Impaired hypoglycaemia awareness in type 1 diabetes: Can CSII help?

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Article points

1. Hypoglycaemia is the most feared side effect of insulin therapy and it is often the greatest barrier that prevents individuals from achieving glycaemic targets.
2. As continuous subcutaneous insulin infusion (CSII) can closely mimic the normal physiology of insulin secretion, it may be an effective means of managing blood glucose levels while minimising the risk of hypoglycaemia.
3. This article discusses the causes of hypoglycaemia unawareness and advantages of using CSII, and includes findings from the author's cohort of individuals initiated onto CSII.

Key words
- Hypoglycaemia
- Unawareness
- Continuous subcutaneous insulin infusion

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Hypoglycaemia is the most feared side effect of insulin therapy and it is often the greatest barrier that prevents individuals from achieving glycaemic targets (Pramming et al, 1991). In addition to the physical risk, the social and psychological impact of hypoglycaemia unawareness on the individual and their family is devastating.

People with insulin-treated diabetes face a daily dilemma. Evidence from the DCCT (1993) demonstrates that strict glycaemic control and intensive insulin therapy prevent the development of complications associated with diabetes; however, such intensive treatment is associated with a three-fold increase in episodes of severe hypoglycaemia. For individuals who have impaired awareness of hypoglycaemia, this risk increases six-fold (Gold et al, 1994).

As continuous subcutaneous insulin infusion (CSII) can closely mimic the normal physiology of insulin secretion, it may be an effective means of managing blood glucose levels while minimising the risk of hypoglycaemia for selected, appropriately educated and supported individuals (Marcus and Fernandez, 1996).

Hypoglycaemia occurs once plasma glucose concentrations are below 3.5 mmol/l (Pampanelli, et al 1996; Bolli et al, 1993). The fall in plasma glucose levels causes the central hypothalamic autonomic centres in the brain to trigger the activation of the peripheral autonomic nervous system and stimulate the sympathoadrenal system (Bolli, 2003). This response is responsible for many classical autonomic reactions such as sweating and tremor and, as a result of an increase in rate and contractibility, the sensation of a 'pounding heart' (Bolli, 2003). The magnitude of this response is further heightened by the secretion of large quantities of adrenaline from the adrenal medullae (Frier and Fisher, 2000). Thus, the warning signs and symptoms that occur in response to an abnormally low blood glucose level provide a useful defence mechanism for the brain by alerting it to impending neuroglycopaenia. Unlike other tissues, such as muscle and liver, the brain is totally dependent on the oxidation of

glucose for its 'fuel' (Bolli, 2003). As the brain is unable to store or synthesise glucose, an inadequate supply of glucose will cause it to malfunction, with cognitive impairment rapidly becoming evident as an overt manifestation of neuroglycopaenia (Bolli, 1999).

Hypoglycaemia in type 1 diabetes

Inappropriate hyperinsulinaemia is the obvious cause of hypoglycaemia in people with type 1 diabetes, with episodes tending to be more prolonged and severe than in people without diabetes (Bolli et al, 1984).

For people with type 1 diabetes, the defence mechanisms against hypoglycaemia are impaired (Bolli, 1990). As a result of the irreversible loss of the glucagon response within 3–5 years of diagnosis (White, 1994) adrenaline becomes the main influence that provides a counter-regulatory response to hypoglycaemia (Bolli, 1990). However, many individuals have a reduced response to adrenaline, particularly those with a long duration of diabetes (Bolli et al, 1984; Bolli, 1990; Fanelli et al, 1994); thus, these individuals are at risk of episodes of severe hypoglycaemia.

Hypoglycaemic unawareness

As defined by Vignesh and Mohan (2004) hypoglycaemic unawareness is 'the reduced ability or failure to recognise hypoglycaemia at the physiological plasma glucose concentrations at which warning symptoms normally occur'.

The exact underlying mechanisms behind impaired awareness of hypoglycaemia are unknown and, in all probability, the key factors are multifactorial and often interlinked (Frier and Fisher, 2000). Possible causes are listed in *Box 1*.

Compromised glucose counter-regulation

People with type 1 diabetes with combined glucagon and adrenaline defects are at greatest risk of severe hypoglycaemia (Bolli, 1990). This hazard is further heightened for certain groups such as those with autonomic neuropathy. Evidence suggests that such individuals will exhibit an additional defect in adrenaline release during hypoglycaemia (Bottini et al, 1997). Paraplegic individuals, who as a result of a high cervical cord transection lose adrenaline secretion, also lose autonomic response to hypoglycaemia (Mathias et al, 1980).

Glycaemic thresholds

The blood glucose level at which symptomatic hypoglycaemia occurs varies between individuals, with the glycaemic threshold for the onset of symptoms higher in people with a long duration of type 1 diabetes (Vea et al, 1992).

A key factor that will affect the threshold for hypoglycaemic symptoms in insulin-treated diabetes is exposure to prolonged hypoglycaemia (Boyle et al, 1994). Recent studies have demonstrated that the brain adapts to chronic exposure to low blood glucose by increasing glucose transporters localised in the microvessels of the blood–brain barrier (such as GLUT-1), as well as the neuron-specific glucose transporter GLUT-3 (Simpson et al, 1999). The implication for clinical practice is that people with insulin-treated diabetes with on-going sub-optimal control will experience symptoms of hypoglycaemia when their blood glucose declines within a hyperglycaemic range (Boyle et al, 1988). Conversely, chronic exposure to 'tight' glycaemic control will modify the glycaemic threshold for the onset of symptoms so that they do not occur until the blood glucose value has declined to a much lower level than that required in the less well-controlled individual. Therefore, during subsequent hypoglycaemic events, the brain is less neuroglycopaenic than normal and does not need to generate autonomic warning symptoms of impending hypoglycaemia. This is a maladaptive response that may not be beneficial to the individual with diabetes.

Antecedent hypoglycaemia

Antecedent exposure to hypoglycaemia can temporarily induce defective counter-regulation as a response to glucose-sensing neurones altering their hypoglycaemic sensitivity in reaction to a recent previous glucose experience (Levin et al, 1999). Indeed, a single hypoglycaemic episode can reduce counter-regulation responses for the next 24–72 hours (Cryer, 1992).

An individual can be placed at additional risk of antecedent hypoglycaemia while sleeping, as neurohumoral responses to hypoglycaemia are less vigorous (Jones et al, 1998). Indeed, nocturnal hypoglycaemia is often not acknowledged (George et al, 1997).

The process of antecedent hypoglycaemia is less operative in long-term diabetes and autonomic neuropathy (Fanelli et al, 1997).

Page points

1. As the brain is unable to store or synthesise glucose, an inadequate supply of glucose will cause it to malfunction.
2. Hypoglycaemic unawareness is 'the reduced ability or failure to recognise hypoglycaemia at the physiological plasma glucose concentrations at which warning symptoms normally occur'.
3. People with type 1 diabetes with combined glucagon and adrenaline defects are at greatest risk of severe hypoglycaemia.
4. The blood glucose level at which symptomatic hypoglycaemia occurs varies between individuals, with the glycaemic threshold for the onset of symptoms higher in people with a long duration of type 1 diabetes.

Box 1. Potential causes of hypoglycaemia unawareness.

- Chronic exposure to low blood glucose levels.
- Recurrent transient exposure to low blood glucose values.
- Central nervous system glucoregulatory failure.
- Peripheral nervous system dysfunction.
- Certain medications.
- Use of human insulin.
- Alcohol.

Page points

1. Antecedent exposure to hypoglycaemia can temporarily induce defective counter-regulation as a response to glucose-sensing neurones altering their hypoglycaemic sensitivity in reaction to a recent previous glucose experience.
2. β-blockers can affect adrenergic mechanisms by 'blunting' the perception of impending hypoglycaemia. ACE inhibitors and hypothyroid agents have also been implicated.
3. The clear aim of any treatment option is to maintain the safety of an individual by avoiding episodes of hypoglycaemia at all costs.
4. Frequent pre- and post-parandial home blood glucose monitoring is essential as it can increase the detection of low blood glucose values.
5. CSII can closely imitate the normal physiology of insulin secretion and can be a proactive means of managing blood glucose levels while minimising the hypoglycaemic risk.

Other factors

Certain drugs have been implicated in increasing the risk of hypoglycaemia or hypoglycaemic unawareness. β-blockers can affect adrenergic mechanisms by 'blunting' the perception of impending hypoglycaemia (Popp et al, 1984; Hirsch et al, 1991). ACE inhibitors and hypothyroid agents have also been implicated (Morris et al, 1997). The impact of ACE inhibitors is disputed, as highlighted in the HOPE trial (Yusuf, 2000), where no increase in hypoglycaemia was detected for individuals using ramipril.

The use of human insulin has been associated with impaired awareness of hypoglycaemia by affecting the adrenalin response (Teuscher and Berger, 1987); however, evidence to support this view is lacking (Airey et al, 2000; Richter and Neises, 2002).

Autonomic peripheral responses are suppressed by alcohol; this will affect the perception of warning signs and symptoms, thus potentiating hypoglycaemic unawareness (Vignesh and Mohan, 2004).

Treatment options

The clear aim of any treatment option is to maintain the safety of an individual by avoiding episodes of hypoglycaemia at all costs. To this end, treatment goals must be personally tailored and, for some individuals, intensive treatment may be contraindicated. Frequent pre- and post-prandial home blood glucose monitoring is essential as it can increase the detection of low blood glucose values.

Both the appropriateness of the current insulin regimen and the need to relax overall glycaemic control must be considered, as the lessening of strict glycaemic control is associated with an improvement in symptomatic and counter-regulatory hormone responses to hypoglycaemia (Liu et al, 1996). In addition, the scrupulous avoidance of hypoglycaemia through meticulous attention to diabetes management can reverse impaired hypoglycaemic awareness and counter-regulatory hormone deficiency (Cranston et al, 1994).

Continuous subcutaneous insulin infusion (CSII) can closely imitate the normal physiology of insulin secretion and can be a proactive means of managing blood glucose levels while minimising the hypoglycaemic risk for selected, appropriately educated and supported individuals (Marcus and Fernandez, 1996).

The Liverpool cohort

All individuals referred for insulin pump therapy in Liverpool are initially seen by the DSN. This assessment is designed to ensure that the individual's current insulin therapy is optimised and that any educational deficits are identified and rectified. At this appointment, the person with diabetes is also fully informed about the realities of insulin pump therapy. Should the prospective candidate still wish to continue with the assessment process, following discussion of the individual case with the insulin pump multidisciplinary team, the person will be seen at a joint appointment with the consultant and DSN. At this review, in partnership with the individual, a decision will be made regarding converting onto insulin pump therapy.

Fifty people with type 1 diabetes and unawareness of hypoglycaemia were initiated onto CSII. All were using optimised multidose injections incorporating analogues, with an average total daily dose of 53.6 units (SD: ±26.5; range: 24–185). The entire cohort met current NICE criteria for CSII (NICE, 2003).

As anticipated, the cohort had a long duration of diabetes, with a mean of 20.3 years (SD: ±12.8; range: 1–65). The group's overall glycaemic control was suboptimal with an average HbA_{1c} of 7.8 % (SD: ±1; range: 5.3–10.6). General characteristics of the cohort included a mean age of 41.1 years (SD: ±12.8; range: 22–69), an average weight of 74.2 kg (SD: ±131' range: 55.6–124.6) and a mean BMI of 26 (SD: ±3.9; range: 20.5–41). The complications of diabetes included retinopathy (12), peripheral neuropathy (7), gastroparesis (3), nephropathy (2) microalbuminuria (5), hypertension (22) and hyperlipidaemia (18). For the ten individuals who required levothyroxin, replacement laboratory reports indicated adequate replacement.

Outcome

Following an in-house structured education programme and 3 months of CSII therapy, our entire cohort had regained awareness of hypoglycaemia. All individuals described episodes of hypoglycaemia as being 'mild and easy to treat'.

Overall glycaemic control had improved with a mean reduction in HbA_{1c} of 0.5 %. There was also a reduction in the average total insulin dose of 7.9 units and an observed weight loss of 1.3 kg. All individuals opted to continue management of their diabetes with insulin pump therapy (see *Box 2* for a case study).

How has CSII helped?

The advantages of CSII are summarised in *Box 3*. CSII is more able to mimic the physiological secretion of people without diabetes, thereby making it easier to prevent hypoglycaemia (Bolli, 1999). The pump achieves this by replicating basal rate secretion by continuously delivering small doses of rapid-acting insulin which is supplemented by manually-delivered bolus doses when the blood glucose value is high. It is therefore a treatment option that gives flexibility for life events and makes it easier to attain normoglycaemia. Thus, as highlighted by Pickup et al (2002) and observed in our study group, glycaemic control is better during the use of CSII compared with multiple daily injections of insulin (MDI).

Intensive therapy for all individuals using pump therapy is conducted in such a way that we aim to prevent exposure to blood glucose values below 4 mmol/l (3.5 mmol/l in pregnancy), and HbA_{1c} results under 6 % are discouraged. As indicated by Pampanelli et al (1996), this strategy aims to ensure that the secretion of adrenaline and generation of symptoms in response to hypoglycaemia are maintained.

For those individuals with impaired hypoglycaemic awareness initiated onto insulin pump therapy, the meticulous prevention of hypoglycaemia has helped to resolve the situation of hypoglycaemic unawareness and impaired release of adrenaline. This, as illustrated by the Liverpool cohort, can be achieved by 3 months post treatment, providing episodes of hypoglycaemia are prevented (Fanelli et al, 1993). Thus, for individuals with hypoglycaemia unawareness, blood glucose values below 7 mmol/l are avoided and the correction of elevated blood glucose levels is only advised once the blood glucose value is 12 mmol/l or above, providing that the reading was taken a minimum of 2 hours following a previous correction dose or ingestion of carbohydrate. Glycaemic control is not intensified further until symptoms associated with hypoglycaemia have returned.

Insulin delivered via a pump has been shown to be more predictably absorbed than injected insulin (Galloway and Chance, 1994; Haakens et al, 1990). We would therefore suggest that pharmacokinetic factors assisted people using insulin pump therapy to develop more glycaemic stability.

Insulin pump therapy utilises small individualised doses of rapid-acting analogue (occasionally soluble) insulin. This prevents hypoglycaemia that could occur from a large subcutaneous depot and the delayed absorption of longer-acting insulin (Marcus and Fernandez, 1996).

Less insulin is required to achieve glycaemic control in individuals who use CSII rather than MDI (Pickup et al, 2002). One advantage of

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2. Overall glycaemic control had improved with a mean reduction in HbA_{1c} of 0.5 %. There was also a reduction in the average total insulin dose of 7.9 units and an observed weight loss of 1.3 kg.

Box 2. Case study of a person with type 1 diabetes who received CSII

Jo, a 30 year old woman with type 1 diabetes of 13 years duration was referred to the insulin pump therapy team for consideration of CSII. She had on-going glycaemic instability which incorporated up to six asymptomatic episodes of hypoglycaemia on a daily basis. As a result of the hypoglycaemic episodes Jo was socially isolated; she was unable to work, she had lost her driving licence and could not leave the house without carer support. She felt 'life was passing her by'

On assessment, despite an optimised multi-dose injection regimen incorporating lispro and glargine with an average daily dose of 59 units, Jo's overall glycaemic control was suboptimal with HbA_{1c} values in the range of 8–9 %. No educational deficits could be identified and glycaemic stability did not improve following hospitalisation. Jo was overweight with a BMI of 33 kg/m^2.

Following three months of CSII utilising lispro, Jo's glycaemic trends were now predictable and her HbA_{1c} was 7.2 %. Occasional hypoglycaemic episodes were noted; however these events were recognised by Jo and described as mild and easy to treat. Jo had lost weight (BMI 28 kg/m^2) and her insulin demand had reduced to a daily average of 30 units.

Box 3. Advantages of CSII.

Closely mimics physiological insulin requirements.

Insulin delivery is individualised and more reproducible.

Greater flexibility for life events.

Reduced insulin requirements.

Lower plasma insulin levels.

Flexible eating.

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1. Many individuals attempt to avoid hypoglycaemia by overeating. CSII allows flexible eating patterns that deter excessive eating and the need to 'feed' the insulin.
2. One of the key factors that will facilitate the success of pump therapy is a partnership between the insulin pump therapy team and the person with diabetes.
3. The key to reversing hypoglycaemia unawareness is a combination of relaxing glycaemic control and scrupulously avoiding episodes of hypoglycaemia.
4. In summary, we would suggest that CSII should be considered as a treatment option for all individuals who have hypoglycaemic unawareness.

this, as highlighted by Bode et al (1996), is that the lower volumes of insulin will be reflected in lower plasma insulin levels, which will reduce the tendency for hypoglycaemia.

All of the participants reported that when their symptoms returned, hypoglycaemic events were less severe and easier to treat. As insulin delivery is individualised and more predictable, the blood glucose level drops more slowly; thus, the pump user has more time to recognise the symptoms of low blood glucose. As the reaction time lengthens, it becomes easier to deal with the situation before it becomes more severe (Walsh and Roberts, 2000).

Many individuals attempt to avoid hypoglycaemia by overeating (Pickup, 2005). CSII allows flexible eating patterns that deter excessive eating and the need to 'feed' the insulin. As observed in the authors' study group, this can facilitate weight loss.

One of the key factors that will facilitate the success of pump therapy is a partnership between the insulin pump therapy team and the person with diabetes (Marcus and Fernandez, 1996). Effective therapy has its origins in appropriate patient selection, education and on-going support from the multidisciplinary team.

Conclusion

It is evident that frequent exposure to hypoglycaemia is associated with the development of unawareness of low blood glucose values. This effect occurs as a result of blunting the release of counter-regulatory hormones. The key to reversing this situation is a combination of relaxing glycaemic control and avoiding episodes of hypoglycaemia.

As illustrated by selected individuals in this study group, insulin pump treatment can be a useful tool that allows the attainment of more stable blood glucose levels than MDI, thereby reducing the risk of low glucose levels that ultimately can reverse hypoglycaemic unawareness. Although the ability to individualise the basal rate and bolus doses according to need undoubtedly helped with the achievement of glycaemic stability, this is not the whole story. CSII therapy demands certain skills and knowledge for its effective use; therefore, the pump user must be appropriately educated and supported by healthcare professionals.

As an added benefit, it is possible to not only re-establish hypoglycaemia awareness but to improve overall glycaemic control despite a reduction in total dose of insulin.

In summary, we would suggest that CSII should be considered as a treatment option for all individuals who have hypoglycaemic unawareness. ■

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