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Impact of clinical factors and CYP2C9 variants for
the risk of severe sulfonylurea-induced hypoglycaemia

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Aims: The established risk factors for severe sulfonylurea-induced hypoglycaemia (SH) include low HbA1c, advanced age, long duration of diabetes, multimorbidity and polypharmacy. As the genetically polymorphic cytochrome P450 (CYP) enzyme CYP2C9 is mainly responsible for the hepatic metabolism of sulfonylureas (SUs), we hypothesized that the slow-metabolizer genotypes *2/*2, *2/*3 and *3/*3 might be overrepresented in type 2 diabetic patients with SH.

Methods: In a prospective population-based case-control study, CYP2C9 allelic variants of 102 diabetic patients with SH were compared to a matched group of 101 SU treated patients but without a history of SH. The 203 Caucasian patients had been treated with the SUs glimepiride, glibenclamide or gliquidone. SH was defined as a symptomatic event requiring treatment with intravenous glucose and was confirmed by a blood glucose measurement of <50 mg/dl (<2.8 mmol/l). 337 Caucasian diabetic patients receiving oral antidiabetic drugs and 1988 healthy Caucasian volunteers who had been genotyped earlier served as further two control groups.

Results: In the univariate analysis only a low HbA1c value ($p=0.0004$) was shown as a risk factor for SH. There was no overrepresentation of the CYP2C9 *2/*2, *2/*3 and *3/*3 variants in the SH group (2%) compared to the control group (5%). However, in the control group, patients with CYP2C9 genotypes predicting slower metabolism of SU drugs were treated with significantly lower doses ($p=0.027$) than extensive metabolizers whereas in the patient group with severe hypoglycaemia, the dose was the same for all genotype groups.

Conclusions: In the present cohort of 102 patients with SH, a low HbA1c value was related to the risk for SH. There was no overrepresentation of the CYP2C9 slow metabolizer genotypes in the hypoglycaemic patients group observed but the drug

exposure in the slow metabolizer genotypes was estimated to be higher in the hypoglycaemic patients which might partly have contributed to their risk for SH.

Key words: type 2 diabetes mellitus - hypoglycaemia - sulfonylureas - CYP2C9 variants

Introduction

Recent results from large interventional studies (1-3) for the prevention of vascular complications and data from observational studies (4) revealed that tight glycaemic control in patients with type 2 diabetes mellitus (T2DM) is of limited value. In particular, severe hypoglycaemia may even increase cardiovascular and all-cause mortality. These inferences apply also for sulfonylurea (SU) treated diabetic patients. Severe sulfonylurea-induced hypoglycaemia (SH) is a life-threatening and pathophysiologically complex, multifactorial event. The established risk factors for SH include low HbA1c, advanced age, long diabetes duration, extensive comorbidity with higher degrees of renal insufficiency, polypharmacy and the use of long-acting versus short-acting preparations (5,6).

Characterizing the individual sensitivity to SUs, pharmacogenetic factors could be of additional critical importance for the risk of SH. SUs such as glibenclamide, glimepiride, gliclazide or gliquidone are metabolized hepatically by the genetically polymorphic cytochrome P450 (CYP) enzyme CYP2C9 (7,8). There have been few studies examining the role of CYP2C9 genotypes for the interindividual variability in drug response (9,10) and mild hypoglycaemia (11). However, previous studies did not capture the significance of CYP2C9 variants in patients with experienced SH. Only in a pilot study with a small sample size we could identify the CYP2C9 genotypes *2/*3 and *3/*3 that are predictive for low enzyme activity as further risk factors for SH in Caucasian individuals (12). In the present study we compared the distribution of different CYP2C9 allelic variants in a by international standards large cohort of patients with T2DM who experienced SH versus a matched control group without SH. Furthermore, the frequency of CYP2C9 genotypes in the cases with SH was compared to a second, previously reported control sample of DNA from 337 Caucasian diabetic patients receiving oral antidiabetic drugs and without a history of

severe hypoglycaemia, and to a further sample of 1988 healthy Caucasian volunteers.

Patients and methods

In this prospective population-based case-control study, 102 consecutive patients with T2DM and SH were genotyped concerning their CYP2C9 allelic variants and compared to a matched control group of 101 SU treated patients but without a history of SH. The hypoglycaemic patients as well as the control group were recruited at the medical department of the Clinic Lippe-Detmold, a large tertiary care hospital in East Westphalia, Germany, between 1 January 2000 and 31.12.2009. As the only hospital in the area, the one at Lippe-Detmold is responsible for the inpatient and outpatient management of all emergencies in a region with 200,000 inhabitants. Our study provided a sensitive detection of hypoglycaemia. As published previously, blood glucose testing was systematically performed in every emergency patient irrespective of the presenting condition, either already prehospitally at the scene of the emergency or immediately after the arrival at the emergency department, respectively. The entire emergency team underwent a structured training program concerning the diagnosis and therapy of diabetic emergencies (6,13).

All investigated 203 Caucasian diabetic patients had been treated with the SUs glimepiride, glibenclamide (glyburide), or gliquidone and were monitored on an inpatient basis. Severe hypoglycaemia was restrictively defined as a symptomatic event requiring treatment with intravenous (i.v.) glucose and was confirmed by a blood glucose measurement of <50 mg/dl (<2.8 mmol/l). Creatinine clearance was calculated by the formula of Cockcroft and Gault (14). Renal impairment was defined as a creatinine clearance of < 60 ml / min.

After informed consent 10 ml EDTA blood samples from all 203 subjects were collected and *CYP2C9* genotyping was performed with the methods described earlier (8). Clinicians and patients were blind to genotype. Frequency of genotypes in the cases with SH was compared to the matched control group. Furthermore, we performed a comparison between our cases with SH and a second control sample of DNA from 337 Caucasian diabetic patients receiving oral antidiabetic drugs and without a history of severe hypoglycaemia, and to a further large sample of 1988 healthy Caucasian volunteers who had given their informed consent for genotyping (12). The protocol was approved by the Ethics Committee of the University of Münster School of Medicine and (for further comparison groups) by the Ethics Committee of the Charité University hospital, University medicine Berlin.

Statistics

Standard descriptive and comparative statistics (χ^2 test, ANOVA) were used to characterize and compare clinical parameters in different groups (cases, controls). Logistic regression analyses were used to calculate the effects of investigated factors on severe hypoglycaemia events, which were reported as odds ratio with 95% CI (confidence intervals). Data were analyzed using the SPSS software package (version 18.0.2; SPSS, Inc., Chicago, IL).

Results

From 2000 - 2009 a total of 1,419 cases of severe hypoglycaemia were registered among the 103,256 patients who attended the emergency department of the Lippe- Detmold Clinic. 39% (552/1,419) of hypoglycaemic events occurred in patients with type 1- and 57% (809/1,419) in those with type 2 diabetes. In 4% (58/1,419) subjects

with secondary diabetes and non-diabetics were affected. 10% (141/1,419) of all cases with severe hypoglycaemia have been treated with SUs. In two cases ingestion of SUs was accidental as two women with dementia took the SU preparations from their husbands. Genotyping could be performed in 102 subjects with SH as another 37 patients were not able to consent due to their demented state or explicitly gave no consent.

All 102 patients with SH demonstrated neuroglycopenic disturbances, their plasma glucose levels were 31.8 ± 10.4 mg/dl (1.76 mmol/l) prior to treatment with i.v. glucose. The distribution and mean daily dose of SU agents were comparable between hypoglycaemic subjects and controls. Table 1 demonstrates the basic characteristics of all hypoglycaemic subjects versus the control group indicating a comparable geriatric and multimorbid state in both groups. The control group without SH had even a higher degree of renal impairment and received more additional co-medication which were main substrates of CYP2C9 than those with SH, in particular torasemide, clopidogrel, phenprocoumon, diclofenac or fluvastatine.

Logistic regression analysis revealed a low HbA1c, presence of coronary heart disease (CHD), the CYP2C9-genotypes (*1/*2 and *2/*3) and comedication with other CYP2C9 main substrates as significant risk factors for SH (Table 2). The effects of these predictors appeared to be independent of each other as they remained statistically significant in logistic regression analysis even upon including all risk factors in the model (HbA1c, presence of CHD and comedication with other CYP2C9 main substrates; all $p < 0.05$). The kind of accommodation of the patients, their previous diabetes education, different comorbidities (dementia, heart failure) or comedication (insulin, metformin, ACE-inhibitors etc.) did not influence the risk of SH. There was no overrepresentation of the CYP2C9 slow metabolizer genotypes *2/*3 and *3/*3 in our group with SH compared to the control group. Accordingly, we found

no significant differences in the distribution of CYP2C9 allelic variants compared with two other previously reported control samples (12) consisting of 337 Caucasian diabetic patients receiving oral antidiabetic drugs and without a history of SH, and to a large cohort of 1988 healthy Caucasian volunteers (Table 3).

By expressing drug dosing as a dose factor with 3.5mg glyburide, 1mg glimepiride, and 30mg gliquidon as normal dose with dose factor 1, we calculated mean doses in the CYP2C9 metabolizer groups extensive (alleles CYP2C9*1/*1, *1/*2), intermediate (CYP2C9*1/*3) and slow (CYP2C9*2/*2, *2/*3 and *3/*3). The mean SU dose was 2.3, 1.8 and 1.7 in the extensive, intermediate and slow metabolizer groups in the control group and 2.5, 2.9 and 2.8 in the hypoglycaemic patients group. A significant lowering of the doses thus could be observed in the control group ($p=0.027$) while in the hypoglycaemic patient group, no such empirical dose adjustment to genotype was seen.

Discussion

The current ten-year population based study suggest that apart from the established clinical risk conditions, CYP2C9 allelic variants do not strongly contribute to the individual susceptibility for severe hypoglycaemia associated with the use of glimepiride and glibenclamide. The frequency of the CYP2C9 slow metabolizer genotypes *2/*2, *2/*3 and *3/*3 in our cohort of 102 Caucasian individuals with SH did not differ from that observed in the control group.

SUs are mainly metabolized by the genetically polymorphic cytochrome enzyme CYP2C9. The rare CYP2C9 genotypes *2/*2, *2/*3 and *3/*3 are predictive for low enzyme activity. In vitro and in vivo studies showed a modest reduction of the enzyme activity in healthy volunteers with the CYP2C9*2 polymorphism and a strong reduction in those with the CYP2C9*3 polymorphism. Compared with the CYP2C9*1/*1 genotype, the tolbutamide clearance in subjects with the CYP2C9*2/*2 genotype was reduced by 25% and in those with the CYP2C9*3/*3 genotype by 84% (7). Pharmacokinetic studies in healthy subjects revealed that clearance of glibenclamide and glimepiride in CYP2C9*3/*3 carriers was only 20% of that in the wild type carriers (8). Also non-diabetic carriers of the CYP2C9*2/*3 genotype had a significantly reduced clearance of glibenclamide and glimepiride (9). Using these SUs, the drug exposure was increased 1.3- to 2.8-fold in volunteers with a CYP2C9*3 allele compared to those with the CYP2C9*1/*1 genotype (9,15,16). In CYP2C9*3 allele carriers using tolbutamide, the prescribed dose was lower compared to patients with the wild-type CYP2C9 genotype. No differences in the prescribed dose were found in tolbutamide users with the CYP2C9*1/*2 or CYP2C9*2/*2 genotype compared to wild-type patients or in patients using glibenclamide, gliclazide, and glimepiride (10). Recent data from the Go-DARTS Study in 1,073 SU treated patients (80% received gliclazide) indicated that patients

with two copies of the CYP2C9*2 or CYP2C9*3 loss-of-function alleles were 3.4 times more likely to achieve a treatment HbA1c level of <7% as compared with wild type carriers resulting in a 0.5% greater reduction in HbA1c (17). Indeed, we observed an empirically lower dosing in patients with the genotypes *2/*2, *2/*3 and *3/*3 within the control group indicating that clinicians and patients got sensibilized to the lower oral clearance of the SU drugs due to the CYP2C9 genotypes and took lower doses. Interestingly, we did not observe these genotype based dosing within the hypoglycaemic patients group. A higher drug exposure, thus, might have contributed to the risk of hypoglycaemia in patients with the CYP2C9 slow metabolizer genotypes.

Our study examined CYP2C9 allelic variants in a typical cohort with experienced SH. As there is no consensus, definition of hypoglycaemia in diabetes is a critical point. Our definition of severe hypoglycaemia as an event with neuroglycopenic symptoms requiring treatment with i.v. glucose and confirmation by a blood glucose measurement of <50 mg/dl (<2.8 mmol/l) was chosen restrictively and indisputable in large degree with the definition of the ADA (18) and comparable studies (19). Whereas in a recent study by Ragia et al. (11) the diagnosis of hypoglycaemia was assessed retrospectively and was not based on accepted standards as it included self-reported unspecific symptoms with incomplete confirmation of a blood glucose concentration of <65 mg/dl (<3.6 mmol/l). The authors demonstrated that the CYP2C9*3 allele was a determinant for mild hypoglycaemia in 92 patients treated with glimepiride or glicazide. However, compared with our cohort their patients were significantly younger (mean age 68 vs. 77 years), less morbid and with a poor metabolic control (HbA1c 7.6 vs. 6.5%), thus predicting an a priori low risk for hypoglycaemia.

Whereas our small sized initial study (12) showed an overrepresentation of *2/*3 and *3/*3 genotypes (10%) in 20 patients with SH as compared to the normal population (2.1%) our current, substantially larger data could not replicate these findings in this dimension. However, a combined effect of genotype and dosing might have contributed to higher drug exposure in patients with low CYP2C9 activity genotypes thereby increasing their risk for hypoglycaemia. Consistently with previous studies (20,21) our results confirmed the established risk factors for SH: low HbA_{1c}, advanced age, long diabetes duration, extensive comorbidity with higher degrees of renal insufficiency and polypharmacy thus highlighting the general representativity and validity of our cohort. Surprisingly, in the Go-DARTS Study there was a lack of effect of the *3/*3 genotype on HbA_{1c} reduction (17) indicating that the individual response to SUs – and also the risk for SH – are pathophysiologically complex and multifactorial. Besides the influence of CYP2C9 variants polymorphisms of other genes might also be involved in the individual response to SUs and the risk of SH. Plausible candidate genes could be those involved in control of β-cell function such as *KCNJ11* (potassium inwardly-rectifying channel, subfamily J, member 11) or Transcription factor 7-like 2 (TCF7L2). In a subgroup of our present 102 individuals with SH we could demonstrate that those carrying the K variant of the E23K polymorphism in *KCNJ11* have reduced response to SU therapy, which results in increased HbA_{1c} and consequently in lower risk for SH (22). Continuing advances in genetic discovery will uncover further loci that are associated with T2DM, including variants that appear to modify responses to SUs.

Additional medication metabolized also through CYP2C9 might reduce the metabolism of SUs and by increasing their hypoglycaemic effects might ultimately result in SH. 24% of subjects with SH versus 49% of our control group received additional medication, which were also main substrates of CYP2C9. So it is unlikely that CYP2C9-dependent comedication would be responsible for the lower HbA_{1c} as well as SH events in our cohort. It is also noteworthy, that the creatinine clearance was significantly lower in our control group. Based on this, the control group would actually have been expected to be at higher risk for SH. Thus, CYP2C9-dependent comedication and higher degree of renal impairment do not explain the higher risk for SH either.

In conclusion, our data suggest that under the conditions of everyday practice, individual susceptibility for SH associated with the use of glimepiride and glibenclamide is complex with HBA1C being the most important clinical risk factor. However, the observed interaction between dose and CYP2C9 genotype leading to potentially higher exposure in slow metabolizers at equal doses, points to the benefit of individualized, and sometimes pharmacogenetics based dosing.

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Table 1: Basic characteristics of type 2 diabetic patients with sulphonylurea-induced hypoglycaemia versus control group

Variable	Severe hypoglycaemia (n=102)	Control (n=101)	p
Sex (female/male)	45/57	51/50	0.36
Age (years)	77.4±9.2	79.3±9.2	0.13
Body-Mass-Index (kg/m ²)	26.7±5.5	27.0±4.4	0.76
Serum creatinine (mg/dl)	1.55±0.87	1.72±1.03	0.19
Creatinine-Clearance (ml/min)	45.8±22.6	38.0±18.1	0.02
HbA1c (%)	6.5±1.2	7.2±1.3	0.0004
Comedication (number of drugs)	7.0±2.8	7.4±2.8	0.28
Duration of diabetes (years)	11.0±9.9	11.5±8.3	0.71
Patients with glimepiride	76 (74.5%)	81 (80.2%)	0.33 (chi ²)
Mean daily dose	2.8±1.6 mg	2.3±1.3 mg	0.04 (t-test)
Patients with glibenclamide	25 (24,5%)	18 (17.8%)	0.2 (chi ²)
Mean daily dose	6.1±3.7 mg	5.0±3.6 mg	0.3 (t-test)
Patients with gliquidone	1 (1.0%)	2 (2%)	0.62
Mean daily dose	30 mg	60 mg	-
Additional treatment with metformin	37 (36%)	43 (43%)	0.36 (chi ²)
Mean daily dose	1731±602 mg	1715±494 mg	0.90 (t-test)
Additional treatment with insulin	29 (28%)	20 (20%)	0.15 (chi ²)
Mean daily dose	36.4±22 I.E.	36.8±21.5 I.E.	0.96 (t-test)
Comedication with other CYP2C9-main substrates	24 (24%)	33 (49%)	0.001 (chi ²)
Comedication with other drugs being at least one CYP2C9-substrate	39 (39%)	32 (47%)	0.30 (chi ²)

Table 2: Risk factors for severe hypoglycaemia in 102 sulphonylurea-treated type 2 diabetic patients with severe hypoglycaemia versus control group (n=101)

Variable	Relative Risk (95% CI)	p
HbA1c (%)	1.56 (1.20-2.04)	0.001
Dose of sulphonylurea	1.00 (0.96-1.04)	0.95
CYP2C9-genotypes *2/*2, *2/*3 and *3/*3	0.58 (0.14-2.50)	0.47
Comedication with other CYP2C9-main substrates	0.34 (0.17-0.65)	0.001
Comedication with other drugs being at least one CYP2C9-substrate	0.72 (0.39-1.34)	0.30
Comedication with insulin	1.61 (0.84-3.09)	0.15
Comedication with ACE-inhibitor	1.35 (0.77-2.34)	0.29
Comedication with analgetics	1.21 (0.59-2.50)	0.60
Comedication with gyrase-inhibitors	0.99 (0.20-5.03)	0.99
Presence of coronary heart disease	2.38 (1.35-4.18)	0.003
Presence of heart failure	1.46 (0.84-2.55)	0.18
Presence of dementia	1.97 (0.94-4.15)	0.09
Previous participation at structured diabetes education	1.09 (0.59-2.00)	0.79
Kind of accommodation (home versus nursing home)	1.29 (0.87-1.92)	0.21

Table 3: Distribution of different CYP2C9 allelic variants in 102 sulphonylurea-treated type 2 diabetic patients with severe hypoglycaemia versus control group without SH and versus previously reported diabetic and healthy control samples

CYP2C9 genotypes	Cases with SH N = 102	Diabetic controls without SH N = 101	p-value*	Diabetic controls without SH (Holstein et al. <i>Br J Clin Pharmacol</i> , 2005) N = 337
CYP2C9 *1/*1	63 (61.8%)	66 (65.3%)		224 (66.5%)
CYP2C9 *1/*2	24 (23.5%)	9 (8.9%)		62 (18.4%)
CYP2C9 *2/*2	1 (1%)	0 (0)	0.04 ⁽¹⁾	5 (1.5%)
CYP2C9 *1/*3	12 (11.8%)	21 (20.8%)		39 (11.6%)
CYP2C9 *2/*3	1 (1%)	2 (2%)	0.28 ⁽²⁾	5 (1.5%)
CYP2C9 *3/*3	1 (1%)	3 (3%)		2 (0.6%)

* - Cases with SH vs. Diabetic controls without SH

** - Cases with SH vs. previously reported Diabetic controls without SH (Holstein et al. *Br J Clin Pharmacol*, 2005)

*** - Cases with SH vs. previously reported Healthy controls (Holstein et al. *Br J Clin Pharmacol*, 2005)

(1) p-values were calculated by using chi-square tests to compare the overall distribution of CYP2C9 allelic variants between cases and controls

(2) p-values were calculated by using Fisher's exact tests to compare the frequencies of CYP2C9 *2/*3 and CYP2C9 *3/*3 allelic variants between cases and controls