Optimal Dosage of Insulin and Glucose in Glucose-Insulin-Potassium Treatment of Acute Myocardial Infarction Remains to Be Established

To the Editor:

The dosage of insulin and glucose plays an important role for the efficacy of GIK (glucose-insulin-potassium) treatment. Until the ECLA study, only 4 trials in acute myocardial infarction (AMI) had used the GIK therapy required to achieve adequate suppression of plasma free fatty acids (FFAs).1 Pooled data from these trials demonstrated a 48% reduction in mortality. In the ECLA study, a significant survival advantage relative to the control group was only found in the “high-dose GIK group.”2 In spite of these encouraging results, we do not yet know the optimal dosage of insulin and glucose in AMI.

To establish appropriate metabolic interventions, these should preferably be evaluated in the relevant clinical settings. Surprisingly little is known about the metabolic consequences of myocardial infarction in humans or the impact of metabolic interventions in this setting. In stable coronary artery disease, an infusion of 30 g of glucose, 50 IU of regular insulin, and 80 mmol of KCl per liter at 1.5 mL/kg body weight reduced myocardial FFA uptake and myocardial oxygen demand, whereas the uptake of glucose and lactate increased.3 In AMI, it was demonstrated that this regimen reduced the level of plasma FFAs substantially.4 However, its impact on myocardial metabolism in this setting remains obscure. The neuroendocrine stress response, for instance, may be expected to influence myocardial metabolism and attenuate the effect of GIK due to insulin resistance. In coronary surgery, where systematic studies on GIK and its effects on systemic and myocardial metabolism have been done by Dr Rolf Ekroth and colleagues at Sahlgrenska University Hospital in Göteborg, Sweden, it has been shown that insulin resistance can be severe early after the operation. Furthermore, substantially higher doses of insulin are required to achieve full metabolic effects than to achieve suppression of plasma FFAs.5 Hence, before large-scale prospective, randomized studies on GIK in AMI are undertaken, further studies of myocardial metabolism in AMI and the impact of different GIK regimens may be advisable.

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Response

In their letter, Dr Svedjeholm and colleagues provide a concise summary of the topic of glucose-insulin-potassium (GIK) therapy. Their comments reflect the current understanding of the metabolic benefit of GIK therapy in acute myocardial infarction (AMI). The spirit of their letter is that dose-finding studies should be performed before a large-scale follow-up trial with GIK is done, with the implication that higher doses of insulin may prove more beneficial.

Should we consider a dose-finding study before the performance of a large-scale clinical trial?

Svedjeholm et al attribute the benefit of GIK in AMI to a metabolic mechanism. However, conceptually limiting the benefit of GIK therapy to its impact on anaerobic myocardial metabolism is a somewhat limited perspective. This assumption fails to consider a number of other potentially beneficial effects of GIK therapy, including a favorable effect on potassium flux, lipid metabolism, hyperglycemia/osmolarity, and plasma volume/hemodynamics. In addition, the extrametabolic effects of acute insulin administration likely contribute to the efficacy of this therapy, including favorable effects on vascular tone, coagulation, arrhythmogenesis, and apoptosis.1

Although a dose-finding study could assess safety and feasibility of different regimens, it would be impractical to power such a study for efficacy assessment. Such a study would have to rely on surrogate markers of efficacy, such as suppression of plasma free fatty acids, as implied by Svedjeholm et al. Although physiologically sound, these measures have never been validated against clinical outcomes and suffer all the limitations of reliance on the “structure-function” relationship outlined in the previous paragraph. One could also make a similar argument that studies to define the optimal duration of therapy and studies of the patient selection parameters would be required. However, we feel that these studies are impractical, if not altogether impossible, due to the financial constraints of studying nonproprietary pharmacotherapy.

Higher insulin doses would potentially come at the expense of safety and tolerability. Higher insulin dosing would likely result in more hypoglycemia. The amount of glucose infused to counter this would incrementally increase the net volume load. Any increase in toxicity of the glucose infusion would likely increase the incidence of local intolerance and phlebitis during peripheral infusion, requiring the placement of a central venous catheter.

Thirty-seven years have elapsed since Sodi-Pallares and colleagues2 introduced GIK therapy as a treatment for AMI in 1962, yet the definitive study has not been done. Given the promising results of our pilot study3 and the consistent results of previous studies using a similar dosing regimen,4 we conclude beyond a reasonable doubt that “the study has come for a large, prospective trial” with GIK in AMI.5 To that end, we have already begun enrollment in the follow-up GIK II trial. If GIK therapy is as efficacious as our pilot study suggests, we feel that any delay of confirmation would only serve to postpone the clinical application of this simple, cheap, widely available, life-saving therapy.

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