Original Article

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Comparative evaluation of aliskiren, ramipril, and losartan on psychomotor performance in healthy volunteers: A preliminary report

Abstract

Aim: To compare the effects of aliskiren, ramipril, and losartan on the psychomotor performance in healthy volunteers. **Materials and Methods:** In this preliminary, single-dose, open-label, cross-over study conducted in 12 healthy volunteers, psychomotor assessment was carried out by four tests: Simple reaction time (SRT), multiple choice reaction time test (MCRT), critical flicker fusion frequency threshold test (CFFT), and tracking performance test (TPT). Each volunteer received a single dose of each of the three test drugs with a washout period of 10 days between different test sessions and then evaluated for post-drug scores at 2-h intervals up to 12 h and then at 24 h. The changes from the baseline scores by the test drug were statistically analyzed. **Results:** All the three antihypertensive drugs caused significant improvement in a similar fashion on SRT, MCRT calculated as error index, CFFT, and TPT. Aliskiren caused numerically more improvement than the other two test drugs, suggesting better cognitive profile. However, inter-drug comparisons were nonsignificant. **Conclusion:** The results of the study highlight improvement of the cognitive functions equally by ramipril, losartan, and aliskiren. The results of the study could be of immense clinical utility in ambulatory hypertensive patients especially engaged in sensory-motor coordination tasks like driving and operating on mechanical tools.

Key words: Aliskiren, cognitive function, losartan, psychomotor performance, ramipril

INTRODUCTION

Hypertension is an important public health issue and a leading risk factor for heart disease, stroke, and kidney failure. The prevalence of hypertension increases with advancing age.[1] It has been found that the average blood pressure (BP) over 20 years is inversely related to cognitive performance.[2]

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Conventional antihypertensives like beta-blockers are well known to cause impairment of psychomotor performance.[3-6] On the other hand, drugs modifying the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), have shown better cognitive outcomes.[7,8] Aliskiren is the first drug in a new class of antihypertensives (renin inhibitors) that inhibit the RAAS by directly targeting the enzyme renin, the first step in the RAAS.[9,10] The drug is indicated for the treatment of high BP, either alone or in combination with other agents.[11,12] Aliskiren's use is likely to increase in the near future like its counterparts, as more and more experience is gained with its use by clinicians.

The scan of the literature did not reveal any report of aliskiren on psychomotor performance tests. Moreover, there is no report comparing the effects of newer antihypertensive, aliskiren, with those of other commonly used drugs in our clinical setup for modifying the RAAS, such as ramipril and losartan, on these parameters. Therefore, the present study was undertaken to assess the effects of aliskiren on psychomotor performances and compare them with the effects of ramipril and losartan.

MATERIALS AND METHODS

In an open-label, randomized, cross-over study, 12 healthy male volunteers (age 25-40 years, weight 50-70 kg) were enrolled after their obtaining informed written consent and Institutional Ethics Committee's (IEC) clearance. Average BP in sitting and supine position was in the normal range as per the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) report[1] and volunteers were literate up to 8th standard at least.

Volunteers with history of intake of psychotropic drugs, antihypertensives, alcohol, any long-term medication, or any drugs known to interfere with psychomotor performance for 4 weeks before commencing the trial were excluded. Those with history of any clinical anxiety, depressive states, diabetes, cardiovascular disease, impaired renal and hepatic functions, or color blindness were also excluded. All volunteers were advised to abstain from caffeinated drinks, cola drinks, and chocolates during the study trial. The drugs under investigation were used as a single dose, i.e. aliskiren (150 mg), ramipril (5 mg), and losartan (50 mg).

After screening the volunteers based on the above-mentioned criteria and before administering any test drug, a detailed clinical history was taken and evaluation of physical characteristics, biochemical estimations, hematological estimations, urine analysis, electrocardiogram, and X-ray chest was conducted in them besides their periodic BP recording. All the volunteers were made to familiarize for 1 week with the psychomotor performance tests or till the performance reached a stable level.

Before commencing the study, baseline scores were obtained on the psychomotor performance tests. Each volunteer received a single dose of either of the three test drugs (aliskiren 150 mg, ramipril 5 mg, losartan 50 mg) with a washout period of 10 days between the different test formulations followed by cross-over. Each subject was then evaluated for post-drug scores on the psychomotor performance tests every 2 hourly up to 12 h and then at 24 h.

Psychomotor assessment

Simple reaction time

Visual reaction time was determined by measuring the latency between presenting a visual stimulus and the response (pressing a key). In one sitting, 20 such stimuli were presented and the mean of these readings was calculated in milliseconds. Increase in SRT indicates impairment of execution of even simple mechanical tasks.[13]

Multiple choice reaction time calculated as error index

Visual reaction time was determined by measuring the latency between presenting a visual stimulus and the response (pressing a key). If the subject responded correctly within 0.5 s, the response was recorded as correct; if the subject responded between 0.5 s and 0.8 s, it was counted as delayed correct; and if the subject pressed a wrong key, the response was recorded as a wrong response. One hundred such stimuli were given at regular intervals. Missed responses were calculated by adding the three and subtracting their sum from 100. At one sitting, four trials were recorded, two with each program, and the error index was calculated from the mean of these four trials by the following formula:[14]

Error index = no. of delayed correct responses + no. of wrong responses × 2 + no. of missed responses × 3.

Critical flicker fusion frequent threshold

Subjects were required to discriminate flicker fusion in a set of four light-emitting diodes placed at a foveal distance of 1 m. Individual thresholds in Hertz were determined on five ascending and five descending frequencies as per the method described by Hindmarch. Decrease in CFFT indicates impairment of sensory-motor integration process in CNS.[15]

Tracking performance task

In this test, eye-to-hand coordination was tested by coordinating the movement of a cursor (by hand) and keeping it in alignment with a target moving around an illuminated circular task at a speed of 6 revolutions/min and the errors made per minute were recorded as per the method described by Raina *et al.*[14]

Statistical evaluation

The data were expressed in mean ± standard error of mean (SEM). The changes from the baseline scores brought about by the test drugs were analyzed by paired *t*-test, whereas inter-drug comparisons were carried out by analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant.

RESULTS

The data obtained with aliskiren, ramipril, and losartan in different psychomotor tests have been summarized in Tables 1-4. All the three drugs caused significant decrease in SRT at 2, 4, and 6 h, except in case of aliskiren where significant values were seen up to 12 h, when compared with their respective baseline values. The effect started at 2 h and lasted up to 6 h, except in case of aliskiren where it lasted up to 12 h, after the intake of drugs [Table 1]. When these drugs were compared with each other, no significant difference, as suggested by ANOVA, was observed, though aliskiren caused more numerical decrease in SRT than ramipril and losartan.

MCRT calculated as error index was significantly decreased on administration of all three test drugs. The effect started at 2 h for all three test drugs and lasted up to 10 h. However, the effect was prolonged by 2 h in case of ramipril. Peak decrease was seen at 4 h in case of ramipril and at 6 h in case of losartan and aliskiren [Table 2]. Inter-drug comparisons calculated by ANOVA were, however, nonsignificant.

CFFT was found to be significantly increased with varied levels of significance with all the three drugs studied, as shown in Table 3. Peak increase in CFFT was observed at 4 h with all three test drugs. When these drugs were compared with each other, ANOVA showed no significant difference, though aliskiren caused more numerical increase in CFFT than ramipril and losartan [Table 3].

TPT increased significantly with all three test drugs with varied levels of significance. Peak increase in TPT was seen at 4 h with all the three test drugs. However, aliskiren caused more increase in TPT numerically as compared to the other test drugs. The inter-drug comparisons were nonsignificant [Table 4].

Table 1: Effects and comparison of ramipril, losartan and aliskiren on SRT (ms) (mean±SEM)

Drug	0 h	2 h	4 h	6 h	8 h	10 h	12 h	24 h
Ramipril	95.67±8.92	89.92±7.82***	85.42±7.82***	88.08±8.20**	92.17±8.81	94.25±8.89	95.33±8.90	95.67±8.94
Losartan	95.67±9.01	90.92±8.16**	87.17±7.16**	87.42±7.35**	91.92±8.83	93.50±9.12	94.67±9.07	95.67±9.05
Aliskiren	95.67±8.86	91.00±8.04**	87.83±7.76***	84.75±8.35**	91.50±8.44**	94.58±8.67**	95.00±8.68*	95.83±8.95
Inter-drug comparison	NS	NS	NS	NS	NS	NS	NS	NS

*P<0.05, **P<0.01, ***P<0.001 in comparison to respective baseline values, SRT = Simple reaction time, SEM = Standard error of mean, NS = Non Significant

Table 2: Effects and comparison of ramipril, losartan, and aliskiren on MCRT (as error index) mean±SEM

Drug	0 h	2 h	4 h	6 h	8 h	10 h	12 h	24 h
Ramipril	140.0±7.17	128.8±10.3*	126.0±10.77**	130.4±10.26*	131.8±9.70*	136.2±8.20*	137.9±7.70*	139.2±7.44
Losartan	139.9±7.33	129.4±7.85*	127.7±9.82**	125.1±9.71***	130.8±8.31***	136.4±7.74*	137.8±7.53	138.5±7.24
Aliskiren	139.6±6.80	132.1±8.35*	128.6±8.66**	126.1±8.29***	130.5±8.30**	135.7±7.44**	138.8±6.86	139.2±6.87
Inter-drug comparison	NS	NS	NS	NS	NS	NS	NS	NS

*P<0.05, **P<0.01, ***P<0.001 in comparison to respective baseline values, MCRT = Multiple choice reaction time test, SEM = Standard error of mean, NS = Non Significant

Table 3: Effects and comparison of ramipril, losartan, and aliskiren on CFFT (in Hertz) (mean±SEM)

Drug	0 h	2 h	4 h	6 h	8 h	10 h	12 h	24 h
Ramipril	30.36±0.54	30.97±0.54**	31.50±0.54***	31.06±0.52***	30.70±0.53*	30.55±0.51	30.49±0.51	30.34±0.54
Losartan	30.39±0.54	31.09±0.55***	31.42±0.51***	31.36±0.58***	30.85±0.52*	30.43±0.59	30.39±0.54	30.38±0.54
Aliskiren	30.38±0.52	31.14±0.55**	32.01±0.62**	31.39±0.55***	30.67±0.56	30.47±0.54	30.36±0.52	30.36±0.52
Inter-drug comparison	NS	NS	NS	NS	NS	NS	NS	NS

*P<0.05, **P<0.01, ***P<0.001 in comparison to respective baseline values, CFFT = Critical flicker fusion frequency threshold test

Table 4: Effects and comparison of ramipril, losartan, and aliskiren on TPT (as error index) (mean±SEM)

Drug	0 h	2 h	4 h	6 h	8 h	10 h	12 h	24 h
Ramipril	19.67±1.17	20.75±1.28***	21.19±1.16***	20.55±1.16**	20.02±1.13	19.8±1.15	19.49±1.17	19.53±1.15
Losartan	19.7±1.14	20.63±1.24***	21.1±1.21***	20.72±1.19**	20.21±1.13**	19.9±1.15	19.65±1.13	19.72±1.15
Aliskiren	19.68±1.16	20.72±1.30***	21.33±1.21***	20.8±1.21***	20.22±1.14**	20.3±1.38	19.73±1.16	19.66±1.15
Inter-drug comparison	NS	NS	NS	NS	NS	NS	NS	NS

*P<0.05, **P<0.01, ***P<0.001 in comparison to respective baseline values, TPT = Tracking performance test,SEM = Standard error of mean, NS = Non Significant

DISCUSSION

In the present study, the effects of aliskiren have been compared with those of ramipril and losartan on psychomotor performance tests to assess any CNS alteration. We chose aliskiren, ramipril, and losartan, all lipophilic in nature, and the latter two are known to cause changes in psychomotor performance test results. A comprehensive battery of tests was employed to elucidate such potential. SRT is an excellent example of tasks which comprise both sensory and motor components. The performance is more dependent upon attentional monitoring abilities in MCRT than in SRT because the number of stimuli is more than one. CFFT, one of the most sensitive psychomotor tests, is the method of choice for measuring the effects of psychotropic drugs on central integrative activity**.** It is a measure of the ability to discriminate between flicker and fusion and vice versa of light. It involves the central mechanism involving cortical arousal or integration and is a more direct measure of CNS activity. TPT is a measure of the visuomotor coordination.

Ramipril and losartan have been reported to cause better cognitive outcomes.[7,8] The main result of the present study indicates that aliskiren, a newer antihypertensive, improves the psychomotor performance tests in a fashion similar to that of ramipril and losartan, suggesting that aliskiren has central effects.

However, there is no report in literature regarding the effect of renin inhibitors, a new class of antihypertensive drugs, on psychomotor performance, though in the past, other drugs like beta-blockers and Calcium channel blockers (CCBs), have been studied. The observations of the present study are contrast to the earlier reported impairment of psychomotor performance tests by beta-blockers, another group of antihypertensive drugs.[5,6] Such an outcome clearly outlines the advantage of aliskiren on the psychomotor functions, compared to beta-blockers.

Calcium channel blockers, another widely used group of antihypertensives, have been extensively studied for their effects on cognitive functions. Verapamil impairs the psychomotor performance tests to a significant extent, such as in auditory reaction time, letter cancellation, and short-term memory. These effects were found to be similar to diazepam. While with nifedipine, impairment was observed only in rapid arithmetic deviation test,[16] nitrendipine, diltiazem, and verapamil have also been shown to significantly impair the psychomotor performance tests including arithmetic ability, verbal learning, and digit symbol substitution test.[17] These reports clearly indicate that calcium channel antagonists impair psychomotor performance.

The basis of improvement of cognitive functions by RAS modification is not clear. However, it is now well established that the independent brain renin-angiotensin system (RAS) has some important central functions besides the vascular ones. Recently, administration of the Ang II blocker captopril has been shown to significantly improve memory tasks (Y-maze task, passive avoidance), increase b oth antioxi dant enzymes, and decrease lipid peroxidation and malondialdehyde (MDA) concentration.[18]

So, it is probable that by altering the neuronal oxidative stress status, the current drugs under study might have resulted in improved psychomotor performance, which remains to be proved in future studies.

Findings of the present study can also be correlated with the lipophilic nature of aliskiren. However, the relevance of these central effects on skilled performance in actual situation involving mechanical and other skills is unclear. Moreover, this study suffers from drawbacks of being a single-dose study in healthy individuals and lacking placebo control. Hence, additional adequately powered studies are needed to elucidate the psychomotor effects of aliskiren in hypertensive patients on chronic treatment.

CONCLUSION

All the three antihypertensive drugs caused significant improvement in a similar fashion on SRT, MCRT calculated as error index, CFFT, and TPT. Aliskiren caused numerically more improvement on SRT, CFFT, and TPT than the other two test drugs, suggesting better cognitive profile. The findings of the present study correlate with the lipophilic nature of aliskiren. The results of the study highlight improvement of the cognitive functions by ramipril, losartan, and aliskiren. Such findings could be of immense clinical utility in ambulatory hypertensive patients especially engaged in sensory-motor coordination tasks like driving and operating on mechanical tools.

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