Diabetologia (1996) 39: 1668–1672

Diabetologia

Short reviews

Safety aspects of oral hypoglycaemic agents

R. Rosskamp

Hoechst Marion Roussel, Clinical Research Metabolism, Bridgewater, USA

Since non-insulin-dependent diabetic (NIDDM) patients represent a high-risk group, the benefits of their drug treatment must be carefully weighed against potential risks. Sulphonylureas are generally well-tolerated with few non-specific adverse effects. Less than 2 % of patients discontinue treatment because of side-effects. Hypoglycaemia is the most common adverse effect (usually mild) and is related to several predisposing factors. Risk of hypoglycaemia is highest within the first month of treatment (5.6 % of glibenclamide-treated patients compared with 1.7 % for glimepiride, a sulphonylurea of the new generation, based on a recent study). Sulphonylureas in reduced doses, can be given, with caution, to patients with liver and renal disease. Metformin, a biguanide drug, used alone does not produce severe hypoglycaemia under normal circumstances. Gastrointestinal reactions are the most common side-effects, leading to discontinuation of treatment in approximately 4 % of cases. Lactic acidosis is a rare but serious metabolic side-effect of biguanide treatment and its risk increases with age and renal dysfunction. Therefore, in elderly patients, renal function should be monitored regularly and metformin is contraindicated in patients, with renal disease or dysfunction. Although still controversial, both sulphonylureas and biguanides bear a special warning for an increased risk of cardiovascular mortality based on the University Group Diabetes Program study in the USA. Acarbose is not associated with life-threatening adverse effects. Its main side-effects are gastrointestinal symptoms in more than 50 % of patients resulting in discontinuation in less than 5 %. At high doses, serum transaminases should be monitored for the first 6 months of treatment. A list of contraindications, mostly gastrointestinal and hepatic diseases, should be maintained.

When diet and education have failed to achieve a good metabolic control in non-insulin-dependent diabetic (NIDDM) patients, oral antidiabetic treatment should be started. First-line drugs are sulphonylureas, biguanides and α-glucosidase inhibitors. A combination of small doses of different drugs including insulin may be used to avoid side effects [1]. Since prevalence of NIDDM increases with age, obesity and dyslipoproteinaemia this population is at high risk for cardiovascular disease and hypertension. Age-specific mortality in these patients is twice that of the general population [2]. Therefore, the benefit of drug treatment in this group of patients must carefully be compared with the possible risks, especially for long-term treatment such as the oral hypoglycaemic agents.

Sulphonylureas

Sulphonylureas have been used in the management of diabetes for 40 years and numerous publications describing their safety and efficacy are available. About 25 years after the introduction of the original compounds (carbutamide, tolbutamide, chlorpropamide), the second-generation sulphonylureas, with greater hypoglycaemic potency per milligram were introduced into clinical practice. Glimepiride is a novel sulphonylurea currently being registered worldwide but is included in this review because of its novel characteristics. Sulphonylureas are still the most-frequently prescribed oral hypoglycaemic agents, testimony to both their acceptable blood glucose-lowering efficacy and general safety. An overview is given in Table 1.

Corresponding author: Dr. R. Rosskamp, Hoechst Marion Roussel, Clinical Research Metabolism, P. O. Box 6800, Bridgewater, NJ 08807, USA

Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study Group.

Table 1. Characteristics of established and recent sulphonylureas (adopted from [3])

Drug	Daily dose range (mg/day)	Dose regimen (daily)	Duration of action (hours)
Tolbutamide	500–2000	once or twice	6–12
Chlorpropamide	100–500	once	24–72
Glibenclamide	2.5–20	once, above 10 mg twice	12–16
Glipizide	2.5–30	once, above 10 mg twice	6–10
Gliclazide	80–320	once, above 160 mg twice	12–18
Glimepiride	1–6	once	15–24

Table 2. Most frequent adverse events in placebo-controlled clinical studies with glimepiride

Event	Glimepiride		Placebo	
	No. of patients	(%)	No. of patients	(%)
All patients evaluated for safety	438	100	245	100
All patients with adverse events	271	61.9	140	57.1
Upper respiratory infection	62	14.2	19	7.8
Hypoglycaemia	52	11.9	4	1.6
Headache	33	7.5	18	7.3
Flu syndrome	24	5.5	10	4.1
Accidental injury	23	5.3	9	3.7
Nausea	22	5.0	9	3.7
Dizziness	20	4.6	7	2.9
Asthenia	18	4.1	7	2.9
Pain in extremity	18	4.1	6	2.4
Back pain	15	3.4	5	2.0
Diarrhoea	13	3.0	13	5.3
Rhinitis	12	2.7	10	4.1
Cough increased	12	2.7	6	2.4
Surgery	12	2.7	6	2.4
Arthralgia	12	2.7	3	1.2
Hyperglycaemia	11	2.5	16	6.5

In general, sulphonylureas are extremely well-tolerated. Gastrointestinal, dermatologic and haematologic reactions are rare and less than 2 % of patients discontinue therapy due to side-effects [4]. Placebo-controlled studies with glimepiride showed similar patterns of adverse events with differences between placebo and the sulphonylurea only for the incidence of hypo- and hyperglycaemia (Table 2).

Hypoglycaemia is by far the most common side-effect of all sulphonylureas. Chlorpropamide and glibenclamide (drugs with a longer duration) are accused of being especially liable to produce hypoglycaemia [5]: in a recent review, chlorpropamide and glibenclamide accounted for 70 % of all severe hypoglycaemic episodes. Since glibenclamide is the most frequently prescribed sulphonylurea, however, the frequency of drug-induced hypoglycaemia is dependent on the actual prescription figure. If the rate of hypoglycaemia is assessed as "hypoglycaemia per million defined daily doses", data from the Swedish Drug Information System between 1980 and 1987 show that glibenclamide overall produces less hypoglycaemia than chlorpropamide and glipizide [6]. In any case, the majority of all hypoglycaemic episodes with sulphonylureas are mild in nature and the incidence of severe episodes has been estimated at 0.19–0.25 per 1000 patient-years [7, 8], while the incidence with insulin therapy was approximately 400 times higher [4]. Mortality in these two reviews of sulphonylurea therapy was calculated as 0.014 to 0.033 per 1000 patient-years, corresponding to a mortality rate of approximately 10 %.

Comparative studies between sulphonylureas are frequently published, but in most instances have limitations, since patient numbers are small or the studies are not double-blind [9]. One open, randomized study, of 2520 patients, is the UKPDS comparing chlorpropamide with glibenclamide treatment amongst other objectives. After 3 years with similar efficacy, the rate of hypoglycaemic episodes of any severity was 13.5 % with chlorpropamide and 27.8 % with glibenclamide. This higher incidence was mainly due to minor hypoglycaemic attacks since similar rates were seen for major episodes. However, the drop-out rate due to side effects was 13 % for chlorpropamide and only for 7 % with glibenclamide [10]. Thus, a positive selection for chlorpropamide patients during the study could have influenced the endpoint results for hypoglycaemia. Double-blind studies have been performed for the registration of the new sulphonylurea drug glimepiride. In a 1 year, double-blind comparison study in 1044 patients, 150 episodes of hypoglycaemia occurred in 14 % of glibenclamide

patients compared with 105 episodes in 11 % of glimepiride patients [11]. There were 3 severe episodes (patients requiring help) of hypoglycaemia in the glibenclamide patients and only 1 in the glimepiride patients. Similarly in another double-blind, glibenclamide-controlled study in 565 NIDDM patients, significantly less hypoglycaemic episodes occurred with glimepiride patients (glimepiride 1.7 %, glibenclamide 5.6 %) during the first month of treatment despite similar reductions in blood glucose. Following a 12-month treatment period, 34 glimepiride (12 %) and 48 glibenclamide-treated patients (17 %) reported episodes of hypoglycaemia (Hoechst AG, unpublished data). A meta-analysis of all glibenclamide-controlled studies confirmed that the risk of hypoglycaemia for glimepiride is almost half that for glibenclamide during the first weeks of treatment (Hoechst AG, unpublished data). A similar result was obtained in a double-blind glipizide-controlled trial with 802 NIDDM patients: although the cumulative occurrences of hypoglycaemia were similar for the two treatments in the first 4 weeks (glimepiride 3.0 vs glipizide 2.8 %, NS), fasting plasma glucose reductions were significantly greater for glimepiride (glimepiride 51.5 vs glipizide 32.1 mg/dl; $p > 0.01$) (Hoechst AG, unpublished data). Glimepiride therefore seems to have a lower risk of hypoglycaemia than other sulphonylureas.

Biguanides

Biguanides differ radically in their chemical structure from sulphonylureas and, therefore, the adverse effects associated with their use are quite different. In contrast to sulphonylureas, therapeutic doses of metformin do not cause hypoglycaemia and do not lower blood glucose in non-diabetic subjects [12]. The major risk of biguanide therapy is lactic acidosis, a metabolic condition with a mortality of about 50 %. The reported incidence of lactic acidosis in metformin treated patients is approximately 0.03 per 1000 patient-years (compared to a rate of 0.64 per 1000 patient-years with phenformin) [13].

Since the risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age, the renal function of older patients has to be monitored regularly. Metformin, therefore, is contraindicated in patients with renal disease as defined by serum creatinine levels ≥ 130 μmol/l (men) or ≥ 120 μmol/l (women). Monitoring of renal function is especially important in NIDDM patients, since advanced age in general is associated with a reduced renal function, and 10–20 % of all NIDDM patients develop proteinuria during the first 5 years after hyperglycaemia is diagnosed suggesting the presence of a glomerular disease other than diabetic nephropathy in these patients [14, 15].

The most common side effects (5–20 % of patients) are gastrointestinal: anorexia, nausea, abdominal discomfort and diarrhoea [16, 12] leading to withdrawal of the drug in less than 5 % of patients. Impaired gastrointestinal absorption of vitamin B 12 and folate are rare [12, 16].

Cardiovascular risk with biguanides and sulphonylureas

A long-term prospective study was conducted by the University Group Diabetes Program (UGDP) to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in 1027 patients with NIDDM. Results showed that patients treated for 5 to 8 years with diet plus tolbutamide (1.5 g per day) or phenformin (100 mg per day) had a rate of cardiovascular mortality approximately 2.5 times that of patients treated with diet alone. Total mortality was increased in both treatment groups (statistically significant only for the phenformin group). These data resulted in a premature discontinuation of both treatment groups [17, 18]. Despite considerable controversy regarding the interpretation of these results [19], the findings of the UGDP study provide a basis for a warning of cardiovascular mortality in the USA for all sulphonylureas and metformin. Renewed interest in this study came from animal studies showing that sulphonylureas impair the recovery of the myocardial function and increase the ultimate infarct size. The mechanism behind this effect is a blocking of cardiovascular K_{ATP} channels resulting in the inhibition of physiological adaptive measures to protect the myocardium [20]. In this respect, glimepiride has a distinctive feature since, unlike glibenclamide, the diazoxide-induced vasodilatation in the human forearm vascular bed is not inhibited by glimepiride [20] indicating no interaction with cardiovascular K_{ATP} channels.

α-glucosidase inhibitors

The α-glucosidase inhibitors reversibly inhibit intestinal α-glucosidase enzymes within the intestinal brush border, thereby delaying the digestion of complex carbohydrates and disaccharides to absorbable monosaccharides. This results in attenuating postprandial blood glucose peak and lowering of postprandial and fasting blood glucose levels in NIDDM patients.

Gastrointestinal problems are the most common side-effects reported in human studies with these drugs. Symptoms are caused by fermentation of unabsorbed carbohydrate in the bowel, which results in increased gas production. In the phase III studies performed in the USA, 76 % of acarbose-treated

Table 3. Incidence of gastrointestinal adverse effects

Adverse event	No. of events (%)			
	Placebo[a] (*n* = 627)	Acarbose[a] (*n* = 618)	Placebo[b] (*n* = 245)	Glimepiride[b] (*n* = 438)
Constipation	22 (4)	15 (2)	4 (1.6)	8 (1.8)
Diarrhoea	63 (10)	192 (31)	13 (5.3)	13 (3.0)
Anorexia	6 (1)	13 (2)	–	1 (0.2)
Dyspepsia	22 (4)	18 (3)	3 (1.2)	5 (1.1)
Eructation	7 (1)	6 (1)	–	–
Flatulence	184 (29)	444 (71)	1 (0.4)	1 (0.2)
Increased appetite	6 (1)	5 (1)	–	1 (0.2)
Nausea	28 (4)	39 (6)	9 (3.7)	22 (5.0)
Vomiting	13 (2)	12 (2)	3 (1.2)	3 (0.7)
Total number of patients with any events effecting the digestive system	235 (37)	468 (76)	74 (16.9)	38 (15.5)

[a] Reference [21]
[b] Hoechst AG, unpublished data

patients and 37 % of placebo-treated patients, reported adverse events affecting the digestive system [21]. If one compares this with the incidence of digestive symptoms in the placebo-group in the Hoechst AG studies with glimepiride, the difference in frequency of flatulence for example, is striking (29 % in the placebo group acarbose vs 0.4 % in placebo group glimepiride) (Table 3). This difference may be readily explained by the awareness of patients in acarbose trials concerning this possible side-effect.

The incidence of gastrointestinal side-effects tend to decrease with combined treatment [22, 23], possibly due to an adequate diet rich in complex carbohydrates and low in simple sugars and individual acarbose doses needed to achieve desirable postprandial blood glucose values [24]. The withdrawal rate in the USA acarbose studies was 15 % in acarbose patients compared with 5 % in the placebo group [21]. The figures for the placebo-controlled patients in the Bayer International Clinical Data Pool (1646 patients) show that 78 (4.7 %) of acarbose-treated patients compared with only 33 (2 %) of the placebo patients withdrew, mainly because of gastrointestinal side effects [21]. Contraindications to acarbose treatment include intestinal malabsorption syndromes, inflammatory bowel disease, intestinal obstruction, hepatic disease and moderate or severe renal impairment [25].

Conclusion

There are three major classes of oral antidiabetic drugs: the sulphonylureas, biguanides and α-glucosidase inhibitors, and all have their own typical safety profiles. Their general role in treatment of NIDDM is well-established. On an individual basis a risk/benefit estimation should be made to decide which drug should be used.

References

1. Alberti KGMM, Gries FA, Jervell J, Krans HMJ for the European NIDDM Policy Group (1994) A desktop guide for the management of non-insulin-dependent diabetes mellitus (NIDDM): An update. Diabet Med 11: 899–909
2. Balkau B, Eschwège E, Papoz L, Richard JL, Claude JR, Warnet JM, Ducimetière P (1993) Risk factors for early death in non-insulin dependent diabetes and men with known glucose tolerance status. BMJ 307: 295–299
3. Peden N, Newton RW, Feely J (1983) Oral hypoglycaemic agents. BMJ 286: 1564–1567
4. Gerich JE (1989) Oral hypoglycemic agents. N Eng J Med 321: 1231–1245
5. Seltzer HS (1989) Drug-induced hypoglycaemia: a review of 1418 cases. Endocrinol Metabol Clin North Am 18: 163–183
6. Krall LP (1988) Sulphonylurea therapy. In: Alberti KGMM, Krall LP (eds) The diabetes annual/4. Elsevier Science Publishers B. V. Amsterdam New York Oxford, pp 80–91
7. Berger W (1985) Incidence of severe side effects during therapy with sulphonylureas and biguanides. Horm Metabol Res 15 [Suppl]:111–115
8. Campbell IW (1985) Metformin and the sulphonylureas: the comparative risk. Horm Metabol Res 15 [Suppl]:105–111
9. Jackson JE, Bressler R (1981) Clinical pharmacology of sulphonylurea hypoglycaemic agents. Parts 1 and 2 Drugs 22: 211–245, 205–320
10. United Kingdom Prospective Diabetes Study Group (1995) United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin-dependent diabetes followed for three years. BMJ 310: 83–88
11. Draeger E (1995) Clinical profile of glimepiride. Diabetes Res Clin Pract 28 [Suppl]:139–146
12. Hermann LS (1979) Metformin: a review of its pharmacological properties and therapeutic use. Diabete Metab 5: 233–245
13. Crofford OB (1995) Metformin. N Eng J Med 333: 588–589
14. Lubran MM (1995) Renal function in the elderly. Ann Clin Lab Sci 25: 122–133
15. Daniels BS, Frederick CG (1991) Diabetes and the kidney. Clin Diab 27: 444–454

16. Bailey CJ, Nattrass M (1988) Treatment – metformin. Baillieres Clin Endocrinol Metab 2: 455–476
17. The University Group Diabetes Program (1970) A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. Mortality results. Diabetes 19 [Suppl 2]:789–830
18. The University Group Diabetes Program (1970) A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. V. Evaluation of phenformin therapy. Diabetes 24 [Suppl 1]:65–184
19. Gilbert JP, Saracci R, Meier P, Zelen M, Rümke C, White C (1975) Report of the committee for the assessment of biometric aspects of controlled trials of hypoglycemic agents. J Am Med Assoc 231: 583–608
20. Smits P, Thien T (1995) Cardiovascular effects of sulphonylurea derivatives. Diabetologia 38: 116–121
21. Hollander P (1992) Safety profile of acarbose, an α-glucosidase inhibitor. Drugs 44 [Suppl 2]:47–53
22. Aubell R, Boehme K, Berchtold P (1982) One year acarbose treatment of diabetic outpatients. Multicentre study part I: Safety. In: Creutzfeld W (ed) Proceedings of First International Symposium on Acarbose. Montreux, October 1981 Excerpta Medica pp 360–362
23. Johnson D (1982) New drugs for diabetes: acarbose. Drug Ther 12: 219–223
24. Toeller M (1992) Nutritional recommendations for diabetic patients and treatment with α-glucosidase inhibitors. Drugs 44 [Suppl 3]:13–20
25. Krentz AJ, Ferner RE, Clifford J, Bailey CJ (1994) Comparative tolerability profiles of oral antidiabetic agents. Drug Saf 11: 223–241