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METFORMIN: THE MIRACULUS DRUG

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INTRODUCTION

Metformin is a biguanide class of antidiabetic drug biochemically known as Dimethyl biguanide. This pharmacological agent has got originated from the French lilac or goat's rue (*Galega officinalis*), a plant that was used in traditional medicine for years. It was first synthesized in 1929 (1). However, it was used in clinical practice for the treatment of diabetes in the late 1950s by the French physician Jean Sterne, who gave it its first trade name, Glucophage ("glucose eater") (1).

Metformin is a hydrophilic base which is absorbed predominately from the small intestine and there is a large inter-individual variability in metformin pharmacokinetics. The drug is widely distributed into body tissues including the intestine, liver, and kidney by organic cation transporters (OCT) (2). The absolute bioavailability of a metformin hydrochloride 500mg tablet given under fasting conditions is approximately 50-60% (3). The half-life of the drug is about 6 hours (3). Metformin is not metabolized in the body. It is excreted unchanged in the urine and active tubular secretion in the kidney is the principal route of elimination (2).

Metformin acts mainly on the liver to reduce gluconeogenesis by inhibiting the enzyme Pyruvate Carboxylase (4). It acts only in the presence of endogenous insulin. However, it has no influence on endogenous insulin secretion and the absence of hypoglycaemia and hyperinsulinaemia is a unique advantage in treating patients with type 2 diabetes mellitus, using this molecule. The molecular mechanisms of metformin action are not fully known. Activation of the enzyme AMP-activated protein kinase appears to be the mechanism by which, metformin lowers serum lipid and blood glucose concentrations (5). It has the ability to lower both basal and postprandial plasma glucose.

Metformin can lower glucose output from the liver by reducing gluconeogenesis, glycogenesis and fatty acid oxidation (5). It reduces glucose absorption from the intestine and increases anaerobic glucose metabolism (6). It also acts at the level of skeletal muscles to increase insulin-mediated glucose uptake, to increase glycogenesis and to reduce fatty acid oxidation (5). All these mechanisms contribute achieving normoglycaemia.

INDICATIONS

Metformin is the drug of choice in type 2 diabetes patients if not contraindicated and if tolerated (7). Metformin is indicated in gestational diabetes mellitus as most recent studies suggest that oral hypoglycemic agents, especifically metformin, are safe to use during pregnancy (8). In a meta-analysis, metformin improved the odds of ovulation in women with polycystic ovary syndrome when compared with placebo and appears more effective for non-clomiphene-resistant women (9).

A meta-analysis has shown that metformin can improve glycaemic control and reduces insulin requirement in patients with type 1 diabetes (7). The clinicians all over the world have been using metformin in combination with insulin in patients with insulin dependent diabetes. However, the FDA has not yet recommended metformin for the treatment of type 1 diabetes (7).

Apart from glucose lowering benefit, there are a number of benefits that metformin offers to a patient with diabetes. Weight reduction property of metformin is of particular advantage when treating patients with type 2 diabetes. Metformin has the ability to lower body fat mass without a change in lean body mass. Lowering of appetite is the probable mechanism. However, there is a suggestion that metformin has an influence on leptin level (10, 11) and also a direct effect on glucose absorption from the intestinal lumen (11), which also contributes to weight reduction property of metformin. Two large studies by the Diabetes Prevention Program Research Group assessed weight loss with metformin. In the study published in 2009 (12), patients randomly assigned to receive lifestyle treatment initially lost weight but gradually regained the lost weight over the 10-year follow-up period. Patients randomly assigned to receive metformin lost less weight at the beginning of the study (2.5 kg) but were able to sustain the weight loss over 10 years. In the study published in 2012, participants in the original study were offered the chance to continue metformin in an open-label fashion. Overall weight loss during the open-label period of 7-8 years was 1.9 kg. In patients considered highly adherent to metformin, the average weight loss was 3.1 kg compared with baseline.

Recent multi-centre randomized controlled trial done with SGLT2 inhibitor, Empagliflozin (Empa-Reg trial), one of the new class of oral hypoglycaemic agents, has shown a cardiovascular benefit apart from the glucose lowering effect of this particular drug (13). Till today, metformin is the only hypoglycaemic

agent that has shown a cardiovascular benefit apart from glucose lowering properties. Lipid lowering action, platelet anti-aggregating effects and reduction of cellular oxidative reactions are thought to be responsible for this (14). The U.K. Prospective Diabetes Studyrandomized 753 adipose type 2 diabetic patients to metformin or placebo. After 10 years, the relative risk reduction in the metformin group was 39% for myocardial infarction and 36% for death (15). Follow-up was continued for an additional 10 years. At this point, the risks reductions were 21% for diabetes-related complications, 33% for myocardial infarction, and 27% for death (16).

Metformin is considered as the first known cancer preventive medication (17). It has anti-carcinogenic activities in breast, colon, pancreatic, ovarian, lung, and prostate cancers (18). It is mediated through activation of AMP-activated protein kinase (AMPK), inhibition of the mammalian target of rapamycin (mTOR) pathway and inhibition of insulin-like growth factors (IGFs), and many others. It has also been shown to be beneficial as an adjuvant therapy in patients with solid cancers and there is a hope as an anticancer agent (19).

SIDE EFFECTS

Short-term effects are mostly gastrointestinal and transient. Anorexia, nausea, vomiting, diarrhoea, abdominal pain, taste disturbances and lactic acidosis are the commonest side effects, which can also be minimized by initiation with the lowest dosage and gradual up-titration.

The most serious and most worrying side effect is the lactic acidosis, despite its rare occurrence. Inhibition of gluconeogenesis, reduced hepatic lactate uptake and inhibition of mitochondrial cellular respiration that occurs with metformin facilitate anaerobic metabolism and lactic acidosis. Therefore, metformin is not recommended in conditions that lead to tissue hypoxia resulting lactic acidosis and in patients with poor renal function. Therefore, this drug has to be used with extreme caution in conditions such as acidosis, dehydration/shock, severe infection/sepsis, acute heart failure, respiratory failure, hepatic impairment, hypoxia, recent myocardial infarction, use of general anaesthesia, renal failure with eGFR<30ml/min/1.73m2 and the use of intravenous contrast agents within 48 hours.

Due to the serious nature of this side effect, lactic acidosis, most of the authorities and guidelines recommend to stop metformin in high-risk situations and when eGFR <30ml/min (20). However, most of the clinicians have been using it even in this extreme situation with careful monitoring without a problem. A Cochrane Systematic Review of over 200 trials evaluated the incidence of lactic acidosis among patients prescribed metformin versus non-metformin anti-diabetes medications. Of 100,000 people, the incidence of lactic acidosis was 5.1 cases in the metformin group and 5.8 cases in the non-metformin group. The authors concluded that metformin is not associated with an increased risk of lactic acidosis. It is assumed that not metformin but the medical conditions associated with diabetes mellitus are responsible for lactic acidosis in metformin-treated diabetic patients. This suggests that risk of using metformin is extreme conditions are not as bad as we thought and one can still consider using it with careful monitoring, if it is really needed.

Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, which occurs due to malabsorption of vitamin B_{12} at its absorption site in the terminal ileum (21). This predisposes to macrocytic and megaloblastic anemia, low haematocrit, peripheral neuropathy and high homocysteine levels.Metformin has an effect on calcium-dependent membrane action in the terminal ileum. Absorption of the vitamin B12-intrinsic factor complex is calcium dependent and metformin interferes with this absorption. Since vitamin B_{12} acts as a potent co-factor in the synthesis of methionine from homocysteine, homocysteinaemia occurs with metformin therapy. Although there is a theoretical risk of B12 deficiency with metformin use, it has not shown as a significant clinical problem (22). However, a recent report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggests that periodic testing of vitamin B_{12} levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy (20).

The major concern among patients as well as the clinicians regarding the possible nephrotoxic effect with the long-term use of metformin. Adverse comments from complimentary medicine practitioners have created even a bigger concern. Down titration of the metformin dosage during renal impairment and withdrawing of the drug when the GFR is <30ml has created an impression that the metformin is withheld due to the nephrotoxic nature of the medication. However, the evidence suggests that metformin is reno-protective. A study conducted by Kim et al. revealed that metformin was able to protect podocytes in diabetic nephropathy in an animal study (23) and Morales et al indicates that metformin shows protective effects against gentamicin nephrotoxicity in another animal study (24).

CONCLUSIONS

Undoubtedly, metformin is a miraculous drug in current medical practice. Due to the multiple benefits that the patient can have, it has become the number one anti-diabetic drug throughout the world and it will remain in the number one position for so many years to come.

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