South Asian consensus guideline: Use of GLP-1 receptor agonists during Ramadan: Update 2016

Revised Guidelines on the use of GLP-1A in Ramadan

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Abstract
This guidance is an update to the South Asian Consensus Guideline: Use of GLP1RA in Diabetes during Ramadan, published in the Indian Journal of Endocrinology and Metabolism in 2012. A five country working group has collated evidence and experience to suggest guidelines for the safe and rational use of glucagon-like peptide1 receptor agonists during Ramadan. The suggestions contained herewith are based upon recently published evidence as well as available basic pharmacological data.

Keywords: Dulaglutide, Exenatide QW, GLP1RA, Hypoglycaemia, Liraglutide, Lixisenatide, Ramadan, South Asia.

Introduction
This communication is an evidence-based update to the 2012 South Asian Consensus guideline on the use of GLP-1 (glucagon-like peptide) analogue therapy in diabetes during Ramadan.1 It lists recently published data to support the rational use of GLP-1 receptor agonists (GLP1RA) as glucose lowering agents in Ramadan. The communication uses modern semantics to remain in line with current trends.

Recent Evidence
Recently published data from the Treat4 Ramadan and LIRA Ramadan trials2,3 provide evidence based support for the experience based suggestions on GLP1RA therapy published by the South Asian consensus group in 2012. Treat 4 Ramadan was one of the first studies to evaluate the use of liraglutide in Ramadan2 Patients were randomized in two groups either receiving sulfonylureas (SU) or liraglutide 1.2 mg OD in addition to metformin. The primary endpoint was composite of HbA1c <7.0%, no weight gain (defined as either weight loss or <1 kg weight increase) and no severe hypoglycaemic events at 12 weeks post Ramadan. The patients achieving composite end point was 20.9% and 38.2% in SU and liraglutide group respectively (p=0.05) at 3 weeks and 10.3% and 26.7% at 12 weeks (p=0.06 NS). Hypoglycaemia rates were significantly lower in the liraglutide plus metformin arm. Hypoglycaemia rate per person year was 10.5 and 3.0 in the SU and liraglutide cohorts respectively (p<0.0001). Treat 4 Ramadan results were not significant for the primary endpoint; however, there was significantly less hypoglycaemia with liraglutide compared with sulphonylureas (p<0.0001). This finding formed the rationale for designing and conducting the LIRA-Ramadan trial.

The primary objective of this multi-national, open-label trial was to compare the effect of liraglutide versus SU, both added on to metformin, on glycaemic control during Ramadan in subjects with type 2 diabetes.2 The secondary objectives were to compare the effect of lira versus SU, both added on to metformin, during Ramadan, from baseline to end of Ramadan and from baseline to end of treatment (EoT) on glycaemic control, body weight, safety and tolerability. Included in this study were adults with type 2 diabetes, BMI ≥20 kg/m², HbA1c 7-10%, on metformin ≥1000 mg/day and SU (gliclazide, glipizide or glyburide/ glibenclamide) (at maximum tolerated dose [at least half maximum approved dose]) or glimepiride (≥2 mg/day or at maximum tolerated dose [at least half maximal approved dose]) ≥90 days and intent to fast during Ramadan.

The primary endpoint was the change in fructosamine from start of Ramadan to end of Ramadan. Key secondary endpoints were change in fructosamine, FPG, HbA1c and body weight from start of Ramadan to end of Ramadan. Number of confirmed hypoglycaemic episodes was also
evaluated. Continuous data were analyzed using a mixed model of repeated measures (MMRM) with visit, treatment, and country, stratification groups as fixed factors and baseline as a covariate, all nested within visit.

More subjects on liraglutide (20) withdrew between randomization and the start of Ramadan than with SU (8). Liraglutide withdrawals were mainly driven by gastrointestinal AEs; approximately 50% occurred during dose-escalation (weeks 1-4). More subjects on SU (11) withdrew during Ramadan than with lira (3). SU withdrawals were driven by subject not fasting during Ramadan and poor glycaemic control.

During Ramadan, similar reductions in fructosamine were observed with liraglutide and SU, despite a lower fructosamine at start of Ramadan with liraglutide vs. SU. Switching from stable SU to liraglutide before Ramadan resulted in a greater reduction in mean HbA1c at end of Ramadan compared to continuing SU. The estimated treatment difference (ETD) was -0.59 [-0.79, -0.38] 95% CI, p<0.001.

The proportion of subjects, who at end of Ramadan (day 29) achieved HbA1c <7.0% (ADA target), was 57.10% in the liraglutide group and 26.40% in the SU group. The odds ratio (lira/SU) of such an achievement was 3.71 [2.18, 6.30] (95% CI, p<0.0001). An HbA1c <7.0% and no confirmed hypoglycaemia, was achieved by 53.91% and 23.54% of liraglutide and SU treated subjects respectively. The odds ratio of 4.90 [2.79; 8.62] (95% CI, p<0.0001).

Treatment with liraglutide induced greater body weight reduction during Ramadan than SU. The ETD was -0.54 kg [-0.94, -0.14] 95% CI, p=0.0091. The ETD in body weight from baseline to end of Ramadan was -3.94 kg [-4.54, -3.33] 95% CI, p<0.0001.

Pre-Ramadan

The pre-Ramadan assessment and risk stratification strategies that are followed for all persons with diabetes apply to those on GLP1RA as well.

The numerous advantages of GLP1RA (Table) make them a preferred class of drugs before and during Ramadan. The 2016 update adds that persons who wish to start short acting, intermediate acting or once-weekly long-acting GLP1RA must do so at least 6 weeks, but preferably 3 months, prior to start of Ramadan. This time period is required to ensure that steady state concentrations are achieved, extent of glycaemic control is assessed, and potential gastrointestinal symptoms are addressed, before start of Ramadan.

The 2016 update reinforces the need to discuss appropriate injection technique with all persons on GLP1RA therapy, and to assess for local site reactions (LSRs). Patients should be encouraged to carry out Self Injection site Examinations (Self IEs), and report LSRs to their diabetes care providers.

Dose Modification

Persons on twice daily exenatide, with the same dose (5mcg or 10mg) being taken at both times, need not change dose or timing of administration. Persons who wish to avoid injecting the evening dose prior to iftaar (evening meal) may do so before a late night snack. Persons on once daily lixisenatide should shift the time of administration to iftar. Persons who wish to avoid injecting the evening dose prior to iftaar (evening meal) may do so before a late night snack.

Persons on once daily liraglutide (0.6mg-1.8mg) need not change their dose. The drug should preferably be administered after iftaar. No specific injection-meal time gap is required.

Persons on once weekly dulaglutide or exenatide QW...
need not change their dose or timing of administration. Those who wish to avoid injecting during the dawn-to-dusk fasting period may change the time of injection as per convenience. Injection of once weekly GLP1RA has no relation to meal timings.

Post-Ramadan Follow Up
Persons who maintain good control on GLP1RA should continue the same therapy after Ramadan as well. Those who require intensification may consider addition of insulin. The availability of fixed ratio combinations of basal insulin and GLP1RA (degludec + liraglutide, glargine+ lixisenatide) will help in convenient intensification of therapy.

Glucose Monitoring
As GLP1RA therapy is associated with a low risk of hypoglycaemia, frequent or self-monitoring of blood glucose (SMBG) is not required. In persons on concomitant insulin or sulfonylurea therapy, appropriate SMBG will have to be performed, to allow safe dose modification.

Summary
The current South Asian Consensus Update utilizes basic and clinical pharmacological knowledge to list the advantages of GLP1RA as glucose lowering strategy during Ramadan; reviews evidence on this topic; and providers succinct, rational suggestions for the safe and effective use of this therapeutic modality. Recently published evidence on liraglutide strengthens the use of GLP1RA during Ramadan. More research is however needed on the use of long acting GLP1RA during Ramadan. We hope that this update will help achieve safe and fulfilling Ramadan for people with diabetes, not only in South Asia, but across the world as well.

References