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Comparative Tolerability of Sulphonylureas in Diabetes Mellitus

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Contents

Abstract

The sulphonylurea drugs have been the mainstay of oral treatment for patients with diabetes mellitus since they were introduced. In general, they are well tolerated, with a low incidence of adverse effects, although there are some differences between the drugs in the incidence of hypoglycaemia. Over the years, the drugs causing the most problems with hypoglycaemia have been chlorpropamide and glibenclamide (glyburide), although this is a potential problem with all sulphonylureas because of their action on the pancreatic β cell, stimulating insulin release.

Other specific problems have been reported with chlorpropamide that occur only rarely, if at all, with other sulphonylureas. Hyponatraemia secondary to inappropriate antidiuretic hormone activity, and increased flushing following the ingestion of alcohol, have been well described.

The progressive β cell failure with time results in eventual loss of efficacy, as these agents depend on a functioning β cell and are ineffective in the absence of insulin-producing capacity. Differences in this secondary failure rate have been reported, with chlorpropamide and gliclazide having lower failure rates than glibenclamide or glipizide. The reasons for this are unclear, but the more abnormal pattern of insulin release produced by glibenclamide may be partly responsible and, indeed, may explain the increased risk of hypoglycaemia with this agent.

Previously reported increased mortality associated with tolbutamide therapy has not been substantiated, and more recent data have shown no increased mortality from sulphonylurea treatment. Indeed, benefit from glycaemic control, regardless of the agent used – insulin or sulphonylurea – was reported by the United

Kingdom Prospective Diabetes Study. Nevertheless, there is still ongoing controversy in view of the experimental evidence, mainly from animal studies, of potential adverse effects on the heart from sulphonylureas, but these are difficult to extrapolate into clinical situations. Most of these studies have been carried out with glibenclamide, which makes comparison of possible risk difficult.

Other cardiovascular risk factors may be modified by gliclazide, which seems unique among the sulphonylureas in this respect. Its reported haemobiological and free radical scavenging activity probably resides in the azabicyclo-octyl ring structure in the side chain. Reduced progression or improvement in retinopathy has been reported in comparative trials with other sulphonylureas, and the effect is unrelated to improvements in glycaemia.

There are differences between the sulphonylureas in some adverse effects, risk of hypoglycaemia, failure rates and actions on vascular risk factors. As a group of drugs, they are very well tolerated, but differences in overall tolerability can be identified.

The introduction of the sulphonylureas in the 1950s was a milestone in the therapy of patients with type 2 (non–insulin-dependent) diabetes mellitus who, until then, had insulin as the only treatment option.[1] The early sulphonylureas and the second generation drugs have, with the exception of glimepiride, been on the market and widely used throughout the world for many years. These agents have been extensively reviewed[2-7] and it could be thought, quite reasonably, that all the problems associated with these agents would be well known by this time. To a large extent, this is true. Much of the information concerning these drugs, however, dates back many years and, while there have been ongoing studies, most of these have been concerned with individual drugs, with few comparative data. Ongoing concerns in some quarters regarding the potential cardiovascular hazards of prescribing these agents are still debated[8-13] and more recent data concerning the structure of the sulphonylurea receptor[14,15] and the kinetic relationships between this receptor and different sulphonylureas require further elucidation.

It is perhaps pertinent now to review these agents and their comparative benefits and problems in treating type 2 diabetes mellitus.

In assessing the comparative tolerability of the sulphonylureas, it is appropriate to look at adverse effects, both general and specific, hazards in relation to associated medical disorders, and benefits, both in their primary action on the β cell and also in their possible extrapancreatic effects.

1. Hypoglycaemia

All the sulphonylureas lower blood glucose by stimulating insulin release from the β cell, and therefore have the potential to cause hypoglycaemia. The sulphonylureas act on a receptor closely associated with ATP-sensitive K^+ (K_{ATP}) channels in the β cell membrane. By closing these channels and reducing potassium conductance, the membrane is depolarised with subsequent activation of voltage-dependent Ca^{2+} channels. The ensuing influx of Ca^{2+} raises the level of free cytosolic Ca^{2+}, eventually causing the exocytosis of insulin.[16]

The incidence of hypoglycaemia differs between these agents, with some having a much greater tendency to cause this adverse effect than others. The reasons are variable, and often pharmacokinetic in origin. Chlorpropamide has a long half-life of >35 hours, and is significantly dependent on renal excretion.[17-21] Patients with diabetes receiving treatment with this agent are more at risk if they miss meals or have renal impairment. Glibenclamide (glyburide) has a relatively long half-life and has metabolites with significant hypoglycaemic activity that depend on renal excre-

tion.[22-25] Several reports have confirmed the increased risk of hypoglycaemia with this agent.[26-30]

By reviewing a cohort of 33 243 sulphonylurea users in the United Kingdom, patients with a diagnosis of hypoglycaemia were identified.[29] Incidence rates per person-year of sulphonylurea therapy were estimated. An annual risk of recorded hypoglycaemia of approximately 1.8% was observed, varying from 1.5% for continuous users to 4.8% for incidental users. This study only included patients who had experienced episodes of hypoglycaemia severe enough to visit a physician or to report the symptoms to a physician during a consultation for other reasons. It is likely, therefore, that the hypoglycaemia rate was greater than observed, as minor episodes of hypoglycaemia were likely to go unrecognised or unreported. The relative risk for recorded hypoglycaemia showed an increased risk for glibenclamide-treated patients compared with other sulphonylureas (adjusted relative risk versus glibenclamide: 0.74, 0.75, 0.60 for gliclazide, tolbutamide and glipizide, respectively). These findings are consistent with other reports also showing sulphonylurea-induced hypoglycaemia to be greater with glibenclamide,[30-33] (table I) and also more liable to be long lasting and dangerous. It was also observed that there was a decreased incidence of symptoms of hypoglycaemia with longer duration of sulphonylurea therapy. Van Staa et al.[29] speculated that this may result from worsening glycaemic control with time, or that patients learn to avoid hypoglycaemia or develop reduced awareness of hypoglycaemia.

Polypharmacy also increased the risk of hypoglycaemia, in keeping with previous reports.[3,22,29] The reasons for this are speculative, and may be related to difficulty in complying with complex treatment regimens[30] or to drug interactions, such as displacement of sulphonylurea from binding sites on plasma proteins, decreased hepatic metabolism, decreased renal excretion and intrinsic hypoglycaemic activity.[34] In addition, patients taking a variety of drugs do so because of other significant medical problems; the effect of these conditions on appetite, food intake and absorption, and physical activity could be variable and unpredictable, with an enhanced risk of hypoglycaemia.

Table I. Standardised incidence ratios for hypoglycaemia with different sulphonylureas compared with glibenclamide (glyburide) set at 100

Sulphonylurea	Standardised incidence ratio	Reference
Chlorpropamide	44	30
Chlorpropamide	89	31
Chlorpropamide	33	32
Chlorpropamide	22	33
Glipizide	42	31
Tolbutamide	19	31
Gliclazide	44	30

2. Nonspecific Adverse Effects

A number of nonspecific adverse effects of sulphonylureas have been reported, but the range of these is limited and they are mainly minor and reversible.[33-37] On the whole, these drugs are very well tolerated (table II). Reports of adverse effects can be difficult to evaluate when comparing drugs, as all adverse events may be included in some reports and hypoglycaemia may also be included in the overall figures. Reports of adverse effects with a newer sulphonylurea, glimepiride, show an 8% incidence compared with 2% in placebo recipients. The incidence in glipizide-treated patients was 8.8%, and in glibenclamide-treated patients 12.4%.[38-42] It seems likely, however, that the incidence of nonspecific adverse effects with glimepiride is similar to that with the other sulphonylureas, and that the incidence of hypoglycaemia is lower than with glibenclamide, again similar to the other agents.

3. Specific Adverse Effects

3.1 Hyponatraemia

The occurrence of hyponatraemia in sulphonylurea-treated patients is almost entirely associated with chlorpropamide,[43-45] although there have been a few reports implicating tolbutamide.[36,46] The mechanism appears to be a combination of stimulation of antidiuretic hormone secretion and sensitisation of the renal tubules to endogenous antidiuretic

hormone.[43] Elderly patients and those treated with diuretics appear to be most at risk; in patients also receiving diuretics the incidence of severe hyponatraemia was more than 10%, in contrast to 3% during treatment with chlorpropamide alone.[45] Interestingly, most patients experiencing this problem were women. The hyponatraemia resolved after discontinuation of the drug.

3.2 Flushing After Alcohol Consumption

Since the introduction of chlorpropamide, there have been reports of unpleasant facial flushing after drinking alcohol, and the subject has been extensively reviewed.[47-51] The mechanism appears to be similar to the effect of disulfiram, with inhibition of hepatic acetaldehyde dehydrogenase leading to an increase in blood acetaldehyde concentrations.[51] The effect has been shown to be dose-dependent, and the plasma concentration of chlorpropamide is critical.[52] One isolated incidence of flushing in a patient treated with gliclazide has been reported.[53] 'Flushers' appear to eliminate acetaldehyde more slowly at a low range of concentrations, suggesting a difference in aldehyde dehydrogenase activity.[54] It is possible that other sulphonylureas might provoke flushing if plasma concentrations were sufficiently high in patients with reduced aldehyde dehydrogenase activity but, clinically, this does not appear to be a significant problem.

4. Secondary Failure

As β cell function deteriorates with time, the ability to respond to sulphonylureas also diminishes. This may also relate to receptor down-regulation, with some selective unresponsiveness of the β cells when exposed to long term sulphonylurea administration.[55] The secondary failure rate with different sulphonylureas varies, and comparisons between chlorpropamide and glibenclamide have shown significantly lower secondary failure rates for chlorpropamide.[56,57] A 5-year study comparing secondary failure rate with 3 sulphonylureas again showed differences, with gliclazide demonstrating a lower failure rate than either glibenclamide or glipizide.[58] The reasons for this are unclear, but may relate to differences in the pattern of insulin release. Some data suggest that glibenclamide produces a prolonged and exaggerated second phase of insulin release, whereas other sulphonylureas, to a variable extent, produce a more physiological pattern.[59] It has also been shown that fasting insulin levels during treatment with glibenclamide are significantly higher than during treatment with glipizide.[60]

Table II. Frequency of nonspecific adverse effects of sulphonylureas[4,5]

System	Drug	Frequency (%)
Cutaneous	Tolbutamide	1.1
	Chlorpropamide	1.4–3.0
	Glibenclamide (glyburide)	0.5–1.6
	Glipizide	0.5
	Gliclazide	0.7
Gastrointestinal	Tolbutamide	1.4
	Chlorpropamide	1.9–2.0
	Glibenclamide	0.5–2.0
	Glipizide	2.2
	Gliclazide	1.7
Haematological	Tolbutamide	0.24
	Chlorpropamide	0.6
	Glibenclamide	0.1
	Glipizide	0.0
	Gliclazide	0.0
Total	Tolbutamide	3.2
	Chlorpropamide	4.1–6.2
	Glibenclamide	1.5–2.9
	Glipizide	4.4
	Gliclazide	2.4

5. Ischaemic Heart Disease

The University Group Diabetes Program (UGDP) Study reported that patients treated with tolbutamide had an increased mortality from ischaemic heart disease.[61] This study has been heavily criticised for a variety of reasons,[8] but has left a legacy of suspicion regarding the safety of sulphonylureas, particularly in patients with ischaemic heart disease.[62] Evidence from clinical studies has been inconclusive, with some suggesting an adverse outcome following myocardial in-

farction in sulphonylurea-treated patients,[63-66] whereas others showed no deleterious effect.[67-69] In a retrospective study in Japan of over 2000 patients, no difference was found in cardiovascular mortality between sulphonylurea-treated patients and those treated with diet or insulin.[69] Participants treated with tolbutamide have been shown to have a reduced mortality from ischaemic heart disease in 2 studies.[70-72]

A major prospective study – the United Kingdom Prospective Diabetes Study (UKPDS) – recently reported its results, which show a reduction in risk for myocardial infarction of 16% in the active treatment group. No difference was noted between patients treated with insulin, chlorpropamide or glibenclamide and, in particular, no deleterious effect was found in sulphonylurea-treated patients.[73]

The cardiovascular system also has K_{ATP} channels[74,75] that have been associated with the cardioprotective mechanism of ischaemia-related preconditioning.[76] Intracellular ATP is a main regulator of K_{ATP} channels, but channel activity is modulated by nucleotides, neurohormones and pharmacological agents, and response sensitivity may vary under different conditions.[77,78] Whether sulphonylurea therapy, by blocking K_{ATP} channels, has an adverse effect on endogenous cardioprotective mechanisms during conditions of ischaemia or cellular metabolic impairment remains controversial.[79,80] The great majority of studies have been carried out *in vitro* or in animals, and glibenclamide has been the most commonly used sulphonylurea. It is difficult to extrapolate to the clinical situation, as the K_{ATP} channel may respond differently under different conditions, and this may modify the sensitivity of the response to sulphonylureas which in themselves may vary in their action on the sulphonylurea receptor.[81]

In human studies, ST segment shifts during a second balloon inflation during coronary angioplasty were unchanged in patients treated with glibenclamide, in contrast with placebo-treated patients where ST segment depression was reduced. This supports the suggestion that glibenclamide may have an adverse effect on ischaemic preconditioning.[82] In contrast, another study in patients with type 2 diabetes mellitus showed a reduction in abnormal arrhythmias in glibenclamide-treated patients.[83]

Other cardiovascular risk factors may be affected by sulphonylurea treatment. Most studies in this area have been conducted with gliclazide but, where other sulphonylureas have been compared, they have generally lacked the specific benefits shown for gliclazide, which are a reduction in thrombotic tendency, enhanced fibrinolysis and increased free radical scavenging activity.[84-86] These effects probably reside in the azabicyclooctyl ring, which is unique to gliclazide. There are, as yet, no clinical data to suggest that cardiovascular outcomes are significantly different between patients treated with different sulphonylureas.

One significant problem in assessing the possible cardiovascular risk of sulphonylureas is the difficulty in extrapolating effects found in animals and *in vitro* where the drug concentration at a cellular level may be significantly different from that achieved by normal oral administration to patients with diabetes. Clinical trials, particularly the UKPDS,[73] are reassuring, but more clinical data are required.

6. Effects on the Sulphonylurea Receptor

More information is now available about the structure of the sulphonylurea receptor on the β cell membrane, and the binding kinetics between the receptor and the sulphonylurea molecule.[15] Comparisons between glibenclamide and glimepiride show that at least 2 subunits exist: a 140kD glibenclamide-binding protein and a 65kD glimepiride-binding protein. Glimepiride associates with, and dissociates from, the receptor more quickly than glibenclamide, which might produce a different pattern of insulin release in response to glucose stimulation of the β cell. Since K_{ATP} channels are found in a wide variety of extrapancreatic tissues, including cardiac muscle cells, drugs that cross-react with different members of the K_{ATP} channel family have the potential to cause adverse

effects. The 2 sulphonylurea receptor subunits possess different binding sites with different affinities, which partly explains the less dramatic effects on cardiac-type K_{ATP} channels.[87] The opposing effects of ATP (a K_{ATP} channel blocker) and MgADP (a channel activator) are also balanced by different sensitivities of the β cell and cardiac ATP channels to sulphonylureas. Although no major adverse effects on cardiac function have been clearly demonstrated in sulphonylurea-treated patients, minor effects may occur, but may be difficult to detect if they are subtle or only evident under conditions of myocardial ischaemia.

7. Conclusions

The sulphonylureas are generally well tolerated, and are well established drugs for the treatment of type 2 diabetes mellitus. The common adverse effects have been well described, and the difference between the sulphonylureas in the frequency of both general and specific adverse effects is generally recognised. The clinical relevance of more recent evidence on the structure of the sulphonylurea receptor and its potential relationship to efficacy on the one hand, and adverse effects, particularly cardiac, on the other, remains to be clarified.

Until clearer evidence emerges, however, current data support the conclusion that the sulphonylureas make an effective and valuable contribution to the management of type 2 diabetes mellitus. They are, as a whole, well tolerated, and the major adverse effects and contraindications are well established. Although there are significant differences between some drugs in these effects, there is sufficient evidence to allow appropriate choices to be made in individual patients. For example, glibenclamide and chlorpropamide should be avoided in elderly patients and those with impaired renal function.

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