Hidden Gems

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Contributing Editor

Shining a light into the past for the articles that continue to shape our diabetes clinical practice today

This issue: Pickup JC, Keen H, Parsons JA, Alberti KG (1978) Continuous subcutaneous insulin infusion: An approach to achieving normoglycaemia. *Br Med J* 1: 204–7

The first documented attempt at a portable insulin pump

As evidence gathered during the 1970s for the benefit of glycaemic control on microvascular complications, novel approaches were developed aiming to normalise blood glucose levels in people with type 1 diabetes. Continuous insulin infusion using open or closed loop feedback techniques were initially confined to inpatient care and usually required intravenous cannulation and bulky equipment. This paper by Pickup et al describes the first attempt to transfer this approach to wider settings using a portable, battery-driven subcutaneous device that became the prototype for future insulin pump technology.

Prior to the Diabetes Control and Complications Trial (DCCT Research Group, 1993), belief in the benefit of glycaemic control on long-term microvascular complications in type 1 diabetes was based largely on observational evidence, at the time still inconclusive. By the late 1970s, attention was focusing on the challenge of optimising glycaemic control (and if possible normalising blood glucose levels) in such individuals, particularly those exhibiting "brittle" patterns clearly associated with poor shorter-term outcomes.

Interest in the "artificial pancreas" concept was emerging also during this time, through which closed-loop feedback techniques could automatically adjust insulin delivery according to requirement (Albisser et al, 1974). But there were problems with this approach, not least the bulkiness of the equipment and the need for intravenous cannulation, making it difficult if not impossible in the "real world" setting. The subcutaneous delivery route offered a much more tolerable cannulation site, reduced infection risk, and portability.

The Hidden Gem

Pickup et al (1978) report a study in which twelve patients were recruited to use a continuous subcutaneous insulin infusion (CSII) device at Guy's Hospital, London over a period of 3–4 days. This was a novel approach at the time. The term "type 1" was not used in this paper but the participants (ages ranging from 19 to 63 years) had all developed diabetes as children or young adults, with just one as old as 35 years at diabetes onset. One patient was newly diagnosed 6 months before the study, while the 63-year-old had been diagnosed 37 years beforehand. All were already established on insulin, mostly using twice-daily regimens combining short-acting and intermediate-acting formulations, as was common practice at that time. Only one individual was taking a lunchtime dose in addition to the twice-daily regimen.

Following admission, the participants were monitored for a "control" day, during which frequent blood glucose measurements were taken on their usual insulin regimen. They were given a standard breakfast (total carbohydrate 50 g) followed by "*the prescribed diabetic diet for that patient*". A subcutaneous cannula was inserted to the abdomen under a local anaesthetic, connected to a small battery driven syringe pump. On the following (insulin infusion) day, a basal rate was set for delivering the insulin and this rate was increased eight-fold for 17 minutes prior to each meal. The infusion rates were estimated both through the patient's overall insulin requirement and the blood glucose levels during the control day.

This study was designed largely to confirm feasibility of the technique but the impact on glycaemic control was also investigated. Measurements of glycaemic variation included not only the mean value from the frequently monitored venous samples, but also the M value, which rises in response to either low or high blood glucose levels. This value is a better measure of

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control adequacy than the mean value alone, as it recognises the detrimental effect of increased hypoglycaemia risk through a general lowering of blood glucose levels.

The "pump" prototype

At 14.5 x 2.2 x 4.2 cm, the device was significantly larger than modern insulin pumps but still compact. The subcutaneous route was a great step forward for the ambulatory setting, but this prototype device still required application by a clinician to the abdominal wall under local anaesthetic, and a bandage around the trunk to keep it in place. In four cases there were problems with cannulation causing loss of data. This tended to happen at night either through kinking of the delivery tube or the cannula simply falling out.

Results

The results of the study were variable in terms of blood glucose response. In one case of a 48-year old woman originally diagnosed at 16 years of age, both mean blood glucose and the range of values were reduced when using the pump. Whereas in five patients, glycaemic control was improved in terms of mean blood glucose value, but not all had improved M values (as the blood glucose in some cases fell too low at times). In a further six patients, the mean value didn't change significantly but the M value improved. And in just two patients, control was worsened through use of the pump, because of difficulties estimating the appropriate infusion rates.

The 12th case in this report was a 39-year-old woman who had developed diabetes at the age of 9 years. She was described as "brittle" (prone to unpredictable glycaemic episodes). Due to poor glycaemic control (with high mean glucose and M values) on the control day, a rate of insulin infusion was set that was nearly twice (193%) her usual overall daily dose. The patient was observed to have much better control based on these two indices, but experienced frequent episodes of hypoglycaemia requiring oral glucose.

The authors concluded that the new technique was feasible and justified further investigation through longer-term studies. These might not only confirm acceptability in more natural settings, but also measure the benefits of maintaining close to normal blood glucose levels for prevention of complications, symptom control and quality of life.

Why it shines today

This short but seminal report ushered in a novel approach to insulin delivery that has become a mainstay of modern type 1 diabetes management. The benefits of glycaemic control for prevention of microvascular complications, described as "controversial" in the opening line, became established in later years through randomised trials, emphasising the value of long-term normoglycaemia where this could be safely achieved. For people with type 1 diabetes treated from a young age or at an early stage of their diabetes, and where risk of hypoglycaemia is not unacceptable, intensive insulin therapy confers benefits in terms of microvascular disease prevention (Fullerton et al, 2014). The use of portable, battery-driven insulin pumps is now widespread among individuals with type 1 diabetes.

While undertaken in controlled conditions, this study confirmed the feasibility and acceptability of the device to the users and its potential for use in everyday settings. The results did not show an overwhelming improvement in glycaemic control in this small sample, but the technique appeared to be safe and important obstacles were identified. These included the difficulties in maintaining cannulation (particularly during the night, when risk of kinking or falling out was increased) and in optimising insulin delivery rates.

In contrast to intravenous infusion, the subcutaneous route carried the advantage of tolerability, portability and reduced risk of infection. It also provided some protection against ketoacidosis in the case of pump failure, as the subcutaneous pool of insulin would offset the otherwise rapid decline in plasma insulin levels seen when an intravenous pump is switched off or fails. However, subcutaneous delivery does not allow rapid response of insulin infusion rates in response to changes in blood glucose levels, a continuing obstacle to closed loop feedback systems.

The report is also historically interesting because it anticipates the development of the basal–bolus approach, in which background (basal) insulin is clearly distinguished from the bolus phase associated with food intake, whose timing can then be varied. This approach was already used during the 1970s, usually using twice-daily intermediate acting insulins (and longer duration formulations were available) with short-acting soluble insulins (such as Actrapid®) to cover meals. But the basal–bolus approach came into its own through even more rapidly acting prandial insulin analogues that (due to short duration of action) avoided overlap of doses if the timing of meals was variable. Only one of the 12 people enrolled in this study was using a regimen involving more than two injections a day. A sample of people with type 1 diabetes today would perhaps include a majority using a more flexible regimen, freeing them somewhat from the need for regularity in the timing of meals.

The device used in the study was a prototype of the "Mill Hill infuser", which became commonly used as a basis for delivering not only insulin but a range of drugs and hormones, and has won a place as an exhibit in the Science Museum in London (http://bit.ly/17pGh4l [accessed 18.02.15]). Later CSII devices were able to replicate natural insulin profiles more accurately. These are designed to recognise that as well as variability in the timing and quantity of carbohydrate intake, requiring flexibility in bolus dosing, the basal component itself may be variable within the individual, e.g. following a diurnal cycle. Modern devices can provide an important function that was still some way in the future at the time of this study – basal delivery rates that are programmed to vary over the 24-hour period.

Much research into pump technology has occurred since this original study, and the devices themselves have become increasingly sophisticated, enabling the patient to tailor insulin delivery to insulin requirement much more effectively. The most recent Cochrane review of CSII in people with type 1 diabetes compared with multiple injections (Misso et al, 2010) synthesised 23 randomised trials and suggested an overall benefit to glycaemic control, reduced risk of severe hypoglycaemia and improved quality of life.

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Fullerton B, Jeitler K, Seitz M et al (2014) Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. *Cochrane Database Syst Rev* **2**: CD009122

Misso ML, Egberts KJ, Page M et al (2010) Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev* **1**: CD005103