Intravenous Glibenclamide Reduces Lesional Water Uptake in Large Hemispheric Infarction

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Background and Purpose—Prior studies have shown a linear relationship between computed tomography (CT)–derived radiodensity and water uptake, or brain edema, within stroke lesions. To test the hypothesis that intravenous glibenclamide (glyburide; BIIB093) reduces ischemic brain water uptake, we quantified the lesional net water uptake (NWU) on serial CT scans from patients enrolled in the phase 2 GAMES-RP Trial (Glyburide Advantage in Malignant Edema and Stroke).

Methods—This was a post hoc exploratory analysis of the GAMES-RP study. Noncontrast CT scans performed between admission and day 7 (n=264) were analyzed in the GAMES-RP modified intention-to-treat sample. Quantitative change in CT radiodensity (ie, NWU) and midline shift (MLS) was measured. The gray and white matter NWU were also examined separately. Repeated-measures mixed-effects models were used to assess the effect of intravenous glibenclamide on MLS or NWU.

Results—A median of 3 CT scans (interquartile range, 2–4) were performed per patient during the first 7 days after stroke. In a repeated-measures regression model, greater NWU was associated with increased MLS (β=0.23; 95% CI, 0.20–0.26; $P<0.001$). Treatment with intravenous glibenclamide was associated with reduced NWU (β=−2.80; 95% CI, −5.07 to −0.53; $P=0.016$) and reduced MLS (β=−1.50; 95% CI, −2.71 to −0.28; $P=0.016$). Treatment with intravenous glibenclamide reduced both gray and white matter water uptake. In mediation analysis, gray matter NWU (β=0.15; 95% CI, 0.11–0.20; $P<0.001$) contributed to a greater proportion of MLS mass effect, as compared with white matter NWU (β=0.08; 95% CI, 0.03–0.13; $P=0.001$).

Conclusions—In this phase 2 post hoc analysis, intravenous glibenclamide reduced both water accumulation and mass effect after large hemispheric infarction. This study demonstrates NWU is a quantitative and modifiable biomarker of ischemic brain edema accumulation.

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Brain edema after large hemispheric infarction (LHI) is a significant complication after ischemic stroke that can lead to neurological deterioration. Malignant cerebral edema usually manifests 2 to 4 days after stroke onset and correlates with a deteriorating clinical condition reflected by a decreasing level of alertness.[1,2] Although its prevalence among all patients with stroke is 2% to 8%,[1,3] malignant cerebral edema occurs in 32% to 50% of patients with LHI.[4,5] The presumed pathological sequence is a difference in ion gradients due to ion channel dysfunction and disruption of blood-brain barrier permeability that leads to excess water accumulation.[6] In turn, the excess water entry causes lesional swelling and mass effect that impinges on adjacent, intact brain tissue.

Although mass effect can be measured by several methods,[7–9] the most common of which is midline shift (MLS),[10,11] few tools are available to directly measure water content using

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clinically acquired imaging studies. In comparison, quantitative radiodensity measurement of noncontrast head computed tomography (CT) in experimental animals and humans has recently emerged as a tool to estimate water uptake in ischemic stroke lesions,[12–15] which can be derived from clinically acquired CT scans. Several recent studies have shown that quantitative radiodensity measurement is a clinically relevant marker in ischemic stroke lesions, after cardiac arrest, and in pediatric traumatic brain injury.[16–18]

Preclinical studies have shown that SUR1 (sulfonylurea receptor 1)-regulated ion channels participate in the formation of ionic and vasogenic edema after stroke.[19,20] Inhibition of SUR1 by intravenous glibenclamide (also known as intravenous glyburide) prevents brain water accumulation and reduces mass effect in animal models of stroke.[19] In the current study, we sought to determine whether water uptake can be modified by an investigational treatment in patients, thereby highlighting water uptake as a potential intermediate end point for clinical studies of edema. We studied patients enrolled in the GAMES-RP Trial (Glyburide Advantage in Malignant Edema and Stroke)[5] (NCT01794182; https://www.clinicaltrials.gov), comparing net water uptake (NWU) on serial CT scans in placebo-treated subjects to patients treated with intravenous glibenclamide.

The purpose of this study was to provide additional insight into the mechanism of action of intravenous glibenclamide on neuroimaging markers of brain edema. We first sought to define the time course and dynamics of water uptake and mass effect and to determine whether the initial water uptake values can predict subsequent malignant cerebral edema. Finally, we sought to address whether intravenous glibenclamide alters the trajectory of brain edema formation over time. We hypothesized that edema formation would rapidly accumulate and then plateau, and that SUR1 inhibition would demonstrate a decrease of edema formation.

Methods

Patient Characteristics

This study was a post hoc analysis of patients who were enrolled in the GAMES-RP Trial.[5,21] The GAMES-RP Trial was done under an Investigational New Drug Application from the US Food and Drug Administration and was approved by the institutional review boards at all participating centers. All participants or their legally authorized representatives provided written informed consent at enrollment. The data that support the findings of this study are available from the corresponding author on reasonable request.

All subjects had a clinical diagnosis of anterior circulation LHI and were randomized to intravenous glibenclamide or placebo. Intravenous tissue-type plasminogen activator was permitted, but endovascular thrombectomy was an exclusion criterion based on the original trial design. Intravenous glibenclamide was given as a 0.13-mg bolus intravenous injection for the first 2 minutes, followed by an infusion of 0.16 mg/h for the first 6 hours and then 0.11 mg/h for the remaining 66 hours. Of the 86 patients randomized, 3 did not receive any drug treatment. Of the remaining 83 subjects (the modified intention-to-treat sample), 2 did not have available CT scans, resulting in a cohort of 81 for the current study.

Demographic data, medical history, and stroke characteristics were all collected as part of the original trial and were obtained from the master trial dataset. All CT scans obtained as part of clinical care at any timepoint within the first 7 days of hospitalization were stored by the neuroimaging core and analyzed (n=323). We excluded CT scans with incomplete files (n=9), motion artifact (n=6), parenchymal hemorrhagic transformation type 1 (n=4), and CT scans obtained after decompressive craniectomy (n=40). All patients who underwent decompressive craniectomy had at least 1 CT scan before surgical decompression. A total of 264 CT scans from 81 patients were included in this analysis. For MLS measurements, we performed a sensitivity analysis that also included the MLS results from the day 4 magnetic resonance imaging. Imputed magnetic resonance imaging MLS values due to early withdrawal of care (n=11) or those obtained after decompressive craniectomy (n=20) were excluded from sensitivity analysis, for a total of 314 MLS values.

Neurological Deterioration and Malignant Cerebral Edema

We used the definition of neurological deterioration that was specified in the original trial protocol.[5,22] Patients with neurological deterioration were determined by participating site investigators, based on meeting at least one of the following criteria: (1) an increase of ≥1 on National Institutes of Health Stroke Scale (NIHSS) subscore 1a, (2) a less brisk response to pain, (3) a new pupillary abnormality, or (4) an increase of ≥4 on the total NIHSS score.

The designation of malignant cerebral edema was determined centrally by a blinded adjudication committee. All relevant patient-level trial data was available to the adjudication committee for review, including serial CT and magnetic resonance imaging, serial NIHSS scores, and free text descriptions of any serious adverse events that included clinically significant changes. Malignant edema was determined using a prespecified definition, which was a clinical sign of large middle cerebral artery infarction with an NIHSS score >18, a level of consciousness of ≥1 on item 1a of the NIHSS, a large space-occupying middle cerebral artery infarction on day 3 to 4 follow-up magnetic resonance imaging or CT with compression of ventricles or MLS, and no other obvious cause for neurological deterioration.[23]

Imaging Analysis

MLS was measured at the level of maximal lateral displacement of the septum pellucidum, using standard approaches.[24] The CT-derived water uptake ratio (NWU) was measured in 13 prespecified regions of interest (ROIs) encompassing both gray and white matter regions. These included 10 ROIs corresponding to the Alberta Stroke Program Early CT Score regions. Because these anatomic areas are predominantly gray matter,[25] we added 3 additional ROIs in the white matter of the corona radiata at the same supraganglionic level as the M4, M5, and M6 areas.

Only ROIs involved in the ischemic brain lesion were recorded and then compared with the corresponding mirrored ROIs on the contralateral hemisphere. The NWU ratio, NWU, was then calculated using the mean Hounsfield units of these ROIs based on the approach from Broocks et al,[12,13] using the following equation:

$$Percent\,NWU = \frac{HUc - HUi}{HUc} \times 100$$

HUi: mean Hounsfield units of affected ROIs ischemic hemisphere.

HUc: mean Hounsfield units of corresponding ROIs in contralateral hemisphere.

The gray matter NWU and white matter NWU were also derived from corresponding affected ROIs and calculated in the same manner.

The estimated volume of gray and white matter within the stroke lesion was calculated on the baseline magnetic resonance imaging. Diffusion-weighted imaging scans of adequate technical quality (n=59) were registered into Montreal Neurological Institute space using FSL 6.0 (Wellcome Centre for Integrative Neuroimaging). The ROI for the stroke lesion was then segmented into gray and white matter using a 50% gray matter tissue probabilistic map. The volume of gray and white matter was then expressed as a percentage of the total stroke volume. Lateral ventricular volume was measured

on the side ipsilateral to the infarction by using a semiautomated thresholding technique with manual supervision, using AnalyzePro (AnalyzeDirect).

Statistics

Demographic data were expressed as number (percentage), mean±SD, or median and interquartile range (IQR), as appropriate. We performed repeated-measures, multilevel, mixed-effects linear regression analyses for NWU in the overall infarct area, in gray matter, in white matter, and for MLS. In these analyses, time was included as a covariate and modeled using logarithmic terms to reflect the hypothesized plateau in water uptake and mass effect over time. The statistical analyses were performed using Stata software, version 15 (StataCorp, College Station, TX). All tests were 2 sided, and a P of ≤0.05 was considered statistically significant.

Results

The study cohort included 81 patients in total, from which we analyzed 134 CT scans from 38 patients treated with placebo and 130 CT scans from 43 patients treated with intravenous glibenclamide. There was a median of 3 CT scans per patient (IQR, 2–4), which were obtained in the first 7 days after stroke. Baseline characteristics of the study cohort are shown in Table 1 and were similar in both intravenous glibenclamide and placebo groups.

Time Course for Edema and Mass Effect

The serial CT scans allowed for modeling the patterns of MLS accumulation and NWU during the critical period of edema development. When MLS (Figure 1A), total NWU (Figure 1B), NWU within the gray matter (Figure 1C), or NWU within the white matter (Figure 1D) were examined over time in the entire cohort, there was a rapid change in the first 12 hours after stroke onset that plateaued between days 3 and 5 (see the online-only Data Supplement). Modeling the accumulation of edema and mass effect as a logarithmic function, the maximum gray matter NWU was 39.5% and the maximum white matter NWU was 29.0%. The time to half-maximal gray matter NWU accumulation was 9.7 hours (95% CI, 9.6–9.9 hours) and the time to half-maximal white matter NWU accumulation was 14.8 hours (95% CI, 14.6–15.0 hours). The time to half-maximal MLS was 14.3 hours (95% CI, 14.3–14.4 hours). We also measured the change in ipsilateral lateral ventricle volume, which is another measure of mass effect, although it is less predictive of clinical outcome.[7] The time to half-maximal ventricular volume change was 9.8 hours (95% CI, 9.7–9.9 hours; see the online-only Data Supplement). We next confirmed the relationship between edema and mass effect; we found that total NWU and MLS were tightly correlated (Figure 2). Accordingly, repeated-measures mixed-effects linear regression revealed an association between overall NWU and MLS (β=0.23; 95% CI, 0.20–0.26; P<0.001). Gray matter NWU was associated with MLS (gray NWU β=0.15; 95% CI, 0.11–0.20; P<0.001) as was white matter NWU but to a lesser extent (white NWU β=0.08; 95% CI, 0.03–0.13; P=0.001). As a percentage of the total stroke lesion, gray matter accounted for 67.8±9% of the stroke volume in the placebo arm and 63.4±14% in the glibenclamide arm (P=0.41).

Table 1. Clinical Characteristics of the Cohort

	Glibenclamide (n=43)	Placebo (n=38)	*P* Value
Age, y	58 (11)	62 (9)	0.045
Women	16 (37%)	10 (26%)	0.30
Ethic origin			
Hispanic	3 (7%)	4 (11%)	0.57
Non-Hispanic	40 (93%)	34 (89%)	
Race			
White	36 (84%)	31 (82%)	0.76
Black	5 (12%)	4 (11%)	
Asian	2 (5%)	2 (5%)	
Medical history			
Ischemic stroke or TIA	6 (14%)	7 (18%)	0.59
Carotid artery disease	6 (14%)	3 (8%)	0.39
Type 2 diabetes mellitus	9 (21%)	8 (21%)	0.99
Hypertension	31 (72%)	25 (66%)	0.54
Hyperlipidemia	25 (58%)	21 (55%)	0.79
Coronary artery disease	8 (19%)	5 (13%)	0.51
Atrial fibrillation	13 (30%)	15 (39%)	0.38
Stroke characteristics			
Cause of stroke			
Large artery atherosclerosis	13 (30%)	11 (29%)	0.46
Cardioaortic embolism	14 (33%)	18 (47%)	
Small artery	1 (2%)	0	
Other	4 (9%)	4 (11%)	
Unknown	11 (26%)	5 (13%)	
Internal carotid artery occlusion	14 (33%)	14 (37%)	0.69
Baseline NIHSS, median (IQR)	20 (16–22)	19 (17–23)	0.59
Baseline DWI lesion volume, cm^3	159 (62)	164 (64)	0.71
IV r-tPA	25 (58%)	24 (63%)	0.65
Number of CT scans, median (IQR)	3 (1–4)	3 (2–4)	0.26
DC status	13 (30%)	9 (24%)	0.51
Symptom onset to study drug bolus, h	8.8 (1.3)	8.9 (1.4)	0.90
Gray matter in infarct lesion, %	63.4 (14)	67.8 (9)	0.41

CT indicates computed tomography; DC, decompressive craniectomy; DWI, diffusion-weighted imaging; IQR, interquartile range; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; r-tPA, recombinant tissue-type plasminogen activator; and TIA, transient ischemic attack.

Temporal Relationships to Clinical Deterioration

Among subjects who had a baseline CT scan (n=59), baseline NWU was higher in those who later developed malignant edema (n=28; median NWU, 8.8% [IQR, 6.2%–12.4%]) compared with those patients who did not (n=31; median, 5.8% [IQR, 2.4%–8.3%]; P=0.012). In contrast, MLS on the baseline CT scan did not differ between those who did and did not later develop malignant edema (median, 1.0 [IQR, 0.0–2.4]

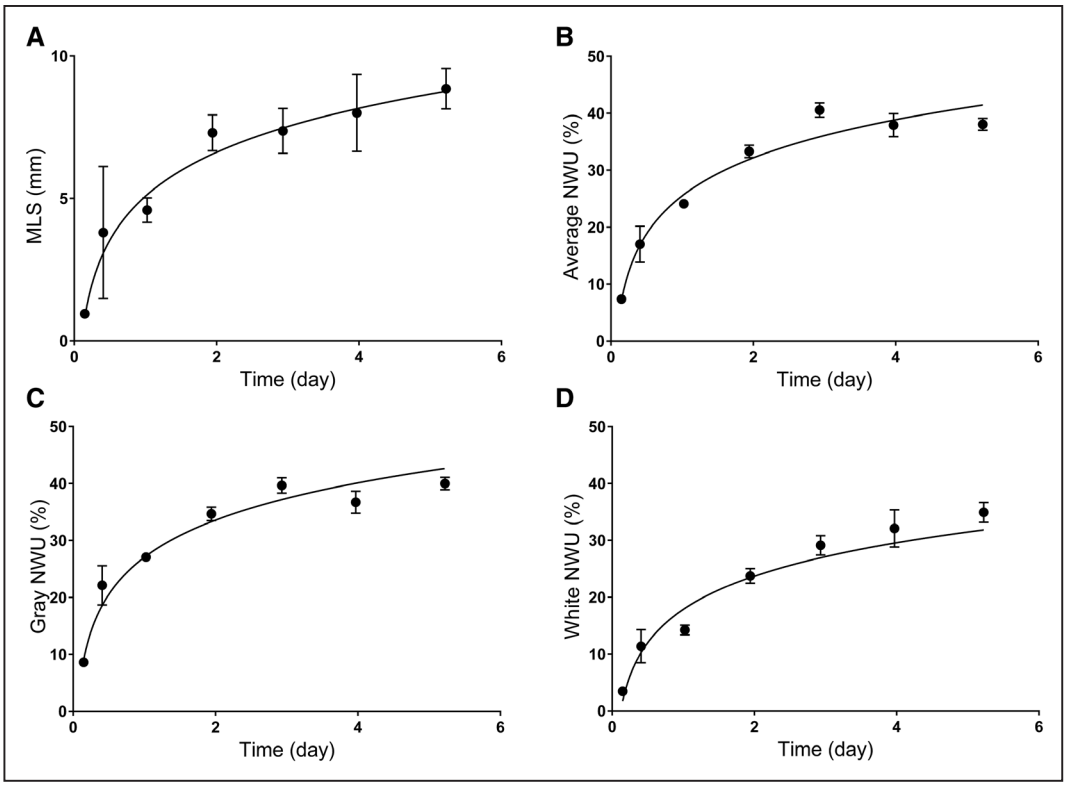

Figure 1. Edema and mass effect accumulate rapidly after large hemispheric infarction. The amount of midline shift (MLS) accumulation over time is shown in **A**. The net water uptake (NWU) is shown in **B**, and separately, the gray matter and white matter water uptake are shown in **C** and **D**, respectively.

versus 0.0 [IQR, 0.0–1.3] mm; *P*=0.08). In multivariable logistic regression, baseline NWU independently predicted malignant edema (OR, 1.16; 95% CI, 1.03–1.32; *P*=0.015) after adjustment for baseline MLS.

We next examined the association between NWU and MLS accumulation over time and malignant cerebral edema. In a repeated-measures, mixed-effects model, NWU and MLS over time were each associated with malignant edema (NWU β=2.87; 95% CI, 0.56–5.17; *P*=0.015; and MLS β=2.81; 95% CI, 1.65–3.96; *P*<0.001). However, in a multivariable model including both imaging markers, only MLS over time was an independent predictor of malignant edema (MLS β=0.49; 95% CI, 0.25–0.73; *P*<0.001; and NWU β=1.48; 95% CI, −0.85 to 3.82; *P*=0.213).

Effect of Intravenous Glibenclamide on Edema and Mass Effect

We next evaluated the effect of intravenous glibenclamide treatment on MLS and NWU (Table 2). In the original trial study results, intravenous glibenclamide reduced MLS in cross-sectional analysis at 4 days after stroke onset.[5] Accordingly, when analyzed over time, patients treated with intravenous glibenclamide had a similar reduction in MLS (Figure 3A; n=264; β=−1.50; 95% CI, −2.71 to −0.28; *P*=0.016). When the day 4 MR-derived MLS measurement was included together with the CT-derived measurements, this result was further strengthened (n=314; β=−1.72; 95% CI, −2.99 to −0.46; *P*=0.008). When examining NWU, intravenous glibenclamide treatment also led to reduced NWU accumulation over time (Figure 3B; β=−2.80; 95% CI, −5.07 to −0.53; *P*=0.016). There was a similar decrease in water uptake in both gray matter NWU (Figure 3C; β=−3.02; 95% CI, −5.04 to −0.99; *P*=0.003) and white matter NWU (Figure 3D; β=−3.59; 95% CI, −6.17 to −1.02; *P*=0.006). Including age in the models for MLS and NWU did not change the independent effect of glibenclamide treatment on edema.

To further evaluate the relationships between intravenous glibenclamide treatment, NWU, and MLS, we conducted mediation analysis (Table 3). Total NWU was a mediator of the effect of intravenous glibenclamide on MLS (24% mediation, Sobel *P*=0.029). Examination of gray and white matter NWU separately revealed that each contributed to this effect (21.3%

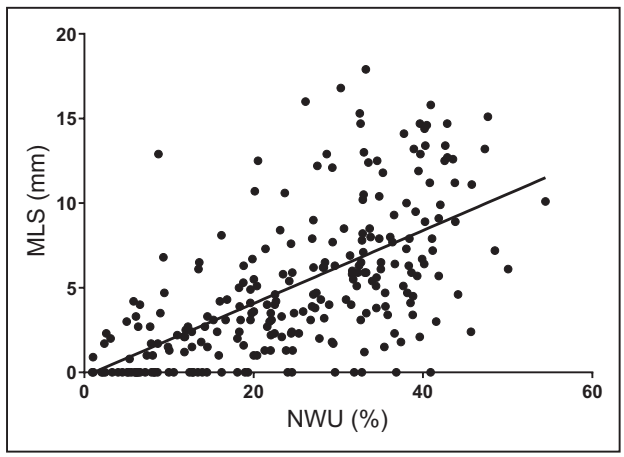

Figure 2. Net water uptake (NWU) and mass effect are correlated. The correlation coefficient between midline shift (MLS) and NWU was r=0.636, *P*<0.0001.

Table 2. Effect of Glibenclamide on Each Edema Imaging Parameter

Parameters	β-Coefficient	95% CI	*P* Value
MLS on CTs (n=264)	−1.50	−2.71 to −0.28	0.016*
MLS on CTs and MLS on day 4 MRI (n=314)	−1.72	−2.99 to −0.46	0.008*
Overall NWU	−2.80	−5.07 to −0.53	0.016*
Gray matter NWU	−3.02	−5.04 to −0.99	0.003*
White matter NWU	−3.59	−6.17 to −1.02	0.006*

CT indicates computed tomography; MLS, midline shift; MRI, magnetic resonance imaging; and NWU, net water uptake.

*$P<0.05$.

mediation, Sobel $P=0.016$ and 21.3% mediation, Sobel $P=0.028$, respectively).

Discussion

This study has 3 principal findings. First, we found that edema accumulated most rapidly in the first 12 hours after stroke. Although the initial NWU value on baseline CT is associated with future clinical deterioration, MLS drives that association thereafter. Second, our observations suggest that early blockade of SUR1 with intravenous glibenclamide reduced brain water accumulation (eg, edema or NWU) and also mass effect (MLS). Finally, through mediation analysis, we found that NWU mediates the effect of intravenous glibenclamide on MLS. Taken together, these data support the hypothesis that water accumulation leads to mass effect and imply that the main determinant of clinical deterioration is tissue displacement.

We found a rapid influx of water into the infarct lesion within the first 12 hours after stroke onset, with a faster accumulation in gray matter than white matter. Furthermore, this water accumulation appears to precede the development of MLS. Similar patterns of rapid, early brain edema accumulation have been shown in rhesus monkey,[26] rats,[15] and in patients with stroke within 4.5 hours of stroke onset.[18] We are not aware of other human studies demonstrating that gray matter edema appears to accumulate more quickly than white matter edema. Edema continued to increase more gradually thereafter, reaching a plateau by about day 4. This time course parallels the known alteration in level of consciousness of malignant cerebral edema that develops within the first 24 to 48 hours after LHI.[27]

Our findings also support a sequential model of early water accumulation that leads to mass effect, followed by clinical deterioration. Interestingly, early NWU was a predictor of future malignant edema, but after the initial baseline scan, MLS was more strongly associated thereafter. This supports the model that mass effect is the main driver of clinical deterioration. These observations are also concordant with a recent study that demonstrated the correlation between water content and MLS in hemispheric stroke rat model.[28] Similarly, our study also showed a significant correlation between MLS and water accumulation in ischemic tissue of patients with stroke. Therefore, both NWU and MLS are complementary quantitative end points that reflect brain edema and predict clinical outcomes.

We also found that NWU was modifiable by intravenous glibenclamide treatment. Given that this compound has been

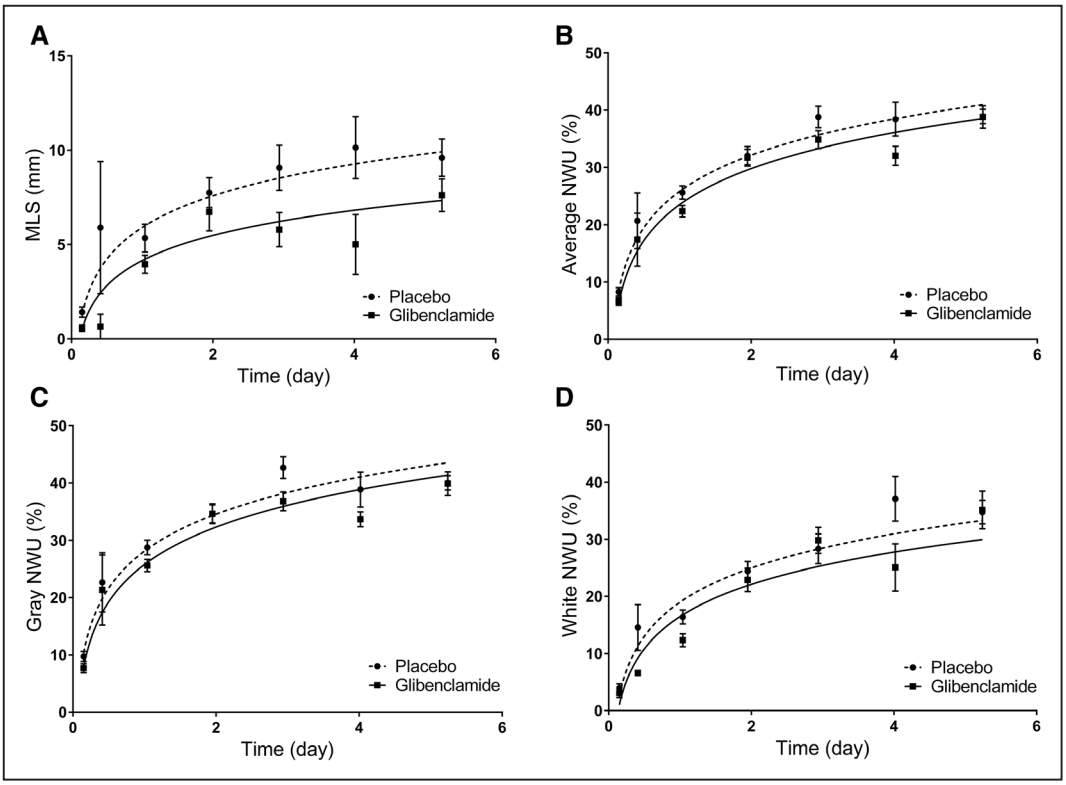

Figure 3. Intravenous (IV) glibenclamide reduces net water uptake (NWU) and midline shift (MLS) over time. **A**, Treatment with IV glibenclamide reduced the amount of MLS over time, reflected by the downward shift in the curve ($P=0.016$). **B**, IV glibenclamide also reduced average NWU ($P=0.016$), (**C**) gray matter NWU ($P=0.003$), and (**D**) white matter NWU, $P=0.006$.

Table 3. Mediation Analysis: Effect of Glibenclamide on Midline Shift

Parameters	β-Coefficient Before Mediation Analysis	β-Coefficient After Mediation Analysis	Percentage Change in β-Coefficient	Sobel Test, *P* Value
Overall NWU	–1.50	–1.14	24%	0.029*
Gray matter NWU	–1.50	–1.18	21.33%	0.016*
White matter NWU	–1.50	–1.18	21.33%	0.028*

NWU indicates net water uptake.
*$P<0.05$.

shown to prevent water content directly in rodent stroke studies,[19,29] our analysis suggests a concordant effect between human and animal studies. Furthermore, our study suggests that intravenous glibenclamide reduced water accumulation in both gray and white matter, resulting in decreased MLS. While intravenous glibenclamide appeared to reduce NWU to a greater extent in white matter consistent with preclinical data,[29] gray matter, which occupies about two-thirds of hemisphere, was a greater mediator of MLS.[30] In accord, a primate study of middle cerebral artery stroke showed greater absorption of water in gray matter compared with white matter.[31]

Our study has limitations. It is a post hoc analysis of randomized trial and thus hypothesis generating, and the results with respect to glibenclamide require further confirmation in a prospective study. This study was not able to provide insight into the effect of glibenclamide in the setting of endovascular thrombectomy, which has an independent effect on edema formation.[32,33] Analysis of CT scans was also limited by the beam-hardening artifact, which can occur in some patients, as this might affect the NWU measurement. Similarly, hemorrhagic transformation can alter the CT radiodensity. However, we minimized the potential effects of these confounding factors by using the contralateral hemisphere to normalize values, and we avoided placing the ROIs in regions of hemorrhagic transformation or beam-hardening artifact.

Our study highlights the potential value of NWU as an intermediate biomarker for brain edema and its relationship to MLS and subsequent clinical deterioration. Modification by an investigational compound, intravenous glibenclamide, provides additional evidence for the utility of NWU as a relevant biomarker. Early administration of intravenous glibenclamide may also be more effective in patients with LHI. Ongoing study of intravenous glibenclamide in patients with LHI may provide definitive evidence for the role of edema modification as a clinically relevant therapeutic target.

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Disclosures

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