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A Clinical Trial of Nifedipine in Schizophrenia and Tardive Dyskinesia

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SUDDATH, R. L., G. M. STRAW, W. J. FREED, L. B. BIGELOW, D. G. KIRCH AND R. J. WYATT. *A clinical trial of nifedipine in schizophrenia and tardive dyskinesia.* PHARMACOL BIOCHEM BEHAV **39**(3) 743–745, 1991.—Effects of the dihydropyridine calcium channel inhibitor nifedipine on chronic schizophrenia and tardive dyskinesia were studied in an 8-week double-blind crossover trial. Four of the ten patients had tardive dyskinesia, and three of these were not receiving neuroleptics. No effects on symptoms of chronic schizophrenia were found using Psychiatric Symptom Assessment Scale ratings. In the four patients with tardive dyskinesia, an average improvement in total Abnormal Involuntary Movement Scale scores of 57% was observed. These data suggest that dihydropyridine calcium channel inhibitors may be effective in the treatment of tardive dyskinesia in schizophrenic patients.

Calcium channel inhibitors Dihydropyridines Nifedipine Tardive dyskinesia Schizophrenia

CALCIUM channel inhibitors (CCIs) have been used experimentally in the treatment of neurological and psychiatric disorders (14). There are indications that CCIs may be effective in treating mania (9), Tourette's syndrome (10, 21, 27), and tardive dyskinesia (1, 2, 5, 7, 8, 19, 20, 23). Previous studies, however, have found CCIs (including nifedipine, diltiazem, or verapamil) to have minimal effects in chronic schizophrenia (1, 13, 18, 22, 25).

In brain synaptosomes, dihydropyridine CCIs such as nifedipine inhibit voltage-sensitive calcium channels (26). Nifedipine crosses the blood-brain barrier in rats (16), inhibits excitatory amino acid neurotoxicity in vitro (28), and inhibits kainic acid-induced seizures in mice (4). Nifedipine is considerably more effective than verapamil (a CCI of the phenylalkylamine class) as an inhibitor of phencyclidine and amphetamine-induced hyperactivity in mice (11,12), and nifedipine also blocks dyskinesia in mice induced by the toxin iminodipropionitrile (IDPN) (6). We have, therefore, examined effects of nifedipine on 10 patients with chronic schizophrenia, four of whom had tardive dyskinesia.

METHOD

Thirteen inpatients (12 male and one female) from the research wards of the National Institute of Mental Health Neuroscience Center at St. Elizabeths gave informed consent to participate in this study. Patients fulfilled DSM-III criteria for chronic schizophrenia. Of the ten patients who completed the study, subtype diagnoses were seven undifferentiated, two residual and one disorganized. Duration of illness ranged from six to 17 (mean = 11.9) years, and the age range was from 24 to 39 (mean = 31.3) years. Four patients also fulfilled clinical criteria for tardive dyskinesia (17). All were free of significant medical illness, and received laboratory screening including EEG, EKG, chest X-ray, CBC, electrolytes, tests for liver and thyroid function, and serology.

Patients were maintained on a stable fixed dose of neuroleptic and benztropine (or neuroleptic and benztropine placebos) for a minimum of six weeks prior to the study, and were maintained at the same dosage throughout. Six patients were on haloperidol and benztropine, one patient was on thiothixene and benztropine, and three were on placebo haloperidol and placebo benztropine. Haloperidol and placebo were given in the form of matched oral concentrate. Benztropine was given in the form of identically appearing active or placebo tablets.

Patients were randomly assigned to begin either active or placebo nifedipine one 10 mg capsule t.i.d. or placebo (identically appearing capsules). Of the ten patients that completed the study, six began on active medication, and four began on placebo. Medication was started at one capsule t.i.d., and the dose was increased every day by three capsules to the final dose of 90 mg/day. Patients were switched and tapered off nifedipine or placebo at the same rate. After four weeks at maximum dose, patients were switched and maintained on placebo or active nifedipine, respectively, for an additional four weeks. Patients were monitored regularly for side effects, and vital signs were monitored twice daily. Liver function tests and EKG were performed during both active and placebo phases. Two patients withdrew from the study, and a third was withdrawn after developing pedal edema while on active medication.

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Clinical outcome was monitored by twice-daily administration of the Psychiatric Symptom Assessment Scale (PSAS) (3) by trained nursing staff who were blind to patient medication status. For this study, the 22 PSAS items were grouped into six subscales indicating anxiety, depression, hostility/suspiciousness, activity, positive symptoms, and negative symptoms. The mean of all 22 individual rating items was also used. The PSAS ratings used for analysis were the average of the daily ratings during the fourth week of active and placebo phases.

Each patient was also rated using the Abnormal Involuntary Movement Scale (AIMS) (15) administered during the last 4 days of each phase by a research psychiatrist blind to medication status who was experienced in administration of this rating scale. The AIMS scale includes ratings of choreoathetosis on a "0" to "4" scale for seven muscle groups: (1) muscles of facial expression, (2) lips and perioral region, (3) jaw, (4) tongue, (5) upper extremities, (6) lower extremities, and (7) trunk. Scores were "0" for none; "1" for minimal or maybe extreme normal, "2" for mild, "3" for moderate, and "4" for severe. Scores used were "total" (the sum of all seven items), "face" (items 1–4), "extremities" (items 5 and 6), and "trunk" (item 7). The sum of items 8 and 9, indicating bradykinesia and rigidity, was also examined. The AIMS scale also includes ratings for other abnormal movements, such as tardive dystonia, tics, and tremor. No patients with movement disorders other than tardive dyskinesia, however, were included. Data were analyzed by two-tailed paired t-tests.

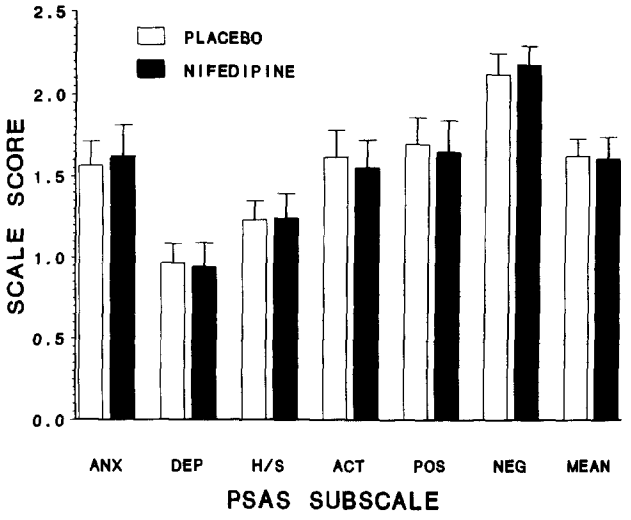

FIG. 1. Psychiatric symptom assessment scale (PSAS) ratings averaged over the final week (week 4) at maximum dose for each phase of treatment. The PSAS subscales used in this study were anxiety (ANX), depression (DEP), hostility/suspiciousness (H/S), activity (ACT), positive symptoms (POS) and negative symptoms (NEG). Mean indicates the mean of all rating items (3). None of the measures were significantly different by two-tailed t-tests for matched pairs.

RESULTS

There was no effect of treatment on total PSAS ratings or on any of six sub-scales (Fig. 1). For the four patients with tardive dyskinesia, however, a significant improvement in total AIMS scores while on active nifedipine was found ($p=0.03$, two-tailed matched pairs t-test; Fig. 2). Total AIMS scores were decreased by $57.2\pm9.0\%$ (mean $\pm$ S.E.M.). The extremities score was also significantly decreased, but the changes in face and trunk scores were not statistically significant (Fig. 2). There was also a tendency for bradykinesia and rigidity to be decreased in these four patients, from a score of 3.0 ± 0.71 during the placebo phase to 1.25 ± 0.25, $t(3)=2.33$, $p=0.10$, during active nifedipine.

Of the four tardive dyskinesia patients, three were on placebo neuroleptic, while only one was on active neuroleptic. Thus the effect is not likely to have been caused by a change in blood neuroleptic levels. The mean total AIMS score for these four patients during the placebo phase was 13.5 ± 3.7, while the mean AIMS score for the nontardive dyskinesia patients was 2.0 ± 0.3.

DISCUSSION

Although nifedipine did not produce a reduction in symptoms in this group of patients, these were long-term chronically ill patients with a history of only partial response to neuroleptic treatment. Most patients were also receiving neuroleptics during the study. The previous trial of nifedipine in schizophrenia employed patients described as refractory to multiple neuroleptics (18). These data, therefore, do not rule out the possibility that nifedipine may be effective in more acutely ill or treatment-responsive patients.

On the other hand, there were positive effects of nifedipine in decreasing tardive dyskinesia, as measured by AIMS scores. Although the number of patients with tardive dyskinesia in the present study was small, this finding is consistent with several previous open studies showing beneficial effects of verapamil and diltiazem in the treatment of tardive dyskinesia (1, 2, 5, 8, 20, 23). In a previous uncontrolled trial, nifedipine was reported to decrease tardive dyskinesia in geriatric patients, most of whom had affective diagnoses (19).

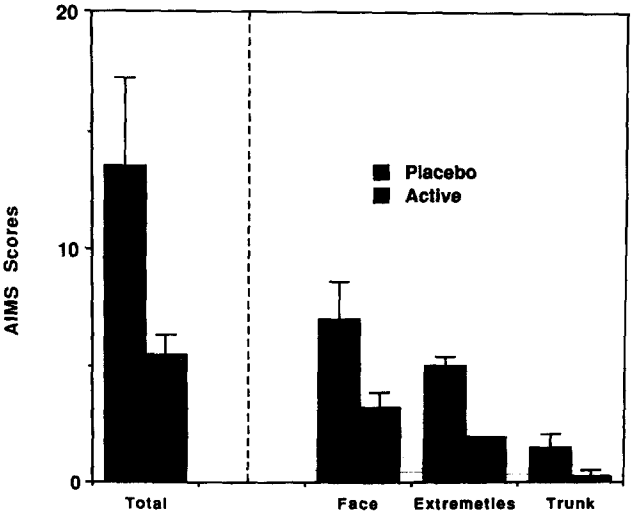

FIG. 2. AIMS ratings from the last week (week 4) of each phase, placebo and active nifedipine, of the trial for the four patients diagnosed as having tardive dyskinesia (total AIMS scores of greater than 10). Total represents the total for all items (numbers 1–7), face represents the total of face, lips-perioral, jaw, and tongue scores (numbers 1–4), extremities represents the total for upper and lower extremities, and the trunk is the score for trunk movements only (item 7). By two-tailed t-tests for matched pairs, the difference was significant for total, $t(3)=3.70$, $p=0.034$, and extremities, $t(3)=7.35$, $p=0.005$, scores, but not for the face, $t(3)=2.1$, $p=0.12$, or trunk, $t(3)=1.7$, $p=0.19$, scores.

In another recently reported single-blind trial, nifedipine was found to decrease AIMS scores in patients with tardive dyskinesia (7), but the average decrease was only 16%, and four of the eight patients showed improvements of two points or less. The average amount of improvement in total AIMS scores observed in the present study was 57%. Possible reasons for this difference in the degree of improvement observed are (1) the maximum dosage of nifedipine used by Duncan and co-workers (7) was 60 mg/day, as compared to 90 mg/day in the present study, and (2) the average duration of treatment at maximum dosage in the study by Duncan et al. (7) was 10 days, as compared to 28 days in the present study. It should also be noted that the only patient in the study by Duncan et al. (7) that was not receiving neuroleptics did not improve; however, three of the four patients with tardive dyskinesia in the present study were not receiving neuroleptics. The results of the present study and the study by Duncan et al. (7) combine, therefore, to suggest that nifedipine can improve tardive dyskinesia regardless of concurrent neuroleptic administration.

It is also interesting that nifedipine decreases IDPN-induced dyskinesia in mice (6) and it is tempting to speculate that the effects of CCIs on both forms of dyskinesia involve similar mechanisms. It should be noted, however, that nifedipine does have actions other than blockade of calcium channels, especially adenosine agonist effects (24), and these could be responsible for the changes seen here. In summary, the cumulative data argue for a role of CCIs, especially dihydropyridines, in the treatment of tardive dyskinesia. Available studies do not give encouragement for the use of nifedipine as an antipsychotic agent in schizophrenic patients.

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