Post-stroke depression: combined treatment with imipramine or desipramine and mianserin

A controlled clinical study

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Abstract. In a 6-week study the efficacy of combined treatment of imipramine plus mianserin was compared to combined treatment of desipramine plus mianserin in patients with post-stroke depression. Patients were required to have a minimum baseline total score of 15 on the 17-item Hamilton Depression Scale (HAMD). The Melancholia Scale (MES) was also used to measure severity of depressive states to show that somatic symptoms had little influence on the evaluation of depression. Out of 120 stroke patients screened, 20 patients fulfilled the inclusion criteria. The doses of the drugs were flexible, using side-effects as a guide during treatment. Both intention to treat analysis and efficacy data (excluding patients who had dropped out during the first 2 weeks of treatment) showed that imipramine (mean dose 75 mg daily) plus mianserin (mean dose 25 mg daily) was superior to desipramine (mean dose 66 mg daily) plus mianserin (27 mg daily). The MES was found to be more sensitive than the HAMD for measuring change in depressive states during treatment. The assessment of side-effects using the UKU scale showed good tolerance in general. The only difference between the two treatment groups was seen in micturition disturbances, where the imipramine treated patients had most complaints after 14 days of treatment, but the symptoms disappeared despite continuous treatment.

Key words: Post-stroke depression – Antidepressants – Imipramine – Desipramine – Mianserin

Mood disorders after stroke have been increasingly studied in recent years and two different theories have been discussed. Thus, Robinson et al. (1983) consider post-stroke depression as an organic affective syndrome which persists for more than a year after the attack and which is unrelated to the severity of the clinical disability induced by the stroke. In contrast, Charatan and Fisk (1979) and Turner and Beiser (1990) consider post-stroke depression as a reaction that is caused by the clinical disability of the stroke, analogous to depression secondary to other somatic disorders such as cancer or arthritis.

Among the arguments identified by Robinson and co-workers (e.g. Lipsey et al. 1984) was the observation that in post-stroke depression treatment with tricyclic antidepressants is superior to placebo. However, in a recent study (Loldrup et al. 1991) we have found that clomipramine was as effective in secondary depression as in primary depression. In other words, antidepressants seem to work as an intermediary factor on the depression syndrome, i.e. independently, whether the syndrome is primary or secondary.

In a previous study on elderly patients with primary depression (Lauritzen et al. 1992) we have shown that combined treatment with imipramine and mianserin was superior to imipramine alone. In the present study we have therefore investigated whether combined treatment with imipramine and mianserin is as effective in patients with post-stroke depression as we found in patients with primary depression. Desipramine has been used as a comparison drug because Robinson and his group have advocated the use of desmethyl tricyclics in post-stroke depression.

Materials and methods

Patient population. Patients with thromboembolic stroke were selected from consecutive admissions to Esboenderup Center Rehabilitation Hospital, Frederiksborg County, in the period between July 1988 and September 1990. In total, 120 patients were evaluated for entry to this study using the Hamilton Depression Scale (HAMD) with the Melancholia Scale (MES) (Bech et al. 1986). Patients with a HAMD score of 15 or more were considered for trial entry. Exclusion criteria were patients with aphasia, patients with previous psychiatric illness, patients with severe cardiac disorder with previous organic brain disorder (clinically verified or by CT scanning) and patients with a present stroke which could not be localized to one hemisphere.

Study design. The trial followed a double-blind, parallel group design. At the start of the treatment period the patients were randomly allocated to either imipramine or desipramine. In addition,
all patients received mianserin. The duration of the treatment was 6 weeks.

Medication. Tablets of identical appearance that contained either 25 mg imipramine (Tofranil) or 25 mg desipramine (Pertofran) were used. The dosage was one tablet twice daily in the first week, subsequently adjusted individually on the basis of side-effects. Maximum dosage was 75 mg twice daily. The mianserin dosage was fixed at 10 mg daily for the first week, and was then adjusted individually (maximum dosage 30 mg daily). In building up the mianserin dose the side-effect of sedation was especially considered.

Rating scales. The Hamilton Depression Scale with the Melancholia Scale was used not only as a screening instrument but also as an outcome measure (Bech et al. 1986). These scales were administered before treatment (baseline) and then after 14, 28 and 42 days of treatment. Furthermore, the UK side-effect scale (Lingjærde et al. 1987) was used to measure unwanted drug effects with the same intervals as the HAMD and MES.

The Newcastle Diagnostic Depression Scale (Carney et al. 1965; Bech 1993) was used at baseline to classify patients as endogenous versus non-endogenous depression. The raters were trained in the use of HAMD, MES, UKU and the Newcastle scale as they had participated in the Danish University Antidepressant Group (DUAG 1990).

Ethical considerations. The trial was performed in accordance with the Helsinki Declaration II, and the protocol was approved by the Danish Health Authorities and the local ethical committee. Before entry informed consent was obtained from each patient.

Statistical analysis. Both the intention-to-treat approach (referring to the idea that all patients whom the doctors intend to treat should be considered, i.e. all randomized patients should be analysed, and for patients who have not completed the planned treatment period of 6 weeks the last observation is carried forward) and efficacy analysis (referring to the idea that only patients who have been treated for at least 2 weeks should be considered for evaluation of drug effects) were used (Pocock 1983). Non-parametric tests were used and the levels of statistical significance were 5 and 1%. Only two-tailed analyses have been considered. Finally, for comparison with other studies a 50% reduction of the pretreatment HAMD and MES was used (Bech 1989). However, because this outcome measure is a purely illustrative response rate, statistical interference analysis has been excluded.

Results

Of the 120 patients considered for entry in this treatment study, 20 patients were randomized, fulfilling the inclusion criteria. The mean score of the 20 patients was 21.0 ± 3.1 on HAMD and 19.5 ± 3.8 on MES. For the non-depressed group (n = 100) the respective scores were 7.4 ± 3.9 and 6.2 ± 3.5.

In the group receiving imipramine and mianserin seven patients had clinical symptoms corresponding to lesions of the right brain and three patients had symptoms corresponding to lesions of the left brain. In the group receiving desipramine and mianserin exactly the same figures were found. The results of the CT scanning will be discussed elsewhere.

Of the 20 patients included in this study, 10 received imipramine and mianserin and 10 received desipramine and mianserin. The demographic characteristics of the study population are shown in Table 1. As indicated, no statistically significant differences between the two groups of patients were seen.

<table>
<thead>
<tr>
<th>Data</th>
<th>Imipramine plus mianserin (n = 10)</th>
<th>Desipramine plus mianserin (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.3 ± 7.0</td>
<td>74.1 ± 9.1</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (% females)</td>
<td>90 %</td>
<td>50 %</td>
<td>ns</td>
</tr>
<tr>
<td>Newcastle Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index (% endogenous)</td>
<td>10%</td>
<td>20%</td>
<td>ns</td>
</tr>
<tr>
<td>Time since stroke (days)</td>
<td>34.0 ± 56.9</td>
<td>43.0 ± 38.4</td>
<td>ns</td>
</tr>
<tr>
<td>Hemisphere stroke (% left)</td>
<td>30%</td>
<td>30%</td>
<td>ns</td>
</tr>
</tbody>
</table>

The mean dose of imipramine was 75 mg daily (range 50–100 mg) and the mean dose of desipramine was 66 mg daily (range 50–125 mg). In the imipramine treated patients mianserin was given in a mean dose of 25 mg daily (range 10–30 mg) and the desipramine treated patients received a mean dose of 27 mg mianserin (range from 20–30 mg).

The mean post-treatment plasma levels of desipramine (last two observations) were 164 nmol/l for desipramine plus mianserin treated patients and 149 nmol/l for the imipramine plus mianserin treated patients. In the latter group of patients the mean plasma level of imipramine was 103 nmol/l. Compared with our previous study on primary depression (Lauritzen et al. 1992) the plasma levels of imipramine plus mianserin treated patients were virtually identical to those obtained in the present study.

During the first 2 weeks of treatment four patients dropped out (early drop-outs). In the imipramine treated patients two patients dropped out, one patient after 2 days of treatment because the family did not accept treatment supervised by a psychiatrist and one patient because of protocol violation. In the desipramine treated group two patients also dropped out, both because of side-effects (one because of severe orthostatic hypotension and one because of A-V block, respectively).

Three patients were late drop-outs. They had all received desipramine plus mianserin. The reasons for dropping out were in two cases side-effects (confusion and appearance of atrial flutter, respectively) and in the last case a deterioration of the stroke disorder.

Table 2 shows the intention to treat analysis, i.e. both early and late drop-outs are included and their last observation has been carried forward. Both the HAMD and MES showed that the imipramine plus mianserin treated group had a better outcome than the desipramine plus mianserin treated group. The difference even after 42 days of treatment was not statistically significant. However, for the MES the difference in change scores (baseline minus endpoint) was nearly twice as high in the imipramine group compared to the desipramine group and this was statistically significant (P < 0.05).

Table 3 shows the efficacy data, i.e. excluding early drop-outs. The same pattern was seen and the changes in MES scores were largest in the imipramine group (P ≤ 0.01).

Using an outcome criterion of 50% reduction of baseline rating scores, no statistically significant difference between imipramine and desipramine treated patients was