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RESEARCH ARTICLE

Comparative evaluation of atorvastatin and simvastatin on critical fusion frequency in healthy volunteers

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ABSTRACT

Background: Atorvastatin and simvastatin are the most frequently prescribed among statins to reduce high lipid levels. Statins are reported to alter cognitive functions. However, the results are equivocal as numbers of studies have shown improvement in the cognitive function, while others have documented impairment. **Aims and Objectives:** The present study was undertaken to compare the effects of atorvastatin and simvastatin on critical flicker fusion frequency (CFFF) which is a most sensitive indicator of cortical arousal. Hence, that outcome of the trial provides evidence of the alterations in cognition in unambiguous terms. **Materials and Methods:** A single-dose, open-label, crossover study was conducted in 15 healthy volunteers. They were familiarized on CFFF test apparatus till they attained plateau level in their values. Predrug score was recorded before giving test drug on the trial day. Volunteers were then given oral single dose of either of drug (atorvastatin 10 mg or simvastatin 10 mg) and then crossed over with 10 days washout period between both treatments. In each arm, volunteers were followed up to 6 h for the postdrug score. **Results:** Both atorvastatin and simvastatin decreased the CFFF significantly during the entire study period ($P = 0.0001$) from their respective predrug values. On comparison, both these drugs produced identical CFFF decline ($P > 0.05$). **Conclusion:** Result of current study highlights the impairment of CFFF with both of these drugs in similar manner in healthy volunteers. However, the trials with long-term treatment in patients are advised to clearly define their role in cognitive function.

KEY WORDS: Statins; Atorvastatin; Simvastatin; Critical Fusion Frequency; Psychomotor Performance

INTRODUCTION

Drugs those are prescribed on longer basis need to be evaluated for their cognitive safety as these are mostly given to ambulatory patients attending their day-to-day activities. Statins are one such group which is part of most of the prescriptions in middle age group. Effects of statins on cognitive functions have been examined by a number of research workers. However, the results of these studies are equivocal. There are studies that have shown improvement in cognitive functions[1-3] and some have documented impairment[4-7] while other has failed to record any alterations.[8-10] Atorvastatin and simvastatin are the most frequently used hypolipidemic drugs and are given for longer duration. Reports regarding the modifications in psychomotor performances by atorvastatin and simvastatin are mostly case reports and pertain to memory and learning. Therefore, due to the paucity of data, the present study was conducted in normal healthy individuals to evaluate and compare the effects of atorvastatin and simvastatin on psychomotor functions. In the light of contradictory reports of statin's effect on psychomotor performance tests, it is hoped that results from the present study shall help to clear this ambiguity.

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In the present study, the effect of these two drugs was examined on critical flicker fusion (CFF) which is the one of the most sensitive psychomotor functions test in evaluating cerebral cortical arousal with the objective that outcome of the study would be useful in clinical practice to assess safety of these drugs while handling complex tasks.

MATERIALS AND METHODS

The present crossover study was conducted in the Department of Pharmacology, Government Medical College, Jammu, after prior approval of Institutional Ethics Committee Government Medical College, Jammu, vide No: ICE/2015/126. The volunteers were screened for inclusion and exclusion criteria. Inclusion criteria included normal, nonsmoker, nonalcoholic individuals without any history of intake of any central nervous system affecting drugs. Volunteers with comorbid conditions, anxiety, depression, history of intake of psychotropic drugs, long-term medication, and drugs interfering with psychomotor functions at least 4 weeks before commencing trial were excluded from the study.

15 healthy volunteers with normal biochemical and pathological laboratory values were selected who fulfilled the eligibility criteria. The volunteers were asked to abstain from caffeinated drinks, cola drinks, and chocolates during the trial period. Volunteers were familiarized with the CFF apparatus for several days until their task values reached a stable level to exclude the learning effect. Written informed consent was obtained from volunteers before their inclusion in the study.

The volunteers were both men and women in age group of 25-35 years with weight between 45 and 55 kg. Each volunteer was given either of the two test drugs (atorvastatin 10 mg, simvastatin 10 mg) orally and followed up to 6 h, with a washout period of 10 days between the drug formulations followed by crossover.

A semi-automatic CFF frequency (CFFF) apparatus was used under standardized conditions, and double-blind technique was employed. Volunteers were required to discriminate the flicker fusion in a set of four light emitting diodes. After a fixed period of 1 min accommodation, the frequency either progressively increased or decreased until the volunteer reported change in his flicker perception (from flicker to fusion or vice versa). The volunteers were tested 5 times with increasing and 5 times with decreasing frequency, and mean of these 10 reading was calculated.[11]

Statistical Analysis

Data obtained were expressed in mean ± standard error of mean. Change from baseline scores brought by test drugs was noted and comparison between two groups was also done. The data were analyzed by statistical *t*-test (intragroup by paired and intergroup by unpaired). The $P < 0.05$ was considered significant.

RESULTS

Both statins led to impairment of CFFF. Oral administration of atorvastatin (10 mg) led to decline in CFFF from the baseline score taken before intake of test drug. The baseline value of 31.83 ± 0.147 Hz decreased to 31.33 ± 0.183 Hz at 1 h, 30.85 ± 0.216 Hz at 2 h, 30.30 ± 0.240 Hz at 3 h, 30.16 ± 0.209 Hz at 4 h, 30.52 ± 0.282 Hz at 5 h ($P < 0.0007$), and 30.37 ± 0.264 Hz at 6 h ($P < 0.0003$). Oral simvastatin (10 mg) also caused decrease in CFFF in similar fashion like atorvastatin. The baseline value of 31.96 ± 0.315 Hz decreased to 30.68 ± 0.268 Hz at 1 h, 30.48 ± 0.219 Hz at 2 h, 29.75 ± 0.196 Hz at 3 h, 30.27 ± 0.212 Hz at 4 h, 30.29 ± 0.292 Hz at 5 h, and 30.26 ± 0.257 Hz 6 h ($P < 0.0001$).

On intergroup comparison, both the drugs showed similar magnitude of impairment of CFFF, and there was no statistically significant difference among them ($P > 0.05$), although numerically more impairment was noted with simvastatin. The results are shown in Table 1.

DISCUSSION

Statins were introduced in 1960s and since then, they have been extensively used in various cardiovascular disorders such as hyperlipidemia, angina, ischemic heart disease, atherosclerosis, diabetes mellitus, and hypertension. Although the statins are generally well tolerated, but in recent past, pharmacovigilance data have suggested neuropsychiatric adverse effects associated with statins.

Tuccori et al.[12] in their review has emphasized occurrence of neuropsychiatric reactions associated with statins like behavioral alterations such as severe irritability, homicidal impulses, threats to others, road rage, depression, violence, paranoia, alienation, antisocial behavior, cognitive and memory impairment, sleep disturbances, and sexual dysfunctions.

However, statins effects on cognition are conflicting. Some reports suggest positive effects on cognitive performance[2,13] while other report reveal decline.[5,7] The impairment of psychomotor functions assumes clinical importance because of increase in accidental risks, handling of mechanical implements, and carrying out daily routine work.

Studies on statins associated with cognitive decline are mostly cased reports.[5,7] There is a paucity of research work on elucidation of the effect of commonly used statins-atorvastatin and simvastatin on these functions. Consequently, the aim of the present was to examine and compare the effect

Table 1: Comparative effect of atorvastatin and simvastatin on CFFF

Drug	Baseline	1 h	2 h	3 h	4 h	5 h	6 h
Atorvastatin (*n*=15)	31.83±0.147 *P*<0.001	31.33±0.183 *P*<0.0001	30.85±0.216 *P*<0.001	30.30±0.240 *P*<0.0001	30.16±0.209 *P*<0.0001	30.52±0.282 *P*<0.0007	30.37±0.264 *P*<0.0003
Simvastatin (*n*=15)	31.96±0.315 *P*<0.0001	30.68±0.268 *P*<0.0001	30.48±0219 *P*<0.0001	29.75±0.196 *P*<0.0001	30.27±0.212 *P*<0.0001	30.29±0.292 *P*<0.0001	30.26±0.257 *P*<0.0001
Intergroup *P* value	0.7090	0.601	0.0999	0.0927	0.7218	0.5819	0.7902

CFFF: Critical flicker fusion frequency

of these drugs on psychomotor functions with their common clinically used dose.

Among the psychomotor function tests, CFF is one of the most reliable methods for measuring the effects of drugs on central integrative activity. It is a measure of ability to discriminate between flicker and fusion or vice versa of light. It involves cortical arousal or integration and is a direct measure of central nervous system activity.[14]

In the present study, oral administration of atorvastatin (10 mg) and simvastatin (10 mg) have led to identical impairment of CFFF values. In a case report, a 64-year-old man developed decline in activities of daily living and instrumental activities after intake of 40 mg daily dose of simvastatin. The worsening of cognition improved within 6 weeks of discontinuation of simvastatin.[15]

Suraweera et al.[7] in their two case reports have reported cognitive deficits with simvastatin in two Asian patients, aged 32-year-old male and 54-year-old woman. They found that this cognitive decline reversed after stopping simvastatin. They underlined the possibility of new-onset cognitive decline and deterioration of already existing cognitive deficits should be considered while advising simvastatin.

Since statins primarily decrease cholesterol, therefore, it is likely that decrease in its level may cause alterations in cognitive functions. Correlation between cholesterol levels and cognitive function is not still well understood.[8,16] Reports in some patients on statins reveal improvement in higher functions; memory and learning[1,3] imply that reduction in cholesterol levels may improve cognitive functions.[2,17] While it has also been suggested that the relationship between cholesterol levels and cognitive function depends on homocysteine levels.[18] However, other reports present strong evidence that statins worsen the cognitive functions[4,6] may be due to hypocholesterolemia.[19]

Statins have been shown to be associated with lower risk of dementia and cognitive decline in some observational studies. However, there is no evidence that statin therapy in late-life has a beneficial effect on cognitive function. Lowering cholesterol levels may impair brain function, as cholesterol is vital for synapse formation, maturation, and regulation of signal transduction.[20] However, the present study was done in individuals with normal cholesterol levels.

Review of literature could not cite any comparative study of atorvastatin and simvastatin on CFFF. Outcome of the current trial could be of clinical importance as statins is mostly part of prescriptions in the middle-aged group for a number of cardiovascular indications. These situations demand long-term statin therapy, and it becomes of utmost importance that patients remain independent and stay active.

Lipophilicity is a determining factor to cause alterations in psychomotor functions. Statins those are less lipophilic (pravastatin and rosuvastatin) may be less likely to cause cognitive impairment due to its limited passage across blood-brain barrier. Therefore, they can be a better choice where the cognitive impairment with other statin is suspected.[7]

CONCLUSIONS

The results of present study underscore the potential of atorvastatin and simvastatin to cause impairment of CFFF. Most of earlier reports demonstrated positive effects on memory in hyperlipidemic patients. Therefore, impairment of psychomotor performance tests obtained in a current study in healthy volunteers must be carefully considered before these results are interpolated in actual clinical situation.

The current study suffers from limitations being a single dose study and having less number of volunteers and is not a *placebo* control trial. It is possible that results may be different with chronic usage of these drugs in patients with hyperlipidemia. Moreover, the psychomotor performance evaluation in current trial is based on CFFF only. Whereas detailed psychomotor evaluation may further require battery of tests including sensory-motor coordination tests.

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