Persistent Hypoglycemia Induced by Long-acting Insulin Degludec

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Abstract:
A 58-year-old Japanese man was brought to the emergency room due to disturbance of consciousness. He regained consciousness on the day of admission and started taking hospital meals, but he needed intravenous glucose administration for eight days. The total amount of glucose administration was 4,464 g. It took over three weeks for exogenous insulin to be almost undetectable. While degludec binds to albumin and exerts glucose-lowering effects for a long time, the above-mentioned period of three weeks was consistent with the half-life of albumin. Hypoglycemia induced by massive dose of insulin degludec is persistent and prominent.

Key words: severe hypoglycemia, insulin therapy, insulin degludec, a pitfall, diabetes care

Introduction
Hypoglycemia is induced by various causes, including overuse of some anti-diabetic drugs or certain disorders, such as insulinoma, insulin autoimmune syndrome and adrenal insufficiency (1-3). It is well known that severe and/or repeated hypoglycemia leads to various clinical problems, such as acute coronary syndrome, fundus hemorrhaging and unconscious hypoglycemia (4, 5). It is also well known that hypoglycemia facilitates the development of dementia, especially in elderly subjects. Therefore, it is very important to prevent hypoglycemia as well as to obtain good glycemic control in subjects with diabetes mellitus. Insulin degludec is a long-acting insulin preparation used very often to obtain good glycemic control in subjects with type 1 and type 2 diabetes mellitus. It is well known that insulin degludec exerts glucose-lowering effects for a longer period of time than other insulin preparations (6-14).

Case Report
A 58-year-old Japanese man was brought to the emergency room in our institution due to disturbance of consciousness. This individual had mental developmental delay and had been in a facility for patients with mental retardation. He had had severe acute pancreatitis in 2013, after which we started insulin therapy for pancreatic diabetes with long-acting insulin degludec and rapid-acting insulin glulisine. When we started insulin degludec, his fasting serum C-peptide immunoreactivity (CPR) had been 0.6 ng/mL, and his CPR index had been 0.52, indicating that endogenous insulin secretion was markedly limited in this subject. Since he repeatedly experienced hypoglycemia, we gradually decreased the insulin dose. In 2020, we stopped insulin degludec, and he took only 4 units/day of insulin glulisine (2 units just before breakfast and supper). Endogenous insulin secretion was low but not depleted, with the following findings: fasting serum C-peptide, 0.8 ng/mL; C-peptide index, 0.65; ΔCPR in glucagon load test, 0.8 ng/mL. We considered him not to need larger amounts of insulin because his endogenous insulin secretion was not depleted. He
addition, inflammation markers were within normal range. Mild liver dysfunction was observed, but the renal function was within the normal range (AST, 54 U/L; ALT 50 U/L; creatinine, 0.79 mg/dL; blood urea nitrogen, 17 mg/dL). In addition, inflammation markers were within normal range.

Abdominal contrast computed tomography (CT) revealed pancreatic tail atrophy, probably due to his history of severe acute pancreatitis, but no malignant findings were noted, including insulinoma. Hypoglycemia is often induced by the overuse of several anti-diabetic drugs, but this subject used only 4 units/day of insulin glulisine, and he did not use any other anti-diabetic drugs. Since his insulin level was not high and anti-insulin antibody was negative, we excluded the possibility of insulinoma or insulin autoimmune syndrome. In addition, since his cortisol level was not low, we excluded the possibility of adrenal insufficiency. Hypoglycemia can be induced by drinking too much alcohol without enough food intake, but this subject had stopped drinking alcohol after severe acute pancreatitis in 2013. To examine the cause of hypoglycemia, we measured the total insulin level (endogenous plus exogenous insulin level). Surprisingly, the total insulin level was as high as 1,856.1 μU/mL.

He regained consciousness on the day of admission and started taking hospital meals (1,600 kcal/day, carbohydrate 260 g/day). Nonetheless, he needed intravenous glucose administration for as long as eight days. The total amount of glucose administration was as large as 4,464 g. As shown in Table 2, even on day 8, the estimated exogenous insulin level (total insulin level - endogenous insulin level) was 37.3 μU/mL. This estimated exogenous insulin level on day 12 and 16 was 18.6 μU/mL and 9.4 μU/mL. It took over three weeks for exogenous insulin to be almost undetectable. The total insulin level was as high as 1,856.1 μU/mL. C-peptide and insulin levels were very low at 0.1 ng/mL and 0.1 ng/mL. Various counter-regulatory hormone levels were increased: ACTH, 667 pg/mL; adrenaline, 424 pg/mL; glucagon level was low (7.8 pg/mL) (5.4-55.0 pg/mL); insulin-like growth hormone, 7.81 ng/mL (0-65.2 pg/mL); cortisol, 39.1 μg/dL (7.07-19.6 μg/dL); growth hormone, 7.81 ng/mL (0-72.2 ng/mL); TSH 2.16 μU/mL; Concentration 189.8 nU/mL; Concentration 189.8 nU/mL.

Table 1. Laboratory Data in This Subject.

| Peripheral blood | Diabetes and endocrine markers | Electrolytes |
|------------------|--------------------------------|--------------|
| RBC 421×10⁴/μL  | Plasma glucose 25 mg/dL        | Sodium 148 mEq/L |
| Hemoglobin 13.5 g/dL | C-peptide 0.1 ng/mL | Potassium 2.9 mEq/L |
| WBC 6,970/μL    | Insulin <0.1 μU/mL            | Chloride 106 mEq/L |
| Neutrophils 79.3% | Total insulin 1,856.1 μU/mL    | Calcium 9.5 mg/dL |
| Lymphocytes 16.6% | HbA1c 8.2 %                  | Phosphorous 3.2 mg/dL |
| Platelets 23.3×10⁴/μL | Glycocalmin 25.7 % | Magnesium 1.9 mg/dL |
| Blood biochemistry | ACTH 65.2 pg/mL               | Lipid markers |
| Total protein 7.6 g/dL | Cortisol 39.1 μg/dL | LDL-cholesterol 86 mg/dL |
| Albumin 4.6 g/dL | GH 7.8 ng/mL                | HDL-cholesterol 57 mg/dL |
| Total bilirubin 0.3 mg/dL | IGF-1 212 mg/dL            | Total cholesterol 180 mg/dL |
| AST 54 U/L | Adrenaline 424 pg/mL          | Triglyceride 70 mg/dL |
| ALT 50 U/L | Noradrenaline 667 pg/mL       | Auto-antibodies |
| GGT 17 U/L | Dopamine 13 pg/mL             | Anti-GAD Ab <5.0 |
| LDH 215 U/L | Glucagon 7.8 pg/mL            | Anti-insulin Ab |
| ALP 96 U/L | TSH 2.16 μg/mL                | Concentration 189.8 nU/mL |
| Creatinine 0.79 mg/dL | FT3 2.81 pg/mL              | Binding rate 0.7 % |
| BUN 17 mg/dL | FT4 0.78 ng/mL               | Anti-IR Ab negative |
| Amylase 113 U/L |                               |              |
| CRP 0.07 mg/dL |                               |              |

RBC: red blood cells, WBC: white blood cells, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, CRP: C-reactive protein, ACTH: adrenocorticotropic hormone, GH: growth hormone, IGF-1: insulin-like growth hormone, TSH: thyroid stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, ACTH: adrenocorticotropic hormone, GAD: glutamic acid decarboxylase, Ab: antibody, IR: insulin receptor.
of three weeks was consistent with the half-life of albumin. We thus considered the possibility that the overuse of degludec was the cause of hypoglycemia. By 3 days after admission, we began to consider the possibility that this subject suffered from hypoglycemia due to degludec, as his insulin level was as high as 1,856 μIU/mL and the hypoglycemia was prolonged, but we failed to confirm such a possibility. We asked the facility staff and his family to check the patient’s room, and they found insulin degludec, which we had stopped prescribing nearly one year earlier. We finally diagnosed this subject with prominent and persistent hypoglycemia induced by the administration of a massive dose of insulin degludec. Needless to say, we explained to the facility staff that a fixed dose of insulin should be injected every day and that the insulin injection should be watched over by the facility staff. However, we cannot exclude the possibility that this subject self-adjusted insulin dose when the facility staff did not watch over insulin injection. In addition, we strictly instructed the facility staff on the necessity of discarding residual insulin preparations and confirmed this point verbally. However, we believe that this was not performed thoroughly, with insulin degludec being actually left in the patient’s room. As he did not appear to have been attempting suicide, why the patient injected such a massive dose of insulin remains unclear. However, since he had mental developmental delay, it was likely that his cognitive function was impaired and this injection was performed in error.

### Discussion

In the present report, we described a subject who had prominent and persistent hypoglycemia induced by the administration of a massive dose of long-acting insulin degludec. Although he regained consciousness on the day of admission and started taking hospital meals, he needed intravenous glucose administration for eight days. The total amount of glucose administration was 4,464 g. Furthermore, it took over three weeks for exogenous insulin to be almost undetectable.

In the present subject, endogenous insulin was measured with an insulin measurement kit FUJIREBIO Inc. (Tokyo, Japan). This measurement principle was based on the one-step sandwich method using ALP-labeled anti-insulin monoclonal antibody. In the cross-reaction test of this method, there was no cross-reactivity with insulin degludec. However, the total insulin was measured with a chemiluminescence immunoassay using an insulin measurement kit (Siemens Healthineers Inc. (Tokyo, Japan). This measurement principle was also based on the one-step sandwich method using acrydinium ester-labeled anti-insulin monoclonal antibody. In the cross-reaction test of this method, we noted cross-reactivity with various kinds of insulin preparations.

It is well known that persistent hypoglycemia leads to various clinical problems, such as acute coronary syndrome, fundus hemorrhaging and unconscious hypoglycemia (4, 5). It is also well known that hypoglycemia facilitates the development of dementia, especially in elderly subjects. Therefore, it is very important to prevent hypoglycemia as well as to obtain good glycemic control in subjects with diabetes mellitus. It is noted here that since insulin degludec forms a multi-hexamer under the skin and exerts glucose-lowering effects for a long time through its binding to albumin in the circulating blood flow, hypoglycemia induced by degludec is considered to be prominent and persistent, as observed in this subject. Given a report showing the time course of the serum insulin level after the injection of 300 doses of degludec (15), we assume that this subject injected quite a large amount of insulin degludec, but it would be very difficult to estimate the injected dose of degludec based on the serum insulin level, as there is marked variation among patients in endogenous insulin secretory capacity and insulin resistance.

In this subject, the glucagon level was as low as 7.8 pg/mL (reference range: 5.4-55.0 pg/mL) despite his severe hypoglycemia (blood glucose: 25 mg/dL), although other counter-regulatory hormone levels were increased. Since the response of serum glucagon levels was reportedly poor under hypoglycemic conditions in subjects with chronic pancreatitis (16), the glucagon response may have worsened due to his history of severe acute pancreatitis. In addition to the above-mentioned characteristics of insulin degludec, we suspect that such a worsened glucagon response was also involved in the prominent and persistent hypoglycemia in this subject.

We feel that the present case report highlights a variety of important messages. First, hypoglycemia triggered by insulin degludec is quite persistent and prominent. Second, we should be careful of triggering hypoglycemia when we use insulin degludec in subjects with a limited glucagon response, such as those with a history of severe pancreatitis. Third, we should give strict instructions concerning the need to discard residual insulin preparations and confirm such actions thoroughly. Fourth, we should bear in mind the possibility of massive insulin injection in subjects experiencing severe acute pancreatitis.

### Table 2. Time Course of Estimated Exogenous Insulin Level (total Insulin Level - Endogenous Insulin Level).

| Blood glucose (mg/dL) | Day 1 | Day 8 | Day 12 | Day 16 | Day 20 | Day 27 |
|-----------------------|-------|-------|--------|--------|--------|--------|
| Total insulin (μIU/mL)| 1,856.1 | 38.7 | 20.3 | 11.8 | 6.4 | 4.2 |
| Endogenous insulin (μIU/mL) | <1.0 | 1.4 | 1.7 | 2.4 | 2.0 | 3.9 |
| Estimated exogenous insulin (μIU/mL) | 1,856.1 | 37.3 | 18.6 | 9.4 | 4.4 | 0.3 |
severe hypoglycemia with marked hyperinsulinemia and lowered C-peptide levels. Finally, this case report underscores the importance of choosing anti-diabetic drugs, including insulin preparations, especially in subjects with a poor condition, in clinical practice. The choice to administer long-acting insulin degludec per se did not appear to have been appropriate for this subject, because severe hypoglycemia in this subject was likely induced by the following reasons: possible poor response of glucagon secretion, presumably due to severe pancreatitis; an insufficient evaluation of the potential decline in his cognitive function, and the insulin preparations being managed by the facility staff rather than his own family.

When we fail to detect the cause of hypoglycemia, we should check the total insulin level in clinical practice. We should also bear in mind that hypoglycemia induced by a massive dose of insulin degludec is persistent and prominent, and we should take care of such subjects very carefully for a long period of time.

The authors state that they have no Conflict of Interest (COI).

Contribution statement: Y.K., F.T., T.K., H.K. researched data and/or wrote the manuscript. M.S., K.K., A.O., S.N., T.M., K.K. contributed to the discussion. All authors have read and approved the manuscript.

Funding: There was no funding for this work.

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