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EFFECT OF TOFISOPAM ON HEART RATE VARIABILITY

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ABSTRACT

We evaluated the effects of tofisopam, a drug that modulates autonomic nerve function, on heart rate variability in 27 patients (12 men and 15 women; mean age, 71 ± 12 years) with a standard deviation of the R-R interval measured at 5-minute intervals (SDANN) of ≤80 msec on 24-hour electrocardiograms (ECGs). After a control 24-hour ECG was recorded, patients were treated with tofisopam at a dosage of 150 mg/day. After 2 weeks of treatment, 24-hour ECGs were recorded again. The total cardiac rate and the number of ventricular extrasystoles on 24-hour ECGs did not differ between the control and treatment periods. The SDANN was ≤80 msec (mean, 62.4 ± 14.7 msec) in all patients during the control period but increased significantly after tofisopam administration (84.8 ± 27.4 msec; $P < 0.0001$). Thus tofisopam improved heart rate variability. This drug may be useful for maintaining normal autonomic nerve activities under stressful conditions, treating autonomic nerve diseases, and preventing sudden cardiac death.

INTRODUCTION

Tofisopam is a 2,3-benzodiazepine derivative that improves functional impairment and organic damage of the autonomic nerve system caused by stimuli such as stress. Its action is central and partly peripheral. Unlike autonomic ganglionic blockers, tofisopam modulates autonomic nerve function by inhibiting its excessive excitation. We have previously reported on the effectiveness of tofisopam for improving sinus cycle variability in patients with cardiac neurosis.[1]

Recent technologic advances in medical engineering permit the accurate measurement of the R-R interval using 24-hour electrocardiography (ECG). As a result, accurate evaluation of the variation in the sinus cycle during a 24-hour period has become possible. Spectral analysis and nonspectral analysis of heart rate variability have been performed in the

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clinical setting.[2–5] In this study, we evaluated the effects of tofisopam on heart rate variability using nonspectral analysis.

PATIENTS AND METHODS

Twenty-seven patients (12 men and 15 women; mean age, 71 ± 12 years) in whom the standard deviation of the R-R interval measured at 5-minute intervals (SDANN) was ≤80 msec, suggesting autonomic imbalance, were enrolled in the study. A total of 16 patients had underlying ischemic heart disease, 3 patients had hypertension, 2 patients each had diabetes mellitus or chronic obstructive lung disease, and 1 patient each had rheumatoid arthritis, laryngeal cancer, Hashimoto disease, and liver cirrhosis. All patients provided informed consent before tofisopam administration.

After a control 24-hour ECG was recorded using a Marquette 8500 recorder, patients were treated with tofisopam* at a dosage of 150 mg/day. After 2 weeks of treatment, a 24-hour ECG was recorded again. The results were analyzed using a Marquette 8000/T, and heart rate variability was simultaneously analyzed. Student's paired t test was used for statistical evaluation. P values of <0.05 were considered significant.

RESULTS

The R-R interval on 24-hour ECGs did not differ significantly between the control period and 2 weeks after tofisopam administration (799 ± 132 msec versus 847 ± 142 msec) (Figure 1). The SDANN was ≤80 msec (mean, 62.4 ± 14.7 msec) during the control period in all patients but significantly increased after tofisopam administration (84.8 ± 27.4 msec; $P < 0.0001$) (Figure 1). The SDRR, which shows the standard deviation of the R-R interval during a 24-hour period, also significantly increased after tofisopam administration (97.9 ± 25.3 msec; $P < 0.0001$) compared with the control period (78.1 ± 23.0 msec). However, no significant differences were observed in the mean value of the standard deviation of the R-R interval for 5 minutes (SD) (39.0 ± 25.4 versus 38.2 ± 14.3 msec), the proportion of adjacent R-Rs more than 50 msec different (pNN50) (7.4 ± 12.2 versus 6.9 ± 8.4%), or the root-mean-square of difference of successive R-Rs (rMSSD) (39.3 ± 42.5 versus 35.3 ± 24.0 msec) before and after drug administration.

The number of ventricular extrasystoles did not differ significantly between the control period and 2 weeks after tofisopam administration (364 ± 829 beats/day versus 544 ± 2010 beats/day). It decreased in 9 of the 27 patients, was unchanged in 13, and increased in 5. The severity of

* Trademark: Grandaxin® (Mochida Pharmaceutical Co., LTD, Tokyo, Japan).

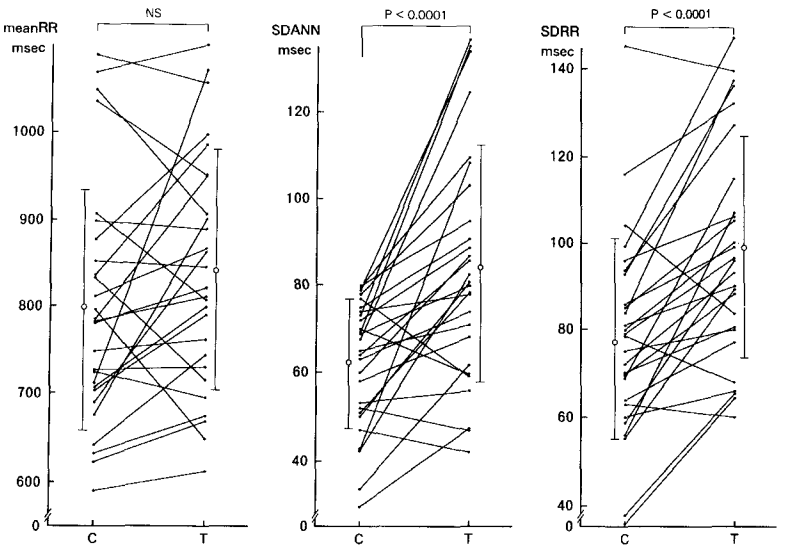

Figure 1. Mean R-R interval during a 24-hour period, the standard deviation of the R-R interval measured at 5-minute intervals (SDANN), and the standard deviation of the R-R interval during a 24-hour period (SDRR) before (C) and after (T) tofisopam administration.

ventricular extrasystoles according to Lown's classification improved in 8 patients, worsened in 4, and was unchanged in 15.

No side effects attributable to tofisopam were observed.

DISCUSSION

Heart rate variability can be used as an index of the effects of the autonomic nerve system on the heart rhythm. Heart rate variability is low in patients at risk for sudden death. Enhanced sympathetic nerve activity promotes the induction of ventricular fibrillation, while vagus nerve activity protects against it.[2–5] Automatic analysis of heart rate variability using 24-hour ECGs has recently become possible. Heart rate variability can be expressed in terms of statistical values (nonspectral analysis), as in this study, or in terms of a graph of the power spectrum, which represents changes in the R-R interval at frequencies of 0 to 1 Hz (spectral analysis). Nonspectral analysis is readily performed in general practice because the calculation method is not complicated, and evaluation is possible in terms of values alone.

Among the parameters of nonspectral analysis, SDANN, which is the standard deviation of the R-R interval on 288 measurements at 5-minute intervals during a 24-hour period, is easy to understand. Kleiger et al[5] have shown that the mortality rate is four times higher in patients with an

SDRR ≤50 msec compared with healthy controls (Figure 2). The SDANN is also known to be low in diseases, such as diabetes mellitus, associated with impairment of autonomic nerve function.[6] We have previously evaluated the effects of caffeine intake and 24-hour work periods without sleep on heart rate variability.[7,8] Caffeine had no effect on SDANN or ventricular extrasystoles in young adults but aggravated these indices in obese middle-aged subjects. Twenty-four–hour work schedules without sleep increased blood catecholamine levels and decreased SDANN. These results suggest that heart rate variability is a useful index in health management.

The SDANN is useful not only for predicting sudden cardiac death but also for evaluating autonomic nerve function. When the SDANN is low, patients should try to avoid stress.

Tofisopam is a 2,3-benzodiazepine derivative synthesized in Hungary. Unlike 1,4-benzodiazepine derivatives such as diazepam, which have N at positions 1 and 4, tofisopam is characterized by modulation of autonomic nerve function rather than action as a minor tranquilizer. We have previously reported on the effectiveness of tofisopam in cardiac neurosis.[1] In the present study, tofisopam significantly improved the SDANN in 27 patients. Thus this drug may be useful for maintaining normal autonomic nerve activity and preventing autonomic nerve diseases or sudden cardiac death, which can result from living in a stressful society.

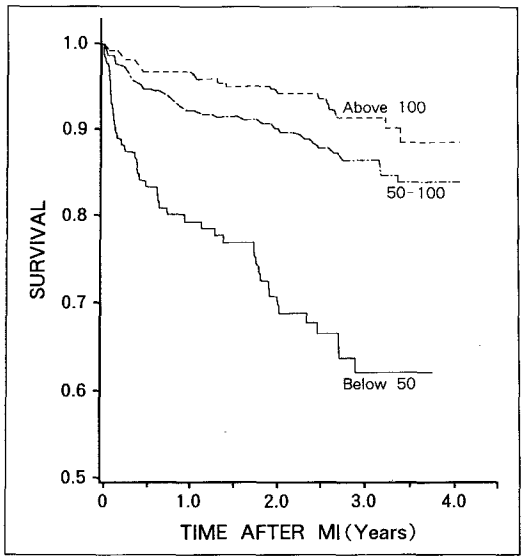

Figure 2. Mortality rate over time after the onset of myocardial infarction (MI) in patients in whom the standard deviation of the R-R interval was 100 msec or more, 50 to 100 msec, or 50 msec or less. Reprinted, with permission, from Kleiger et al.[5]

References:

1. Nakanishi T, Nishimura M, Kubota S, Hirabayashi M. The influence of the autonomic nervous system on cardiac sinus rhythm. *Curr Ther Res* 1990; 48:853–865.
2. Singer DH, Martin GJ, Magid N, et al. Low heart rate variability and sudden cardiac death. *J Electrocardiol* 1988; Suppl:S46-S55.
3. Lombardi F, Sandrome G, Pernpruner S, et al. Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. *Am J Cardiol* 1987; 60: 1239–1245.
4. Martin GW, Magid NM, Meyers G, et al. Heart rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. *Am J Cardiol* 1987; 60:86–89.
5. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; 59:256–262.
6. Lshner M, Akselrod S, Mor Avi V, et al. Spectral analysis of heart rate fluctuations. A non-invasive sensitive method for the early diagnosis of autonomic neuropathy in diabetes mellitus. *J Autonom Nerv Syst* 1987; 19:119–125.
7. Nakanishi T, Nishimura M, Takahashi H, et al. Effects of caffeine on heart rate variability and arrhythmia. Proceedings of the 12th Congress of the Japanese Society of Obesity, November 30, 1991, Yokohama, Japan. 1992:380–381.
8. Nakanishi T, Nishimura M, Takahashi H, et al. Effects of overwork on the cardiovascular system in healthy adults. (Abstract) *Electrocardiology* 1992; 12:561.