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Sulfonylureas and the risk of myocardial infarction

Henriette Thisted[a,b], Søren Paaske Johnsen[a], Jørgen Rungby[b,c,*]

[a]*Department of Clinical Epidemiology, Aarhus University Hospital, DK-8000 Aarhus C, Denmark*
[b]*Department of Clinical Pharmacology, Aarhus University Hospital, DK-8000 Aarhus C, Denmark*
[c]*Department of Endocrinology C, Aarhus University Hospital, DK-8000 Aarhus C, Denmark*

Abstract

Patients with diabetes mellitus have an increased risk of coronary artery diseases such as myocardial infarction. Sulfonylureas are used in the treatment of diabetes mellitus and have been linked with adverse cardiovascular effects due to an apparent effect on myocardial ischemic preconditioning. Individual sulfonylureas differ pharmacologically and may have different effects. Although the hypotheses were stimulated by animal studies and experimental studies using intermediate end points, data on the possible clinical implications in humans remain sparse. However, recent data seem reassuring.

1. Introduction

The hypoglycemic effect of sulfonamides was first discovered in 1942 by Jambon and colleagues, both in experimental animals and in patients treated with sulfonamides for typhoid fever. This led to the development of early sulfonylurea (SU) drugs, carbutamide and tolbutamide, of which the latter proved clinically useful and remains an option for the treatment of type 2 diabetes mellitus in 2005.

Although a number of extrapancreatic effects of SUs may be of some clinical relevance [1], the main effect of SUs on glycemia is the result of the interaction of the drugs with the SU receptor 1 (SUR1) in beta cells, resulting in closure of adenosine triphosphate (ATP)–sensitive K^+ channels (K_{ATP}), Ca^{2+} influx, membrane depolarization, and eventually release of beta-cell secretory vesicle contents into the extracellular compartment. Thus, SUs cause insulin secretion and thereby repair one of the fundamental problems in type 2 diabetes mellitus. Because of the many years of experience, the well-documented antihyperglycemic effects, and the reassuring safety profiles, SUs, in our opinion, remain a mainstay in the treatment of type 2 diabetes mellitus as long as a sufficient beta-cell response can be expected.

2. Sulfonylureas and myocardial ischemia

Apart from hypoglycemia, the major concern with the SUs has been the presence of SURs in the vasculature and in cardiomyocytes. The binding of SUs to vascular and cardiac SURs, like the binding to beta-cell receptors, has a number of physiologic consequences. In cardiac myocytes, ischemia results in K_{ATP} opening, K^+ efflux, reduced Ca^{2+} influx, and via these mechanisms reduced contractility and, consequently, a decreased need for oxygen. In vascular cells, K_{ATP} opening decreases muscular tone resulting in increased flow. Thus, theoretically, SUs, by closing K_{ATP} channels, may cause double jeopardy to the myocardium during ischemia. On the other hand, some SUs may enhance fibrinolysis and reduce platelet activity and oxidative stress [2], properties that might reduce myocardial ischemic damage. Furthermore, some SUs may reduce arrhythmias during ischemia [3].

The phenomenon of ischemic preconditioning (IP) has received particular attention. Ischemic preconditioning self-protects the myocardium if exposed to repeated ischemic episodes (as is often the case in clinical myocardial infarction [MI]). K_{ATP} opening results in IP. Thus, inhibition of K_{ATP} by SUs could further damage the myocardium because IP reduces infarct size [4].

3. Individual SUs and the heart

There is preclinical and clinical evidence suggesting that SUs differ pharmacologically and that this may be relevant

* Corresponding author. Departments of Endocrinology C and Clinical Pharmacology, Aarhus University Hospital, DK-8000 Aarhus C, Denmark. Tel.: +45 89497657; fax: +45 89497659.
E-mail address: jr@farm.au.dk (J. Rungby).

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Table 1
Current SU use and MI case fatality in the United Kingdom Prospective Diabetes Study [39]

	MI case fatality
SU use	142/277 (51%)
No SU use	209/397 (53%)

to the cardiovascular system. Firstly, the affinity for the cardiac SUR2A receptor is high for glibenclamide and glimepiride compared with tolbutamide and gliclazide [5,6]. However, even with comparable receptor affinities, post-receptor events differ. Thus, the maximal inhibitory concentrations for closing K_{ATP} are 4 times lower for glibenclamide than for glimepiride [7].

Furthermore, in preclinical studies, gliclazide appears to possess favorable effects that may affect pre- and postinfarct events (see above). In vivo studies on the heart, ischemia, and SUs have largely been performed with glibenclamide. A number of studies reviewed in reference [8] confirm the possible negative effects of this particular substance on IP. Data on other SUs, however, are sparse. In animal models, gliclazide did not abolish IP [9]. Two SUs, glimepiride and glibenclamide, have been compared in clinical angiography studies showing that patients on glimepiride were able to maintain the ability for IP during repeated balloon inflations compared with patients on glibenclamide in whom IP was practically abolished [10,11].

4. Epidemiologic data

We know that patients with type 2 diabetes mellitus have an increased risk of coronary artery disease, such as MI, and an adverse prognosis after MI when compared with their nondiabetic counterparts [12-14]. Some have suggested that use of SUs in patients with type 2 diabetes mellitus could contribute to the increased risk and case fatality rate (CFR) after an MI. Concerns about the cardiovascular safety of SUs were initially based on results from the University Group Diabetes Program in 1970, in which treatment with tolbutamide appeared to be associated with an increase in cardiovascular mortality when compared with treatment with insulin and placebo [15]. The literature on SUs and cardiac mortality besides the University Group Diabetes Program is characterized by varying conclusions; thus, some studies suggest that SUs are detrimental to the heart [13,16-24], some suggest a decreased cardiac mortality with SUs [25-29], and some suggest that SUs are neutral in this respect [30-40]. Recent data, however, seem reassuring. In particular, the United Kingdom Prospective Diabetes Study group, in an analysis of 674 MIs, found comparable fatality rates among SU-treated patients and their non–SU-treated counterparts [39] (Table 1), and similar results appeared in an analysis of 562 MI patients, of which 77 SU-treated patients did not fare worse than their controls [40]. Finally, in a 7-year follow-up of 2275 diabetic patients with coronary artery disease, the Bezafibrate Infarction Prevention Study Group found comparable mortality rates with metformin and glibenclamide; however, combination therapy with the 2 drugs was associated with an increased mortality [41].

Recently, in an epidemiologic study, we examined the association between use of SUs and other antidiabetic drugs and the risk and CFR of MI in a population-based case-control and follow-up study, respectively. A total of 6738 cases of first-time MI, and 67 374 age- and sex-matched population controls were identified from the Hospital Discharge Registry and the Civil Registration System of North Jutland County, Denmark, in the period 1994 to 2002 [42].

The risk of MI appeared higher among users of "old" SUs (adjusted odds ratio [OR], 2.07; 95% confidence interval [CI], 1.81-2.37) than among users of "new" SUs (adjusted OR, 1.36; 95% CI, 1.01-1.84). The adjusted ORs among users of non-SU oral antidiabetic drugs, insulin, and patients with diabetes mellitus not receiving pharmacother-

Table 2
Crude and adjusted ORs with 95% CIs for MI according to prescriptions for antidiabetic drugs filled within 90 days before hospitalization compared with nondiabetic subjects

Antidiabetic medication	Cases (n = 6636)	Controls (n = 66 839)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
New SUs	56	322	1.96 (1.47-2.61)	1.36 (1.01-1.84)
Glimepiride	35	205	1.93 (1.34-2.77)	1.36 (0.93-1.99)
Gliclazide	21	117	2.01 (1.26-3.21)	1.37 (0.84-2.22)
Old SUs	305	1.306	2.59 (2.28-2.95)	2.07 (1.81-2.37)
Glibenclamide	206	889	2.57 (2.20-3.01)	2.08 (1.77-2.45)
Glipizide	72	317	2.51 (1.94-3.25)	1.97 (1.50-2.58)
Tolbutamide	27	100	3.02 (1.97-4.64)	2.32 (1.48-3.64)
Non-SU oral antidiabetic drugs	31	177	1.88 (1.25-2.82)	1.38 (0.90-2.11)
Insulin	235	737	3.55 (3.03-4.16)	2.56 (2.16-3.03)
Any combination	51	183	1.09 (0.77-1.55)	1.02 (0.70-1.47)
Diabetes without pharmacotherapy	189	423	4.96 (4.16-5.90)	3.51 (2.92-4.22)

[a] Adjusted for discharge diagnoses of hypertension, chronic bronchitis and emphysema, alcoholism, and liver cirrhosis, and prescriptions for antihypertensive drugs, lipid-lowering agents, high-dose aspirin, platelet inhibitors, oral anticoagulants, hormone replacement therapy, and nitrates before the date of hospitalization for MI.

Table 3
Thirty-day CFRs and ORs of case fatality after first-time MI compared with nondiabetic subjects

Antidiabetic medication[a]	No. of users	Deaths	30-d CFR (%)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
New SUs	56	14	25.0	1.06 (0.58-1.95)	1.00 (0.53-1.90)
Glimepiride	35	12	34.3	1.66 (0.83-3.35)	1.65 (0.78-3.47)
Gliclazide	21	2	9.5	0.34 (0.08-1.44)	0.30 (0.07-1.32)
Old SUs	305	103	33.8	1.62 (1.27-2.07)	1.29 (1.00-1.67)
Glibenclamide	206	67	32.5	1.54 (1.14-2.07)	1.32 (0.96-1.80)
Glipizide	72	26	36.1	1.80 (1.11-2.93)	1.30 (0.79-2.15)
Tolbutamide	27	10	37.0	1.88 (0.86-4.11)	1.20 (0.53-2.72)
Non-SU oral antidiabetic drugs	31	7	22.6	0.83 (0.34-2.03)	0.69 (0.27-1.76)
Insulin	235	71	30.2	1.33 (0.98-1.80)	1.27 (0.92-1.74)
Any combination	51	17	33.3	1.31 (0.68-2.52)	1.34 (0.67-2.68)
Diabetes without pharmacotherapy	189	47	24.9	1.06 (0.76-1.48)	1.04 (0.73-1.49)

[a] Antidiabetic use was measured in the 90 days before hospitalization for first-time MI.
[b] Adjusted for age, sex, discharge diagnoses of hypertension, chronic bronchitis and emphysema, alcoholism, and liver cirrhosis, and prescriptions for antihypertensive drugs, lipid-lowering agents, high-dose aspirin, platelet inhibitors, oral anticoagulants, hormone replacement therapy, and nitrates before the date of hospitalization for MI.

apy were 1.38 (95% CI, 0.90-2.11), 2.56 (95% CI, 2.16-3.03), and 3.51 (95% CI, 2.92-4.22), respectively (Table 2). The overall 30-day CFR was 24.6%, but varied between 9.5% to 37.0% among the different categories (Table 3).

We found a reduced risk of MI when comparing users of gliclazide and glimepiride with users of other SUs. Furthermore, in this study, we found trends suggesting that CFRs after MI were also dependent on the particular SU used by the patients. Our data indicate the need for further examination of the cardiovascular safety of antidiabetic drugs, and the differences we observed need confirmation in larger-scale studies [42].

Emerging data may thus allow us to identify SUs with particularly positive cardiac risk profiles. There is an urgent need for such studies because the increasing burden of type 2 diabetes mellitus will enhance the need for effective, cheap, and safe hypoglycemic agents [43].

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