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Long-term efficacy of sulfonylureas: a United Kingdom Prospective Diabetes Study perspective

Rury R. Holman*

Diabetes Trials Unit, OCDEM, University of Oxford, Oxford OX3 7LJ, UK

Abstract

The United Kingdom Prospective Diabetes Study shows sulfonylureas to be an effective first-line therapy for people with type 2 diabetes mellitus. The durability of the glycemic control obtained is dependent on the degree to which beta-cell function can be maintained, but sulfonylureas appear neither to increase nor to decrease the underlying rate of loss of beta-cell function. As sulfonylureas act by enhancing insulin secretion, they are probably best used close to the time when diabetes is diagnosed when beta-cell function is at its greatest and their utility can be extended by judicious use in combination with agents that improve glycemia by different modes of action, including insulin.

1. Introduction

Sulfonylureas have remained one of the major therapies for type 2 diabetes mellitus since they were first introduced in the 1950s, and the landmark diabetes trial, the United Kingdom Prospective Diabetes Study (UKPDS) [1], has provided extensive insights into their efficacy and clinical utility. The UKPDS primary results published in 1998 confirmed that a more intensive glucose control policy, using sulfonylurea or insulin therapy, could reduce the risk of diabetic microvascular complications [2]. The UKPDS showed sulfonylureas to have an excellent safety profile, promoting less weight gain than with insulin therapy and with lower risks of minor or major hypoglycemia [2]. Since the publication of the UKPDS results, guidelines worldwide have continued to recognize sulfonylureas as first- or second-line therapy for glycemic control. With the advent of novel therapies, such as glitazones and incretin mimetics, it is appropriate to review the value of sulfonylurea therapy for type 2 diabetes mellitus in the 21st century.

2. Hyperglycemia and diabetic complications

The UKPDS observational analyses confirmed that an increased glycemic exposure, assessed as mean updated HbA_{1c}, is an independent risk factor for diabetic complications and coronary heart disease [3]. Fig. 1 shows that the incidence of myocardial infarction approximately doubles over the observed range of updated mean HbA_{1c} values, whereas for microvascular disease the increase is more than 10-fold. The UKPDS demonstrated that, over a median 10-year follow-up from diagnosis of type 2 diabetes mellitus, the risk of "any diabetic complication" could be reduced by 12% when HbA_{1c} levels were maintained 0.9% lower on average by a more intensive glucose control policy using insulin or sulfonylurea therapy [2]. The study also showed an important 25% reduction in the risk for microvascular disease ($P = .0099$) and a borderline significant 16% reduction in the risk for myocardial infarction ($P = .052$). The results of the ACCORD (Action to Control CardiOvascular Risk in Diabetes) study are awaited to know for certain whether glucose lowering can reduce independently the risk of cardiovascular disease [4]. Other trials evaluating the impact of lower glucose levels on cardiovascular outcomes include the ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) and ORIGIN (Outcome Reduction with Initial Glargine INtervention) studies [5,6]. Although UKPDS data suggest that sulfonylurea therapy is likely to reduce the risk of myocardial infarction overall, concerns have been raised that those which act on myocardial sulfonylurea receptors (SUR) may diminish ischemic injury responses at the time myocardial infarctions occur and increase case fatality. Additional UKPDS analyses have been undertaken

* Diabetes Trials Unit, OCDEM, Churchill Hospital, Headington, Oxford OX3 7LJ, UK. Tel.: +44 1865 857240; fax: +44 1865 857241.

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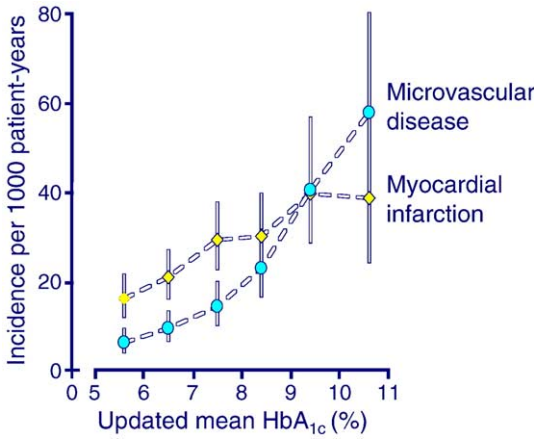

Fig. 1. Incidence rates and 95% confidence intervals for myocardial infarction and microvascular complications by category of updated mean HbA_{1c} concentration, adjusted for age, sex, and ethnic group, expressed for white men aged 50 to 54 years at diagnosis and with mean 10 years' duration of diabetes.

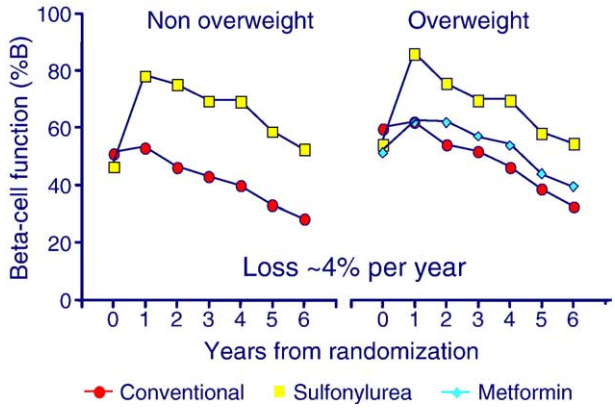

Fig. 3. Mean HOMA estimates of beta-cell function (%B) over the first 6 years from diagnosis of type 2 diabetes mellitus in nonoverweight and overweight patients allocated to, and remaining on, conventional (diet alone) or intensive (sulfonylurea or metformin [overweight subjects only]) monotherapies.

[7] to help address this issue and have shown that there is no difference in the proportion of patients failing to survive a myocardial infarction when taking chlorpropamide, glibenclamide, or glipizide (53%) compared with those not taking a sulfonylurea at the time of the event (51%).

3. The challenge of progressive hyperglycemia

An early UKPDS finding was the appreciation that type 2 diabetes mellitus is a progressive disorder with an inexorable rise in mean HbA_{1c} values over time [8]. Fig. 2 shows the substantial drop in HbA_{1c} seen during the initial 3-month run-in dietary period, followed by a steady upward HbA_{1c} trend observed in patients then randomized to a conventional glucose control policy, primarily with diet alone. In those randomized to a more intensive glucose control policy with chlorpropamide, glibenclamide, metformin, or insulin monotherapy, a substantial further improvement was seen in HbA_{1c} levels, but after 1 year, all groups had the same upward HbA_{1c} trend as the diet-alone group. By 3 years from therapy initiation, only 23% of patients allocated to diet were able to maintain HbA_{1c} values of less than 7.0% compared with substantially greater proportions of those allocated to sulfonylurea, metformin, or insulin monotherapy, although no group achieved greater than 50% success [9]. At 6 and 9 years, a similar progressive drop in the ability to maintain this degree of glucose control was seen with all treatment regimens.

4. Loss of beta-cell function

Progressive hyperglycemia in type 2 diabetes mellitus appears to be caused primarily by a progressive decline in

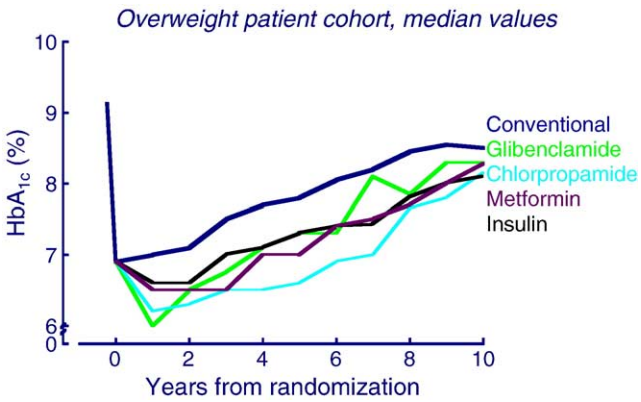

Fig. 2. Median HbA_{1c} over 10 years in cohorts of overweight patients with newly diagnosed type 2 diabetes mellitus by assigned treatment with conventional (diet alone) or intensive (chlorpropamide, glibenclamide, metformin, or insulin) therapies.

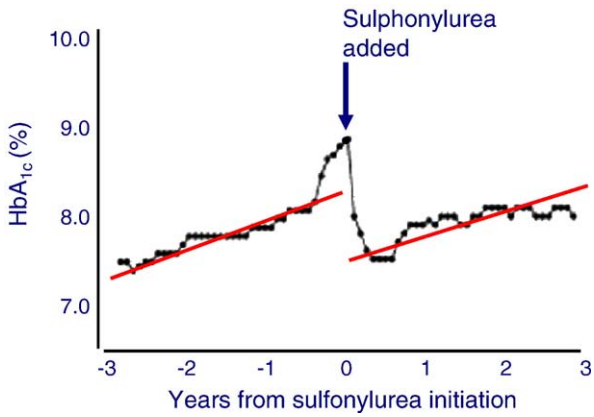

Fig. 4. Rolling 3-month median HbA_{1c} levels before and after the addition of sulfonylurea therapy to metformin. Red lines highlight rate of glycemic progression first on metformin and then on metformin plus sulfonylurea therapy.

beta-cell function. This was shown by UKPDS analyses [8] using homeostatic model assessment (HOMA) [10] of insulin sensitivity (%S) and beta-cell function (%B). These analyses demonstrated mean %S estimates essentially were stable over 6 years from allocation to therapy with diet alone, but that there was a steady 4% per year decline in mean %B estimates, from 53% to 28%, that mirrored rising HbA_{1c} values (Fig. 3). By contrast, patients allocated to therapy with sulfonylureas had a substantial initial 24% absolute increase in their beta-cell function (Fig. 3), reflecting their concurrent improved glycemic control. After 1 year, however, an identical downward trend in mean %B was observed to that seen in the diet-alone group. This finding refutes a widely held view that sulfonylureas will "stress" beta cells by increasing insulin secretory demand and thereby hasten their loss of function. Equally, allocation of overweight patients to the insulin-sparing agent metformin did not slow down the rate of loss of beta-cell function in type 2 diabetes mellitus, showing a modest but helpful 9% increase in mean %B followed, after 1 year, by the same downward trend seen for both diet and sulfonylurea therapy.

5. Sulfonylurea plus metformin therapy

After the realization that monotherapy was becoming less effective over time, a UKPDS substudy was introduced to examine the effect of allocating patients on sulfonylurea monotherapy randomly to the addition or not of metformin [11]. In those given metformin, a similar drop in mean fasting plasma glucose and HbA_{1c} levels was observed to that seen in patients randomized initially to metformin alone, but after 1 year they resumed their previous rate of increase, albeit from a lower glucose level than the comparator group not allocated metformin. This finding has been supported by an observational analysis using UK General Practice Research Data [12], which demonstrated that when sulfonylureas are given to patients whose type 2 diabetes mellitus is inadequately controlled on metformin therapy, the initial drop in median HbA_{1c} levels is followed by reinstatement of the same rate of increase as on metformin alone (Fig. 4). A concern generated by the UKPDS substudy was the lower than expected rate of diabetes-related deaths in those remaining on sulfonylurea therapy alone, which gave the impression that there was an increased risk in those allocated combination therapy. This finding remains to be explained but appears to be the play of chance on the small number of events that occurred in this 6-year substudy.

6. Sulfonylurea plus insulin therapy

Of 23 UKPDS clinical centers, 8 used a modified protocol in which insulin could be given in addition to sulfonylurea in patients whose fasting plasma glucose levels were not maintained to less than 6.0 mmol/L despite maximally tolerated sulfonylurea therapy with chlorpropamide or glipizide [13]. By 6 years, 53% of patients allocated to the combined therapy arm required insulin in addition to their sulfonylurea. Over this time, their median HbA_{1c} values were 0.5% lower (6.6% vs 7.1%; $P = .0066$) than observed in those allocated to insulin monotherapy with substantially more patients having HbA_{1c} values of less than 7.0% at 6 years (47% vs 35%; $P = .011$). Those allocated to the combination therapy arm had similar changes in body weight to those allocated insulin alone, but their median insulin doses were 20% less and they reported fewer major hypoglycemic episodes (1.2% vs 3.2% per year; $P = .017$, respectively).

7. Conclusion

The UKPDS results confirm that first-line therapy with sulfonylureas in newly diagnosed type 2 diabetes mellitus is a safe and effective treatment for glycemic control. The progressive hyperglycemia seen over time, secondary to the observed pathophysiologic decline in beta-cell function, was similar irrespective of whether patients were treated with diet, sulfonylureas, metformin, or insulin. These UKPDS data demonstrate that the use of sulfonylureas does not hasten the loss of beta-cell function. The study showed also that improved glycemic control with sulfonylureas or insulin reduced the risk of diabetic complications and that the chances of surviving a myocardial infarction did not differ whether patients were taking a sulfonylurea or not at the time of the event. Guidelines worldwide continue to recognize the importance of sulfonylurea therapy, alone or in combination, in people with type 2 diabetes mellitus.

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