Intra-operative blood glucose and serum insulin concentrations in the surgical management of insulinoma

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Summary: The surgical management of insulinoma is frequently complicated by difficulty in pre- and intra-operative localization of the tumour. An early and reliable post-operative indicator of successful surgery would therefore be useful in the management of this condition.

In a prospective, controlled study serial measurements of blood glucose and serum insulin concentrations were performed in 5 patients with insulinoma during surgical removal of the tumour. Results were compared with 5 patients, matched for age and body weight, undergoing abdominal surgery for non-malignant disease. Serum insulin (mean $\pm$ s.e.m.) was significantly elevated in the insulinoma patients at the start of surgery (32.1 ± 3.1 vs 6.1 ± 2.2 mU/l; $P < 0.01$). A significant fall ($P < 0.01$) to levels comparable with the control patients (7.5 ± 1.8 vs 10.0 ± 3.3 mU/l) occurred following removal of the tumour. We conclude that serial intra-operative measurements of serum insulin concentration are technically simple to perform and provide useful retrospective corroboration of successful surgery in patients with insulinoma.

Introduction

Surgical removal of insulinoma abolishes symptoms of neuroglycopenia and is therefore the treatment of choice for this condition.¹ Post-operatively serum insulin concentrations fall to normal² although high post-operative values occasionally have been reported.³ It is unclear whether the latter results are observed following successful removal of the tumour or arise as a consequence of the well recognized difficulties of identifying small tumours with certainty.⁴ A reliable, early post-operative indicator of successful surgery would therefore be useful in the surgical management of insulinoma.

The aim of this controlled study was to determine whether serial intra-operative measurements of blood glucose and serum insulin concentrations would provide corroborative retrospective evidence that removal of the tumour had been successfully accomplished in patients with insulinoma.

Patients and methods

Five patients presenting with neurological symptoms were diagnosed as having an insulinoma

following the demonstration of fasting hypoglycaemia in the presence of an inappropriate elevation of serum insulin concentration. Four of the patients underwent partial distal pancreatectomy and local excision of the tumour was carried out in the remaining patient. Surgery resulted in the complete abolition of neuroglycopenic symptoms in all the patients during follow-up periods of between 1.5 and 3 years. Histological confirmation of the diagnosis was obtained in each case. Peri-operative blood glucose and serum insulin concentrations were determined as detailed below.

A control group of 5 patients undergoing abdominal surgery for non-malignant disease (4 cholecystectomies and 1 repair of incisional hernia and apronectomy) were also studied. There were no significant differences between the insulinoma patients and controls in age, body weight or percentage ideal body weight. None of the control patients had a family history of diabetes nor were any receiving medication known to interfere with insulin secretion or carbohydrate metabolism. Random pre-operative blood glucose concentration was normal in each case.

To prevent intra-operative hypoglycaemia in the insulinoma patients an intravenous infusion of 5% dextrose was commenced the night before operation and maintained throughout surgery at a rate of approximately 100 ml/h. The control group

received an identical infusion of dextrose overnight and during surgery. Informed verbal consent was obtained from all patients.

Immediately following the induction of anaesthesia a Teflon® cannula was inserted into an antecubital vein of the arm contralateral to the dextrose infusion. Free-flowing blood samples were withdrawn immediately and at approximately 10–15 minute intervals thereafter throughout surgery. The stage of the operation (induction of anaesthesia, skin incision, opening of peritoneal cavity etc) was noted at each sampling time point. Between samples the cannula was kept patent by flushing with 2 ml saline (0.15 mol/l). At each sampling time-point approximately 7.5 ml of blood was withdrawn; 2.5 ml was placed in a tube containing fluoride oxalate for assay of blood glucose and 5 ml was allowed to clot in a glass tube and serum subsequently separated and stored at -20°C for subsequent assay of insulin. Blood glucose concentration was determined by a glucose dehydrogenase method on a Cobas-Bio centrifugal analyser. Serum insulin was determined by a double antibody radio-immunoassay³ with a lower limit of detection of 2.0 mU/l. The intra-assay coefficient of variation (CV) was 5.2% at a plasma insulin concentration of 5.0 ± 1.4 mU/l (mean $\pm$ s.d.). Inter-assay CVs were 8.7% and 12.5% at 10.0 ± 0.9 and 38.0 ± 4.8 mU/l respectively. For statistical purposes serum insulin values below the level of detection of the assay were assigned an arbitrary value of 1 mU/l.

In order to compare the results of blood glucose and serum insulin between the two groups the results from samples taken at corresponding stages of operation were matched as closely as possible (Figures 1 and 2). Statistical differences between groups were sought using the Mann-Whitney U-test and changes within groups with Wilcoxon's signed rank sum test. Results are expressed as mean $\pm$ s.e.m.

Figures 1 Blood glucose concentration (mean and s.e.m.) during operation in the insulinoma patients (O---O) and controls (●---●). The arrow indicates the time of insulinoma removal.

Figure 2 Serum insulin concentration (mean and s.e.m.) during operation in the insulinoma patients (O---O) and controls (●---●). The arrow indicates the time of insulinoma removal.

Results

Following induction of anaesthesia blood glucose concentration was normal in both insulinoma patients and controls at 6.4 ± 0.8 vs 5.6 ± 0.3 mmol/l (Figure 1). Blood glucose rose significantly in the insulinoma patients following removal of the tumour to 9.7 ± 0.9 mmol/l ($P < 0.05$) but was unchanged in the control group (6.9 ± 0.5 mmol/l; Figure 1). Serum insulin at the start of surgery was significantly elevated in the insulinoma patients at 32.1 ± 3.1 vs 6.1 ± 2.2 mU/l ($P < 0.01$; Figure 2) and fell significantly following removal of the tumour to 7.5 ± 1.8 mU/l ($P < 0.01$; Figure 2). Serum insulin at a similar stage of surgery was unchanged in the control patients at 10.0 ± 3.3 mU/l (Figure 2).

Discussion

Even in experienced hands the surgical management of insulinoma is often complicated by difficulties in pre- and intra-operative tumour localization.⁴ Insulinomas are palpable at operation in more than 20% of cases and in about 10% of cases the tumours are multiple.⁴ Recent work has concentrated on developing techniques to improve pre- and intra-operative insulinoma localization. These include the use of a modified version of the artificial endocrine pancreas,⁶ intra-operative ultrasound scanning^{7,8} and portal venous sampling techniques.^{9,10} Relatively quick (30 minute) insulin radioimmunoassays have been described which may facilitate the intra-operative localization of insulinomas.^{9,10} Our study was prompted by the limited availability of such techniques outside specialized centres and the consequent need to provide an early post-operative indicator of the effectiveness of surgery.

Previous studies have demonstrated a rise in blood glucose concentration and a fall in serum

insulin concentration following the removal of insulinomas.^{11,12} We have confirmed that tumour removal is followed by a significant rise in blood glucose concentration in insulinoma patients. However, the reliability of blood glucose as a marker of successful surgery has been questioned since similar rises in blood glucose have been observed in patients subsequently documented to have retained tumour or multiple adenomatosis.¹²

In addition to the rise in blood glucose a significant fall in serum insulin concentration was observed after excision of the insulinomas. Following removal of the tumours serum insulin concentrations in the insulinoma patients fell to levels comparable to the control group. Endogenously secreted insulin has a half-life of less than 5 minutes in the circulation^{14,15} though a significant proportion of the circulating radio-immunoassayable insulin in insulinoma patients is proinsulin which has a plasma half-life of about 25 minutes.¹⁵⁻¹⁷ We consider that the prompt fall in serum insulin concentration provides convincing corroborative evidence of successful tumour removal in our patients.

Body weight,¹⁸ counter-regulatory hormone responses to surgery¹³ and intravenous glucose infusion may all affect circulating glucose and insulin concentrations. To examine these factors a control group of patients undergoing abdominal surgery was studied under identical conditions. No significant changes in blood glucose or serum insulin concentration were observed in this group during the operative period. While we acknowledge the limitations of our control group, patients with any other condition necessitating partial pancreatectomy would clearly have been unsuitable as

controls due to their inherent pancreatic disease. It is therefore not possible to perform a valid assessment of the effect of an acute 50% reduction in pancreatic volume on circulating glucose and insulin concentrations in man. We consider that such a marked fall in circulating insulin concentrations would be highly unlikely if an insulin-secreting tumour had been missed during partial pancreatectomy and it is of note that the changes in glucose and insulin concentrations observed in the patient who underwent local tumour excision were indistinguishable from those of the patients who underwent partial pancreatectomy. None of the patients has had a recurrence of neuroglycopenic symptoms during up to 3 years of post-operative follow-up. A larger prospective study will be required to determine the relative false positive and false negative rates of this technique. However, the marked fall in serum insulin in all our patients suggests that in an individual case failure to remove the functioning tumour tissue would be readily apparent.

In summary, we conclude that serial measurements of blood glucose and serum insulin concentrations during surgery are technically simple to perform and provide useful retrospective corroboration of successful surgery in patients with insulinoma.

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