Hypoglycemia Probably Due to Accidental Intake of Repaglinide

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This report focuses on a 16-year-old girl afflicted with hypoglycemia after administration of medications for gastrointestinal symptoms. Repaglinide-induced hypoglycemia was suspected when a tablet of repaglinide was noted in the drug package that she had been given. As the use of various types of oral hypoglycemic agents has increased, a definitive diagnosis of drug-induced hypoglycemia has become difficult. It is dangerous for a patient to take oral hypoglycemic agents without the knowledge of hypoglycemic symptoms and initial management. We present this case and review the characteristics of repaglinide to remind physicians and pharmacists to pay more attention to this situation. *(Chang Gung Med J 2002;25:783-6)*

Key words: drug-dispensing error, hypoglycemia, repaglinide, Novonorm®.

Hypoglycemia is an emergent medical problem which requires quick management upon diagnosis. Drug-induced hypoglycemia, especially by oral hypoglycemic agents, is an important cause and should be kept in mind. We report on a case with initial presentations of vomiting and diarrhea, whose medications prescribed for relieving those symptoms resulted in hypoglycemia. It turned out that she took repaglinide which had been incorrectly dispensed by the pharmacy. This is a new class of insulin-augmenting agents with a relatively short active duration and which has lower risks of producing severe hypoglycemia than do sulfonylurea drugs.[1-3]

CASE REPORT

A 16-year-old girl presented with loss of consciousness during an episode of hypoglycemia. According to statements by her family, she had been well until March 6, 2001, when she suffered from vomiting and diarrhea after she had eaten a bowl of noodles. She was brought to a hospital, where a gastrointestinal disorder was diagnosed, and several medications were prescribed and then dispensed from the pharmacy of the same hospital. She took the tablets 3 times as indicated after the afternoon of March 7. The symptoms of diarrhea and vomiting improved but she felt a little hungry and tired on the following day. She thought that this resulted from the sickness, so she did not pay much attention to it. Before going to bed that night, she consumed an additional cup of soup.

She could not be awakened by her mother in the morning on March 9, and was brought to the emergency room of the same hospital. Laboratory analysis revealed a plasma glucose level of 19 mg/dl. After intravenous glucose administration, her consciousness returned. Afterwards, no hypoglycemic sequelae occurred, so she was discharged from the emergency room without determination of the definitive cause of the hypoglycemia.

She visited our hospital for further evaluation on

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March 12. The list of drugs on the previous prescription included Novamine® (prochlorperazine), Ditopax® (magnesium and aluminum), KBT® (kaolin-bismuth subcarbonate and tannalbin), and Trancolon® (mepenzolate). Laboratory analysis revealed normal liver and renal functions. The fasting plasma glucose was 79 mg/dl. At the same time, the plasma concentration of insulin was 7.6 (normal range, 2.6-24.4) μU/ml, and C-peptide was 2.49 (normal range, 0.9-4.0) ng/ml. Other hormone studies, including evaluation of TSH and cortisol, showed no abnormal findings. The drugs that she had received were brought to the hospital at our request. In contrast to the prescription, a 1-mg Novonorm® (repaglinide) tablet instead of novamine was identified in each package. She recalled having taken only 3 of this type of tablet before the episode of hypoglycemia, although she had taken regular meals. After the drugs were discontinued, there were no further hypoglycemic attacks during the follow-up period.

DISCUSSION

Plasma glucose concentration remains within a narrow range (usually between 65 and 140 mg/dl) in healthy people. A decrease in plasma glucose concentration results from excessive glucose efflux from the circulation or deficient glucose influx into the circulation, or both. Hypoglycemia endangers the brain because glucose is its primary energy source.[4] There are various manifestations of low plasma glucose concentration.[5,6] Pathologic hypoglycemia should not be diagnosed merely by measuring plasma glucose or individual symptoms. To establish a diagnosis of hypoglycemia, Whipple's triad must be present: low plasma glucose concentration, hypoglycemic symptoms, and rapid relief of symptoms with administration of carbohydrates.[7]

The causes of hypoglycemia can be classified into 3 categories: drug-induced hypoglycemia, disorders associated with fasting hypoglycemia, and disorders associated with postprandial hypoglycemia.[8] Drugs, especially oral hypoglycemic agents, are an important cause of hypoglycemia.[9,10] A high clinical suspicion and demonstration of plasma drug concentration are necessary for a definitive diagnosis of drug-induced hypoglycemia.[11] It is helpful in determining whether it resulted from hyperinsulinemia by analyzing the plasma concentrations of insulin and C-peptide during a hypoglycemic episode. For this purpose, the reappearance of hypoglycemia can be induced by a prolonged fast for fasting hypoglycemia or a mixed meal test for postprandial hypoglycemia.[4] Fasting hypoglycemia due to insulinoma, insulin receptor autoantibodies, or anti-insulin antibodies may be associated with an excessive insulin effect, but on the other hand congestive heart failure, combined with endocrine deficiency, severe liver disease, renal failure, or sepsis are not associated with an excessive insulin effect.[8] Postprandial hypoglycemia can result from gastric surgery or early type 2 diabetes mellitus.[4]

Repaglinide, 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl) phenyl]-butyl] amino]-2-oxoethyl] benzoic acid, is an insulinotropic agent with a structure different from that of sulfonylurea drugs.[1] After administration of 1 mg repaglinide before a meal, the maximal postprandial plasma glucose concentration is lessened by a mean of about 28.8 mg/dl in comparison with the administration of a placebo.[2] It is characterized by rapid absorption and relatively fast elimination. The half-life of repaglinide in type 2 diabetic patients is about 1 hour, and there is nearly no effect during the secondary meal period (240-480 min).[1,2] For this reason, a lower risk of severe hypoglycemia has been noted in comparison with sulfonylurea.[1,3]

Sulfonylurea-induced hypoglycemia in non-diabetic patients due to drug-dispensing error has been well documented.[10] Look-alike or sound-alike drug names are a factor in inadvertent drug-dispensing errors.[12] However, errors with repaglinide (Novonorm®), a new class of oral hypoglycemic agents with a name similar to novamine, have seldom been reported (Fig. 1). Findings of increased serum insulin and repaglinide concentration during the episode of hypoglycemic symptoms are necessary to establish a definitive diagnosis of repaglinide-induced hypoglycemia. It had been reported that factitious hypoglycemia was successfully defined by determining the repaglinide serum concentration during hypoglycemia.[11] However, in our case, the episode of hypoglycemia occurred 5 days before the patient visited our hospital, thus we were unable to obtain a serum sample during the hypoglycemic episode and failed to detect an abnormal plasma concentration of glucose, insulin, or C-peptide at our

Fig. 1 The two drugs involved in the drug-dispensing error.

hospital. The half-life of repaglinide is relatively short, at about 1 h in type 2 diabetic patients,[1] so there was no reason to measure the repaglinide concentration in her blood 5 days after the episode. The clues that we found were the repaglinide tablets in her drug package, and no recurrent hypoglycemia after the drugs were discontinued. Instead of further studies, we suggested close follow-up after educating her about hypoglycemia.

The severe hypoglycemic episode that this patient experienced probably resulted not only from repaglinide but also from the medications for gastrointestinal disorder. Although it has not been reported that the gastrointestinal drugs which she took, including Ditopax®, KBT® and Trancolon®, can induce hypoglycemia alone, the anticholinergic agent has resulted in hypoglycemia in a few subjects, especially those with advanced age, impaired renal function, or malnutrition.[13] In fact, an anticholinergic agent can also increase the severity of hypoglycemia by inhibiting gastric emptying.[14] A young female with a regular diet developing severe hypoglycemia after administration of 1 mg repaglinide due to a dispensing error has never been reported. We present the case to remind physicians and pharmacists to pay more attention to this situation.

In conclusion, a diagnosis of factitious hypoglycemia is difficult, and the physician should keep it in mind. Leaving it undiagnosed is dangerous, because the patient may not have knowledge of hypoglycemic symptoms or its initial management. Delay in treatment may result in sequential complications of hypoglycemia. When physicians write a prescription and pharmacists dispense drugs to patients, they should be careful, especially when there is a chance to confuse similar-sounding names.

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疑似誤用Repaglinide導致低血糖

李奕德　許惠恒　林時逸

我們報告一位16歲女性因腸胃不適就醫並服用藥物後產生低血糖現象。直到在她帶來未服用完的藥袋中，發現repaglinide錠劑後，才懷疑是藥物引起的降低血糖作用。隨著降血糖藥物種類的增多，要確定診斷藥物引起低血糖更加困難。若病人不知低血糖的症狀及處理方式，將造成嚴重的後遺症。因藥名類似造成發藥時的錯誤，在國外已被廣泛的報告過。Repaglinide爲一新型降血糖藥物，藉此病例我們討論repaglinide的特性並提醒醫師及藥師特別注意。(長庚醫誌 2002;25:783-6)

關鍵字：配藥錯誤，低血糖，repaglinide，諾和隆®。

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