Short Communication

Neurochemical Monitoring of Glycerol Therapy in Patients With Ischemic Brain Edema

Christian Berger, MD; Oliver W. Sakowitz, MD; Karl L. Kiening, MD; Stefan Schwab, MD

Background and Purpose—Osmotic agents such as glycerol are used to treat brain edema in stroke patients. We investigated the pharmacokinetics of glycerol in brain tissue by cerebral microdialysis.

Methods—Patients experiencing large middle cerebral artery infarction were included in this prospective study. The following variables were assessed before and every 10 minutes until 80 minutes after intravenous administration of 25 g of glycerol: intracranial pressure (ICP), serum osmolarity, and cerebral microdialysate concentrations of glycerol, glutamate, pyruvate, and lactate.

Results—During 16 ICP crises in 7 patients, cerebral glycerol concentrations (baseline 73.9±17.0 μmol/L) increased immediately after glycerol administration by up to 350%. Conversely, ICP (baseline 25±2.4 mm Hg) rapidly decreased by almost 50%. Both effects lasted for 70 minutes. Serum osmolarity (baseline 305±5.6 mOsm/L) was only briefly raised, whereas glutamate, lactate, and pyruvate remained unaffected.

Conclusion—Treatment of stroke patients with intravenous glycerol has only a brief effect on plasma osmolarity, but a more sustained effect on ICP, which is, however, accompanied by a rapid glycerol accumulation in brain tissue. (Stroke. 2005;36:e4–e6.)

Key Words: brain edema ■ infarction ■ intracranial pressure ■ middle cerebral artery

Osmotic agents are used in acute cerebral ischemia to treat brain edema, particularly in space-occupying stroke where the mass effect may cause further clinical deterioration. Other than mannitol, glycerol is commonly used to treat increased intracranial pressure (ICP). However, a potential rebound effect with increasing ICP following glycerol administration may restrict its use in treating brain edema.

We studied the pharmacokinetics of glycerol in brain tissue using cerebral microdialysis in patients requiring ICP treatment with intravenous glycerol. Additionally, we investigated potential effects of glycerol therapy on glutamate, lactate, and pyruvate concentration in cerebral microdialysate.

Patients and Methods

From October 2003 to April 2004, 7 consecutive patients with 16 episodes of increased intracranial (ICP) crises and space-occupying middle cerebral artery infarction were included in this study. Neuromonitoring through an ipsilateral frontal bolt catheter consisted of cerebral microdialysis (CMA/70 custom probe, CMA/Microdialysis; perfusion velocity 2 μL/min) and of ICP measurements (Codmann, Johnson & Johnson) in nonischemic tissue adjacent to the infarct as confirmed by follow-up cranial computed tomography.

We administered glycerol if standard therapy with 15 g mannitol had only insufficient effects and either spontaneous ICP increase >20 mm Hg persisted >10 minutes or pupillary functions were disturbed. Then 25 g of glycerol (250 mL 10% Glycerosteril, Fresenius Kabi) were infused through a central venous catheter over 15 minutes. The following variables were assessed before and every 10 minutes until 80 minutes after drug application: ICP and serum osmolarity and microdialysate concentrations of glycerol, glutamate, pyruvate, and lactate, which were analyzed enzyme-photometrically (CMA 600 Autoanalyser). To account for varying baseline values of glycerol, ICP, and osmolarity, we calculated relative changes at all subsequent time points.

We used the Wilcoxon signed rank test to detect differences between each time point and baseline values. Statistical analyses were performed with StatView statistical software. A P<0.05 was considered statistically significant. Data are presented as mean±SEM.

Results

A total of 16 episodes with ICP crises in 7 patients (3 female, 4 male) experiencing large middle cerebral artery infarction were included in this study. Their mean age was 51.7 with a range between 35 and 65 years.

Cerebral glycerol concentrations rose immediately after intravenous glycerol administration from 73.9±17.0 μmol/L by a maximum of 350% within 20 minutes. Subsequently, glycerol decreased gradually to a nonsignificantly different level at 60 minutes after the infusion had ended. Conversely, ICP (baseline 25±2.4 mm Hg) rapidly decreased by almost 50% and remained significantly lower for 50 minutes with a short rebound at 40 minutes. In contrast, serum osmolarity (baseline 305±5.6 mOsm/L) increased only briefly by ≈3% (Figure 1).
Microdialysate concentrations for glutamate, pyruvate, and lactate were within normal ranges and remained unchanged during the measurements (Figure 2) as did blood gases, hemoglobin, hematocrit, pH, electrolytes, and mean arterial blood pressure (Table). No hemolysis or electrolyte disturbances were noted.

**Discussion**

Intravenous glycerol reduces ICP promptly and significantly for up to 60 minutes without large and long-lasting effects on serum osmolarity. Instead, glycerol rapidly accumulates in brain tissue until 20 minutes after the infusion, before it subsequently decreases gradually and almost linearly to previous concentrations.

These results suggest that glycerol readily moves across the blood brain barrier into the brain. This was confirmed in a study using glycerol as enema for paralytic ileus in brain-injured patients, though after oral administration the peak concentration occurred 3 to 5 hours later. In CSF, rapid glycerol accumulation after intravenous infusion preceded a temporary reversal of the serum/cerebral spinal fluid concentration gradient during glycerol elimination. This reversal may be the cause of a rebound effect that describes an increase in ICP after repeated administration of an osmotic agent. The brief ICP rebound at 40 minutes in our series may be indicative of this effect.

No changes in cerebral glutamate, lactate, and pyruvate concentrations occurred after glycerol administration, which may argue for a pharmacological rather than ischemic effect. The latter would have been accompanied by an increase in pyruvate concentration in ischemic brain tissue. Potentially, the implantation of microdialysis probes altered the blood brain barrier, which may have alleviated the permeation of a hyperosmotic solution into brain tissue. However, animal experiments suggest that glycerol readily enters even intact brain tissue.

Other than a potential adverse rebound effect, glycerol may also be beneficial for ischemic brain tissue: first, by offering an alternative source of energy for neuronal tissue which can metabolize glycerol if glucose is lacking; second, by redistribution of cerebral blood flow with increase in regional cerebral blood flow and regional cerebral blood volume in ischemic brain secondary to reduction in focal cerebral edema, though no reduction of healthy brain volume was observed in MRI studies; and third, glycerol may modulate the leukocyte-endothelium interaction by preventing leukocytes from interfering with the blood cell and plasma flow, thus improving cerebral blood flow.

In conclusion, glycerol can reduce ICP in stroke patients though its main mechanism does not consist of creating a sustained osmotic gradient. Instead, glycerol accumulates in brain tissue with potential rebound effects on ICP if frequently administered. Therefore, its general use in stroke therapy with a lack of evidence of benefit in long term survival cannot be recommended.

**Acknowledgments**

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**Physiological and Laboratory Results Before and After Glycerol Infusion**

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<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At 15 Minutes After Glycerol Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>97 ± 3</td>
<td>103 ± 5</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>67 ± 4</td>
<td>82 ± 6</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>101 ± 15</td>
<td>105 ± 12</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>41 ± 3</td>
<td>42 ± 1</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.4 ± 1.7</td>
<td>12.1 ± 1.5</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>34 ± 4</td>
<td>34 ± 3</td>
</tr>
<tr>
<td>pH</td>
<td>7.396 ± 0.021</td>
<td>7.401 ± 0.034</td>
</tr>
<tr>
<td>Na+, mmol/L</td>
<td>139 ± 4</td>
<td>141 ± 4</td>
</tr>
<tr>
<td>K+, mmol/L</td>
<td>4.1 ± 0.3</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>Cl–, mmol/L</td>
<td>117 ± 6</td>
<td>115 ± 3</td>
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MAP indicates mean arterial blood pressure; CPP, cerebral perfusion pressure.
References

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