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Sulfonylureas Improve Outcome in Patients With Type 2 Diabetes and Acute Ischemic Stroke

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Abstract

Background and Purpose—The sulfonylurea receptor 1-regulated NC_{Ca-ATP} channel is upregulated in rodent models of stroke with block of the channel by the sulfonylurea, glibenclamide (glyburide), significantly reducing mortality, cerebral edema, and infarct volume. We hypothesized that patients with type 2 diabetes mellitus taking sulfonylurea agents both at the time of stroke and during hospitalization would have superior outcomes.

Methods—We reviewed medical records of patients with diabetes mellitus hospitalized within 24 hours of onset of acute ischemic stroke in the Neurology Clinic, Charité Hospital, Berlin, Germany, during 1994 to 2000. After exclusions, the cohort comprised 33 patients taking a sulfonylurea at admission through discharge (treatment group) and 28 patients not on a sulfonylurea (control group). The primary outcome was a decrease in National Institutes of Health Stroke Scale of 4 points or more from admission to discharge or a discharge National Institutes of Health Stroke Scale score of 0. The secondary outcome was a discharge modified Rankin Scale score ≤ 2 .

Results—No significant differences, other than stroke subtype, were observed among baseline variables between control and treatment groups. The primary outcome was reached by 36.4% of patients in the treatment group and 7.1% in the control group ($P=0.007$). The secondary outcome was reached by 81.8% versus 57.1% ($P=0.035$). Subgroup analyses showed that improvements occurred only in patients with nonlacunar strokes and were independent of gender, previous transient ischemic attack, and blood glucose levels.

Conclusion—Sulfonylureas may be beneficial for patients with diabetes mellitus with acute ischemic stroke. Further investigation of similar cohorts and a prospective randomized trial are recommended to confirm the present observations.

Keywords

cerebral ischemia; diabetes mellitus; glibenclamide; stroke; sulfonylurea

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Acute stroke is the second leading cause of death in industrialized countries and is the leading medical cause of acquired adult disability. At present, thrombolysis is the only approved therapy, and for a variety of reasons, it is administered to less than 5% of patients with stroke.¹ There is an ongoing search for better prevention and treatment for acute stroke.

The NC_{Ca-ATP} channel is a nonselective cation channel that is expressed in the central nervous system only under conditions of injury or ischemia.²⁻⁴ Channel opening, which is triggered by adenosine triphosphate depletion, results in cytotoxic edema, oncotic cell death, and cerebral edema.⁵ Like the K_{ATP} channel in pancreatic β cells, it is regulated by sulfonylurea receptor 1 (SUR1) and is blocked by sulfonylureas such as glibenclamide (glyburide). Recently, Simard et al⁴ reported that this channel is upregulated in rodent models of ischemic stroke, and that postevent block of the channel with glibenclamide reduces mortality, cerebral edema, and infarct volume by half.

In patients with type 2 diabetes mellitus (DM), prior use of sulfonylureas at the time of stroke has been shown not to adversely influence initial stroke severity, in-hospital outcome, or mortality.⁶ In the same study, a nonsignificant benefit was observed among patients taking sulfonylureas, but the study did not distinguish between patients who remained on these agents after stroke and those in whom they were discontinued.

Given that the study by Simard et al⁴ used continuous infusion of glibenclamide poststroke, we hypothesized that patients who are on sulfonylurea agents both pre- and poststroke would have improved outcomes compared with patients not on sulfonylureas. Apart from effects on SUR1, glibenclamide can also inhibit SUR2, which forms the regulatory subunit of cardiovascular K_{ATP} channels. The potency of glibenclamide at SUR2 is one to 2 orders of magnitude less than at SUR1.⁷ However, cerebrovascular SUR2-regulated K_{ATP} channels have been shown in rodents to be important for hypoxic/hypercarbic cerebral vasodilation,^{8,9} which in turn may be important for optimizing collateral blood flow after stroke. We hypothesized that potential vasoconstriction through this mechanism, if present, would not cause a deleterious effect.

The aim of the present study was to determine whether the use of a sulfonylurea agent both at the time of stroke and during hospitalization resulted in better neurological and functional outcomes in patients with DM. The primary outcome was defined as a decrease in the National Institutes of Health Stroke Scale (NIHSS) score of 4 points or more from baseline to discharge or a discharge NIHSS score of 0. This outcome has been previously used for short-term recovery in Part 1 of The National Institute of Neurological Disorders and Stroke rtPA Stroke Trial.¹⁰ An improvement of 4 points or more on the NIHSS is regarded as "major neurological improvement."¹¹ The secondary outcome was defined as a modified Rankin Scale (mRS) score ≤ 2 at the time of discharge, signifying functional independence.¹²

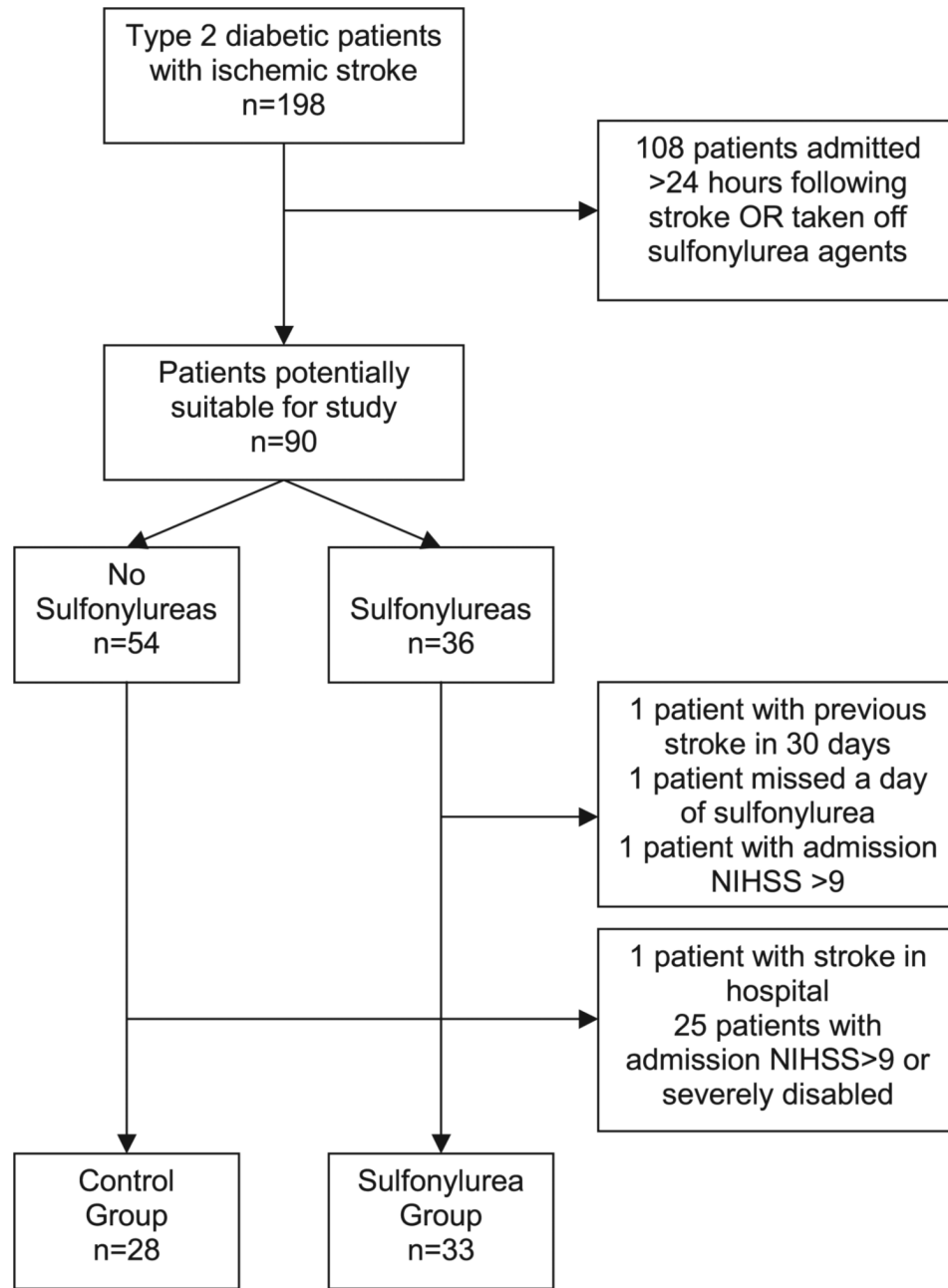
Methods

Patients and Data Collection

A blinded chart review was performed of all patients with DM who were admitted and hospitalized with an acute ischemic stroke in the Neurology Clinic of Charité Hospital, Berlin, from January 1994 to May 2000, which had previously been screened and analyzed in the study by Weih et al.⁶ The Figure summarizes the algorithm used for patient selection. Of the 198 charts reviewed, 90 patients were admitted within 24 hours of their acute ischemic stroke and were considered for inclusion in the present study. A total of 36 patients were on the sulfonylureas glibenclamide (glyburide), glimepiride, or glibornuride at admission through discharge, all of which act on SUR1 and were thus potentially efficacious. The remaining 54

patients were not on sulfonylurea agents. Patients who were on a sulfonylurea at the time of stroke but who were taken off their sulfonylurea at admission were excluded from the present study. In a separate, preliminary analysis of 16 patients who had their sulfonylurea treatment discontinued, 15 patients had the agent discontinued on the day of admission and one on the day after admission. Although the severity of stroke may have influenced whether the sulfonylurea was discontinued, the decision to discontinue the agent was made early in the hospital stay. Therefore, the decision to discontinue the agent was made before knowledge of clinical deterioration or improvement. This is important, because it indicates that patients whose condition worsened were not transferred from sulfonylurea to insulin, and therefore there was no intended bias of the treatment group toward better recoveries.

Relevant demographic and clinical data for the 90 patients were extracted from the charts. Two individuals were responsible for transcribing these data, after which they covered the sections of the charts reporting medications so that the 2 neurologists (H.K., S.S.) performing the NIHSS and mRS scoring, independently of each other, were blinded as to whether the patients were in the treatment or control groups. The same 2 neurologists compared their scores once completed and, when differences were found, reached a consensus score that was used in the analysis. The cause of stroke (ie, stroke subtype) was determined retrospectively using TOAST criteria based on all available medical information, including documented clinical presentation, MRI, intracranial and extracranial vessel imaging,



Patient selection algorithm.

cardiac monitoring, hypercoagulability serum panels, and echocardiography reports.¹³

Of the 90 patients, 29 were excluded. Only one patient in the sulfonylurea group had a baseline NIHSS score >9, whereas 18 control patients had such a score. To make valid comparisons between the 2 groups, patients with a baseline NIHSS score >9 were excluded. A further 7 patients in the control group were severely disabled at admission as a result of various causes, including somnolence and dementia. It was argued that because of their medical condition, had these patients been prescribed oral medications, such medications would have been interrupted or halted. As a result of these further exclusions, the analyses in the present study consisted of 33 patients in the treatment (sulfonylurea) group and 28 patients in the control group.

Statistical Analyses

The primary outcome was defined as a decrease in the NIHSS score of 4 points or more from baseline to discharge or a discharge NIHSS score of 0. The secondary outcome were defined as a mRS score ≤ 2 at the time of discharge signifying functional independence. Pearson's χ^2 test and Fisher exact test were used to compare the proportion of patients reaching these outcomes between the 2 groups. Multivariable logistic regression was used to assess whether age, admission NIHSS, and admission glucose level were potential confounders.

Lacunar infarcts (small-artery atherosclerosis) have been reported to be associated with milder deficits compared with nonlacunar (large-artery atherosclerosis, cardioembolism, and other/undetermined) causes of stroke.¹⁴ For this reason, an analysis was performed to assess whether the cause of stroke modified the effectiveness of sulfonylurea using the Breslow-Day statistic as a test for interaction. Because of the study's small sample size, patients with large-artery atherosclerotic, cardioembolic, other, and unknown causes were grouped together for this analysis.

Female gender¹⁵ and the occurrence of a previous transient ischemic attack (TIA)^{16,17} have been found to influence stroke outcome. Post hoc analyses were thus performed to test whether gender or previous TIA modified the effectiveness of sulfonylurea. Primary and secondary end points were reanalyzed for the designated subgroups, and a test for interaction was performed using the Breslow-Day statistic. Only the presence or absence of TIA was available from the charts with no information available as to which hemisphere or at what time the TIA occurred.

Because sulfonylurea drugs reduce blood glucose levels, and lower blood glucose levels are associated with better stroke outcomes,^{18,19} an analysis was performed to determine whether the outcomes were influenced by baseline, day 1 minimum and maximum, or day 3 minimum and maximum glucose levels. Glucose levels were dichotomized at 140 mg/dL and analyzed using multiple logistic regression.

Results

Baseline demographic and clinical characteristics are summarized in Table 1. No significant differences were observed between groups other than stroke subtype, in which patients in the control group were more likely to present with a lacunar stroke (46.4% versus 21.2%, $P=0.037$). The median hospital stay was 13 and 14 days for control and treatment groups, respectively ($P=0.86$). One patient in the control group died versus none in the treatment group.

Patients who were on sulfonylureas were significantly more likely to have a better neurological outcome (NIHSS improvement ≥ 4 or NIHSS=0; $P=0.007$) and a better functional outcome (mRS ≤ 2 ; $P=0.035$) at the time of discharge (Table 2). Multiple logistic regression analysis did not identify any confounders, and because the adjusted and unadjusted results were similar, only the simpler, univariate results are presented.

The cause (subtype) of stroke significantly modified the effectiveness of sulfonylurea for the NIHSS outcome ($P=0.032$, Table 2). A large difference in the primary outcome, in favor of sulfonylurea, was observed among patients who presented with a nonlacunar stroke (42.3% versus 0.0%), in particular large-artery atherosclerosis (7 of 13 versus zero of 11, $P=0.006$, Fisher exact test). A similar pattern was observed for the mRS outcome, but the test for interaction was not statistically significant.

The effect of gender and the occurrence of a previous TIA were assessed, because these variables have been found to influence stroke outcome.^{15–17} For both variables, the 2 end points still favored sulfonylurea, and the test for interaction was not statistically significant

(for gender, $P=0.13$ and 0.44 for primary and secondary outcomes; for previous TIA, $P=0.55$ and 0.70 for primary and secondary outcomes).

From multiple logistic regression analysis, glucose levels at baseline, day 1, and day 3 did not influence patient outcome.

Discussion

The present study is the first to show that prior use plus postevent use of sulfonylurea agents could have a beneficial effect on stroke outcome. Patients on sulfonylureas were significantly more likely to have favorable neurological and functional outcomes at the time of discharge with the magnitude of the effect being large. These improvements occurred during hospitalizations that lasted an average of 14 to 17 days.

Use of sulfonylureas was not equally effective in all subgroups of patients. Beneficial effects were observed preferentially in patients with nonlacunar strokes, ie, patients with large-artery atherosclerosis or cardioembolic causes of stroke. In contrast, patients with lacunar strokes did not appear to benefit from the use of sulfonylureas. This finding is comparable to the previous observation that patients on statins show smaller infarct volumes when nonlacunar middle cerebral artery infarctions are involved, but not with lacunar infarcts.²⁰ The striking results with large-artery atherosclerosis are reminiscent of the TOAST study, which reported efficacy of low-molecular-weight heparin only in the large-artery atherosclerosis subtype.²¹ The reasons for such observations are not entirely clear, but they may relate to the greater potential availability of collaterals when large vessels are involved compared with the relative paucity of collaterals for territories supplied by microvessels or end arterioles. This interpretation would fit with data from animal models, in which reduction in edema by glibenclamide, resulting in improved leptomeningeal collateral flow, is believed to be responsible for cortical sparing observed after proximal large-vessel occlusion.⁴

Currently, treatments for stroke are severely limited with plasminogen activators being the mainstay of acute intervention. New treatment strategies and new compounds continue to be evaluated, but identification of successful treatments for humans continues to be elusive. Assessing new stroke therapies for patients with DM is reasonable, because DM is an important risk factor for stroke. Compared with the general population, patients with DM have a higher incidence of stroke, a poorer prognosis after stroke, and are more likely to have atherothrombotic stroke and lacunar infarcts.^{22,23}

Sulfonylurea agents such as glibenclamide are not without potentially deleterious effects in the context of stroke. Glibenclamide exerts its most potent effect on SUR1, which forms the regulatory subunit of both the K_{ATP} channel in pancreatic β cells and the NC_{Ca-ATP} channel that is upregulated in cerebral ischemia.^{3,4} Thus, consideration must be given to the potential side effect of hypoglycemia, which could be harmful in stroke.²⁴ However, in rodent models of stroke,⁴ beneficial effects of glibenclamide are observed at doses that are lower than those typically administered to patients with DM and lower than those typically required to develop critical hypoglycemia. The positive results of the present study make it unlikely that a deleterious effect working through SUR2 was operating in the patient cohort, possibly because cerebrovascular K_{ATP} channels in humans are less sensitive to glibenclamide than in other species²⁵ or because the potency of glibenclamide inhibition is reduced by diabetes.²⁶

The present study has several limitations. First, it was a retrospective chart review, thus limiting the type and details of the data that could be collected. Specifically, the NIHSS and mRS scores were ascertained retrospectively from reading the charts, although the neurologists performing the scoring were blinded to treatment group. Second, because of the small sample size, it will be necessary to replicate the study in other groups of patients to confirm whether the results

may be generalized. However, it is worth noting that despite the sample size, the treatment and control groups were well balanced with the exception of the high proportion of lacunar strokes in the control group, which favored outcomes in the control group and thus increased the bar for demonstrating efficacy. Third, outcomes were assessed at the time of discharge, thus precluding long-term follow up out to 90 days and beyond. This is not ideal but is also not uncommon in proof-of-principle neuroprotectant and thrombolytic stroke trials as seen in Part 1 of The National Institute of Neurological Disorders and Stroke rtPA Stroke Trial, which looked at neurological improvements at 24 hours posttherapy. Finally, the results do not apply to all patients with acute stroke, because all patients in the present study had DM. This is somewhat mitigated by the effect being demonstrated to be independent of glucose levels and the mechanism of action of sulfonylureas in stroke being unrelated to DM.

In summary, the use of sulfonylureas before and during the acute phase of stroke may have a significant, clinically meaningful effect on stroke outcome in patients with DM. Future studies will be required to determine whether postevent treatment with sulfonylureas is as beneficial as was observed here when treatment was ongoing before the ischemic event. It also remains to be determined whether starting sulfonylurea treatment after stroke in patients without DM is beneficial and whether the short-term benefits reported here are maintained at longer-term follow up. However, the findings from the present study, combined with the previous report that postevent treatment with glibenclamide is beneficial in rodent models of stroke, suggest that sulfonylureas may be useful in the acute care of patients with stroke. The current data suggest that further investigation of similar cohorts should be performed and that a prospective, randomized trial of sulfonylureas is justified.

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TABLE 1

Demographic and Clinical Characteristics*

	Sulfonylurea (N=33)	Control (N=28)	P Value [‡]
Age ≥75 years [†]	27.3	17.9	0.38
Male sex	69.7	57.1	0.31
Lacunar stroke	21.2	46.4	0.037
Prior TIA	30.3	10.7	0.063
Admission NIHSS score 4–9	66.7	75.0	0.48
Glucose ≥140 mg/dL	77.4	80.8	0.76
Admission ≥6 hours	56.3	50.0	0.63
Received reperfusion	0.0	7.1	0.21
Time to discharge ≥14 days	51.5	46.4	0.69

* Values indicate percent of the group.

[†] Mean (SD) age: 66.8 (11.3) and 67.1 (9.9) years, respectively.

[‡] P value computed from Pearson's χ^2 test comparing 2 groups.

TABLE 2

Favorable Outcome at Time of Discharge, Overall and by Cause of Stroke*

	Sulfonylurea (N=33)	Control (N=28)	P Value
NIHSS improvement ≥ 4 or NIHSS=0	36.4 (12)	7.1 (2)	0.007 [†]
Lacunar stroke	14.3 (1/7)	15.4 (2/13)	0.032 [‡]
Nonlacunar stroke [§]	42.3 (11/26)	0.0 (0/15)	
mRS ≤ 2	81.8 (27)	57.1 (16)	0.035 [†]
Lacunar stroke	71.4 (5/7)	69.2 (9/13)	0.17 [‡]
Nonlacunar stroke	84.6 (22/26)	46.7 (7/15)	

* Values indicate percent of the group (no. of patients).

[†] P value computed from Pearson's χ^2 test comparing 2 groups.

[‡] P value corresponding to test of interaction between cause of stroke and group.

[§] Includes large-artery atherosclerosis (7 of 13), cardioembolic (one of 6), and other/undetermined (3 of 7) in the sulfonylurea group; and large-artery atherosclerosis (zero of 11), cardioembolic (zero of 3), and other/undetermined (zero of one) in the control group.

^{||} Includes large-artery atherosclerosis (13 of 13), cardioembolic (5 of 6), and other/undetermined (4 of 7) in the sulfonylurea group; and large-artery atherosclerosis (5 of 11), cardioembolic (one of 3), and other/undetermined (one of one) in the control group.