Practice Point

Oral Anti-diabetic Agents

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A. Sulfonylurea (SU) – back bone in the management of type 2 diabetes mellitus (T2DM) in our country

Indications of SU

1. SUs may be prescribed as first-line agents in case of metformin intolerance or contraindication, MODY 3/HNF-1α and MODY 1/HNF-4α.
2. Prescribe SU as second or third-line agent after other drug classes (eg metformin) fail to achieve glycaemic control.
3. If prescribed, SUs should be initiated early in the course of T2DM when there is good β cell reserve.
4. SUs are preferred in patients who are not overweight.

Contraindications of SU and their use in co-morbid and special conditions

1. Avoid SU in children, adolescents, pregnancy, lactation and sulphur sensitivity. SUs with low risk of hypoglycaemia (gliclazide MR, glimepiride) are recommended in the elderly.
2. In CKD stage 3-5, avoid chlorpropamide, tolbutamide, glibenclamide; reduce dose of glimepiride; can use usual dose of glipizide and glicazide.
3. In mild to moderate hepatic impairment, reduce dose and frequency of SU. In moderate to severe hepatic impairment, avoid SU.
4. Modern SUs (glimepiride, glicazide MR) are preferred over conventional SUs in patients at increased risk of hypoglycaemia, patients who are overweight, and those with increased cardiovascular risk.

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Guidelines for the use of SU

1. Assess cardiovascular health, presence of renal and hepatic impairment.
2. If no contraindication, start with low dose of SU.
3. Uptitrate slowly every 2-4 weeks.
4. If hypoglycaemia occurs or there is no further improvement in glycaemic status, return to previous dose.
5. Change the treatment regime when patient is on more than 50% of maximum dose of SU and HbA1c has not reached the target.
6. During SU use, blood glucose can be monitored once in 2 weeks in responders and once in a week in non-responders.
7. Administer SU as morning dose – half an hour before meal.
8. Glimepiride is given once daily, maximum dose 6 mg. Glicazide can be given once or twice daily with a maximum dose of 320 mg.
9. SU can be used with sensitizers, DPP4 inhibitors, α-glucosidase inhibitor and basal only insulin regimen.
10. Avoid using SU with other secretagogues (other SU and meglitinides).
11. Consider risk of drug interaction with other protein bound drugs (eg. salicylates, sulfonamides, warfarin).
12. Adjust the dose when patient is taking concomitant enzyme inducers or inhibitors.

Advice to give patients on SU

1. Educate patient about hypoglycaemia, its symptoms and management.
2. Advise 3+3 meal pattern. Caution against missing meals.
3. Monitor weight, cardiovascular health, liver function, renal function and blood glucose at every clinic visit.

*Before prescribing SU, please ask about sulphur hypersensitivity.

B. Metformin – a safe, effective, non-hypoglycaemic, cardioprotective, cancer reducing and weight neutral drug used in all patients with type 2 diabetes mellitus provided there is no contraindication

Indications of Metformin

1. Prescribe Metformin as first-line agent if no contraindication or intolerance.
2. Preferred in overweight patients. Can also be given to normal weight patients.
3. Metformin mainly lowers fasting hyperglycaemia.

Contraindications of Metformin and use in co-morbid and special conditions

1. Avoid Metformin when eGFR is below 45 ml/min/1.73m2 or serum creatinine is above 1.4 mg/dl in females and 1.5 mg/dl in males.
2. Avoid in conditions associated with hypoxia (eg. severe cardiac or respiratory insufficiency, septicaemia, hypotension, liver disease and history of metabolic acidosis).
3. Avoid Metformin in children under 10 years, pregnancy (except PCOS) and lactation.
4. Temporarily stop Metformin during intercurrent illness, major surgery, investigations with intravenous radiographic contrast media and interventions.

Guidelines for the use of Metformin

1. Start with low dose (eg. 500 mg daily).
2. Uptitrate slowly – 500/850 mg at a time every 1-2 weeks until target is reached.
3. If gastrointestinal symptoms develop, return to previous dose.
4. Metformin can be given once daily, 12 hourly or 8 hourly. Slow release formulations should be given once daily (if necessary, twice daily).
5. Do not exceed the maximum dose of 2500 mg/d.
6. Well tolerated dose is 850 mg 12 hourly.
7. It is given after meal.
8. It can be given in combination with other oral and injectable anti-diabetic medication.
9. Monitor renal function every 3 months if eGFR is 45-60 ml/min/1.73m2 and yearly if eGFR >60 ml/min/1.73m2.

*Avoid in conditions associated with or leading to hypoxia.

C. DPP-4 inhibitor – a new, safe, effective but costly drug especially for hypoglycaemia prone patients

Indications of DPP-4 Inhibitors

1. Prescribe DPP-4 inhibitors as add-on therapy in patients inadequately controlled on metformin or other agents.
2. Can also be given as monotherapy to patients not responding to lifestyle measures, or with contraindication to SU and metformin.
3. Should be initiated early, but also effective late in the course of disease.
4. DPP-4 inhibitors mainly lower post prandial hyperglycaemia. Preferred in patients with risk of or having conditions associated with hypoglycaemia.
5. Preferable for overweight patients. Can also be given to normal weight patients.

Contraindications of DPP-4 inhibitors and use in co-morbid and special conditions

1. Reduce dose of Sitagliptin to 25 mg/d when eGFR is below 30 ml/min/1.73m2, and to 50 mg/d when eGFR is between 30 and 50 ml/min/1.73m2. In case of Vildagliptin, avoid when eGFR is below 50 ml/min/1.73m2.
2. Avoid Vildagliptin and Sitagliptin when liver enzymes are > 3X upper limit of normal.
3. Use cautiously in heart disease (due to drug interaction with digoxin).
4. Avoid in children, pregnancy, lactation, pancreatitis and medullary carcinoma of the thyroid.
5. Linagliptin can be used in renal and hepatic impairment.

Guidelines for the use of DPP-4 inhibitor

1. Sitagliptin is given once daily in the morning, maximum dose is 100 mg. Vildagliptin is given twice daily with a maximum dose of 100 mg. Linagliptin 5 mg is given as a single dose. Saxagliptin is taken 2.5 to 5 mg once daily.
2. It can be taken with or without food.
3. It can be given in combination with other oral anti-diabetic medications and insulin.
4. Monitor renal and pancreatic function periodically.

D. α-Glucosidase inhibitor – a safe, non-hypoglycaemic, less potent oral agent in the management of type 2 diabetes mellitus

Indications of α-Glucosidase inhibitors

1. Prescribe as add-on therapy in patients with primarily post-prandial hyperglycaemia.

Contraindications of α-Glucosidase inhibitors and use in co-morbid and special conditions

1. Avoid in any condition associated with gastrointestinal upset, chronic intestinal disease, hepatic and renal impairment.
2. Avoid in children, pregnancy and lactation.

Guidelines for the use of α-Glucosidase inhibitor

1. Start with a low dose (25 mg 8 hourly)
2. Slowly uptitrate over several weeks.
3. Can be given up to 3 times a day.
4. Maximum dose is 100 mg tds.
5. Should be taken with meals (eg. take with first bite).
6. Advise patient to take diet rich in complex carbohydrate.
7. Miglitol is better tolerated than Acarbose.

E. SGLT2 inhibitor – a new but costly drug used in special situations

1. Reserved drug, can be used as add-on therapy with any other anti-diabetic treatment at all stages of diabetes when control of diabetes is difficult with other agents, especially if patient is overweight.
2. Helps to control hypertension and reduces weight.
3. There is risk of repeated UTI, fluid and electrolyte imbalance. Patients should be cautious about development of ketoacidosis.
4. Diabetes control should be monitored by checking blood glucose and not urine sugar.

****Take Home Message**

- Right regime
- Right drug
- Right approach (patient centered)
- Right follow up
- Right patient education

- Key to the successful management of diabetes mellitus