

PHARMACOLOGICAL MANAGEMENT

Oral anti-diabetics in Ramadan

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Abstract

A large proportion of Muslim patients with type 2 diabetes fast during the month of Ramadan worldwide. Hypoglycaemia is one of the major complications associated with long periods without food during the fasting hours. There is also a risk of hyperglycaemia due to over indulgence in food during the two main meals of Suhur and Iftar. Healthcare providers need to be cognizant of the risk of fasting and be competent to provide Ramadan adjusted diabetes care particularly adjustment of oral anti diabetics. This review article has taken into consideration observational studies, randomized trial data, pathophysiology and practical experience in recommending adjustment in oral anti-diabetics during fasting in type-2 diabetics. Metformin and Thiazolidinediones (TZD'S) being insulin sensitizers need minimum adjustment with low risk of hypoglycaemia. Older generation Sulphonylureas (SU) pose a high risk of hypoglycaemia but the newer generations of Sulphonylureas have a reasonable safety profile. Alpha- Glucosidase inhibitors are safe during fasting but their use is limited due to the side effects.

Keywords: Type-2 Diabetes Mellitus, hypoglycaemia, Ramadan Fasting and oral anti-diabetics.

Introduction

Muslims constitute approximately 25% of the world population and globally there are about 1.6 billion Muslims.¹ It is obligatory for all healthy adult Muslims to fast during the month of Ramadan which is the ninth lunar month of Islamic/Hijri calendar. Fasting involves abstinence from food and water from dawn to dusk (sunset). This fasting period varies from a minimum of 6-7 hours up to a maximum of 20 hours depending upon the

geographical location and season of the year. Most Muslims consume two major meals during this month; one before dawn the Suhur and one after breaking the fast at sunset, the Iftar. Some Muslims take a third meal as well before going to bed in the form of a late dinner or snack. Fasting is a challenge not only for the people with diabetes who observe fasts but also for the healthcare professionals.

The epidemiology of diabetes and Ramadan (EPIDIAR), is a population based study conducted in 13 Islamic countries which enrolled 12,243 patients.² The EPIDIAR study highlighted certain important facts i.e. approximately 79% of people with type 2 diabetes observed fasts during Ramadan but only 25% of them had their oral anti diabetics adjusted during this month. This study also revealed that only 2% of the people with type 2 diabetes had at least one episode of severe hypoglycaemia and only 4% of them had one episode of severe hyperglycaemia needing hospitalization.

Recently newer therapeutic options for treating type 2 diabetes have emerged but the experience of these new drugs during Ramadan is very limited. On the other hand older agents have been modestly studied in the diabetic population with clear understandings. In this review we provide an update on the use of oral anti diabetics in Ramadan for people with type 2 diabetes who would be fasting.

Biguanides

Metformin is the only biguanide available in the world these days. It is an insulin sensitizer and by virtue of its mechanism of action the possibility of hypoglycaemia is minimal. Although hypoglycaemia has been reported with Metformin in people with diabetes who are not fasting however severe hypoglycaemia is not reported unless given in combination with insulin secretagogues or insulin. People on Metformin can safely fast during

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Recommended changes in treatment regimens in patients with type 2 diabetes who fast during Ramadan

Medications	During Ramadan
Biguanides	2/3rd of the daily dose at Iftar and 1/3rd at Suhur. Sustained release metformin be taken at Iftar in the same dose.
Thiazolidinediones	No change needed
Alpha glucosidase inhibitors	No change needed
Sulfonylureas once a day	Dose should be given before the sunset meal. Adjust the dose based on the glycaemic control and the risk of hypoglycaemia
Sulfonylureas twice a day	Use the smaller evening dose at Suhur and the higher morning dose at Iftar. The Suhur dose may be further reduced if the pre Ramadan diabetes control is good.
Meglitinides	To be taken at Suhur and Iftar and a 3rd dose in patients who also take late night dinner. Suhur dose may need be reduced slightly based on glycaemic control and risk of hypoglycaemia.

Ramadan but it is advisable that one-third of the total dose be taken at Suhur and two-third at Iftar to decrease any chance of hypoglycaemia without reducing the total dose of Metformin.³ In case the individual is on a maximum dose of Metformin 1gm tid, then it should be 1 gm. at Suhur and 1 gm. at Iftar as it is not recommended to give more than 1 gm. of Metformin at one time. Slow release formulations of Metformin are a better choice in this group with diabetes who are fasting and it may be given once daily at Iftar time.³

Thiazolidinediones (TZD'S)

Similar to Metformin TZD's a PPAR- γ agonist is unlikely to cause hypoglycaemia but can potentiate the hypoglycaemic effect of insulin secretagogues or insulin. Pioglitazone has been studied in randomized controlled trials in people with diabetes fasting during Ramadan and no increase of hypoglycaemic event was reported.⁴ It is recommended that the dose of TZD's should be unchanged and preferably taken at Iftar. If TZD's are being considered as an addition or substitution to other oral anti diabetics, they should be started at least 3-4 weeks before the start of Ramadan as it takes many weeks for the action of TZD's to take effect.

Meglitinides

This group of drug which includes Repaglinide and Nateglinide, have very short duration of action and thus are very useful in people with type 2 diabetes fasting during Ramadan. Nateglinide has the shortest duration of action and thus possibly has the lowest risk of hypoglycaemia among the secretagogues. A randomized multicenter trial found that Repaglinide was associated with lower risk of hypoglycaemia in comparison with Glibenclamide during Ramadan (0.03 hypoglycaemic events versus 0.05 hypoglycaemic events).⁵ In another study using Repaglinide thrice daily along with insulin Glargine in low risk type 2 diabetics fasting during Ramadan reported no increase in hypoglycaemia or any change in glycaemic control or weight. It is recommended

that Meglitinides be used twice daily before the two main meals or thrice in some subjects taking late night meal during the month of Ramadan.

Sulphonylureas

This group of drugs, a classical secretagogues, cause glucose independent stimulation of insulin release from β -cells. A few newer Sulphonylureas have some relatively glucose dependent insulin release. This group of drugs have been in use for several decades, but the risk of hypoglycaemia, weight gain and some concern about cardiovascular safety is well known. Despite this adverse effect it is an effective agent with long global experience. As they are economical with a low cost they are widely used in the developing world despite the introduction of newer and safer agents. Chlorpropamide, the longest acting Sulphonylurea, is not recommended for people with type 2 diabetes, fasting during Ramadan due to the risk of prolonged hypoglycaemia. Glibenclamide was shown to be safe in an earlier study by Belkhadir J et al⁶ during Ramadan but subsequent studies have suggested that Glibenclamide may be associated with higher risk of hypoglycaemia in comparison with second and third generation Sulphonylureas like Gliclazide and Glimepiride. The GUIDE study, a double blind randomized trial, comparing once daily Gliclazide MR and Glimepiride in people with type 2 diabetes who were fasting, showed 50% lower risk of hypoglycaemia with Gliclazide MR in comparison with Glimepiride.⁷ Zargar et al⁸ in their study used Gliclazide MR as a monotherapy in 136 male diabetic subjects who fasted during Ramadan. His study showed no change in status of diabetes control, which remained well controlled, with no weight gain and few hypoglycaemic events. A prospective observational study from six countries showed that once daily evening dose of Glimepiride taken at Iftar did not alter hypoglycaemic rates or glycaemic control.⁹ It is recommended that Chlorpropamide should be avoided altogether in persons with type 2 diabetes who are fasting but Glibenclamide

can be used with caution. If the glycaemic control before the start of Ramadan is good, then those taking twice daily equal doses of Sulphonylureas are recommended to take the usual evening dose at Iftar but the morning dose should be reduced to half at Suhur time. If the person is taking sulphonylureas twice daily with higher doses in the morning and a smaller dose in the evening, the higher morning dose should be shifted to Iftar and the smaller evening dose to Suhur, which may be reduced further if the control of diabetes is good. Individuals on once daily Glimepiride or Gliclazide-MR should take their medications at Iftar and the dose may remain unchanged or reduced depending upon their pre-Ramadan glycaemic control. However it is important to assume that long acting oral antidiabetic drugs should be used more cautiously than their short acting counterparts during the month of Ramadan.¹⁰

Alpha Glucosidase Inhibitors

This group of drug which includes Acarbose, Voglibose and Miglitol, by virtue of the mechanism of action of inhibiting the alpha glucosidase enzyme at the intestinal border, is unlikely to cause hypoglycaemia. Despite a lower risk of hypoglycaemia its use in clinical practice is limited due to high incidence of gastro intestinal side effects particularly flatulence. No clinical trial has evaluated this group of drugs used in Ramadan. It is recommended that no change in dose of this group is required during fasting and it should be taken with Suhur and Iftar.

Conclusion

In general insulin sensitizer Metformin and TZD'S may be the drugs of choice for use during fasting in people with type-2 diabetes because they carry a very low risk of hypoglycaemia. Older generation SUs should be avoided whereas newer generation SU like Gliclazide and Glimepiride are relatively safe. Meglatinides are a good option due to their ultra short duration of action with

negligible risk of hypoglycaemia. The use of Alpha-Glucosidase inhibitors is limited during Ramadan. In general oral anti-diabetics should be shifted to the Iftar time or relatively higher doses be administered at this time as compared to the Suhur. Lastly individualization should be an essential part of the management plan of people with type-2 diabetes who fast during the month of Ramadan.

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