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Is Diltiazem Effective in Treating the Symptoms of (Tardive) Dyskinesia in Chronic Psychiatric Inpatients? A Negative, Double-Blind, Placebo-Controlled Trial

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Calcium channel blockers, antiarrhythmic drugs, such as verapamil and diltiazem, may decrease the symptoms of tardive dyskinesia. The efficacy and safety of administering 60 mg diltiazem hydrochloride, four times daily for a period of 3 weeks, was studied in a random, double-blind, crossover trial in which the drug was compared with placebo in 17 neuroleptic-treated, chronic psychiatric inpatients of both genders with (tardive) dyskinesia. The severity of the dyskinesia was assessed using the Abnormal Involuntary Movement Scale. Neither diltiazem nor placebo produced a significant decrease in the severity of the dyskinesia. Diltiazem did not influence the psychiatric state of the patients, nor did it have a significant effect on either the blood pressure or electrocardiographic parameters. No significant adverse drug reactions were elicited.
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THE LONG-TERM use of neuroleptic drugs (antipsychotics) is generally hampered by the possible development of the involuntary movement disorder tardive dyskinesia (TD).[1,2] Recently, calcium antagonists such as verapamil,[3–5] diltiazem,[6,7] and nifedipine[8,9] have been reported to decrease the symptoms of TD. The mechanism of their beneficial effect may be a reduction of nigrostriatal dopaminergic neuron activity. It is currently hypothesized that hypersensitivity of dopamine (DA) receptors, resulting in an imbalance between dopaminergic and cholinergic activities in the basal ganglia, might play a role in the development of TD. Animal experiments have shown that Ca^{2+} is involved both in DA release from nigrostriatal DA terminals and in DA synthesis.[10] Indeed, calcium antagonists are known to inhibit neurosecretory processes, and it has been demonstrated *in vitro* that verapamil, diltiazem, and ryosidine decrease the release of DA from rabbit caudate nucleus slices.[11] Moreover, the high density of calcium antagonist binding sites found in the substantia nigra[12] has led to speculation that these receptors are the primary site of action.[13]

The present pilot study was undertaken to investigate whether diltiazem effectively suppresses symptoms of (tardive) dyskinesia. A second objective was to assess the tolerability of diltiazem compared with placebo in chronic psychiatric inpatients.

Methods

Patient sample

The patients were recruited from the long-stay wards of the Psychiatric Hospital Reinier van Arkel, Vught, The Netherlands. Inclusion criteria were (1) clinical diagnosis of (tardive) dyskinesia based on (i) a history of neuroleptic drug treatment over a period of at least 4 months; (ii) either moderate or severe hyperkinesia according to the UKU definition (i.e., "Involuntary movements, most frequently affecting the oro-facial region in the form of the so-called bucco-linguo-masticatory syndrome. However, it is often also seen in the extremities, especially the fingers, more rarely in the musculature of the body and the respiratory system. (2) Moderate hyperkinesia, present most of the time. (3) Severe hyperkinesia, present most of the time, with for instance marked tongue protrusion, opening of the mouth, facial hyperkinesia, with or without involvement of the extremities.")[14] and (iii) preferably, a history of aggravation due to dose reduction of the neuroleptic or addition of an antiparkinson drug (i.e., the AMDP-criterion)[15] (2) hyperkinesia present for at least 6 months; and (3) clinical condition stable for at least 3 weeks.

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The following subjects were excluded from the trial: pregnant or lactating women, women of child-bearing potential, patients known to be incompliant or insufficiently cooperative, and patients suffering from or with a history of a medical condition which would prevent them from entering a drug trial[16] or contraindicate the use of diltiazem.

Requirements were that the dosage of concomitant medication possibly influencing tardive dyskinesia, e.g., neuroleptic, anticholinergic, antihistaminic, or anxiolytic drug, had been stable for at least 3 weeks before entry until the end of the trial, and in the case of long-acting neuroleptics, the preceding 3 doses and dosage intervals had been constant, or the last administration had been at least 7 weeks before entry. Informed consent was obtained from all patients or, when appropriate, from a legal representative, close relative, friend or guardian.

Study design

Patients who entered the study were randomly allocated to treatment group I or II by application of the random permuted block technique with a block size of 2. Patients in group I initially received one diltiazem HCl 60 mg tablet orally four times daily for 3 weeks. Thereafter they were switched double-blindly to placebo tablets which looked identical, for another three weeks. Patients in group II first received placebo four times daily, and after a period of 3 weeks they were switched to diltiazem, which was then continued for another 3 weeks.

Assessments

At the beginning of the trial, all patients underwent a general medical examination, specific attention being paid to neurologic and cardiovascular signs and symptoms. Dyskinesias were assessed by applying the first eight items of the Abnormal Involuntary Movement Scale (AIMS) as translated by Kief.[17] This was performed six times: on 2 separate days with an interval of at least 3 days before the start of the trial and after 1 and 3 weeks of treatment with either diltiazem or placebo. In every patient, all assessments were made at the same time of the day and (when relevant) 60 ± 15 min after drug intake. The investigator made a general assessment of the possible changes in behavioral and psychic state and the drug tolerability during the 3-week period by applying the Clinical Global Impressions (CGI)[18] and the Systematic Assessment for Treatment Emergent Events–Systematic Inquiry[19] on entry and at the end of each treatment period. When relevant, the nursing staff was consulted to obtain additional information. An electrocardiogram was recorded and routine laboratory tests were performed before entry and at the end of each 3-week treatment period. The baseline blood pressure and pulse were taken on 2 separate days before the start of the trial or at least 1 week after terminating trial drug intake. During the trial period, systolic and diastolic blood pressure and radial pulse were measured at weekly intervals.

Data processing

Unless specified otherwise, all data are presented as the mean ± SD. The results of the various assessments found in the diltiazem period were compared to those found in the placebo period, before and after subtracting the (averaged) pretreatment period values. The two-tailed Wilcoxon Matched-Pairs Signed-Ranks Test or the two-tailed Fisher's Exact Test were used.[20] The blood pressure measurements and the AIMS ratings were performed more than once during each study period. In these assessments the period averages for every patient were also calculated and compared.

To calculate stability differences in the effects of diltiazem on the AIMS assessments, we also subtracted the total AIMS score (i.e., the sum of item 1–7 scores) after 3 weeks of treatment from the total AIMS scores after 1 week.

Results

Description of population

Eighteen patients with TD entered the study. During the study, three subjects terminated prematurely. Two of them showed an obvious lack of compliance unrelated to trial medication; these subjects were replaced. One patient developed atrial fibrillation, which required digitalization. When the double-blind code of this patient was broken, it appeared that the atrial fibrillation had started during the placebo period. Thus, the number of subjects who completed the study was 17 (6 men and 11 women). The mean age of the subjects was 57.2 ± 9.30 years (range, 37–69). The average height was 163.5 ± 12.01 cm, and the mean weight 68.7 ± 12.81 kg. One patient was black, the others were caucasian. Fourteen patients had a DSM-III-R first axis diagnosis; in 14 cases there was a second axis diagnosis, and none of the patients had no psychiatric diagnosis at all. The concomitant medication comprised antipsychotics (n = 17; short-acting, n = 10; long-acting, n = 8), anticholinergics (n = 9), benzodiazepines (n = 2), anticonvulsants (n = 2), and diuretics (n = 2), whereas single patients received a variety of somatic drugs unlikely to affect trial results.

Assessments

AIMS. Table 1 reports the mean total AIMS scores of the trial population during the baseline, the diltiazem, and the placebo periods. When differences between the mean AIMS item scores and the mean total AIMS scores during the diltiazem period (total score = 7.97 ± 5.55) and that at entry (7.53 ± 4.47) were compared with differences

TABLE 1. Mean (±SD) total AIMS scores

Group	Preentry	Diltiazem	Placebo
Total trial population			
First assessment	7.00 (4.26)		
Second assessment	8.06 (5.06)		
Mean	7.53 (4.47)		
Week 1		7.65 (5.53)	7.71 (6.45)
Week 3		8.29 (5.76)	8.53 (5.78)
Mean		7.97 (5.55)	8.12 (6.02)
Subgroup starting with diltiazam or placebo			
Diltiazem first (n=8)		7.31 (5.26)	8.88 (6.05)
Placebo first (n=9)		8.56 (5.93)	7.44 (6.13)
Subgroup with schizophrenia or other diagnosis			
Schizophrenia (n=9)		7.56 (6.15)	6.22 (5.40)
Other (n=8)		8.44 (5.01)	10.25 (6.18)

between the mean item scores and the mean total scores during the placebo period (8.12 ± 6.02) and that at entry, none of the differences was significant at the $p < 0.05$ level. Nor did we find differences at the $p < 0.05$ level when we compared scores after 1 and 3 weeks of treatment.

The mean total AIMS scores of the subjects who were first treated with diltiazem and then with placebo do not differ greatly from scores in the patients who first received placebo followed by diltiazem. Diltiazem did not have an obvious effect on TD in the subgroup of schizophrenic subjects nor on TD in the subgroup of patients with another psychiatric diagnosis.

CGI. In comparing the CGI results, none of the differences is significant at the $p < 0.05$ level. Mean scores of severity did not change much during the diltiazem (6.29 ± 0.59) and the placebo periods (6.18 ± 0.39) compared with the preentry score (6.06 ± 0.66). No change in condition was noted in any of the cases.

Laboratory tests, electrocardiography, blood pressure and side effects. No significant differences were found between the effects of diltiazem and placebo on distinct laboratory tests or on clusters of laboratory tests (blood chemistry, hematologic tests, and urinalysis). Furthermore, no significant differences were found in effects of diltiazem and placebo on electrocardiogram parameters or on blood pressure.

Diltiazem was tolerated well by all trial subjects. Only minor events were reported that could not be considered to be related to diltiazem.

Discussion

The differential diagnosis of TD can be difficult because dyskinesias can also occur spontaneously in drug-free patients, and TD can coexist with a variety of both extrapyramidal and psychopathologic symptoms.[21-23] Jenner and Marsden's description of TD[21] may serve as a reference for making a differential diagnosis. Our inclusion criteria did not differ greatly from the frequently used research diagnostic criteria proposed by Schooler and Kane,[24] and because our criteria were more restrictive, our subjects did meet their definitions. In the present trial, diltiazem did not affect TD. This is true for the total trial population and for the subgroups of schizophrenics and subjects with another psychiatric diagnosis. The preentry period, the diltiazem period, and the placebo period scores are almost equal. This contrasts the obvious and immediate improvement of TD after the administration of diltiazem in 3 patients reported by Ross and colleagues.[6] These patients showed a decrease in total AIMS scores within 1 day of the first diltiazem administration. In addition, Leys and associates[7] observed a significant reduction of the frequency of involuntary movements ($p < 0.05$) 30, 60, and 90 min after the administration of a single oral dose of diltiazem HCl 60 mg in 6 patients with TD. Therefore, the fact that in our study we did not find any effect of diltiazem on TD is probably not due to the trial period being too short or the timing of the assessments being incorrect. It is also unlikely that the lack of a positive effect of diltiazem on TD in our trial is a matter of dosages being too low (240 mg daily in all patients), because Ross and coworkers[6] reported that improvement occurred when the daily administration was only 120 mg. Perhaps the patients who showed the improvement differ in certain important aspects. For example, all 3 patients in the study by Ross and colleagues were on lithium, and according to the very high initial AIMS scores of these patients, they suffered from severe TD, which was not the case in our patients. Adler and associates reported a reduction in severity of TD after treatment with verapamil (mean AIMS scores decreased from 10.1 ± 3.6 to 8.2 ± 2.8; $n = 9$; $p < 0.05$) and diltiazem (mean AIMS scores decreased from 11.5 ± 3.6 to 10.2 ± 3.6; $n = 12$; p value not significant). Duncan and associates[8] found a significant ($p < 0.01$) reduction of mean AIMS scores (12.9 ± 2.0 at baseline to 10.8 ± 2.7) after treatment with nifedipine.

In our trial, the sample size was relatively small, but

from the data reported it does not appear that larger numbers would have led to significant results. None of the members of the nursing staff nor the investigators noticed even the slightest reduction in severity of TD during the trial. No carry-over effects were observed. Diltiazem did not have any effect on the general psychic state of our subjects. Nor were the laboratory investigations, the blood pressure, or the electrocardiographic assessments affected by diltiazem. No major adverse drug reactions occurred during the trial period.

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