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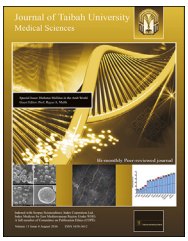

Review Article

Diabetes and oral therapies
A review of oral therapies for diabetes mellitus

Mohamad S. Alhadramy, FRCP

Department of Medicine, Taibah University, Almadinah Almunawwarah, KSA

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الملخص

تستخدم الأدوية الفموية الخافضة لسكر الدم لعلاج النوع الثاني من داء السكري منذ عقود، نظرا لفاعليتها وسهولة استعمالها. الأدوية الخافضة لسكر الدم الأكثر تجربة هي متفورمين وسلفونيل يوريا منذ أكثر من ٥٠ عاما. تلى هذه الأدوية تقديم مركبات أخرى من أدوية خفض سكر الدم مثل الجلينيدات، وثيازولدين ديونات، ومثبطات ألفا جلوكوسيديز، ومثبطات ديببتديل ببتديز ٤—، ومثبطات الناقل المشارك لصوديوم —جلوكوز —٢. ويعتبر المتفورمين الدواء المفضل للعلاج المنفرد، مالم يكن هناك مانع من استخدامه أو وجود آثار جانبية له. وقد أدى نقص السكر في الدم الناجم عن السلفونيل يوريا إلى تراجع استخدمه لصالح بعض المركبات الجديدة، ولكن الوصفة العامة لسلفونيل يوريا مع ميتفورمين رخيصة جدا ومازالت فاعلة. والجدير بالذكر أن مخاطر القلب والأوعية الدموية للعديد من الأدوية هي مصدر قلق كبير للأطباء وهيئات التشريع. كما يجب على الطبيب المعالج أن يضع في اعتباره حالة المريض الصحية، والآثار الجانبية للأدوية، والتكلفة، وما يفضله المريض عند اختيار الأدوية الخافضة لسكر الدم للعلاج المزدوج أو الثلاثي. تستعرض هذه المقالة المزايا والعيوب لمجموعة من الأدوية الفموية الخافضة لسكر الدم وتطبيقاتها للعلاج المنفرد أو المتعدد.

الكلمات المفتاحية: سلامة الدواء؛ علاج نسبة السكر في الدم؛ أدوية خفض سكر الدم؛ حوادث القلب والأوعية الدموية؛ العلاجات الجديدة المضادة للسكري

Abstract

For decades, antihyperglycaemic agents have been used for the treatment of type 2 diabetes mellitus given their effectiveness and convenience. Metformin (MET) and sulphonylureas (SU) are time-tested antihyperglycaemic agents that have been administered for more than 50 years. These agents were followed by the introduction of other antihyperglycaemic agents such as glinides (GLN), thiazolidinediones (TZD), alpha-glucosidase inhibitors (AGI), dipeptidyl peptidase-4 inhibitors (DPP-4I), and sodium–glucose cotransporter-2 inhibitors (SGLT2I). MET is recognized as the drug of choice for monotherapy unless contraindicated or unwanted side effects occur. SU-induced hypoglycaemia is losing ground to various new agents, but the generic formulae of SU together with MET are cheap and effective. The cardiovascular hazards of several agents are a major concern to physicians and legislating bodies. In choosing antihyperglycaemic agents for dual or triple therapy, the treating physician must keep in mind the health status of the patient, medication side effects, cost, and patient preference. This review addresses the advantages and disadvantages of a range of antihyperglycaemic agents and their applications in monotherapy or combination therapy.

Keywords: Cardiovascular events; Drug safety; Glycaemic management; Hypoglycaemic agent; New antidiabetic therapy

Introduction

Oral antihyperglycaemic agents have been the mainstay of treating type 2 diabetes mellitus (T2DM) for numerous decades given their efficacy and convenience. Metformin (MET) and sulphonylureas (SU) have been in use for more than 50 years, and their major side effects are widely

Corresponding address: Department of Medicine, Taibah University, PO BOX 2591, Almadinah Almunawwarah 41461, KSA.
E-mail: alhadraamy@hotmail.com

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known. The last two decades have witnessed the introduction of many classes of these agents, and their optimal use and side effects are gradually recognized. Seven approved major classes of oral antihyperglycaemic agents are currently available: MET, SU, glinides (GLN), thiazolidinediones (TZD), alpha-glucosidase inhibitors (AGI), dipeptidyl peptidase-4 inhibitors (DPP-4I), and the most recent sodium−glucose cotransporter-2 inhibitors (SGLT-2I). This review summarizes the characteristics of each class and their use in T2DM management. The cardiovascular safety of these medications has received more attention in the last few years after the United States Food and Drug Administration (FDA) reported unexpected cardiovascular outcomes and made new requirements for licensing new antidiabetic drugs. These outcomes are discussed in the section on TZD.

Metformin

Traditional medicine used French lilac for treating diabetes for centuries, and guanidine compounds were derived from its extract in 1920s.[1] These compounds exhibited hypoglycaemic effects in animals but were later withdrawn due to hepatotoxicity in patients. The biguanides, phenformin and MET are derived from guanidines and were introduced in 1950's.[2] However, phenformin was withdrawn in the late 1970s, as it was linked to fatal lactic acidosis.[3]

Mechanism of action and efficacy

Metformin works by reducing hepatic gluconeogenesis and increasing glucose uptake in the peripheral tissues, especially in muscles,[4,5] thus improving insulin sensitivity. As it does not stimulate insulin secretion, metformin monotherapy rarely causes hypoglycaemia. Metformin also enhances the action of glucagon-like-peptide-1 (GLP-1), but the clinical significance of this agent is not established.[6]

Metformin is recognized as the first agent to be used as monotherapy with life-style modification to treat T2DM unless intolerance or a contraindication for its use is noted.[7,8]

The United Kingdom Prospective Study (UKPDS) demonstrated that overweight patients allocated to the MET group exhibited reduced median HbA1C compared with the conventional group (7.4% vs 8%), with 32% risk reduction for any diabetes related endpoints.[9] A systemic review analysing the results of 15 controlled studies on treatment with MET versus control reported a weighted mean absolute difference (WMAD) in HbA1C levels of −1.14%.[10] Many reports refer to a reduction of HbA1C by 1−2%.[11] Despite this finding, metformin gradually loses efficacy with a cumulative incidence of secondary failure as a monotherapy of 21% at 5 years, which is better compared with SU.[12] However, starting MET monotherapy in T2DM was less likely to require intensification by another agent compared with SU, TZD, or DPP-4I.[13]

Analysis of 8 controlled trials reported the weighted mean difference (WMD) in body weight between the treatment and control as 0.3 kg.[10] Although some studies reported weight reduction, the treatment is generally considered weight neutral.[11]

Side effects and contraindications

The most frequently reported side effect, which may force the patient to discontinue usage, is gastrointestinal (GI) upset, which could be due to the release of 5-hydroxytryptamine and other substances within the duodenal mucosa.[14]

GI upset may be managed by a starting dose of 500 mg daily with meals. The dose is then increasingly titrated by 500 mg every 1−2 weeks in two to three divided doses until the desirable dose is achieved. Another method involves the use of the extended release formula of MET. The extended release formula was well tolerated by 97.4% of patients in a study of 3556 patients.[15] Vitamin B12 deficiency may develop with prolonged MET use, especially in elderly diabetic patients administered high doses.[16]

Lactic acidosis is a lethal complication that causes the withdrawal of phenformin, but this condition rarely occurs with MET. An extensive systematic review showed no increase in lactic acidosis in 70,490 MET users years compared to non users.[17] However, one should avoid using MET in conditions that predispose to lactic acidosis, such as severe renal failure. Metformin should be avoided in patients with chronic liver disease, heart failure, renal failure, sepsis and shock.[11] However, there is debate about avoiding MET in heart failure. Analysis of nine cohort studies concluded that MET is as safe as other oral hypoglycaemic agents in patients with heart failure.[18]

The FDA advises to avoid MET if serum creatinine is $\geq$1.5 mg/dl in males and $\geq$1.4 mg/dl in females.[19] However, an observational study over approximately 4 years revealed no increase in the risk of severe side effects, including acidosis, in patients administered MET with a creatinine clearance of 30−45 ml/min/1.73 m^2.[20]

The FDA also advises to avoid MET before, during and 48 h following radiologic studies involving IV iodinated contrast.[19] However, the American College of Radiology does not recommend holding MET dosing in relation to IV iodinated contrast studies if the patient does not have acute kidney injury and has an eGFR $\geq$30 ml/min/1.73 m^2 nor in relation to gadolinium in the typical dose range of 0.1−0.3 mmol/kg.[21]

The side effects of MET are summarized in Table 1.

Cardiovascular safety

Metformin was associated with 42% reduction in diabetes-related deaths and 36% reduction of all-cause mortality in the UKPDS.[9] In the intensive blood-glucose control group, patients treated with MET exhibited a greater effect for all-cause mortality, stroke and diabetes related endpoints compared with those treated with SU. The reduction of myocardial infarction and mortality gained by MET use in overweight patients in the UKPDS was maintained 10 years after the end of the study.[8]

Dosage

Table 2 shows the dose of MET and relation to food intake.