Initiating oral anti diabetic drug: alternatives to metformin

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Abstract

While most published articles on oral anti diabetic therapy approve of metformin, few discuss what should be done if metformin is contraindicated or not tolerated. This article defines metformin intolerance, and discusses various pharmacological options available for persons with type 2 diabetes who cannot take metformin and do not accept/require insulin.

Keywords: Metformin intolerance, type 2 diabetes, sulfonylureas, alpha glucosidase inhibitors, pioglitazone, SGLT2 inhibitors, DPP4 inhibitors.

Introduction

Most persons with type 2 diabetes initiate oral therapy with metformin. However, some patients have contra-indications to metformin, or cannot tolerate the drug, In such cases, an alternative is required. This alternative may be an oral anti diabetes drug (OAD), or an injectable therapy (insulin, glucagon-like peptide 1 receptor agonist [GLPIRA]). More often than not, an OAD is chosen for this purpose.[1]

Tiributes of A Good Drug For Initiation of Therapy

The diagnosis of diabetes, and the institution of pharmacotherapy, both are associated with significant psychological burden, exposure to drug therapy also brings with it the risk of side effects such as hypoglycaemia. One should, therefore, choose an initial OAD which is easy to use, needs less dose titration, requires less frequency of administration, causes less hypoglycaemia and other side effects, does not need frequent monitoring of glucose or other biochemical parameters, and is economical.

Initolerance to Metormin

Metformin intolerance is defined as the inability to tolerate clinically meaningful doses of metformin after all possible pharmaceutical preparations (IR, SR), timings of administration (before and after meal), dose distributions (once daily, twice daily, at bed time), and all possible co-medication designed to improve gastrointestinal tolerance (eg, antacids, proton pump inhibitors, H2 receptors blockers) have been tried for an adequate period of time. Metformin intolerance should be labeled as such only after optimal counseling has been done regarding the benefits of this molecule. This diagnosis should be arrived at after a process of shared decision making between patient and physician.

Oral Alternatives to Metformin

Oral alternatives to metformin included the sulfonylureas, pioglitazone, alpha-glucosidase inhibitors and gliptins. Bromocriptine and colesevalam are other oral drugs which are approved for the management of type 2 diabetes, and SGLT2 inhibitors are a novel class of OADS which have recently been approved for use.[1-3]

Sulfonlyureas

There seem to be hardly any justification for using sulfonylurea monotherapy today. An extremely unlikely situation would be a person who needs oral therapy, but cannot tolerate any other class of drugs because of gastrointestinal symptoms.[2] Yet another possibility for sulfonylurea monotherapy is in markets where sulfonylureas are cheaper than metformin. This however, is not a valid defence, as the pleiotropic benefits of metformin easily outweigh the potential adverse effects of older (cheaper) sulfonylureas.[3] Dose titration with sulfonylureas needs significant training and experience. Sulfonylureas should be avoided in patients at high risk of hypoglycaemia. These include persons with renal impairment, hepatic impairment and hypothyroidism.

Pioglitazone

Pioglitazone may be considered as initial therapy of choice in freshly diagnosed type 2 diabetes patients who do not tolerate metformin and who wish to gain weight. Pioglitazone does not cause hypoglycaemia, and needs minimal dose titration at monthly intervals, as it takes time for the drug effects to set in. One should keep a close watch for oedema and unwanted weight gain.[3] Pioglitazone is contraindicated in persons with, or at risk of, congestive cardiac failure.

Alpha-Glucosidase Inhibitors

The alpha glucosidase inhibitors (AGIs), eg, acarbose and

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Table-1: Dosage of commonly used oral anti-diabetic drugs.

Drug	Initial dose	Maximal dose	Frequency of dosage
SULPHONYLUREAS			Once-twice daily, before meals
Glipizide	2.5 – 10 mg	40 mg	
Glimepiride	1 – 4 mg	8 mg	
Gliclazide	40-160 mg	320 mg	
PIOGLITAZONE	7.5 -15 mg	45 mg	Once daily
ALFAGLUCOSIDASE INHIBITORS			
Acarbose	25 mg with each meal	100 mg with each meal	With each major meal (Breakfast, lunch, dinner)
Voglibose	0.2 mg with each meal	0.3 mg with each meal	With each major meal (Breakfast, lunch, dinner)
DPP4 INHIBITORS			DPP-4 inhibitors can be prescribed
Vildagliptin	50 mg OD/BD	50 mg BD	as a once daily pill (except vildagliptin: od/bd)
Saxagliptin	5 mg OD	5 mg OD	given at any time of the day, without
Sitagliptin	100 mg OD	100 mg OD	regards to time of meals
Linagliptin	5 mg OD	5 mg OD	
Alogliptin	12.2- 25 mg OD	25 mg OD	
SGLT2 INHIBITORS			
Canagliflozin	100 mg/day	300 mg/day	Before breakfast
Dapaglifozin	5 mg/day	10 mg/day	Before breakfast

voglibose, are suitable alternatives to metformin for initiation of therapy. They have excellent tolerance used in low doses, do not cause hypoglycaemia, and have proven cardiovascular safety.[1] Dose titration is simple, and timing of administration is flexible i.e, acarbose can be administered immediately before or after meals. The frequency of administration (with each meal) may be a barrier for some patients.

Gliptins (DPP4 Inhibitors)

The gliptins, or DPP4 inhibitors, are a suitable class of drug for initiating OAD therapy. Flexibility in timing of administration, lack of side effects, low risk of hypoglycaemia, little or no dose titration requirement and minimal drug- drug interactions make DPP4 inhibition a prepared choice for initiation of OAD therapy.[1,2]

SGLT2 Inhibitors

The SGLT2 inhibitors, are a novel class of OADs, which may emerge as an alternative to metformin, simple or nonexistent dose titration, low risk of hypoglycaemia and high tolerability are advantages of this drug. However, these drugs promote glycosuria, and this fact should be explained to primary health care providers while promoting its use. SGLT2 inhibitors have favourable impact on blood pressure and weight as well.[4]

Conclusion

There will be a small minority of recently diagnosed type 2 diabetes patients in whom metformin is contraindicated, or not tolerated, and who do not require or accept insulin. In such patients OADs such as pioglitazone, AGIs DPP4 inhibitors and SGLT2 inhibitors may be suitable alternatives in certain situations [1,2]. A careful medical assessment is required, however before such therapy is instituted.

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