Mini Review

Where do conventional OADs stand

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ABSTRACT

The last two decades have witnessed unprecedented activity in the field of OADs with many new drugs becoming available. Concerns with OAD include cardiovascular safety, fear about hypoglycemia, weight gain etc. In this article we attempt to review OADs , sulfonylureas in particular, in the light of the newer agents.

Key words: Conventional OADs, sulfonylureas, new roles

Introduction

The era of sulfonylureas in the treatment of diabetes was first ushered in by the fortuitous discovery of Marcel Janbon and his co-workers who discovered that the compound sulfonylurea induced hypoglycemia in animals, when they were working on sulfonamide antibiotics. Biguanide compounds are even older and date back to the use of *Galega officinalis* (French lilac), which has been used for treating diabetes in traditional medicine for centuries. In the 1920s, guanidine compounds were discovered in *Galega* extracts and these compounds were found to lower blood-glucose levels in animal studies. Initially, derivatives like synthalin A and synthalin B, were used for diabetes treatment, but after the discovery of insulin, they were forgotten for the next few decades. Biguanides were reintroduced into Type 2 diabetes treatment in the late 1950s. Initially, phenformin was widely used, but its potential for sometimes fatal lactic acidosis resulted in its withdrawal from pharmacotherapy in most countries in the 1970s. Metformin, which has a much better safety profile, is still the single most important oral anti-diabetic drug in use worldwide.

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New Sun on the Horizon

However, the last two decades have witnessed unprecedented activity in the field of oral anti diabetics (OADs) with many new drugs becoming available. Drugs like alpha-glucosidase inhibitors, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists, bromocriptine, and SGLT-2 inhibitors have provided new means of tackling diabetes. Even more effective drugs are on the horizon, which prompts the question: What is the relevance of conventional OADs in today's diabetic practice? Multiple factors like concerns about cardiovascular safety, fears about hypoglycemia and availability of more efficacious alternatives have prompted this question, more so for sulfonylureas, which are perceived as having many disadvantages.

Risks with sulfonylureas

Concerns about sulfonylureas were first expressed in the University Group Diabetes Program (UGDP) study,[1] in which cardiovascular mortality rates of Type 2 diabetic patients treated with the sulfonylurea tolbutamide exceeded those of patients treated with placebo or insulin. While an intense debate ensued, criticism of the study design and lack of concrete evidence about the dangers of tolbutamide from other studies and supplantation of tolbutamide by newer sulfonylureas led to partial alleviation of concern about these drugs. The single most important concern about sulfonylureas in general and glibenclamide in particular, is their effect on ischemic pre-conditioning. This is a mechanism by which transient ischemia "conditions" the myocardium in a protective fashion, allowing greater

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tolerance of subsequent ischemia. This has been shown to reduce irreversible tissue injury, reduce anginal pain and protect cardiac tissue from myocardial function. ATP-dependent potassium (KATP) channels in myocardial cells are vital to this process. Agents like diazoxide, that open the KATP channels have an effect similar to prior ischemia, while agents like sulfonylureas, which close this channel, can potentially abolish this protective effect. This issue was first raised by the UGDP study. However, the subsequent United kingdom prospective diabetes study group (UKPDS)[2] temporarily laid this controversy to rest, when it reported that treatment with sulfonylureas exhibited a trend toward protection against myocardial infarction rather than enhancement of cardiovascular mortality. However, in 1999, a study by Garratt *et al*.[3] reopened this controversy when they reported increased early mortality (odds ratio 2.7 after adjustment for a number of co-variates) in 67 persons taking sulfonylureas versus 118 using insulin or lifestyle therapy alone. This study, on the surface, seems to condemn sulfonylureas unequivocally. However, a critical re-appraisal of this study reveals a few interesting facts. This study was a retrospective and not a prospective study; randomization was lacking and sulfonylureas taken by patients in this study were not specified. Furthermore, the study sample was too small to reach a decision about the cardiovascular risks of sulfonylureas. Further, even if glibenclamide treatment leads to some decrease in ischemic preconditioning, this is probably counteracted by other beneficial effects of the drug like good glycemic control and a reported anti-arrhythmic action,[4] thus leading to neutral or beneficial cardiovascular outcomes. The results from the UGDP study were based on the effects of tolbutamide, a relatively short-acting drug. Consequently, ingestion of a single early morning of tolbutamide would result in a short burst of high plasma levels of the drug. This burst might have been responsible for the avid binding to KATP channels and abolition of ischemic preconditioning. It is highly debatable whether such bursts or high drug levels can be seen with longer-acting sulfonylureas such as extended-release glipizide, extended-release gliclazade, and glimepiride. Another study by Lee *et al*.[5] concluded that protection by preconditioning occurred with glimepiride but not with glibenclamide in diabetic patients. The values for lactate balance further suggested that diabetes itself may have impaired preconditioning. Glimepiride mainly inhibits SUR 2A, rather than SUR 1 and hence does not interfere with the ischemic preconditioning. In light of these above findings, it is still not clear whether diabetes itself or glibenclamide contributes to cardiovascular mortality. Moreover, glimepiride clearly does not abolish myocardial protection afforded by ischemic preconditioning and it is very likely that gliclazide and glipizide exhibit the same effects, even though very few studies have been published about these two drugs. Hence, it would be very premature to condemn sulfonylureas based on a very tenuous connection with cardiovascular risk.

The second major concern expressed with sulfonylureas is hypoglycemia. While it is true that sulfonylureas can cause severe and long lasting hypoglycemia, they are rarely dangerous when prescribed appropriately. Most episodes of hypoglycemia occur in people with renal or hepatic impairment, in the geriatric population or in those who do not comply with dietary precautions. Further, if hypoglycemic episodes alone are the benchmark for deciding the efficacy and safety of a drug, then the rate of major hypoglycemic episodes per year with insulin was 1.8%, contrary to 1.0% with chlorpropamide and 1.4% with glibenclamide. This in itself, should preclude the use of insulin in treatment of diabetes. On the contrary, insulin still continues to be the most effective therapy for diabetes. This demonstrates that the way a drug is prescribed, rather than its perceived side effects play a major role in its safety profile and efficacy. The newer sulfonylureas like glimepiride, glipizide, and gliclazide are also faster in onset of action, safer even in mild renal and hepatic impairment and are also associated with fewer adverse episodes. Moreover, glibenclamide has been shown to cause a 50% greater suppression of hepatic glucose output than newer sulfonylureas like glipizide, which can also explain the lower incidence of hypoglycemia associated with the newer drugs.

A third bone of contention with sulfonylureas has been the weight gain. This has been attributed to sulfonylureas enhancing insulin secretion, and reducing its hepatic clearance, leading to hyperinsulinemia. However, during long-term therapy, plasma insulin concentrations usually return toward pretreatment levels, while blood-glucose reduction persists. This is due to multiple factors, including initial reduction of glucose stimulated insulin secretion, improved insulin action and consequent reduction of glucotoxicity. Equivalent weight gain or even greater weight gain have also been noted with use of glitazones and insulin. In fact, among the presently used drugs, only GLP-1 analogs and metformin can truly cause weight loss. All the other drugs are either weight neutral or cause weight gain and are also further beset with their own side effects and contraindications.

A lack of incretin like effect is also often quoted. While β-cell mass seems to be well preserved with DPP-IV inhibitors and GLP-1-analogs, the effective and sustained euglycemia produced by use of sulfonylureas, especially when started early, can lead to amelioration of glucotoxicity and lipotoxicity leading to improved beta cell survival.

Differences between sulfonylureas in their effects on β-cell survival may also exist, with animal studies suggesting that glimepiride and glibenclamide may increase the generation of reactive oxygen species and induce β-cell apoptosis, whereas gliclazide lacks such adverse effects and may actually have a benefit in the preservation of functional β-cell mass.[6] Rapidly reversible binding of gliclazide to the SUR receptor is also likely to further enhance its β-cell protective effects.

The overall frequency of other adverse effects of sulfonylureas like nausea, dizziness, skin reactions, headache, agranulocytosis, thrombocytopenia, and jaundice are low, and they are usually mild and reversible.

Benefits of Sulfonylureas

Looking at the other side of the coin, sulfonylureas have many benefits. (1) Efficacy: They are among the most potent OADs, especially when used appropriately with reduction in HbA1C of up to 1.5%, in contrast to drugs like alpha-glucosidase inhibitors (≃ 0.5%), DPP-4 inhibitors (≃ 1%) and GLP-1 analogs (≃ 0.8-1.1%). (2) Safety: Sulfonylureas have been in use far longer than any other OAD and during this period have reported very little teratogenecity or carcinogenic effects. When contrasted with drugs like glitazones which are facing the axe for cardiac side effects, fractures, weight gain, and fluid retention and incretin mimetics, which have been persistently dogged by reports of pancreatitis, sulfonylureas enjoy an exemplary safety record. (3) Compliance: Most sulfonylureas are also prescribed once a day, which helps ensure patient compliance. Oral intake is also a factor contributing to good compliance. (4) Cost: Sulfonylureas, along with metformin are the cheapest OADs, which has particular relevance in a country like India. (5) Combination: These drugs are also very useful in combination with metformin, basal insulin, and alpha-glucosidase inhibitors.

Metformin

The case for metformin is much more straightforward. It has been in use for over 50 years and it still is the drug of first choice for initiating treatment in almost all the guidelines. It has other benefits, including weight loss, an incretin effect leading to preservation of β-cell mass, reduction of hepatic glucose production and a reduction in hyperinsulinemia. It can also be used in combination with all the other OADs and retains its beneficial effects and acts in a synergistic manner with the other drugs. The risk of hyperglycemia is also almost non-existent. The only major side effect of metformin is lactic acidosis, which can be prevented by reducing the dose or stopping the drug in people with hepatic or renal dysfunction. Gastro-intestinal side effects are mild and usually short lived. Prescribing a drug after meals and use of sustained-release preparations have increased the acceptability of metformin.

New Role for Conventional OADs

Oral agents are a more practical alternative to insulin therapy in pregnancy on account of their oral route of administration, compliance, and patient acceptability. Langer *et al*.[7] first recommended glibenclamide in pregnancy in 2000. Since then, multiple studies and guidelines[8-10] have endorsed the use of glibenclamide as an alternative pharmacological therapy to insulin during pregnancy. These recommendations are based on the sound logic that glibenclamide does not cross the placenta and has been safely used in pregnancy without adverse effects on the fetus. Further, when insulin and glibenclamide were compared, similar success rates were reported and were comparable to insulin in glycemic control and pregnancy outcome.[11,12]

Metformin has also been used for treatment of gestational diabetes. Data from retrospective studies in patients with polycystic ovary syndrome first suggested its utility and safety in treatment of gestational diabetes mellitus. Oral metformin is a logical option for women with Gestational diabetes mellitus (GDM). It improves insulin sensitivity and is not associated with weight gain or hypoglycemia. Some of the most favorable evidence for metformin was provided by the metformin in GDM study,[13] which found no significant increase in a composite measure of neonatal complications among women with GDM who were randomly assigned to metformin as compared with those who were assigned to insulin. Severe hypoglycemia also occurred significantly less often in infants of women taking metformin. More women in the metformin group than in the insulin group stated that they would choose to receive their assigned treatment again (76.6% vs. 27.2%). In the first follow-up to this study, Rowan *et al*.[14] found that the offspring exposed to metformin in utero had increased subscapular and biceps skinfolds when compared with the unexposed infants, while total body fat was similar. They hypothesized that this represents a possible benefit, as this may signal a healthier fat distribution. Thus, further large-scale studies are immediately needed to confirm the suitability of these conventional OADs in treating GDM.

In conclusion, a requiem for conventional OADs seems premature at this point of time. Their low-cost, convenience, compliance and long-term safety have ensured that they still form the mainstay of therapy for Type 2 diabetes. The most important caveat in using these drugs is to

exercise judgment in prescribing them, based on patient profile and side-effects. Furthermore, a preference for newer sulfonylureas, rather than glibenclamide, especially in older patients at risk for prolonged hypoglycemia and cardiovascular morbidity, could be a more pragmatic option. All said and done, conventional OADs are here to stay and there is no wishing them away.

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