CASE REPORT

Intraperitoneal insulin therapy for a patient with type 1 diabetes with insulin injection site inflammation

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SUMMARY

A 36-year-old man with type 1 diabetes developed skin inflammation at the site of subcutaneous insulin injection after 10 years of basal bolus subcutaneous insulin therapy. This inflammation led to poor insulin absorption, poorly controlled blood glucose and subsequently to ketoacidosis. The problem persisted despite a trial of continuous subcutaneous insulin infusion. The patient went on to be treated with continuous intraperitoneal insulin infusion. Three months after the procedure, he was achieving good glucose control and was able to resume his normal life, with the only complication being an episode of cellulitis surrounding the port site.

Figure 1 Previous area of lipohypertrophy on anterior abdominal wall.

BACKGROUND

Continuous intraperitoneal insulin infusion (CIPII) is an alternative route of insulin delivery for patients with injection site issues relating to subcutaneous insulin. However, it is not frequently utilised. We report a case of CIPII use to demonstrate effectiveness and raise awareness of its availability.

CASE PRESENTATION

We present a case of a 36-year-old Caucasian man with a 14-year history of type 1 diabetes (T1D). He first presented with weight loss, polyuria and polydipsia. His mother has type 2 diabetes and he has a cousin with T1D. The only diabetic complication he had was erectile dysfunction; this is managed with tadalafil. The other medical condition he had was hay fever. He led an active life and ran a home refurbishment business.

For the first 10 years, his diabetes was treated with a basal bolus insulin regime. He used his abdomen as the primary insulin injection site. However, he developed two areas of significant lipohypertrophy around his umbilicus, which did not resolve despite years of avoiding injections there (figure 1). He subsequently injected insulin into his upper and lower limbs. Ten years following his diagnosis with T1D, while attending a structured education course for T1D (Dose Adjustment For Normal Eating—DAFNE course), he described local inflammation and stinging pain at his injection sites. This was associated with poor diabetes control. The application of hydrocortisone cream to the injection sites did not help. His diabetes became increasingly difficult to manage (glycated haemoglobin (HbA1c) 94 mmol/mol) and he had an admission with diabetic ketoacidosis.

The patient was then treated with continuous subcutaneous insulin infusion (CSII, Accu-Check Spirit Combo Infusion Pump, Roche). This initially helped achieve good glucose control (HbA1c 73–76 mmol/mol) for a year but the local inflammation recurred. The cannula sites for CSII did not last for more than 48 h (sometimes less than an hour) before his glucose values began to rise—suggesting that the cannula was inserted into an area of previous inflammation and possible fibrosis. Over a period of a few months, he exhausted all his cannula insertion sites such that he had to attend the diabetes clinic several times a week for the cannula to be inserted at sites that he was unable to reach himself.

As a consequence of the need for frequent clinic attendance and problems with injection site inflammation, the patient had to give up his employment. He scored 67 of 80 in the Problem Areas in Diabetes (PAID) questionnaire, indicating high levels of diabetes-related distress, requiring referral to the diabetes psychologist for support. As the cannula insertion sites for CSII became further limited, he became hyperglycaemic and was admitted with another episode of diabetic ketoacidosis 15 months after initiating CSII.

INVESTIGATIONS

The patient had tolerated insulin aspart (Novorapid) as his short acting meal time insulin for the first 10 years and had no known drug allergies. He was switched to insulin glulisine (Apidra) when the problem with skin inflammation started, but this did not lead to improvement. The possibility of IgE-mediated insulin allergy was investigated. He underwent skin prick testing against a range of

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common insulins but these were all negative: insulin lispro (Humalog), soluble insulin human prb (Humulin S), soluble insulin human pyr (Actrapid), soluble insulin bovine highly purified (Hypurin Bovine), soluble insulin porcine highly purified (Hypurin Porcine), insulin glulisine (Apidra), insulin detemir (Levemir), insulin aspart (Novorapid), biphasic insulin lispro (Humalog Mix 25), insulin glargine (Lantus) and isophane insulin bovine highly purified (Isophane Hypurine Bovine). The test for insulin autoantibody was also negative.

The possibility of allergies to the CSII delivery components were then contemplated but the manufacturer (Roche) advised that an allergy to the cannula was unusual. Various different cannulas were trialled, including FlexLink, TenderLink and metal Rapid-D cannula but with no success.

The histopathology of the skin biopsy taken from the areas of affected skin on the abdomen only showed scarring and mild chronic inflammation (figure 2).

TREATMENT

In view of the difficulty delivering insulin subcutaneously, a few alternatives were considered. A pancreas transplant can offer insulin independence, but in addition to possible complications associated with major surgery, it requires lifelong immunosuppression. Post-transplantation, it usually takes the patient a number of months to return to normal activities.¹ The latest UK data reported that the graft survival rate at 1 year was 68% and the patient survival rate at 1 year was 94% from a brain dead donor.²

Inhaled insulin was also a possibility but one of the first forms to be marketed, Exubera, had been discontinued.³ Although studies had shown it to be clinically effective, there was not enough long-term data for its safety profile.⁴ Reported adverse events included cough and decline in lung function.³ Alternative forms of inhaled insulin are currently undergoing clinical trials.⁵ Oral insulin was contemplated but this is also in the early stages of development.⁶

The final option was a CIPII delivery system.⁷ One such device, Accu-Check DiaPort (Roche), has recently been approved for use in Europe.⁸ This percutaneous port system consists of a metal body with a catheter placed intraperitoneally.⁷ Hitherto, in the UK there is only one informal report of a patient who had been using CIPII with good effect for over 9 years.⁹

Figure 2 Histopathology of skin biopsy from affected area on the abdomen showing mild scarring, sparse inflammation and no eosinophils.

Figure 3 Primary incision for insertion of intraperitoneal insulin port.

Our patient went on to undergo surgical insertion of the CIPII device (figure 3). Insuman Infusat (soluble insulin, 1.100 strength, Sanofi INS 1450) was used with the pump in place of insulin glulisine (Apidra). This insulin formulation is not widely available in the UK, but it is the only one currently recommended for use with the Accu-Check DiaPort by the manufacturer.

OUTCOME AND FOLLOW-UP

After the first bolus of intraperitoneal insulin, the patient commented that the most notable change was the lack of pain—a side effect he had had to endure for many years previously. Two months post-insertion, he developed cellulitis around the port but this settled with a course of intravenous flucloxacillin. At 3 months' follow-up, his HbA1c was 63 mmol/mol compared with 73 mmol/mol pre-CIPII. His PAID score had also improved from 67/80 pre-CIPII to 33/80 post-CIPII.

The patient continued to make good progress and was able to return to his self-run business. He was taught to recognise the early signs of cellulitis and on the importance of taking oral antibiotics should it recur. He was also educated about port care and strict hygiene by the tissue viability nurse.

DISCUSSION

In summary, we present the use of CIPII as an alternative route of insulin delivery in a young adult with T1D. We believe the only alternative approach for this patient would have been a pancreas transplant. Overall, CIPII is a better alternative to a pancreas transplant because it is associated with fewer complications and does not require lifelong immunosuppression.

In health, insulin is secreted from the pancreas into the portal venous system before reaching the peripheral circulation.¹⁰ This leads to a high concentration of insulin in the liver, where it stimulates glucose storage and, more importantly, inhibits hepatic basal glucose release.¹⁰ A significant proportion of insulin undergoes first-pass clearance in the liver; on average, 50% of insulin delivered to the liver is removed. This portal/peripheral gradient is reversed with subcutaneous or intravenous insulin delivery.¹⁰

CIPII closely approximates the physiological secretion of insulin because insulin is absorbed from the peritoneal space into the portal circulation.^{11–13} Duckworth *et al*¹⁰ have highlighted the benefits of the intraperitoneal route of insulin delivery, including rapid insulin absorption, near physiological carbohydrate and lipid metabolism and avoiding of peripheral hyperinsulinaemia. The latter may be linked to an increased risk of arteriosclerosis.

Clinically, the advantages of CIPII had been demonstrated by a Dutch crossover study that reported greater HbA1c reduction, improvement in quality of life and greater patient satisfaction

when comparing CIPII against CSII.^{14 15} Efficacy in lowering HbA1c and acceptable morbidities with CIPII were also reported in a French 5-year retrospective review of 181 patients and in a recent systematic review.^{16 17} Two recent trials on the therapeutic effectiveness of CIPII have been conducted in the USA and the Netherlands; results are awaited.^{18 19} Preliminary results from the USA trial again showed better HbA1c control with CIPII compared with CSII.¹⁹

The most commonly reported complication of CIPII is catheter obstruction secondary to insulin aggregates. This is usually managed with diluent flushing, laparoscopic repair or catheter replacement.^{20–22} Other complications included pump dysfunction, infection and pain at pump site.²³ Cost and complications may have limited CIPII use despite the technology being available for the past 2 decades.^{14 15} Only a few specialist centres in the USA, France and the Netherlands had reported experience in CIPII.^{15 20 21 24}

As pumps with better design and safety profile become available, CIPII can be considered as an alternative route of insulin delivery in patients with insulin injection site problems. This had been reported in Australia, Germany and France in cases of lipodystrophy and subcutaneous insulin infusion resistance.^{25–28}

Although preliminary results are promising, there is a need for long-term good quality data regarding clinical effectiveness, complications, insulin requirements and metabolic benefits of CIPII. Certainly, in the UK there is a need to raise the awareness of the availability of CIPII as an alternative management.

Patient's perspective

- ▶ Excerpts from the local hospital newsletter interview with the patient:
 - When his diabetes control was at its worst, he was forced to close down his home refurbishment business and move back to live with his parents. In his own words “I was desperate for something to be sorted, it was not a life.” Now well on the road to recovery, the patient is aiming to revive his business and looking forward to socialising ‘like normal people’. “I feel back in control and massively positive about life now. It took so long to sort because of the tests and it was frightening but thankfully a way was found to fix it.”
 - The patient's Problem Areas in Diabetes (PAID) score improved from 67/80 to 33/80 after the initiation of continuous intraperitoneal insulin infusion.

Learning points

- ▶ Continuous intraperitoneal insulin infusion (CIPII) can be considered as an alternative insulin delivery route when subcutaneous insulin injection and infusion fail to achieve good blood glucose control.
- ▶ In some patients, sites available for insulin injection can become exhausted even with site rotation.
- ▶ Education for patients with a CIPII port is very important to reduce the risk of infection.

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