LOW DOSE LEVODOPA IN TARDIVE DYSKINESIA

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SUMMARY

Efficacy of low dose levodopa in treatment of TD has been studied on 30 male inpatients with predefined selection criteria. The preliminary results are encouraging but long term double blind studies in larger samples are needed.

Tardive dyskinesia severe enough to interfere with talking, swallowing or mobility is relatively rare. But even in mild cases they may constitute a severe social handicap. Jeste and Wyatt (1982) after reviewing 285 treatment studies involving more than 3000 patients concluded that no satisfactory treatment for persistent TD is available. The traditional hypothesis of dopamine (DA) overactivity and receptor supersensitivity (Casey and Robins, 1978; Christensen et al., 1970; Tarsy et al., 1979) has dominated and shaped various treatment approaches.

An alternative approach to the treatment of TD is levodopa, a metabolic precursor of dopamine. It has been proposed that low doses of levodopa leads to stimulation of presynaptic DA receptors, which in turn reduces the synthesis and turnover of DA, thereby inhibiting DA neurotransmission (Caroll et al., 1977). Alpert and Friedhoff (1980) on the other hand, suggest that treatment with levodopa temporarily increases DA levels and thus reduces dopamine receptor supersensitivity. The use of levodopa or other DA agonist may have additional advantage in their ability to counteract the initial extrapyramidal side effects e.g. akathisia and rigidity with consequent greater emotional participation and feeling of well-being. The incidence of a worsening of psychosis is reported to be high but this may be particularly seen with high dose levodopa administration.

The present study was conducted to find out the efficacy of low dose levodopa treatment in TD.

Material and Methods

The study was conducted at the Central Institute of Psychiatry, Ranchi. As a first step all chronically hospitalized male inpatients were screened for the presence of any movement disorder. 30 patients were selected for the study using the following inclusion criteria—(1) a firm diagnosis of TD on administration of the Abnormal Involuntary Movement Scale (AIMS) twice a week for two weeks (2) no change in neuroleptic treatment during the last three months (3) physically fit to undergo the trial (4) cooperative enough to take oral medication (5) baseline investigations within normal limits (6) informed consent. The exclusion criteria were (1) age more than 60 years (2) presence of schizophrenic mannerisms and stereotypies (3) those suffering from neurological movement disorders. 

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disorders like Huntington's chorea or organic brain syndrome.

All the 30 patients thus selected were assessed on the Rockland Research Institute Abbreviated Dyskinesia Rating Scale (Simpson et al., 1980) and Brief Psychiatric Rating Scale (Overall and Gorham, 1962). All patients received a placebo for 6 weeks and then after a wash out period of one week they received levodopa (1500 mg/day).

Intervention was in the form of a single tablet of placebo or levodopa (500 mg) thrice a day following meals. The dose and type of neuroleptic used was kept constant during the entire period of study.

During the period of study, dyskinesia rating scale was administered at weekly intervals for 14 weeks from the onset of placebo administration to one week following the discontinuation of levodopa. This method was adopted in order to account for the spontaneous improvement seen in many patients with TD (Rex Roth and Berger, 1980). BPRS was readministered at the end of the trial with placebo and levodopa.

The side effects and symptom checklist of WHO was used once a week to record any side effect.

Results

The mean age of the sample was 46.7 years with a standard deviation of 8.8 (range 32 to 57 years). The mean duration of illness was 24.5 (±8.8) years. They were on neuroleptic therapy for a mean duration of 15 (±7.07) years, with a mean total neuroleptic dose of 1277.17 (±734.39) gm of chlorpromazine equivalent. The mean number of drug holidays were 8.8 (±6.22).

Out of the 30 patients selected, 29 completed the study. One patient while on levodopa showed an exacerbation of psychiatric symptomatology severe enough to warrant increase in the dose of neuroleptic and was dropped from the study. Another patient showed aggressive behaviour once during the trial period but could complete the study satisfactorily. No patient showed any physical side effects during the trial period.

In order to determine the number of cases who responded favourably, improvement was defined as a minimum of 50% reduction in symptoms, as suggested by Jeste and Wyatt (1982). Data was processed and analysed using two tailed t-test for significance.

No significant change was seen with placebo. Levodopa administration however led to improvement in TD scores in 79.3% of the sample. The difference was statistically significant. One week following discontinuation of levodopa administration there was no significant increase in TD scores (Table I).

| Phase of the study          | Mean | SD  |
|-----------------------------|------|-----|
| On Placebo                  |      |     |
| Initial score               | 31.5 | 9.71|
| Final score                 | 31.6 | 10.30|
| \( t = 0.33, \) d.f. =28, N. S. |      |     |
| On Levodopa                 |      |     |
| Initial score               | 33.6 | 10.30|
| Final score                 | 17.6 | 5.80 |
| \( t = 8.33, \) d. f. =28, p<0.01 |      |     |
| On Discontinuation of Levodopa | |     |
| Initial score               | 17.6 | 5.80 |
| Final score                 | 18.0 | 5.16 |
| \( t = 1.4, \) d.f. =28, N. S. |      |     |

Discussion

Jeste and Wyatt (1982) found 11 studies on the effects of oral administra-
tion of levodopa in patients with TD. Only 33% of the patients treated had improved; in others dyskinesia was either unimproved or worsened. They concluded that the hypothesis behind levodopa administration is attractive but the incidence of various side effects (including of psychosis) is rather high.

Several investigators have suggested that there may be a biphasic response to levodopa administration (Smith et al., 1977, Carroll et al., 1977). Worsening of psychosis is also seen more often with high doses. Tarsy et al. (1979) gave levodopa in different doses to 10 patients with TD and reported improvement with low doses and worsening at high doses. Friedhoff and Alpert (1975) using higher doses reported initially a worsening of tardive symptoms but after repeated administration with a subsequent withdrawal, a decrease in abnormal movements.

The present study used a fixed low doses levodopa treatment strategy throughout the 6 week trial period, and in order to take care of natural variation seen in many patients with TD, a 6 week trial with placebo preceded the levodopa treatment. Significant improvement (defined as more than 50% reduction in symptoms) was found in 79.3% of patients with tardive dyskinesia. Care was taken not to make any change in the current neuroleptic treatment. Serious worsening of psychosis was seen in only one case. However, the study sample consisted of only male patients as gender is thought to be an important risk factor. Similarly, compared to earlier studies, the mean age of the sample is lower (46.7±8.8 years). Age related changes in the brain is recognised as an important non-pharmacological phenomena contributing to the etiology of TD. Some of the discrepancies in therapeutic trials in TD could be accounted towards these factors.

Though the preliminary results are encouraging, long term double blind studies using larger samples of both sexes are needed in order to establish low doses levodopa administration as a valid therapeutic strategy in patients with TD.

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