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Critical path

FDA's proactive role in the development of an artificial pancreas for the treatment of diabetes mellitus

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One of the critical path initiatives of the Food and Drug Administration (FDA) is to accelerate the development and availability of a safe and effective artificial pancreas for the treatment of diabetes mellitus. The FDA has established a multidisciplinary group of scientists and clinicians, in partnership with the National Institutes of Health (NIH), to address the clinical, scientific and regulatory challenges related to this unique medical product.

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Background information

The incidence of diabetes mellitus is growing at an alarming rate in the United States and throughout the world. Long-term medical consequences of diabetes include microvascular (blindness, kidney failure and neuropathy) and macrovascular (cardiovascular disease, stroke and peripheral vascular disease) complications. Improved glycemic control in patients with diabetes has been shown to reduce the risk for the development and progression of some of these major complications [1,2]. Therefore, excellent glycemic control is an important goal for all patients with diabetes.

Why an artificial pancreas is needed and what FDA is doing to help

Despite the availability of increasingly effective treatment modalities, including insulin analogues and continuous glucose monitors (CGMs), a substantial proportion of patients with diabetes cannot achieve adequate glycemic control. Compounding this difficulty is the trade-off between improved glycemic control and an increased risk for hypoglycemia (low blood glucose levels), which can cause seizure, coma and death.

Many experts believe that the best therapeutic option for the treatment of diabetes is a system (termed an artificial pancreas or closed-loop) that can mimic normal pancreatic beta cell function thereby restoring normal metabolic

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homeostasis without causing hypoglycemia. The design of any system capable of achieving this goal is complex and raises novel scientific, clinical and regulatory challenges.

To accelerate availability of a closed-loop system, the FDA has identified the artificial pancreas as one of its critical path initiatives and has formed the Interagency Artificial Pancreas Working Group (IAPWG). The IAPWG collaborates with stakeholders, including private organizations, patient groups, academic researchers, product developers, industry and other government groups to find ways to accelerate and optimize research and development efforts. Two examples of IAPWG activities include earlier and more frequent interactions with product developers and a public workshop (targeted for 2008) to provide a forum for openly discussing the unique challenges pertaining to the development of an artificial pancreas. By promoting cross-fertilization of diverse resources, the IAPWG is identifying obstacles and developing innovative strategies to address them. The multidisciplinary group includes FDA scientists who regulate components of the artificial pancreas and NIH scientists who oversee and coordinate research on diabetes, biomedical imaging and bioengineering. This article focuses on some of the issues being discussed by the group, in order to assist those developing an artificial pancreas.

What an artificial pancreas might look like

The term 'artificial pancreas' refers to an automated system of controls intended to supplement or replace the functionally impaired endocrine pancreas in patients with diabetes. Conceptually, a mechanical artificial pancreas consists of inputs (e.g. glucose readings) continuously fed to a controller where a mathematical algorithm applies a set of rules to generate an output (e.g. for an infusion pump to deliver a set amount of insulin). Subsequent information from inputs would result in adjustments to the output. Other drugs (e.g. glucagon) may be included in the system to counter the hypoglycemic effects of insulin or to slow the rate of carbohydrate absorption following a meal (e.g. incretin-based therapies). Components might be external or implantable and may integrate wireless telemetry to enhance communications.

An artificial pancreas can also be entirely biological (e.g. islet transplantation), a mechanical–biological hybrid, or a semiclosed system that involves actions by the patient (e.g. patient administration of a premeal bolus of insulin). This article focuses on the mechanical artificial pancreas. At present, there is only one such system that has been approved by the FDA, the Biostator® (Miles Laboratories, Inc., Elkhart, Indiana). However, its large size and the intravenous sampling and delivery components limit its use to in-clinic settings.

Current technology

Despite FDA's approval of several CGMs, their robustness and reliability are still in need of improvement. The approved devices measure glucose in interstitial fluid using needle-type, enzyme-based sensors which utilize a glucose oxidase reaction. These devices require calibration using a traditional blood glucose meter, are inserted subcutaneously, and must be periodically removed and replaced. Sensor readings are transmitted to a pager-like device where an algorithm converts the information to blood-equivalent glucose results. Current and previous glucose results are displayed to the user to assist with tracking of glucose concentrations and monitoring for trends. Limitations of these devices include biological and physical changes at the sensor interface; for example, errors may be caused by an inflammatory response at the site of insertion or by mechanical movement of the sensor. There are also time delays of the output signal in relationship to changes in blood glucose concentrations. Sensor performance is typically poorest at critically low blood glucose concentrations and there are unexplained periods when sensor readings vary significantly from blood glucose readings. It is not clear whether some of the problems are because of limitations in the sensor or differences that often exist between interstitial fluid and blood glucose concentrations. These limitations make the current CGMs suitable only for adjunctive use in diabetes management. Under certain circumstances, existing technology might conceivably be adequate for closed-loop input if the system is set to turn off insulin release at a relatively high glucose level (e.g. 120–140 mg/dl at night).

Insulin pumps are often used to provide continuous subcutaneous insulin delivery (CSII). Currently approved extracorporeal pumps consist of an insulin-loaded syringe that delivers the insulin via a catheter. The continuous infusion mimics the basal function of a real pancreas. Limitations of CSII include slow and variable absorption of insulin into the circulation from the subcutaneous space. Development of insulin and delivery devices with rapid onset/offset pharmacokinetics would benefit artificial pancreas system development.

To compensate for the variable lag times for entry of glucose from blood into the interstitial compartment, a number of insulin-dosing algorithms are currently under development. Algorithms attempt to mimic normal pancreatic beta cell glucose-induced insulin responses by using either reactive or predictive mathematical models. An example of the former is the Proportional-Integral-Derivative algorithm, which incorporates current glucose concentrations, the area under the glucose–time curve, and the rate of change of glucose concentrations [3]. However, reactive algorithms alone may not offer sufficient postprandial glycemic control [4]. Other algorithms, such as Model Predictive Control, may provide control in settings where long delays occur between insulin delivery and insulin action [3]. Algorithms will need to factor in sensor inaccuracies and the inherent lag time between insulin delivery and pharmacokinetic action.

Many components that may be incorporated into a mechanical system are driven by software. When integrating those components, software validation of the whole system is an important consideration. The FDA has several guidance documents to assist developers in this area [5–8].

Concepts of clinical trial design

At least in theory, an artificial pancreas could benefit any patient with diabetes who cannot maintain adequate glycemic control despite optimal medical treatment. However, because of safety issues relating to system design challenges, initial development of an artificial pancreas could target a patient population with the greatest need and the potential for maximum benefit (e.g. patients with brittle Type 1 diabetes, those experiencing frequent hypoglycemic episodes or diabetic ketoacidosis, or those who are not aware of their hypoglycemic state). As clinical experience with the artificial pancreas accrues, adequately designed studies could allow expanded testing in other patient populations, such as:

- All adult patients with Type 1 diabetes mellitus.
- Children: young children and adolescents are expected to derive the most benefit from prevention of the hyperglycemia-related long-term complications of diabetes (automated control of blood glucose in the absence of hypoglycemia would also improve quality of life for patients and families).
- Adult patients with Type 2 diabetes: because of progressive beta cell dysfunction, these patients may require insulin or insulin secretagogues that increase the risk of hypoglycemia and metabolic instability.
- Gestational diabetes: an artificial pancreas may rapidly achieve and maintain excellent glycemic control required for successful pregnancy outcomes in patients with gestational diabetes who require insulin.
- Recipients of islet cell transplantation: patients with a functional graft remain free from severe hypoglycemia but may require exogenous insulin. A mechanical artificial pancreas could provide adequate insulin to cover blood glucose excursions above a preset value (e.g. 120–140 mg/dl), which would reduce the effect of glucose toxicity to the graft and improve glycemic control and quality of life.

Initial clinical studies for high risk devices are typically conducted in adults because of ethical and practical considerations. Subjects with baseline characteristics (lifestyle, medical and concomitant medications) that may interfere with efficacy or safety outcome measurements should be excluded in early trials.

Enrollment criteria might be based on the degree of metabolic instability, such as the inability to achieve hemoglobin A1c levels $<7.0\%$ in the absence of severe hypoglycemia. More quantitative data from Mean Amplitude of Glycemic Excursion (MAGE) scores [9], Lability Indices [10] or from CGMs could also form the basis for trial enrollment and efficacy outcomes measurements.

Trials to evaluate an artificial pancreas should begin in a safe, controlled environment, such as a Clinical Research Center. This permits close and frequent monitoring of plasma glucose and an evaluation of the overall system. These initial outcomes could be compared to data and medical decisions obtained from conventional means. Within this controlled environment, the system can be stressed with external glucose and insulin infusions to measure performance at extremes of the glucose range. It can also allow an evaluation of the system while the patient is sleeping. Success in highly controlled environments may be followed by testing in monitored settings that progressively simulate real-life use (e.g. inpatient settings that simulates home use and specialized summer camps for adolescents or children with diabetes).

Relevant endpoints for trials could include improvement in glycemic control with a reduction in hypoglycemia. Complete data sets derived from CGMs or conventional blood glucose determinations, or outcome measures (e.g. hemoglobin A1c or occurrences of hypoglycemia) may be used to evaluate system performance, which could be compared to conventional therapy in a cross-over or parallel-group trial design.

Developing technologies

New technologies could impact each element of an artificial pancreas and, in turn, improve the overall system performance. Blood glucose concentration is an important system input but is not the only variable that might be utilized. It is possible to measure other outcome variables, such as physical activity, food consumption, onset of hypoglycemia, and brain metabolic function. An example of a glucose signal under development involves otoacoustic emission (OAE), a low-intensity sound generated by the cochlea in response to acoustic stimuli. Preliminary data from the University of Oregon suggests that suppressed OAEs may provide a robust correlation with glucose concentrations because the suppression is a result of peripheral neural feedback, and neural activity is affected by glucose concentrations [11].

Other sensors are being developed that measure blood glucose indirectly. For instance, one technology uses a laser to create microscopic holes through the outer layer of skin. Interstitial fluid flows out of the holes into a patch that contains a standard glucose sensor. Other technologies involve optical coherence tomography [13], impedance spectroscopy, boronic acids to make polyacrylamide hydrogels, holographic sensors and contact lenses for measuring glucose [14,15]. These methods have limitations, such as competition with interfering analytes (e.g. fructose), tissue movement, environmental interferences and time-consuming fabrication.

The most successful direct optical measurements of glucose concentration have been based upon either the absorption or polarization properties of glucose. Noninvasive optical polarimetry technique for measuring glucose concentrations in the eye have shown promise, however, *in vivo* measurements have been compromised by birefringence of the cornea and optical activity of confounding agents such as albumin and ascorbate [16]. Measurements based upon the chiral nature of glucose in other tissues have proven even more difficult due mainly to collagen which is ubiquitous and highly birefringent. Another direct glucose measurement is based upon the near- and mid-infrared absorption of glucose. Implantation of the sensor such that the infrared radiation passes directly through a venous vessel has shown some promise however this requires a surgical procedure for sensor placement, and biocompatibility issues exist.

A number of product developers have been working with noninvasive near infrared diffuse reflectance spectroscopy systems. Although important progress has been made, an instrumental signal-to-noise ratio needs to be optimized and investigators are working to establish a unique spectral signature for glucose relative to tissue matrix [17].

A technology that is showing significant promise is based on Surface Enhanced Raman Spectroscopy. It seems likely that an advanced version of this sensor could be passed through the skin into the subcutaneous space, in a manner similar to the placement of insulin-pump-based catheters. The nanoparticle-based system may provide a continuous and direct measure of glucose concentration, and like all Raman-based analysis is relatively specific to glucose [18].

One company has developed an insulin delivery system that is regulated by glucose concentrations. This 'smart insulin' is a once daily injectable formulation of insulin. It consists of a nanostructured material (hydrogel) that selfassembles from two biomolecular building blocks: a glycosylated insulin–polymer conjugate and a multivalent glucose-binding molecule. Investigators have shown promising results when studying this technology in animals [12].

Conclusion

In summary, a mechanical artificial pancreas system has enormous potential benefit for a substantial proportion of patients with diabetes. Current obstacles are mostly technological, including glucose-sensing inaccuracies (mismatches between blood and interstitial glucose levels), imperfect algorithms for calculating the appropriate dose of insulin, and the time delay from subcutaneous insulin infusion to pharmacologic effect. Several new and promising technologies may solve some of these problems. The FDA is playing an active role in collaborating with stakeholders to develop strategies to overcome the scientific obstacles and to streamline regulatory processes.

Different subpopulations of patients with diabetes have unique physiological and pathological conditions that may impact the system's effectiveness and which must be considered when designing clinical trials. Clinical studies will require a progressive and staged approach, starting in a well-controlled inpatient setting that evolves to independent operation in a home setting. The studies must be carefully constructed considering both the target population and how the system will be used. Product developers are urged to consult with the FDA before conducting studies involving an artificial pancreas and frequently throughout clinical development.

More information regarding the critical path initiative can be found at http://www.fda.gov/oc/initiatives/criticalpath/.

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