Original Article

Experience with enteral sulfonylurea monotherapy for extremely low birth weight infants with hyperglycemia

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Highlights

- This is the first case series of SU treatment in hyperglycemic ELBWIs
- SU can be helpful in decreasing blood glucose levels in hyperglycemic ELBWIs
- Further studies are required to evaluate efficacy and safety of SU in ELBWIs

Abstract: Limited data are available on the effects of enteral sulfonylurea (SU) monotherapy in extremely low birth weight infants (ELBWIs) with hyperglycemia. Therefore, we report our experience with enteral SU monotherapy for hyperglycemic ELBWIs. We retrospectively evaluated 11 hyperglycemic ELBWIs (seven male infants, median gestational age = 24.9 wk) who received SU between January 2016 and December 2019. Blood glucose (BG) levels were monitored before and after SU initiation and evaluated for the occurrence of adverse effects. We administered SU at a median of 15 d (interquartile range [IQR]: 12–20 d) after birth, with the median maximum dose of 0.2 mg/kg/d (IQR: 0.125–0.3 mg/kg/d). Hyperglycemia improved in all patients, and the target BG levels were achieved without severe side effects at a median of 6 d (IQR: 4–8.5 d) after initiation of treatment. The incidence of hypoglycemia during SU treatment was observed in 18 events per 1000 patient hours; however, the patients were asymptomatic. Based on these results, enteral SU monotherapy may be considered as an option for hyperglycemic ELBWIs.

Key words: glyburide (glibenclamide), hyperglycemia, infant, extremely low birth weight, sulfonylurea

Introduction

The incidence rate of hyperglycemia in extremely low birth weight infants (ELBWIs) is 32%–88% during the first 14 d of life, which is significantly higher than its incidence in infants with normal birth weight ($\geq$ 2500 g) (1, 2). ELBWIs that develop hyperglycemia during the postnatal period show increased short- and long-term mortality rates. Early intervention to regulate blood glucose levels is essential because persistent hyperglycemia increases the risk of adverse events, such as sepsis, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP) and death (1–4).

A protocol that allows timely management of hyperglycemia in ELBWIs should be established. However, to date, no valid evidence-based criteria to ensure effective interventions for hyperglycemia or blood glucose (BG) levels in ELBWIs exists (5). Stress is a possible cause of hyperglycemia; therefore, it must be ruled out first. Several studies have reported that certain strategies, such as discontinuing hyperglycemia-causing drugs, reducing dextrose infusion rate, administering intravenous amino acids, and promoting enteral feeding, are effective in improving hyperglycemia in ELBWIs. The American Academy of Pediatric Nutrition recommends insulin administration to control hyperglycemia in low birth weight infants to maintain a sufficient caloric intake for their growth (6); however, insulin therapy presents an increased risk of hypoglycemia (7–9). Moreover, it is difficult to achieve euglycemia in infants born at a gestational age < 28 wk because intravenous infusion and insulin dosage typically require multiple changes in protocol (5, 10). Therefore, safe alternative drugs with efficacy rates equivalent to or better than those of insulin are required for treating hyperglycemia in ELBWIs (11, 12).

Conversely, sulfonylureas (SUs) are known to decrease the BG levels in infants with neonatal diabetes mellitus (NDM) in the early postnatal period, and presently considered as an established treatment for this disease (13). SUs enhance the secretion of endogenous insulin by binding to the SU receptor subunit of the ATP-sensitive potassium (K_{ATP}) channel on pancreatic β-cells. These drugs have been used to treat type-2 diabetes mellitus for several years. Pearson *et al.* reported the efficacy of SU in NDM caused by *KCNJ11* mutations (14); and consequently, the efficacy and safety of SUs have been further demonstrated in NDM that is also associated with other genetic mutations (15).

Although SUs are effective even in cases of non-K_{ATP} channel genetic mutations (16), there have been no reports regarding their use for the treatment of hyperglycemia in ELBWIs. Therefore, in this study, we report our experience with SU monotherapy for ELBWIs who developed hyperglycemia in the early postnatal period.

Materials and Methods

We retrospectively evaluated the medical records of all hyperglycemic ELBWIs who received SU between January 2016 and December 2019 at our institution. We excluded patients who were treated with SU for less than 48 h, referred to another hospital, or had congenital malformations. This study was conducted according to the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Studies issued by the Ministry of Health, Labor and Welfare, of our country. The study was approved by the Central Ethics Board of our institution. Adequate explanations about the risks and benefits of SUs were provided to all patients' families at the time of the initial decision to use.

We collected data on the demographic and clinical characteristics of the patients, including sex, gestational age (wk), birth weight (g), comorbidities, maternal information, insulin administration before SU treatment, age (d) at initiation and discontinuation of SU, duration from the diagnosis of hyperglycemia to SU treatment, dose of SU, daily amount of enteral nutrition, rate of increase in weight for 28 d after SU treatment, weight at 37 wk of postmenstrual age, presence of ROP, and abnormalities on brain magnetic resonance imaging (MRI) at discharge. We considered the MRI abnormalities to be intracranial hemorrhage or abnormal signal intensity in the white matter. We also collected data on concomitant medications known to influence circulating blood glucose levels (e.g., steroids, dopamine hydrochloride, dobutamine hydrochloride, xanthine, caffeine, or indomethacin). Laboratory data included arterial and venous blood gas analysis, complete blood count, blood biochemistry and urine analysis.

We initiated enteral SU in patients with persistent hyperglycemia (defined as BG levels $\geq$ 180 mg/dL on at least two occasions) (17) who were receiving milk feed $\geq$ 100 mL/kg/d. We administered SU by enteral tube. The prescribed dosage of SU was according to the discretion of the attending physician and based on the previous reports (14, 16). We used crushed glibenclamide with added lactose as SU treatment which was dissolved in sterile water before administration.

Before SU administration, we measured the BG levels at least every 24 h until postnatal day (PD) 5, and every 3 days after PD 6. The target BG level was 47–180 mg/dL (7). In cases of hyperglycemia, we first excluded infection as a cause and reduced the amount of medication that may have been responsible for it. When hyperglycemia persisted and the quantity of enteral nutrition was 100 mL/kg/d, we considered treatment with SU.

We monitored BG at least three times a day for 1 wk after the initiation of or increase in SU dosage, and once a day after stabilization of BG. Additional BG monitoring was performed at the discretion of the attending physician. In cases of hypoglycemia we immediately administered intravenous dextrose or enteral milk, and resumed SU treatment according

to the attending physician's opinion. Discontinuation was defined as the absence of SU administration for > 48 h. The BG levels were measured using RAPIDPoint 500 (Siemens Healthcare Diagnostics K.K., Tokyo, Japan), ABL-90 FLEX analyzer (Radiometer Medical ApS, Brønshøj, Denmark), or FreeStyle Freedom Lite (NIPRO Corporation, Osaka, Japan). Adverse events (AEs) were defined as symptoms that appeared from the first day of SU administration to 24 h after the end of SU administration. The most important AE, hypoglycemia, was defined as follows (18, 19):
· Hypoglycemia: BG levels < 47 mg/dL
· Severe hypoglycemia: BG levels < 47 mg/dL with severe cognitive impairment (including coma and seizures) that required aggressive carbohydrate administration.

Other AEs were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (20). We conducted descriptive analyses for the baseline and follow-up periods. Continuous variables are expressed as medians and interquartile ranges (IQRs), whereas categorical variables are expressed as frequencies and proportions. All analyses were performed using STATA 16.0 (StataCorp, College Station, TX, USA).

Results

A total of 55 ELBWIs were born during the study period, of whom 30 (55%) developed hyperglycemia within 28 d of life. We performed SU treatment using glibenclamide in 11 patients (**Fig. 1**). **Table 1** summarizes the baseline characteristics of the study cohort. The median gestational age was 24.9 wk (IQR: 23.9–25.3 wk), and the median birth weight was 655 g
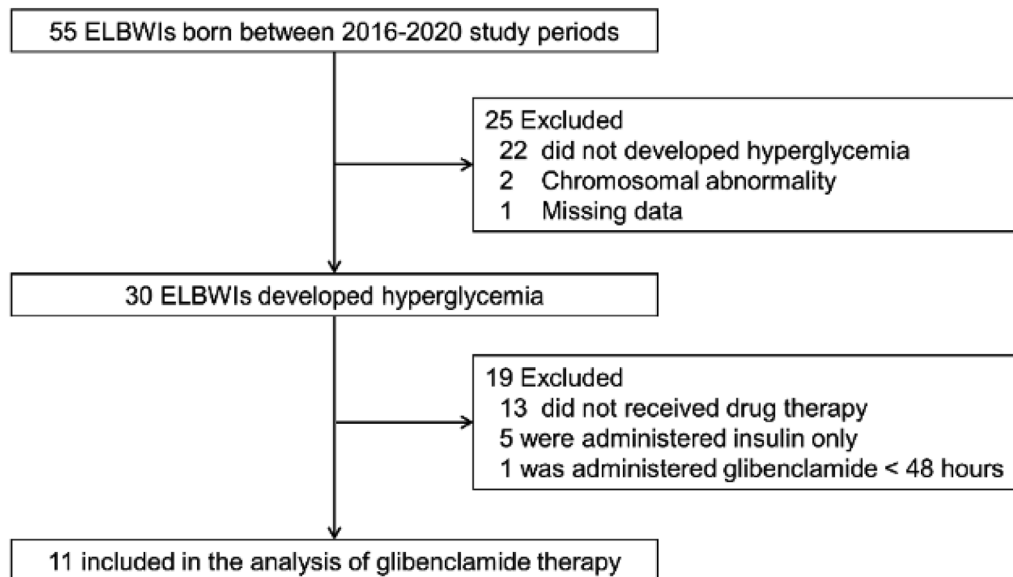

Fig. 1. Patient flow chart.

Table 1. Baseline characteristics of the study population

Case ID	Sex	GA at birth (wk, d)	BW (g)	Number of antenatal betamethasone	Pregnancy-related complications	Onset of hyperglycemia (PD)	Maximum BG levels (mg/dL)	Serum insulin levels (IU/mL)	At initiation of SU treatment		
									Comorbidities	Milk intake (mL/kg/d)	Concomitant medications
1	F	23w4d	571	2	PROM, CAM	3	371	2.3	–	132	Caffeine
2	F	25w0d	660	0	–	18	305	18.4	IVH grade IV	136	HDC
3	M	26w5d	795	2	PROM, CAM	5	316	6.3	–	50	Caffeine
4	M	23w1d	339	2	PROM, CAM	1	385	–	Sepsis	117	–
5	M	23w1d	513	2	PROM, CAM	4	399	–	–	125	HDC
6	M	24w4d	655	2	PROM, CAM	14	388	–	–	105	–
7	M	25w2d	681	2	PROM, CAM	4	336	–	–	100	DOA
8	F	25w2d	583	2	CAM	4	302	–	–	116	–
9	F	25w4d	763	2	PROM	2	480	–	–	102	–
10	M	22w6d	620	0	PROM, CAM, GDM	14	467	–	IVH grade II	94	HDC, DOA
11	M	24w6d	657	2	PROM, CAM	1	248	12.1	IVH grade II	120	Caffeine

BG, blood glucose; BW, body weight; CAM, chorioamnionitis; DOA, dopamine hydrochloride; GA, gestational age; GDM, gestational diabetes mellitus; HDC, hydrocortisone; ID, identification; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PD, postnatal day; PROM, premature rupture of membranes; SU, sulfonylurea.

Table 2. Detailed description of the sulfonylurea therapy for each patient

Case ID	Age at initiation of SU (PD)	Initiation SU dose (mg/kg/d)	Maximum SU dose (mg/kg/d)	SU dose before discontinuation (mg/kg/d)	Time to achieve the target BG levels (d)	Age at discontinuation of SU (PD)
1	93	0.15	0.15	0.15	8	145
2	26	0.10	0.10	0.05	4	32
3	7	0.10	0.20	0.05	11	68
4	15	0.25	0.25	0.10	3	100
5	11	0.50	0.75	0.70	8	23
6	14	0.10	0.40	0.02	13	128
7	9	0.20	0.30	0.025	9	76
8	13	0.22	0.30	0.10	6	44
9	20	0.10	0.10	0.05	5	35
10	19	0.17	0.15	0.05	4	67
11	15	0.10	0.10	0.10	3	19

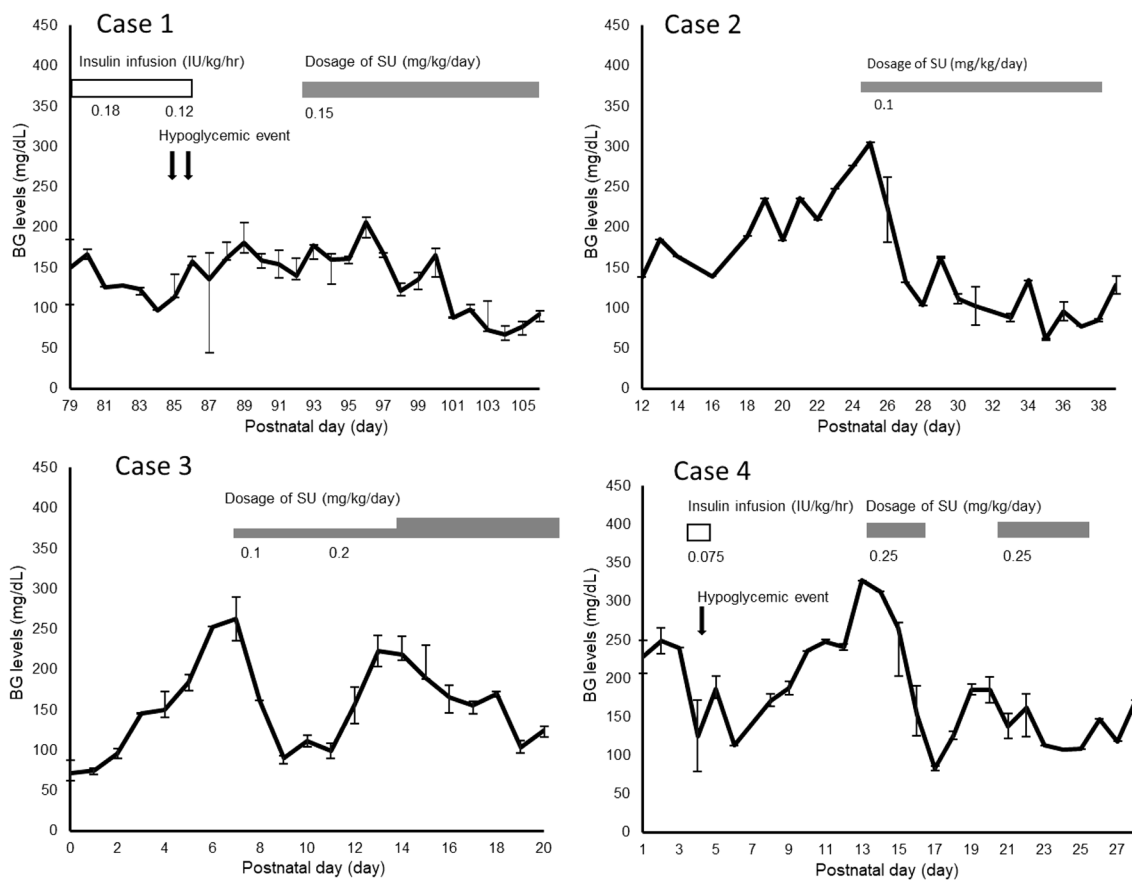BG, blood glucose; ID, identification; PD, postnatal day.

Fig. 2. Daily blood glucose levels for 14 d before and after the introduction of sulfonylurea (SU). Cases 1 and 4 patients received intravenous insulin before SU treatment. The blood glucose (BG) levels decreased within a few days after SU administration in all patients. Cases 5, 6, and 9 patients required reintroduction of SU because their BG levels were elevated after SU discontinuation. Hypoglycemic events during SU treatment occurred in six patients, all of whom were asymptomatic.

(IQR: 577–670 g). Seven patients (64%) were male. Cases 4 and 5 involved dichorionic diamniotic twins. Only one patient received partial parenteral nutrition combined with enteral nutrition at the start of SU treatment. Of the 11 patients, nine were intubated at the initiation of SU, but all patients had recovered from acute respiratory distress.

Patients developed hyperglycemia at a median age of PD 4 (IQR: 2.3–4.5). The highest median BG level before SU treatment was 371 mg/dL (IQR: 311–396 mg/dL). We measured the serum insulin levels in four patients, in whom the median serum insulin level was 9.2 mIU/mL. Two patients had received insulin before SU treatment: case 1 patient received intravenous insulin
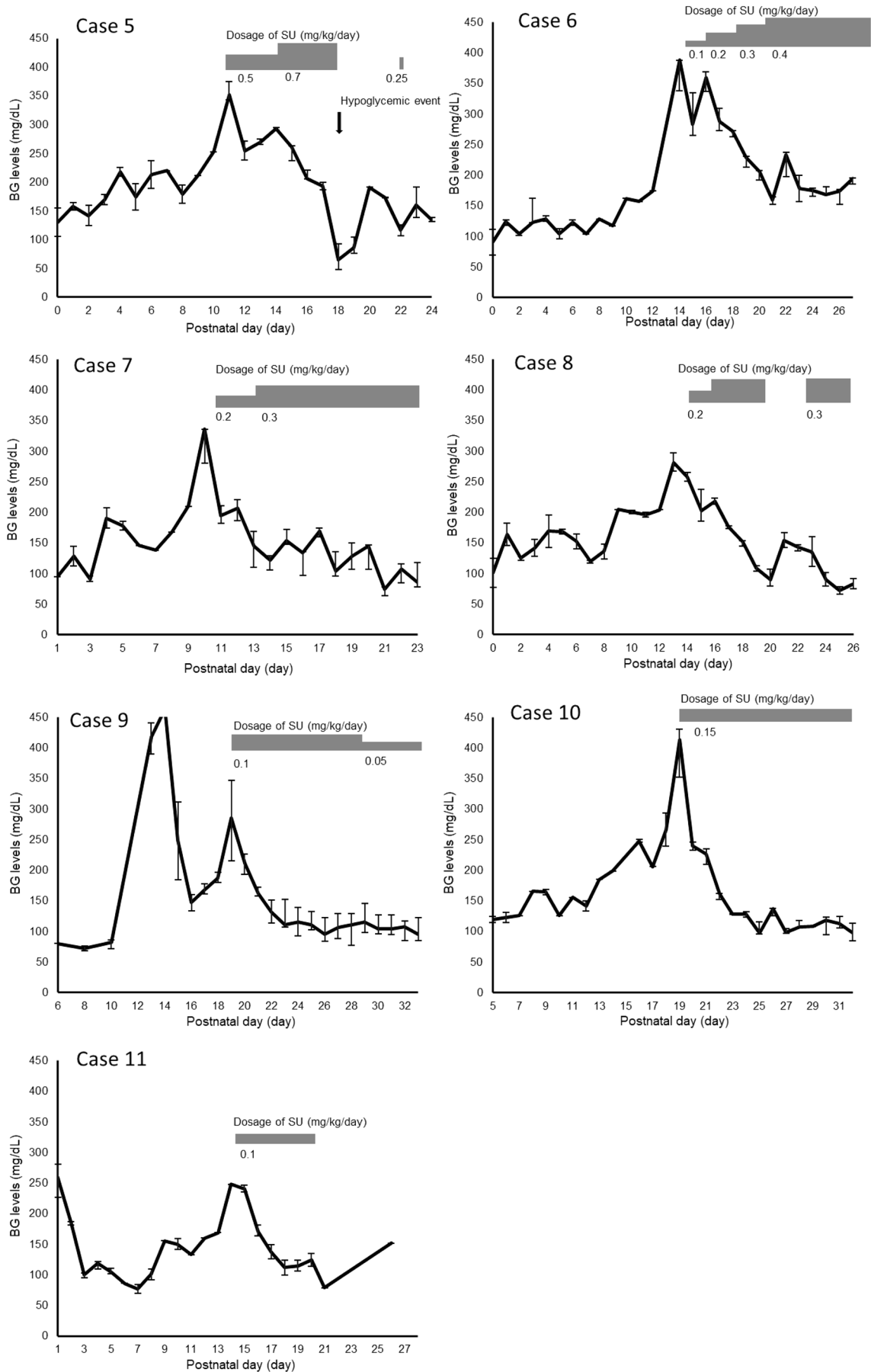
Fig. 2. continued.

Table 3. Detailed description of hypoglycemia during sulfonylurea therapy

Event No.	Case ID	BG levels at hypoglycemia (mg/dL)	Time from start of SU therapy (d)	SU dose at hypoglycemia (mg/kg/d)
1	1	43	13	0.15
2 *	1	39	37	0.15
3 *	3	38	22	0.20
4 *	5	20	8	0.70
5 *	6	46	29	0.30
6	6	40	31	0.30
7	6	39	32	0.15
8 *	6	41	46	0.02
9 *	7	37	35	0.15
10	8	46	24	0.10

* Patients with recurrent hyperglycemia after discontinuation of sulfonylurea therapy. BG, blood glucose; PD, postnatal day.

for hyperglycemia from PD 58 to PD 86, which was discontinued because of frequent hypoglycemia; and case 4 patient received insulin between PD 3 and 4 as glucose-insulin therapy for hyperkalemia. Contrarily, out of the ten patients who did not receive SU therapy, five died early in life. Three patients had hyperglycemia that improved without hypoglycemic agents by treatment of sepsis, medium-chain triglyceride oil suspension, and reduced rate of glucose infusion. In the remaining two patients, hyperglycemia improved spontaneously within 3 to 6 d. The median maximum blood glucose level in the five patients who survived was 281 mg/dL.

Detailed information related to SU treatment is provided in **Table 2**. We started SU at a median age of PD 15 (IQR: PD 12–20); and the median initial dose was 0.15 mg/kg/d (IQR: 0.1–0.2 mg/kg/d). All patients received SU by an enteral tube. None of the patients developed ketoacidosis at the time of SU introduction. The median maximum dose of SU was 0.2 mg/kg/d (IQR: 0.125–0.3 mg/kg/d). Hyperglycemia improved in all patients (**Fig. 2**), and the median time to reach the target BG levels after initiation of SU was 6 d (IQR: 4–8.5 d). All patients were able to discontinue SU because of normalization of BG levels, and the median total treatment period was 49 (IQR: 14.5–65.5) d.

ROP (≥ stage 3) occurred in five patients. MRI findings after SU treatment showed post-hemorrhagic ventricular dilatation in case 2 patient; however, none of the patients had a new onset of IVH (≥ stage 3). Although periventricular leukomalacia (PVL) was found in case 4 patient, there were no abnormal signals in the cerebral parenchyma due to hypoglycemia (21).

Hypoglycemia occurred in six patients, with a total of 10 hypoglycemic events (**Table 3**). The incidence of hypoglycemia during SU treatment was 18 events per 1000 patient hours. The median BG level at the time of onset of hypoglycemia was 40 mg/dL (IQR: 38–41 mg/dL). None of the patients had any symptoms, such as seizures or coma. Hypoglycemia occurred at a median of 29 d (IQR: 22–34 d) after SU initiation. Breast milk or formula was immediately administered to patients who developed hypoglycemia, and consequently the

condition improved without any additional treatment. SU was discontinued in four patients. Laboratory findings revealed that neutropenia occurred in four patients and low platelet levels occurred in two patients. None of the patients developed liver dysfunction, agranulocytosis, or hemolytic anemia. None of the patients discontinued treatment because of side effects other than hypoglycemia.

Discussion

This case series illustrates the change in BG levels after initiation of SUs in ELBWIs that develop hyperglycemia during the early postnatal period. To the best of our knowledge, detailed reports on the use of SU as a treatment for hyperglycemia in ELBWIs are lacking, and there is limited information even in normal or low birth weight infants. The most common causes of hyperglycemia in ELBWI are infections such as sepsis and inadequate nutrition. In the patients reported in this study, hyperglycemia persisted even after these causes were eliminated, followed by a marked improvement within a few days after SU treatment initiation. These observations suggest that SU may be considered as one of the treatment options for hyperglycemia in ELBWIs. Carmody *et al.* retrospectively analyzed nine patients with NDM (eight of whom had genetic abnormalities) who were treated empirically with SU before the results of genetic testing were available. The results showed that six patients could be switched safely from insulin within 6 d after initiation of SU, and the remaining patients could be switched from insulin within 14 d (15). However, when SU treatment was started before genetic testing, the author recommended not to proceed with a trial, provided there was a clear history of pancreatic hypoplasia/agenesis. In two other case reports, BG levels normalized within 14 d after starting SU, regardless of the presence or absence of genetic abnormalities (16, 22). In these reports, BG levels were controlled in all the patients without any severe side effects. Similarly, in the present study, the target BG level was achieved without serious side effects in ELBWIs, within a median

of 6 d after SU initiation. These results suggest that SU can normalize BG levels within a few days in ELBWIs; however, SU administration should be discontinued when the patient has insulin deficiency.

Guidelines for dosing and titrating SU in ELBWIs have not yet been published. A previous study demonstrated that body weight was significantly correlated with the clearance and volume of distribution of glibenclamide, suggesting that body weight-based dosing is reliable (23, 24). According to the Best Pharmaceuticals for Children Act (BPCA) in the USA, the mean dose of SU administered to children with type-2 diabetes mellitus is 0.18 mg/kg/d (25). Contrarily, in patients with NDM because of *KCNJ11* mutation, the median SU dose required for insulin independence is 0.45 mg/kg/d (14). In our study, the median SU dose needed to achieve the target glucose level in ELBWIs was 0.2 mg/kg/d. The SU dose in ELBWIs was similar to the maximum dose required for the treatment of type-2 diabetes in adults and children, but less than the dose required for NDM with *KCNJ11* mutation. This is reasonable because hyperglycemic preterm neonates are relatively resistant to insulin (26). Considering pharmacokinetics, glibenclamide is metabolized mainly by CYP3A4 and CYP2C9 (24). Although CYP enzyme activity at birth is approximately 50%–70% of adult levels (27), CYP2C proteins develop in the first few weeks after birth, irrespective of the gestational age at birth (28). In the neonatal period, it is better to initiate a lower dose of glibenclamide to reduce the risk of hypoglycemia.

None of our patients had symptomatic hypoglycemia, which involves seizure or coma. Previous reports on infants with gene mutation-related NDM have shown that the incidence of hypoglycemia (BG levels < 60 mg/dL) during SU treatment was ≤ 5%, which did not increase when compared with insulin treatment (14, 29). This determines that SU is not inferior to insulin in terms of the occurrence of side effects.

Managing ELBWIs who require maintenance insulin therapy is a significant challenge for pediatricians. The initial pharmacological management of ELBWIs with hyperglycemia is intravenous insulin infusion; however, evidences for dosing and titrating insulin infusions in ELBWIs are unreliable. Moreover, securing vascular access in ELBWIs is often difficult, additional manpower is required, and costs are incurred to prevent insulin absorption in intravenous lines (5). In addition, multistep dilution is required because of the low body weight of these infants which makes titration of insulin dose difficult, thus making BG levels prone to wide fluctuations (30). Conversely, the BG levels in patients who received oral SU were within the physiological range in comparison to insulin treatment (31, 32). In our patients, the BG levels did not show wide fluctuations and after starting SU treatment, the dose could be easily titrated. Therefore, we consider that enteral SU treatment can be administered in patients in whom achieving vascular access or glycemic control by insulin treatment is difficult. However, SU treatment is also associated with a risk of hypoglycemia; therefore, considering this, clinicians should be particular while prescribing high doses of SUs for longer periods in ELBWIs.

This study had several limitations that need to be acknowledged. First, the patients who developed hyperglycemia in our study may have had spontaneous remission without treatment, since post-natal hyperglycemia in ELBWIs often resolves within 2 wk without drug treatment (2). The patients showed marked improvement in hyperglycemia within a few days after the initiation of SU administration, suggesting that SU treatment could have helped to normalize the BG levels earlier. Therefore, further studies are required to demonstrate that SU is effective in ELBWIs with hyperglycemia. Second, we did not perform a genetic analysis for NDM during or after hospitalization, and we cannot exclude the possibility that some of our patients may have had NDM due to genetic mutations. Although genetic testing is important to accurately diagnose NDM, obtaining sufficient blood required for testing is a challenge in ELBWIs; moreover, the long waiting periods to obtain the results may delay the treatment. Thus, distinguishing hyperglycemia in ELBWIs from NDM remains a challenge. Third, the attending physician checked the BG levels at their discretion and we did not perform continuous glucose monitoring (CGM), which may have resulted in an underestimation of the frequency of hypoglycemia. Fourth, crushed glibenclamide was used for SU treatment, because glibenclamide is not available in a suspension form in Japan. Although BG levels decreased after administration of crushed glibenclamide tablets, drug potency and stability of glibenclamide were unknown (16). In Europe, the EMA approved the glibenclamide suspension as Amglidia in 2018 (33). Recommendation is provided to administer the suspension 15 minutes before the child's milk feed; however, this cannot be directly applied to crushed tablets, because comparative pharmacokinetic data following the application of glibenclamide suspension and micronized tablets are not available.

This is the first report of SU administration in ELBWIs with hyperglycemia in the early postnatal period. On the basis of these results, enteral SU monotherapy may be considered as an option for ELBWIs with hyperglycemia. However, further studies are required to compare various insulin treatments and to investigate the risks of comorbidities and long-term neurodevelopmental outcomes.

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