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SHORT COMMUNICATION

The role of continuous subcutaneous insulin infusion therapy in patients with diabetic gastroparesis

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Abstract
Aims/objective To describe the effectiveness of continuous subcutaneous insulin infusion (CSII) in patients with symptomatic diabetic gastroparesis and unstable glycaemic control.
Methods Data from 26 patients with symptomatic diabetic gastroparesis and unstable glycaemic control using multiple-dose insulin (MDI) regimens, and subsequently managed with CSII, were analysed.
Results Following initiation of CSII, the median length of inpatient bed days associated with hospital admissions related to gastroparesis and glycaemic instability was reduced from 8.5 (range 0–144) days patient^{-1}year^{-1} prior to CSII to 0 (range 0–15) days patient^{-1}year^{-1}.

The median HbA_{1c} reduction with CSII was 1.8% (22 mmol/mol; $p<0.05$). The median capillary blood glucose (CBG) with CSII was significantly lower than with MDI: 7.7 mmol/l (range 3.8–15.4 mmol/l) vs 9.8 mmol/l (range 2.3–27 mmol/l), respectively, $p<0.001$. Glycaemic variability with CSII was significantly reduced compared with MDI: CBG CV 0.37 vs CV 0.53, respectively, $p<0.001$.
Conclusions/interpretation CSII therapy in patients with diabetic gastroparesis results in significant improvement in glycaemic control and reductions in glycaemic variability and number of hospital inpatient bed days.

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Keywords CSII · Gastroparesis · Glycaemic instability · Hospital admissions · Insulin pump · Length of stay

Abbreviations
CBG Capillary blood glucose
CSII Continuous subcutaneous insulin infusion
MDI Multiple-dose insulin

Introduction

Gastroparesis, a disorder of delayed gastric emptying in the absence of mechanical obstruction of the stomach, is a well-recognised complication of diabetes mellitus [1]. Though most patients with diabetic gastroparesis remain asymptomatic, a significant proportion (8–12%) suffers with variable degrees of upper gastrointestinal symptoms that adversely affect their quality of life, glycaemic control and nutritional status [2]. Moreover, some patients may have periods of intractable and debilitating symptoms requiring frequent and prolonged hospital admissions [3]. Acute variations in blood glucose concentration have been found to affect gastric motility in healthy people and patients with diabetes [4, 5]. Multiple-dose insulin (MDI) injections characteristically provide flexibility in adjustment of insulin dose and injection timing according to meals. However, in patients with gastroparesis, a mismatch between insulin action and glucose absorption can still result in wide fluctuations in glucose level despite the use of MDI injections [6]. We present our experience of using continuous subcutaneous insulin infusion (CSII) therapy in a group of patients with diabetic gastroparesis.

Methods

The data presented in this case series were collected from 26 patients (two men) with type 1 diabetes mellitus

diagnosed with gastroparesis, managed with CSII at two centres (Royal Liverpool University Hospital, Liverpool, UK and Countess of Chester Hospital NHS Foundation Trust, Chester, UK). Caldicot guardians of both of the institutes have approved the publication of the manuscript. All the patients had a diagnosis of gastroparesis based on their symptoms and established by demonstrating delayed gastric emptying on scintigraphic studies as per the standard protocol. Other structural abnormalities that may cause similar symptoms were excluded by upper abdomen ultrasound and oesophagogastroduodenoscopy. All patients were assessed by a multidisciplinary team consisting of a consultant physician, a specialist nurse, a dietitian and a psychologist.

Cohort characteristics Patients' demographic characteristics and diabetic complications are summarised in Table 1.

Prior to switching to CSII therapy, all patients were following an MDI regimen, with an average total daily insulin dose of 49 U (range 24–110 U). Despite optimised prokinetic therapy, all patients reported profound gastroparesis-related symptoms—such as nausea, vomiting and loss of appetite—and frequent episodes of hypoglycaemia. The BMI of the cohort was 23.9 kg/m^2 (range 16–33 kg/m^2), with a mean reported weight loss of 6.0 kg in the 6 months prior to starting CSII therapy. Patients had frequent hospitals admissions and the group as a whole, in the year leading up to the initiation of CSII, had a total of 1,013 inpatient days to manage gastroparesis related symptoms and associated glycaemic instability.

Table 1 Characteristics of the study group

Characteristic	Mean (range) or number of patients
Mean age (years)	38.4 (24–53)
Men:women	2:24
Diabetes duration (years)	21 (8–34)
Weight (kg)	65.4 (42–99)
BMI (kg/m^2)	23.9 (16–33)
HbA_{1c}	
%	9.9 (6–15.3)
mmol/mol	85 (42–144)
Retinopathy, *n* (%)	20 (77)
Laser treated (*n*)	15
Partially sighted (*n*)	2
Registered blind (*n*)	2
Nephropathy, *n* (%)	10 (38)
Renal replacement therapy (*n*)	8
Proteinuria (*n*)	2
Peripheral neuropathy, *n* (%)	19 (73)
Charçot's arthropathy (*n*)	2
Postural hypotension, *n* (%)	8 (30)
Neurogenic bladder, *n* (%)	7 (27)
Bowel symptoms, *n* (%)	8 (30)

n=26 in the group

Adaptation of CSII Insulin pump therapy was initiated using a flat basal rate to provide 24 h insulin delivery that was subsequently tailored according to the individual requirement. Bolus doses of insulin were delivered to cover meals, generally using 1 U insulin for each 10 g carbohydrate, except in patients with BMI below 17 kg/m^2 where a dose of 1 U to every 15 g carbohydrate was used. The first-phase component of the bolus insulin was omitted. The boluses were given in extended form with the extension times determined by the composition of the food, severity of symptoms and the results of the gastric-emptying studies. As symptoms improved, bolus doses for carbohydrate were modified by shortening the extension times or by adopting a multi-wave delivery whereby 10% of the total insulin dose was infused as first-phase insulin.

Statistical analysis Data were analysed by using GraphPad PRISM software, version 5.04 for Windows (GraphPad software, San Diego, CA, USA). Results are expressed as mean and range unless specified. A two-tailed significance test was used to test the significance at a significance level of 0.05. The glycaemic variability with MDI and CSII were compared by calculating the CV of the CBG.

Results

During the first 12 months following instigation of CSII, the median number of inpatient bed days associated with hospital admissions related to gastroparesis and glycaemic instability decreased to 0 (range 0–15) days patient^{-1}year^{-1} compared with 8.5 (range 0–144) days patient^{-1}year^{-1} prior to CSII ($p<0.05$).

There was a significant improvement in glycaemic control (median HbA_{1c} 8.0% [range 5.6–14.3%]; 62 mmol/mol [range 38–133 mmol/mol]) with CSII in comparison with MDI (median HbA_{1c} 9.8% [range 6–15.3%]; 84 mmol/mol [range 42–144 mmol/mol], $p<0.05$). Glycaemic variability ($n=20$) was significantly reduced with CSII as shown by: a lower median CBG with CSII than with MDI, 7.7 mmol/l (range 3.8–15.4 mmol/l, $n=142$) vs 9.8 mmol/l (range 2.3–27 mmol/l; $n=87$; $p<0.001$); and a lower CV for CBG with CSII (0.37) compared with MDI (0.53; $p<0.001$).

The total daily dose of insulin was reduced to 33.7±12.3 U (mean±SD) with CSII, compared with 49.3±27.7 U (mean±SD) with MDI ($n=25$, $p<0.005$). The mean weight

gain in 6 months post CSII was 2.9 kg, with 1.0 kg/m^2 mean improvement in BMI.

Discussion

This study demonstrates that CSII is an effective method of delivering insulin in patients with difficult to manage diabetic gastroparesis. Glycaemic control improved and there was a significant reduction in the number of hospital inpatient bed days following initiation of CSII.

Delayed gastric emptying in patients with gastroparesis alters glucose absorption and the mismatch between glucose absorption and insulin action results in wide excursions in blood glucose concentrations with MDI regimens [7]. In addition, patients with severe symptomatic gastroparesis are unable to have regular meals and frequently omit their insulin in an attempt to avoid the risk of hypoglycaemia. This results in severe glycaemic instability, deterioration in glycaemic control and further worsening of gastroparesis. A recent meta-analysis has established that the rate of episodes of severe hypoglycaemia in type 1 diabetes is reduced by CSII, leading to improvements in HbA_{1c} [6]. However, this case series is probably the first to show the value of CSII in patients with gastroparesis for improving glycaemic control and reducing glycaemic variability and the frequency and severity of hypoglycaemic episodes. Improved glycaemic stability with CSII was achieved through greater flexibility, which allowed basal insulin profiles to be individually tailored and bolus insulin doses modified to an extended form by omitting first-phase insulin, depending on meal composition. The ability to modify insulin dose delivery can be especially advantageous for individuals with gastroparesis, in which there is often a mismatch between insulin action and the absorption of glucose following meals.

Gastric emptying is a complex process involving coordinated motor activity of the proximal part of the stomach, the antrum and the pylorus. Acute fluctuations in glucose concentration adversely affect gastric function, resulting in worsening of upper gastrointestinal symptoms [5]. Acute hyperglycaemia has been shown to induce relaxation of the proximal stomach, suppression of the frequency and propagation of antral pressure waves, and an increase in pyloric tone. Moreover, marked hyperglycaemia can also produce tachygastria and un-coordinated motor activity of different parts of the stomach [8, 9]. Studies have also shown that acute hyperglycaemia slows gastric emptying of both solid and liquid nutrients in patients with established autonomic neuropathy and can also attenuate the prokinetic effect of intravenous erythromycin on gastric emptying [5, 10]. It could be hypothesised that reduction in day-to-day glycaemic variability could help to optimise gastric motility in patients with diabetic gastroparesis.

We conclude that, when used in combination with appropriately tailored prokinetic therapy, CSII is an effective insulin delivery system in patients with diabetic gastroparesis, improving glycaemic control and reducing hospital admissions and the number of inpatient bed days. The initial costs of CSII therapy are relatively high, but overall reduction in length of hospital stay may prove it to be cost effective.

Duality of interest The authors declare that there is no duality of interest associated with the manuscript.

Contribution statement DS, PJW, TSP, FJ and GM are responsible for the conception and design of the study. DS is the primary author of the manuscript with additional responsibility for analysis and interpretation of the data while PJW, GM, FJ and TSP have contributed to the re-drafting and revision of the manuscript in addition to the care of the patients. All authors have contributed to the final approval of the version of the manuscript.

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