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Evaluation of cilazapril in vasovagal syncope treatment

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Abstract: Objective: to evaluate cilazapril in vasovagal syncope treatment. Method: eighty-six cases of VVS patients found positive in TTT tilt were medicated with 2.5 mg cilazapril daily for three months and followed up by TTT. Results: seven cases quit due to cough or unexplained reason; 79 VVS patients had no more fainting spells; 75.95% of TTT results of patients changed to negative after 3 months therapy. The before and after cilazapril treatment average blood pressures (taken in lying position) were 121/73 mm Hg (1 mm Hg=0.133kPa) and 120/76 mm Hg respectively ($P>0.05$); and mean heart rates were 68.63±12.37/min and 70.13±13.15/min respectively with no significant changes ($P>0.05$). Conclusion: Cilazapril was effective in treatment of VVS; did not affect normal blood pressure and heart rate; was safe; and had little side effect.

Key words: Vasovagal syncope(VVS), Cilazapril, Blood pressure & heart rate, Tilt table test
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INTRODUCTION

Vasovagal syncope (VVS) is a common frequently occurring clinical problem, which does not seriously affect work and life. β-blockers, cheophylline, and scopolamine have been used and shown to have curative effect (Guan et al., 1999; Roul et al., 1997). While the pathophysiology of vasovagal syncope remains imcompletely understood, appropriate treatment remains uncertain. Enapril was reported to be excellent for treating VVS(Zeng et al., 1998). Medical experience showed that cilazapril (angiotensin converting enzyme inhibitors) often used to decrease blood pressure could also be used just like enapril to treat VVS.

PATIENTS AND METHODS

Patients

All patients who were admitted via clinic and medical ward had experienced syncope from 1 to 42 years and had severe fainted 3 times weekly. Each patient with a history of recurrent syncope underwent thorough clinical investigation including clinical history, physical examination, electrocardiogram, echocardiogram, 24-hour Holter ambulatory monitoring and electroencephalogram, to exclude cardiac or neural origin diseases. In this study, 86 patients (32 males and 54 females, aged 15 to 67 years, mean age 39.18 years) who had unexplained syncope and positive tilt table test (TTT) results were diagnosed as VVS. Of these 86 patients, 5 had hypertension (3 were diagnosed recently, 2 had taken nifedipine or felodipine irregularly for 3 years); 2 had carotid atherosclerosis; 2 had intermittent second-degree atrioventricular block. In these cases, 13 patients had slower than 60 beats/min heart rate; 5 patients' baseline blood pressure was lower than 100/60 mm Hg.

Methods

1. Three months after 2.5 mg cilazapril (inhibace) was given daily to each patient, they were given TTT again. Before TTT, all patients were told to stop taking antiarrhythmia drugs, vasoactivity drugs and drugs which affect the autonomic nervous system for at least 5 half life.

2. TTT procedure(Han et al., 2001; Ge et al., 2000)

1) Basic TTT: TTT was performed fol-

lowing a 6-hour fast. The patients remained in a supine position for 15 minutes, and intravenous cannula was inserted. Heart rate and ECG were monitored continuously and recorded on magnetic tape. Blood pressure was recorded every five minutes. The test was conducted in a commodious room with temperature of 25 − 30 centigrade and low lighting. The patients were belted on torso and thigh to prevent tumbling and then tilted to 70 degrees angle within 10 seconds. The end points of the test were: (1) Positive reaction: including occurrence of syncope or presyncope with heart rate slower than 50 beats/min, and/or blood pressure lower than 80/50 mm Hg; (2) The patients had severe discomfort and could not intolerate the test; (3) The basic test had been taken for 45 minutes and multistage isoproterenol TTT had been taken for 30 minutes; (4) The heart rate exceeded 140 beats/min for over ten minutes during multistage isoproterenol TTT, or frequent ventricular premature beat resulted in paroxysmal ventricular tachycardia. Syncope is defined as a transient loss of consciousness and inability to maintain postural tone. Presyncope is defined as paleness, sweat, dyspnea, hyperventilation, then followed by amaurosis, hypoacusis, unresponsive, unsteadiness, etc.

2) Multistage isoproterenol TTT: Preparations and monitoring indices were the same as those in the basic tilt test. The test proceeded in three grades, every grade tilted for 10 minutes. If the patients remained asymptomatic and were negative during a former grade, isoproterenol concentration was then increased successively by 1 μg/min, 3 μg/min, 5 μg/min (Ren et al., 1998).

3) Data Management using FoxBASE. Chi-squared analysis and t-test were used to analyze the differences of blood pressure and heart rate before and after the therapy. For all analyses $P<0.05$ was taken as statistically significant.

RESULTS

1. Of the 86 patients, 7 patients (4 males, 3 females) were excluded from the study group: 2 changed to taking benazepril as cilazapril was out of stock, 2 discontinued therapies because of cough; we lost contact with 3, so their cases could not be followed up. Among the 79 out of 86 control patients, 38 (48.1%) showed vasodepressor response, 17 (21.52%) showed cardioinhibitory response and 24 (30.38%) showed mixed response. None of the control patients had recurrent syncope while receiving therapy. After 3 months of cilazapril treatment, we reevaluated the patients' response to TTT showing that 62 of the initial 79 patients (75.95%) had negative test results. The remaining 17 again experienced syncope, lasting around 10 minutes in average or the dose of isoproterenol to syncope was increased 2μg/min over that of the first TTT. Among the 17 positive TTT patients, 8 (47.06%) showed a vasodepressor response, 4 (23.53%) a cadioinhibitory response and 5 (29.41%) mixed response.

2. Twenty-three of 28 males had a negative second test, while 39 of 51 females had a negative second test. The results were assessed with Chi-squared analysis, showing that there was no significant difference between the male and female subgroups ($P>0.05$). This suggests that sex has no effect on cilazapril therapy. Chi-squared analysis of the effect of age rank (<40, 40 − 59, >59) on therapy showed there was also no significant difference ($P>0.05$).

3. The before and after therapy mean arterial pressure of 79 patients were 121/73 mm Hg and 120/76 mm Hg respectively. The difference of blood pressure failed to reach statistical significance (t-test, $P>0.05$). There was also no differences between heart rate before and after therapy (68.63 ± 12.37 beats/min vs. 70.13 ± 13.15 beats/min, $P>0.05$). But in the case of 13 patients with bradycardia (heart rate was lower than 60 beats/min in supine position), cilazapril caused a significant increase in heart rate (55.23 ± 3.14 beats/min to 64.18 ± 7.56 beats/min, $P<0.001$); all of whom had a negative second test.

4. Five patients had baseline blood pressure lower than 100/60 mm Hg in supine position before TTT (when systolic BP was

96.24 ± 3.07 mm Hg and diastolic BP 55.16 ± 3.94 mm Hg), with 3 of them often complaining of dizziness. After initiation of cilazapril treatment, their repeatedly measured blood pressure did not significantly change. Three months later, during the repeat TTT, their blood pressure in supine position or tilted position did not change significantly (systolic BP was 98.52 ± 6.72 mm Hg and diastolic BP 63.31 ± 5.22 mm Hg), but the diastolic pressure of 4 patients increased and one patient's dizziness was alleviated. In addition, the second-degree atrioventricular block of 2 patients did not change in degree after therapy.

DISCUSSION

VVS is a common syncope type clinically. Although the pathophysiologic characteristics are still unclear, it is believed that the patient is hypersensitive to the decreased ventricular preload in upright position, which causes an exaggerated catecholamine response, resulting in the hypercontractile state of the ventricle. The hypercontractile state stimulates C-fibers located primarily in the inferoposterior wall of the left ventricle. Then the transfer of the nerval impulse (it is similar to sympathetic signal of blood pressure elevation) to the vagus center causes excessive stimulation of the vagus nerves to counteract sympathetic nerves. The outcome is inappropriate peripheral vasodilation and heart inhibition, resulting in cerebral ischemia and syncope. (Kochiadakis et al., 1997; Lippman et al., 1994). It is thought that the mechanism of cilazapril treatment of VVS is through the decrease in the concentration of angiotensin II in the cardiac tissue, which stops the excessive stimulation of the mechanoreceptor in the ventricle. In addition, whether cilazapril has a direct effect on cerebral autonomic outflow needs further investigation.

We studied the results of cilazapril therapy in 86 cases of VVS patients shown positive in TTT for 3 months. No patients had recurrent syncope while receiving therapy. Some (75.95%) patients had a negative second test 3 months later. Adverse effects: 2 cases quit the study due to cough; no other adverse effects were found. Although cilazapril is an antihypertension drug, blood pressure did not change significantly before and after therapy in our study. This may suggest that cilazapril has no prominent effect on normal or low blood pressure, and even has modulatory effect. On the other hand, our study showed that the heart rate of bradycardia patients increased dramatically during cilazapril treatment. This point needs further studies. In conclusion, cilazapril has the same effect as β-blockers in treating VVS, and it is not restricted by low heart rate (Guan et al., 1999). When cilazapril is used on low blood pressure patients, their blood pressure should be monitored closely.

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