Article *NIMHANS Journal*

Nifedipine in the treatment of tardive dyskinesia: A one year follow up

Volume: 15 Issue: 01 January 1997 Page: 39-43

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Reprints request
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Abstract

Attempts to develop effective therapies for tardive dyskinesia (TD) have met with limited success. The majority of interventions have been of brief duration. We report a 1 year follow up of a cohort of patients who had shown significant (80.7%) improvement of TD with the calcium channel blacker, Nifedipine. Fifteen subjects (9 male, 6 female) with a mean age of 37.73 (8.34) years were selected from the inpatient facilities of the National Institute of Mental Health & Neuro Sciences . Fifteen subjects fulfilled Research Diagnostic Criteria for persistent TD. All subjects received oral Nifedipine (40-80 mg/day) and were rated on the TD Rating Scale (TDRS) at intake and after 2 weeks of treatment. Eleven subjects were followed up for 1 year on the same dose and rated at the end of that period. Paired t-tests were done between the total TDRS scores at intake after 2 weeks after 12 months. TDRS scores were significantly decreased after 2 weeks of treatment ($t = 8.42$, < 0.001). The scores continued to be significantly improved and the effects were seen to persist even after 1 year of treatment.

Key words -
Tardive dyskinesia,
Nifedipine
Tardive Dyskinesia,
Nifedipine

Neuroleptic-include tardive dyskinesia (TD) is a serious heterogenous disorder in psychopharmacology. Approximately 20% of patients receiving long-term neuroleptic treatment develop TD. Attempts to develop effective therapies have met with only limited success. Numerous classes of medications have been studied, and as multiple studies of a given drug or class are reported, results often conflict [1]. Also, though a number of treatment modalities were reported to be useful in short term treatment of TD, no treatment was effective in the long run [2].

There have been a few reports on the use of calcium-channel antagonists as possible treatments for TD. Barrows and Childs [3] found improvement in one patient after treatment with verapamil. Ross [4] reported 3 patients who reported improvement on 120-240 mg/day of diltiazem. Subsequently other researchers have conducted therapeutic trials of Nifedipine [5], [6], verapamil [7], [8], diltiazem [9]. These studies are largely preliminary, involving few patients, very short durations of therapy, no control groups and open or single blind designs. The studies have generally shown either

minimally significant reductions or no change in dyskinesia scores, with no patients showing reductions or no change in dyskinesia scores, with no patients showing reductions of 50% or greater. Nifedipine (20-80 mg/day) appeared somewhat more effective in treating TD in a longer term (1-8 month) uncontrolled trial in eight geriatric patients. Abnormal Involuntary Movement Scale (AIMS) scores of six patients were reduced by a least 50%, although hypotension and increased hostility forced discontinuation in 5 patients. Here we present a single blind (rater-blind) investigation of Nifedipine in the treatment of tardive dyskinesia and a one year follow up of a part of the original cohort.

Material and Methods

Subjects were selected from the inpatient facilities of the National Institute of Mental Health & Neuro Sciences, (NIMHANS) Bangalore, if they met the Research Diagnostic Criteria (RD-TD) for persistent Tardive Dyskinesia [10]. Only those subjects whose psychopathology had stabilized and were on a stable dose of maintenance medication or were off medication because their psychotic symptoms had remitted were taken out from the study.

Each patient gave informed consent before entering the trial and received a physical examination and an electrocardiogram and routine blood test were done. These were repeated at 3 month intervals. Patients were excluded if they had any contraindications to receiving calcium-channel antagonists (e.g. hypotension or cardiac conduction delays or block), cardiovascular illness requiring medication, any neurological disorder other than TD or any systemic or infectious disorder were the other exclusion criteria.

Nifedipine was prescribed by a physician who did not rate the patients. Nifedipine was started at 30 mg p.o.t.i.d and increased to a maximum of 80 mg p.o.t.i.d or to an intermediate dose at which the rater (VB) who was blind to the dosage indicated that there was significant improvement over a 14 day period. The dosage obtained at the end of 2 weeks was then continued for 1 year.

TD was assessed on the Tardive Dyskinesia Rating Scale (TDRS) [11]. Ratings were performed on alternate days over a 14 day period, by the blind rater (B). Subsequently the patients who were followed up for a total period of 1 year were rated at 1 month intervals. All ratings were discarded except those obtained immediately prior to treatment, on day 14 and after 1 year of treatment. (The TDRS is a 43 item scale, rated as 1 = absent, 2 = probable, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = very severe; so even patients without TD rate a baseline score of 43. Therefore the derived score is the raw score-43).

Statistical analysis was performed by paired t-tests on total TDRS scores baseline Vs. Total scores on day 14. Similarly, the day 14 scores were compared to the scores after 1 year. The percent changes was calculated as Total Change ÷ Maximum possible change (Baseline score-43) × 100

Results

15 subjects (9 male, 5 female) with a mean age of 37.73 (8.34) years were studied. Of these, 11 subjects were followed up and 1 subject had to discontinue Nifedipine as he developed pedal edema. The duration of TD in the group varied from 3 months to 96 months (Table-I)

Table I - Changes in TDRS scores with Nifedipine

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Average % age change in TD (after 14 days): 80.78%
Day 0 vs. Day 14, $t = 8.42$, $p < 0.001$
Day 0 vs. Day 365, $t = 6.73$, $p < 0.001$
Day 14 vs. Day 365, $t = 0$
t: Paired T-test

TDRS scores were significantly decreased even after 12 months ($t = 6.73$, $p < 0.001$). There was no significant difference between the day 14 scores and the 1 year scores ($t = 0$) (Table I: Fig.1).

Discussion

In our study, Nifedipine appears to cause significant improvement in persistent TD, and the therapeutic effect seems to persist even after 1 year of therapy. The aggregate reduction in TD scores was 80.78% which is well above the 50% reduction in symptoms suggested by Jeste & Wyatt [12] as the 'improvement' criterion in treatment studies of TD.

This marked response to Nifedipine is distinct from the relatively less robust reductions seen in the Western studies. It is possible however that this is may be a function of the relatively lower doses of neuroleptics generally in use and the relatively lower prevalence of TD seen in the Indian population.

Most patients seemed to tolerate the high doses of Nifedipine. It is not clear whether the therapeutic effect is reversible on stopping Nifedipine. One patient who was poorly compliant, developed prompt reappearance of TD every time medication was stopped whereas another patient who stopped the medication after 6 months of therapy continued to maintain her improvement.

Calcium is an ubiquitous second messenger linking membrane excitation with subsequent intracellular enzymatic responses. Changes in the Cytosolic calcium system located mainly on ion influx voltage sensitive and receptor operated calcium channels. There appear to be four different voltage sensitive and receptor operated calcium channels designated as L, T, N and P. Only the L type channel, in the nervous system located mainly on the neuronal cell bodies is considered sensitive to calcium channel inhibitors (CCI). CCI's are chemically and functionally heterogenous compounds categorized as group 1: Phenylalkylamine derivatives (e.g. verapamil) group II: 1, 4 dihydropyridine derivatives (DHP e.g. nifedipine etc.; group III: benzothiazepines (diltiazem) and group IV: p perazines (e.g. flunarizine). CCI's receptors on the calcium channel protein. Interestingly, some CCI's (especially DHP's like nifedipine) have been found to protect against behavioural sensitization to dopaminergic agonists brought about by chronic neuroleptic administration, in animal studies. There is evidence to indicate a reciprocal interaction between dopaminergic D2 receptors and CCI binding sites through a common suppressant effect on lower last CAMP formation. Theoretically then, when D2 receptors are down regulated as a result of neuroleptic treatment, CCI receptors multiply or change conformation to a high affinity state, taking over functional control of adenylate cyclase. A reciprocal situation occurs when chronic DHP treatment leads to DHP receptor down-regulation. These adaptive reciprocal situation occurs when chronic DHP treatment leads to DHP receptor down-regulation. These adaptive changes could perhaps explain the mechanism of action of Nifedipine in over-riding the state of super-sensitization that the dopamine receptors are hypothesized to attain to produce tardive dyskinesia

[13].

There have been no previous attempts too look at the effects of calcium channel inhibitors in the Indian literature. Moreover, we have also tried to look at the long term stability of the observed improvements in TD in this cohort for a period of one year. A weakness of our study design has been the use of a single blind, non placebo-controlled design and future studies would have to be planned around a double blind, placebo-Nifedipine crossover design. If this response of persistent TD to Nifedipine can be widely replicated, it will provide a solution to this common, disfiguring iatrogenic disorder.

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