# Effect of sulfonylureas on the changes in QTc interval in non-insulin dependent diabetes mellitus

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The diabetic subjects with prolonged QT interval in electrocardiogram associated with autonomic neuropathy may die suddenly and unexpectedly[1~3]. Thus, the QT interval prolongation has been suggested to predict cardiovascular mortality not only in healthy population but also in diabetes mellitus with autonomic neuropathy[4,5]. In a previous study[6], we reported that the QTc interval in diabetic subjects treated with glibenclamide, one of hypoglycemic sulfonylurea drugs, was significantly longer than that treated with diet alone independently of diabetic autonomic neuropathy, and that glibenclamide treatment has been suggested to prolong the QT interval. Because of being simple and crosssectional, the previous study has remained equivocal results. Therefore, we made sure by the investigation of the QTc-interval change during two years if it is true or not that the prolongation in diabetic subjects occurs by glibenclamide.

## Materials and methods

*Subjects*

Ninety-one subjects (aged 50-70 yr) with non-insulin dependent diabetes mellitus were enrolled for the study, in whom the mode of therapy (for insulin, sulfonylureas, or diet) had not been changed over the last two years. Their diabetic condition was stable, and they were treated neither with diuretics, digitalis, $\beta$-blockers, nor antiarrhythmic drugs that could potentially interfere with the QT interval. They had no hypertension or abnormal findings on the electrocardiogram monitoring [recent or past myocardial infarction, right or left ventricular hypertrophy (RV4>45 min), arrhythmias, or ST-T changes]. Thirty-one subjects had been treated with insulin, 34 with sulfonylureas (20 with glibenclamide and 14 with gliclazide), and 26 with diet alone. Clinical features of the subjects were shown in Table 1.

*Measurements of QT interval*

All subjects had received every year a standard 12-lead electrocardiogram. In them, 91 subjects with QTc-interval of 380-420 msec were selected from the ECG records in 1992. The records in 1992 were compared with those in 1994. The longest QT interval was measured in leads I, II, or III, which consists of the length from 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: $QTc=QT/\sqrt{RR}$[6]. Coefficient of variation for the R-R interval ($CV_{R-R}$) was

determined from 150 systoles by the off-line calculator of an R-R interval measuring device.

*Statistical analyses*

The data were expressed as the means ±SD. Analysis of variance was used and two-tailed Student's nonpaired *t* test was also used for statistical evaluations.

## Results

The age and the duration of diabetes were not significantly different from those among the four groups as shown in Table 1. The prevalence of diabetic complications was higher in diabetic subjects treated with insulin or sulfonylureas than in those treated with diet alone. $HbA_1c$ value in diabetic subjects treated with insulin was significantly higher than that treated with diet alone. $CV_{R-R}$in diabetic subjects treated with insulin (1.78±0.80%) was significantly lower than that treated diet alone (2.68±1.22%). QTc interval was not significantly different among the four groups, although the QTc interval in the subject treated with gliclazide was slightly longer than in other groups.

Table 1 Clinical features of non-insulin dependent diabetes mellitus

| | insulin (n=31) | diet (n=26) | glibenclamide (n=20) | gliclazide (n=14) |
|---|---|---|---|---|
| age(yr) | 61.9±6.2 | 62.4±5.7 | 61.8±5.6 | 61.6±6.4 |
| duration of diabetes (yr) | 17.3±7.4 | 12.9±7.2 | 13.7±7.1 | 12.8±8.2 |
| peripheral neuropathy | 26/31 | 15/26 | 16/20 | 9/14 |
| retinopathy | 20/31 | 7/26 | 12/20 | 6/14 |
| nephropathy | 10/31 | 5/26 | 4/20 | 3/14 |
| serum K (mEq/l) | 4.6±0.4 | 4.4±0.4 | 4.6±0.3 | 4.5±0.3 |
| serum Ca (mg/dl) | 8.3±0.6 | 8.5±0.6 | 8.6±0.5 | 8.5±0.5 |
| $HbA_1c$(%) | | | | |
| 1992 | 8.7±2.1* | 7.4±1.0 | 7.8±0.9 | 7.6±1.1 |
| 1994 | 9.0±2.2 | 7.4±1.1 | 7.9±1.1 | 8.1±1.2 |
| $CV_{R-R}$(%) | 1.78±0.80* | 2.68±1.22 | 2.22±0.80 | 2.36±0.88 |
| QTc(msec) | | | | |
| 1992 | 410±27 | 410±25 | 413±12 | 411±23 |
| 1994 | 417±20 | 416±31 | 415±11 | 421±31 |

The data are expressed as means ± SD.
* $p<0.05$, significantly different from diet.

## Discussion

The present study clearly demonstrated that the QTc interval gradually and naturally prolonged in diabetic subjects, and that the sulfonylurea drugs did not influence the prolongation of the QTc interval. The present results were contradictory to the result of our previous report that the QTc interval was significantly longer in the diabetic subject treated with glibenclamide[6]. Our previous report was a cross-sectional study, and it is possible that diabetic subjects who initially had prolonged QTc interval were included in glibenclamide-treated diabetic groups. Thus, the reexamination of our previous study revealed that three subjects who initially had prolonged QTc interval (>420 msec) were included in glibenclamide-treated groups although such subjects were not included in diet- or insulin-treated groups. This may mainly be responsible for the previous results.

We conclude that sulfonylurea drugs do not enhance the natural lengthening of the QTc interval in NIDDM subjects.

## Summary

In a previous study, we reported that QTc interval in diabetic subjects treated with glibenclamide, one of hypoglycemic sulfonylurea drugs, was significantly longer than that treated with diet alone independently of diabetic autonomic neuropathy. We pursued the two years QTc-interval changes in diabetic subjects to elucidate whether or not glibenclamide lengthen the interval. Ninety-one subjects (aged 50-70 yr) with non-insulin dependent diabetes mellitus were enrolled for the study, who had received unchanged therapy (for insulin, sulfonylureas, or diet) over the last two years. The subjects were divided into four groups; 1) 31 subjects treated with insulin, 2) 20 with glivenclamide, 3) 14 with gliclazide, and 4) 26 with diet alone. After 2 years, there were no significant differences in the QTc interval among the four groups, although the QTc interval naturally and slightly prolonged in all groups during the same periods.

These results suggest that sulfonylurea drugs do not enhance the natural lengthening of the QTc interval in NIDDM subjects.

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