvement was 90.9%. The combination of drugs proved to be effective in improving both thinking and mood of the patients. Although some authors claimed that pericycine has weak antipsychotic effect, it was found in this study that a combination of pericycine and trimipramine showed definite antipsychotic effect. This may be due to synergistic effect of both drugs.

SIDE-EFFECTS

There were no serious side-effects. A few complained of dry mouth, constipation, drowsiness, palpitation and blurring of vision. One case showed mild degree of parkinsonism which needed no corrective agent. Almost all of the cases showed mild degree of hypotension without symptoms.

The follow up study in 6 months showed that 5 out of 21 cases had dropped out, 4 cases refused to take the medication and resulted in re-admission.
Figure 1.

- Mean total target symptoms score.
- Mean total depression scores.

Table 4 Results of improvement

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No of cases</th>
<th>Results of improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manic – depressive psychosis, depressive phase.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Involutional Melancholia</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Schizo-affective, depressed</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Schizophrenia, paranoid type with depressive symptoms</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>17</td>
</tr>
</tbody>
</table>

*E.C.T. was required to control depression.*
DISCUSSION

The combination of pericyazine and trimipramine showed definite antipsychotic and antidepressive effects. The results are sufficiently encouraging to warrant controlled clinical trial.

CONCLUSION

1. The antidepressive effect of pericyazine and trimipramine is comparable to that of E.C.T.\(^\text{[36]}\)
2. The superior results may be due to synergistic effect of both drugs.
3. There are no serious side effects.
4. The results are sufficiently encouraging to warrant controlled clinical trial.

SUMMARY

The history, pharmacology, toxicity, mode of administration and dosage, side-effects and therapeutic effects of pericyazine and trimipramine were reviewed. Uncontrolled pilot study was done in 25 cases of newly admitted or re-admitted psychotic patients with depressive symptoms. The results of this clinical trial showed that the combination of such drugs was beneficial to psychotic patients with depressive symptoms for controlling both psychotic and depressive symptoms. There were no observable serious side-effects.

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การทดลองยาเพอร์อีฟซิลโคนร่วมกับไตรมีตรีม

ในป่วยโรคติดต่อมาเร็วมีศรี; การศึกษา

วัฒน์ วิชยาธิ, ภ., พ.บ.

ในระยะเวลา ๑๐ ปีแล้วที่ผ่านมาได้มีการใช้ยาเพอร์อีฟซิลโคนร่วมกับไตรมีตรีมผู้ป่วยโรคติดต่อมาเร็วมีศรี ยาเพอร์อีฟซิลโคนและยาไตรมีตรีม ช่วยควบคุมและป้องกันการเกิดและการแพร่กระจายของโรคติดต่อมาเร็วมีศรี ยาเพอร์อีฟซิลโคนมีผลในการป้องกันและป้องกันการเกิดและการแพร่กระจายของโรคติดต่อมาเร็วมีศรี.

จากการทดลองในระยะเวลายาวนาน ๑๐ ปีมีผลการทดลองที่ดี ยาเพอร์อีฟซิลโคนมีผลในการป้องกันและป้องกันการแพร่กระจายของโรคติดต่อมาเร็วมีศรี ยาเพอร์อีฟซิลโคนมีผลในการป้องกันและป้องกันการแพร่กระจายของโรคติดต่อมาเร็วมีศรี.

ผลการทดลองในระยะเวลายาวนาน ๑๐ ปีมีผลการทดลองที่ดี ยาเพอร์อีฟซิลโคนมีผลในการป้องกันและป้องกันการแพร่กระจายของโรคติดต่อมาเร็วมีศรี ยาเพอร์อีฟซิลโคนมีผลในการป้องกันและป้องกันการแพร่กระจายของโรคติดต่อมาเร็วมีศรี.

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