

Original article

Effect of Nitrendipine, Diltiazem and Verapamil on psychomotor performance in human volunteers

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Abstract

Background: Calcium channel blockers are amongst the commonly used drugs in the treatment of cardiovascular disorders. They produce their action by blocking voltage regulated calcium channels. **Methodology:** Present study evaluated the effects of three structurally dissimilar calcium channel blockers Nitrendipine (a dihydropyridine) in a single dose of 10 mg and 20 mg, Diltiazem (a benzothiazepine) in a single dose of 30 mg and 60 mg and Verapamil (a phenylalkylamine) in a single dose of 40 mg and 80 mg on psychomotor performance in human volunteers. For evaluation of psychomotor performance, the tests used were arithmetic ability, verbal learning, letter cancellation, digit symbol substitution and card sorting test. **Results:** Nitrendipine both in low dose (10mg) and high dose (20mg) as well as Diltiazem in high dose (60mg) and Verapamil in high dose (80mg) were found to impair the psychomotor performance in human volunteers to a statistically significant extent in all the tests employed except letter cancellation test. Whereas Diltiazem in low dose (30mg) and Verapamil in low dose (40mg) showed statistically significant impairment of psychomotor performance using arithmetic ability, verbal learning, and digit symbol substitution test. **Conclusion:** Thus calcium channel blockers namely Nitrendipine, Diltiazem and Verapamil significantly impaired the psychomotor performance of human volunteers in our study.

Key words: calcium channel blockers, psychomotor performance

Introduction

Calcium channel antagonists constitute a heterogeneous class of agents with unrelated structural, electrophysiological and pharmacological properties¹.

Structurally different Calcium channel blockers including Nitrendipine, Diltiazem and Verapamil show varied sensitivity towards Calcium channels at different sites in the body. They have been demonstrated in a variety of tissues including brain^{2,3}.

Some of the Calcium channel blockers namely Nifedipine, Diltiazem and Verapamil have been reported to block Calcium channels in the neurons. Blockade of neuronal Calcium channels might be responsible for the inhibition of seizure spread⁴. Similarly they may interfere with calcium mediated neuronal activities namely propagation of impulses and release of neurotransmitters⁵.

In addition to their Calcium channel blocking effects in the neurons, they have a direct effect on the central nervous system^{4,6}. At therapeutic doses Nifedipine and Diltiazem show penetration into the brain⁶.

Doran et al (1985)⁷ have measured levels of Verapamil and the active metabolite Norverapamil in cerebrospinal fluid in schizophrenic patients.

Besides cardiovascular disorders, calcium channel antagonists are used in neurological disorders like migraine, subarachnoid hemorrhage, cerebrovascular accidents, vertigo, intractable hiccough and epilepsy⁸.

Calcium channel blockers also have a place in the treatment of psychiatric disorders like manic depressive psychosis, depression, schizophrenia and tardive dyskinesia⁵.

Jaguste, Dadkar and Dhar (1990)⁹ showed that Nifedipine and Verapamil impaired psychomotor performance in human subjects.

With this background the present study was undertaken to evaluate the effects of three structurally dissimilar Calcium channel blockers Nitrendipine (second generation Calcium channel blocker) Diltiazem and Verapamil in single low and high dosages on psychomotor performance in normal healthy human

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volunteers using conventional psychomotor performance tests.

Material & Methods

The present study was carried out in clinical pharmacology division- Department of pharmacology. It was a single blind randomized trial. Fifteen normal healthy human volunteers in the age group of 18 to 21 years of either sex having a body weight that did not deviate from the normal by more than 10% were included in the study.

Those volunteers who have history of drug allergy, diabetes mellitus, tuberculosis, asthma, epilepsy, HBV and HIV positive cases, gastrointestinal, renal, hepatic and cardiac diseases were excluded from the study.

Informed written consent was obtained from all the volunteers after explaining the study pattern and related hazard involving drug allergies and possible adverse reactions. The study was approved by institutional ethical committee of Government medical college and Hospital.

Routine investigations of each volunteer such as complete hemogram, urine analysis, random blood sugar, liver function test (serum bilirubin, SGOT, SGPT), kidney function tests (blood urea, serum creatinine), electrocardiogram, HBV and HIV testing, X-ray chest were carried out before the study.

Prior to the study sessions all volunteers underwent detail medical examination. Volunteers selected for the study had no clinically significant abnormal findings.

The volunteers were well versed with the various psychomotor performance tests, they were given practice till consistent scores were obtained for all the tests to be performed prior to the study day.

On the study day the volunteers were asked to come in the clinical pharmacology division- Department of Pharmacology at 8 a.m. on an empty stomach and zero hour (before giving drug) readings were taken. Following this they were provided a light breakfast. The drugs used were tablet Nitrendipine (Nitrepin) 10mg single dose, tablet Nitrendipine (Nitrepin) 20mg single dose, tablet Diltiazem (Dilzem) 30mg single dose, tablet Diltiazem (Dilzem) 60mg single dose, tablet Verapamil (Calaptin) 40mg single dose,

tablet Verapamil (Calaptin) 80mg single dose.

The drugs were administered in a single dose with 50 ml of water orally to the volunteers according to a randomized chart. All the psychomotor tests were performed at ^{1,2,3,4,5,6,7} and 8 hours (post dose) after drug administration.

Standard lunch was provided four hours after the drug was given to the volunteers.

After the washout period of one week the same procedure was repeated and readings were taken pre and post dose respectively for each drug groups.

Psychomotor Performance Tests Used:

Following are the details of psychomotor performance tests used.

Arithmetic Ability test:

Summation test was performed to test arithmetic ability. For this purpose eight vertical columns (sums) were prepared, each column containing ten figures (between 10 and 99) which were to be added up. Score – The number of wrong sums were recorded¹⁰.

Verbal Learning test:

In this test 10 words were shown to the volunteers. One word at a time for 5 seconds at one second intervals. After the final word was presented, a 6 digit number was shown (to eliminate a recency effect). The volunteers were asked to write down that number and as many words as they could remember in 60 seconds¹¹.

Score – The score being the total number of correctly recalled words in 60 seconds.

Letter Cancellation test:

In this test, the volunteer cancels particular letter (digit) in a line of numbers, the frequency of letter being 40 in 400 numbers. The volunteer was asked to cancel a particular letter by a single vertical stroke.

Score – The score being the time taken to cancel particular letters^{12,13}.

Digital Symbol Substitution test:

In this test 10 symbols were taken to represent 10 digits (0 to 9). The symbols and digits are randomly

tabulated and repeated in different sequences many times. The volunteer has to match as many digits to the symbols as he can over a time period of 2 minutes.

Score – The scores being the total number of correctly substituted digits in two minutes^{12,14}.

Card Sorting test:

For this test it was initially confirmed that all the volunteers were familiar with playing cards. The volunteers were shown a set of four cards arranged randomly. They were allowed to view each card for a period of 10 seconds. The set of cards was shown three times in succession without changing the times for viewing. Immediately after they were asked to remove all the same four cards shown by the tester in one minute⁹.

Score – The score being the total number of correctly removed cards in one minute.

Version:

Volunteers received different set of versions at each reading for each test. 15 such versions were prepared for each test.

Sample size:

Fifteen volunteers were used for individual drug group (Nitrendipine, Diltiazem, Verapamil) for low and high doses respectively. Total 45 volunteers were enrolled in the study.

Statistical Analysis:

The changes in the psychomotor performance observed after single drug administration to that with basal value (before giving drug) were analyzed by paired student's 't' test.

To compare the alteration in the psychomotor performance for low dose and high dose of individual drug group, unpaired student's 't' test was applied.

Statistical significance was indicated by conventional symbols.

** (P < 0.05)

NS (P > 0.05) not significant

Results and Discussion

Cardiovascular disease is a major health problem that affects a large segment of adult population in world, a significant portion of the adult work force may be expected to be under treatment with cardiovascular medications including Calcium channel blockers.

The present study evaluated the effects of Nitrendipine 10mg and 20mg, Diltiazem 30mg and 60mg and Verapamil 40mg and 80mg on psychomotor performance in normal healthy human volunteers using conventional psychomotor performance tests.

Psychomotor performance tests were selected in such a manner that arithmetic ability, short term memory, concentration, learning, discrimination and motor activity were evaluated.

Results of the present study showed Nitrendipine in single low dose 10mg as well as in single high dose 20mg significantly impaired psychomotor performance in volunteers using arithmetic ability test, verbal learning test, digital symbol substitution test and card sorting test (P<0.05).

Experimental evidence suggests that Nitrendipine produces impaired psychomotor activity in rats¹⁵.

Impaired learning and memory with Nifedipine has been reported in some elderly hypertensive patients by skinner et al (1992)¹⁶.

David Spurgeon (1999)¹⁷ and Maxwell, Hogan and Ebly (1999)¹⁸ in their study have shown that declines in cognitive function were significantly greater among elderly people using calcium channel blockers (Nifedipine, Diltiazem and Verapamil) than among those using other antihypertensive agents. Similarly Payne R(1990)¹⁹ reported that analgesic adjuvants (coanalgesics) like Calcium channel blockers may impair psychomotor functioning.

In the present study Diltiazem in single low dose 30mg as well as Verapamil in single low dose 40mg showed significant impairment of psychomotor performance in volunteers using arithmetic ability test, verbal learning test, digital symbol substitution test (P<0.05).

Diltiazem in single high dose 60mg as well as Verapamil in single high dose 80mg showed significant impairment psychomotor performance in volunteers using arithmetic ability test, verbal learning test, digital symbol substitution test and card sorting test (P<0.05).

Effect of Nitrendipine, Diltiazem and Verapamil on psychomotor performance

The above results of Diltiazem and Verapamil are consistent with the results obtained by Jaguste, Dadkar and Dhar (1990)⁹, David Spurgeon (1999)¹⁷, Maxwell, Hogan and Ebly (1999)¹⁸ and Payne R (1990)¹⁹.

Though low as well as high dose of Nitrendipine, Diltiazem and Verapamil significantly impaired psychomotor performance but there was not significantly greater impairment with high dose possibly due to the learning phenomenon of psychomotor performance tests²⁰. While individual drug Nitrendipine, Diltiazem and Verapamil showed significant impairment of psychomotor performance but their results were not significantly different when compared amongst themselves.

In conclusion- Nitrendipine, Diltiazem and verapamil in low dose and high dose impaired the psychomotor performance of human volunteers. Although these agents are used safely most of the

time by the patients in acute or chronic diseases at intervals of 8 to 12 hours over several days or weeks, Nitrendipine, Diltiazem and Verapamil in the dosage used are not very safe drugs for those who are engaged in tasks requiring higher skill and motor activity.

Therefore patients taking drugs which produce psychomotor impairment may be at risk or lapses and significant errors that may lead to potential hazards and decreased work productivity more specifically those involved in skilled work like driving vehicles, pilots and machine operators etc²¹⁻²³.

Conflict of interest- None to declare

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Table No. 1

Effects of Calcium channel blockers on psychomotor performance in human volunteers

Mean ±S.E.M. * (n=15)

| Treatment group | Psychomotor performance tests | | | | | | | | | |
|-------------------|-------------------------------|----------------------|----------------------|----------------------|--------------------------|----------------------|----------------------------------|----------------------|---------------------|----------------------|
| | Arithmetic ability test | | Verbal learning test | | Letter cancellation test | | Digital symbol substitution test | | Card sorting test | |
| | Pre treatment score | Post treatment score | Pre treatment score | Post treatment score | Pre treatment score | Post treatment score | Pre treatment score | Post treatment score | Pre treatment score | Post treatment score |
| Nitrendipine 10mg | 0.6±0.213 | ** 1.51±0.221 | 8.53±0.244 | ** 7.58±0.275 | 54.33±2.19 | 54.08±1.95 | 9.6±0.288 | ** 8.31±0.319 | 4±0 | ** 3.42±0.107 |
| Nitrendipine 20mg | 0.46±0.132 | ** 1.38±0.282 | 9.06±0.252 | ** 8.11±0.322 | 44.93±2.86 | 44.27±2.13 | 9.4±0.244 | ** 9.21±0.126 | 3.93±0.066 | ** 3.58±0.101 |
| Diltiazem 30mg | 1.06±0.140 | ** 1.75±0.148 | 8±0.337 | ** 7.50±0.174 | 59.06±2.34 | 59.37±1.88 | 10±0 | ** 8.84±0.370 | 3.6±0.130 | 3.38±0.105 |
| Diltiazem 60mg | 1.06±0.205 | ** 1.79±0.170 | 8.46±0.396 | ** 7.58±0.177 | 49.73±2.92 | 48.89±2.19 | 9.86±0.090 | ** 9.61±0.138 | 3.93±0.066 | ** 3.60±0.126 |
| Verapamil 40mg | 2.06±0.298 | ** 2.70±0.213 | 8.6±0.201 | ** 8.01±0.209 | 51.13±2.24 | 50.29±1.52 | 9.6±0.248 | ** 9.14±0.111 | 3.66±0.159 | 3.46±0.099 |
| Verapamil 80mg | 1.73±0.352 | ** 2.74±0.182 | 8.86±0.284 | ** 7.92±0.255 | 43.6±2.06 | 44.19±1.80 | 9.86±0.133 | ** 9.21±0.120 | 4±0 | ** 3.54±0.121 |

*Standard error of mean. ** Statistically significant (p<0.05)

Score:

- 1] Arithmetic ability test (Number of wrong sums done)
- 2] Verbal learning test (Number of words correctly recalled)
- 3] Letter cancellation test (Time required to cancel letter in seconds)
- 4] Digital symbol substitution test (Number of digits correctly substituted)
- 5] Card sorting test (Number of correctly removed cards)

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