Potential Impact of Sulfonylureas in the Outcome of Type 2 Diabetic Patients With Ischemic Stroke

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See related article, pages 2526–2530.

Type 2 diabetes mellitus is a well known independent risk factor for coronary heart disease and stroke. Diabetes accelerates the clinical course of atherosclerosis and contributes to increased cardiovascular morbidity and mortality. Moreover, diabetes is the cerebrovascular risk factor associated with greater in-hospital mortality either in patients with ischemic stroke or primary intracerebral hemorrhage. However, the reason for an increased early mortality and worse prognosis in diabetic patients with cerebral infarction is not well understood. Diabetic patients with stroke had atrial fibrillation more often than nondiabetic patients. Congestive heart failure and atrial fibrillation are major aggravating factors in this population and are likely to further increase substantially the risk of stroke, cardiac events, and sudden death, indicating that diabetic stroke patients may have larger cerebral infarcts than nondiabetics. In addition, the worse prognosis may probably be related to metabolic derangement caused by hyperglycemia. Data from experimental studies show that hyperglycemia exacerbates ischemic lesions by increasing acidosis-related damage and is associated with an increase in cerebral edema and infarct volume. Cerebral edema is a complex pathophysiological process that causes brain swelling, complicates ischemic stroke, worsens neurological dysfunction, and can lead to brain herniation and death. Malignant cerebral edema after a large ischemic stroke in the territory of the middle cerebral artery is responsible for the high mortality (60% to 80%) of the patients.

Recent experimental studies have shown that sulfonylureas may have a beneficial effect on cerebral edema. Sulfonylurea derivatives constitute the pharmacological class of oral hypoglycemic agents most frequently used in the treatment of type 2 diabetes. Sulfonylurea derivatives act by depolarizing pancreatic β cells by inhibiting ATP-dependent potassium channels (K<sub>ATP</sub>). Simard et al have recently identified a nonselective cation channel, the NC (Ca-ATP) channel, in ischemic astrocytes that is regulated by sulfonylurea receptor 1 (SUR1), is opened by depletion of ATP and, when opened, causes cytotoxic edema, oncocytic cell death, and cerebral edema. Like the K<sub>ATP</sub> channel in pancreatic β cells, the NC (Ca-ATP) channel is regulated by SUR1 and is blocked by sulfonylureas. The channel is upregulated in rodent models of ischemic stroke, and block of SUR1 with constant infusion of low-dose glibenclamide caused only a slight reduction of serum glucose, but was highly effective in reducing cerebral edema, infarct volume, and mortality by 59% in rodent models of stroke. Accordingly, the NC (Ca-ATP) channel is crucially involved in the development of cerebral edema, and that targeting SUR1 may provide a new therapeutic approach to stroke. However, up to the present time these promising and novel experimental findings have not been replicated in human studies.

The research of Kunte and associates published in this issue of Stroke has the important merit of showing for the first time that treatment with sulfonylureas before cerebral ischemia and maintained during the acute phase of infarction (similarly to therapy in experimental studies) had a beneficial effect on the short-term prognosis of patients with type 2 diabetes and cerebral infarct. The authors studied a cohort of 33 diabetic patients with cerebral ischemia treated with sulfonylurea derivatives (glibenclamide, glimepiride, or glipizide) at admission to discharge (treatment group) and 28 diabetic patients with cerebral infarction not on a sulfonylurea (control group). A decrease in National Institutes of Health Stroke Scale (NIHSS) of ≥4 points from admission to discharge, or a discharge NIHSS score = 0 was reached by 36% of patients in the treatment group compared with 7.1% in the control group (P = 0.007). At the time of discharge, a modified Rankin Scale score ≤ 2 was obtained by 81.8% in the treatment group and 57.1% in the control group (P = 0.035). Improvement was independent of gender and previous transient ischemic attack, and it is remarkable that it was only observed in the subset of patients with cerebral infarction of nonlacunar type. In this respect, previous studies have shown that patients with nonlacunar ischemic stroke treated with HMG-CoA reductase inhibitors (statins) before or early after infarction had a more favorable outcome than those untreated. The beneficial effect of transient ischemic attack before definite cerebral infarction, probably attributable to a mechanism of ischemic tolerance, is usually restricted to nonlacunar stroke. The lack of efficacy in the subgroup of patients with lacunar stroke may be explained by the small size of lacunar infarcts in which maximum diameter of the lesion is <15 mm and the well known short-term good prognosis of this stroke subtype, so that it is difficult to assess differences in neurological recovery in this subgroup of patients who spontaneously present a good outcome. On the other hand, the preparatory recruitment of collateral pathways is not feasible in lacunar infarction because this type of cerebral ischemia is characterized by occlusion of the
terminal perforating arterioles with no possibility of mobilization of collateral pathways.\textsuperscript{12,16}

Effective therapies for acute stroke are scarce, and numerous neuroprotective strategies have failed in human trials.\textsuperscript{17} For this reason, the study of Kunte and coworkers\textsuperscript{11} is highly relevant because it provides evidence of the potential beneficial effects of sulfonylurea derivatives in the management of type 2 diabetic patients with acute cerebral infarction. Moreover, the favorable effects of these agents were independent of the serum glucose concentration, suggesting that the mechanism through which sulfonylureas exert their beneficial effects is not only limited to the metabolic control of diabetes.\textsuperscript{18} Although these findings cannot be generalized to all patients with acute stroke and should be interpreted taking into account the limitations of the study, such as its observational, unmatched, retrospective design and the lack of information on concomitant treatment (it may be possible that other medications may confer neuroprotection, as just recently reported for statins or angiotensin-converting enzyme inhibitors),\textsuperscript{17} the piece of work by Kunte et al\textsuperscript{11} opens new encouraging perspectives for the treatment of patients with type 2 diabetes and ischemic stroke. In agreement with the authors, a prospective randomized trial of sulfonylureas is justified and, in my opinion, urgently needed.

**Disclosures**

None.

**References**


**Key Words:** cerebral infarction ■ diabetes mellitus ■ type 2 ■ stroke management ■ stroke outcome ■ sulfonylurea compounds
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