Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): a randomised, double-blind, placebo-controlled phase 2 trial

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Summary

Background Preclinical models of stroke have shown that intravenous glyburide reduces brain swelling and improves survival. We assessed whether intravenous glyburide (RP-1127; glibenclamide) would safely reduce brain swelling, decrease the need for decompressive craniectomy, and improve clinical outcomes in patients presenting with a large hemispheric infarction.

Methods For this double-blind, randomised, placebo-controlled phase 2 trial, we enrolled patients (aged 18–80 years) with a clinical diagnosis of large anterior circulation hemispheric infarction for less than 10 h and baseline diffusion-weighted MRI image lesion volume of 82–300 cm³ on MRI at 18 hospitals in the USA. We used web-based randomisation (1:1) to allocate patients to the placebo or intravenous glyburide group. Intravenous glyburide was given as a 0·13 mg bolus intravenous injection for the first 2 min, followed by an infusion of 0·16 mg/h for the first 6 h and then 0·11 mg/h for the remaining 66 h. The primary efficacy outcome was the proportion of patients who achieved a modified Rankin Scale (mRS) score of 0–4 at 90 days without undergoing decompressive craniectomy. Analysis was by per protocol. Safety analysis included all randomly assigned patients who received the study drug. This trial is registered with ClinicalTrials.gov, number NCT01794182.

Findings Between May 3, 2013, and April 30, 2015, 86 patients were randomly assigned but enrolment was stopped because of funding reasons. The funder, principal investigators, site investigators, patients, imaging core, and outcomes personnel were masked to treatment. The per-protocol study population was 41 participants who received intravenous glyburide and 36 participants who received placebo. 17 (41%) patients in the intravenous glyburide group and 14 (39%) in the placebo group had an mRS score of 0–4 at 90 days without decompressive craniectomy (adjusted odds ratio 0·87, 95% CI 0·32–2·32; p=0·77). Ten (23%) of 44 participants in the intravenous glyburide group and ten (26%) of 39 participants in the placebo group had cardiac events (p=0·76), and four of 20 had serious adverse events (two in the intravenous glyburide group and two in the placebo group, p=1·00). One cardiac death occurred in each group (p=1·00).

Interpretation Intravenous glyburide was well tolerated in patients with large hemispheric stroke at risk for cerebral oedema. There was no difference in the composite primary outcome. Further study is warranted to assess the potential clinical benefit of a reduction in swelling by intravenous glyburide.

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Introduction

Malignant cerebral oedema can develop as a complication of large hemispheric infarction and leads to abrupt neurological deterioration within 24–48 h after stroke onset.[1,2] Brain swelling, which is the mass-occupying consequence of cerebral oedema, can cause further ischaemic damage and, if left untreated, can result in brain herniation. The horizontal tissue shifts that occur as a consequence of brain swelling manifest clinically as a reduction in the level of arousal.[3] Medical treatment to reduce the brain volume includes supportive care and osmotic drugs. Nevertheless, herniation and death occur in up to 50% of patients with brain swelling.[1,4] Neurosurgical treatment with decompressive craniectomy can reduce mortality and might improve outcomes in patients younger than 60 years.[5] However, decompressive craniectomy is associated with substantial morbidity.[6] Moreover, surgery is done only after substantial tissue injury, brain shift, and neurological deterioration have already occurred.[1,3] Although treatment of oedema is reactive in clinical practice, no drug therapy has been assessed to prevent oedema.[7]

Results of preclinical studies[8,9] suggest that blockade of the inducible sulfonylurea receptor 1 (SUR1)-transient receptor potential melastatin 4 (TRPM4) channel in neurons, astrocytes, and endothelium substantially reduces cerebral oedema in rodent models of stroke. Further preclinical studies and retrospective studies in human beings have shown that a continuous parenteral infusion of the SUR1 inhibitor glyburide (glibenclamide) decreases water accumulation in the brain, improves survival, and facilitates neurological recovery in

Research in context

Evidence before this study

We searched PubMed for randomised controlled trials published in only English between Jan 1, 2000, and March 4, 2016, with the search terms "ischemic stroke", AND "brain edema", AND "glyburide", OR "glibenclamide", OR "sulfonylurea". We found 12 preclinical studies that showed that continuous glyburide administration led to a reduction in brain oedema and mortality in rodent models of stroke. A pilot trial of intravenous glyburide in patients with acute, large hemispheric stroke showed feasibility and initial safety of treatment of critically ill stroke patients at high risk for oedema. Interpretation of these retrospective and prospective pilot data is limited by the absence of double-blind, placebo controlled trials.

Added value of this study

To our knowledge, this is the first trial to assess the effect of early (within 10 h) and continuous administration of an intravenous glyburide for the prevention of brain oedema after a large hemispheric stroke in a randomised, double-blind, placebo-controlled trial. Treatment was well tolerated, hypoglycaemia was uncommon and successfully treated with a prespecified hypoglycaemia protocol. Although the percentage of people who had a modified Rankin Scale score of 0–4 at 90 days without decompressive craniectomy (primary endpoint) was not significantly different in the glyburide and placebo groups, and mortality was non-significantly reduced overall, functional outcome measured by the modified Rankin Scale was improved in patients treated with the active drug. There was an association with a reduction in midline shift of the brain and lower plasma matrix metalloproteinase-9 concentrations in patients treated with intravenous glyburide compared with placebo.

Implications of all the available evidence

Our findings suggest that the sulfonylurea receptor pathway is implicated in the formation of brain oedema after stroke in patients. Early and continuous intravenous administration of glyburide favourably affects markers of brain oedema and suggests that there might be a clinical effect on mortality and functional outcome at 90 days. These findings need to be replicated in a larger phase 3 trial in patients with large hemispheric infarction.

experimental settings.[10] This evidence suggests that the SUR1–TRPM4 channel is a candidate target for prevention of cerebral oedema after large hemispheric stroke in patients.[8] A phase 2A clinical trial showed the feasibility and safety of administering intravenous glyburide to critically ill stroke patients.[11,12]

The Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP) trial was designed to test the safety and efficacy of intravenous glyburide in a critically ill, acute ischaemic stroke population at high risk for brain swelling.[13] On the basis of the GAMES-Pilot data,[11,12] we hypothesised that intravenous glyburide would safely diminish brain swelling, decrease the need for decompressive craniectomy, and improve clinical outcome.[11,12] An additional objective was to provide information for the design of a phase 3 trial of intravenous glyburide in patients at high risk for developing brain oedema.

Methods

Study design and participants

GAMES-RP was a double-blind randomised, phase 2 trial —done at 18 hospitals in the USA—of intravenous glyburide in patients with a large anterior circulation hemispheric infarction who were at risk to develop malignant oedema. The design of the GAMES-RP trial has been previously reported.[13] The study was done under an Investigational New Drug Application from the US Food and Drug Administration. The study was approved by the institutional review boards at all participating centres. All participants or their legally authorised representatives provided written informed consent at enrolment.

Participants were aged 18–80 years and had a clinical diagnosis of large anterior circulation hemispheric infarction for less than 10 h from the time last known to be neurologically healthy, confirmed by a baseline diffusion weighted image (DWI) lesion volume of 82–300 cm³. The ABC/2 method was used locally to assess the baseline DWI lesion volume for enrolment purposes.[14] Treatment with alteplase was permitted for up to 4·5 h after symptom onset.[15] Participants undergoing endovascular thrombectomy were not eligible, because the efficacy of this process is uncertain in strokes with a baseline DWI lesion volume of more than 70 cm³.[16] The full exclusion criteria are listed in the appendix.

See Online for appendix

Randomisation and masking

Eligible participants were randomly assigned to receive intravenous glyburide or placebo in a 1:1 ratio from a centralised, web-based randomisation algorithm. Patients were screened by clinical teams at each site and enrolled by site study personnel. Minimisation combined with biased coin were used to control for clinical site, age (≤60 years *vs* >60 years), and alteplase treatment. The funder, principal investigators, site investigators, patients, imaging core, and outcomes personnel were masked to treatment. Drug vials, preparation bags, and tubing were identical in appearance for both treatment groups.

Procedures

The bolus and the infusion concentrations of the study drug were both 5·3 µg/mL. A 0·13 mg bolus intravenous injection was given during the first 2 min of treatment. Subsequently, an intravenous infusion was administered