Clinical outcomes of 20 Japanese patients with insulinoma treated with diazoxide

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Abstract. Diazoxide is recognized as an effective medical treatment for insulinoma. However, due to its adverse effects, such as fluid retention, it is sometimes difficult to employ diazoxide at an effective dose in clinical practice. This study aimed to clarify the clinical factors, which may affect efficacy and safety of the diazoxide treatment. We retrospectively evaluated the medical records of 20 patients with insulinoma including 4 malignant cases. The patients were divided into two groups according to the presence or absence of favorable outcomes or adverse effects, and the clinical features of both groups were compared. Diazoxide was effective and ineffective in each 9 patients, respectively. In other 2 cases, the efficacy could not be determined. In the effective group, all patients had benign insulinoma. Additionally, the tumor size determined by imaging test was tended to smaller than the ineffective group but not statistically significant when malignant cases were excluded (p = 0.065). Fluid retention was observed more frequently in females than in males (p = 0.025). Five patients displayed unacceptable thrombocytopenia within a few weeks after the administration of diazoxide. In these patients, the diazoxide dose was significantly higher than that in the other patients (400 mg/day (250–500 mg/day) vs. 225 mg/day (50–425 mg/day), p = 0.027). These findings may be informative in determining the indication and dose of diazoxide against insulinoma. In addition, a careful evaluation of platelet count would be required for a few weeks after the initiation of diazoxide treatment.

Key words: Insulinoma, Diazoxide, Fluid retention, Thrombocytopenia
therapeutic dose of diazoxide is wide ranging (200–600 mg/day) [6] and an appropriate method to optimize the dose has not been established. For these reasons, it is difficult to determine the maximal permissible dose for each patient in clinical practice.

Therefore, it is useful to determine the clinical factors, which may predict the outcomes of the diazoxide treatment. In the current study, we aimed to identify the factors by retrospectively evaluating the clinical characteristics, imaging features, and therapeutic outcomes of 20 Japanese patients with insulinoma treated with diazoxide.

Patients and Methods

Patients

This retrospective study evaluated the medical records of patients with insulinoma who were admitted during 2008–2016 to Tokyo Medical and Dental University Hospital, Yokohama City Minato Red Cross Hospital and Tokyo Metropolitan Tama Medical Center. One case has been reported [7]. Patients with diabetes who had developed hypoglycemia secondary to insulin or oral hypoglycemic agent intake, hypoglycemia due to insulin antibodies, hypopituitarism, or hypoadrenalism were not included in the study. As a result, 20 Japanese patients treated with diazoxide were recruited for this study.

Diagnosis and treatment

The presence of Whipple’s triad was confirmed in all patients. In addition, a diagnosis of insulinoma was based on the patients meeting at least one of two criteria described as follows: 1. presence of hyperinsulinemic hypoglycemia (plasma glucose concentrations <55 mg/dL and plasma insulin concentrations ≥3 μU/mL) and a pancreatic tumor identified the location by computed tomography (CT) or magnetic resonance imaging (MRI), and 2. presence of insulin secreting cells by histological analysis following the surgical resection of the pancreatic tumor and disappearance of hypoglycemia following surgery. The tumor was considered to be malignant when extra-pancreatic metastasis (overall liver and/or lymph node metastases) was observed by imaging analyses. In most cases, diazoxide was initiated at a low dose and increased up to 20 mg/kg/day until normalization of glucose levels was achieved, unless unacceptable side effects were observed. Seventeen patients were taking diazoxide because of preoperative glycemic control. Metastatic disease (two patients) and rejection of surgery (one patient) were other indications. This study complied with the principles laid by the Declaration of Helsinki and was approved by the ethics committee of Tokyo Medical and Dental University (M2016-274).

Outcome variables

Data regarding age, sex, body weight, imaging findings, complicated diseases, dose and side effects of diazoxide, and concomitant drugs for hypoglycemia were collected from the patients’ medical records. Failure to respond to diazoxide was defined according to a past report [8]; inability to fast >10–12 hours keeping plasma glucose levels >70 mg/dL without glucose infusion at maximal permissible dose of diazoxide. Edema and congestive heart failure were categorized as fluid retention. Fluid retention, rash, and thrombocytopenia were recognized as side effects of diazoxide when these symptoms developed after administration and disappeared after discontinuation of the medication.

Statistical analysis

Statistical analysis was performed using programs available in the SPSS version 21.0 statistical package (SPSS Inc., Chicago, Illinois, USA). Data are presented as median with range. Patients were divided into two groups according to effectiveness or tolerability of diazoxide. Mann–Whitney U-tests and Chi-Square tests were performed to compare the clinical characteristics between these two groups. Differences were considered to be statistically significant at p values less than 0.05.

Results

Table 1 summarizes the clinical characteristics of 20 patients with insulinoma. The median age of presentation was 57.5 years (18–85 years) and the male to female ratio was 9:11. The median body weight was 60.55 kg (40.0–78.8 kg). Tumors were identified with CT or MRI in all but two patients, where its presence was confirmed in the pancreas by surgical exploration. Seventeen patients underwent surgery, and insulin secreting cells were identified in the resected tumors by histological analysis in all cases. Four patients displaying metastatic lesions were diagnosed with malignant insulinomas. The median duration of diazoxide treatment was 29.5 days (10–705 days). In 4 cases, diazoxide was administered in combination with other drugs, such as octreotide (cases 13 and 16) and sunitinib (cases 14, 15, and 16), to control severe hypoglycemia or to shrink the tumor. The median estimated glomerular filtration rate was 73.8 mL/min./1.73 m² (47.2–186.3 mL/min./1.73 m²).

In the current series, diazoxide was effective in 9 patients and ineffective in another 9. In case 14, efficacy could not be determined because we failed to increase the diazoxide dose to the maximal permissible dose until the day of surgery. In case 20, diazoxide treatment was discontinued due to the development of a rash prior to the confirmation of efficacy. Although treatment with
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Diazoxide was initially effective in case 12, it failed to sufficiently control hypoglycemia approximately 2 years after diagnosis. In this patient, MRI revealed an increase in tumor size from 15 to 19 mm during the period of diazoxide treatment. Intravenous glucose infusion was administered to 4 patients in the effective group during the dose-adjustment period, but it was able to finally stop infusion without the recurrence of hypoglycemia. Table 2a outlines the characteristics related to the efficacy of diazoxide. A significantly lower dose of diazoxide was administered to the effective group than the ineffective group [200 mg/day (50–300 mg/day) vs. 325 mg/day (200–500 mg/day), \( p = 0.013 \)]. Fajans’s score (immuno-reactive insulin/fasting blood glucose) was not statistically significant between both groups (\( p = 0.895 \)). The tumor size, as determined by imaging test, was smaller in the effective group than the ineffective group [10 mm (0–15 mm) vs. 19 mm (8–110 mm), \( p = 0.010 \)]. This difference was not statistically significant when malignant cases were excluded from the analysis (\( p = 0.065 \)). Among the 4 patients with malignant insulinoma, diazoxide was ineffective in controlling hypoglycemia in 3 and efficacy was undetermined in the remaining 1 patient.

Overall, adverse effects were recorded in 13 patients; 11 of those were deemed to have unacceptable side effects and they discontinued diazoxide treatment. Fluid retention was confirmed in 10 patients; in these patients, leg edema accompanied by an increase in the cardio-thoracic ratio was recorded after the administration of diazoxide. The frequency of fluid retention in females was significantly higher than that in males (\( p = 0.025 \)). The proportion of patients administered intravenous glucose infusion was not statistically significant between the patients with presence and absence of fluid retention (70\% vs. 40\%, \( p = 0.178 \)) (Table 2b). In our series, unacceptable thrombocytopenia occurred in 5 patients, with platelet counts reaching the nadir 13–23 days after the administration of diazoxide; reversal of this effect was immediately observed after treatment discontinuation in all cases (Fig. 1). These 5 patients were administered significantly higher doses of diazoxide than the other patients [400 mg/day (250–500 mg/day) vs. 225 mg/day (50–425 mg/day), \( p = 0.027 \)] and had significantly larger tumors [34 mm (12–110 mm) vs. 12 mm (0–86 mm), \( p = 0.018 \)] (Table 2c). Additionally, the frequency of thrombocytopenia in patients with malignant insulinoma was significantly higher than in those with benign insulinoma (\( p = 0.010 \)). A rash was confirmed in 2 patients and disappeared after the discontinuation of diazoxide.

**Discussion**

This report analyzed the clinical characteristics of 20 patients with insulinoma diagnosed in three hospitals in Japan. Past clinical reviews have reported that diazoxide provides a reasonably good control of hypoglycemia in approximately 50\% of patients; however, edema, weight gain, and hirsutism complicate an equal number of patients [6]. Another report of a case series described diazoxide as being of minor benefit to malignant insulinomas due to poor tolerance, especially at higher doses [9]. Our results largely agree with these past findings; additionally, we identified certain factors associated with the efficacy and side effects of diazoxide.

Our investigation of the efficacy indicated that the effective group was administered a significantly lower dose of diazoxide than the ineffective group. Considering the fact that the dose of diazoxide was increased until unacceptable side effects were confirmed, this finding indicates that the final dose in the ineffective group (200–500 mg/day) is a putative maximal practical dose in Japanese patients. In congenital hyperinsulinism, some mutations in the genes encoding the ATP sensitive K+ channel contributing to diazoxide resistance have been identified [10, 11]. Conversely, to the best of our knowledge, no factor has been identified to be a predictor for diazoxide responders in patients with insulinoma. Interestingly, in our case series, 7 of the 9 patients in the ineffective group had tumors larger than 15 mm, even though tumor sizes were not larger than 15 mm among all patients in the effective group (Table 1). However, as the difference of tumor size was not statistically significant among patients with benign insulinoma (\( p = 0.065 \)), it could be more likely the association between the tumor size and diazoxide response demonstrated in this study was due to the drug resistance of malignant insulinoma. However, in case 12, hypoglycemia became refractory to diazoxide in parallel with the growth of a benign tumor. Therefore, tumor size may be associated, in some way, with the efficacy of diazoxide.

Fluid retention is a common adverse effect of diazoxide treatment [4], especially in Japanese patients [5]. Diazoxide reduces vascular resistance in all circulatory beds through direct relaxation of arteriolar smooth muscle and causes sodium and water retention [12]. Severe fluid retention leads to congestive heart failure or significant weight gain, both of which result in the discontinuation of diazoxide. Large volumes of fluid therapy could induce fluid retention. In our series, intravenous glucose infusion was administered more frequently in patients with fluid retention than in those with absence of the symptom, although statistically insignificant. The dose of diazoxide among patients with fluid retention was wide.
ranging (50–500 mg/day). Therefore, it appears to be difficult to determine an appropriate regimen of diazoxide treatment in Japanese patients with insulinoma. Conversely, fluid retention was observed significantly more frequently in females than in males, suggesting a susceptibility of females to edema. These findings suggest that fluid retention should be carefully evaluated, especially in females.

It is notable that thrombocytopenia was observed in 5 of the 20 patients (25%) treated with diazoxide in this case series. Although several cases have been reported on diazoxide-induced thrombocytopenia [7, 13, 14], hematological adverse effects are rare not only in patients in insulinoma [4] but also in those with congenital hyperinsulinism [15], who are treated with diazoxide as the first choice. In terms of drug-induced thrombocytopenia, it has been proposed that the sensitizing drugs typically contain structural elements that enable them to bind to both the antibody and platelet surface proteins [16]. In this model, the drugs bind to platelets and strengthen the connection between the antibody and platelet epitope. Drug-dependent antiplatelet antibodies typically occur following the exposure to a new drug for 1–2 weeks. Another characteristic aspect is the recovery from thrombocytopenia after the suspected drug is stopped without discontinuing the other drugs administered prior to thrombocytopenia. In our series, the platelet counts reached the nadir 13–23 days after the administration of diazoxide and were immediately reversed after its discontinuation in all 5 patients with thrombocytopenia. Conversely, 2 of these 5 patients (cases 15 and 16) were treated with sunitinib prior to the administration of diazoxide. Thrombocytopenia has been reported as a common adverse effect among Japanese patients treated with sunitinib [17]. However, even in these cases, thrombocytopenia was reversed after diazoxide was stopped in the absence of the discontinuation of sunitinib and other drugs. Therefore, including these two cases, thrombocytopenia is thought to occur as a result of diazoxide. In this study, patients with thrombocytopenia were administered a significantly higher dose of diazoxide than the other patients. Although it is unknown whether the dose

| Case | Age (years) | Gender | BW (kg) | Glucose (mg/dL) | Insulin (μU/mL) | C-peptide (ng/mL) | eGFR (mL/min/1.73 m²) | Imaging test |
|------|-------------|--------|---------|----------------|----------------|------------------|------------------------|-------------|
| 1    | 31          | Man    | 67.2    | 34            | 7.5            | 1.8              | 107.0                  | CT          |
| 2    | 52          | Man    | 62.2    | 39            | 14.9           | 3.8              | 65.3                   | CT          |
| 3    | 70          | Man    | 60.2    | 41            | 11.1           | 3.4              | 59.9                   | CT          |
| 4    | 60          | Man    | 68.0    | 11            | 21.4           | 4.4              | 74.4                   | CT          |
| 5    | 63          | Woman  | 57.5    | 35            | 9.5            | 2.8              | 80.7                   | CT          |
| 6    | 71          | Man    | 66.8    | 35            | 5.7            | 1.8              | 53.0                   | CT          |
| 7    | 65          | Woman  | 45.1    | 42            | 1.8            | 0.8              | 81.6                   | CT          |
| 8    | 85          | Woman  | 51.8    | 39            | 13.4           | 2.3              | 65.3                   | CT          |
| 9    | 83          | Man    | 75.0    | 56            | 28.4           | ND               | 54.6                   | CT          |
| 10   | 71          | Man    | 78.8    | 40            | 57             | 5.3              | 95.7                   | CT          |
| 11   | 70          | Woman  | 69.3    | 43            | 14.8           | 6.2              | 47.2                   | CT          |
| 12   | 55          | Woman  | 44.6    | 58            | 1.7            | 1.8              | 53.3                   | MRI         |
| 13   | 71          | Woman  | 68.7    | 47            | 22.5           | 2.7              | 74.3                   | CT          |
| 14   | 39          | Man    | 65.0    | 46            | 39.0           | 3.4              | 72.4                   | CT          |
| 15   | 18          | Man    | 52.0    | 48            | 8.1            | 1.8              | 127.0                  | CT          |
| 16   | 31          | Woman  | 49.0    | 46            | 72.9           | 4.5              | 73.3                   | CT          |
| 17   | 23          | Woman  | 53.3    | 35            | 9.9            | 2.0              | 133.2                  | CT          |
| 18   | 45          | Woman  | 40.0    | 39            | 8.3            | 3.3              | 186.3                  | CT          |
| 19   | 42          | Woman  | 47.7    | 47            | 5.9            | 1.6              | 130.1                  | CT          |
| 20   | 49          | Woman  | 60.9    | 45            | 4.8            | 2.0              | 65.2                   | CT          |

Tumor sizes were documented ‘0’ in cases if imaging tests failed to detect the tumors.

Abbreviations: BW, body weight; eGFR, estimated glomerular filtration rate; ND, not determined; CT, computed tomography; MRI, magnetic resonance imaging.
of diazoxide is associated with decreasing platelet count, the mean reported diazoxide dose in the cases of thrombocytopenia is 600–1,200 mg/day [13, 14]. Therefore, a high dose of diazoxide may be a potential contributor to the development of thrombocytopenia.

However, our study has some limitations. First, in this retrospective study, we assessed the therapeutic outcomes by evaluating the past medical records of the patients. Therefore, unrecorded hypoglycemia or adverse effects may have occurred in the patients. Second, in the evaluation of thrombocytopenia, other etiologies were not excluded (e.g., bone marrow examination) before the discontinuation of diazoxide. Third, we defined diazoxide was ineffective unless plasma glucose levels were kept >70 mg/dL without glucose infusion over 10–12 hours. However, in some cases among ineffective group, diazoxide might be “partially effective” in a sense of preventing severe hypoglycemia even if intravenous glucose infusion or nocturnal intake of high-caloric foods could not be discontinued completely. Fourth, the number of eligible patients was not large enough to avoid sample bias. For example, although previous research revealed that malignant insulinomas account for only approximately 5%–10% of insulinomas [18], a higher percentage (20%) of patients with malignant insulinoma was included in this case series. In contrast to benign cases, most patients with malignant insulinoma were administered octreotide or sunitinib as concomitant drugs, which may affect the favorable and adverse outcomes. Therefore, generalization of our findings may be limited by such differences in clinical characteristics. Nevertheless, to the best of our knowledge, detailed case analyses regarding the clinical outcomes of diazoxide treatment have not been carried out so far. Our results are meaningful in that they offer a new point of clinical observation during the treatment of insulinoma as a rare disease. Further large and homogeneous cohort studies including multivariate analyses are needed to reach a clear conclusion about the predictors for the outcomes of the diazoxide treatment.

In summary, helpful information with regards to the control of hypoglycemia could be extracted from the treatment of insulinoma with diazoxide. Diazoxide could not be expected to prevent hypoglycemia in patients with

| Case | Diazoxide Dose (mg/day) | Diazoxide Duration (day) | Diazoxide Effect | Side-effects | Concomitant medication | Surgical resection |
|------|-------------------------|--------------------------|------------------|-------------|------------------------|-------------------|
| 1    | 300                     | 80                       | +                |             |                        |                   |
| 2    | 225                     | 17                       | +                |             |                        |                   |
| 3    | 75                      | 316                      | +                |             |                        |                   |
| 4    | 300                     | 30                       | +                |             |                        |                   |
| 5    | 200                     | 52                       | +                |             |                        |                   |
| 6    | 75                      | 137                      | +                |             |                        |                   |
| 7    | 200                     | 29                       | +                |             |                        |                   |
| 8    | 50                      | 22                       | +                |             |                        |                   |
| 9    | 300                     | 42                       | +                |             |                        |                   |
| 10   | 400                     | 15                       | +                |             |                        |                   |
| 11   | 425                     | 21                       | +                |             |                        |                   |
| 12   | 250                     | 705                      | +                |             |                        |                   |
| 13   | 300                     | 23                       | +                |             |                        |                   |
| 14   | 300                     | 144                      | ND               |             |                        |                   |
| 15   | 250                     | 13                       | –                |             |                        |                   |
| 16   | 400                     | 14                       | –                |             |                        |                   |
| 17   | 500                     | 10                       | –                |             |                        |                   |
| 18   | 325                     | 33                       | –                |             |                        |                   |
| 19   | 200                     | 63                       | –                |             |                        |                   |
| 20   | 50                      | 15                       | ND               |             |                        |                   |

Abbreviations: ND, not determined.

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Table 2  Comparison of clinical characteristics according to the difference of outcomes after diazoxide administration

(a) diazoxide-effective or diazoxide-ineffective

|                      | Effective (n = 9) | Ineffective (n = 9) | p value |
|----------------------|------------------|---------------------|---------|
| Age (years)          | 65 (31–85)       | 45 (18–71)          | 0.121   |
| Men/Women            | 6/3              | 2/7                 | 0.058   |
| Body weight (kg)     | 62.2 (45.1–75.0) | 50.2 (40.0–78.8)    | 0.354   |
| Dose of diazoxide (mg/day) | 200 (50–300) | 325 (200–500)         | 0.013   |
| Fajans’s score       | 0.27 (0.04–1.95) | 0.28 (0.03–1.58)    | 0.895   |
| Tumor size (mm)      | 10 (0–15)        | 19 (8–110)          | 0.010   |
| Tumor size (mm) excluding malignant cases | 10 (0–15) | 16.5 (8–66) (n = 6) | 0.065   |
| Benign/Malignant tumor | 9/0            | 6/3                 | 0.058   |

(b) present or absent of fluid retention

|                      | Present (n = 10) | Absent (n = 10) | p value |
|----------------------|------------------|-----------------|---------|
| Age (years)          | 67.5 (23–85)     | 50.5 (18–71)    | 0.120   |
| Men/Women            | 2/8              | 7/3             | 0.025   |
| Body weight (kg)     | 52.55 (40.0–78.8)| 61.55 (49.0–68.0)| 0.650   |
| Dose of diazoxide (mg/day) | 300 (50–500) | 237.5 (50–400)       | 0.207   |
| Fajans’s score       | 0.31 (0.03–1.43) | 0.27 (0.11–1.95) | 0.650   |
| Tumor size (mm)      | 15.5 (8–110)     | 12 (0–86)       | 0.448   |
| Benign/Malignant tumor | 8/2             | 8/2             | 1.000   |
| eGFR (mL/min/1.73 m²) | 77.95 (47.2–186.3)| 72.85 (53.0–127.0)| 0.571   |
| Intravenous glucose infusion | 7/3 | 4/6       | 0.178   |

(c) present or absent of thrombocytopenia

|                      | Present (n = 5) | Absent (n = 15) | p value |
|----------------------|-----------------|-----------------|---------|
| Age (years)          | 31 (18–71)      | 60 (31–85)      | 0.294   |
| Men/Women            | 2/3             | 7/8             | 0.795   |
| Body weight (kg)     | 53.3 (49.0–78.8)| 60.9 (40.0–75.0)| 0.760   |
| Dose of diazoxide (mg/day) | 400 (250–500) | 225 (50–425)         | 0.027   |
| Fajans’s score       | 0.48 (0.17–1.58)| 0.27 (0.03–1.95)| 0.150   |
| Tumor size (mm)      | 34 (12–110)     | 12 (0–86)       | 0.018   |
| Benign/Malignant tumor | 2/3             | 1/14            | 0.010   |

Data are presented as n or median with range. p values were obtained from Chi-square test or Mann–Whitney U test.

Fig. 1  Profile of platelet count in patients with thrombocytopenia after the administration of diazoxide. Large symbols indicate the date when diazoxide treatment was discontinued in each patient.
malignant insulinoma. Fluid retention was more frequently recorded among females than males. Diazoxide-induced thrombocytopenia may occur more frequently than previously thought in patients with insulinoma. Finally, our findings suggest that the patient’s platelet count should be frequently checked, at least in 2 or 3 weeks after the administration of diazoxide.

Disclosure

The authors declare that they have no competing interests.

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