# Safety, Tolerability, and Efficacy of a Glucose-Insulin-Potassium-Magnesium-Carnitine Solution in Acute Myocardial Infarction

Michael A. Arsenian, MD, Peter S. New, MD, and Cynthia M. Cafasso, RPH

Major strides in the management of acute myocardial infarction (AMI) have occurred over the past quarter century; however, the possibility of favorably manipulating myocardial metabolism during ischemia has been virtually ignored. Glucose-insulin-potassium (GIK) therapy was used to treat AMI in the 1960s with ostensibly favorable results.[1-3] After the 1967 publication of a multicenter trial of 840 patients showing no benefit of GIK in AMI, interest in this form of therapy waned.[4] Small trials from a single center in the 1970s continued to suggest beneficial effects of GIK.[5,6] A recent report of glucose and insulin therapy in 620 diabetic patients with AMI has shown a significant reduction in mortality rates at 1 year.[7] There is a strong theoretical biochemical basis for the use of GIK, as well as experimental data on animals that support its efficacy.[8,9] GIK enhances glycolytic flux and the potential for anaerobic adenosine triphosphate production

From the Addison Gilbert Hospital, Gloucester, Massachusetts. Dr. Arsenian's address is: Cape Ann Medical Center, 2 Blackburn Park, Gloucester, Massachusetts. Manuscript received January 8, 1996; revised manuscript received and accepted March 7, 1996.

**TABLE 1** Concomitant Therapy in 54 Patients Receiving MgCICK

| Form of Therapy | Number of Patients |
|---|---|
| Tissue plasminogen activator | 36 |
| Streptokinase | 8 |
| Aspirin | 52 |
| Nitroglycerin | 30 |
| $\beta$ blockers | 18 |
| Heparin | 46 |

MgGICK = glucose, insulin, potassium, phosphate, magnesium, and carnitine.

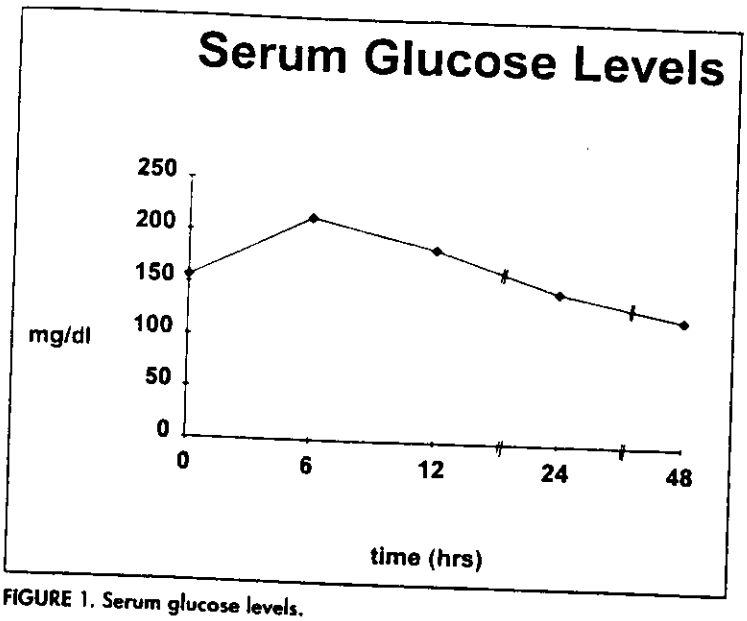


**FIGURE 1. Serum glucose levels.**

while decreasing the generation of toxic free fatty acids and myocardial oxygen demand. This form of therapy warrants reevaluation as the trials that led to abandonment of GIK gave inadequate doses, often orally and belatedly. They also lacked the statistical power to support their conclusions.

Magnesium represents another treatment of AMI for which enthusiasm has lessened based on the results of the International Study of Infarct Survival IV trial, an enormous multicenter study.[10] Although the statistical strength of this trial is conclusive, the disparate results of smaller clinical trials raise questions of methodologic differences.[11-13] Indeed, there is evidence that magnesium attenuates ischemic injury only when administered early in the course of myocardial infarction.[14] Recent editorials have challenged the dismissal of magnesium in the treatment of AMI.[15,16] Mechanisms by which magnesium may attenuate hypoxic injury are multiple.[17] Furthermore, the relation between magnesium and insulin is complex, because magnesium may act as a second messenger for insulin.[18]

Carnitine is an essential cofactor used as a nutritional supplement and in the treatment of carnitine deficiency syndromes. Exogenous carnitine reduces the intracellular accumulation of toxic long-chain fatty acid esters and enhances glucose oxidation in ischemia by reversing inhibition of pyruvate dehydrogenase.[19] In conventional doses, carnitine lacks hemodynamic effect and is devoid of significant toxicity.[20] Small trials have reported beneficial effects with carnitine therapy in myocardial infarction.[21,22]

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We treated 54 nonconsecutive patients with a diagnosis of AMI with a hypertonic solution of glucose, insulin, potassium, phosphate, and magnesium and carnitine (MgGICK) administered by peripheral infusion. The solution consisted of 300 g glucose, 50 U humulin R insulin, 60 mEq potassium chloride, 10 mM potassium phosphate, 18 g magnesium sulfate, and 3 g L-carnitine and sterile water to achieve a volume of 1 L. The solution was infused at 200 ml/hour for 1 hour, 150 ml/hour for the next 2 hours, 100 ml/hour for the next 2 hours, and then 30 ml/hour for 10 hours. Serum potassium, glucose, and magnesium were measured at 6, 12, 24, and 48 hours. Phosphorus and calcium were measured at 24 hours. The infusion was stopped if: heart rate was <40 beats/min, pauses were >3 seconds, serum glucose was >600 mg/dl, potassium was >6 mmol/L, and magnesium was >5 mg/dl. Forty milligrams of furosemide was given intravenously if urine output was <400 ml at 6 hours or if signs of pulmonary congestion developed. Patients were treated with all usual therapy (Table 1). Treatment was started immediately in the emergency department in most cases. Patients were excluded if they had renal failure (serum creatinine >3 mg/dl), were in shock, or had significant hyperkalemia (serum potassium >5.5 mmol/L). Patients were also excluded if they were thought to have a low clinical likelihood of AMI or if they presented at >12 hours from onset of symptoms. While this series is nonconsecutive, it includes 44 consecutive patients receiving thrombolytic therapy. Supplemental insulin was given at the discretion of the attending physician. If the patient complained of pain at the infusion site, the infusion rate was decreased by 50%. If significant pain persisted, the infusion was discontinued. The subgroup receiving thrombolytic therapy was compared with a historical control group made up of the last 50 patients receiving thrombolytic therapy before use of concomitant metabolic therapy. Patients in the historical control group who did not meet the eligibility criteria for metabolic therapy were excluded from analysis.

MgGICK was given by a peripheral intravenous cannula, preferably using the antecubital vein. In 1 of 54 patients the infusion had to be stopped because of pain, and in 2 others the infusion rate had to be decreased. Ten patients required supplemental insulin, and 17 were given intravenous furosemide. Mild hyperglycemia frequently developed. Three patients developed glucose levels >500 mg/dl and 1 had a glucose level <60 mg/dl. Figure 1 shows serum glucose levels. No instances of significant hyperkalemia

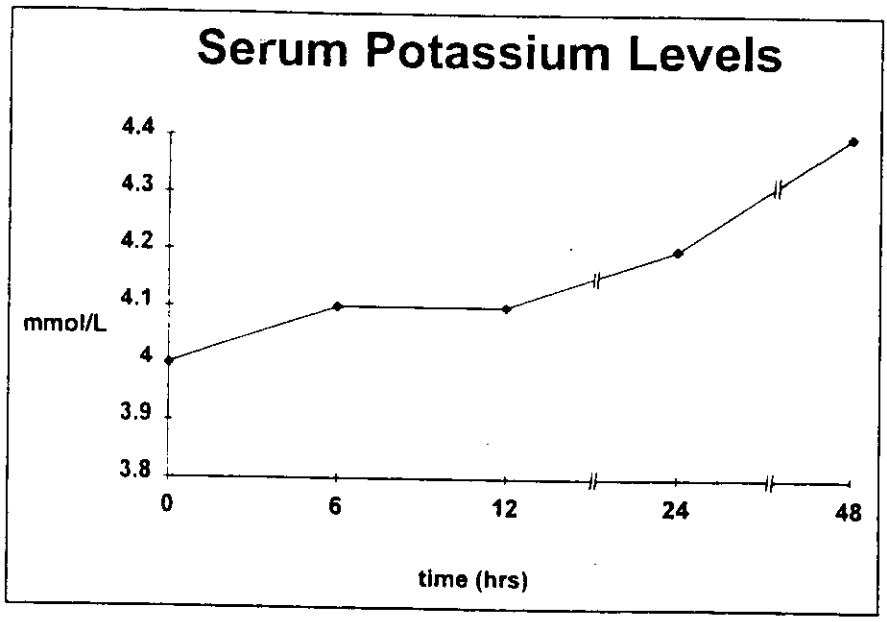


FIGURE 2. Serum potassium levels.

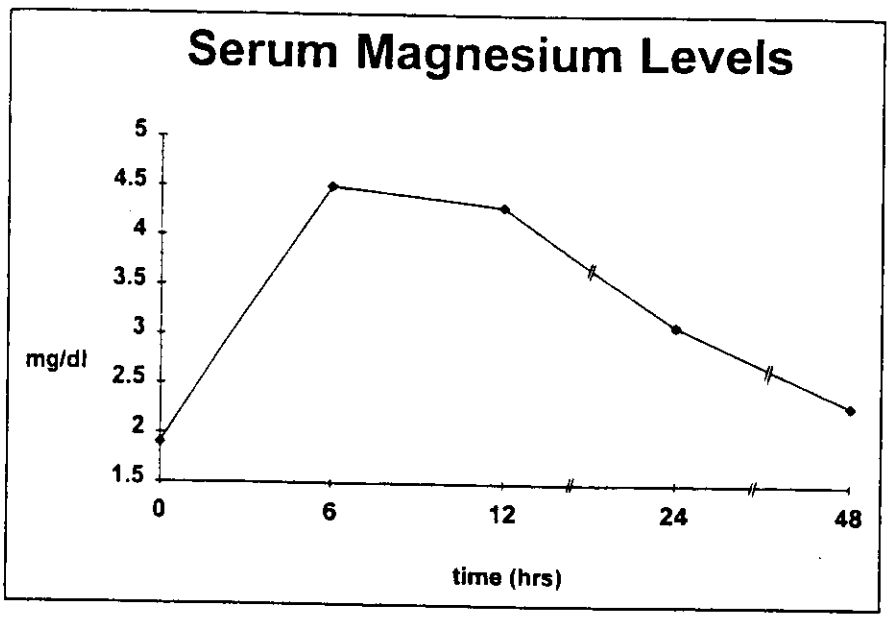


FIGURE 3. Serum magnesium levels.

(serum potassium >6 mmol/L) or hypokalemia (serum potassium <3 mmol/L) were observed (Figure 2). Hypermagnesemia occurred in all patients (Figure 3). Two patients had magnesium levels >6 mg/dl, and 18 had magnesium levels that peaked between 5 and 6 mg/dl. Mild hypocalcemia developed in most patients; however, serum calcium levels <7 mg/dl were not seen. Mean serum calcium fell from 9.4 mg/dl at baseline to 8.5 mg/dl at 24 hours. There were no significant changes in serum phosphorus levels (3.3 mg/dl at baseline and 3 mg/dl at 24 hours). Blood urea nitrogen decreased slightly in most, presumably due to the anabolic effects of insulin. The mean blood urea nitrogen was 17 mg/dl at entry and 14 mg/dl after 24 hours.

Forty-four consecutive patients receiving thrombolytic therapy and meeting the eligibility criteria for metabolic therapy outlined above were treated with MgGICK. These patients were compared with a historical control group as described above. Table II shows the baseline characteristics of the treatment group (MgGICK and thrombolytic therapy) and the

**TABLE II** Baseline Characteristics of Treatment and Control Groups

| | MgGICK | Control |
|---|---|---|
| Number of patients | 44 | 50 |
| Men/women | 33/11 | 39/11 |
| Age >75 yr | 8 | 8 |
| Tissue plasminogen activator/streptokinase | 36/8 | 39/11 |
| Prior myocardial infarction | 7 | 10 |
| Diabetes mellitus | 7 | 10 |
| Preexisting heart failure | 7 | 7 |

Abbreviation as in Table I.

| TABLE III Adverse Outcomes of Therapy | | |
|---|---|---|
| | MgGICK (n = 44) | Control (n = 50) |
| Death | 0 | 4 |
| New heart failure | 2 | 5 |
| Emergency revascularization | 10 | 10 |
| Pacemaker required | 1 | 0 |
| Death or development of heart failure | 2 | 9* |

* $p < 0.05$.
Abbreviation as in Table I.

historical control group (thrombolytic therapy only). Table III shows the incidence of morbid outcomes in these groups. When the incidences of death or development of new congestive heart failure are combined, there is a significant benefit of MgGICK therapy. There were no significant changes in the need for pacemakers or emergency coronary revascularization. Ten patients were treated with MgGICK but did not receive thrombolytic therapy and are not included in this comparison. In this group there were also no in-hospital deaths, and no patients developed heart failure.

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Previous studies with GIK have used central venous infusion and were associated with complications, including hyperkalemia, hyperglycemia, hypoglycemia, and hypophosphatemia.[23,24] All patients in this study received metabolic supplementation via a peripheral intravenous catheter. Despite the hypertonic nature of the solution, it was well tolerated. We observed metabolic/electrolyte abnormalities frequently—chiefly hyperglycemia and hypermagnesemia. These were well tolerated, readily treated, and without significant clinical sequelae. In older studies of GIK in AMI, a higher concentration of potassium was given solely as potassium chloride for a longer period of time. The current protocol was associated with no significant changes in potassium or phosphorus levels. This protocol resulted in a large volume of intravenous fluid in the first few hours; 31% of patients were given intravenous furosemide. We found the early volume loading well tolerated, given the concomitant use of multiple vasodilating drugs (nitroglycerin, $\beta$ blockers, streptokinase). Supplemental insulin was given to 18% of our patients, most of whom had preexisting diabetes. MgGICK therapy was started as early as possible (usually in the emergency department) and continued for 15 hours, although 70% of the solution was given in the first 5 hours. The beneficial effects of MgGICK—if they exist—are probably due to cytoprotection and contingent on early administration either before or with reperfusion therapy. This form of treatment is safe, inexpensive, well tolerated, and worthy of further study.

**Fifty-four patients with AMI were treated with a front-loaded 15-hour infusion of hypertonic glucose, insulin, potassium, magnesium, and L-carnitine in addition to usual therapy. This metabolic solution was well tolerated, free of serious side effects, and reduced the incidence of morbid events.**


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