Original Article

Safety and effectiveness, including intelligence prognosis, of diazoxide in pediatric patients with hyperinsulinemic hypoglycemia: special survey in Japan (long-term, all-case survey)

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Abstract. To evaluate the safety and effectiveness of the long-term administration of diazoxide in patients with hyperinsulinemic hypoglycemia, a post-marketing surveillance study was conducted. Between 2008 and 2015, with a maximum observation period of 7 yr, 384 patients were monitored; 117 (30.5%) experienced at least one adverse drug reaction (ADR). The most commonly observed ADR was hypertrichosis (8.6%). The incidence of water retention-related ADRs and cardiac failure-related ADRs was 8.3% and 3.4%, respectively, and many of these occurred within the first 2 mo of treatment. The mean fasting blood glucose level was 44.9 mg/dL at baseline and was maintained at > 70 mg/dL, the control target, for 4 yr. A total of 113 infants < 1 yr of age were evaluated for the prognosis for intelligence, and a majority (77.9%) were assessed as “normal” at the final evaluation. Most ADRs occurred at an early stage of treatment and blood glucose levels were well controlled during long-term administration. The proportion of “normal” patients tended to be higher in those who started treatment at a younger age. However, because of the exploratory nature of this analysis, potential effects of coexisting or underlying diseases and the age of onset or diagnosis should not be ignored.

Key words: diazoxide, hyperinsulinemic hypoglycemia, pediatric, glycemic control, intelligence prognosis

Introduction

Hyperinsulinemic hypoglycemia (HH) is caused by excessive insulin. Many cases occur in childhood (mainly in neonates and infants) as a congenital disorder (1, 2). Congenital HH in children can be transient or persistent (2, 3). Transient HH is often associated with certain factors, such as maternal diabetes mellitus, low birth weight, and neonatal respiratory or cardiovascular disease, and most cases are considered non-inherited. However, most cases of persistent HH are considered to be caused by genetic factors. The results of a nationwide survey for the fiscal year 2009–2010 supported by the Health and Labour Sciences Research Grants showed that approximately one individual in 17,000 births developed transient HH and approximately one individual in 35,400 births developed persistent HH (4). Symptoms of HH include hypoglycemia-associated sweating,
tachycardia, tremor, lethargic tendencies, difficulty in thinking, disturbed consciousness, and convulsion. The symptoms of transient HH can improve within 3 or 4 mo of onset, whereas persistent HH, which tends to improve with age, requires years of treatment (2, 3). Given that persistent or recurrent hypoglycemia can cause a high incidence of severe central nervous system-related sequelae, such as epilepsy and developmental delay, adequate long-term glycemic control is critical for patients with HH (5, 6).

The Guideline for the Diagnosis and Management of Congenital Hyperinsulinemia (hereinafter, the Guideline) (2) recommends that patients should at first be administered a continuous infusion of glucose; subsequently, if they fail to maintain sufficient blood glucose levels despite the infusion, an oral dose of diazoxide should be administered unless contraindicated (e.g., in patients with cardiac failure or pulmonary hypertension). Other treatment options include medical procedures, such as a subcutaneous injection of octreotide, which are not covered by health insurance in Japan and are considered second-line therapies for patients unresponsive to diazoxide.

Diazoxide, a benzothiadiazine derivative that can be administered orally, opens ATP-sensitive potassium channels in pancreatic beta cells and increases blood glucose levels through the inhibition of insulin secretion (7). This agent, developed overseas in the 1960s, was approved in the U.S. in 1976 for the indication of HH (7). In Japan, prior to its market launch in July 2008, diazoxide was imported privately and used.

As the sample size in the Japanese pre-approval clinical trial of diazoxide was limited (23 patients), a special survey (long-term, all-case survey; hereinafter, referred to as “the survey”) on diazoxide use in post-marketing clinical practice was conducted. Diazoxide is known to cause water retention when used for a prolonged period and attention should also be paid to the potential for the occurrence of cardiac failure in patients administered the drug (2, 8, 9). However, the available information is limited with regard to patients who develop these events, and there have been no reports on the probability of their actual clinical occurrences. Moreover, there are no published papers on any study of the effect of glycemic control by diazoxide on the intelligence prognosis in infants with HH. Based on data obtained from the survey, we investigated the safety and effectiveness of diazoxide in pediatric patients, with a focus on adverse drug reactions (ADRs) related to water retention and cardiac failure, as well as the intelligence prognosis in infants.

Methods

Survey population and study population

All patients with HH who started treatment with diazoxide (DIAZOXIDE Capsules 25 mg “MSD”) after the launch of the agent and patients of all age groups, including adults and the elderly, were included in the survey population. Based on the survey population, this study comprised pediatric patients < 15 yr of age who had not received any dose of privately imported diazoxide.

Survey period

From July 2008 to September 2015

Observation period

Patients were observed for up to 7 yr from the starting day of treatment with diazoxide to the day of completion of the survey, in principle. Patients continued to be observed even after completion or discontinuation of treatment with diazoxide.

Survey methods

Patients to be surveyed were registered by the central registration method at medical institutions with which a written contract was concluded. The survey was conducted in accordance with the “Ministerial Ordinance on Good Post-Marketing Study Practice” (Ministry
Survey of diazoxide in pediatrics

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Survey items

Data on sex, age (mo) at the start of treatment with diazoxide (hereinafter, baseline), coexisting diseases, underlying diseases, previous treatment for HH, concomitant drugs, use status of diazoxide, changes in blood glucose levels, glycemic control status, prognosis for intelligence, and adverse events were collected. Choice answers by check box was used for sex, underlying diseases, glycemic control status, and prognosis for intelligence. For the underlying diseases, one of the following were selected based on the physician’s diagnosis: “leucine sensitive hypoglycemia,” “nesidioblastosis,” “insulinoma,” and “extrapancreatic tumor.” If the diagnosis was not included in the above choices, the physician was free to describe the diagnosis. The condition was specified by a free descriptive answer. Previous medications for HH were glucose, glucagon, or octreotide, as specified in the therapeutic guideline (1).

In the survey, an adverse event was defined as any untoward medical occurrence in a patient administered diazoxide, irrespective of its causal relationship with the drug.

Safety and effectiveness evaluation criteria

In the safety evaluation, an ADR was defined as an adverse event for which a causal relationship to diazoxide could not be excluded. ADRs were classified on the basis of preferred terms (PTs) of MedDRA ver. 18.1. If the same ADR (when classified using PT) occurred more than once in the same patient, the ADR was counted as 1 event occurring in 1 patient. Events classified as fluid retention, generalised oedema, oedema, oedema peripheral, ascites, pleural effusion, pulmonary oedema, or fluid overload were counted as “water retention-related ADRs,” and those classified as cardiac failure or cardiac failure congestive were counted as “cardiac failure-related ADRs.” In cases in which the distinction between generalised oedema and peripheral oedema was unidentifiable, the event was classified as “oedema.”

As effectiveness endpoints, the changes from baseline in blood glucose levels after treatment and the glycemic control status were evaluated. The glycemic control status was based on the attending physician’s impression of “well-controlled,” “not controlled,” or “not evaluable” for each year after the start of treatment with diazoxide. For each annual observation time period, the number of patients evaluated, the number of patients by glycemic control status, and the complete response rate (“well-controlled” patients/“well-controlled” patients + “not controlled” patients × 100%) were recorded.

Prognosis for intelligence was also assessed in infants < 1 yr of age at baseline. Based on the intelligence quotient (IQ) or the developmental quotient (DQ) measured annually during the observation period and evaluated at the final point, prognosis for intelligence was assessed by attending physicians with reference to the following criteria: IQ/DQ of ≥ 70: “normal,” 50–<70: “slight mal-prognosis (MP),” 35–<50: “moderate MP,” 20–<35: “severe MP,” <20: “very severe MP,” and not assessed: “unknown.” The time point of the last evaluation by the physician for each patient was considered to represent the final evaluation.

Statistical analyses

Overall ADRs: the percentage of patients with at least 1 ADR was reported, and water retention- and cardiac failure-related ADRs by time of onset were analyzed using the Kaplan-Meier method, in which the initial onset of ADR was considered the event. Any ADR with an unknown time of onset was excluded from analysis.

Summary statistics for the fasting blood glucose levels for each time point were calculated. With regard to changes from baseline in the fasting blood glucose levels, the numbers of
patients, mean changes, mean change ratios, and the 95% confidence intervals for mean change ratios were obtained, and a paired-t test was performed. The mean changes and change ratios were calculated by using data from patients whose baseline and post-treatment measurements were available. Intelligence prognosis in infants at the final evaluation was determined in an exploratory manner using IQ or DQ. With regard to the prognosis for intelligence, the Wilcoxon rank-sum test was used to analyze the effect of patients’ age at the start of treatment with diazoxide. Fisher’s exact test was used for patients with a baseline blood glucose level of < 40 mg/dL and for diseases that could possibly affect the prognosis for intelligence. A pooled t-test was used for the minimum baseline blood glucose level to analyze the effect on prognosis for intelligence.

**Survey Results**

**Patient disposition**

In the survey, case report forms were collected from 432 pediatric patients < 15 yr of age, who had not received any dose of privately imported diazoxide (Fig. 1). Of these, 384 patients and 376 patients were included in the safety analysis and the effectiveness analysis populations, respectively. From the effectiveness analysis population, 199, 368, and 113 patients were included in the fasting blood glucose analysis population, glycemic control analysis population, and intelligence prognosis analysis population, respectively.

**Patient baseline characteristics and use status of diazoxide**

Of the 384 patients included in the safety analysis population, patients < 1 yr of age accounted for 94.5% (363 patients), and those with underlying diseases accounted for 20.8% (80 patients) (Table 1). The underlying diseases reported consisted of nesidioblastosis in 9 patients (2.3%), insulinoma in 1 patient (0.3%), and other diseases in 71 patients (18.5%). The underlying other diseases or conditions reported in ≥ 10 patients included low birth weight baby (24 patients), small-for-dates baby (14 patients), and Beckwith–Wiedemann syndrome and foetal growth restriction (12 patients each).

The mean administration period (mean ± SD; hereinafter, the same shall apply) was 238.7 ± 438.3 d; the mean initial dose was 7.4 ± 2.8 mg/kg/d for patients <1 yr of age and 4.3 ± 2.2 mg/kg/d for patients ≥1 yr of age; and the mean dose was 6.9 ± 3.1 mg/kg/d for patients <1 yr of age and 5.6 ± 2.8 mg/kg/d for patients ≥1 yr of age (Table 1). The minimum and maximum doses were 0.9 and 16.9 mg/kg/d for patients <1 yr of age and 1.7 and 10.8 mg/kg/d for patients ≥1 yr of age (Table 1).

**Safety**

**ADRs:** The percentage of patients who had at least 1 ADR was 30.5% (117 of 384 patients) (Table 2a). The commonly observed ADRs included hypertrichosis (8.6%), oedema (5.5%), anaemia (2.3%), and cardiac failure (2.3%) (Table 2b).

**ADRs of special interest:** In the safety analysis population, water retention-related ADRs and/or cardiac failure-related ADRs occurred in 40 patients (10.4%); specifically, water retention-related ADRs occurred in 32 patients (8.3%) and cardiac failure-related ADRs occurred in 13 patients (3.4%). The water retention-related ADRs reported consisted of 21 cases of oedema, five cases of fluid retention, three cases of generalised oedema, and two cases of pulmonary oedema (data not shown). The cardiac failure-related ADRs consisted of nine cases of cardiac failure and five cases of cardiac failure congestive (Table 2b). The results of the Kaplan-Meier analysis indicated that most cases of water retention- and cardiac failure-related ADRs tended to occur within 2 mo of the start of treatment with diazoxide (Fig. 2). A total of 23 cases of serious water retention-
or cardiac failure-related ADRs occurred in 20 patients (5.2%). These 20 patients comprised 11 patients who had perinatal abnormality (e.g., low birth weight baby and premature baby) and/or cardiovascular malformation (e.g., Fallot’s tetralogy and atrial septal defect). The outcomes of serious water retention- or cardiac failure-related ADRs were “resolved” or “improved” in
### Table 1  Patient baseline characteristics

| Patient Baseline Factors                                      | Number of patients (%) |
|-------------------------------------------------------------|-------------------------|
| Safety analysis population                                  | 384 (100.0)             |
| **Sex**                                                    |                         |
| Male                                                       | 235 (61.2)              |
| Female                                                     | 149 (38.8)              |
| **Age**                                                    |                         |
| < 1 yr                                                     | 363 (94.5)              |
| 0 mo                                                       | 205 (53.4)              |
| 1 mo                                                       | 118 (30.7)              |
| ≥ 2 mo                                                     | 40 (10.4)               |
| 1–< 6 yr                                                   | 14 (3.6)                |
| ≥ 6 yr                                                     | 7 (1.8)                 |
| **Underlying disease ¹**                                   |                         |
| Yes                                                        | 80 (20.8)               |
| Insulinoma                                                 | 1 (0.3)                 |
| Nesidioblastosis                                           | 9 (2.3)                 |
| Other                                                      | 71 (18.5)               |
| No                                                         | 243 (63.3)              |
| Unknown or not entered                                     | 61 (15.9)               |
| **Previous treatment for HH**                              |                         |
| Yes                                                        | 166 (43.2)              |
| No                                                         | 216 (56.3)              |
| Unknown or not entered                                     | 2 (0.5)                 |
| **Concomitant drug treatment for HH**                      |                         |
| Yes                                                        | 277 (72.1)              |
| No                                                         | 106 (27.6)              |
| Unknown or not entered                                     | 1 (0.3)                 |
| **Administration period**                                  |                         |
| Mean ± SD (d)                                              |                         |
| ≤ 1 mo                                                     | 152 (39.6)              |
| > 1–3 mo                                                   | 74 (19.3)               |
| > 3–6 mo                                                   | 53 (13.8)               |
| > 6 mo–1 yr                                               | 40 (10.4)               |
| > 1 yr                                                     | 65 (16.9)               |
| **Initial dose (mg/kg/d)**                                 |                         |
| Aged < 1 yr ²                                              |                         |
| Mean ± SD                                                  | 7.4 ± 2.8               |
| Min, Max                                                   | 0.3, 17.4               |
| < 5                                                        | 66 (18.2)               |
| 5–10                                                       | 204 (56.2)              |
| 10–20                                                      | 79 (21.8)               |
| Unknown or not entered                                     | 14 (3.9)                |
| Aged ≥ 1 yr ³                                              |                         |
| Mean ± SD                                                  | 4.3 ± 2.2               |
| Min, Max                                                   | 0.5, 9.9                |
| < 3                                                        | 3 (14.3)                |
| 3–5                                                       | 10 (47.6)               |
| > 5–20                                                     | 5 (23.8)                |
| Unknown or not entered                                     | 3 (14.3)                |
| **Mean dose (mg/kg/d)**                                    |                         |
| Aged < 1 yr ²                                              |                         |
| Mean ± SD                                                  | 6.9 ± 3.1               |
| Min, Max                                                   | 0.9, 16.9               |
| < 8                                                        | 238 (65.6)              |
| 8–15                                                       | 104 (28.7)              |
| > 15–20                                                   | 5 (1.4)                 |
| Unknown or not entered                                     | 16 (4.4)                |
| Aged ≥ 1 yr ³                                              |                         |
| Mean ± SD                                                  | 5.6 ± 2.8               |
| Min, Max                                                   | 1.7, 10.8               |
| < 3                                                        | 5 (23.8)                |
| 3–8                                                       | 7 (33.3)                |
| > 8–20                                                     | 4 (19.0)                |
| Unknown or not entered                                     | 5 (23.8)                |
| Renal impairment                                           |                         |
| Yes                                                        | 9 (2.3)                 |
| No                                                         | 374 (97.4)              |
| Unknown or not entered                                     | 1 (0.3)                 |
| Hepatic impairment                                         |                         |
| Yes                                                        | 11 (2.9)                |
| No                                                         | 372 (96.9)              |
| Unknown or not entered                                     | 1 (0.3)                 |

¹ If a patient had more than one underlying disease, then the patient was counted for each relevant underlying disease. ² N = 363. ³ N = 21. HH = Hyperinsulinemic hypoglycemia.
Table 2  Adverse drug reactions in the safety analysis population

a: Overall ADRs

|                                | 165 |
|--------------------------------|-----|
| Number of institutions         | 165 |
| Number of patients in Safety analysis population | 384 |
| Number of patients with ADRs   | 117 (30.5%) |
| Number of events of ADRs       | 230 |

b: ADRs ≥ 0.5% by preferred term (N = 384)

| System organ class | preferred term                      | n  | (%) |
|--------------------|-------------------------------------|----|-----|
| Infections and infestations | Bronchitis                       | 4  | (1.0) |
|                      | Gastroenteritis                    | 3  | (0.8) |
|                      | Pharyngitis                        | 2  | (0.5) |
| Blood and lymphatic system disorders | Anaemia               | 9  | (2.3) |
|                      | Anaemia neonatal                   | 2  | (0.5) |
|                      | Iron deficiency anaemia            | 4  | (1.0) |
| Metabolism and nutrition disorders | Fluid retention                | 5  | (1.3) |
|                      | Hyperkalaemia                      | 2  | (0.5) |
|                      | Hyperuricaemia                     | 2  | (0.5) |
|                      | Hyponatraemia                      | 3  | (0.8) |
| Nervous system disorders   | Epilepsy                           | 2  | (0.5) |
|                      | Febrile convulsion                 | 3  | (0.8) |
|                      | Seizure                            | 2  | (0.5) |
| Cardiac disorders        | Cardiac failure                    | 9  | (2.3) |
|                      | Cardiac failure congestive         | 5  | (1.3) |
|                      | Cardiac hypertrophy                | 2  | (0.5) |
| Vascular disorders       | Circulatory collapse               | 2  | (0.5) |
| Respiratory, thoracic and mediastinal disorders | Asthma          | 2  | (0.5) |
|                      | Pulmonary hypertension             | 2  | (0.5) |
|                      | Pulmonary oedema                   | 2  | (0.5) |
| Hepatobiliary disorders  | Hepatic function abnormal          | 3  | (0.8) |
|                      | Hyperbilirubinaemia                | 2  | (0.5) |
| Skin and subcutaneous tissue disorders | Hypertrichosis          | 33 | (8.6) |
|                   | Muscle, and connective tissue disorders | Rickets | 2 | (0.5) |
| Renal and urinary disorders | Oliguria                        | 2  | (0.5) |
| Congenital, familial and genetic disorders | Patent ductus arteriosus | 5  | (1.3) |
| General disorders and administration site conditions | Generalised oedema | 3  | (0.8) |
|                      | Oedema                             | 21 | (5.5) |
|                      | Pyrexia                            | 3  | (0.8) |
| Investigations        | Blood pressure decreased           | 3  | (0.8) |
|                      | Neutrophil count decreased         | 4  | (1.0) |
|                      | Platelet count decreased           | 3  | (0.8) |
|                      | Weight increased                   | 3  | (0.8) |
|                      | Blood alkaline phosphatase increased | 3 | (0.8) |
|                      | Urine output decreased             | 5  | (1.3) |
|                      | Hepatic enzyme increased           | 2  | (0.5) |

MedDRA ver 18.1. ADR = Adverse drug reaction.
22 of 23 cases, including 14 cases assessed as “resolved” or “improved” after the discontinuation or completion of treatment with diazoxide.

Effectiveness

Fasting blood glucose levels: In the fasting blood glucose analysis population, the mean fasting blood glucose level (mean ± SD) was 44.9 ± 24.0 mg/dL at baseline, which improved to 78.1 ± 22.5 mg/dL after 1 mo and 88.3 ± 25.2 mg/dL after 3 mo and was maintained at > 70 mg/dL, the control target, for 4 yr, resulting in 79.1 ± 20.7 mg/dL at the final evaluation. Patients with a fasting blood glucose level of ≥ 70 mg/dL at the final evaluation accounted for 74.9% (149 of 199 patients). The mean fasting blood glucose level at any time point was < 110 mg/dL, with no further increases over time. The mean change from baseline in the fasting blood glucose level (mean ± SD) was 31.4 ± 27.5 mg/dL after 1 mo and 39.2 ± 33.5 mg/dL after 3 mo, which was significantly different from baseline at both time points (Fig. 3). A statistically significant increase in the fasting blood glucose after treatment with diazoxide continued for 3 yr; the mean change from baseline at the final evaluation was 34.3 ± 28.2 mg/dL, which was also statistically significant.

Glycemic control status: In the glycemic control analysis population, the complete response rate was 96.7% (356 of 368 patients) after 1 yr and 96.5% (273 of 283 patients) at the final evaluation. Of 356 patients assessed as “well-controlled” after 1 yr, three patients were assessed as “not controlled” after 2 yr based on the results of a subsequent glycemic control assessment performed during the observation period.

Prognosis for intelligence: Of 113 infants included in the intelligence prognosis analysis population, the majority (88 patients; 77.9%) were assessed as “normal” (hereinafter, “normal patients”) at the final evaluation, and those assessed as “slight MP,” “moderate MP,” “severe MP,” or “very severe MP” (hereinafter, “MP patients”) accounted for 22.1% (25 patients).
As potential patient-related factors that could affect the prognosis for intelligence, the patient’s age at the start of treatment with diazoxide, baseline blood glucose levels, coexisting diseases, and underlying diseases were investigated. As potential treatment factors, the timing of the start of treatment with diazoxide and the glycemic control status were investigated.

1) Patient’s age at the start of treatment with diazoxide, baseline blood glucose levels, coexisting diseases, and underlying diseases

The “normal patients” accounted for 90.0% of the infants 0 mo of age at baseline (54/60 patients), 70.5% of those 1 mo of age at baseline (31/44 patients), and 33.3% of those ≥ 2 mo of age at baseline (3/9 patients). The “MP patients” accounted for 10.0% of the infants 0 mo of age at baseline (6/60 patients), 29.5% of those 1 mo of age at baseline (6/60 patients), 29.5% of those ≥ 2 mo of age at baseline (6/9 patients). The prognosis for intelligence showed a tendency to be poorer for patients who were treated with diazoxide when older (p < 0.0001).

Of all evaluated patients, 73.9% (65/88 patients) of “normal patients,” and 76.0% (19/25 patients) of the “MP patients” were treated with diazoxide.
patients) of “MP patients” were infants with a baseline blood glucose level (measured for diagnosis of hypoglycemia) of < 40 mg/dL. The mean value for the minimum baseline blood glucose level was 29.9 mg/dL for “normal patients” and 31.6 mg/dL for “MP patients.” Statistically significant differences were not observed between “normal patients” and “MP patients” for the percentage of patients with baseline blood glucose level of < 40 mg/dL (p = 1.0000) and the mean minimum baseline blood glucose level (p = 0.5506).

Of the coexisting diseases and reported underlying diseases, nesidioblastosis, insulinoma, Beckwith-Wiedemann syndrome, hypoglycaemic encephalopathy, neonatal asphyxia, encephalomalacia, epilepsy, periventricular leukomalacia, Costello syndrome, trisomy 13, trisomy 21, apneic attack, convulsion neonatal, postresuscitation encephalopathy, cerebral palsy, Klinefelter’s syndrome, and Sturge-Weber syndrome were evaluated as diseases that may affect the prognosis for intelligence (prognosis-for-intelligence-related diseases, hereafter). Prognosis-for-intelligence-related diseases were observed in 18.2% (16/88 patients) in “normal patients,” and 56.0% (14/25 patients) in “MP patients.” The percentage of patients with prognosis-for-intelligence-related diseases was significantly higher in “MP patients” compared with “normal patients” (p = 0.0004). Among patients who were assessed as “severe MP” or “very severe MP,” some had hypoglycemic encephalopathy, periventricular leukomalacia, or trisomy 13. The percentage of patients with multiple prognosis-for-intelligence-related diseases was 1.1% (1/88 patients) in “normal patients” and 16.0% (4/25 patients) in “MP patients.”

The demographic characteristics of patients without prognosis-for-intelligence-related diseases were tabulated by prognosis for intelligence (Table 4). With regard to the patient’s age at the start of treatment with diazoxide, the majority of the infants were 0 mo of age (59.7%) for “normal patients,” and 1 mo of age (54.5%) for “MP patients.” The age at the start of treatment was significantly higher in “MP patients” (p = 0.0112). Statistically significant differences were not observed in the number of patients with baseline blood glucose level of < 40 mg/dL, the number of days from the diagnosis of hypoglycemia to the start of treatment, or the glycemic control status at final evaluation.

2) Timing of start of treatment with diazoxide and glycemic control status

With regard to the timing of start of treatment with diazoxide, the number of days

### Table 3 Results of assessment of prognosis for intelligence in infants

| Prognosis for intelligence (At the final evaluation) | Number of patients aged < 1 yr | 0 mo | 1 mo | 2–11 mo |
|-----------------------------------------------------|--------------------------------|------|------|---------|
| Normal                                              | n | % | n | % | n | % | n | % |
| MP                                                  | 88 | 77.9 | 54 | 90.0 | 31 | 70.5 | 3 | 33.3 |
| Normal                                              | 25 | 22.1 | 6 | 10.0 | 13 | 29.5 | 6 | 66.7 |
| Slight MP                                           | 9 | 8.0 | 2 | 3.3 | 5 | 11.4 | 2 | 22.2 |
| Moderate MP                                         | 7 | 6.2 | 3 | 5.0 | 4 | 9.1 | 0 | 0.0 |
| Severe MP                                           | 4 | 3.5 | 0 | 0.0 | 2 | 4.5 | 2 | 22.2 |
| Very severe MP                                      | 5 | 4.4 | 1 | 1.7 | 2 | 4.5 | 2 | 22.2 |

MP = Mal-prognosis.
from the diagnosis of hypoglycemia to the start of treatment was counted. The mean number of days was 3.9 (maximum of 29 d) for “normal patients” and 6.9 for (maximum of 43 d) for “MP patients”; this difference was not significant (p = 0.1166). At the final evaluation for glycemic control status, 97.6% (41/42 patients) and 100.0% (16/16 patients) were “well-controlled” in “normal patients” and “MP patients,” respectively.

**Discussion**

Analyses were performed on data on pediatric patients < 15 yr of age extracted from the results of the survey conducted to investigate the long-term safety and effectiveness of diazoxide in daily clinical practice. Case report forms were collected from 432 pediatric patients who had not received any dose of privately imported diazoxide; 384 of 432 patients were included in the safety analysis population.

The percentage of patients who had at least 1 ADR was 30.5% (117/384 patients). The most commonly observed ADR was hypertrichosis (8.6%), which was followed by oedema (5.5%) and anaemia and cardiac failure (2.3% each). A total of 40 patients (10.4%) experienced water retention- and/or cardiac failure-related ADRs. These ADRs are indicated in the package insert as clinically significant ADRs for diazoxide (9). To be more specific, water retention-related ADRs, including 21 cases of edema and 5 cases of fluid retention, were reported in 32 patients (8.3%), and cardiac failure-related ADRs, including 9 cases of cardiac failure and 5 cases of cardiac failure congestive, were reported in 13 patients (3.4%). The results of a Kaplan-Meier analysis showed that most of these ADRs tended to occur within 2 mo of the start of treatment with diazoxide. Of the water retention- and cardiac failure-related ADRs, 23 cases reported in 20 patients (5.2%) were assessed as serious. The outcomes of these serious ADRs were “resolved” or “improved” in 22 cases, of which 14 cases were “resolved” or “improved” after the discontinuation or completion of treatment with diazoxide. Approximately half (11 patients) of the patients with relevant serious ADRs had a perinatal abnormality (e.g., low birth weight baby and premature baby) and/or cardiovascular

| Prognosis for intelligence | Normal patients | MP patients |
|---------------------------|----------------|------------|
| Number of patients without prognosis-for-intelligence-related diseases | 72 | 11 |
| Age in mo at the start of treatment with diazoxide | | |
| 0 mo | 43 | 3 | 27.3% |
| 1 mo | 27 | 6 | 54.5% |
| 2–11 mo | 2 | 2 | 18.2% |
| Baseline blood glucose level of < 40 mg/dL | 54 | 9 | 81.8% |
| Number of days from the diagnosis of hypoglycemia to the start of treatment (d) | 4.1 | 4.1 | |
| Glycemic control status* (At the final evaluation) | | |
| Well-controlled | 35 | 9 | 100.0% |
| Not controlled | 1 | 9 | 0.0% |

* N = “well-controlled” + “not controlled.” MP = Mal-prognosis.
malformation (e.g., Fallot’s tetralogy and atrial septal defect). Although no trends in ADRs were clarified in the Japanese clinical trial owing to its small sample size, the above results were obtained from the more substantial number of patients reported in this survey.

The mean fasting blood glucose level statistically significantly increased to 158.4% of the mean baseline level (44.9 ± 24.0 mg/dL) after 1 mo and continued to increase significantly and numerically until 3 mo, after which it was maintained until 4 yr. Thus, the mean fasting blood glucose level remained > 70 mg/dL between 1 mo and 4 yr and at the final evaluation, thereby achieving the control target (> 70 mg/dL) specified in the Guideline (2). We have conducted an exploratory study and investigation of the actual situation of the prognosis for intelligence for HH in Japan, on account of the limitations for the investigation of the prognosis for intelligence, namely, the absence of control group because of the nature of the survey being held in daily clinical practice. Among the 113 infants who were assessed on the prognosis for intelligence at the final evaluation, 88 infants (77.9%) were “normal patients” and 25 infants (22.1%) were “MP patients.” Although a simple comparison is challenging owing to the differences in the sample population and assessment methods on the prognosis for intelligence, the percentage of “MP patients” in this study (22.1%) tended to be lower than that in the study conducted with a small population size overseas (10), in which 34% of the population had hypoglycemic symptoms during the neonatal period and 63% of the population had hypoglycemic symptoms during infancy.

First, as factors of demographic characteristics, the age at the start of treatment with diazoxide, baseline blood glucose level, and prognosis-for-intelligence-related diseases were evaluated. The percentage of “normal patients” tended to be higher when treatment with diazoxide was started at an earlier age. Significant differences were not observed in the percentage of patients with baseline blood glucose level of < 40 mg/dL between “normal patients” and “MP patients,” and statistical difference between the two groups was also not observed for the minimum baseline blood glucose level. These results implied that the baseline blood glucose level was not a factor that causes a reduced prognosis for intelligence. The number of patients with prognosis-for-intelligence-related diseases was significantly higher in “MP patients” compared with “normal patients.” There were no notable differences in the demographic characteristics of “normal patients” and “MP patients,” when the evaluation was performed only on patients without prognosis-for-intelligence-related diseases.

The results in this study were similar to that of the study overseas (10), including the higher incidence of mental retardation in HH infants compared with HH neonates, and minimum baseline blood glucose level with no statistical differences between the group of patients with psychomotor or mental retardation and the group of normal patients.

Second, as treatment factors, the promptness of the treatment and complete response rate of glycemic control were evaluated. Statistically significant differences were not observed between “normal patients” and “MP patients” for the number of days from the diagnosis of hypoglycemia to the start of treatment with diazoxide or the complete response rate of glycemic control.

Patients with aggravated prognosis for intelligence were observed, despite the success in early glycemic control. The possible factors were speculated to be the age of onset along with coexisting or underlying diseases. However, a firm conclusion cannot be drawn as the population size evaluated for prognosis for intelligence was small; therefore, factors other than survey items could affect the prognosis for intelligence.

Given that the survey was performed in daily clinical practice and complete information may not have been obtained, the survey population included patients with acquired hypoglycemia, and various concomitant drugs were used with
diverse administration methods, there are limitations to the interpretation of its results. In contrast, the data obtained on the safety and effectiveness of diazoxide used in daily clinical practice in pediatric patients with a variety of baseline characteristics are considered significant.

**Conclusion**

Of the results of the special survey of diazoxide in patients with HH, data from pediatric patients < 15 yr of age were analyzed. Many cases of ADRs, including water retention- and cardiac failure-related ADRs, occurred at an early stage of treatment with diazoxide. Blood glucose levels after the start of treatment were well controlled. Although the efficacy of diazoxide in the treatment of central nervous system symptoms caused by severe hypoglycemia has not been demonstrated, this study, despite its exploratory nature, showed that coexisting or underlying diseases and the time of onset are likely to be factors that could impact the prognosis for intelligence.

**Conflict of Interest:** Authors are employees of MSD K.K., Tokyo, Japan, a subsidiary of Merck & Co., Inc., Kenilworth, N. J., U.S.A., and potentially own stock and/or hold stock options in the company.

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