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NOTE

Safety and tolerability of diazoxide in Japanese patients with hyperinsulinemic hypoglycemia

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Abstract. Diazoxide is a non-diuretic benzothiadiazine derivative, one of a group of substances introduced into clinical practice in the 1950s for the treatment of hypertension. Fajans reported the use of diazoxide for the treatment of insulinoma in 1979. Although patients with hyperinsulinemic hypoglycemia worldwide have been treated with diazoxide for more than 30 years, there are no recent reports about the adverse effects of this drug in Asian patients, including Japanese patients. Herein, we report the results of our retrospective clinical record review of 6 Japanese patients (3 females and 3 males, ranging in age from 58 to 91 years) with hyperinsulinemic hypoglycemia and inoperable insulinoma treated with diazoxide. Diazoxide improved control of hypoglycemic symptoms and maintained normoglycemia in 5 of the 6 patients, and was ineffective in one patient. Surprisingly, although all 6 patients received diazoxide according to the treatment strategy recommended in Western patients, 5 of the 6 patients developed edema and two developed congestive heart failure. Thus, when starting treatment with diazoxide in Japanese patients, the symptoms and signs of fluid retention should be evaluated carefully. Also, appropriate protocols for treatment with diazoxide should be evaluated by means of clinical trials in Japanese patients with hyperinsulinemic hypoglycemia.

Key words: Diazoxide, Hyperinsulinemic hypoglycemia, Fluid retention

HYPERINSULINEMIC hypoglycemia present with symptoms of hypoglycemia due to hypersecretion of insulin by pancreatic beta cells. In adults, insulinoma is the most cases of hyperinsulinemic hypoglycemia though noninsulinoma pancreatogenous hypoglycemia syndrome has also been reported, in those have undergone gastric bypass surgery for morbid obesity and in those with mutations in the insulin receptor [1]. Surgical removal is the ideal therapeutic managementns for insulinoma, however, it is not always possible. Because they are usually small, with 40% being less than 1 cm in diameter, 50% being between 1 and 5 cm in diameter and only a rare few exceeding 5 cm in diameter [2], their localization in the pancreas may be extremely difficult. Also, some patients are too old and debilitated at presentation to be suitable candidates for major surgery. In such cases, diazoxide or somatostatin analogues are prescribed for the patients [3].

Diazoxide is a non-diuretic benzothiadiazine derivative, one of a group of substances introduced into clinical practice in the 1960's for the treatment of hypertension [4]. Diazoxide inhibits insulin secretion from the pancreatic beta cells by causing opening of ATP-sensitive K^+ channels and reduced opening of Ca^{2+} channels, resulting in a potent hyperglycemic effect [5]. Fajans reported the use of diazoxide for the treatment of insulinoma in 1979 [6], and a national UK survey revealed the efficacy of diazoxide in the management of insulinoma [7]. Although patients worldwide have been treated for more than 30 years with diazoxide, there have been no recent reports about the adverse effects of this drug. Moreover, since most previous investigations have been conducted in western patients, it is unclear whether diazoxide may have a different adverse effect profile in Asian patients, includ-

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ing Japanese patients. Here, we report the results of a review of 6 Japanese patients with hyperinsulinemic hypoglycemia and inoperable insulinoma treated with diazoxide, including the safety and tolerability of diazoxide in Japanese patients.

Patients and Methods

We conducted a retrospective review of the clinical records of inpatients with hyperinsulinemic hypoglycemia treated with diazoxide at the Chigasaki City Hospital, Fujisawa City Hospital, Yokohama City University medical center, Yokohama City University Hospital, Kanagawa, and Hokkaido University hospital, Hokkaido, from 1995 to 2011. Three females and 3 males were included in the study. The clinical and biochemical features of these patients are summarized in Table 1. All six patients fulfilled the criteria for the Whipples triad sign during the episodes of hypoglycemia, and insulin secretion was not suppressed. In patients 1–4 and 6, selective arterial calcium stimulation and hepatic venous sampling (ASVS) were performed. Although the ASVS showed hypersecretion of insulin from the tail of the pancreas in patient 4 and from the head of the pancreas in patient 6, these patients were still considered as being unsuitable for surgery due to their advanced age. The other patients were considered to be unsuitable surgical candidates due to the poor localization of the tumors. In patient 5, a tumor was removed from the tail of the pancreas by partial pancreactomy, however, since abdominal computed tomography (CT) performed one year later revealed a liver metastasis, partial hepatectomy was performed. The diagnosis of malignant insulinoma was confirmed by histopathological analysis. A year later, another repeat further abdominal CT revealed multiple liver metastases. Diazoxide treatment was started for the aforementioned reasons in the 6 patients.

Results

Patient 1 needed frequent meals at short intervals, continuous infusion of 10% glucose and administration of prednisolone, and diazoxide treatment was started at 75 mg/day (1.6 mg/kg/day), with the daily dose increased gradually. Glucose control was restored and the glucose infusion was stopped. However, the dose of diazoxide needed to be reduced, because leg edema appeared and the body weight increased by 5.5 kg after 5 days on diazoxide treatment. We gradually reduced the dose of diazoxide from 175 to 100 mg/day (3.8 mg/kg/day) and started concomitant administration of furosemide and spironolactone. The patient was maintained near euglycemia, and the leg edema and weight gain improved.

In patient 2, diazoxide treatment was started at 150 mg/day (2.8 mg/kg/day), with the daily dose increased gradually. After 4 days on the therapy, he developed nausea, which settled with metoclopramide. Twenty days after the start of therapy, leg edema appeared at 400 mg/day of diazoxide. The leg edema improved with a small dose of furosemide.

In patient 3, diazoxide treatment was started at 150 mg/day (2.5 mg/kg/day), with the daily dose increased gradually. After 14 days on the therapy, she developed hyperglycemia with 225 mg/day of diazoxide. Therefore, we reduced the dose of diazoxide to 150 mg/day after which euglycemia was maintained.

In patient 4, treatment was started with octreotide, however, glucose infusion could not be stopped. Initiation of diazoxide administration in combination with octreotide resulted in maintenance of euglycemia with no glucose infusion. Diazoxide was started at the dose of 150 mg/day (4.6 mg/kg/day), with the dosage increased gradually. After 5 days on the therapy, at 250 mg/day of diazoxide, although euglycemia was still maintained, the patient developed congestive

Table 1 Clinical features and biochemical data of the six Japanese patients of hyperinsulinemic hypoglycemia treated with diazoxide.

Case	Age	Sex	Clinical symptom	Symptom duration (months)	Glucose (mg/dL)	C-peptide (ng/mL)	Insulin (μU/mL)
1	62	Female	Confusion	7	37	6.2	33.8
2	58	Male	Confusion	6	41	2.8	3.8
3	80	Female	Confusion	4	30	3.5	11.1
4	91	Female	Coma	2	25	1.2	4
5	62	Male	Palpitation, weight gain	1	31	6.7	60.5
6	87	Male	Confusion	1	55	1.9	2.7

heart failure. Therefore, the diazoxide administration was stopped. Thereafter, she was continued on treatment with octreotide, and euglycimia was maintained.

In patient 5, diazoxide treatment was started at 150 mg/day (2.5 mg/kg/day), with the dose increased to 475 mg/day, and octreotide administration was also started. The dosage of diazoxide was gradually increased. However, 12 days after the start of diazoxide administration, the patient developed severe leg edema. Although furosemide administration was started, the patient gained 10 kg and euglycemia could not be maintained. Therefore, the diazoxide therapy was stopped.

In patient 6, diazoxide treatment was started at 150 mg/day (2.6 mg/kg/day), with the daily dose increased gradually. After 4 days on the therapy, the patient developed congestive heart failure and needed oxygen supplementation. Diazoxide administration was stopped, and octreotide was started. However, without diazoxide, it was impossible to prevent hypoglycemia. After he recovered from the heart failure, diazoxide administration was started again at 75 mg and, with the dose increased gradually. Although nausea and leg edema appeared, administration of furosemide and reduction of the diazoxide dose settled these symptoms. Since 125 mg of diazoxide was not sufficient to prevent hypoglycemia, prednisolone was started at 5 mg. Thereafter, euglycemia was maintained.

The initial dose, maintenance dose and adverse effects of diazoxide in our cases are summarized in Table 2.

Discussion

In the present study, of the 6 patients with hyperinsulinemic hypoglycemia treated with diazoxide, five developed edema and two developed congestive heart failure. In a national UK survey, diazoxide side-effects were recorded in 17 of 36 (47%) patients with insulinoma, and fluid retention was the most common (11/36). Moreover, diuretics were needed with the diazoxide in 20 of the 36 (55%) patients [7]. Also, Peter *et al*. reported that the main side effects were hirsutism (56%), ankle edema (50%), weight gain (38%) and nausea (11%) [8]. Diazoxide therapy should be initiated at the daily dose of 150 to 200 mg given in two to three divided doses, and the dose can be increased up to a maximum of 600 to 800 mg per day [2]. Although our patients received diazoxide treatment according to this recommended strategy, edema and congestive heart failure caused by fluid retention developed at high rates in our patients. Laboratory studies on admission of developed edema patients (patients 1, 2, 4-6) revealed that proteinuria was negative, mean eGFR was 65.0 mL/min/1.73m^2, and mean serum albumin was 4.1 g/dL. Whereas, those without edema (patient 3) revealed that proteinuria was negative, eGFR was 46 mL/min/1.73m^2, and serum albumin was 3.4 g/dL. Also, all 6 patients had no history of congestive heart failure, severe hepatic or renal dysfunction.

Why did edema develop at such a high rate in our patients? Diazoxide, which produces vasodilatation, causes sodium and water retention [9]. Many mechanisms for the increased sodium reabsorption have been proposed: increased antidiuretic hormone secretion, alteration of the intrarenal blood flow, changes in peritubular physical factors, reduction in the renal perfusion pressure, and stimulation of the renal sympathetic nerve activity [10]. The higher mean daily intake of sodium in Asian than in Western populations [11], may explain the higher incidence of edema caused by fluid retention developing in Asian patients with hyperinsulinemic hypoglycemia treated with diazoxide according to the treatment strategy recommended overseas. Set the keyword associated with the Diazoxide, we per-

Table 2 Initial dose, maintenance dose and adverse effects of diazoxide in the six Japanese patients with hyperinsulinemic hypoglycemia.

Case	Initial dose (mg/kg/day)	Maximum dose (mg/kg/day)	Maintenance dose (mg/kg/day)	Adverse effect
1	1.6	3.9	2.1	Edema
2	2.8	7.5	7.5	Nausea, appetite loss, edema
3	2.5	3.9	2.5	Hyperglycemia
4	4.6	7.7	- *	Edema, congestive heart failure
5	2.5	7.7	- *	Nausea, appetite loss, edema
6	2.6	3.5	2.1	Edema, congestive heart failure

* See text.

formed a literature search of the electronic databases Igaku Chuo Zasshi, which is the largest medical literature database in Japan. We found 76 cases of reports treated with diazoxide due to hyperinsulinemic hypoglycemia in Japanese adult patients. Age was 18-93 years, dose of diazoxide was described in 46 cases (25-600 mg/day). The presence or absence of adverse effects was described in 32 cases, and adverse effects were recorded in 29 patients. The main adverse effects were fluid retention (16 cases (55%)), hematologic abnormalities (5 cases), such as cytopenia, erythema (3 cases) and hirsutism (3 cases), gastrointestinal symptoms (2 cases), and hyperglycemia (1 case). Although there was no description of the presence or absence of adverse effects in the other 44 cases, the frequency of fluid retention in Japanese patients were higher than that of Western patients according to the national UK survey [7]. Mean diazoxide dose in Japanese patients was 182 ± 131 mg/day (range 25-600 mg/day), which was less than that in the Western patients (267 ± 138 mg/day (range 100-600 mg/day) [7], or 400 mg/day (range 40-1500 mg/day) [8]). Moreover, mean dose of diazoxide with fluid retention patients was 215 ± 206 mg/day (range 50-600 mg/day), which was also less than that in the Western patients. Therefore, appropriate diazoxide treatment protocols should be evaluated by means of clinical trials in Japanese patients with hyperinsulinemic hypoglycemia.

In conclusion, edema and congestive heart failure caused by fluid retention developed at high rates during diazoxide treatment in Japanese patients with hyperinsulinemic hypoglycemia. Thus, when starting treatment with diazoxide in Japanese patients with hyperinsulinemic hypoglycemia, the symptoms and signs of fluid retention should be evaluated carefully. Especially, use in the elderly should be careful due to high frequency of heart dysfunction.

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Disclosure

No other potential conflicts of interest relevant to this article were reported.

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