

ALTEA THERAPEUTICS TRANSDERMAL PASSPORT™ SYSTEM: FREEDOM FROM INSULIN INJECTIONS FOR SUPERIOR DIABETES MANAGEMENT

While starting insulin therapy is often the best way for people with diabetes to ensure that they stay healthy, many factors including fear of needles, make many resistant to starting injected insulin. Factors associated with injecting insulin also lead to poor compliance. In this article, Yogi Patel, PharmD, Manager, Business Development, Altea Therapeutics, examines some of these problems and describes how transdermal insulin can overcome them.

It is a challenge for people with diabetes to keep track of their blood sugar levels and to take the right amount of insulin throughout the day. For a child these tasks can be extremely difficult or simply impossible without help. That is the case for eleven-year-old Taja. She has diabetes, which for most of her life has been under control – but not lately. “She woke up in the middle of the night and her glucose levels were a little

Taja was admitted to the hospital. “I talked to your parents yesterday,” says Dr Goo, “and they said that last weekend you had a sleep-over at your friend’s house and you may have forgotten to take your insulin. Is that what happened?” Taja nods yes.

Children like Taja who suffer from diabetes have to check their blood sugar and give themselves shots of insulin 3-6 times a day.

Furthermore, they have to calculate the correct dose of both basal and meal-time insulin for

PHARMACEUTICAL COMPANIES HAVE BECOME MORE INNOVATIVE IN ORDER TO RESPOND BETTER TO THE NEEDS OF PEOPLE WITH DIABETES

low – at about 67 mg/dL. When she got up the next morning, her blood glucose level was over 400 mg/dL,” her mother recalls.

Normal blood sugar is around 90 to 120 mg/dL, but that was not her only problem. “She was in what we call diabetic keto-acidosis,” explains Dr David Goo, Emergency Paediatrics, Children’s Healthcare of Atlanta. “That means that the acid in her blood was building up because she wasn’t getting enough insulin to convert sugar into nutrition, making her weak and nauseous.” If not caught and treated, unchecked keto-acidosis can be life threatening. But for Taja, what was the cause? “It’s kind of a puzzle,” says Dr Goo. “It could be triggered by an infection, emotional or physical stress, shifting hormone levels, or even by missing a dose of her medication.” To find out,

each injection. “For a young child that’s a lot of work, a lot of pain from the injections and finger-stick blood sampling and a lot of trouble. If they’re feeling good, playing and having fun, it is easy for a child to forget to do something they don’t really want to do to start with,” says Dr Goo. (Source: Diabetes Maintenance (ER). Newsfeed November 2, 2005. www.connectingwithkids.com/tipsheet/2005/253_nov2/diab.html (December 14, 2005)).

As reported by the World Health Organization (WHO), Taja was just one of the reported 200 million people around the world suffering from diabetes in 2005.¹ Diabetes is a serious condition and its rapidly increasing prevalence on the global scale is a significant cause for concern. By 2030, the WHO estimates that the number of people with diabetes will



Yogi R Patel, PharmD
Manager, Business Development

T: +1 678 495 3125
F: +1 678 495 3130
E: ypatel@alteatherapeutics.com

Altea Therapeutics
2056 Weems Road
Tucker, GA 30084
USA

www.alteatherapeutics.com

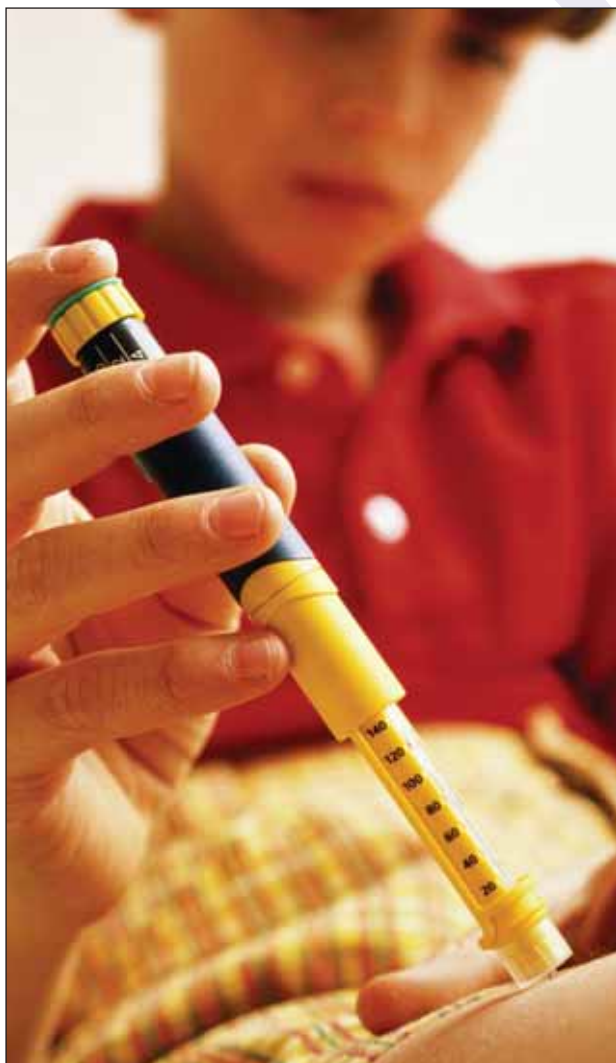


Figure 1: The new transdermal insulin patch, PassPort™ System, replaces injections thereby enhancing compliance in patients with diabetes

almost double to 366 million.²

About 40% of people with diabetes rely on insulin to maintain control of their blood glucose levels.³ Patients with Type 1 diabetes are completely dependent on insulin injections. For patients with Type 2 diabetes, which comprises 90% of the world's diagnosed cases of diabetes, about one-third of them rely on insulin as part of their regimen for controlling their blood glucose levels.

Patients with Type 1 diabetes require both basal and bolus (or mealtime) insulin to control their glucose levels effectively. Basal insulin provides the body with a steady, low level of insulin throughout the day and night. Bolus insulin is the faster-acting insulin that provides the boost of insulin needed to stop the rise in blood glucose level that occurs after meals. Bolus insulin is usually given as a before-meal injection.

For patients with Type 2 diabetes using insulin, the majority of them use only the long-acting basal insulin injections taken once or twice daily, frequently in combination with other medications. Most physicians agree that patients with

Type 2 diabetes are resistant to starting injected insulin therapy for a variety of reasons, especially the fear of needles. Medical facts, however, support that the sooner a person with Type 2 diabetes begins insulin therapy, the longer they will stay healthy and free of the long-term complications of the disease.

There are more than 20 types of insulin products available, each with a different time of onset and duration of action.⁴ The worldwide insulin market had sales of over \$5 billion in 2004 and yearly growth of almost 10%.¹ However, insulin is a fragile protein drug that requires refrigeration for storage, possesses a relatively short shelf life and can be potentially life threatening in case of an overdose. This requires patients with diabetes to inject themselves with carefully calculated insulin doses often several times per day (see figure 1), a procedure that is difficult, painful and impractical in many situations. These factors often lead to noncompliance in patients.

Lack of adherence to proper therapy in patients with diabetes can lead to life threatening conditions such as keto-acidosis (such as Taja's case) and various complications including blindness, kidney failure, heart disease, limb amputations and many more.³ These complications lead to a poor prognosis and significantly increase the cost of healthcare and the loss of productivity associated with diabetes.

Along with lack of compliance due to pain, needles and syringes present the risk for accidental injury. These injuries can occur at any time when people improperly use or dispose of needles. Infected needles can become concealed in linen or garbage and injure other workers or caregivers who encounter them. Most reported needle-stick injuries involve nursing staff, but laboratory staff, physicians, housekeepers, and other healthcare workers are also injured.

These injuries expose workers to bloodborne pathogens that may cause an infection. In the World Health Report 2002, the WHO reported that of the 35 million healthcare workers, 2 million experience percutaneous exposure to infectious diseases each year.⁵

The most important of these infectious, which are potentially life threatening, include HIV, Hepatitis B virus (HBV) and Hepatitis C virus (HCV).⁶

As a result of challenges associated with using injections for insulin, pharmaceutical companies have become more innovative in order to respond better to the needs of people with diabetes. In particular, companies are developing non-injection based insulin delivery alternatives for alleviating any pain and complication associated with injections and enhancing compliance in patients with diabetes – such as Taja.

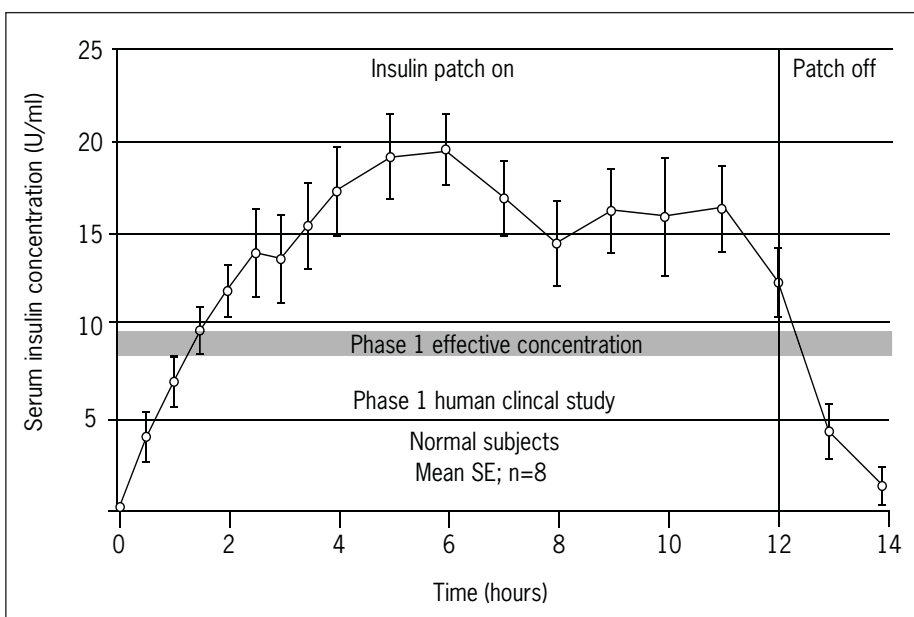


Figure 2: Results of Phase I insulin trials in humans using the PassPort™ System show sustained delivery of therapeutic levels of insulin over a 12-hour application period



Figure 3: The PassPort™ System is comprised of an applicator (on the left) and a reservoir patch; the latter is placed on the skin and provides for painless delivery of insulin

Altea Therapeutics has developed an innovative technology that provides convenient and painless delivery of basal insulin for people with diabetes.

A NEW TRANSDERMAL PATCH

The Altea Therapeutics PassPort™ System was the first product in development shown in US FDA clinical trials to provide a non-invasive, controllable and efficient way to deliver insulin via a patch on the skin. The PassPort™ System enables fast, controlled drug delivery without the pain of an injection or the possible complications associated with inhaled medications. It also avoids the first-pass gastro-intestinal and liver metabolism that occurs often after oral administration. It creates an effective, economical and patient-friendly delivery of insulin as well as the delivery of drugs for a wide variety of conditions.

Using the PassPort™ System, Altea Therapeutics has demonstrated effective delivery of insulin via the skin in Phase I clinical trials (see figure 2). The basal insulin skin patch, the first non-injectable daily insulin product, is

AQUEOUS MICROPORES PERMIT THE RAPID AND SUSTAINED FLOW OF PROTEINS, PEPTIDES, CARBOHYDRATES, AND SMALL MOLECULES INTO THE BODY WITHOUT THE USE OF NEEDLES OR PUMPS

designed to achieve normal basal levels of insulin to enable patients with diabetes to maintain better control of their blood glucose levels.

The insulin transdermal patch maintains constant basal levels while avoiding skin depots of insulin common with subcutaneous injections. As a safety feature, if a patient begins to

experience the hypoglycaemia associated with an inadvertent overdose of insulin, they may simply remove the insulin transdermal patch, thus immediately ending the influx of insulin. In contrast, if a patient experiences an overdose of injected insulin, there is no practical way to stop the build-up of serum insulin levels.

The patient-friendly insulin patch is designed to encourage early adoption of insulin therapy by people with Type 2 diabetes and thus increase compliance with insulin therapy in all patients, particularly those with needle phobia. Early adoption and increased compliance will help delay disease progression and reduce the complications associated with poorly controlled diabetes.

In addition to improved compliance and safety profile, the insulin transdermal patch presents several significant advantages over injected long-acting insulin formulations. Some of the important advantages include the elimination of complex training to administer subcutaneous injections and improved safety through steady basal levels. Moreover, there is no risk of nee-

dle-stick injuries with a patch, eliminating the potential of transmitting blood-borne infections and the general difficulty associated with the correct disposal of needles.

HOW IT WORKS

Conventional transdermal systems are normally limited to very potent, lipid-soluble drugs with a molecular weight of less than 500 Daltons. The PassPort™ System can be used for small water-soluble drugs as well as water-soluble macromolecular drugs and vaccines at doses ranging up to tens of milligrams that cannot be delivered via the skin using conventional passive transdermal patch systems.

The PassPort™ System uses extremely short bursts of focused thermal energy to create hundreds of tiny channels, or micropores, in the surface of the skin. The process is painless, as the short yet rapid delivery of these measured amounts of thermal energy ensures that none penetrates deep enough into the skin to reach the heat-sensing nerve endings in the dermis. These aqueous micropores permit the rapid and sustained flow of proteins, peptides, carbohydrates, and small-molecules into the body without the use of needles or pumps.

The delivery method can be configured to achieve systemic or local action of a therapeutic agent.

The PassPort™ System is comprised of an applicator and a PassPort™ Patch (see figure 3). The PassPort™ Patch contains a reservoir of drug and a tiny screen made of wafer-thin metallic filaments, known as the porator.

Using the PassPort™ System is easy:

1. Clip a PassPort™ Patch onto the Applicator and place against the skin
2. Press the activation button of the Applicator
3. Remove the Applicator, thereby leaving the transdermal patch on the skin
4. Fold over the transdermal drug patch to initiate drug delivery.

When the patient places the PassPort™ Patch against the skin using the Applicator and

Human clinical studies (US):

- Insulin
- Interferon-alpha
- Parathyroid hormone
- Hepatitis B surface protein antigen
- Hydromorphone hydrochloride
- Morphine salts

Preclinical studies:

- Influenza HA protein antigen
- Avian Influenza antigen
- Tetanus protein antigen
- DNA vaccines
- Erythropoietin
- Apomorphine hydrochloride
- Fentanyl citrate

Figure 4: Altea Therapeutics has shown the delivery of therapeutic levels of many compounds in human clinical trials and in animal studies

presses the activation button, a single pulse of electrical energy is released to the porator, where it is converted to thermal energy. The rapid conduction of this thermal energy into the surface of the skin painlessly ablates the stratum corneum under each filament to create micropores. Once the Applicator is removed, the transdermal drug patch remains behind on the skin, and a simple fold-over design aligns the transdermal patch with the newly formed micropores.

PRODUCT PORTFOLIO

Along with developing insulin in Phase I clinical trials, Altea Therapeutics is developing the first non-injectable product to deliver rapid onset and sustained therapeutic levels of hydro-morphine hydrochloride for the management of moderate-to-severe acute and chronic pain. The company has concluded a Phase II study and is preparing for Phase III clinical trials of this product.

Altea Therapeutics is also developing a fentanyl citrate transdermal patch for moderate-to-severe acute and chronic pain. In several pre-clinical studies, the company has demonstrated delivery of sustained therapeutic levels with drug utilisation of 90%.

In addition Altea Therapeutics is developing a daily apomorphine patch for managing Parkinson's disease, with plans for initiating clinical development in 2006.

Several pilot studies in human subjects have demonstrated the use of the PassPort™ System to deliver protein drugs, vaccines and highly water-soluble small-molecule drugs. This research includes the delivery of interferon-alpha, parathyroid hormone 1-84 and 1-34, hepatitis B protein antigen vaccine, and morphine (see figure 4).

CONCLUSION

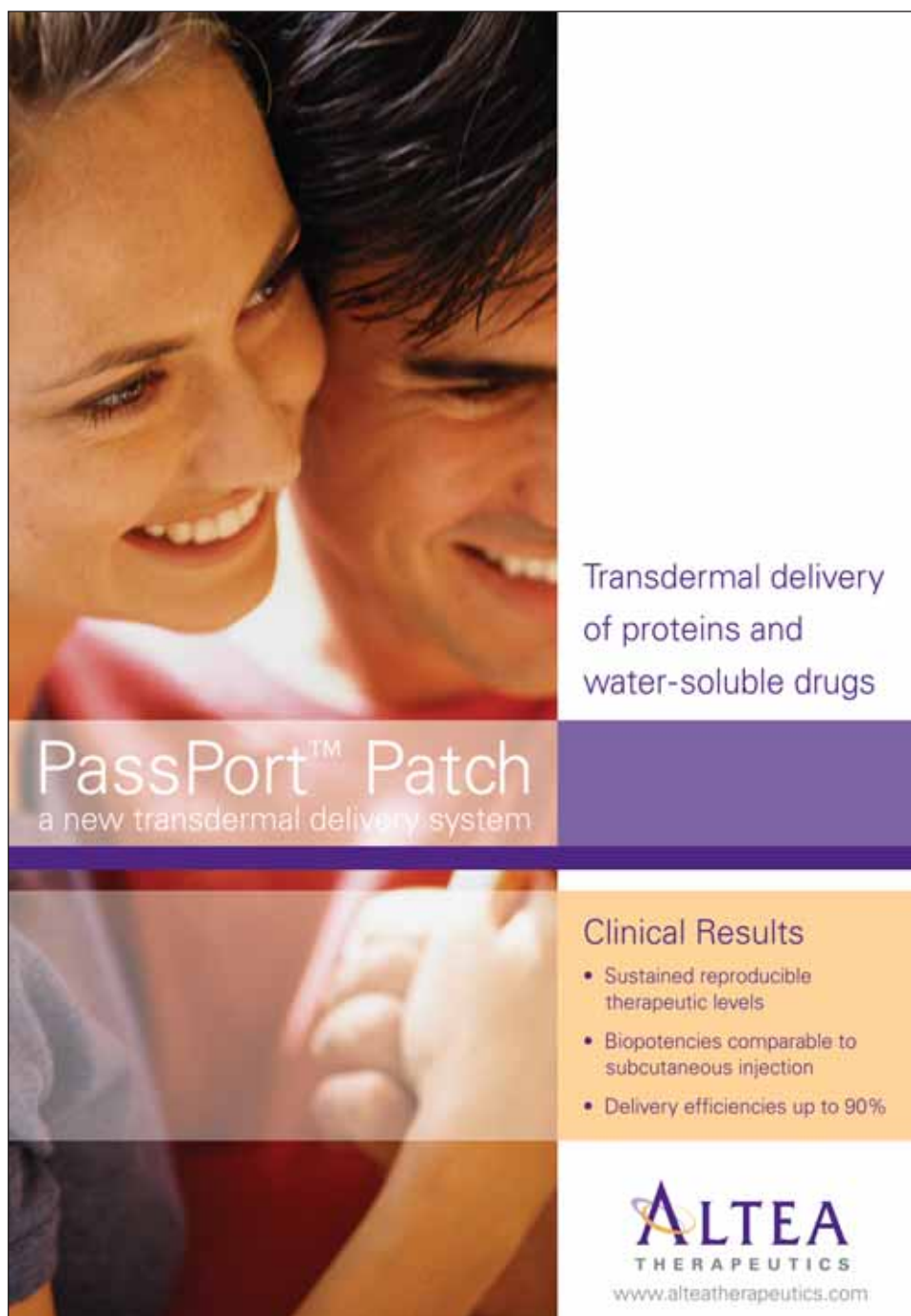
Altea Therapeutics has made a key scientific and commercial breakthrough in the delivery of drugs and vaccines via the skin with its proprietary technology, the PassPort™ System. The PassPort™ System enables the affordable, non-invasive, and controllable delivery of a wide range of drugs via the skin that cannot be delivered using conventional patches.

This breakthrough technology is about freedom from needles and pumps and costly, complicated devices.

Imagine one day children like Taja will be able sleep over at their friend's home without having to worry about taking their painful insulin injections. A simple glance at their patch will tell them that all is well, sleep tight!

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Transdermal delivery of proteins and water-soluble drugs

PassPort™ Patch
a new transdermal delivery system

Clinical Results

- Sustained reproducible therapeutic levels
- Biopotencies comparable to subcutaneous injection
- Delivery efficiencies up to 90%

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