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MEETING PROCEEDINGS

Insulin Delivery Route for the Artificial Pancreas: Subcutaneous, Intraperitoneal, or Intravenous? Pros and Cons

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Abstract

Insulin delivery is a crucial component of a closed-loop system aiming at the development of an artificial pancreas. The intravenous route, which has been used in the bedside artificial pancreas model for 30 years, has clear advantages in terms of pharmacokinetics and pharmacodynamics, but cannot be used in any ambulatory system so far. Subcutaneous (SC) insulin infusion benefits from the broad expansion of insulin pump therapy that promoted the availability of constantly improving technology and fast-acting insulin analog use. However, persistent delays of insulin absorption and action, variability and shortterm stability of insulin infusion from SC-inserted catheters generate effectiveness and safety issues in view of an ambulatory, automated, glucose-controlled, artificial beta cell. Intraperitoneal insulin delivery, although still marginally used in diabetes care, may offer an interesting alternative because of its more-physiological plasma insulin profiles and sustained stability and reliability of insulin delivery.

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The development of an artificial endocrine pancreas aims to restore stable near-normoglycemia in insulin-deficient diabetic patients. Three crucial components are needed to achieve this optimal replacement therapy: a glucose sensor, a control system, and an insulin delivery device.[1] The glucose sensor's duty is to generate almost continuously a signal corresponding to blood glucose level. This signal serves as input for the algorithm of the control system that is expected to compute the amount of insulin to be delivered to keep glucose in a narrow, close-to-normal range. The question of the most appropriate delivery route to be used by the insulin infuser is still debated.[2] Indeed, the answer must take into account both pharmacokinetic and -dynamic factors, but also the feasibility and the availability of the infusing devices, so that ultimately an ambulatory use of the artificial beta cell can be sustained safely and at an affordable cost. Since the 1990s various options have included intravenous (IV), intraperitoneal (IP), and subcutaneous (SC) insulin delivery routes. The present paper analyzes the pros and cons of these different pathways.

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Abbreviations: (CSII) continuous subcutaneous insulin infusion, (IP) intraperitoneal, (IV) intravenous, (MPC) model predictive control, (PID) proportional-integral-derivative, (SC) subcutaneous

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Intravenous Insulin Delivery: A Historical Background

In the 1970s, IV insulin infusion was almost naturally selected as the best way to deliver insulin during the elaboration of the bedside artificial pancreas.[3,4] Tuning of insulin action is helped by the easy modulation of IV insulin delivery; no delay due to absorption and short duration of action allow for rapid changes if needed. In the hospital setting, IV insulin infusion raises no problem of vascular access, which can be changed as needed. Moreover, high reactivity of insulin action according to delivery rate allows quick corrective measures related to potential glucose sensor errors. Use of IV glucose sensing and insulin delivery has been shown to be effective on glucose control in patients showing brittle diabetes, thanks to proportional-derivative algorithms. Although still used for investigational purpose, the bedside artificial pancreas cannot, however, be considered for ambulatory use.

Because of the pharmacokinetic and -dynamic advantages of the IV route, it has been tested with implantable insulin delivery devices from the 1970s up to the early 1990s.[5] The first models were nonprogrammable and infused insulin using a peristaltic mechanism. The constantly positive pressure in the infusing central IV catheter minimized clotting issues.[6] Newer pump models that use a pulsatile infusion mechanism have experienced frequent catheter problems, including IV migrations and obstructions by fibrin clots that could even lead to intravenous subclavian thrombosis, and have an average 1-year catheter survival rate of 64%, .[7] The lack of constant positive pressure inside the catheter likely promoted these recurrent events. Although effectiveness of glucose control by IV insulin infusion from these implanted pumps led to near-normoglycemia, the limitations caused by catheter complications stopped the development of this route of insulin delivery in favor of intraperitoneal infusion. No further attempt of IV insulin delivery for ambulatory use has been reported.

The current conclusion is that in spite of pharmacokinetic and -dynamic benefits, IV insulin delivery for an artificial pancreas model does not seem to be feasible for expected home use.

Subcutaneous Insulin Delivery: A Widespread Experience

Since the late 1990s, continuous subcutaneous insulin infusion (CSII) has become the usual mode of insulin pump therapy worldwide. Moreover, availability of fast-acting analogs has provided significant improvements in terms of pharmacokinetics and -dynamics. In contrast to regular insulin infusion, an increase in delivered dose as a bolus does not alter the time to peak and the duration of action.[8] Variability of insulin action related to both the basal rate and the bolus infusion is significantly reduced by fast-acting analogs.[9] As a consequence, postmeal spikes can be reduced and incidents of severe hypoglycemia are significantly lowered.[9]

When using model predictive control (MPC) or proportional-integral-derivative (PID) algorithms, tuning of CSII based on subcutaneous glucose sensing has been shown to be effective for basal "out-of-meal" periods because it keeps blood glucose in a tight narrow normal range.[10,11] However, permanent closed-loop control has been reported to be unsuccessful in addressing insulin needs at meal periods.[11,12] Indeed, the rapid rise of postmeal glucose cannot be averted when there is a delay in subcutaneous insulin absorption and action.[13] All reported trials show an unavoidable glucose peak well above the normal range. Moreover, delayed insulin action, while blood glucose decreases, results frequently in secondary glucose lows.[11] Partial reduction of these postmeal deviations can be obtained by the handheld programming of a priming bolus around 15 minutes before food intakes.[12]

In view of ambulatory use, insulin pumps have already improved a lot in terms of safety and miniaturization. Further comfort is expected from the "patch pumps" that have become available.[14] Of note, gradually altered absorption of insulin at subcutaneous insulin delivery sites still needs specific attention to avoid underdelivery.

By now, pros of subcutaneous insulin delivery route for the artificial beta cell include easiness of management and wide availability, whereas cons are related to a poor compatibility with rapid changes in insulin needs.

Intraperitoneal Insulin Delivery: A Physiological Model

From initial experiments performed in animals in the 1970s, a clearly predominant absorption of IP-infused insulin via the portal venous system has been demonstrated. When compared to IV-infused insulin after a portal glucose load in pancreatectomized dogs, IP insulin delivery showed the same efficacy on peripheral blood glucose levels.[15] While IP insulin needs were somewhat higher than IV ones, peripheral plasma insulin levels were lower than when using the IV route.

Later investigations in diabetic humans confirmed the lower peripheral insulinemia at steady state when using the IP vs SC route.[16] However, plasma insulin levels increased more quickly after enhanced basal rate of insulin infusion.[16] These investigations documented the more physiological plasma insulin profiles that could be obtained with the IP route.[17]

Safety, effectiveness, and reduction of blood glucose variability associated with longterm IP insulin delivery have been reported in the experience of implantable programmable insulin pumps from the 1990s.[18,19,20] The dramatic reduction of severe hypoglycemic events, which is the most impressive benefit of the clinical use of implanted insulin pump using IP insulin delivery,[21] has been related to the good reproducibility of insulin absorption, the combined quicker time to peak and return to baseline, and the closer-to-physiological insulin levels after IP vs SC bolus administration.[22] Moreover, restoration of glucagon response to hypoglycemia and exercise has been reported after several months of IP insulin infusion.[23,24]

Clinical use of implantable, programmable insulin pumps is, however, still limited because of the cost associated with this technology. This cost is related to the device cost itself, but also to the man-time cost needed to refill the pump reservoir with insulin at hospital every 6–8 weeks and to maintain reliable insulin delivery. Indeed, iterative insulin aggregation in the system requires specific procedures to get rid of the aggregates.[25]

An alternative option to benefit from IP insulin delivery at a lower cost and with higher patient autonomy is represented by the DiaPort® system (Mannheim, Germany) developed by Roche Diagnostics. This system includes a port that is implanted in the abdominal wall, to which an IP catheter is connected on one side and an external insulin pump on the other side. Clinical investigations have reported close-to-physiological blood glucose and plasma insulin profiles while using such ports for intraperitoneal insulin delivery.[26]

Closed-loop control trials using IV glucose sensing, proportional-derivative algorithms, and IP insulin delivery have been reported by our team.[27,28] While out-of-meal glucose control was tight, high blood glucose deviations characterized postmeal periods. However, the reason for these postmeal spikes was not related to a delay in IP-infused insulin action but to an unexpected delay in IV glucose sensing. This delay was due to the structure of the sensor itself, which is designed for longterm use. An internal sensor delay results from the large glucose oxidase amounts that are needed to maintain sensor operating time while submitted to shear forces of the blood stream in the vena cava superior or right atrium.[13]

Another issue that may occur while using intraperitoneal insulin delivery is related to the increased production of antiinsulin antibodies in some patients.[29] When these antibodies have a medium-low affinity for insulin, they form neutralizing complexes with insulin when plasma insulin levels increase after meals, and these complexes dissociate and release insulin when plasma insulin levels decrease at nighttime. Since it is noncontrollable, this process alters the pharmacodynamics of insulin and results in high postmeal spikes with glucose lows at night, whatever the tuning of insulin delivery.[27]

So far, the advantages of the intraperitoneal route are plasma insulin profiles and insulin action closer to physiology, except in patients showing high antiinsulin antibody levels. The still limited availability of insulin delivery devices using this route and the necessity of implantation represent the main limits for the development of an artificial pancreas using the intraperitoneal route.

Considerations for Present and Future

Among the three considered routes of insulin delivery for the development of an artificial pancreas, none has shown an overall superiority. Until an IV insulin infuser becomes available for ambulatory use, which would provide requested pharmacodynamics for meal coverage of insulin needs, a full, closed-loop, artificial pancreas seems nonconceivable. Priming handheld insulin delivery before meals or so-called "meal announcement" cannot be circumvented. The current pragmatic approach has selected SC insulin delivery as the leading one to develop models for "semi-closed-loop" systems, allowing automated control for basal, out-of-meal insulin needs. However, because of the inherent variability and shortterm stability of SC infusion, specific attention must be paid to safety concerns. Hyperglycemic alarms will have to be thoroughly scheduled to prevent a ketosis trend in case of gradual insulin underdelivery related to the unavoidable SC reaction around the catheter tip at the infusion site. These problems may even increase with time, as we frequently experience in CSII-treated patients. Although remaining limited to a few patients in Europe, continuous intraperitoneal insulin delivery by implanted devices provides specific advantages in terms

of stability of infusion and insulin pharmacodynamics. Accordingly, a combination of intraperitoneal insulin infusion and fast—hopefully 7–10 day stable—sensors represents an alternative approach to be considered for the development of an artificial beta cell, and may constitute a promising "think different" option.

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