Innovations in Insulin

Oral delivery of insulin has often been regarded as a more favourable alternative to daily injections. A new method that combines a liquid formulation of insulin with absorption enhancers may be set to benefit sufferers of diabetes

Since the pioneering discovery and demonstration by Banting and Best at the University of Toronto of insulin’s ability to save lives, followed by the subsequent commercialisation of the treatment in 1922, scientists and physicians have searched for a method to deliver insulin without the problems and pain of using a needle and syringe. People with diabetes bound to a regimen of multiple daily injections have always been strong proponents and vocal advocates of this quest.

Attempts have been made to deliver insulin orally, first by just administering large dosages, then by coating the molecule with protective layers to prevent digestion of the insulin peptide. A second method was the inhalation of either a liquid or dry formulation of insulin through the mouth and into the lungs. The third method was using the vasculature of the buccal mucosa to deliver insulin to the blood stream by using aqueous formulations of insulin. These methods have not achieved dramatic success.

Recently, a method has been developed that utilises both a liquid formulation of insulin with absorption enhancers and a propelled delivery system that deposits insulin on the buccal mucosa (the inside lining of the mouth and throat), but does not produce particles of a size that can get into the respiratory system.

The buccal mucosa overlies a tremendous number of small blood vessels, allowing the buccal insulin to be absorbed very rapidly, producing an onset of insulin activity that is much faster than subcutaneously (SC) administered insulin and almost resembles insulin injected intravenously. This fast absorption makes buccal insulin an ideal pre-prandial insulin (before meal insulin) for both

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insulin-requiring patients with Type 1 or 2 diabetes who benefit from insulin therapy.

A major safety concern with inhaled (also known as pulmonary) insulin was the development of both benign and malignant tumours hidden within the lung, as well as general questions about the effect of pulmonary insulin on normal lung function. Since buccal insulin does not enter the lung, as proven with radiologic studies using radiolabelled buccal insulin, and is deposited on the buccal mucosa, if a tumour were to develop, it could easily be seen by simply looking in the mouth. In the entire history of buccal insulin use, both in animal studies and in all of the clinical studies, no tumour has ever been reported.

The illustrations demonstrate the clinical pharmacokinetic/pharmacodynamic (pK/pD) studies that used a glucose clamp technique, in which the fasted patient’s blood sugar is kept at a constant level while an intravenous infusion of glucose replaces the glucose used by the buccal insulin or injected insulin. The more effective the insulin, the more glucose is required to be infused. These studies were conducted by Professor Itamar Raz, MD, Head of the Center for the Prevention of Diabetes, Hadassah Medical Center, Jerusalem. They document the fast absorption of buccal insulin; the rapid onset and offset of buccal insulin entering the bloodstream; the dose response curves based on five, 10, and 20 sprays; the placebo- or SC-injected insulin controls; the effective metabolism of glucose (with timing appropriate to the plasma insulin pK); and the dose response seen with the glucose utilisation, that is, the more buccal insulin given the greater the effect on glucose reduction:

- Plasma insulin values demonstrate significant, dose-dependent absorption of administered buccal insulin
- Glucose infusion rates (GIR) represent the amount of glucose being infused necessary to keep the plasma glucose constant. This is an indirect measure of the amount of glucose being metabolised by the buccal insulin or injected insulin absorbed
- The GIRs demonstrate a significant, dose-dependent, glucose metabolising effect of the buccal insulin

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The first study is the pK/pD evaluation of a buccal spray insulin formulation in comparison to SC regular insulin in healthy volunteers. Buccal insulin (15 sprays or puffs) was administered on each of two days and a single SC dose of 0.1U/kg regular insulin was given on a third day, with each line representing the mean glucose infusion rate required to maintain a constant plasma glucose value from baseline to six hours using a glucose clamp technique.

In Figure 1, the x-x-x line represents the change in plasma insulin following the first administration of buccal insulin. The o-o-o line represents the second day that buccal insulin was given. The greater response may reflect the fact that the subject better understood the administration procedure the second time they took buccal insulin (suggesting a learning process that is seen in other studies). The ☐-☐-☐ line presents the plasma insulin achieved with injected insulin.

In this study, using the same labelling scheme, Figure 2 presents the amount of glucose metabolised by the buccal insulin or the injected insulin treatments. The peak glucose response rate was comparable for both buccal insulin treatments and the injected insulin treatment. Note that with buccal insulin, there is a more physiologic return to basal rate by 2.5-3 hours, while the injected insulin produces a prolonged response past five hours, creating the potential for hypoglycaemia in a patient.

The next study, shown in Figure 3, demonstrates the ability of buccal insulin to work in seven patients with Type 1 diabetes mellitus. These patients are unable to produce any insulin of their own. With the same design as the previous study done in volunteers without diabetes, the dose-ranging effects of buccal spray insulin formulation (placebo, five, 10, and 20 puffs) were compared to SC-injected regular insulin in patients with Type 1 diabetes.

Greater insulin concentrations are achieved as the number of sprays are increased from placebo (line o-o-o) to five puffs basal insulin (line ☐-☐-☐) to 10 puffs (line x-x-x) and then 20 puffs (line o-o-o). The 20 puffs produced a more rapid peak in insulin concentration though comparable in level to the injected insulin (line △-△-△) and with the more physiologic return to basal concentrations. Since these volunteer patients could not produce any insulin of their own, the insulin concentrations achieved are solely due to the buccal insulin.

The key observation from these pharmacokinetic studies is that buccal insulin can produce glucose control equivalent to injected insulin, but, to be therapeutically equivalent to injected regular insulin, 20 sprays of buccal insulin be must be given.

Based on the studies described, a medical/scientific decision was made to enhance the buccal insulin formulation so that the patient with diabetes would only have to use three to five sprays of insulin before meals to achieve good metabolic control. This more concentrated buccal insulin formulation would allow dosing in the average patient to be
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reduced to fewer sprays, which would increase convenience, compliance, and safety.

Using new techniques in protein chemistry and formulation science, with minimal changes in the production process and content of the components, efforts succeeded in increasing the insulin concentration in the product by approximately 400-500%, as confirmed by a variety of in vitro testing procedures while preserving the solubility, stability, biologic activity, and potency of the insulin in the formulation.

A study of the relative bioavailability of the enhanced formulation in dogs was conducted for proof of concept, safety, toxicity, and efficacy. The enhanced buccal insulin formulation was compared with the original formulation in a blinded, parallel, controlled study involving fasted, awake, healthy, mature beagle dogs. Each dog received three sprays of either the enhanced formulation or the original formulation. Each dog was observed with assessments of serum insulin and glucose measured over a two-hour period. No adverse events were observed in any of the animals. No dogs were harmed or sacrificed in this study.

In the dogs given the enhanced buccal insulin formulation, the serum insulin had a nine-fold increase at 15 minutes and almost 500% greater absorption of insulin over the two-hour test period compared to dogs given the original formulation. The serum glucose decreased by 33% at 30 minutes in dogs treated with the enhanced buccal insulin formulation, compared to a 12% increase in serum glucose in dogs treated with the original formulation.

These outstanding results of the dog studies, coupled with the positive findings from the in vitro work, provide support and confidence to move forward as quickly as possible with the remaining clinical and regulatory work necessary to achieve global approval of the enhanced buccal insulin formulation. The combined results provide evidence that the enhanced buccal insulin can be used by people with either Type 1 or Type 2 diabetes mellitus as a safe, simple, fast, flexible, and effective alternative to pre-prandial insulin injections with easy dosing of only three to five sprays required before meals.