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Hypoglycaemia during Treatment of Type 2 Diabetes: Dangerous Complication….. But Avoidable with Modern Non-Insulin Therapy

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ABSTRACT

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Hypoglycaemia is a dangerous complication that could occur while treating diabetes. Inpatients with type 2 diabetes, avoidance of hypoglycaemia is desirable in all; and absolutely necessary in many. Currently, clinicians have access to a variety of medications that achieve the dual objective of reaching targets and avoiding hypoglycaemia.

This brief review aims to highlight the dangers of hypoglycaemia and to familiarize clinicians with non-insulin based medications that avoid hypoglycaemia while treating patients with type 2 diabetes mellitus.

Keywords: Hypoglycaemia, Type 2 diabetes, Pioglitazone, GLP-1 mimetics, DPP4 inhibitors, SGLT2 inhibitors

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A major challenge in the management of patients with diabetes mellitus is to achieve glycaemic and HbA1C targets without producing hypoglycaemia. Hypoglycemia in diabetes has been defined[1]as "all episodes of abnormally low plasma glucose concentration that exposethe individual to potential harm". In practice, hypoglycaemia is diagnosed when plasma glucose is less than 70 mg/dl. Certain terms have been defined[1] as follows. Severe hypoglycaemia is defined as hypoglycaemia that requires the assistance of another person to actively administer carbohydrate (or glucagon) or other resuscitative measures. Symptoms of hypoglycaemia, accompanied by low blood glucose, is termed documented symptomatic hypoglycaemia. Event where typical hypoglycaemic symptoms are presumed to be due to low plasma glucose, but glucose is not measuredis called probable symptomatic hypoglycaemia. When hypoglycaemia is documented, without typical symptoms, it is termed asymptomatic hypoglycaemia. When a person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration that is not low, the term relative (or pseudo) hypoglycaemia is used.

CONSEQUENCES OF HYPOGLYCAEMIA

Hypoglycaemia should never be underestimated as it is dangerous. It can rarely cause death, increase cardiovascular events, impair judgment, behavior and performance of simple tasks.[1,2] In the elderly, while symptoms due to hypoglycaemia may be less pronounced than in younger adults,[1] the morbidity from hypoglycaemia is higher.[3] A single episode of severe hypoglycaemia, increases 12 month mortality[4] (the precise mechanism unclear). Among type 2 diabetics surviving severe hypoglycaemia, 12 month mortality rate was 22.1% (27.4% in patients aged ≥75 years).[4] Clinicians must appreciate that hypoglycaemia can greatly impair the emotional wellbeing and quality of life of not just the patient but also their next of kin.[1] Further, fear of hypoglycaemia can significantly affect the quality of life of diabetic patients.[1] Therefore, patients and their next of kin must be provided sufficient knowledge to suspect, diagnose and treat hypoglycaemia. These must be periodically reinforced. Further, during follow-up visits, clinicians must specifically enquire about episodes of hypoglycaemia.

Certain situations demand complete avoidance of hy-

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poglycaemia. Examples include people living alone, senior citizens (above 65 years), professional drivers, people working at heights, and people working in situations where effects of hypoglycaemia are totally undesirable.

The consequences of hypoglycaemia, must compel clinicians to choose appropriate strategies for minimising or avoiding hypoglycaemia. Sulfonylureas, glinides and insulins are the medications eminently capable of causing hypoglycaemia.In patients with type 2 diabetes, metformin has stood the test of time and continues to be first line drug. Metformin does not cause hypoglycaemia. It should be used with caution if eGFR (estimated glomerular filtration rate) is below 45ml/Kg/1.73m^2. Should eGFR fall below 30 ml/Kg/1.73m^2, metformin should be stopped[5].

THE OLDER APPROACH NEEDS TO BE RECONSIDERED

For decades, sulfonylureas were the most widely used second line oral hypoglycaemic agent. This historic reality, was primarily due to non-availability of safer drugs in the past. Sulfonylureas have almost as much chance for causing hypoglycaemia (including severe hypoglycaemia) as insulin.[6] Among sulfonylureas, Glibenclamide has a high chance of causing hypoglycaemia.[7] Glimepiride is safer, Gliclazide has the least chance for hypoglycaemia. When safer medications are available, why are sulfonylureas widely prescribed? It may be that sulfonylureas are relatively less expensive and widely available. Glibenclamide is provided free of cost through government run hospitals and health centres in Kerala.

In selected situations, when insulins are indicated, choice of the appropriate analogue insulin prevents hypoglycaemia. A detailed discussion on newer insulins is beyond the purview of this paper.

Currently, a wide range of medications are available to control glucose without causing hypoglycaemia. These include pioglitazone, GLP-1 mimetics, DPP4 inhibitors, alpha glucosidase inhibitors and SGLT2 inhibitors. Clinicians must be familiar with their use.

Pioglitazone:

The only currently available "glitazone" (thiazolidinedione) – pioglitazone, is not likely to cause hypoglycaemia, unless used in combination with sulfonylureas or insulin. Its major advantage is the relatively low cost. Pioglitazone does cause weight gain and fluid retention. A small increase in incidence of fractures is observed in patients taking pioglitazone. The side effect of major concern is small increase in chance of bladder cancer. This risk increases with duration of use and cumulative dosage. Incidence is highest among those using the drug for more than 24 monthsand those receiving cumulative dosages greater than 28000 mg.[8] Pioglitazone must not be started or continued in patients whohave heart failure or a history of heart failure, hepatic impairment, diabetic ketosis, uninvestigated microscopic hematuria and current or previous bladder cancer.[5]

GLP-1 Mimetics and DPP4 Inhibitors:

Incretins[9] are glucagon like hormones, released from the GI tract, in response to ingestion of glucose and fat. GLP-1 is an important member of this family. They stimulate pancreatic insulin release and inhibit glucagon release. They are rapidly destroyed by the enzyme dipeptidyl peptidase 4 (DPP-4); and have a half-life of less than 2 minutes. Both DPP-4 inhibitors and GLP-1 mimetics are hypoglycaemic agents. As they act only when blood glucose level is high, they are not likely to cause hypoglycaemia.

GLP-1Mimetics (Incretins):[9]

These do not cause hypoglycaemia. A major benefit is weight loss. These should therefore be considered for obese type 2 diabetics. Marketed in "pens", they are administered as subcutaneous injection. Dose is not titrated to blood glucose.Reversible, mild nausea, observed in the initial week or two can be minimised by using a lower dose during initiation. Examples of such agents include Liraglutide, Dulaglutide and Albiglutide. Liraglutide needs to be administered once daily. Dulaglutide and Albiglutide are administered once a week. A gradual fall in blood pressure is commonly observed. Hence blood pressure needs to be checked and dose of antihypertensives reduced if necessary. Though very effective in obese diabetics, high cost limits their use in India. They should be continued beyond 6 months only if the patient has beneficial clinical response – defined as reduction in HbA1C of at least 1% and reduction in weight loss of at least 3% of initial body weight.[5]

DPP-4 Inhibitors:

Also known as Gliptins, they are administered orally. Sitagliptin, Vildagliptin, Saxagliptin and Teneleglitin are administered daily, whereas Omarigliptin (not yet available in India) is administered once a week. They are generally well tolerated. When used as the sole agent, or in combination with metformin, they do not cause hypoglycaemia. Combining DPP-4 inhibitors with sul-

fonylureas, may cause hypoglycaemia.[10] In India, they were relatively expensive at the time of launch. Subsequently, cost has decreased.

Alpha glucosidase Inhibitors:

Acarbose and Voglibose are examples. These competitively block digestion of large carbohydrates to monosacharides, thereby retarding absorption from the gut. Their primary role is in reducing postprandial hyperglycaemia. They can be combined with metformin when hepatic or mild renal impairment prevents the use of other oral hypoglycaemics. Their effect on HbA1C is minimal. Presence of undigested carbohydrate in the gut can cause abdominal discomfort and flatulence.

SGLT2 inhibitors:

Selective sodium-glucose co-transporter-2 (SGLT-2) inhibitor, lowersblood glucose in people with type 2 diabetes by blocking the reabsorption of glucose in the kidneys and promoting loss of excess glucose in the urine. They do not cause hypoglycaemia.[11,12] Dapagliflocin, Empagliflocin and Canagliflocin are examples of SGLT2 inhibitors. As per NICE guidelines,[12] dual therapy with SGLT2 inhibitor (and metformin) should be considered if a person cannot tolerate sulfonylurea or the person is at the significant risk of hypoglycaemia or its consequences. Triple therapy with SGLT2 inhibitors is indicated in combination with metformin plus pioglitazone or metformin plus sulfonylurea.

eGFR less than 60ml/kg/1.73m2 is currently a contraindication for commencing SGLT2 inhibitors.[12] Their use is associated with a slight increase in urinary tract infection. They do not cause volume depletion, or higher incidence of fractures.

SUMMARY

The use of sulfonylureas is associated with hypoglycaemia. Hypoglycaemia is dangerous. Severe hypoglycaemia steeply increases one year mortality. While avoiding hypoglycaemiais desirable in all patients with type 2 diabetes, in selected groups, hypoglycaemia is totally undesirable. Currently, clinicians have access to a variety of medications that do not cause hypoglycaemia, when used alone or in combination with metformin. Clinicians must familiarise themselves with these medications.

END NOTE

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