Prolonged QT interval in non-insulin dependent diabetes mellitus patients treated with glibenclamide

Tadasu IKEDA

The Department of Nursing, Tottori University, College of Medical Care Technology, Nishi-machi 133-2, Yonago 683

Diabetic subjects with clinical features of autonomic neuropathy may die suddenly and unexpectedly[1]. In diabetes mellitus with autonomic neuropathy, QT interval prolongation in electrocardiogram has been reported by authors in a few groups[2,3]. The QT interval prolongation in electrocardiogram is associated with a lowered ventricular fibrillation threshold and with an occurrence of ventricular arrhythmias[4]. Thus, the QT interval prolongation has been expressive of predicting cardiovascular mortality in apparently healthy population[5]. Ewing et al.[6] have reported a significant association between the QT interval prolongation and the risk of dying unexpectedly in diabetes mellitus with autonomic neuropathy. Glibenclamide, one of sulfonylurea drugs widely used for the treatment of non-insulin dependent diabetes millitus (NIDDM), is well known to be a specific blocker of K^+_{ATP} channels, and potentially has antiarrhythmic properties[7,8]. These suggest that glibenclamide influence the QT interval independently of diabetic neuropathy. In the present study, QT interval in NIDDM subjects treated with glibenclamide was compared with that in the subjects treated with insulin or diet alone.

Subjects and methods

Subjects

Sixty NIDDM patients (30 men and 30 women, aged 50-70 yrs) were enrolled in the present study, in whom the mode of therapy (insulin, glibenclamide, or diet alone) had not been changed for recent two years. Their diabetic condition was stable. They had not been treated with digitalis, β-blockers or antiarrhythmic drugs that will influence QT interval. They had no hypertension and no abnormal findings in electrocardiogram (fresh or old myocardial infarction, right or left ventricular hypertrophy, arrhythmias or significant ST-T changes). Twenty (10 men and 10 women) had been treated with insulin, twenty (10 men and 10 women) with glibenclamide (1.25-5.0 mg/day), and twenty (10 men and 10 women) with diet alone. Clinical features of these patients were shown in Table 1.

Measurements of QT interval

All subjects were registered a standard 12-lead electrocardiogram two times in a different day, and the longest QT interval in leads I , II or III was measured from the beginning of the first deflection of the QRS complex to the end of the T top,

where it merges with the electric baseline. Adjustment for heart rate was made according to Bazett's formula; $QTc = QT/\sqrt{RR}$[9]. The mean of the two QTc intervals was calculated. If the intervals measured fluctuated more than 10 msec, the standard electrocardiogram was taken one more time in another day to accept the mean interval calculated from the nearest interval out of three trials. In the same electrocardiogram, coefficient of variation of R-R interval (CV_{R-R}) in resting was also calculated.

Statistical analyses

The data were expressed as the mean ± SD. Analyses of variance and two-tailed Student's nonpaired *t* test were used for statistical evaluation.

Results

Clinical features

The age and the duration of diabetes were not significantly different from each other among three groups, as shown in Table 1. The number of subjects with diabetic peripheral neuropathy and retinopathy was greater in NIDDM subjects treated with insulin or glibenclamide than that in the subjects treated with diet alone; and that with nephropathy was greater in NIDDM subjects treated with insulin than that in the subjects treated with glibenclamide or diet alone. Glycosylated

Table 1 Clinical features of NIDDM subjects

	treatment		
	insulin (n=20)	diet (n=20)	glibenclamide (n=20)
age(yr)	59.8±5.9	63.6±5.4	62.6±5.3
duration of diabetes(yr)	16.9±7.6	13.2±7.3	13.5±7.2
peripheral neuropathy	18/20	12/20	16/20
retinopathy	15/20	5/20	12/20
nephropathy	7/20	3/20	4/20
HbA_1c(%)	8.5±2.0*	7.3±1.0	7.7±0.8
CV_{R-R}(%)	1.78±0.80*	2.68±1.22	2.22±0.80
QTc(msec)	407.9±15.5	399.8±16.4	411.2±15.0*

The values are means ± SD.
peripheral neuropathy : loss of deep tendon reflex.
retinopathy : background or proliferative retinopathy.
nephropathy : urine albumine above 300 mg/day.
* $p < 0.05$, significantly different from diet alone.

hemoglobin concentration (HbA_1c) in NIDDM subjects treated with insulin (8.5±2.0%) was significantly higher than that in the subjects treated with diet alone (7.3±1.0%). CV_{R-R} in NIDDM subjects treated with insulin (1.78±0.80%) was significantly lower than that in the subjects treated with diet alone (2.68±1.22%).

QTc interval

QTc interval in NIDDM subjects treated with glibenclamide (411.2±15.0 msec) was significantly longer than that in the subjects treated with diet alone (399.8±16.4 msec). The number of subjects with moderate QTc prolongation (420<QTc≦440 msec) was 8 in the insulin treated group, 2 in the diet, and 7 in the glibenclamide-treated; and the number of subject with extensive QTc prolongation (>440 msec) was 1 only in the glibenclamide treated group (omitted in Table 1).

Discussion

The present study clearly demonstrated that QTc interval in NIDDM subjects treated with glibenclamide was significantly longer than that in the subjects treated with diet alone. Slightly prolonged QTc interval in NIDDM subjects treated with insulin may be due to the diabetic autonomic neuropathy, because CV_{R-R}, which is known to decrease coincidentally with the severity of diabetic autonomic neuropathy, was significantly lower in NIDDM subjects treated with insulin than that in NIDDM subjects treated with diet alone. However, CV_{R-R} in NIDDM subjects treated with glibenclamide was not significantly different from that in the subjects treated with diet alone, suggesting that the significant prolongation of the QTc interval in NIDDM subjects treated with glibenclamide was not resulted from diabetic autonomic neuropathy.

The results of previous studies[7,8] that glibenclamide has an antiarrhythmic effect are contradictory to our present results that glibenclamide caused the prolongation of the QTc interval that may be associated with an occurrence of ventricular arrhythmias[6]. Although the QTc interval is well known to be influenced by electrolyte abnormalities, the present subjects did not have any electrolyte abnormalities in routine laboratory examinations.

As the present study was the cross-sectional study, the changes of QTc interval before and after the treatment with glibenclamide in the same patient remain to be elucidated. In the previous UGDP study[10], tolbutamide, one of sulfonylurea drugs, has been reported to increase the incidence of ischemic heart disease in adult diabetic subjects, suggesting that sulfonylurea drugs have a cardiotoxic effect. Although the mechanism by which glibenclamide lengthens the QTc interval remains to be elucidated, careful observation should be necessary to evaluate whether or not the QT prolongation in NIDDM patients treated with glibenclamide has a clinical significance.

Summary

To evaluate the possible role of glibenclamide, one of hypoglycemic sulfonylurea agents and a specific blocker of K^+_{ATP} channels, in QTc interval in diabetes mellitus, QTc interval in a standard 12-lead electrocardiogram was compared in 60 NIDDM patients treated either with insulin, glibenclamide or diet alone. The QTc interval in the group treated with glibenclamide was 411.2 ± 15.0 msec (means±SD), and was significantly longer ($p < 0.05$) than that, 399.8 ± 16.4 msec, in the group treated with diet alone. CV_{R-R} in the group treated with glibenclamide, however, was not significantly different from that in the group treated with diet alone. These results indicate that glibenclamide lengthens the QTc interval in NIDDM subjects independently of autonomic neuropathy.

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