USEFULNESS OF GIK INFUSIONS IN ACUTE MI

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Mortality rates from acute MI (AMI) remain 1.5–2 times higher in patients with diabetes than in those without diabetes. Although patients with diabetes may have more extensive concomitant cardiovascular risk factors, poor cardiac reserve and diffuse coronary artery disease, it is likely that metabolic factors, including poor glycaemic control at the time of AMI, contribute to poor outcomes. Where chronic hypoglycaemia results in the development of diabetic cardiomyopathy, acute hyperglycaemia may also cause injury to the myocardium. In-vitro studies have demonstrated stimulation of pro-apoptotic events in cardiomyocytes, reduced cardiomyocyte contractility, generation of reactive oxygen species and impairment of collateral flow in coronary vessels during periods of acute hyperglycaemia in low insulin states. Indeed, such pathophysiological mechanisms may explain the increase (3–4 fold) risk of death in patients without diabetes who were hyperglycaemic at the time of their AMI compared with those with normal glucose levels. Patients with this 'stress hyperglycaemia' also have a 3-fold increased risk of congestive cardiac failure. Such a relationship between hyperglycaemia and adverse cardiac outcome has been noticed in the pre-thrombolytic and the more recent revascularisation era.

The rationale for use of glucose/insulin/potassium (GIK) infusions is to maintain normal glucose levels, stimulate potassium uptake, suppress free-fatty acid metabolism and enhance glycolysis in the ischaemic myocardium. Increased glycolytic flux results in higher free energy yield and the ATP thus derived maintains myocardial calcium and sodium haemostasis in times of ischaemia. Increased levels of free-fatty acids after AMI depress myocardial contractility, suppress glycolysis and increase myocardial oxygen demands. Insulin per se may also have cardioprotective effects, being vasodilatory for coronary artery and potentially improving myocardial contractility and reducing cardiomyocyte apoptosis.

A number of early trials examined the effect of GIK. Though these studies were inconclusive they suggested an approximately 25% reduction in mortality in patients with or without diabetes who received GIK therapy. Other studies, using higher doses of insulin, resulted in a reduction of mortality by 48%. In the DIGAMI study (Malmberg K et al, 1997) patients with an AMI in the preceeding 24 h and plasma glucose values succeeding 11 mmol/l, even if not previously diagnosed with diabetes, received high dose insulin/glucose infusion for at least 24 h to keep plasma glucose values between 7–10 mmol/l. Subcutaneous insulin using multiple injection regimens was used for at least 3 months after AMI. A total of 87% in the treatment group received subcutaneous insulin at discharge compared with 43% in the control group. However, there was a difference in HbA_{1c} of 1.1% between the two groups, with more hypoglycaemia in the insulin treated group. Mortality was not significantly different between the two groups at discharge and at 3 months, though at 12 months there was a 29% mortality reduction in the treatment group. However, the study was unable to differentiate between the benefits of insulin/glucose infusions from improved glycaemic control over the 12 months.

The ECLA study (Diaz R et al, 1998) examined the effects of high and low dose GIK infusion over 24 h. High dose GIK was considered sufficient to suppress pre-fatty acid production, though levels were not measured. Patients with or without diabetes were included in the study. The mean plasma glucose level for patients prerandomisation was 8.6 mmol/l, though only 16% of the patients had prediagnosed diabetes. A 66% reduction in mortality was noted in the revascularisation combined with the GIK group at hospital discharge compared with control. At 1 year, the high dose GIK group had a 63% reduction in mortality compared with control, though the low dose GIK group did not produce similar benefits.

The Polish-GIK Trial evaluated a low dose GIK infusion over 24 h (Ceremuzynski L et al, 1999). Thrombolysis was administered in 60% though only 6.3% of all enrolled patients had known diabetes. Limitations of the study were that patients with insulin-requiring diabetes and congestive cardiac failure were excluded and that the dosage of insulin infusion was low. Higher total mortality was observed in the GIK group at 35 days and 6 months. Cardiac deaths were similar in the insulin receiving and non-insulin receiving groups.

Thus, where does the clinician progress to in terms of GI(K) in AMI? Although overall there is a significant pathophysiological basis for using glucose/insulin infusions with or without potassium, the situation is somewhat muddied by two positive (DIGAMI and ECLA) and one negative (Pol-GIK) trials. The number of patients with diabetes enrolled in the ECLA and Pol-GIK trials was relatively small. The studies do, however, indicate that patients' metabolic status is an important determinate in survival in the acute and long-term post-AMI period. Data certainly exist supporting the use of insulin/glucose infusions with or without potassium in the acute peri-AMI period, but there is no data to support the long-term use of insulin therapy over and above improvement in glycaemic control. Disagreement continues as to who should receive such therapy and as to whether it should be confined to patients with diabetes, those with stress hypergylcaemia or extended to all patients after AMI (given recent data from intensive insulin therapy in gravely ill patients). Clarity is also required on the composition of infusion regimen to be administered, specifically in relation to the dose of insulin used, and as to whether this should just achieve normoglycaemia or suppress free-fatty acid levels. We all eagerly await the results of DIGAMI 2 and ECLA-GIK-2 trials, which may assist the clinician in deciding on the utility of these infusion regimens.

Ceremuzynski L, Budaj A, Czepiel A et al (1999) Low-dose glucose-insulin-potassium is ineffective in acute myocardial infarction: results of a randomised multicentre pol-GIK trial. *Cardiovascular Drug Therapy* **13**: 191–200

Diaz R et al, on behalf of the ECLA collaborative group (1998) Metabolic modulation of acute myocardial infarction: ECLA glucose insulin potassium pilot trial. *Circulation* **98:** 2227–34

Malmberg K, for the DIGAMI Study Group (1997) Prospective randomised study of intensive insulin treatment on long-term survival after myocardial infarction with diabetes mellitus. *British Medical Journal* **314**: 1512–15