Insulin pump users would not rule out using an implantable artificial pancreas

Abstract
The aim of this survey was to establish the limitations of open loop continuous subcutaneous insulin infusion (CSII) as perceived by current users of the technology, and to ascertain their interest in and requirements for a non-electronic implantable closed loop insulin pump, INSsmart, currently under development for the treatment of type 1 diabetes. INSsmart has been surgically implanted in the peritoneum in animal models and continuously restored normoglycaemia.

A bottom-up survey design was used to determine both positive and negative experiences of patients currently using CSII to define the performance characteristics they would require from a non-electronic, implantable closed loop insulin pump.

A total of 360 insulin pump users completed the survey. All respondents had type 1 diabetes, were predominantly from English-speaking countries and had been diagnosed before age 34 years. Most had well controlled blood glucose (BG) according to their self-reported HbA1c results. They reported a reduction in this value after transferring to CSII from multi-dose injections. However, 70% of pump users had more than three hypoglycaemic episodes per week. Eighty percent reported self-measured BG values >10mmol/L three or more times per month; 94% of respondents considered a (non-electronic implantable) closed loop insulin pump would make their BG management easier and improve their quality of life.

The majority of respondents felt there were still many disadvantages to current external insulin pumps such as their constant visible presence, rotation of insertion sites and skin inflammation. These shortfalls could be overcome by a device, such as INSsmart, that provides a relatively instant feedback mechanism for controlling insulin release due to its proposed location in the peritoneal cavity. Copyright © 2014 John Wiley & Sons.

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Key words
insulin delivery; implantable insulin pump; CSII; type 1; artificial pancreas

Introduction
Successful glycaemia management in diabetes requires mean blood glucose (BG) concentrations that result in HbA1c values close to the normal range, while avoiding hypoglycaemia. Although of proven efficacy, it is difficult to achieve this chronically using multidose insulin injections or open loop continuous subcutaneous insulin infusion (CSII), as evaluated in the Diabetes Control and Complications Trial (DCCT).1,2 for patients with type 1 diabetes (T1DM).

The attraction of a closed loop insulin delivery system which can maintain normoglycaemia is obvious to both patients and health care services that have to deal with the costs of poor diabetes control around the world.3 In order to produce an effective closed loop system, insulin needs to be released and metabolised over an appropriate time scale to minimise fluctuations in BG levels. Several methods for accomplishing closed loop control have been developed in both human and animal models, but the ‘perfect’ artificial pancreas remains elusive,7,8 because of limitations in one or more of the contributory components of a closed loop system, namely delivery devices and sensors.

External insulin pumps or CSII are driven by mechanical force and provide a continuous infusion of a short-acting insulin delivered from a soft cannula under the skin. The major drawbacks to this therapy, however, are primarily the slow absorption of insulin into the plasma, the need to re-site subcutaneous (SC) cannulas every 48 hours in order to minimise the risk of tube blockages, and skin infection at the insertion sites. These contribute to delays and failures in response and have contributed to the difficulty in converting a CSII system to a closed loop system. Similarly, SC glucose sensors which have become part of some integrated CSII systems rely on the difference between SC glucose and BG being proportional to the
rate of change taking place in BG; this time lag limits the sensitivity of continuous glucose monitors to detect hypoglycaemia; algorithms can be produced to mitigate this where there are sufficient data from sequential readings to give the BG/time gradient.

Intraperitoneal insulin infusion offers a more physiological route for insulin delivery devices, producing greater porto-systemic and hepatic insulin gradients, and controls hepatic glucose metabolism more efficiently. Recent research in our laboratory has focused on producing an implantable insulin delivery device (INSmart) which would deliver insulin to the peritoneum in an automated fashion linked to changing glucose levels (Figures 1a and b). INSmart delivers insulin via a glucose-sensitive gel which acts as both a sensor and controller of the amount of insulin released (Figure 1c). The glucose-sensitive gel comprises polymerised derivatives of dextran and a glucose-sensitive lectin, concanavalin A. The highly viscous gel that forms due to the equilibrium binding between the dextran and the lectin binding sites impedes insulin release. This changes in the presence of glucose as the binding sites are disrupted resulting in a reduction in the viscosity of the gel that facilitates insulin release. This process is both reversible and repeatable, being sensitive to the changes in glucose levels that occur in the peritoneal cavity. The gel layer is therefore both the sensor and the delivery port in this design and contains no electronics or moving parts.

The benefits of an INSmart device for the treatment of diabetes are that it could provide automated control preventing hypoglycaemia and also the long-term harm from hyperglycaemia. However, the associated risks from an implantable device could arise from surgery, leakage of the insulin reservoir and infection. A prototype design was used to demonstrate the feasibility of this novel approach by restoring normoglycaemia in diabetic rats and pigs for up to five weeks but would require some redesign to provide it with biocompatibility, reliability and security to be optimal for clinical use.

In designing a clinically-testable prototype it is important to understand the needs of the market, i.e. potential users, and to assess their reaction to it. To gain these insights it was decided to conduct a survey of current users of CSII.

Method

We surveyed CSII users to determine their current approach to glucose management and their appreciation of its importance, and to understand the practical difficulties of achieving desired control with their current pump therapy. Questions were multiple choice or open ended and addressed various aspects of diabetes management, basal and bolus delivery, diet, hypo- and hyperglycaemia as well as short- and long-term insulin pump management.

We also wanted to know what they thought about the concept of a surgically implantable pump such as INSmart, if it could bring the advantage of closed loop functionality. A closed loop INSmart device or ‘artificial pancreas’ could present an alternative to pancreatic or islet transplants, and to electronic-sensor controlled pumps, assuming biocompatibility, predictability and security can be assured.

Survey design, distribution and response collection. An international survey of patients with diabetes currently using CSII was carried out. This was aimed at gauging their opinions of whether a closed loop implantable insulin pump was an attractive proposition, the premise being that since this group of patients already managed their diabetes in a partly automated way, they might offer unique insights about the concept.

The questionnaires were produced in English and distributed to insulin pump users through various channels. Advertisements were placed in various local and national media (such as newspapers) within the UK, and in publications from various diabetes charities such as Diabetes UK. An interactive web-based version of the survey (Survey Monkey) was also available via a dedicated website for participants who wanted to submit responses via the internet. The UK Diabetes Network and ‘Pumpers’ also distributed copies to members on their databases. Finally, we used social networking sites such Twitter and Facebook to publicise the survey.

Participants answered 56 questions which were either multiple choice or open ended, relating to their background; the insulin pump brand being used; the type of insulin used in the pump; basal and bolus doses; infusion set; insertion sites; the current quality of glycaemic control as evidenced by self-reported HbA1c concentration and the frequency and severity of hypo- and hyperglycaemic events; and self-reported diabetes complications.
Attitudes toward a non-electronic implantable closed loop insulin pump (INSmart)

Specifically, they were asked about the practical difficulties they experienced with CSII in achieving their glucose targets. Finally, they were asked to respond to a description of the implantable closed loop insulin pump, INSsmart, which could make automatic adjustments to the amount of insulin being delivered in response to changing blood sugar and whether this would be an attractive proposition to them. Further open ended questions sought responses about whether an INSmart device implanted under the skin and which was refillable would still appeal to them.

Analysis of responses. The responses from Survey Monkey were downloaded in Microsoft Excel and then coded before inputting into SPSS. All postal responses were entered manually using the same coding directly into SPSS.

Results
In all, 360 completed surveys were received and analysed; 30.4% of responses were from the UK, which is predominantly where the survey was widely distributed and advertised. Many responses were also collected from the USA (39.9%), Canada (2.8%) and 0.35% of the total responses each from Australia, France, India, Israel and Switzerland; however, 25% of respondents did not disclose which country they lived in.

About 88% of the survey respondents were below the age of 34 at diagnosis of diabetes; 36.4% were between the ages of 0–11 years, 27.5% between the ages 12–21, and 24.4% between 22–34 years of age and are thus likely to have T1DM. All responses collected from respondents under the age of 17 were completed by their parents.

Insulin pump users’ current approach to glucose management. Figure 2a shows the most commonly used pump was the Medtronic Paradigm device (57.6%), and insulin aspart (Novorapid) and insulin lispro (Humalog) were the insulins most commonly infused (Figure 2b). Respondents were asked whether the pump they used was chosen by them, or had been given to them by their medical advisors. As 44% had been given the pump by their medical advisors, this suggests that the choice was made by diabetes physicians and/or diabetes specialist nurses rather than patient choice.

When insulin pump users were asked about the amount of insulin they infused over a 24-hour period 50.6% used 20–40 units, 24.4% used 40–60 units and 12.7% have used more than 60 units. Most (57.3%) reported infusing a basal rate of 0.5–1 units/hr, with 29.3% using 1–2 units/hr and 18.4% using 0.5 units/hr. Only 3.2% of respondents infused a basal rate of more than 2 units/hr. Most respondents (52.2%) used the standard or ‘sweep’ bolus to cover meals.

The majority of respondents (65.7%) had an HbA1c value between 42–64mmol/mol (6.0–8.0%), a broadly acceptable range; 13.9% had HbA1c values between 32–42mmol/mol (5.1–6.0%), indicative of overly tight control, associated with a significant risk of hypoglycaemia; 2.8% had HbA1c values >76mmol/mol (9.1%) and 0.3% had values >86mmol/mol (10.0%) which indicates very poor glucose control. In all, 77.8% of people could recall their HbA1c result before starting CSII; 57.3% reported that it had improved subsequently.

About 70% of the respondents reported having a hypoglycaemic episode at least once a week. In most cases (39.9%) respondents were able to sense that they were hypoglycaemic and 51.6% of these respondents confirmed that this occurred at BG <4mmol/L. In all, 79.4% of the respondents reported BG values >10mmol/L more than three times in the month preceding the survey, and most (68.7%) claimed that they would respond by taking a correction bolus straightaway. However, 9.8% reacted to elevated BG by waiting 60–90 minutes before re-testing their BG and 10.1% by drinking water. Some respondents would change their infusion set, in case it had become blocked.
Insulin pump users’ reaction to a description of an implantable closed loop insulin device (INSmart).

Table 1 summarises the responses from an open question asking the respondents what they thought about closed loop insulin delivery from a device like INSmart, which removes the necessity to adjust insulin in response to changes in BG but possibly not to eliminate entirely the need for routine BG tests. Over 90% of respondents were in favour of closed loop insulin delivery and gave reasons for these views; 31.5% of respondents thought that having a closed loop system would provide them with better BG control than their current insulin pump treatment. In particular, 10% of the respondents thought that a closed loop system would offer the best possible chance of achieving glycaemic control in the non-diabetic range. The majority of respondents felt there were still many disadvantages to current external insulin pumps such as their constant visible presence, rotation of insertion sites, cannula site irritation/infection and skin inflammation. The concept of a so-called artificial pancreas is widely acknowledged by interested parties as the ‘holy grail’ in insulin delivery and BG management and, although only 10% of respondents actually selected this answer, many of the other responses encompassed elements of the concept. Other common responses included: ‘It would fit into my lifestyle more easily’ suggesting that they would be able to forget about the constant vigilance required from BG testing and insulin administration; and ‘It would be accurate, safe and sensitive’ which highlights that most people with diabetes still have issues relating to BG control as well as safety.

Only 4% of respondents did not think that closed loop delivery would be an attractive proposition. The main concern from these responses related to a possible failure of the device indicating that they would not feel safe or comfortable allowing a device to deliver their insulin automatically. Other responses included concerns that the device would not allow the user to make their own adjustments and that they would constantly worry that the device would fail. A more obvious reason for not finding this type of device attractive for respondents was they would find the insertion surgery invasive and undesirable. These responses suggest insulin pump users tend to be well adapted to the demands of running a pump safely and effectively and it is not surprising that they would identify not only the advantages, but also the potential disadvantages and hazards of an implantable closed loop system.

Table 2 shows the positive responses to a question where respondents were asked what their opinions would be regarding a closed loop insulin pump that needed to be implanted under the skin. It can be seen that the main concerns about an implantable closed loop delivery device relate to the surgery and the refilling of the insulin in such a device. The main negative responses to an implantable insulin pump related to concerns about the surgery itself and possible resulting infection, as well as device safety, the concept of an implanted device and the impact on others including children.

Figure 3 shows the general preference for refilling an implantable insulin pump, such as INSmart, was weekly (40.5%). This was a deliberately open ended question and the reason most respondents opted for this preference was that they felt this would allow them to remember to refill the reservoir on a set time every week.

Discussion

The bottom-up survey was designed to gain an understanding of insulin pump therapy together with users’ experiences of their condition and treating it with infused insulin. This was aimed at gauging their opinions of whether a closed loop implantable
Attitudes toward a non-electronic implantable closed loop insulin pump (INSmart)

![Figure 3. Responses to the question 'How often would you prefer the pump to be filled?' (Numbers above bars denote the percentage of respondents)](image)

An insulin pump was an attractive proposition, the premise being that, since they already manage their diabetes in a partly automated way, they might be particularly perceptive about the prospect in ways not obvious to others.

Many of the background responses implied that pump users were all type 1 and that they had been diagnosed early in life. The majority of the respondents were from the UK and North America. The lack of responses from France may have been as a result of the survey being written in English, as Sulmont et al.16 have reported that insulin pump use in France, especially for children and adolescents with T1DM, increased 10-fold between 2001 and 2007. A higher proportion of patients with T1DM in the USA use pumps compared with UK residents and these are funded by the medical insurance companies. In the UK, the criteria for pump use are somewhat different and depend more on the local commissioners implementing NICE guidelines17 for pump use.

Clear choices emerged for the pump brand and the insulin type. Bartalo et al.18 have shown that there are no pharmacokinetic or pharmacodynamic differences in the absorption profiles of insulin lispro and aspart and conclude that the use of short-acting insulin in CSII therapy provides a small but statistically significant improvement in glycaemic control compared with regular insulin. Glycaemic control was also dependent on the infusion line and has been shown to deteriorate after 48 hours of use leading to an incremental loss of glycaemic control.19

In this survey, quantities of insulin used per day and the dose rate used were variable but within expected ranges. In general terms, pump users are reported to need about 80% of the dose given to T1DM people by injection, and this relates to the efficiency of converting long-acting insulins to diffusible insulin that can reach the plasma. Basal insulin needs were found to be <1 unit/hr for most of the respondents. Insulin requirements are believed to increase during the night and early morning (dawn phenomenon) due to a decrease in insulin sensitivity caused by cortisol and growth hormone secretion. Basal insulin requirement begins peaking in juveniles (<20 years) before midnight and maintains a relative high throughout the night,20 drops in the morning and increases again from noon to midnight. Basal needs for adults (>20 years) show a more abrupt peak in the morning followed by a drop off until noon and gradually increasing in the evening. Basal rates thus require fine tuning by those on insulin pump therapy.

The bolus pattern, although subject to variation depending on the circumstance, tended towards the standard spike bolus for the respondents in this survey. A spike bolus delivers the incremented dose of insulin in a short time similar to an SC injection and, as most insulin pump users were well versed in judging their insulin input in response to their meals, this method gave adequate blood glucose control. An extended square wave bolus, used by 5.1% of respondents, delivers a larger dose of insulin spread over a longer period of time such as an hour or two and is useful when eating foods high in protein. The delay in the delivery of carbohydrates from the digestive system when eating and digesting protein can approach the insulin duration-of-action, so in these cases the blood glucose level is better controlled by a slow extended release of insulin that matches the profile of carbohydrates entering the bloodstream. In all, 24.4% of respondents used a combination bolus (standard + extended), as often one method of bolusing does not fit the elevated BG levels from the different types of carbohydrates present in their meal. This provides a large initial dose of insulin, and extends the tail of the insulin action. It is appropriate for high carbohydrate and high fat meals such as pizza and chocolate cake.

A super bolus (1.6% of respondents) considers the basal rate delivery of insulin following the bolus, as part of the bolus and can be borrowed ahead and given together with the bolus. This type of bolus is often used to prevent hypoglycaemia. Cukierman-Yaffe et al.21 have reported that there is a significant relationship between glycaemia indices and the use of a bolus calculator (a feature in several insulin pumps). Diabetes patients who used the bolus calculator in 50% of their boluses had a lower HbA1c and mean BG value suggesting better glucose control.

Most responders had very well controlled glucose as described by their HbA1c and reported an improvement after transferring from MDI. However, 70% had more than three hypoglycaemia per week. Frequent troublesome hypoglycaemia with MDI is an indication for CSII and we did not ask whether this frequency had reduced since starting CSII. However, 90% of pump users said they could detect an oncoming hypo and that, for them, it became a problem only if the BG dropped below 4mmol/L.

Continuous glucose monitoring (CGM) using a Guardian sensor has been shown to improve HbA1c values...
over a 12-week period and lower the incidence of hypoglycaemia compared with self-monitoring of BG in CSII users.22–23 There was, however, a high incidence of drop outs for CGM due to patient discomfort. These findings are similar to those reported by a Juvenile Diabetes Research Foundation trial24 which also found a significant improvement in Hba1c of young diabetes patients who used a sensor, although they did not find an alteration in the incidence of hypoglycaemic events.

By contrast, 80% of respondents had BGs >10mmol/L three or more times per month and their remedy was either to give an additional bolus (70%) or watch and wait (10%) or drink water (10%). While 10mmol/L is the upper limit of normal BG levels, this may in practice indicate that levels are much higher. Together, this information about glucose control reveals that, while convenient, pump therapy might be less effective than reported, although not necessarily less effective than MDI therapy. It may be that an anonymised survey elicits information that differs from other sources for a variety of reasons that relate to surveys in general as well as to diabetes. It also implies that despite being on a reliably constant basal dose of insulin and with boosts conveniently selected for delivery to a tailored pattern coupled with features such as electronic memory and safety lockout features, respondents were commonly above the target BG range. An increase in BG with CSII may result from an occlusion of the infusion line or cannula, although more commonly problems arise from human error, for example inaccurate carbohydrate estimation, inaccurate insulin carbohydrate ratios, insulin sensitivity factors, as well as lifestyle factors such as exercise and stress. Whether the postprandial BG peak would be detected would depend on the user testing at the relevant times.

The positive attitude towards an artificial pancreas such as INSIMART focused on the control of BG and user independence as well as improved quality of life. Negative responses were perceptions about relying on an automated system that could possibly fail or not be reliable. The concept of an implantable device rather than an external (and therefore easily-removable) pump was clearly worrying to some. There were comments about the need for comfort, the safety of implantation and maintenance including refill which would all need to be demonstrated for an INSIMART type device to secure approval from the Medical Devices Directive in the UK25 (FDA in the USA).

The behaviour, attitude and use of existing external pump users from the open ended questions from this survey provided some useful feedback toward a redesign of the existing device which has now successfully been implanted into diabetic pigs. It is apparent that current external pumps have shortcomings which an implantable INSIMART device could overcome:

- Automated delivery of insulin to real time changing glucose levels by the fast uptake of glucose in the peritoneum.
- No changing of infusion lines, rotation of sites and not visible.
- No moving parts or electronic power requirements.
- No need to regularly check BG levels.
- No need to bolus for meal times.

However, an implantable INSIMART device would still need to overcome risks such as leakage of insulin or smart gel, infection and surgery.

**Key points**

- A bottom-up survey design was used to determine current experiences of diabetes management by insulin pump users and their attitude toward a non-electronic implantable closed loop insulin pump, INSIMART, currently under development for the treatment of type 1 diabetes. INSIMART has been surgically implanted in the peritoneum in animal models and continuously restored normoglycaemia
- The majority of respondents felt there were still many disadvantages to current external insulin pumps such as their constant visible presence, rotation of insertion sites and skin inflammation. These shortfalls could be overcome by a device, such as INSIMART, that provides a relatively instant feedback mechanism for controlling insulin release due to its proposed location in the peritoneal cavity.
- A closed loop INSIMART device or ‘artificial pancreas’ could present an alternative to pancreatic or islet transplants, and to electronic-sensor controlled pumps, assuming biocompatibility, predictability and security can be assured.

**Conclusion**

The general consensus from the survey was that most respondents felt that an implantable artificial pancreas would be a close match to a functioning healthy pancreas and therefore appealing. The vast majority of respondents felt that there are many disadvantages to using current external insulin pumps such as its constant visible presence, rotation of insertion sites and skin inflammation, the need for frequent BG testing and adjustment of insulin flow in the absence of feedback from an SC implanted sensor. These shortfalls could be overcome by a device, such as INSIMART, that provides a relatively instant feedback mechanism for controlling insulin release due to its location in the peritoneal cavity. Its performance would be a much closer match to a fully functioning healthy pancreas and therefore very appealing to the pump users surveyed. The key requirements of an INSIMART like device identified by the survey are that it needs to be comfortable to ‘wear’, safe and reliable and easily refilled on a weekly basis.

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**Declaration of interests**

There are no conflicts of interest declared.

**References**

References are available in Practical Diabetes online at www.practicaldiabetes.com.
Attitudes toward a non-electronic implantable closed loop insulin pump (INSmart)

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