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Dorothy Hodgkin Lecture 2013: Artificial Pancreas Project at Cambridge 2013

R. Hovorka^{1,2}

¹Wellcome Trust–MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK

²Department of Paediatrics, University of Cambridge, Cambridge, UK

Abstract

The development and clinical testing of closed-loop systems (the artificial pancreas) is underpinned by advances in continuous glucose monitoring and benefits from concerted academic and industry collaborative efforts. This review describes the progress of the Artificial Pancreas Project at the University of Cambridge from 2006 to 2014. Initial studies under controlled laboratory conditions, designed to collect representative safety and performance data, were followed by short to medium free-living unsupervised outpatient studies demonstrating the safety and efficacy of closed-loop insulin delivery using a model predictive control algorithm. Accompanying investigations included assessment of the psychosocial impact and key factors affecting glucose control such as insulin kinetics and glucose absorption. Translation to other disease conditions such as critical illness and Type 2 diabetes took place. It is concluded that innovation of iteratively enhanced closed-loop systems will provide tangible means to improve outcomes and quality of life in people with Type 1 diabetes and their families in the next decade.

Introduction

This review outlines the progress of the Artificial Pancreas Project at the University of Cambridge. Initial studies under controlled laboratory conditions, designed to collect representative safety and performance data, were followed by short to medium free-living unsupervised outpatient studies demonstrating the safety and efficacy of closed-loop insulin delivery using a model predictive control algorithm. Accompanying investigations included assessment of the psychosocial impact and key factors affecting glucose control such as insulin kinetics and glucose absorption. Translation to other disease conditions such as critical illness and Type 2 diabetes took place.

The justification for the research into the artificial pancreas is clear-cut. Intensive insulin therapy, the standard of care in the management of Type 1 diabetes in the last two decades, is limited by increased risk of hypoglycaemia. Closed-loop systems may improve glucose

Correspondence to: Roman Hovorka.rh347@cam.ac.uk.

Competing interests

RH reports having received speaker honoraria from Minimed Medtronic, Lifescan, Eli Lilly, BBraun, and Novo Nordisk, serving on advisory panel for Animas, Minimed Medtronic, Merck, and Eli Lilly, receiving license fees from BBraun, Medtronic, and Becton Dickinson, having served as a consultant BBraun, Sanofi-Aventis, and Profil, and patent applications.

control and simultaneously reduce the risk of hypoglycaemia, and differ from conventional pump therapy through the use of a control algorithm that automatically reduces and increases subcutaneous insulin delivery according to sensor glucose levels.

Comprehensive reviews of the underlying concepts and summaries of the clinical results of work carried out globally are available elsewhere [1–3].

Inpatient overnight and day-and-night studies

Cambridge inpatient studies assessed the safety and efficacy of closed-loop insulin delivery under lifestyle conditions known to affect glucose metabolism. We used a single continuous glucose monitor, calibrated according to the manufacturer's instructions, without recalibration even in the case of large sensor errors. This mimicked home conditions where frequent reference glucose measurements and recalibration are not feasible. We collected representative safety data allowing us to progress to home unsupervised studies without the need for transitional hotel/camp investigations or remote monitoring.

Initially, we focused on the overnight closed loop and performed three randomized control studies in 19 children and adolescents aged 5–18 years [4] and two randomized control studies in 24 adults aged 18 years and older [5]. The effects of large evening meals, 40-min-long late afternoon exercise and evening alcohol intake on overnight glucose control were evaluated. Closed loop increased the time that plasma glucose was within the target range of 3.9–8.0 mmol/l in both young (mean 40% vs. 60%, $P = 0.002$) and adults (mean 50% vs. 76%, $P < 0.001$) compared with conventional pump therapy. Pooled analysis showed an increase in time in target from mean 43% to 71% ($P < 0.001$), and reduced time spent < 3.9 mmol/l from median 4.1% to 2.1% ($P = 0.01$) and > 8.0 mmol/l from median 33% to 20% ($P = 0.03$). Overnight closed loop in 11 young children aged 3–6 years documented comparable glucose control using standard strength insulin aspart (U100) and diluted insulin (U20) [6] with good overnight glucose control and a tendency towards reduced hypoglycaemia and reduced glucose variability using diluted insulin.

A randomized control study investigating a 36-h day-and-night closed loop, applying algorithm-driven insulin delivery overnight and between meals with manual prandial boluses delivered using a standard bolus calculator, in 12 adolescents undertaking unannounced moderate intensity exercise on a stationary bicycle in the morning (40 min) and afternoon (20 min) showed increased percentage time when glucose was in the target range between 3.9 and 10 mmol/l (median 84% vs. 49%; closed loop vs. conventional pump therapy, $P = 0.02$), reduced mean plasma glucose levels (mean 7.1 vs. 9.1 mmol/l, $P = 0.02$), and comparable time spent in hypoglycaemia ($P = 0.85$). Hypoglycaemia occurred on ten occasions during control visits and nine occasions during closed-loop delivery (five episodes were exercise related, and four occurred within 2.5 h of prandial bolus). Follow-up investigations evaluated 36 h day-and-night closed loop with prandial boluses reduced by 25% in eight adolescents to investigate whether this approach prevents postprandial hypoglycaemia. Despite lower overall insulin delivery (median 62 vs. 73 U; reduced boluses vs. standard boluses, $P = 0.01$) leading to lower mean plasma insulin concentration (186 vs. 252 pmol/l, $P = 0.002$), mean glucose using the two bolus delivery approaches was identical

(8.4 vs. 8.4 mmol/l, $P = 0.98$) and time in target ($P = 0.87$) and below target ($P = 0.88$) were similar. Hypoglycaemia occurred once 1.5 h post-meal during closed loop with standard bolus. Closed loop during reduction and omission of meal insulin boluses was investigated over 24 h in 12 suboptimally controlled adolescents [7]. Plasma glucose was in target between 3.9 and 10 mmol/l for median 74% of the time during closed loop and median 62% of the time during conventional insulin pump therapy ($P = 0.26$). Time above ($P = 0.88$) and below ($P = 0.24$) target and plasma glucose (mean 8.0 vs. 7.7 mmol/l, $P = 0.79$) were also similar. The study documented the safety and efficacy of closed loop in scenarios mimicking non-compliant behaviours in a group of adolescents with poorly controlled diabetes.

A multicentre randomized 23-h day-and-night loop study in 46 adults compared Cambridge control algorithm, iAP algorithm and conventional pump therapy [8]. The Cambridge algorithm was detuned to account for sensor over-reading and applied prandial insulin boluses reduced by 25%. In an intention to treat basis, time spent in the target range was similar (mean 62.6% conventional pump therapy vs. 59.2% iAP algorithm vs. 58.3% Cambridge algorithm). Although the glucose level was significantly lower in conventional pump therapy (mean 7.19 vs. 8.27 vs. 8.26 mmol/l, $P = 0.001$), percentage of time spent in hypoglycaemia (< 3.9 mmol/l) was reduced during closed loop (median 6.4% vs. 2.1% vs. 2.0%, $P = 0.001$). The amount of delivered insulin was lower using Cambridge algorithm (mean 1.8 vs. 1.7 vs. 1.6 U/h, $P = 0.001$) documenting its ability to titrate insulin efficiently.

Ten women were studied over 24 h during early (15 weeks) and late pregnancy (28 weeks) [9]. During day-and-night closed-loop insulin delivery, plasma glucose levels were median 6.5 mmol/l in early gestation and median 7.0 mmol/l in late gestation ($P = 0.72$). There were no differences in overnight time in target ($P = 0.09$), overnight time spent hyperglycaemic ($P = 0.25$) and hypoglycaemic ($P = 0.18$) between early and late pregnancy. Another 12 pregnant women underwent day-and-night closed loop and performed normal daily activities (standardized meals, snacks and exercise) for 24 h on two occasions at 19 and 23 weeks' gestation [10]. Plasma glucose time in target (3.5–7.8 mmol/l) was comparable for closed-loop and conventional insulin therapy (median 81% vs. 81%; $P = 0.75$). Less time was spent hypoglycaemic [< 2.5 mmol/l (median 0.0 vs. 0.3%); $P = 0.04$] during closed-loop insulin delivery.

Free-living overnight and day-and-night home studies

In 2012, we initiated unsupervised free-living closed-loop studies and confirmed findings from inpatient studies. Overnight closed-loop insulin delivery over 3–4 weeks reduced overnight glucose by a mean of 0.8 mmol/l in 16 adolescents in a single-centre randomized study ($P < 0.001$) [11] and 24 adults in a multicentre randomized control study ($P < 0.005$) [12]. After pooling data (total 850 closed-loop nights) and adopting intention to treat analysis, the proportion of time spent overnight in hypoglycaemia below 3.9 mmol/l was reduced from median 2.9% to median 1.9% ($P = 0.014$), and the proportion of time spent in the target glucose range from 3.9 to 8 mmol/l was increased from mean 41% to mean 59% ($P < 0.001$) [13]. Twenty-four hour mean glucose was reduced by 0.5 mmol/l ($P = 0.016$) despite unchanged overall 24 h insulin delivery ($P = 0.84$) [13].

A multicentre multinational trial in 17 adults investigating day-and-night free-living closed loop over one week documented reduced 24 h glucose by mean 0.7 mmol/l ($P = 0.027$), although time spent in hypoglycaemia below 3.9 mmol/l was unchanged ($P = 0.34$) [14]. The proportion of time spent with glucose in the target range from 3.9 to 10 mmol/l increased from median 62% to median 75% ($P = 0.005$) with a trend towards reduced total daily insulin dose from mean 45 U/day to 39 U/day ($P = 0.11$) [14]. This suggests that insulin can be more efficiently and sparingly titrated by an automated control algorithm than by pre-programmed pump delivery.

In the overnight adolescent study, no severe hypoglycaemia event was observed. In adult home studies, no severe hypoglycaemia events were observed during control therapy and three events during closed-loop period, but none were attributed to closed loop, which was turned off when these events occurred. One event likely resulted from incorrect pump priming, another nocturnal event was compounded by increased physical activity during the day, and another likely resulted from stacked insulin during an insulin bolus correction.

Characteristics of our early home studies include no remote monitoring or close supervision, unlike in other transition, diabetes camp or outpatient studies. Participants started and stopped closed loop on their own volition with no restrictions on diet. They were instructed not to use closed loop during vigorous exercise or during intercurrent illness. They used a standard bolus wizard for prandial insulin delivery and could co-administer correction boluses while closed loop was turned on.

Psychosocial outcomes

Prior to performing home studies, we examined parenteral attitudes to overnight closed loop in families with children and young people with Type 1 diabetes [15]. In focus group settings, we explained the concept of closed loop and presented plans regarding the Artificial Pancreas Project at Cambridge. Nineteen parents (12 mothers and 7 fathers) anonymously completed a questionnaire. Achieving good glucose control represented major challenge for carers (83%) with night-time being the most difficult period to manage (56%), worrying most parents (71%) particularly because of fear of hypoglycaemia (33%). The development of closed loop to manage diabetes was welcomed by all parents (100%). All parents were ready to respond to additional alarms at night with 90% parents not worried about their child's overnight insulin delivery being controlled by a computer [15].

These positive attitudes towards closed loop were confirmed in semi-structured interviews with 15 adolescents aged 12–18 years and 13 parents participating in a three-week home overnight closed-loop study [16]. Key positive themes included reassurance/peace of mind, confidence, time off from diabetes demands, safety and improved diabetes control. Key negative themes included difficulties with calibration, alarms and the size of the devices. A similar investigation in 24 adults undergoing home overnight closed loop identified key positive themes: improved blood glucose control ($n = 16$), reassurance/reduced worry ($n = 16$), improved overnight control leading to improved daily functioning and diabetes control ($n = 16$), and improved sleep ($n = 8$) [17]. Key negative themes were technical difficulties (n

= 24), intrusiveness of alarms ($n = 13$) and size of equipment ($n = 7$). Twenty participants (83%) would recommend the closed-loop technology.

Insulin absorption

Our inpatient closed loop enabled us to investigate the kinetics and variability of insulin aspart absorption known to affect safety and effectiveness of closed-loop insulin delivery. Pooled analysis of 5804 plasma insulin concentrations measured in 70 participants (39 females, 46 young) aged 6 years and older attending closed-loop studies documented time-to-peak of aspart plasma concentration of mean 66 min and 33% between-subject variability [18]. Inter-occasion variation accounted for 37% of the total variance documenting low reproducibility and predictability of the rate of insulin absorption. BMI, total daily dose, age, glycated haemoglobin and duration of diabetes could explain only 13% of total variance in the absorption rate by a linear regression model [18], documenting that the rate of absorption is difficult to relate to common anthropometric and biomedical factors.

Investigations of 1302 plasma insulin measurements in 22 pregnant women attending closed-loop studies documented time-to-peak of aspart concentration of mean 55 min with a faster absorption of mean 40 min after breakfast followed by moderate physical exercise [19]. There was strong evidence of delayed aspart absorption with advancing pregnancy. The time-to-peak aspart concentration was delayed by 1.6% per week; absorption appears ~ 50% slower at 38 weeks compared with 8 weeks of gestation. The percentage of inter-occasion variation out of total variation for time-to-peak was high at 83%, implying that most variability is occasion specific rather than individual specific. This suggests that aspart pharmacokinetics is considerably less reproducible in pregnancy.

Absorption of standard strength aspart (100 U/ml) and diluted aspart [1 : 5 dilution with saline (154 mmol/l NaCl); 20 U/ml] was investigated in 11 young children aged 3–6 years [20]. No change in time-to-peak was observed between standard (mean 59 min) and diluted (mean 62 min) aspart although reduced inter-subject variability of time-to-peak was documented with diluted aspart ($P = 0.047$) suggesting that the use of diluted aspart may provide a more consistent plasma insulin concentration and may be preferable for closed loop in young children requiring small insulin doses.

Gut absorption

The rate of total glucose appearance in postprandial conditions exceeds the capacity of prandial insulin to augment glucose disposal and suppress endogenous glucose production, resulting in hyperglycaemia due to the mismatch between total glucose appearance and total glucose disappearance, particularly following the consumption of large meals. Attempts to overcome meal-related hyperglycaemia by increased prandial insulin often results in late postprandial hypoglycaemia due to relatively slow absorption of rapidly acting insulin analogues. Using an innovative two-visit multiple stable-label tracer dilution approach, we measured glucose appearance attributable to meals containing complex and simple carbohydrates in eight adolescents [21]. We documented differences between absorption patterns of meals with low- and high-glycaemic load affecting optimum prandial insulin dosing. Glucose attributable to the high glycaemic load meal appeared significantly faster

compared with the low glycaemic load meal ($P < 0.003$). However, higher apparent bioavailability (by 15%; $P = 0.037$) was observed after the low-glycaemia meal.

A simpler experimental approach using a single stable-label tracer to measure total glucose appearance following digestion of mixed meals over 24 h without the ability to distinguish between gut absorption and endogenous glucose production was utilized in 10 pregnant women [22] and 8 adolescents undergoing closed-loop studies. In late gestation, we found that postprandial glucose control was impaired by significantly slower glucose disposal. In adolescents with inadequate glucose control, we found that following 25% reduction of prandial insulin boluses, total glucose appearance and disappearance over 24 h were similar despite lower 24 h plasma insulin concentration.

Model predictive control

We developed a control algorithm based on the model predictive control paradigm and used it in all our inpatient and outpatient studies. The treat-to-target algorithm calculates a new insulin infusion rate utilizing a compartment model of glucose kinetics describing the effect of rapid-acting insulin and the carbohydrate content of meals on glucose levels. The algorithm is initialized using pre-programmed basal insulin delivery, participant's weight and total daily insulin dose.

The algorithm adapts itself to a particular subject. Several competing models differing in the absorption of subcutaneous insulin and oral carbohydrates ran in parallel. The algorithm aims to achieve glucose levels between 5.8 and 7.2 mmol/l and adjusts the actual level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions. Safety rules limit maximum insulin infusion and suspend insulin delivery at a sensor glucose level at 4.2 mmol/l or when the sensor glucose level is rapidly decreasing.

Beyond Type 1 diabetes

We applied the closed-loop approach to the intensive care setting [23]. Twenty-four critically ill adults (predominantly trauma and neuroscience patients) were randomized to receive either fully automated closed-loop therapy (model predictive control algorithm directing insulin and 20% dextrose infusion based on frequently recalibrated continuous subcutaneous glucose values [24], $n = 12$) or a local protocol ($n = 12$) with intravenous sliding-scale insulin, over a 48-h period. The time when reference plasma glucose was in the target range was significantly increased during closed-loop therapy (median 54% vs. 19%, $P = 0.001$). Reference glucose was significantly lower during closed loop (mean 7.8 vs. 9.1 mmol/l, $P = 0.001$) without hypoglycaemia during either therapy [23].

In preparation for testing closed loop on the general ward in patients with Type 2 diabetes, we performed a feasibility study in 12 insulin-naïve subjects with Type 2 diabetes who underwent two 24 h visits (closed loop and control) in a randomized crossover design [25]. Compared with conventional therapy, closed loop increased the time in target plasma glucose (3.9–8.0 mmol/l) from median 24% to 40% ($P = 0.016$). The benefit of the closed-loop system was more prominent overnight, with greater time in target glucose (median 78%

vs. 35%; $P = 0.041$) and less time in hyperglycaemia (median 22% vs. 65%; $P = 0.041$). There was no hypoglycaemia during either intervention [25].

Bigger picture and way forward

Closed-loop glucose control is nearing translation to clinical practice. Low-glucose suspend, termed threshold suspend in the USA, interrupting insulin delivery at hypoglycaemia threshold has been shown to be effective in reducing the risk and duration of hypoglycaemia in hypoglycaemia-prone individuals [26] and is used clinically. Low-glucose predictive suspend, interrupting insulin delivery when hypoglycaemia is predicted, is undergoing home testing.

The research into outpatient active above-basal insulin dosing by closed-loop insulin delivery systems is buoyant. Studies have been carried out in camp settings overnight [27], during hotel/supervised translational settings [28], and overnight in remotely monitored home settings [29]. Several studies documented reduced rates of hypoglycaemia as the major effect and some documented increased time glucose was in the target range. Longer and larger studies evaluating the effect on HbA_{1c} are the next step, as well as delineating safety and efficacy in various subpopulations including young children, poorly controlled, newly onset, elderly, hypoglycaemia unaware and pregnancy.

Glucagon co-administration shows promise, as demonstrated by studies in diabetes camp and closely supervised outpatient settings, with improved glucose control and reduced risk of hypoglycaemia, albeit with aggressive insulin dosing and large glucagon doses [30]. An alternative use of glucagon to prevent hypoglycaemia without deliberately augmenting insulin delivery has been studied and its benefits over single-hormone insulin-only delivery documented during the day, but not overnight [31]. Co-delivery of other hormones such as analogue of amylin pramlintide [32] and a glucagon-like peptide-1 agonist exenatide [33] may enhance closed-loop performance.

The accuracy of advanced continuous glucose monitors with mean absolute relative deviation of 10% or less no longer poses a barrier to closed-loop glucose control and factory-calibrated continuous glucose monitoring, albeit not yet suitable for integration into the closed-loop system, will further increase convenience and reduce burden-associated device wear. Additional innovations may include single-port glucose sensing/insulin delivery, highly anticipated ultrafast insulin analogues, dual-chamber pumps for dual-hormone closed-loop systems, improved insulin infusion sets and room temperature-stable glucagon formulations.

Conclusions

The future for closed-loop systems is bright. Although not perfect or curative, in the next decade, closed-loop systems will undergo incremental refinements underpinned by innovation potential. Given the challenges and developmental timelines faced by other treatment modalities such as immunotherapy and cell-based therapies, closed-loop systems provide a relatively fast-track to translation offering means to improve outcomes, increase

quality of life and allowing flexible management approaches for people with Type 1 diabetes and their families.

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