Exenatide implant therapy in diabetes
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Abstract
This review describes a recent advance in diabetes pharmacotherapeutics and drug delivery. ITCA 650 is an implantable device which delivers sustained and stable concentrations of the glucagon-like peptide 1 receptor agonist exenatide, when inserted subcutaneously. The article discusses the pharmacodynamics and pharmacokinetics of ITCA 650, and suggests how it's benefits can be utilized in clinical practice. It lists the advantages and limitations of the device, and shares tips for its rational use in type 2 diabetes care.

Keywords: Exenatide, GLP1RA, subcutaneous implant, type 2 diabetes.

Introduction
Glucagon like peptide 1 receptor agonists (GLP1RA) are available as subcutaneous injections, which may be administered once daily, twice daily or weekly. The injectable nature of these drugs may limit their acceptance, even though they are demonstrated to have excellent glucose lowering, weight reducing and cardio beneficial effects.1

Newer delivery systems are being tried to administer GLP1RA, so as to achieve therapeutic benefit while avoiding injections. These include implantable devices being developed by Intarcia, Delpor, Nanoprecision medical, and Microchips Biotech.2-5

This review describes the basic and clinical pharmacology of ITCA 650, a miniature implantable osmotic pump system, which delivers zero-order continuous subcutaneous exenatide at a precise, preset rate, for up to 12 months.

Administration and Removal
A short outdoor based procedure, lasting 5 minutes, is required to insert the ITCA 650. The match stick sized sterile pump is placed in the subcutaneous tissue of the abdomen, using a sterile single use tool, after cleaning the skin. Once placed sub dermally, extracellular fluid diffuses through a semi-permeable membrane directly into an osmotic engine, entering the pump device at one end. The space expands to drive a piston at a controlled rate, which in turn releases the drug at a steady, consistent rate through the other end of the device. While the product’s life comes to an end, it is removed under sterile conditions.6

Clinical Trials
A randomized open label 28 day study was performed to assess the pharmacodynamics, pharmacokinetics and tolerability of ITCA 650 in persons with type 2 diabetes who were on stable regimens of lifestyle modification ± metformin regimens and/or thiazolidinedione therapy. Forty four participants were randomized to either 10μg, 20μg, 40μg or 80 μg/day release from ITCA 650. Significant reduction in fasting plasma glucose, 2 hour post prandial glucose, glucose area under curve and HbA1c were noted with all doses. Significant weight loss was seen in the 40μg and 80μg/day groups. Exenatide levels reached detectable range within 12-24 hours of ITCA 650 insertion, reached steady state by 24 hours and remained constant till device removal. They declined to undetectable levels within 24 hours of removal of the pump. Most adverse events were mild or moderate, and were related to gastrointestinal symptoms or local site reactions. Anti exenatide antibodies were noted in 12/14 participants, but this did not alter the pharmacokinetics.7

ITCA 650 was studied in a randomized, two stage, 24 week open label, phase 2 study in 155 participants with type 2 diabetes who were inadequately controlled on metformin. In the 12 week long first stage, participants were randomized to either 20 or 40 μg/day of ITCA 650, or 5 to 10μg/day twice daily of injectable exenatide. In the dose finding second stage, 131 persons were re randomized to 20, 40, 60, or 80μg/day of ITCA 650.8 At 12 weeks, mean HbA1c fell (from a baseline of 7.9-8.0%) by 0.98%, 0.95% and 0.72% in the 20μg/day ITCA 650, 40μg/day ITCA 650, and injectable exenatide groups respectively. In the second stage, significant HbA1c reductions (1.4% from baseline) were noted in the 60 μg/day and 80μg/day
ITCA 650 groups. The proportion of participants achieving an HbA1c \(<7\% at 24 weeks was 86\% with 60 \(\mu\)g/day and 78 with 80 \(\mu\)g/day. Weight reduction of 2.8-3.7 kg was noted in the 40 \(\mu\)g, 60 \(\mu\)g and 80 \(\mu\)g groups at 24 weeks. Nausea was reported transiently, with 60 \(\mu\)g/day ITCA providing the best efficacy and tolerability profile.

Henry et al studied the effect of ITCA 650 on glycaemic control and weight loss in 86 metformin treated participants with type 2 diabetes over 48 weeks. ICTA 650 mg was used to deliver exenatide as 20, 40, 60 or 80 \(\mu\)g/day. HbA1c reduction varied from 0.85\% to 1.51\%. Of all participants who achieved an HbA1c \(\leq 7\% at week 24, >64\% were able to maintain it at week 48. Adverse events were dose related, and ranged from 13.3\% (20 \(\mu\)g/day dose) to 31.5\% (80 \(\mu\)g/day) dose. Most adverse events were mild and transient, and declined in incidence as the study progressed. This study was a follow up of a 24 week long phase 2 study which assessed the efficacy and safety of ITCA 650.

Henry et al also studied the treatment satisfaction posted on ITCA 650, as compared to twice daily injectable exenatide, the participants had type 2 diabetes and were on metformin. Using the Diabetes Medication Satisfaction Tool (DM-SAT), ITCA 650 was associated with better treatment satisfaction by 8 weeks in this 24 week long pen label trial. Satisfaction score was not influenced by nausea/ vomiting or the sub dermal implantation procedure.

Indications and Limitations
The indications of exenatide are similar to those of other GLP1RA. Exenatide can be used as a first line agent in persons with type 2 diabetes in whom metformin is not tolerated or contraindicated. It is a preferred second line and third line option in persons who do not respond to mono therapy or dual therapy.

ITCA 650 is a unique delivery system which can be used in all situations where exenatide is indicated. It obviates the need for frequent injections, and thus reduces the level of “intrusion” into the patient's lifestyle. The difference between invasion and intrusion must be highlighted. While ITCA 650 is an ‘invasive’ therapy, it is a non-intrusive one, as it facilitates easy adherence to therapy, and does not involve fixed or meal-related times of administration.

The advantages and limitations of ICTA 650 are mentioned in Table.

ITCA 650 may find great acceptance in persons who are unwilling or unable to self-inject regularly. It will also benefit persons who are unable to follow or remember specified injection meal time gaps for subcutaneous exenatide. Thus, the population segments which may prefer ITCA 650 will range from busy young professionals to elderly persons with limited neuro cognitive function or self care ability.

The contraindications and caveats for exenatide apply to ITCA 650 as well. Presence of extensive active injection, infestation, burns, acute trauma or ulcer over the anterior abdominal wall is a contraindication to ITCA 650 initiation.

Monitoring
There is no consensus regarding frequency of glycaemic monitoring in persons with implanted ICTA 650. The most relevant guidance that exists pertains to once weekly GLP1RA usage and monitoring. Frequent self glucose monitoring will not be required with this mode of therapy, and occasional monitoring with HbA1c may suffice.

Summary
This brief communication describes the basic and clinical pharmacology of ITCA 650(exenatide implant). This unique delivery device should prove to be of great utility in persons with type 2 diabetes who wish to use GLP1RA, but are unwilling or unable to inject regularly.

References


