Insulin degludec and insulin degludec/insulin aspart in Ramadan: A single center experience

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ABSTRACT

This study aimed to document the utility and safety of insulin degludec (IDeg) and insulin degludec aspart (IDegAsp) in persons with type 2 diabetes, observing the Ramadan fast. An observational study was conducted at a single center, in the real world setting, on six persons who either switched to IDeg or IDegAsp a month before Ramadan or changed time of administration of IDegAsp at the onset of Ramadan, to keep the fast in a safe manner. Subjects were kept under regular monitoring and surveillance before, during, and after Ramadan, and counseled in an opposite manner. Four persons, who shifted from premixed insulin to IDegAsp, experienced a 12–18% dose reduction after 14 days. At the onset of Ramadan, the Suhur dose was reduced by 30%, and this remained unchanged during the fasting month. The Iftar dose had to be increased by 4 units. One person who shifted from neutral protamine hagedorn to IDeg demonstrated a 25% dose reduction at 20 days, without any further change in insulin requirement during Ramadan. One person who changed time of injection of IDegAsp from morning to night reported no change in dosage. No episode of major hypoglycemia was reported. IDeg and IDegAsp are effective, safe, and well-tolerated means of achieving glycemic control in persons with type 2 diabetes who wish to fast.

Key words: Co-formulation, degludec, hypoglycemia, insulin degludec/insulin aspart, ultra-long acting insulin

INTRODUCTION

Insulin degludec (IDeg) is a new ultra-long-acting insulin, with flat time-action profile, which has a lower risk of hypoglycemia and nocturnal hypoglycemia, and can be injected at any time of the day.[1] IDeg is also available as a co-formulation with the rapid-acting insulin aspart – insulin degludec/insulin aspart (IDegAsp).[2] These attributes allow its use in situations where the risk of hypoglycemia is high.

One such scenario is encountered during the Ramadan month, when Muslims fast from dawn to dusk, abstaining from both fluid and solid foods. Ramadan is associated with a higher risk of hypoglycemia, hyperglycemia, and increased glycemic variability.[3] Islam allows exemptions in specific situations where fasting may pose a danger to health.[4] Consensus driven guidelines are available for risk stratification, which allows health care providers to offer religion-sanctioned, biomedically appropriate advice as to whether to fast or not.[4]

Many insulin users, however, choose to observe the Ramadan fast for spiritual wellbeing. In such people, it becomes a challenge to adjust insulin regimens, to ensure a safe and healthy fasting experience. Current guidelines mention regimen and dose adjustments that should be made in type 1 and insulin-using type 2 patients.[5,6] Expert opinion mirrors this advice.[7] No evidence-based guidance

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has been shared, however, regarding the use of IDeg and IDegAsp in Ramadan. IDeg can be used as a once-daily basal insulin, or as part of a basal-bolus regimen.[5] IDegAsp can be prescribed once daily (with the major meal), twice daily, or as part of a three dose regime (one IDegAsp and two insulin aspart doses).[3]

**Materials and Methods**

We report our experience with six subjects who switched to IDeg or IDegAsp before the Ramadan month of 2015 and were able to observe a fulfilling fast. An observational study was conducted in the real world setting, on insulin users who expressed the desire to fast, in spite of difficulties encountered in previous Ramadans.

Five adults (4 women) with type 2 diabetes, aged 34–56 years, on premixed insulin analog twice daily \( (n = 4) \), or neutral protamine hagedorn \( (NPH) \) insulin once daily \( (n = 1) \), for periods ranging from 2 to 6 years, with normal renal, hepatic, and thyroid function, were included. None was planning conception. All had tried to observe Ramadan the previous year but had failed in doing so for over 15 days, because of severe hypoglycemia and physical fatigue. One subject (48 years, male) was well controlled on one daily dose of IDegAsp, taken with breakfast, his heaviest meal, and wished to observe Ramadan. He reported having to break his fast while on sulfonylurea + metformin combination.

All six subjects were counseled regarding the risks and benefits of fasting, 6–8 weeks before Ramadan. The availability of newer insulins, IDeg, and IDegAsp was shared with the subjects on premixed/NPH insulin. All five voluntarily consented to an observational trial with IDeg or IDegAsp, to assess if this would help them achieve a safe fasting experience.

Four subjects were switched from premixed insulin analog twice daily to equal doses of IDegAsp twice daily. They were followed up with twice weekly plasma glucose assessment before breakfast and dinner. Titration was done using simple published algorithms[1] to achieve target premeal glucose values, in the month preceding Ramadan. During Ramadan, the dose of IDegAsp was titrated on the phone, using once weekly pre-Suhur and pre-Iftar values alone. Target glucose values were kept similar to those in clinical practice, and a pre-Suhur value of 100 mg%, and pre-Iftar value of 110–140 mg% was aimed for.

One subject was switched from NPH at night, to an equal dose \( (20 \text{ units}) \) of IDeg once daily, to be injected at any time of the day. Her oral therapy of linagliptin + metformin fixed dose combination, taken twice daily, was not changed. The person on a morning IDegAsp dose was advised to change timing of injection upon the start of Ramadan fasting. In both these patients, fasting glucose was performed twice weekly for 20 days, and weekly thereafter, with dose titration being done on phone.

All six subjects were contacted weekly on the telephone by a paramedical worker and physician during Ramadan. They were encouraged to report any unexpected symptoms to the health care team. Post-Ramadan, a repeat counseling and debriefing session, which reviewed symptomatic well-being, dietary and physical activity patterns, as well as glycemic control, with a view to improving next year’s fasting experience, was done.

**Results**

**Subjects switched to twice daily insulin degludec**

Four subjects were switched from premixed insulin analog twice daily to equal doses of IDegAsp twice daily. The mean and range of doses are mentioned in Table 1. These subjects were followed up with twice weekly plasma glucose assessments before breakfast and dinner. Titration was done using a simple algorithm[1] to achieve target premeal glucose values. By day 7, adequate fasting control had been attained. Postprandial glucose was also monitored at twice weekly to weekly intervals, based upon patient convenience and acceptance.

By day 14, the dose of IDegAsp had reduced by 12–18%. The same dose was maintained, with minor changes, until

| Subject | Age/gender | Pre-IDeg/IDegAsp therapy | Pre-Ramadan therapy | Ramadan therapy | Net change (units) |
|---------|------------|--------------------------|---------------------|----------------|-------------------|
|         |            | Insulin               Dose (units) | Insulin               Dose (units) | Insulin               Dose (units) |                      |
| 1       | 34 female  | BIAsp                 20-20       | IDegAsp              20-20      | IDegAsp              15-24       | -1                 |
| 2       | 46 female  | BIAsp                 24-16       | IDegAsp              24-16      | IDegAsp              18-20       | -2                 |
| 3       | 46 female  | BIAsp                 24-16       | IDegAsp              24-16      | IDegAsp              18-18       | -4                 |
| 4       | 48 male    | BIAsp                 16-16       | IDegAsp              16-16      | IDegAsp              12-20       | 0                  |
| 5       | 56 female  | NPH                   20 hs        | IDeg                 20 OD      | IDeg                 15 OD       | -5                 |
| 6       | 48 male    | IDegAsp               25 OD       | IDegAsp              25 OD      | IDegAsp              25 hs       | 0                  |

OD: Once daily, BD: Twice daily, hs: Hours of sleep, NPH: Neutral protamine Hagedorn, BIAsp: Biphasic insulin aspart, IDeg: Insulin degludec, IDegAsp: Insulin degludec/insulin aspart
the onset of Ramadan. At the start of Ramadan, the evening dose was kept constant, while the morning dose was reduced by 30%. This was done as a safety precaution, to avoid daytime hypoglycemia during the prolonged period of fasting.

By the end of the month, the Iftar dose had increased by a mean of 4 IU. The morning time dose, which was reduced by 30% to form the Suhur dose, remained almost unchanged throughout the month.

Subject switched to once daily insulin degludec
One subject was switched from NPH at night, to an equal dose (20 units) of IDeg once daily, to be injected at any time of the day. Her oral therapy (linagliptin + metformin, twice daily) was not changed. Fasting glucose was performed twice weekly until 20 days and weekly thereafter. At 10 days, the dose of IDeg had to be reduced to 18 units and at 20 days, to 15 units. No change in dose was required after 20 days of IDeg usage, including during the month of Ramadan.

Subject on once daily insulin degludec/insulin aspart
One patient, who administered his single daily dose of IDegAsp with breakfast, was requested to inject with Iftar, from day 1 of Ramadan. His earlier night time dose of sustained release metformin 1 g was not changed. Fasting and predinner glucose values remained within normal limits during Ramadan.

Safety
No episode of severe hypoglycemia was reported among these six patients. A total of three episodes of confirmed hypoglycemia, all minor, and corrected by self-administration of glucose, were reported in the nonfasting period. Three subjects reported a total of 11 episodes suggestive of hypoglycemia during the fasting period but chose not to check glucose values or break the fast. A mean weight gain of 1600 g was observed in the IDegAsp patients while no weight change was observed in the IDeg using subject.

Post-Ramadan follow-up
Patients expressed satisfaction at being able to fast in a fulfilling manner, without major hypoglycemia. Three subjects elected to continue their IDegAsp-based regimens, while one reverted to premix analog based regimen, because of financial constraints. The subject who had switched from NPH to IDeg preferred to continue with IDeg therapy. The single daily dose of IDegAsp user restarted injecting himself at breakfast from the morning after Eid.

**Discussion**

This is perhaps the first reported usage of IDeg and IDegAsp in Ramadan. This was an observational study conducted during routine clinical practice. The data adds to existing literature on insulin use in Ramadan. It highlights subtle differences in use of IDeg and IDegAsp, as compared to other basal and dual action insulins, in Ramadan. For example, the need to reduce dose in persons shifting from other basal insulins, and the simpler formula of adjusting/reducing Suhur dose by 30%, while keeping Iftar dose of IDegAsp the same, are different from strategies employed with earlier insulins.

HbA1c, other metabolic markers, and quality of life were not measured in this study. However, based on this data, IDeg and IDegAsp in once daily and once/twice daily dosing respectively provide a safe and effective alternative for glycemic control in Ramadan, with minimal glycemic monitoring. These insulins may help insulin-using persons observe Ramadan in a healthy and fulfilling manner.

**Summary**

Our case series reinforces the following observations made earlier:

- IDeg and IDegAsp are safe and effective means of achieving good glycemic control
- These drugs should be initiated at least 4–6 weeks before start of Ramadan, to ensure dose stabilization is complete before Ramadan begins
- The IDeg dose may need to be reduced by 25%
- A dose reduction of about 25–30% in the Suhur dose of IDegAsp is suggested. No change is needed in the Iftar dose of IDegAsp
- Persons on once daily injection of IDegAsp with breakfast may shift their dose to the evening meal without changing dose
- This study did not include any persons on IDeg based intensive regimes.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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