Targeting Glucose in Acute Myocardial Infarction

Has glucose, insulin, and potassium infusion missed the target?

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Proinflammatory mechanisms may contribute to hyperglycemia-associated adverse outcomes in acute myocardial infarction (AMI) (1–3). Insulin exerts anti-inflammatory effects in ST elevation myocardial infarction and coronary artery bypass graft patients (4–6). Inflammation plays an important role in the pathogenesis of atherosclerosis and thrombosis (7,8). Thus, insulin infusion in AMI should be beneficial. However, glucose, insulin, and potassium (GIK) infusion was neutral in its benefit in the Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–Estudios Cardiologicos Latinoamerica (CREATE-ECLA) study (9).

The GIK regimen (fixed combination of 1 l of 25% dextrose with 50 units regular insulin and 80 meq/l potassium) used in CREATE-ECLA is known to lower serum free fatty acid concentrations (10) and to reduce mortality by 18% in AMI, as previously reviewed (11). However, the infusion of 30 g/h glucose without titration of glucose or insulin in CREATE-ECLA led to a significant increase in blood glucose concentrations. Mehta et al. suggested that the adverse effect of GIK-induced hyperglycemia may have neutralized any potential benefit of insulin in the GIK regimen. However, Mehta et al. did not comment on the magnitude of the potential contribution of hyperglycemia to neutralize benefits of GIK. Since admission hyperglycemia was predictive of mortality in AMI in CREATE-ECLA, we have estimated the potential effects of GIK-induced hyperglycemia on mortality in this study.

RESEARCH DESIGN AND METHODS — Based on the admission blood glucose–related mortality rates in control subjects in CREATE-ECLA, we have constructed a model: 30-day % mortality = $100\% \times [1 - c \times \exp(-d \times BG)]$ predicting 30-day mortality as a function of admission blood glucose, where exp = exponential function and BG = blood glucose. The constants c and d were estimated using a regression involving 3 points from this constructed curve. This model was then applied to the blood glucose at admission and at 6 and 24 h for both the GIK and control groups, assuming that the relationship between glycemia and mortality is maintained even after admission in AMI. This assumption is probably valid because for every 0.6-mmol/l reduction in glucose postadmission, there is an 8% reduction in mortality in patients with AMI (12) and because glucose levels after admission predict mortality in AMI (13,14).

The projected mortality at 0, 6, and 24 h (Table 1) yielded trapezoids of which the areas were calculated. After dividing by 24 h, the following weighted average formula for mortality was obtained: % mortality (average) = (0.125) × % mortality at 0 h + (0.5) × % mortality at 6 h + (0.375) × % mortality at 24 h.

RESULTS — In our model, the estimated 30-day mortality for control subjects based on blood glucose achieved during 24 h is 9.9%, which is similar to the observed mortality of 9.7% for the control subjects in CREATE-ECLA. However, the estimated mortality rate for the GIK group on the basis of the GIK-induced hyperglycemia during 24 h was 12.2%, which was 2.2% higher than the observed mortality of 10% for the GIK group.

CONCLUSIONS — We suggest that the insulin in the GIK infusion used in CREATE-ECLA might have neutralized the 2.2% (12.2% [expected] − 10% [observed]) increase in mortality that should have been observed in the GIK group because of the effect of hyperglycemia induced by this infusion. Thus, if hyperglycemia was not induced by the GIK infusion used in CREATE-ECLA, the administration of insulin in this trial could have resulted in a 2.2% absolute and a 22% relative reduction in mortality in the GIK group. Indeed, CREATE-ECLA investigators have recently reported an excess mortality and congestive cardiac failure in the GIK group in the first 3 days, when GIK-induced hyperglycemia was present and probably had its maximal effect. In contrast, there was a reduction in mortality and congestive cardiac failure between 4 and 30 days (15), when glucose levels had probably approximated the levels in the control group. In a canine model of AMI, low-dose insulin alone reduced the infarct size, while glucose and potassium (16) caused hyperglycemia and increased infarct size. These find-

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Received for publication 28 May 2007 and accepted in revised form 4 September 2007.

Published ahead of print at http://care.diabetesjournals.org on 11 September 2007. DOI: 10.2337/dc07-1220.

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Abbreviations: AMI, acute myocardial infarction; CREATE-ECLA, Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–Estudios Cardiologicos Latinoamerica; GIK, glucose, insulin, and potassium.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Hyperglycemia-related mortality in CREATE-ECLA based on relationship of admission glucose to mortality in control subjects*

	Control group		GIK group	
Time	Blood glucose (mmol/l)	Mortality	Blood glucose (mmol/l)	Mortality
0	9	11.4	9	11.4
6 h	8.2	10.2	10.4	13.4
24 h	7.5	9.1	8.6	10.8

Data are percentages unless otherwise indicated.

ings and the proinflammatory, prothrombotic effects of hyperglycemia may explain how GIK-induced hyperglycemia can neutralize the potential benefits of insulin (2).

A limitation of our study is that our analysis is based on the published data in CREATE-ECLA. Because of the absence of detailed data and the derivational nature of our methodology, which arrives at 12.2% expected mortality, we are not in a position to provide a *P* value or SEs. However, based on the level of the expected precision in a large study like CREATE-ECLA, a potential absolute reduction in mortality of 2.2% or relative reduction of 22% would be statistically significant and well outside the confidence bounds (95% CI 9.4–10.6) of the observed mortality of 10% for the GIK. Although our model accurately predicted the death rate for the control subjects, it is possible that we could have overestimated the death rate for the GIK patients. We have also speculated that the adverse effects of the reactive hyperglycemia observed following AMI are equivalent to the iatrogenic hyperglycemia induced by the GIK infusion. Iatrogenic hyperglycemia is known to induce proinflammatory cytokines and endothelial dysfunction (17,18). These mechanisms may be responsible for the adverse cardiovascular outcomes associated with hyperglycemia. The important point for discussion is not whether the model is fundamentally wrong but whether, if these assumptions are "essentially correct," is there then a factor (insulin) that protected the GIK patients from the toxic effects of hyperglycemia? Using the model based on the observations in CREATE-ECLA, the answer is probably in the affirmative. Thus, hyperglycemia needs to be avoided when designing studies investigating whether insulin administration is beneficial in AMI.

We have now designed a trial to test the hypothesis that insulin is cardioprotective in AMI because of its anti-inflammatory, profibrinolytic, antioxidant, antiapoptotic, vasodilatory, and antiaggregatory actions and that these effects are enhanced by lowering glucose into the normoglycemic range. We are using intravenous insulin infusion to lower glucose to 90–130 mg/dl in ST elevation myocardial infarction patients. To allow us to infuse a minimal dose of 2.5 units/h (the anti-inflammatory dose of insulin) in this trial, ~7 g/h dextrose appropriately titrated will be infused simultaneously to maintain euglycemia (R.N., P.D., personal communication). With sucn an insulin infusion regimen, the anti-inflammatory and potentially cardioprotective effect of insulin is likely to be observed.

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