

Glyburide in Treating Malignant Cerebral Edema. Blocking Sulfonyl Urea One (SUR1) Receptors

Tony V Pallan, MD¹ and Iftekhar Ahmed, MD²

¹ Department of Family Medicine, Research Family Medicine Program, Kansas City, Missouri

² Research Medical Center department of Neurology, Associate Professor of Neurology, University of Missouri, Kansas City, Missouri

Abstract

Cerebral edema is a serious side effect of malignant stroke. On average 70,000 patients are diagnosed with malignant cerebral edema every year, of those patients, approximately 60-80% results in fatalities. The treatment of cerebral edema includes multimodality approaches.

In this article, we discuss our experience with glibenclamide in the treatment for malignant cerebral edema. Our study indicates that glibenclamide may decrease cerebral edema by blocking SUR1 receptors in ischemic stroke and non-ischemic etiologies.

Introduction

Cerebral edema results from increased brain cellular permeability, resulting from neurological insults including head injuries, infection and stroke which lead to severe disability and or death. In the past, various modalities have been tried with little success; this includes osmotic diuretics, steroids, mannitol, hypertonic saline, hyper-ventilation, glycerol, pentobarbital/propofol and craniotomy. All treatments have variable results in decreasing cerebral edema. In a recent animal study by Simard et al has shown the significance of SUR1 receptors blockade by glibenclamide and resulted in decreasing cerebral edema.

The discovery of the SUR1 as a regulatory subunit that associates with Kir6.x pore-forming subunits to form heterooctameric KATP channels¹. SUR1 confers sensitivity to sulfonylurea inhibitors such as glibenclamide and to channel activators such as diazoxide¹. The non-selective cation channel, SUR1/TRPM4, is regulated by the SUR1 and requires nanomolar concentrations of Ca²⁺ and the depletion of ATP to open the receptors. SUR1/TRPM4 allows sodium into the cell when Adenosine triphosphate (ATP) is depleted which occurs with an injury to the central nervous system which leads to apoptosis. The depolarization and blebbing induced by depletion of ATP are prevented by glibenclamide, and are reproduced without depletion of ATP by diazoxide, consistent with a crucial role for NC_{Ca-ATP} channels in

cytotoxic edema¹. In rodent models of massive ischemic stroke with malignant cerebral edema associated with high mortality (68%), glibenclamide reduced mortality and cerebral edema by half¹. In a model of subarachnoid hemorrhage, glibenclamide attenuates the inflammatory response due to extravasated blood². Clinical trials of an intravenous formulation of glibenclamide in traumatic brain injury (TBI) and stroke underscore the importance of recent advances in understanding the role of the SUR1-regulated NC_{Ca-ATP} channel in acute ischemic, traumatic, and inflammatory injury to the CNS.²

In patients with type 2 diabetes mellitus, prior use of sulfonylureas at the time of stroke has been shown to improve initial stroke severity, in-hospital outcome, or mortality³. SUR1 is the target of sulfonylurea drugs used to treat diabetes mellitus type 2, neonatal diabetes, and some forms of congenital hyperinsulinism². The purpose of our study is to investigate the role of glibenclamide in improving the neurological outcomes of patients with cerebral edema from various etiologies including stroke after an initial treatment of steroids and mannitol. The primary outcome of our study is a Rankin score of approximately 2 at the end of three months.

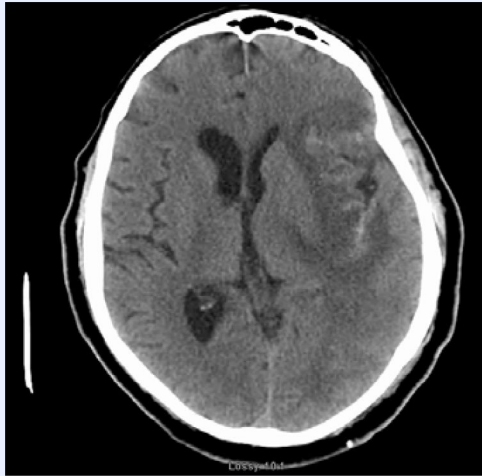
Methods

A total of seven patients with high glucose levels and various neurological ailments who were hospitalized at

Published November, 2014.

All Rights Reserved by JVIN. Unauthorized reproduction of this article is prohibited

Address correspondence to: Tony V Pallan.



(a)



(b)

Figure 1. a) a typical CT scan of patients prior to administering glibenclamide. It shows the cerebral edema after patients were treated with only mannitol and steroids. b) a typical CT scan of patients after the administering glibenclamide. It shows a significant reduction in the cerebral edema with a treatment with glibenclamide despite which etiology of cerebral edema the patient suffered from and far more effective than the traditional treatments of mannitol and steroids.

Table 1. Patient Clinical Profile

Age	22-68 yrs
Gender	4 Males, 3 Females
Hypertension	3 patients
Blood Pressure Range	130-210 mm Hg systolic
Diabetes	3 Diabetic, 4 non-Diabetic
Blood Sugar	132-280 mg/dl
Glibenclamide Average Dose	10 mg

Research Medical Stroke Care center, Kansas City, Missouri from 2009 to 2011 were selected. They were of various age ranges from 22 to 68 years.

The seven patients selected, three suffered strokes, two suffered from closed head injury and two had HIV infection and fungal meningitis. Three patients were hypertensive with blood pressure ranges from 130-210 mm Hg systolic. All patients had elevated blood glucose levels ranging from 132-280 mg/dl. In addition, all patients had an increased intracranial pressure (ICP) and were initially treated with the traditional treatment of steroids and mannitol. All patients were closely monitored in a neurointensive care unit for a week and their ICP was monitored via an ICP monitor. It showed that steroids and mannitol failed to decrease the ICP and cerebral edema. Glibenclamide was then introduced orally via a feeding tube and administered at 2.5 mg and gradually increased to 12.5 mg over the course of two days. All patients were closely monitored in the neurointensive care and the standard ICU workup was followed with ICP monitor, blood sugar levels and electrolytes.

Results

Prior to treatment with glibenclamide, the average initial ICP readings were 32 cm. After treatment all patients exhibited a significant decrease in ICP readings averaging to 12 cm. The effectiveness of glibenclamide in reducing the effects of cerebral edema from different etiologies became apparent. Regardless of the type of cerebral edema suffered by the patient, glibenclamide reduced the effects of cerebral edema and proved to be a safe treatment for patients with elevated blood glucose levels. All patients selected were either diabetic or had elevated blood glucose levels, after treatment with glibenclamide none of the patients suffered from hypoglycemia.

All patients were monitored for three months to see if the effects of the treatment would be consistent over time. Three months after the initial treatment, two patients died from medical complications. Three patients were withdrawn from treatment due to severe aphasia and poor neurological status. The results showed sustained progress in two of the patients after three months who achieved a Rankin score of 2.4 at 3-4 months. Of those two patients, one of the patients suffered from a stroke and the other suffered from a closed head injury.

Below is a CT scan

Conclusion

Our study finds the clinical and radiological effects of the SUR1 receptors in regulating the nonselective cation channel, NCCA-ATP channel. The SUR1 are not transporters and, by themselves, perform no recognized function². Instead, they undergo obligate association with heterologous pore-forming subunits to form ion channels². The upregulation of SUR1 receptors are linked to the activation of transcription factor Sp1 and is associated with expression of function NCCA-ATP but not KATP channels. Although both KATP and SUR1-NC_{Ca}-ATP channels are regulated by SUR1, the two have opposite functional effects in the central nervous system (CNS) injury-opening of KATP channel hyperpolarizes the cell and may be neuroprotective, whereas opening of SUR1-NC_{Ca}-ATP channel depolarizes the cell and, if unchecked, is associated with oncotic (neurotic) cell death². Glibenclamide blocks the SUR1 receptors which decreasing cerebral edema. The inhibitory effect of glibenclamide on channel opening is prevented by an antibody directed against one of the cytoplasmic loops of Sur1². The potency of block by glibenclamide is increased ~8-fold at pH 6.8, compared with pH 7.4, consistent with the weak acid needing to enter the lipid phase of the membrane to cause block, paralleling observations with the KATP channels². The NCCA-ATP channel is crucially involved in development of cerebral edema. Glibenclamide block of Cs⁺ currents also is observed when SUR1-NC_{Ca}-ATP channels are induced in brain microvascular endothelial cells by exposure the TNF α .

Given the study by Kunte et al, we arrived at the same conclusion, which is that 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 large³. Glibenclamide exerts its most potent effect on SUR1, which forms the regulator subunit of both the KATP channel in pancre-

atic β cells and the NCA-ATP channel that is upregulated in cerebral ischemia³. In the rodent models of stroke, beneficial effects of glibenclamide are observed at doses that are lower than those typically administered to patients with diabetes and lower than those typically required to develop critical hypoglycemia. Although our study is small, it showed similar conclusion about glibenclamide to be effective similar to the Kunte et al study, who suffered from ischemic stroke compare to those patients did not receive glibenclamide³. Our findings show that glibenclamide is effective in reducing other types of neurologic disorders other than ischemic strokes with patients who are hyperglycemic and is significantly more effective than traditional treatments of mannitol and steroids. Since our study is based on a small sample size, several studies with larger sample sizes will need to be implemented to confirm these results in non-ischemic stroke cases. This treatment shows a significant reduction in cerebral edema in non-ischemic stroke patients. Our study findings are similar to the previous studies in rodent models suggesting that sulfonylureas may be useful in acute care of patients with stroke.

References

1. Marc, Simard; Mingkui, Chen, et al. Newly expressed SUR1 NCCA-ATP channel mediates cerebral edema after ischemic stroke. *Nat Med* 2006;12:433–440.
2. Simard, J Marc; Woo, S Kyoon; Schwartzbauer, Gary; Gerzanich, Volodymyr. Sulfonylurea receptor 1 in central nervous system injury: a focused review. *J Cereb Blood Flow & Metab* 2012;32(9): 1699–1717.
3. Kunte H, Schmidt S, et al. Sulfonylureas improve outcome in patients with type 2 Diabetes and Acute Ischemic Stroke. *Stroke* 2007;38:2526–2530.
4. Martini SR, Kent TA. Hyperglycemia in acute Ischemic Stroke; a vascular perspective. *J Cereb Blood flow Metab* 2007;27:435–451.
5. Simard J.M, Tsybalyuk N, et al. Glibenclamide is superior to decompressive craniotomy in a rat model of malignant stroke. *Stroke* 2010 mar;41(3):531–7.