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SHORT COMMUNICATION

COMPARATIVE EFFECTS OF CONVENTIONAL B-BLOCKERS AND NEBIVOLOL ON PSYCHOMOTOR PERFORMANCES IN HEALTHY VOLUNTEERS : A PRELIMINARY REPORT

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Abstract : The present study was under taken to assess the comparative effects of nebivolol with propranolol and atenolol on psychomotor performances. Thirty healthy volunteers were randomized into three groups with n=10 in each group. Each subject received single dose of one of the three medications (nebivolol 5 mg, atenolol 50 mg and propranolol 40 mg) in morning (9.00 AM). Just before administering the drug, the pre-drug scores were taken, followed by post drug score obtained for consecutive six hours. Psychomotor assessment was carried out by three tests Simple Reaction Timer (SRT), Critical Flicker Fusion Frequent Threshold (CFFT) and Digit Cancellation Test (DCT). The results of present study indicate that single doses of atenolol and propranolol produced significant impairment of psychomotor performance. Nebivolol also impaired psychomotor performance tests in the similar fashion to atenolol and propranolol. Hence, the findings of the present study correlate with the lipophilic nature of the nebivolol.

Key words : nebivolol atenolol propranolol psychomotor CNS

INTRODUCTION

Nebivolol is a newer highly cardioselective β_1-receptor antagonist, which differs from traditional β-blockers by its peculiar pharmacodynamics profile and kinetics. It is an effective drug for the treatment of hypertension, congestive heart failure and stable angina (1–2). Its tolerability profile is highly favorable compared with the classical beta-blockers, with less fatigue and dyspnea in hypertensive subjects, and with an improvement of functional capacity and exercise tolerance in patients with left ventricular dysfunction. Furthermore, contrary to atenolol and propranolol,

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nebivolol does not diminish specific airway conductance (3). Hence, its use is likely to increase.

In spite of the fact that β–blockers are extensively used for variety of cardiovascular ailments they have significant central effects on cognitive and psychomotor performance irrespective of lipophillic or hydrophilic antagonist of beta receptors (4). Moreover, nebivolol like carvedilol, metoprolol and bucindolol is highly lipophilic compounds (5) and is expected to have central effects and affect psychomotor performances. However, from the available reports nothing conclusively can be said about central actions of the drugs as Mangrella et al (6) in there review suggested few central nervous system (CNS) adverse affects such as dizziness, headache and fatigue, whereas Van Bortel et al (7) showed nebivolol to be devoid of CNS adverse effects.

Since, caridovascular conditions in which nebivolol find therapeutic place need prolonged therapy and the situation may be compounded by the fact that most of these patients are ambulatory. Scan of literature (Pubmed-with key words nebivolol, psychomotor performances) did not reveal any report regarding the effect of nebivolol on psychomotor performance tests. Therefore, the present preliminary study for the first time was under taken to assess the effect of nebivolol on psychomotor performances and compare them with conventional â-blockers like propranolol and atenolol.

METHODS

Thirty healthy volunteers (age 28–35 yrs, wt 55–65 kg and M: F 16:14) were enrolled for the study after obtaining informed consent and Institutional Review Board (IRB) clearance. The volunteers were in normal physical health with no history of cardiovascular, renal, hepatic or psychiatric ailment. All subjects had normal biochemical and laboratory values (Hb, TLC, DLC, LFT, RFT, lipid profile and blood sugar). The volunteers were non smoker and non alcoholic and had no history of any β-blocker use or psychopharmacologic treatment two weeks prior to study and were advised to abstain from caffeinated drugs, cola drinks and chocolates during study trial.

Prior to the entry in study volunteers were familiarized with test procedure for a week to obtain stable values. The study subjects were randomized into three groups according to a block permuted randomization plan, with 10 healthy volunteers in each group. Each subject received single dose of one of the three medications (nebivolol 5 mg, atenolol 50 mg and propranolol 40 mg) in morning (9.00 AM). Just before administering the drug, the pre-drug scores were taken, followed by post drug score obtained for consecutive six hours.

Psychomotor assessment

1. Simple Reaction Timer (SRT) : Visual reaction time was determined by measuring the latency between presenting a visual stimulus and the response (pressing a key). The mean of five measurements to each stimulus were recorded in two sessions and the results of the sessions averaged. Increase in SRT indicates impairment of execution of even simple mechanical tasks (8).

2. *Critical Flicker Fusion Frequent Threshold (CFFT)* : Subjects were required to discriminate flicker fusion in a set of 4 light emitting diodes placed at foveal distance of 1m. Individual thresholds in Hz were determined on five ascending and five descending frequencies as per the method described by Hindmarch (9). Decrease in CFFT indicates impairment of senseriomotor integration process in CNS

3. Digit Cancellation Test (DCT) : In a matrix of 400 arithmetic digits a particular digit was distributed randomly 40 times and the subject was required to cancel the digit as fast as he could. The number of digits cancelled per minute was recorded (10). Decrease in DCT indicates impairment of perceptual processing of the central sensory information with regards to current information and matching with previous stored information.

Statistical evaluation

The data was expressed in Mean ± SEM. The changes from the baseline score by medication or drug was analyzed by paired t-test, whereas inter drug comparison was carried out by one-way analysis of variance ANOVA (P-value<0.05 has been taken as significant).

RESULTS

The data obtained with propranolol, atenolol and nebivolol in different psychomotor tests have been summarized in Table I to III. All the three drugs (propranolol, atenolol and nebivolol) caused significant increase with P<0.001 at 1, 2, 3 hr and P<0.01 at 4 hr by propranolol and nebivolol and with P<0.01 at 1, 2 & 3 hr by atenolol in SRT when compared with there respective baseline values. The effect started at 1 hour and lasted up to 4 hours except in atenolol where it lasted up to 3 hours after intake of drugs (Table I). When these drugs were compared among each other, no significant difference as suggested by non-significant ANOVA was observed, though propranolol caused more numerical increase in SRT than atenolol and nebivolol.

TABLE I: Comparative effect of Propanalol, Atenolol and Nebivolol on SRT.

n=10 (mg, P.O, Single dose)	*SRT (msec) Mean ± SEM*						
	0 hr	*1 hr*	*2 hr*	*3 hr*	*4 hr*	*5 hr*	*6 hr*
Propranolol (40)	0.582 ± 0.027	0.674*** ± 0.026	0.657*** ± 0.030	0.635*** ± 0.026	0.611** ± 0.022	0.598 ± 0.022	0.574 ± 0.027
Atenolol (50)	0.586 ± 0.027	0.619** ± 0.022	0.624** ± 0.027	0.620** ± 0.029	0.604 ± 0.026	0.592 ± 0.026	0.584 ± 0.027
Nebivolol (5)	0.589 ± 0.027	0.653*** ± 0.027	0.641*** ± 0.021	0.633*** ± 0.025	0.622** ± 0.026	0.594 ± 0.029	0.589 ± 0.028
One way ANOVA		F=3.354 df=2, 27 p=NS 0.327	F=3.354 df=2, 27 p=NS 0.68	F=3.354 df=2, 27 p=NS 0.913	F=354 df=2, 27 p=NS 0.87	F=3.54 df=2, 27 p=NS 0.98	F=3.35 df=2, 27 p=NS 0.928

*P<0.05; **P<0.01; ***P<0.001 in comparison to respective baselines.

Critical Flicker Fusion Frequent Threshold (CFFT) was found to be significantly decreased with varied levels of significance with the entire three drugs studied as shown in Table-II. The decrease with nebivolol lasted up to 5 hours whereas with propranolol and atenolol, the effect lasted up to 4 hours. Peak decrease in CFFT was observed at 2 hours with propranolol whereas; with both atenolol and nebivolol peak effect was observed at 3 hours (Table II). No significant difference was observed amongst these drugs when they were compared with each other as suggested by non-significant ANOVA.

On DCT, less number of digits were cancelled after intake of nebivolol and atenolol. (P<0.01 to 0.001) as shown in Table-III. Significant affect with atenolol lasted

TABLE II: Comparative Effect of Propanalol, Atenolol and Nebivolol on CFFT.

n=10 (mg, P.O, Single dose)	*CFFT(in hertz) Mean ± SEM*						
	0 hr	*1 hr*	*2 hr*	*3 hr*	*4 hr*	*5 hr*	*6 hr*
Propranolol (40)	35.5298 ± 0.96	34.354*** ± 0.86	33.894*** ± 0.88	34.473** ± 0.90	34.828* ± 0.96	35.111 ± 0.97	35.291 ± 01.02
Atenolol (50)	35.51 ± 0.98	34.5*** ± 0.88	34.01*** ± 1.02	33.74*** ± 0.98	34.3** ± 0.91	33.38 ± 0.91	35.33 ± 1.10
Nebivolol (5)	35.492 ± 0.97	34.963** ± 0.91	34.557** ± 0.93	34.369** ± 0.93	34.797** ± 0.96	35.095* ± 0.96	35.44 ± 1.008
One way ANOVA	F=0.54 df=2, 27 p=NS 0.94	F=1.3 df=2, 27 p=NS 0.97	F=0.17 df=2, 27 p=NS 0.84	F=0.111 df=2, 27 p=NS 0.89	F=0.02 df=2, 27 p=NS 0.97	F=0.005 df=2,27 p=NS 0.99	

*P<0.05; **P<0.01; ***P<0.001 in comparison to respective baselines.

TABLE III: Comparative effect of Propranolol, Atenolol and Nebivolol on DCT.

n=10 *(mg, P.O, Single dose)*	*DCT (Digits cancelled per minute) Mean ± SEM*						
	0 hr	*1 hr*	*2 hr*	*3 hr*	*4 hr*	*5 hr*	*6 hr*
Propranolol (40 mg)	47.6 ± 0.702	47.1 ± 0.674	46.9 ± 0.706	47.4 ± 0.635	47.5 ± 0.670	47.5 ± 0.670	47.7 ± 0.650
Atenolol (50 mg)	47.9 ± 0.690	46.8*** ± 0.696	47.2*** ± 0.711	47.8 ± 0.663	48 ± 0.714	47.9 ± 0.690	47.8 ± 0.755
Nebivolol (5 mg)	48 ± 0.649	46.4*** ± 0.541	47.5 ± 0.521	47.9 ± 0.622	48 ± 0.649	48 ± 0.649	48 ± 0.649
One way ANOVA		F=0.300 df=2, 27 p=NS 0.74	F=0.211 df=2, 27 p=NS 0.81	F=0.170 df=2, 27 p=NS 0.84	F=0.180 df=2, 27 p=NS 0.83	F=0.155 df=2, 27 p=NS 0.85	F=0.04 df=2, 27 p=NS 0.95

*P<0.05; **P<0.01; ***P<0.001 in comparison to respective baselines.

upto 2 hours, while with nebivolol effect was observed at 1 hour. While propranolol did not significantly modify DCT however, the numerical decrease was observed. All the three drugs did not differ from each other when they were compared with each other as evident from non-significant ANOVA (Table III).

DISCUSSION

In the present study the effects of nebivolol have been compared with atenolol and propranolol on psychomotor performance tests to assess any CNS alteration. We chose propranolol, lipophillic in nature and atenolol a selective hydrophillic â-blocker both known to alter psychomotor performance tests. A comprehensive battery of tests was employed to elucidate such potential. SRT is an excellent example of tasks which comprises of sensory and motor components. The CFFT is a measure of ability to discriminate between flicker and fusion and vice-versa of light and involves central mechanism involving cortical arousal or integration and is more direct measure of CNS activity. While DCT is a measure of perceptional processing of central sensory information with regards to current information and matching with previous stored information (11).

Atenolol and propranolol have been reported to cause appreciable impairment of psychomotor performance test like SRT, CFFT, and DCT (12–15). In the present study atenolol and propranolol affected the psychomotor performance tests in concurrence with above authors Betts et al (12), McDevitt(13), Salem & McDevitt (14) and our own previous report (15). McDevitt (13) in accordance to our study, suggested that with single doses of atenolol, a cardioselective hydrophilic beta-blocker and lipophilic non-selective beta-blocker propranolol, produce significant impairment of psychomotor tests. The results of present study further support the findings of Currie et al (4) that β-blockers both lipophillic and hydrophillic can modify the CNS function.

The main result of present study indicate that nebivolol a newer highly cardioselective β_1-receptor antagonist impairs psychomotor performance tests in the similar fashion to atenolol and propranolol suggesting nebivolol to have central effects. These findings are in agreement with Mangrella et al (6) who suggested few CNS adverse affects such as dizziness, headache and fatigue with nebivlol, whereas the findings are contradictory to findings of Van Bortel et al (7) who showed nebivolol to be devoid of CNS adverse effects. Findings of the present study can also be correlated with the lipophilic nature of the nebivolol (5). 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, short study done in healthy individuals, & lacks placebo control. Hence, additional adequately powered studies are needed to elucidate the psychomotor effects of nebivolol in hypertensive patients on chronic treatment.

Conclusion

Nebivolol, a newer highly cardioselective β_1-receptor antagonist also impairs psychomotor performance tests in the similar

fashion to atenolol and propranolol in healthy volunteers. Hence, the findings of the present study correlate with the lipophilic nature of the nebivolol.

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