Action of Magnesium Sulfate in the Treatment of Preeclampsia-Eclampsia

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Recent evidence supports the concept that cerebral vasospasm is involved in the pathogenesis of eclampsia. Magnesium, which has a beneficial effect in eclampsia, may act by opposing calcium-dependent arterial constriction, thereby relieving vasospasm. Magnesium may also antagonize the increase in intracellular calcium concentration caused by ischemia and thus prevent cell damage and death. Magnesium might have a role in the treatment of cerebral vasospasm and ischemia, such as occurs in subarachnoid hemorrhage, ischemic stroke, and brain trauma. (Stroke 1989;20:1273-1275)

Magnesium sulfate has been advocated for treating toxemia of pregnancy since 1925,1-2 and despite controversy surrounding its mode of action, is still considered, especially in the US, to be the drug of choice for the control and prevention of eclamptic convulsions. A suggestion that magnesium sulfate controls convulsions by blocking peripheral neuromuscular transmission was based on animal studies by Hilmy and Somjen,3 in which raised serum magnesium levels caused skeletal muscle paralysis but failed to cause anesthesia in humans.4 The authors concluded that the brain is protected from hypermagnesemia by a barrier mechanism. However, many clinical studies and widely accumulated experiences have since shown that the antieclamptic effect is attained at serum levels of magnesium below those depressing neuromuscular transmission.5 Borges and Gucer6 found magnesium sulfate to be effective in suppressing topical penicillin-induced epileptic activity in animals at serum levels similar to those reported to control seizures in eclamptic patients. However, the relevance of the experimental technique of these authors to eclampsia is uncertain. Donaldson7 suggested that eclampsia is a hypertensive encephalopathy and argued against the use of magnesium in eclampsia because it is not an antihypertensive agent. However, eclampsia may be seen with blood pressure below the range that produces encephalopathy. Sibai et al8 found no correlation between blood pressure and electroencephalographic (EEG) abnormality in preeclampsia-eclamptic patients or between the percentage rise in mean arterial blood pressure from the last prenatal visit to the time of EEG recording and EEG changes. These findings do not suggest any direct relation between the degree of hypertension and eclamptic convulsions.

Evidence of Cerebral Vasospasm

Sheehan and Lynch9 described the cerebral pathologic findings in eclampsia, including cortical petechial hemorrhages; multiple, widespread, small necrotic areas; small periventricular hemorrhages; or large hemorrhages in the white matter, basal ganglia, and pons. The authors suggested that these changes resulted from periods of vasoconstriction inducing focal necrosis and hemorrhages. Recent cerebral angiography studies in toxemia have demonstrated severe arterial vasospasm.10-13 Findings in five such patients included widespread diffuse narrowing of all intracranial arteries with poor filling of cortical branches, especially in the parietal and occipital regions, whereas computed tomograms (CT scans) in these patients demonstrated areas of decreased attenuation in the major blood vessels' border zones. In other reports on patients with eclampsia, CT scans showed hypodense areas in the basal ganglia and cortex.14-16 The evidence of cerebral vasospasm agrees with that of systemic vasospasm,17 with increased peripheral vascular resistance and increased sensitivity of the blood vessels to vasoactive substrates such as angiotensin II and catecholamines.

Mechanism of Action of Magnesium on Vasospasm

Zaret19 has suggested that magnesium sulfate given in preeclampsia-eclampsia may prevent vasospasm by acting as a calcium antagonist. Mg2+ is a bivalent ion resembling Ca2+ and is therefore a competitive antagonist of the latter. The blockade of neuromuscu-
lary synapses and consequent skeletal muscle paralysis in hypermagnesemia is due to magnesium's competition with calcium in the presynaptic membrane and hence inhibition of acetylcholine-Ca$^{2+}$-dependent release. This effect may be corrected by increasing Ca$^{2+}$ concentration at the synapse, with calcium glutamate injection recommended as an antidote to magnesium intoxication.\(^{20}\)

Ca$^{2+}$ and Mg$^{2+}$ also have opposite effects on vascular tone. Ca$^{2+}$ plays an essential role in regulating blood vessel caliber or resistance, even in the absence of neurohumeral substances.\(^{21}\) Increased Ca$^{2+}$ concentration has been shown to induce vasospasm in isolated cerebral arteries; vasospasm is amplified by lowering Mg$^{2+}$ concentration and alleviated by increasing it.\(^{22}\) Hypomagnesemia causes increased cerebral vascular tension, whereas hypermagnesemia reverses vasospasm induced by hallucinogens, alcohol, serotonin, and potassium chloride.\(^{22}\) Calcium channel blocking agents have a potent dilating effect on cerebral blood vessels\(^{23}\) and have been used to treat vasospasm in subarachnoid hemorrhage.\(^{24}\)

The pathogenesis of cerebral vasospasm in eclampsia is unknown. It is assumed, however, that Ca$^{2+}$ is involved by its activation of smooth muscle contraction, the final common pathway in the mechanism of vasoconstriction of various causes. As is the case with nimodipine,\(^{24}\) the transient minor effect of magnesium sulfate treatment on blood pressure, as opposed to its persistent cerebral effect, may be explained by differential sensitivity of cerebral and systemic arteries to calcium blocking. Altura and Altura\(^{22}\) concluded that this was consistent with levels of free Mg$^{2+}$ in the cerebrospinal fluid that were threefold that in plasma and with the almost-double content of Mg$^{2+}$ in the walls of cerebral arteries compared with systemic arteries.

**Antagonism of Intracellular Calcium**

The increased intracellular Ca$^{2+}$ concentrations induced by cerebral ischemia with consequent cell damage and cell death has recently received scientific attention.\(^{25-28}\) Ischemia leads to increased Ca$^{2+}$ concentration by lowering the transmembrane potential and opening calcium channels and by releasing Ca$^{2+}$ from mitochondria and the endoplasmic reticulum. Increased levels of Ca$^{2+}$ activate phospholipases that hydrolyze membrane phospholipids.\(^{29}\) This membrane damage increases calcium influx and induces a positive feedback mechanism by which ischemia produces high cellular Ca$^{2+}$ levels.\(^{30}\) A high Ca$^{2+}$ concentration poisons mitochondrial oxidative phosphorylation. Activation of calcium-dependent processes and increased load on the Na$^{+}$-K$^{+}$ pump uses large amounts of adenosine triphosphate (ATP), which, together with decreased ATP production, leads to depletion of ATP reserves and eventually to irreversible cell damage.\(^{28,30}\)

One route of calcium influx during ischemia is through the ion channels linked to the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor.\(^{21}\) An increased Mg$^{2+}$ concentration has blocking effects on inward current flow through these channels.\(^{32,33}\) Goldman and Finkbeiner\(^{24}\) have recently suggested that a large part of the magnesium sulfate effect in eclampsia may be exerted by blocking NMDA receptors, especially since their involvement in epileptiform bursting has been demonstrated.\(^{35}\)

Calcium channel blocking agents have been used to overcome ischemic damage in animals\(^{36}\) and in humans.\(^{37}\) However, these agents have no direct effect on intracellular calcium release and only a limited effect on calcium channels and calcium influx in damaged membranes. It is tempting to speculate that Mg$^{2+}$ competes with Ca$^{2+}$ on intracellular sites, antagonizes the intracellular calcium effect, and prevents or reverses the positive feedback pathways described above. Magnesium sulfate could in this way prove superior to calcium channel blockers because its action would be mediated by more than membrane receptors and might be effective even with membrane dysfunction. This view is supported by the prevention of death in cultured hippocampal neurons due to exposure to an anoxic atmosphere by treatment with magnesium\(^{38}\) and to the protective effect of magnesium against irreversible cell damage in an experimental model of central nervous system ischemia.\(^{39}\)

**Clinical Implications**

Recently, magnesium infusion has been demonstrated to reduce mortality rates when given immediately on admission to patients with acute myocardial infarction.\(^{40}\) Although the authors ascribed this result to a decrease in the number of arrhythmias requiring treatment, the main cause of death in the untreated group was cardiogenic shock, which did not occur in the magnesium-treated group. These results may therefore also be explained by reduced coronary artery spasm and myocardial necrosis due to the dual effect of magnesium treatment on spasm and cell death.

If the basic assumptions of these theories are correct, then magnesium sulfate may be helpful in treating other disorders associated with cerebral vasospasm and ischemia. A notable example is subarachnoid hemorrhage, in which vasospasm is a serious and even lethal complication despite some beneficial effect of calcium channel blocker treatment.\(^{24}\) Other possible applications are in ischemic strokes\(^{37}\) and severe head trauma, in which areas of ischemic injury are a common finding at autopsy,\(^{41}\) and have already lead to a trial of calcium channel blocking agents.\(^{42}\)

**References**


**Key Words** • calcium • cerebral vasospasm • eclampsia • magnesium sulfate
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Stroke. 1989;20:1273-1275
doi: 10.1161/01.STR.20.9.1273

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