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Experience using high-dose glucose-insulin-potassium (GIK) in critically ill patients

Elise M.A. Slob [a,b], Rob Shulman [b,*], Mervyn Singer [c,d]

[a] Division of Pharmacology, Faculty of Science, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands
[b] Pharmacy Department, University College London Hospitals NHS Foundation Trust, London 2W1 2BU, United Kingdom
[c] Department of Critical Care, University College London Hospitals NHS Foundation Trust, London NW1 2BU, United Kingdom
[d] Bloomsbury Institute of Intensive Care Medicine, Division of Medicine, University College London, Gower Street, London WC1E 6BT, United Kingdom

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ABSTRACT

Purpose: To audit the use of GIK in terms of safety, haemodynamic effects, and impact on catecholamine dosage.
Materials and methods: A retrospective, descriptive, evaluative audit of GIK use within the adult ICU of a London teaching hospital was conducted. Rescue therapy of GIK (up to 1.0 Units insulin/kg/h) was administered to improve cardiac function. Outcomes were ICU survival, change in cardiac index (CI) and blood lactate levels, events of hypoglycaemia, hyperglycaemia, hypokalaemia and hyperkalaemia, and discontinuation time of catecholamine inotropes.
Results: Of 85 patients treated with GIK, 13 (15.3%) survived their ICU stay and 9 (10.5%) were discharged home. In patients surviving until 72 h, a trend of improved CI and lactate levels was seen, often with reductions in catecholamine dosing. Inotropes were discontinued in 35 (54%) patients. Severe hypoglycaemia (<2 mmol/l), hyperglycaemia (>20 mmol/l), hypokalaemia (<2.5 mmol/l) and hyperkalaemia (>7 mmol/l) during GIK affected 1, 6, 8 and 1 patients, respectively. These abnormalities were quickly identified. No measurable harm was noted.
Conclusions: High-dose GIK can be safely used in critically ill patients, though blood glucose and potassium levels must be monitored frequently. GIK was associated with improved CI and blood lactate levels. Impact on survival requires prospective evaluation.

1. Introduction

Heart failure is a severe disease with a high morbidity and mortality. In 2012/2013, 0.74% of all inpatient episodes in National Health Service hospitals in the United Kingdom were caused by heart failure [1]. In that year, 9.4% of the heart failure patients in England died in-hospital, and 24.6% died within a 1 year follow-up period [2]. Critically ill patients with heart failure and cardiogenic shock are typically treated with catecholamine inotropes as these increase myocardial contractility and myocardial perfusion, and improve cardiac output. If vascular tone is low, drugs with a predominant vasoconstrictor action (norepinephrine, vasopressin, terlipressin) are generally given, whereas inotropes such as epinephrine and dobutamine are commonly used to enhance cardiac output [3].

Use of catecholamines can however be harmful in multiple ways including immunomodulation, increased bacterial growth and virulence, decreased metabolic efficiency, myocardial damage, increased cardiac work, and pro-thrombotic and pro-arrhythmogenic tendencies [4]. Indeed, even adjusting for severity and other factors, these agents are associated with a significantly increased risk of greater morbidity, mortality and rehospitalisation [5-7]. Other options for treating low cardiac output states include phosphodiesterase inhibitors such as enoximone or calcium sensitizers such as levosimendan. Both agents can sometimes cause excessive vasodilation [8], while phosphodiesterase inhibitors have been associated with worse outcomes [9,10].

Because of the putative beneficial effects of glucose-insulin-potassium (GIK) infusions in patients with low cardiac output states [11], we started to use low dose GIK (with 0.075 Units insulin/kg/h) within our intensive care unit 8 years ago [12]. This showed promising results in terms of improving arterial lactate levels and augmenting cardiac output. More recently, case series, predominantly in patients being treated for overdoses with beta-adrenergic blockers and/or calcium channel

Abbreviations: GIK, glucose-insulin-potassium infusion; ICU, intensive care unit; CI, cardiac index; CO, cardiac output; IV, intravenous; K^+, potassium; BG, blood glucose; G50%, glucose 50% infusion; ICIP, IntelliVue Clinical Information Portfolio; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology Age Chronic Health Evaluation; FFA, free fatty acids; ATP, adenosine-tri-phosphate; APT-1, acyl palmitoyltransferase I.

* Corresponding author at: Pharmacy Department, University College London Hospitals NHS Foundation Trust, 235 Euston Road, London NW1 2BU, United Kingdom.
E-mail address: robert.shulman@uclh.nhs.uk (R. Shulman).

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blockers, have used much higher doses of insulin (usually 0.5–1 Units/kg/h but, sometimes, up to 3 Units/kg/h or even higher) to augment low output states [13,14]. Haemodynamic benefits with an excellent safety profile were reported. These positive data encouraged us to move to a high-dose GIK regimen (0.25–1.0 Units insulin/kg/h) from 2012 onwards as a treatment strategy for patients with low cardiac output who were not responding effectively to high-dose catecholamines. Clearly, the risk of hypo- or hyperglycaemia, as well as hypo- and hyperkalaemia would likely be increased with the use of these high doses. A protocol was thus developed to manage the high-dose GIK regimen safely with a staff education campaign preceding. As this strategy has become adopted into our routine clinical practice, we decided to audit the use of high-dose GIK, with a focus on safety and haemodynamic effects.

2. Material and methods

2.1. Setting and study population

This retrospective, descriptive evaluative audit of usual practice was carried out in the mixed adult 35-bed ICU of University College London Hospital, a tertiary care teaching hospital in the United Kingdom. Our protocol aimed to treat patients with myocardial depression who had not responded to conventional catecholamine therapy, with high-dose GIK. All patients treated with GIK with an ICU admission between December 2012 and March 2015 were included, there were no exclusion criteria.

To implement high-dose GIK, staff were asked to follow a protocol aiming to increase cardiac index (CI) (Table 1). This protocol was adapted from Marini et al. who applied a GIK strategy for treating calcium channel and bèta blocker overdoses (Dr. John Marini, personal communication). The protocol requires patients to be treated with catecholamines and have serum glucose levels >7 mmol/l and potassium levels >4 mmol/l prior to commencing the GIK infusion. After giving glucose and insulin boluses, separate infusions were started at a rate of 0.25 Units insulin/kg/h, 10 ml/h 50% glucose solution and 10 mmol/h potassium. For patients in whom no significant improvement was seen, the insulin dose could be up-titrated after 1 h to 0.5 Units/kg/h and, if needed, to 1.0 Units/kg/h. The 50% glucose infusion rate could be uptitrated to 15 ml/h and 20 ml/h, respectively. Glucose and potassium levels were required to be monitored hourly and the infusion rates adjusted to achieve normal blood glucose (4–10 mmol/l) and potassium levels (3.8–5.0 mmol/l). Once stabilised, the frequency of monitoring could be reduced. When stopping the GIK infusion, insulin should be reduced to half its previous infusion rate at 8–24 hourly intervals. After GIK discontinuation, glucose should be continued for 12–24 h.

Patient outcomes were manually collected from the Philips IntelliVue Clinical Information Portfolio (ICIP) Electronic Health Record and MUSE Cardiology Information System. Blood gas measurements were carried out with a Roche Cobas B221 blood gas analyser. Cardiac output was monitored using oesophageal Doppler ultrasonography (Deltex Medical, Chichester, Sussex, UK); CI was calculated subsequently by dividing cardiac output by body surface area. We considered 2.6–4.2 l/min/m^2 as a normal range for CI. The underlying reason to start GIK was recorded. Sepsis was defined using standard definitions [15]. A Sequential Organ Failure Assesment (SOFA) score was calculated for each patient [16]. As the central nervous system score could not be defined for sedated patients, they were scored 0 (normal) unless evidence of prior abnormality existed.

Patient consent and Ethical Committee review is not required in the UK for research limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection), provided that the patients or service users are not identifiable to the research team in carrying out the research [17].

Table 1
UCLH ICU GIK protocol (adapted from Marini et al.).

Monitoring

- Do NOT change insulin dose in response to blood glucose (BG) or potassium (K^+) levels
- Monitor BG every 10 min and titrate glucose 50% infusion (G50%) to achieve target of 4–10 mmol/l. If BGs are stable, monitor the BG every hour
- Monitor blood potassium levels every hour

Step 1	Step 2	Step 3	Step 4	Step 5	GIK discontinuation	Hypoglycaemia
Indication for GIK Low cardiac output (CO), on inotrope	Bolus	Stop other crystalloids. Start infusion (first hour)	If no improvement after 1 h[a]	If no improvement after 2 h[a]	Consider when inotrope weaned and CO restored[a]	Continue insulin at same dose Glucose BG 2.5–3.9 mmol/l: give 10 ml 50% G centrally; recheck BG every 15 min, repeat as needed. BG < 2.5 mmol/l: give 25 ml 50% glucose centrally; recheck BG every 15 min, repeat as needed. Increase G50% rate by 5 ml/h
Stabilise the patient with conventional therapy e.g. mechanical ventilation, inotropes, fluids as needed. Hold feed, inform Dietitian- to review nutrition	Insulin 0.25 U/kg intravenous (IV) 5–10 min	Insulin 0.25 U/kg/h Syringe 300 U/50 ml N/S	Insulin 0.5 U/kg/h	Insulin 1.0 U/kg/h	Halve rates of GIK infusions every 8–24 h[a]. Continue this if CO and perfusion maintained	
Ensure glucose >7 mmol/l (if not: give 15 ml 50% bolus centrally)	Glucose 20 ml 50% IV 5–10 min	Glucose 50% 10 ml/h centrally	Glucose 50% Increase previous dose by 5 ml/h and adjust to normal target	Glucose 50% Increase previous dose by 5 ml/h and adjust to normal target	Give glucose after insulin discontinuation for 12–24 h. Monitor BG/K^+ every 0.5–2 h (depending on degree of concern about abnormal values – adjust dosing as needed)	
Ensure $K^{\pm}$ >4 mmol/l (if not: give 20 mmol K^+ over 1 h centrally)		$K^{\pm}$ 40 mmol/100 ml 10 mmol/h centrally. Adjust to achieve normal levels (3.8–5.0 mmol/l)	$K^{\pm}$ Titrate to achieve normal levels (3.8–5.0 mmol/l)	$K^{\pm}$ Titrate to achieve normal levels (3.8–5.0 mmol/l)		

[a] Consultant/senior doctor decision.