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RESEARCH ARTICLE

Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide

Andreas Holstein*
Armin Plaschke
Eick-Hartwig Egberts

1st Department of Medicine, Klinikum Lippe-Detmold, Detmold, Germany

*Correspondence to: Dr. Andreas Holstein, 1st Department of Medicine, Klinikum Lippe-Detmold, Röntgenstrasse 18, D-32756 Detmold, Germany.
E-mail: Andreas.Holstein@t-online.de

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Abstract

Background Severe hypoglycaemia is a potentially life-threatening condition. The aim of the present study was to compare the frequency of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide.

Methods This prospective, population-based, 4-year study examined the incidence of severe hypoglycaemia in a region of Germany with 200 000 inhabitants. The blood glucose of all 30 768 patients who attended the emergency department of the region's central hospital was determined to detect severe hypoglycaemia, which was defined by the requirement for intravenous glucose or glucagon injection and blood glucose value of <2.8 mmol/l. Additionally, 6631/7804 patients (85%) attended to by the emergency medical services received a blood glucose test at the emergency site. The regional prescribing frequency of both sulphonylureas was determined by an independent external institute.

Results Despite glimepiride being prescribed more frequently than glibenclamide (6976 vs 6789 person-years), glimepiride induced fewer episodes of hypoglycaemia (6 vs 38 episodes); one episode occurred with a combination of the two preparations. The incidence of severe hypoglycaemia was 0.86/1000 person-years for glimepiride and 5.6/1000 person-years for glibenclamide. The characteristics of the 45 patients who presented with sulphonylurea-associated hypoglycaemia were as follows: mean age 79 years (95% CI 75.2; 82.6); glycosylated haemoglobin 5.4% (95% CI 5.1; 5.7); impaired renal function in 62%.

Conclusions In people with type 2 diabetes, glimepiride was associated with fewer episodes of severe hypoglycaemia than glibenclamide in routine clinical use. However, severe hypoglycaemia did occur with glimepiride and may be minimised if treatment targets are determined on an individual basis.

Keywords type 2 diabetes; sulphonylureas; glimepiride; glibenclamide; hypoglycaemia

Introduction

The sulphonylurea, glimepiride, was introduced in the USA in 1995 and in Germany in 1996, where it is currently the most frequently prescribed sulphonylurea [1]. Glibenclamide remains the global market leader of the

sulphonylurea class of oral hypoglycaemic agents and is the reference drug for comparison with new sulphonylureas. Glimepiride has different receptor kinetics and pharmacokinetics from glibenclamide [2,3] and is more expensive. However, the innovative importance of a new hypoglycaemic agent such as glimepiride is determined largely by the incidence of severe hypoglycaemic episodes.

Hypoglycaemia is considerably more common with treatment with a long-acting sulphonylurea such as glibenclamide or chlorpropamide than with short-acting preparations such as gliclazide, glipizide, or gliquidone [4,5]. Severe glibenclamide-associated hypoglycaemia is fatal in 1.4% to 10% of cases and may necessitate long, expensive hospital admissions [6–8]. Comparative studies have shown the equivalent antihyperglycaemic efficacy of glibenclamide and glimepiride [9]. In controlled clinical studies with administration of maximal daily doses (8–16 mg glimepiride and 12–20 mg glibenclamide), significantly lower rates of mild (self-treated) hypoglycaemia were recorded with glimepiride than for glibenclamide only during the 4-week titration phase but not for the entire study duration [10]. However, in these studies, hypoglycaemia was based on a subjective assessment and was not confirmed by simultaneous measurement of blood glucose [10]. No investigations to date, other than controlled clinical studies, have examined the incidence of severe hypoglycaemia associated with glimepiride and glibenclamide during everyday practice.

Up to 58% of cases of severe hypoglycaemia in patients with type 2 diabetes are not initially detected by the primary physician, and the neuroglycopenic signs and symptoms are frequently misinterpreted as cerebral ischaemia [7]. The aim of the present prospective population-based study was, therefore, to determine the incidence of severe hypoglycaemia associated with glimepiride and glibenclamide using a sensitive procedure for the diagnosis of hypoglycaemia. Recognised risk factors for severe sulphonylurea-induced hypoglycaemia include the initial phase of therapy, advanced age, renal/cardiovascular co-morbidity, interactions with other medications [angiotensin-converting enzyme (ACE) inhibitors, beta-adrenoceptor blockers, sulphonamides], changes in diabetes therapy or lifestyle, and inadequate patient education [4,5,7,8,11]. An additional aim of the present study was to describe the clinical characteristics of those patients with diabetes who presented with severe sulphonylurea-induced hypoglycaemia.

Subjects and methods

Study design

This prospective, population-based study evaluated the incidence of severe hypoglycaemia in patients with type 2 diabetes. The diabetes prevalence in Germany on the basis of retrospective data from the sickness funds is 4.8% [12], while a prospective study based on the randomised measurement of glycated haemoglobin found a prevalence of 8.2% [13]. It can therefore be assumed that in the region of investigation, which has a population of 200 000, there are likely to be at least 10 000 patients with type 2 diabetes.

Detection of severe hypoglycaemia

Severe hypoglycaemia was defined as a symptomatic event requiring treatment with intravenous glucose or glucagon im/sc [14] and was confirmed by a blood glucose measurement of <2.8 mmol/l. In the present prospective study, all episodes of severe hypoglycaemia were documented among the 30 768 patients who attended the medical emergency department of the Klinikum Lippe-Detmold, a large tertiary care hospital in East Westphalia/Germany (urban–rural catchment area of 200 000 inhabitants) between 1 January 1997 and 31 December 2000. As the only hospital in the catchment area, this hospital is responsible for the inpatient and outpatient management of all emergencies in the region. Irrespective of the patient's presenting condition, blood glucose was measured in every patient immediately after their arrival at the emergency department as one of the routine laboratory tests. Blood glucose was determined in venous whole blood using the hexokinase method.

In addition, in order to identify unsuspected severe hypoglycaemia in patients attended to by the emergency services, a pre-hospital blood glucose was measured using a reflectometric method with the GlucoTouch™ meter at the emergency site. This blood glucose measurement used venous whole blood from the introducer needle for obtaining intravenous access before treatment, and allowed subsequent confirmation of hypoglycaemia. A sub-study conducted in 522 emergency patients, including 90 patients with severe hypoglycaemia, confirmed the high level of accuracy of this method in the emergency setting [15]. For ethical and methodological reasons, blood glucose was not determined in 1173 emergency patients (deaths, resuscitations, and small children) so that 6631/7804 (85%) emergency-site patients were tested for hypoglycaemia at the site of emergency. Of these 6631 patients, 6013 (90.7%) were transported to the hospital emergency department where a further blood glucose measurement was made. In the present study, all patients with sulphonylurea-associated hypoglycaemia were taken to the hospital for treatment.

A detailed history and blood laboratory profile were obtained for each patient. Creatinine clearance was calculated by the formula of Cockroft and Gault [16]. In order to establish the progress of patients with diabetes, who experienced sulphonylurea-induced hypoglycaemia, after hospital discharge we contacted either the patients themselves or their family doctors by telephone (cut-off date 31 January 2001). All serious diseases or deaths that had occurred in the interim were

documented, together with the cause of death where applicable.

Prescribing frequency of sulphonylureas

The national and regional prescribing frequency of drugs in Germany is documented by the independent commercial Institute of Medical Statistics in Frankfurt am Main. The regional pharmaceutical market is estimated from sales of drugs by the wholesalers to local pharmacies. These data are generally accepted by the German pharmaceuticals industry and are used as a basis for market analyses. Our estimate of the quantities of sulphonylureas prescribed in the catchment area of our hospital during the period 1997–2000 was based on the numbers of packs of glimepiride and glibenclamide supplied to the pharmacies in the catchment area. To infer what number of people with diabetes were being treated with the respective sulphonylureas, the total quantity of the drug sold was divided by its defined daily dose, i.e. the amount of active drug which is typically used for the main indication in an adult with type 2 diabetes. In accordance with World Health Organization guidelines, we chose 2.0 mg as the defined daily dose for glimepiride and 7.0 mg for glibenclamide [1]. With once-daily administration, the recommended glimepiride dose is 1–6 mg for Europe and 1–8 mg for the USA; doses higher than 6 mg are only more effective in exceptional cases [9,10].

Statistics

Comparison of treatment groups was performed by calculating treatment differences and corresponding 95% confidence intervals (CI). If these intervals did not include '0' the treatment difference was statistically significant at the 5% level.

Results

A total of 264 cases of severe hypoglycaemia, 145 (55%) of them in patients with type 2 diabetes, were identified in the period of investigation. Of the 145 episodes of severe hypoglycaemia occurring in patients with type 2 diabetes, 100 episodes involved patients receiving insulin therapy and 45 episodes occurred in patients treated with sulphonylureas. Of these sulphonylurea-associated episodes, four occurred in patients taking glimepiride as monotherapy, 28 occurred in patients taking glibenclamide as monotherapy, seven in patients taking glibenclamide in combination with metformin (850–2550 mg/day) and three in patients taking glibenclamide in combination with acarbose (150 mg/day); two episodes occurred in patients taking glimepiride in combination with metformin (500 and 1700 mg/day) and one in a patient taking a combination of glibenclamide 3.5 mg and glimepiride 2 mg. The basic characteristics of the three groups of patients with diabetes who experienced sulphonylurea-associated hypoglycaemia are shown in Table 1. Figure 1 clearly indicates that there was no dose–effect relationship for glibenclamide-associated hypoglycaemia, with severe hypoglycaemia being associated with low dose of the drug.

This cohort of 45 patients who had experienced drug-associated hypoglycaemia had an average age of 79 years and marked co-morbidity. Twenty-eight diabetic patients (62%) had a creatinine clearance of <60 ml/min (34.5 ml/min (95% CI 23.0; 53.6) [range 8.3–59]) and, were considered to have impaired renal function. Cardiac failure was present in 36% (16/45) of patients, coronary heart disease in 29% (13/45), and neoplasms, cerebral

Table 1. Basic characteristics of the diabetic patients presenting with sulphonylurea-induced hypoglycemia[a]

Characteristic	Glibenclamide + glimepiride ($n=1$)	Glibenclamide ($n=38$)	Glimepiride ($n=6$)	Treatment difference and 95% CI glibenclamide vs glimepiride
Age (years)	84	83.5 [44–94] (73.0; 83.0)	83.5 [62–93] (67.9; 96.1)	0 (−17.1; 9.1)
Sex (% female)	0%	63.2% (46.6; 79.8)	66.7% (20.6; 112.7)	−3.5 (−44.1; 37.3)
Diabetes duration (years)	4	6.0 [0–33] (6.6; 13.8)	16.0 [10–32] (4.5; 34.2)	−10 (−19.0; 0.8)
BMI (kg/m^2)	24.8	22.9 [17.8–32] (21.9; 25.1)	28.2 [22.8–38.4] (19.8; 39.0)	−5.3 (−10.7; 1.1)
Sulphonylurea dose (mg)	3.5 and 2	4.4 [1.75–10.5] (4.9; 7.3)	3.0 [1–3] (1.5; 3.5)	1.4 (0.6; 6.6)
Initial venous blood glucose (mmol/l)	2.24	1.7 [0–4.00] (1.4; 2.14)	1.8 [0.78–2.72] (0.95; 2.60)	−0.1 (−0.97; 0.95)
HbA_{1c} (HPLC; non-diabetic range 3.4–4.9%)	5.6	5.25 [4.1–7.5] (5.1; 5.9)	4.7 [4.6–4.7] (4.6; 4.8)	0.55 (−0.3; 1.9)
Patients with impaired renal function	1/1 (100%)	23/38 (60.5%) (43.7; 77.4)	4/6 (66.7%) (20.6; 112.7)	−6.1% (−46.9; 34.7)
Co-medication (number of drugs)	7	3.0 [0–16] (2.4; 4.9)	3.5 [1–10] (−0.8; 8.5)	−0.5 (−3.7; 3.1)
Participation in diabetes education programmes (%)	0%	3% (1/38)	0%	Not done

[a]Values are presented as median [range] (95% CI).

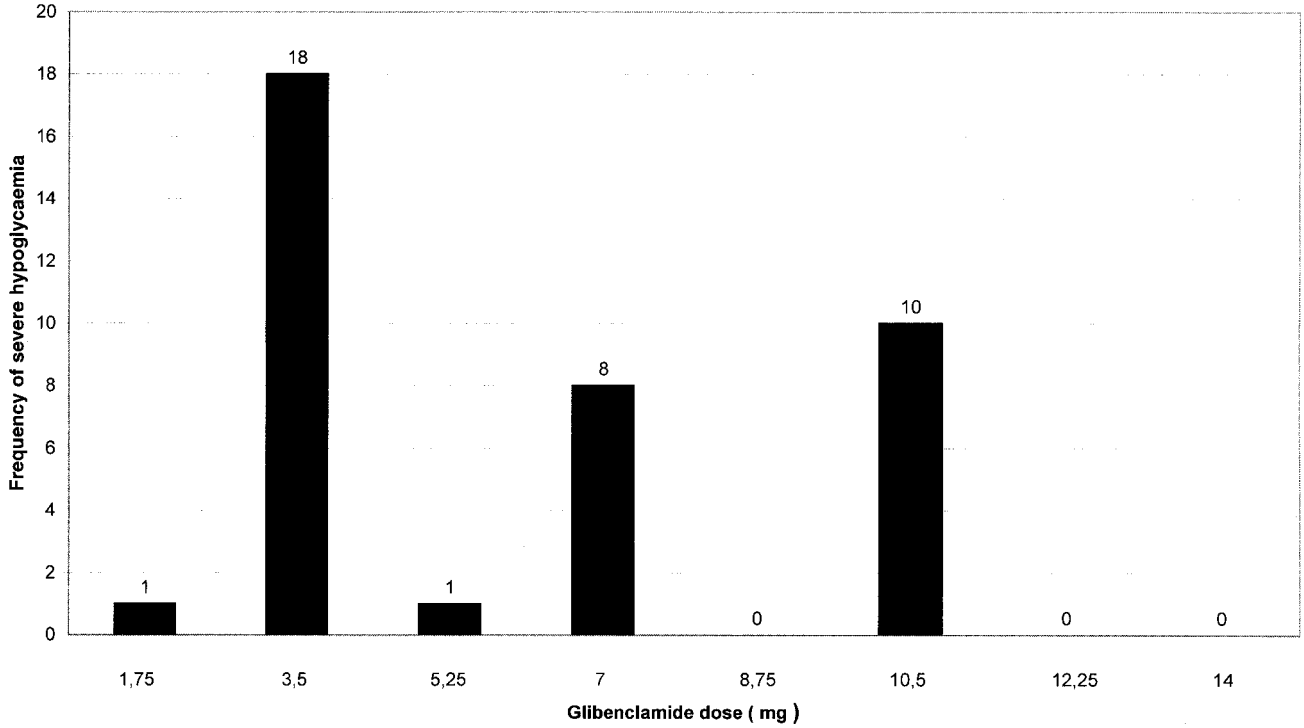

Figure 1. Dose–effect relationship for glibenclamide-associated severe hypoglycaemia ($n = 38$)

ischaemia, alcoholism, and dementia each occurred in 16% (7/45). This group of patients was found to have glycated haemoglobin (HbA_{1c}) values of 5.4% indicating that their diabetes was well controlled. Only one of the patients had taken part in a structured patient education programme for type 2 diabetes, and none performed regular blood glucose self-monitoring; there was only one patient in whom blood glucose was regularly monitored by family members. One-third of the patients lived in nursing homes or were cared for by a home nursing service.

Thirty-one (69%) episodes of sulphonylurea-induced hypoglycaemia were diagnosed and treated out-of-hospital by the emergency medical services, while the remaining 14 (31%) were diagnosed and treated at the emergency department. No cases of hypoglycaemia had already been definitively treated by the family members of the diabetic patients. The clinical presentations in all 45 of the patients with sulphonylurea-induced hypoglycaemia were: coma in 23 (51%), disorientation in eight (18%), somnolence in five (11%), paralysis in four (9%), cerebral seizures in three (7%), and psychological disturbances in two (5%). Six patients (13%) sustained soft tissue injuries or bone fractures as a result of falls associated with hypoglycaemia. No hypoglycaemia-associated deaths were identified.

The cause of hypoglycaemia could only be established unambiguously in 15 episodes (33%): omission of meals in seven, excessive alcohol consumption in six, and dosing errors by patients or nursing staff in two episodes. In addition to the sulphonylurea, the diabetic patients were taking an average of 3.9 (95% CI 2.7; 4.7) [range 0–16] additional drugs, mainly cardiovascular preparations. With regard to drugs that may potentially increase the risk of sulphonylurea-induced hypoglycaemia, 16 (36%) of the diabetic patients were taking ACE-inhibitors, four (9%) beta-blockers, seven (16%) sedatives or morphine, and one (2%) non-steroidal anti-inflammatory drugs (NSAIDs).

In the follow-up period, which averaged 22.8 (95% CI 17.7; 26.9) [range 0.5–49] months after the severe hypoglycaemic episode, 16 (36%) of the 45 hypoglycaemic patients had died. The causes of death were: myocardial infarction, heart failure, cerebral ischaemia, acute renal failure, hypertensive cerebral haemorrhage, septicaemia, and metastatic cancer.

Incidence of severe hypoglycaemia

For our region, the incidence of severe sulphonylurea-associated hypoglycaemia was 5.6/100 000 inhabitants/year. It was estimated that 1768 patients were being treated with glimepiride and 1721 with glibenclamide in the 4-year period of the survey. There were 38 cases of hypoglycaemia in patients receiving glibenclamide and six cases of glimepiride-associated hypoglycaemia. Figure 2 shows the development of hypoglycaemia in the period studied in relation to the regional prescribing frequency of the two sulphonylureas. It is clear that despite a prescribing frequency 1.4% higher than that of glibenclamide (6976 vs 6789 person-years), glimepiride caused considerably fewer episodes of hypoglycaemia. The incidence of hypoglycaemic episodes for glimepiride was 0.86/1000 person-years, compared with 5.6/1000 person-years for glibenclamide. Concomitant with a continuous decline in the prescribing frequency of

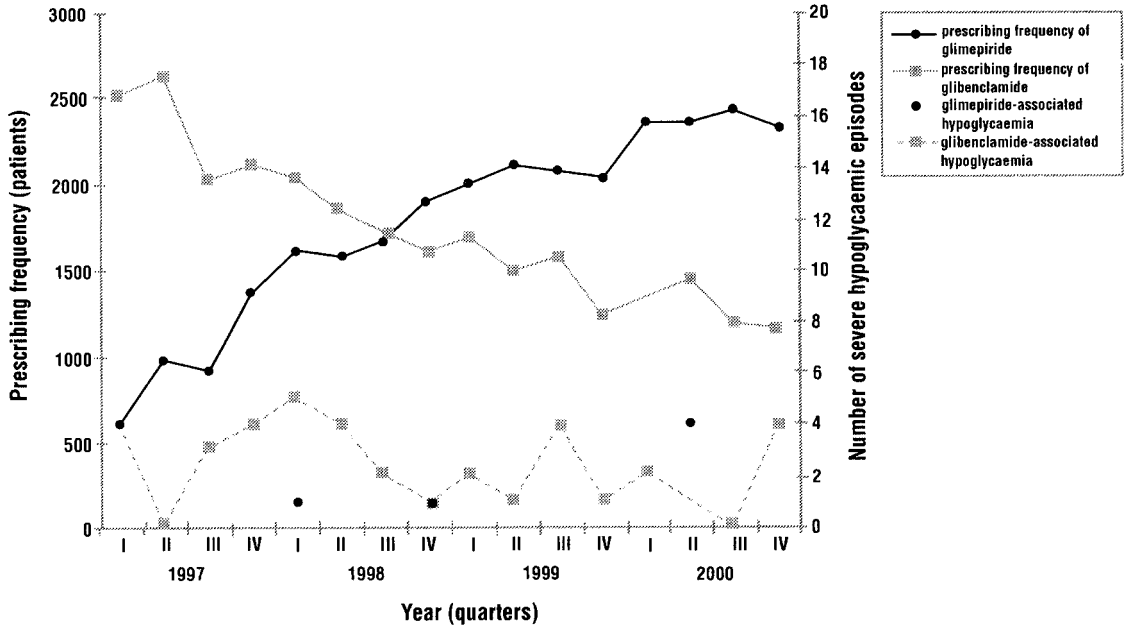

Figure 2. Regional prescribing frequency of sulphonylureas and prevalence of sulphonylurea-associated severe hypoglycaemia

glibenclamide, there was a progressive decline in both the incidence of glibenclamide-induced hypoglycaemic episodes and the total number of sulphonylurea-associated hypoglycaemic episodes. Contrary to this clear trend, in the second quarter of 2000 there was an unusual increase in glimepiride-associated hypoglycaemia. However, this represented an isolated and exceptional departure from the overall downward trend.

Discussion

Sulphonylureas are one of the first-line oral anti-diabetic agents for the treatment of type 2 diabetes. Glibenclamide is a widely prescribed drug of this class and its hypoglycaemic efficacy and positive effects on clinically relevant endpoints have been confirmed [17]. Positive effects of the newer sulphonylurea, glimepiride, on patient-oriented endpoints have not, as yet, been demonstrated, the clinical–therapeutic advantages of this more expensive drug are still open to debate.

Using pharmaco-epidemiological data, the present study has demonstrated a lower incidence of severe hypoglycaemia for glimepiride than glibenclamide. The study design allowed the collection of blood glucose data from emergency patients in this region throughout the 4 years of the study. Although the prescribing frequency of glimepiride was 1.4% higher than that of glibenclamide, there were only six episodes of severe hypoglycaemia in patients treated with glimepiride compared with 38 for glibenclamide. This corresponds to an incidence of severe hypoglycaemia of 0.86/1000 person-years for glimepiride versus 5.6/1000 person-years for glibenclamide. Thus, the incidence of severe hypoglycaemia for glimepiride was comparable with that of short-acting second-generation sulphonylureas such as glipizide and gliclazide [5]. Although our estimation of prescribing patterns could be limited by the poor compliance with oral hypoglycaemic agents, recent studies have demonstrated that patients with type 2 diabetes who are prescribed more than one preparation have a reduced adherence to taking their oral hypoglycaemic agents [18]. Poor adherence should affect glibenclamide in multiple dosage more than glimepiride which is taken once daily, yet the incidence of glibenclamide-associated severe hypoglycaemia was higher.

The definition of severe hypoglycaemia in the present study was restrictive and precise but omits episodes treated with oral carbohydrate. Therefore some hypoglycaemic episodes with both sulphonylureas could have been under-reported. In agreement with another prospective study [7], the present study shows a considerably higher incidence of severe sulphonylurea-associated hypoglycaemia than retrospective analyses [5] (Table 2). In addition to regional differences in prescribing, the main reason for this may be the careful screening for hypoglycaemia. As many as 14% of our hypoglycaemic sulphonylurea-treated patients with diabetes presented with neurological symptoms or psychological abnormalities. These incidences of hypoglycaemia were identified only as a result of routine blood glucose measurement, allowing rapid treatment. This confirms the desirability of blood glucose testing in any patient with type 2 diabetes treated with sulphonylureas who experiences an impaired state of consciousness or a neuropsychiatric deficit.

The reasons for the discrepant hypoglycaemia rates are multifactorial; essential factors are the distinct receptor and pharmacoprofiles of the two substances. Compared with glibenclamide, glimepiride has a considerably lower binding affinity to the beta-cell receptor with a high exchange rate [2,19]. Glimepiride results, in the fasting state [9] and postprandially [20], in the secretion of

Table 2. Incidence of severe sulphonylurea-induced hypoglycaemia in type 2 diabetes in other studies

Reference	Region/population	Period	Design	Hypoglycaemia/drug	Incidence/1000 person-years (PY)	Mortality
Sugarman (1991) [8]	Navajo Reservation/USA (190 000)	5 years (1983–1988)	Retrospective	49 chlorpropamide, 14 glibenclamide	5.8/1000 PY chlorpropamide, 16.0/1000 PY glibenclamide	1.4%
Bachmann *et al.* (1995) [7]	Kronach/Germany (76 000)	7 years (1985–1991)	Prospective	79 glibenclamide	6.8/1000 PY glibenclamide	10%
Spranger and Bachmann (1999) [6]	Kronach/Germany (76 000)	2 years (1994–1995)	Retrospective	26 glibenclamide	Not stated	5.9%
Stahl and Berger (1999) [5]	Basel/Switzerland (200 000)	12 years (1986–1997)	Retrospective	15 glibenclamide, 1 chlorpropamide, 10 glibornuride, 2 gliclazide	2.24/1000 PY long-acting sulphonylureas, 0.75/1000 PY short-acting sulphonylureas	0%
Holstein *et al.* (2001)	Detmold/Germany (200 000)	4 years (1997–2000)	Prospective	38 glibenclamide, 1 glibenclamide + glimepiride, 6 glimepiride	5.6/1000 PY glibenclamide, 0.86/1000 PY glimepiride	0%

smaller amounts of insulin than glibenclamide with no loss of glucose-lowering efficacy. This pharmacodynamic characteristic of glimepiride minimises the risk of hypoglycaemia to the patient. Animal studies suggest that glimepiride has additional extrapancreatic effects that increase insulin sensitivity [21]. In addition, significant suppression of endogenous insulin secretion in response to acute exercise has been demonstrated in patients receiving glimepiride [22]. It has previously been suggested that glimepiride is more suitable than glibenclamide for patients with moderately impaired renal function [23].

Glimepiride not only has theoretical advantages over glibenclamide with regard to its clinical and pharmacological profile, but also appears to be associated with considerably fewer episodes of severe hypoglycaemia under everyday conditions. Glibenclamide should be avoided in elderly people with type 2 diabetes, as they are more susceptible to hypoglycaemia which may have serious consequences in this age group [11,24,25]. Attention must also be paid to the predisposing risk factors for hypoglycaemia with glimepiride. Frequent and uncritical prescribing of sulphonylureas [7] remains a challenge and will not be solved by the introduction of new preparations. In order to avoid severe hypoglycaemia in elderly patients with diabetes, it is important, while taking into account individual quality of life and life expectancy, to set appropriate therapeutic targets and define the indications for hypoglycaemic therapy more closely. Education of patients and their family members must also receive more emphasis.

The clinical characteristics of this group of sulphonylurea-treated patients who experienced hypoglycaemia included the recognised risk factors identified in previous studies: advanced age, marked co-morbidity, and extensive co-medication. In the present study, the subsequent mortality in individuals who had received treatment for severe hypoglycaemia was 36% due to co-morbidity. Thus, it was confirmed that patients who require hospital admission for the treatment of hypoglycaemia represent a high-risk group with a poor long-term prognosis [26].

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