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Short Communication

The addition of insulin to home parenteral nutrition for the control of hyperglycaemia: A case series

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SUMMARY

There is little data on the safety or efficacy of insulin added to parenteral nutrition in the homecare setting. We report the use of this route of insulin administration in a series of 4 patients spanning 39 patient years in which it appeared effective, safe and well tolerated.

1. Introduction

Hyperglycaemia frequently complicates parenteral nutrition (PN) and often requires treatment with exogenous insulin [1,2]. Designing effective insulin regimens in patients on home PN (HPN) is challenging – patients may receive all their carbohydrate calories intravenously overnight and may receive different formulations during the week. One possible solution is the addition of insulin directly to PN, which ensures a proportionate supply of insulin to match PN carbohydrates and may reduce the frequency of additional insulin injections in patients lacking subcutaneous tissue [3]. Studies have found insulin availability from PN to range widely from 44 to 95% [4–7] with this difference likely accounted for by differing PN container material, assay methods and type of insulin used in the analyses. Availability and consistency of insulin in PN may also be affected by differing PN compositions including the types of amino acid [5] or presence of lipid emulsion [8]. Moreover, the availability of insulin in PN may decrease during the course of the infusion [6]. There are very few studies examining this method of insulin administration in patients on HPN and, consequently, many home care providers are not prepared to accept the risk. In one reported cohort of non-diabetic patients who developed hyperglycaemia on commencement of HPN, survival was not affected by the addition of insulin to the PN solution but glycaemic control was not evaluated [9]. In order to initiate a debate in this area and to encourage others to describe their practice, we hereby outline our experiences of the use of insulin in HPN in 4 patients amounting to 39 patient years of experience.

2. Methods

At our institution, patients with intestinal failure requiring long term HPN that develop hyperglycaemia commence insulin therapy in an inpatient setting. Insulin is only added to PN when BG values have stabilised for at least 24 h on variable rate intravenous insulin infusion (VRIII). Usually, two thirds of the insulin required in the subsequent 24 h period is added to PN. The remaining insulin requirements are provided by once daily injection of long-acting subcutaneous insulin. If the patient is able to eat, then additional rapid acting subcutaneous insulin may be administered prior to food. Dosing changes are reviewed on a daily basis by the hospital's diabetes team. PN is mixed by specialist pharmacists and only short acting human insulin (Actrapid®, Humulin S®) is added to the PN solution. Home care companies deliver PN to the patient's home but do not add insulin to PN themselves. Therefore, prior to discharge, the patient or carer must be able to inject the required dosage of insulin directly into the bag of PN prior to starting each infusion using aseptic technique.

We describe 4 patients from our cohort between 1998 to the present day who met the criteria for the addition of insulin to HPN and received their insulin via this route for three years or more. Clinical data including insulin prescriptions, PN prescriptions and glycaemic control (HbA1c values) were reviewed from hospital records. Episodes of hypoglycaemia were defined as hospital admissions where the chief compliant was a BG value of <70 mg/dL and associated sympathoadrenal and neuroglycopenic symptoms.

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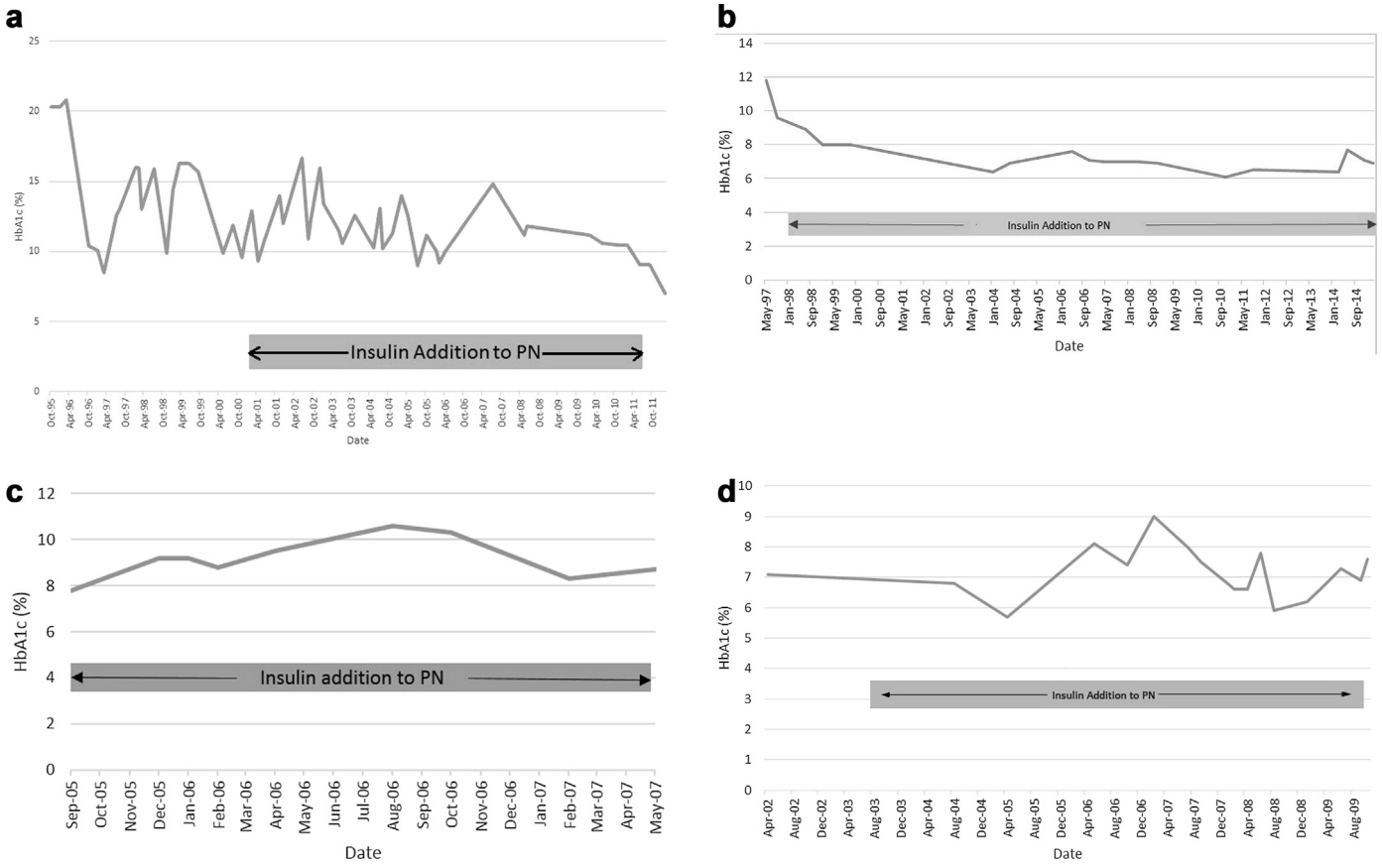

Fig. 1. Graphs demonstrating HbA1c levels expressed as % for patients receiving insulin added to their home parenteral nutrition. a) Case 1, b) Case2, c) Case 3, d) Case 4. Details of individual cases are shown in Table 1.

3. Results

4 patients received insulin added to PN at home to control hyperglycaemia. Their HbA1c levels (expressed as %) are shown over time (Figs. 1a–d). ESPEN guidelines recommend an HbA1c target of 6.5–7.5% in this setting [3]. Table 1 summarises the PN indications, duration of insulin added to PN, initial body weight & BMI, daily calorie requirements, PN composition and weekly regimens and insulin types and doses for each case.

3.1. Case 1

A female with a prior history of Grave's Disease and an eating disorder who developed type 1 diabetes mellitus at the age of 29 years. Diabetes was poorly controlled as a result of her eating disorder and she consequently developed early microvascular complications (proliferative retinopathy, nephropathy, peripheral and autonomic neuropathy of bladder and gastrointestinal tract). She became significantly malnourished and after multiple failed attempts to establish enteral feeding was commenced on HPN at the age of 35 and continued until her death at age 48 years.

Her weight was 56 kgs with a body mass index (BMI) of 19 kg/m^2. Approximately 75% of estimated calorie requirements were delivered parenterally. The PN schedule included an infusion of 1.5 L of PN 7 nights a week over 12 h containing approximately 275 g carbohydrate: 3 infusions a week also included lipid emulsion. Glycaemic control on PN was challenging with repeated line infections and glycaemic control was poor. 2 years following PN commencement, she started to add insulin directly to PN bags with additional background insulin (Insulatard®) injections subcutaneously. Short acting insulin (Actrapid®) was added directly to the PN bag at approximately 1 unit of insulin per 10 g carbohydrate. In addition to the insulin in PN, doses of long acting insulin (Insulatard®, subsequently Levemir®) from 6 to 22 units were administered subcutaneously. Additional short acting insulin was administered subcutaneously dependent on oral intake in periods off PN.

She continued to add insulin to PN for 10 years, interrupted briefly for a trial of Continuous Subcutaneous Insulin Pump (CSII) therapy that was hindered by her eyesight and compliance issues. In periods off parenteral nutrition she reverted to oral/enteral intake coupled with subcutaneous basal-bolus insulin therapy. HbA1c levels remained above target during this time, and the only instance of recorded severe hypoglycaemia was attributed to a miscalculated correction dose of subcutaneous insulin. She also experienced rebound hypoglycaemia at the end of PN cycles, possibly related to her progressive renal failure, poor compliance with her cortisol replacement therapy or varying basal insulin requirements. This was successfully managed by tapering the PN rate towards the end of infusions. The inability to effect overall better glycaemic control was influenced by her complex personal and psychological state, multiple co-morbidities and sepsis episodes. The addition of insulin to her PN terminated one year prior to her death, due to severe visual impairment. Glycaemic control was notably better with the addition of insulin to the PN and deteriorated significantly after the reversion to subcutaneous insulin administration.

3.2. Case 2

A male who developed Type 1 diabetes when 4 years old. In his 20's he developed severe gastrointestinal dysmotility due to enteric

Table 1
Patient details for cases 1–4.

	Case 1	Case 2	Case 3	Case 4
HPN indication	Enteric dysmotility	Enteric dysmotility	Short bowel syndrome	Short bowel syndrome
Cause of diabetes	Type 1 diabetes	Type 1 diabetes	Pancreatectomy	Pancreatectomy
Year of HPN commencement	1999	1994	2003	2000
Years insulin added to HPN	2001–2012	1995–2015	2004–2007	2003–2009
Weight, kg (BMI kg/m^2) at initiation of HPN	56 (19)	60 (21)	59 (19)	51 (21.8)
HPN volume, mls	1500	2500	2500	3500
% estimated daily calorie requirements delivered parenterally	75	70	100	100
Dextrose, g content	275	300	400	400
Weekly PN regimen	7 nights a week – 3 including lipid; 12 h infusions	7 nights a week – 2 including lipid; 12 h infusions	7 nights a week – 3 including lipid; 12 h infusions	7 nights a week – 3 including lipid; 12 h infusions
Grams of PN dextrose per unit insulin	10	9 initially, subsequently 15	20	18
Long acting insulin	Insulatard, Levemir (6–22 units)	Insulatard 10u	Insulatard 10u	Insulatard 10u
Other subcutaneous insulin	Novorapid (dose titrated to carbohydrate content of meals)	Novorapid (dose titrated to carbohydrate content of meals)	n/a	n/a

neuronitis and underwent several laparotomies and subtotal colectomy. He commenced HPN at age 24 and insulin was added directly to his PN a year later. This practice was continued to his death at the age of 45 from a presumed pulmonary embolus.

Body weight was maintained at 60 kgs and BMI at 21 kg/m^2. Approximately 70% of estimated calorie requirements were delivered parenterally. The PN schedule included an infusion of 2.5 L of PN 7 nights a week over 12 h containing 300 g Carbohydrate: 3 infusions a week also included lipid emulsion. He initially administered insulin entirely subcutaneously for the PN load but 4 years later started short acting insulin (Humulin S®) added directly to the PN bag. Initially 35 units were added to the PN resulting in 1 unit of insulin per 9 g carbohydrate. Subsequently however background insulin was increased to 10 units of long acting insulin (Insulatard®) and the amount of insulin added to the PN was reduced to provide approximately 1 unit of insulin to 15 g carbohydrate. 4 units of quick acting insulin (Novorapid®) were administered subcutaneously for correction doses.

Excellent glycaemic control was maintained for 17 years until his death. He had no recorded admissions for hypoglycaemia.

3.3. Case 3

A female with inherited familial adenomatous polyposis who underwent prophylactic panproctocolectomy at the age of 22. Two years later, a desmoid tumour encasing the superior mesenteric artery required total enterectomy and pancreatectomy with bile duct anastomosis to the stomach and venting gastrostomy. Two years later she was commenced on intravenous hydrocortisone replacement for hypoadrenalism that made her glycaemic control additionally challenging. Insulin was added to PN following the pancreatectomy in 2004 and continued until her death from intestinal failure associated liver disease whilst awaiting multivisceral transplantation in 2007.

Initial body weight was 59 kg at HPN commencement giving a BMI of 19 kg/m^2 100% of estimated nutritional requirements were delivered parenterally. Her PN regimen consisted of 2.5 L of PN 7 nights a week, each over 12 h overnight: 3 infusions a week included lipid emulsion and all bags contained approximately 400 g carbohydrate. Short acting insulin (Actrapid®) was added directly to the PN bag to provide 1 unit of insulin to 20 g carbohydrate. In addition to the insulin in PN, 10 units of long acting insulin (Insulatard®) and 4 units of correction quick acting insulin (Novorapid®) were administered subcutaneously.

No hospital admissions with hypoglycaemia were recorded during this time and she was able to maintain a good quality of life, undergoing teacher training and enjoying foreign holidays.

3.4. Case 4

An unrelated female with Familial Adenomatous Polyposis coli, she underwent total enterectomy, pancreatectomy, colectomy, bile duct anastomosis to the stomach and venting gastrostomy at age 46. Remnant pancreatectomy and splenectomy was carried out at age 50. 100% of estimated nutritional requirements were delivered parenterally. Insulin was added directly to PN a year prior to the completion pancreatectomy.

Initial body weight was 51 kg at HPN commencement giving a BMI of 21.8 kg/m^2 100% of estimated nutritional requirements were delivered parenterally. Her initial PN regimen consisted of 2.5 L of PN 7 nights a week, each over 12 h overnight: 3 infusions a week included lipid emulsion and all bags contained approximately 400 g carbohydrate. Short acting insulin (Actrapid®) was added directly to the PN bag at 1 unit insulin to 18 g carbohydrate. In addition to the insulin in PN, 10 units of long acting insulin (Insulatard®) and 4 units of correction quick acting insulin (Novorapid®) were administered subcutaneously.

Blood glucose readings remained well controlled while on PN (4–9 mmol/l) and background insulin was progressively titrated to reduce inter-feed hyperglycaemia. She continued this practice until her death at age 56 liver disease.

4. Discussion

In theory, the addition of insulin to PN offers an attractive method of mitigating against the complications of hyperglycaemia. Providing a steady supply of insulin alongside the PN infusion allows a smoother glycaemic profile by reducing discordance between insulin dosing and PN administration [3]. However, there remain legitimate concerns about the availability and delivery of insulin and thereby the efficacy as well as risks of hypoglycaemia for this mode of insulin delivery. In the hospital setting, the available clinical data has not highlighted evidence of increased harm with this method of insulin delivery when adequate precautions are taken [2]. However, there is no information available on the safety or efficacy of insulin in PN in patients at home with only one report suggesting that this approach may be safe in patients without pre-existing diabetes who experience feed related hyperglycaemia [9]. Acknowledging the lack of evidence based data on the addition of insulin to HPN, ESPEN have stated that a recommendation on this insulin technique is not possible [3].

In this case series, we have presented our experience of this method of insulin delivery in four patients on HPN. These four patients, two with type 1 diabetes and two following total pancreatectomy, received insulin in PN at home for periods ranging from 3 to

17 years. No significant episodes of hypoglycaemia were recorded. When combined with good self-management behaviours, good control was achieved in 3 of the 4 patients (cases 2 to 4). In two cases where insulin was delivered separately prior to the use of insulin in the PN, glycaemic control appeared to be improved by the addition of insulin to the bag (case 1 and 2). In the other two cases, addition of insulin to the bag was found to provide the best control of their brittle post-pancreatectomy diabetes during prolonged post-operative hospital admissions. It is striking that relatively small amounts of insulin were required in most patients giving a ratio of one unit of insulin for every 10–20 g of carbohydrate in the PN. The two patients with type 1 diabetes appeared to require a greater amount of insulin proportionate to the PN carbohydrate than those after pancreatectomy. This may reflect that in those cases the PN was being supplemented by oral intake and provided a relatively smaller proportion of total estimated calories. It was also notable that over the long duration of the insulin added to these patients' intravenous feeds, the insulin requirements remained relatively stable in most cases. All patients expressed a preference for this route of administration which minimised the impact on their lifestyle as it resulted in more stable blood sugar control, fewer symptoms and reduced the need for blood glucose checks and subcutaneous injections.

5. Conclusion

This report demonstrates that this route of insulin administration in PN-related hyperglycaemia can be safe and effective in the homecare setting. Further studies are needed in the HPN cohort to make safe recommendations for the application of this technique in clinical practice.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2018.11.014.

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