Starting titrating and intensifying metformin

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Abstract

Most persons with type 2 diabetes are treated with oral anti diabetic drugs (OADs). The drug of choice for initiating OAD therapy, in most cases, is metformin. This communication discusses how to start, titrate, and intensify metformin therapy in primary care. It discusses ways of improving tolerance to, and enhancing acceptability of, metformin in people with diabetes.

Keywords: Oral anti diabetic drugs, Metformin.

Aims of Treatment

Most persons with type 2 diabetes are treated with oral anti diabetic drugs (OADs). The drug of choice for initiating OAD therapy, in most cases, is metformin.[1] The aim of pharmacotherapy is to help the person with diabetes live a life which is symptom- free, complication-free, productive, and of optimal quality. OAD therapy should be chosen keeping these aims in mind. While there is no controversy regarding the utility of metformin, its use can certainly be made more efficient and effective, by following a few basic rules of science and art of medicine.

Characteristics of Suitable OAD in Primary Care

Patient-friendly and physician- friendly OADs, which require least trouble shooting on both sides of the consultation table, should be preferred in primary care. OADs chosen for primary care practice should be effective, safe and well- tolerated.[2] There should be minimal drug-drug interactions, and few side effects. The chances of hypoglycaemia, especially, should be low. The OADs should not require frequent investigations before onset or during therapy. Dose titration should be minimal or should be easily done by paramedical staff or by patients themselves. Timing of administration should be flexible.

The list of contraindications to a particular drug should be limited. Preferably, the drug should be affordable, and be available as fixed dose combination.

Starting Therapy

Current guidelines recommend use of metformin at

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Table-1: Strategies to improve metformin tolerance.

Patient selection
- avoid patients with contraindications
Dosage
- use sustained release preparations
- start low, go slow
- frequent divided doses
- bedtime doses
- post meal doses
- taking tablets during meals
Concomitant management
- manage Gastroparesis
- proton pump inhibitors
- H2 blockers
-antacids
Supportive therapy
- explanation of effects of metformin
- empowerment
- reassurance about self-limiting nature of symptoms
- reinforcement of benefits of metformin
- drug holiday

diagnosis. Metformin therapy should be started in all persons, provided it is tolerated, and is not contraindicated.[1]

Metformin is available in many formulations, and can be started in a dose of 500 mg to 1000mg daily, as a single or in divided doses, usually after meals. An acceptable starting dose for a person with average fasting plasma glucose (FPG) of 150mg% postprandial plasma glucose (PPG) of 250mg%, and HbA1c of 7.5% may be 500mg bd. In case fasting hyperglycaemia predominates, the entire daily dose can be given after dinner. A high FPG with low post prandial excursion (PPE) (difference between PPG and FPG <40mg%) should prompt a prescription of metformin 1000mg at night.

Tolerability

Some patients complain of gastro intestinal upset or uneasiness after initiating metformin.[3] This can be managed by reducing the dose of metformin, changing the timing of administration, asking the patient to take metformin after having consumed half the meal, changing the formulation (from IR to SR preparation), adding a short course of proton pump inhibitors, or giving

a brief drug holiday. Reassurance, that these symptoms will be short-lived; reinforcement, that metformin has multiple beneficial effects; explanation, that metformin is a calorie restriction mimetic, and empowerment, i.e., allowing the patient to self-titrate doses in case side effects occur, are important tools in preventing and managing intolerance (Table-1).

Follow Up

The frequency of follow up in primary care often depends on psychosocial and environmental factors. The attitude and motivation level of the patient, his family support, the expense incurred in consulting the health care provider, and the ease (or difficulty) of travel, all impact the frequency of titration.

A fair strategy, for an asymptomatic or relatively less symptomatic person, would be to schedule fortnightly follow up visits, for the first month. Follow up can be made less regular if there is no strong indication for frequent testing and titration of dose. In fact, metformin is one of the safer drugs to use (along with alpha-glucosidase inhibitors and gliptins) in primary care, if regular follow-up is doubtful or uncertain.

Titration

Inadequate glycaemia response should prompt an increase in the dose of metformin, in increments of 500mg/day at 2-4 weekly intervals. Excellent glycaemic control with or without symptoms suggestive of hyperglycaemia, can be a cue for dose reduction, in decrement of 250mg or 500 mg /day. The maximum dose of metformin allowed varies from 2.5-3g/day. Minimum improvement in glycaemic control is achieved after 1.5g/day.

Response

About 10% of patients may not respond to metformin at all. This is termed primary failure Inability to achieve glycaemic control with half-maximal (1500mg/day) metformin, in spite of adequate lifestyle modification, in the absence of other modification or reversible factors causing hyperglycaemia can be termed as metformin non-response.

It would be beneficial to add another drug to metformin in such cases, instead of continuing to up-titrate the metformin dose.

Over the years, as beta cell function decreases, persons who were earlier well controlled on metformin (primary responders) may find their glycaemic control deteriorating (secondary failure or secondary non-response). This, too, should prompt addition of a second drug.

Trouble Shooting

Common issues with metformin therapy include lack of tolerance, and inadequate control. Both these have already been discussed.

Hypoglycaemia is very rare with metformin monotherapy, but is known to occur. Patient listening ("diabetes therapy by the ear"), a regular meal pattern, and hypoglycaemia awareness training (HAT) can help manage this condition. If required, metformin can be spilt into smaller, but more frequent doses, or the total dose can be reduced.

Documented hypoglycaemia on metformin use should prompt investigations for renal dysfunction, hepatic dysfunction, and hypothyroidism.

Contraindications

Metformin should be avoided in cachexia, and in malnourished individuals, as it works as a calorie restriction mimetic. It is contraindicated in severe hepatic or renal dysfunction, and in ketonuria.

Limitations

Metformin monotherapy will not work without adequate lifestyle modification, it also may not work in settings where the patient is highly symptomatic or has severe hypoglycaemia. Combination oral therapy, or insulin, may be preferable in such cases,

References

1. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: A patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012; 55: 1577-96.
2. Scheen AJ, Paquot N. Metformin revisited: A critical review of the benefit-risk balance in at-risk patients with type 2 diabetes. Diabetes Metabol 2013; 39: 179-90.
3. Ferrannini E. The Target of Metformin in Type 2 Diabetes. N Eng J Med 2014; 371: 1547-8.