The relationship between risk of hypoglycemia and use of cibenzoline and disopyramide

Abstract Objective: A case-control study was carried out to compare the risks of hypoglycemia caused by disopyramide and cibenzoline.

Methods: We selected 91 subjects with hypoglycemia from among 14,156 outpatients who consulted the National Cardiovascular Center (NCVC) and received drug therapy between September 1997 and February 1998. We used the fasting blood sugar (FBS) level of 75 mg/dl or less as the cut-off level to screen for hypoglycemia. For each case, five controls matched for gender and age were selected from the clinical division consulted by relevant subjects.

Results: Ninety-one cases and 455 controls were enrolled in this study. Of 91 cases with hypoglycemia, 8 (8.8%) were treated with cibenzoline and 3 (3.3%) with disopyramide. The percentage of cases treated with cibenzoline was greater than that in the controls (1.5%), and the prescription frequency of cibenzoline during the study period was 2%. With adjustment for potential confounding factors using conditional logistic regression, hypoglycemia was significantly correlated with the use of cibenzoline [OR 8.0 (95% CI 1.7–36.8)], insulin [OR 48.4 (95% CI 8.8–267.2)], and thyroid agents [OR 13.0 (95% CI 1.1–160.4)]. An increased risk of hypoglycemia associated with the use of sulfonylureas was not detected. In additional logistic regression analysis, including the variables with individual sulfonylureas, glibenclamide but not gliquidone significantly increased the risk of hypoglycemia. The use of disopyramide did not affect the risk of hypoglycemia. In separate analyses for diabetic and non-diabetic patients, the risks of hypoglycemia associated with the use of drugs other than β-blocking agents in non-diabetic patients were estimated to be lower than those in diabetic patients.

Conclusion: The use of cibenzoline was significantly correlated with an increased risk of hypoglycemia.

Key words Hypoglycemia · ATP-sensitive K+ channel · Cibenzoline

Introduction

Hypoglycemia, which is a major side effect of some drugs, results in coma or psychological damage and is observed frequently in patients treated with insulin or oral antidiabetic agents. Therefore, diabetic patients treated with insulin or oral antidiabetic agents are followed up closely for hypoglycemia and educated in the prevention and treatment of this adverse effect.

It is well known that some other drugs also can cause hypoglycemia [1, 2]. Vaughan-Williams class-Ia antiarrhythmic agents, such as disopyramide and cibenzoline, are known to cause hypoglycemia during treatment [3–7]. The major target of class-Ia antiarrrhythmic agents is considered to be the fast sodium channel, which determines the conduction of ventricular and atrial action potentials. However, some class-Ia agents possess non-specific effects that block other ionic channels. Disopyramide and cibenzoline block the ATP-sensitive K+ channels [8–10]. The K+ channels in pancreatic β cells play a crucial role in regulating insulin secretion. Closure of K+ channels in pancreatic β cells depolarizes β cells and promotes Ca2+ influx through the voltage-dependent Ca2+ channels, thereby stimulating insulin secretion [11]. Although such an effect could be
beneficial for diabetic patients, it may also increase the risk of hypoglycemia in both non-diabetic and diabetic patients.

The National Cardiovascular Center (NCVC) is a highly specialized medical center that treats cardiovascular diseases and related disorders, including cardiac diseases, hypertension, renal diseases, cerebrovascular diseases and vascular disorders. Seventy percent of the patients at the NCVC are residents of Osaka Prefecture, 16% reside in the surrounding prefectures such as Kyoto, Hyogo and Nara, and the remaining patients come from all over Japan. The treatment of arrhythmia is an important task in the NCVC. Class-Ia antiarrhythmic agents, including disopyramide, cibenzoline, quinidine, procainamide, bepridil and pirmenol, are used frequently to treat atrial and ventricular tachyarrhythmias in Japan. Disopyramide is the most frequently used among the class-Ia antiarrhythmic agents, followed by cibenzoline. In Japan, disopyramide and cibenzoline account for about 25% and 8% of prescribed antiarrhythmic agents, respectively. The defined daily doses (DDDs) of disopyramide and cibenzoline are 300 mg/day, each. Hypoglycemia often occurs as an adverse effect of the clinical use of cibenzoline.

Disopyramide also occasionally causes hypoglycemia. However, it is not clear whether there is a difference in the risks of hypoglycemia between these two drugs. The comparison between the risks of hypoglycemia of disopyramide and cibenzoline has not yet been reported. Therefore, we carried out a matched case-control study on outpatients who received drug therapy in the NCVC to compare the risks of hypoglycemia arising from the administration of disopyramide and cibenzoline.

**Methods**

**Study population**

The accessible populations were selected from among outpatients who consulted the NCVC and received drug therapy between 1 September 1997 and 28 February 1998. We used filled prescriptions as a proxy for drug therapy, which yielded the data of 14,156 outpatients who received drug therapy during the study period. Cases and controls were selected from the same accessible population. As our study was based on information from the prescription database, we did not include patients who received no medication during the study period.

**Selection of cases**

We used the fasting blood sugar (FBS) level of 75 mg/dl or less as the cut-off point to screen for hypoglycemia. We selected patients who developed fasting hypoglycemia once or more from the FBS database which contained data of 11,179 measurements of FBS level among the outpatients who consulted the NCVC during the study period. FBS levels were below 75 mg/dl on 116 occasions in a total of 109 patients. Of 109 patients, 91 were included in the accessible population. Selection criteria for cases were hypoglycemia and medication in the study period. These patients met the selection criteria and were considered eligible for matching and analysis. Eighteen patients did not meet the selection criteria, because they did not receive medication during the study period. We used the first episode during the study period to identify the cases. The index date for each case was defined as the first date on which the FBS level of 75 mg/dl or less was observed during the study period. The presence or absence of an episode of hypoglycemia before the study period was not taken into account in the selection of cases.

**Selection of controls**

For each case, five matching controls were selected from the same accessible population. Selection criteria for controls was medication during the study period. A total of 455 controls were enrolled in the study. The controls were selected within a month of detecting hypoglycemia in the corresponding case. The controls were matched for age and gender, and selected from the clinical division consulted by the relevant subject. If a sufficient number of controls could not be obtained, then the age range was widened. Consequently, the cases matched the controls within 7 years of their age.

Matching was based on information from the prescription database file constructed in the prescription order entry system, which contains all prescriptions filled for the outpatients. It also contains information on the prescription date, clinical division consulted and demographic characteristics, including the date of birth and gender. The index date for each control was defined as the date of the visit. The controls were selected from patients without hypoglycemia during the study period, including those whose FBS levels had not been measured. In the selection of the controls, the frequency of FBS measurement for each subject during the study period was not taken into account.

**Information on prescribed drug therapy and diagnosis**

Information on the prescribed drug therapy was obtained from the computerized prescription database. Although disopyramide and cibenzoline were the main variables of interest in this study, we also included the following drugs or classes of drugs for adjustment and comparison: insulin, sulfonylureas, biguanides, insulin action enhancers, α-glucosidase inhibitors, angiotensin-converting-enzyme (ACE) inhibitors, diuretics, β-blocking agents and thyroid agents. Exposure was defined as at least one prescription for these drugs filled in the 1-month period before the index date, since, in general, prescriptions were written every month. From the computerized receipt files, we retrieved each subject’s information regarding the presence or absence of diseases that might have affected glucose metabolism (diabetes mellitus, hypertension, hyperlipidemia, hypothyroidism, hyperthyroidism and renal failure). The information regarding the degree of compliance with treatment and the diet recommendations for diabetic patients could not be obtained.

**Statistical analysis**

The prevalence of each diagnosis was tested using chi-square analysis, unless the expected cell frequencies were less than 5, in which case the Fisher exact test was used. We calculated the odds ratio (OR) using the conditional logistic regression analysis for the matched case-control study by means of the LogXact computer program (CYTEL Software Corporation, Mass.). The probability ($P$) values of ≤0.05 were considered statistically significant. We also calculated the 95% confidence intervals (95% CI). The model contained potential confounding variables for adjustment, including the following multiple classes of drugs besides cibenzoline and disopyramide: insulin, sulfonylureas (glibenclamide and gliclazide), biguanides (buformin), insulin action enhancers (tolbutamide), α-glucosidase inhibitors (acarbose and voglibose), ACE inhibitors (captopril, enalapril, alacepril, delapril, cilazapril, lisinopril, benazepril, imidapril, temocapril, quinapril, trandolapril and perindopril), diuretics (trichlormethiazide, hydrochlorothiazide, furosemide and azosemide), β-blocking agents (propranolol, pin-
dolol, bopindolol, carteolol, acebutolol, celiprolol, metoprolol, atenolol, bisoprolol, betaxolol, labetalol, carvedilol, ar tinolol, nipradilol and tilisolol), and thyroid agents (levothyroxine), as well as