Hypoglycemia Induced by Interaction between Clarithromycin and Disopyramide

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SUMMARY

A 59-year-old man receiving hemodialysis was hospitalized due to severe hypoglycemic attack. The patient had been treated with disopyramide (50 mg/day) because of paroxysmal atrial fibrillation. Hypoglycemia occurred after taking clarithromycin (CAM, 600 mg/day), a macrolide antibiotic. The serum disopyramide concentration reached 8.0 μg/ml (23.6 μM) in the presence of CAM, while it was 1.5 μg/ml before the addition of CAM. A 75 g oral glucose tolerance test and daily profiles of blood glucose value showed that blood glucose levels were significantly lower in the presence of CAM and disopyramide compared to that in the absence of these drugs. The Turner index in the presence of CAM and disopyramide was significantly higher than that in the absence of these drugs, suggesting that a toxic concentration of disopyramide enhanced insulin secretion, resulting in the induction of hypoglycemic attacks, in which the inhibitory effects of CAM on the hepatic cytochrome P-450 might be involved. QT and QTc intervals were prolonged in the presence of CAM and disopyramide, but torsades de pointes were not observed in this patient receiving nicorandil (15 mg/day). Thus, it should be taken into account that life-threatening hypoglycemia may result from the interaction between clarithromycin and disopyramide. (Jpn Heart J 1999; 40: 91–96)

Key words: Hypoglycemia, Disopyramide, Clarithromycin, Pancreas ATP-sensitive K⁺ channels, Macrolide, Chronic renal failure

ATP-sensitive K⁺ channels, composed of K⁺ channel (Kir₆.2) and sulfonylurea receptors (SUR₁),¹⁻³ exist in pancreatic β-cells, which play an essential role in secreting insulin. Class Ia antiarrhythmic agents such as disopyramide have been reported to inhibit the pancreatic ATP-sensitive K⁺ channels,¹⁻³ and promote insulin secretion,⁵⁻⁶ which may be involved in these agent-induced hypoglycemias reported in rare cases.⁷⁻¹⁰ Antibiotic agents belonging to the

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macrolides, such as erythromycin, have been shown to combine with and inactivate hepatic cytochrome P-450.\textsuperscript{11-13} Subsequently, they may disturb the metabolism of certain drugs such as disopyramide, resulting in increased serum concentrations of the drug. Ragosta et al.\textsuperscript{14} reported two cases who developed torsades de pointes due to an interaction between erythromycin and disopyramide, where cytochrome P-450 might be involved. Here, we describe a patient receiving hemodialysis in whom severe hypoglycemia might have resulted from an interaction between clarithromycin and disopyramide.

**Case Report**

A 59-year-old man receiving hemodialysis was hospitalized due to hypoglycemic shock. He had been under treatment with disopyramide (50 mg/day) because of paroxysmal atrial fibrillation since 1987. Then in 1994, he was suspected of having angina pectoris, and had been administered isosorbide dinitrate (120 mg/day), nicorandil (15 mg/day) and later metildigoxin (0.05 mg/day). On June 23, 1997, he was started on clarithromycin (600 mg/day) because of chronic bronchitis. On the 14th day of treatment with clarithromycin, he fell into a coma. The serum level of potassium was within normal range. Blood urea nitrogen and creatinine were 60.0 mg/day and 9.1 mg/dl, respectively. The blood glucose value was 21 mg/dl, but plasma levels of cortisol and ACTH were within normal ranges. He was intubated and administered glucose, following

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Effects of clarithromycin (CAM) on serum concentration of disopyramide (DP). The data examined is shown in the lower part of each panel. HD = hemodialysis.
which he recovered. However, he continued to suffer from hypoglycemic attacks, and on July 31 he again fell into a coma. At this time, his serum disopyramide concentration was 8.0 μg/ml (6.7 after hemodialysis), while it was 1.5 before the start of treatment with clarithromycin (Figure 1). Thus, he seemed to have developed hypoglycemia due to a toxic concentration of disopyramide. Therefore, both disopyramide and clarithromycin were discontinued. The serum level of metildigoxin (3.9 ng/ml on July 31) was also higher compared with the level after stopping these agents (0.9 ng/ml on September 10). The blood glucose value in a 75 g oral glucose tolerance test (Figure 2A) and the daily levels of blood glucose (Figure 2B) measured while on disopyramide and clarithromycin were lower than those measured after withdrawal of these agents. HbA1c (4.9%) and the serum level of fructosamine (248 μmol/l) were within normal ranges. Thus, it is likely that disopyramide and clarithromycin interacted which led to the development of hypoglycemia. The Turner index (Figure 3A) was higher in the presence of clarithromycin and disopyramide than that observed in their absence, suggesting that hypersecretion of insulin might have been involved in the development of hypoglycemia. The QTc interval in the presence of clarithromycin (0.49 on July 16) was longer than that in its absence. However, torsades de pointes were not detected in 24 hr Holter ECG and ECG monitoring. After discontinuing these
agents, the QTc interval and blood glucose value returned to normal levels, and he never developed a hypoglycemic attack again. However, after discontinuing disopyramide, 24 hr Holter ECG revealed paroxysmal atrial fibrillation. He was treated with aprindine (40 mg/day) and left the hospital (Figure 3B).

**DISCUSSION**

The present case suggests that hypoglycemia might be induced by an interaction between clarithromycin and disopyramide in patient receiving hemodialysis, and this is, to our knowledge, the first report described in the literature. Until now, it has been reported in rare cases that hypoglycemia devel-
oped following treatment with class Ia antiarrhythmic drugs such as disopyramide and cibenzoline. The mechanism for this agent-induced hypoglycemia remains to be clarified since the serum concentrations of these drugs were not necessarily elevated in these cases. In our case, the serum level of disopyramide reached a toxic concentration, and after withdrawal, the patient did not fall into a hypoglycemic attack again, indicating that the hypoglycemia was induced by the increased serum concentration of disopyramide. Class Ia drugs have been reported to inhibit pancreatic ATP-sensitive K+ channels, thereby enhancing insulin secretion by pancreatic β-cells. In fact, disopyramide has been shown to increase insulin secretion with an \( EC_{50} \) value of 23.3 \( \mu \)M, which is close to the 23.6 \( \mu \)M in our case. The Turner index was elevated, suggesting that insulin secretion might be enhanced during hypoglycemic conditions. Macrolide antibiotic clarithromycin, as erythromycin, is known to bind to and inactivate a specific hepatic cytochrome P-450 called CYP3A4. Since several drugs including disopyramide can be substrates for this enzyme, and macrolides may interfere with the metabolism of these drugs in the liver. Clarithromycin elevated the concentration of disopyramide in our patient with hemodialysis, possibly due to the inhibitory effects of clarithromycin on cytochrome P-450. Severe hypoglycemia developed on the 14th day of treatment with clarithromycin. Thus, if the drugs need to be used for a long time, these side effects should be taken into consideration, especially in patients with renal failure. Two cases in which torsades de pointes were induced by the interaction between disopyramide and erythromycin have been reported. They showed a marked prolongation of the QT interval which was related to an increased disopyramide concentration. Antiarrhythmic drugs such as disopyramide exert their antiarrhythmic action by inhibiting cardiac K+ channels, however, at toxic concentrations, they produce proarrhythmic effects, i.e. torsades de pointes. The QT interval was prolonged in our case, but torsades de pointes were not induced. He has been under treatment with nicorandil, a K+ channel opener as shown in Figure 3B, which might shorten the QT interval and prevent the appearance of torsades de pointes. In conclusion, severe hypoglycemia might be induced by an interaction between clarithromycin and disopyramide, where the inhibitory effects of clarithromycin on hepatic cytochrome P-450 might be involved.

**References**


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