Continuous subcutaneous insulin infusion therapy (CSII) is becoming an increasingly utilized treatment modality around the world for Type 1 diabetes. As our experience of it grows, so too does our knowledge of what we can realistically expect to achieve, what its limitations are and what black clouds we should look out for.

In our unit, we have started over 220 patients on pump therapy since 1998 with numbers growing each year. Financial restraints due to the United Kingdom (U.K) funding system restrict access to this form of insulin delivery and experience over the years has led us to rethink some of the criteria for selecting patients appropriate for such treatment who are likely to gain significant benefit.

Reimbursement for CSII is regulated by National Institute of Health and Clinical Excellence (NICE 2008) criteria one of which is failure to achieve HbA1c <8.5% (69mmol/mol) despite use of modern analogue insulins (MDI) with an understanding of carbohydrate counting (1). It has been previously documented that the greatest decrements in HbA1c occur in those who started at the higher levels initially (Figure 1) (2). From our experience, the greatest fall in HbA1c occurs in the first 6 months of starting CSII and levels then tend to plateau out.

We have now managed 2 patients whose excellent glycaemic response on initiation of pump therapy was however on starting insulin pump therapy accompanied by distressing, unpleasant symptoms highly suggestive of autonomic neuropathy reminiscent of...
the symptom complex occasionally described in early type 1 diabetes on insulin initiation.

Case 1

A 19 year old student with a 4 year history of type 1 diabetes was referred for consideration of CSII therapy due to erratic glucose control. She enrolled in our intensive education program (www.b-dec.co.uk) in July 2005 with an HbA1c of 12.1%. Although she coped well with carbohydrate counting and her blood sugars improved, she continued to have significant hypoglycaemic episodes and started on insulin pump therapy in November 2005. She had a good response to CSII in terms of improvement in HbA1c and reduction in hypoglycaemic episodes and blood glucose variability.

In April 2006, she was urgently referred back to us with profound weight loss of 15kg, intermittent vomiting and profuse diarrhoea. Her HbA1c at that time had fallen to 6.3%. Initial investigations showed negative stool culture, normal liver function tests, normal tissue transglutaminase and CRP. There was no clinical suggestion of an eating disorder and no evidence of laxative abuse.

On admission routine biochemistry and imaging were normal. An OGD during the admission showed considerable food residue after a 12 hour fast and a barium meal assessment confirmed gastroparesis. Autonomic function testing was reported as normal although she did have a resting tachycardia averaging 110bpm.

Following use of a prokinetic her vomiting abated and weight stabilised. Unfortunately, her diarrhoea persisted which resolved after treatment for small bowel bacterial overgrowth (3).

Case 2

A 28 year old lady with type 1 diabetes, diagnosed aged 7, had been referred for consideration of insulin pump therapy after many years of struggling with recurrent hypoglycaemia, poor control with HbA1c 10% and lately osmotic symptoms on MDI. She was known to have established retinopathy and peripheral neuropathy. After attending the Intensive Insulin Education course she started on pump therapy in June 2010. Initially, she was delighted with the result and with the improved quality of life.

She was referred back to see us urgently with symptoms of hypotension and a significant postural drop in blood pressure (>30mmHg) and symptoms although again formal autonomic function testing revealed only a resting tachycardia. She was started on fludrocortisone and metoclopramide. After 3 weeks there was a significant improvement in postural and GI symptoms. Retinal photography demonstrated no deterioration in her retinopathy over this time period.

Both of these clinical scenarios would be classic of “insulin neuritis” first described by Caravati early in the last century as a case of painful neuropathy after introduction of insulin (4). Neuropathy induced by rapid correction in glycaemic control in chronic hyperglycaemia is not a well recognized entity and with its myriad of presentations is easily overlooked. Since this original description there has been documentation of similar clinical pictures developing after initiation either insulin therapy for type 2 diabetes, improvement of diabetes control in type 1 diabetes and indeed in insulinomas (5-8). The usual clinical scenario is one of classic painful peripheral neuropathy with either worsening of ongoing neuropathic pain or the development of new symptoms within one to two months of the change in glycaemic control. If the clinical picture resembles that of the recognized deterioration in retinopathy following improved HbA1c then one could expect a resolution of symptoms over 12 to 18 months (9). In a recent case series of 16 patients with treatment-induced neuropathy in both type 1 and type 2 diabetes symptoms, signs and objective measures of nerve fibre dysfunction were shown to improve over 18 months (10).
showed some improvement fairly rapidly within 3-6 months but these people are under active follow up and much more data is required to clarify the natural history of this possibly iatrogenic complication.

Neuropathy as a microvascular complication of diabetes is under reported and hence cases of treatment induced neuropathy due to a change in diabetes control may also be. What is the pathophysiological process which underlies this condition? Experimental evidence points to a role for both hypoglycaemia and hypoxia in neuronal injury with support available for multiple hypoglycaemic episodes leading to attenuation in neural perfusion of up to 40% (10,11). However, CSII usually leads to a reduction in hypoglycaemia and a more likely explanation may be endoneurial hypoxia induced by arterio-venous shunting (12). In the poorly controlled diabetic state hypoxia induced endoneurial damage is relatively protected by the hyperglycaemic environs but this protection is lost under conditions of improved blood glucose control with triggering of neural damage (13). Clearly the term “neuritis” is inappropriate as there is no evidence of an inflammatory component.

Currently, there is little to suggest additional risk factors for this phenomenon other than chronically elevated Hba1c but at what level of Hba1c? Is duration of diabetes relevant or age? Are there early nerve fibre or autonomic function markers to predict those at risk? Is there a “safe” rate of improvement in Hba1c?

It is at this early stage of recognition of this entity difficult to determine the magnitude of the problem. Greater recognition of “pump associated autonomic neuropathy (PAAN)” will hopefully lead to a growing body of evidence. Clinicians involved in starting patients on pump therapy, which can lead to rapid reductions in Hba1c are well placed to collect such data (Figure 2). There is a paucity of evidence to suggest what is a safe rate of decline in Hba1c and guidelines should be established to recommend individualised targets over specified timelines to minimize the risk of neuropathy for any given patient (14).

Continuous advancement in pump therapy, with and without sensor augmentation will allow us to offer the hope of improvement in diabetes control and with this hope for a reduction in recognized diabetes complications. With this silver lining, however, comes the cloud of potential iatrogenic complications which we need to be aware of and be prepared to treat as required.

References

1. Continuous Subcutaneous Insulin Infusion for the treatment of diabetes mellitus (review of technology appraisal guidance 57) NICE 2008
3. Partridge H, Kerr D Gastrointestinal upset following improvement in Hba1c on initiation of insulin pump therapy. Practical Diabetes 2009;26:14-15
The Implantable Insulin Pump
The Perspective of Two Patients

Greg Peterson (1) and Anne Nordyke (2)

(1) Martinez, California, (2) Livermore, California

We are long-term members of a small group of fewer than five hundred type 1 diabetics worldwide who get their insulin from a surgically implanted pump that delivers insulin directly into our peritoneal cavities (the space enclosing the intestines and organs such as the spleen, pancreas and liver). We and our peers believe that this method of insulin delivery has immensely improved our health and the quality of our lives. Our belief is based upon our personal experiences and the remarkable testimonials of the other patients, the commitment of our physicians to this solution, and scientific theory confirmed by extensive research data. Finally, we are deeply concerned over the fact that this technology, for reasons unrelated to its effectiveness, is in danger of being lost.

The story we are about to tell seems unbelievable even to us and we have lived it for the last twenty years. Here is the bottom line: Type 1 diabetes patients who convert from subcutaneous insulin (injections or continuous infusion pumps) to the implantable insulin pump report nearly immediate, life-changing improvements beginning with a feeling of well-being that has led many to ask; “Is this how it feels to be normal?” They uniformly report that it is far easier to control their blood sugars and that insulin boluses act far more quickly, more predictably and for shorter duration -- allowing much finer blood sugar control. Many also report that as they strive for an ideal blood sugar level they seem to hit a “sweet spot” where blood sugars seem to lock in and stabilize. Erratic work schedules are easy to handle as are spontaneous changes in exercise routines and irregular timing of food intake or periods of not eating. Real life unpredictability is no longer as much of a challenge. They experience far fewer episodes of dreaded hypoglycemia and the episodes they do encounter are milder, easier to correct and they resolve more rapidly. The chronic, negative impact and overall burden of living with diabetes is so diminished that they say, “I almost forget that I have diabetes.” Our doctors, experienced and highly respected endocrinologists who have authored numerous scientific research papers focusing on this method of insulin delivery, wholeheartedly agree with us.

Of course, it is not uncommon for patients to fall in love with whatever their current treatment happens to be. In the case of the implantable insulin pump however there is a well-established physiological basis as to why these patients should feel this way and to top it off there is a large body of published research that also validates what we have experienced. There is a profound difference between the treatment of diabetes with subcutaneous insulin and the treatment of diabetes with the implantable insulin pump delivering insulin to the peritoneum.

If, after reading this article, you would like to know more about this remarkable technology, we have recently created a web site www.theiipump.com to provide information about the implantable insulin pump and to act as a focal point for an effort to save this valuable technology.

Twenty years and counting

We, along with eight other type 1 diabetics volunteered for an implantable insulin pump study in Northern California in January of 1992. The implantable pump had followed a long and difficult developmental path that began in 1980 and the version we were to receive was a product of MiniMed, an innovative company launched by the legendary entrepreneur, Alfred Mann, and staffed by a remarkable group of scientists and engineers. Throughout the decade following our enrollment, numerous technical challenges arose to threaten the viability of the implantable insulin pump. Battery life was too short, electronic circuits were inefficient and not reliable enough, manufacturing processes were inefficient, improved diagnostic capabilities were needed, and communication protocols were lacking. The special, highly stabilized insulin used in our pumps at the start of the study was developed by Hoechst and it worked superbly. That is, until 1994, when an environmental group forced a change in the manufacturing process. Suddenly, the insulin began to precipitate within the pumps and at the time no one knew why. The problem was eventually identified and by 1997 a new variant of insulin had been developed. It seemed to work well at first but turned out to be overly sensitive to the pressures generated by the piston that propelled the insulin out of the pump. Titanium pressure transducers, customized valves, a catheter with an added access port and a procedure for clearing damaged insulin from the pump without removing it from the
patient were developed to deal with this problem. Meanwhile, the surgeons and attending physicians were designing techniques and procedures to prevent surgical and post surgical complications and improve the refill and maintenance procedures. For us, it was both a wonderful and an awful decade. When things were going smoothly (pumps, refills, surgeries and insulin working as they should) life was a dream. When something went wrong and we had to return to subcutaneous insulin, life was not so great. Despite this back and forth, we never considered leaving the study because life was so much better with the implantable pump. In fact, we were so committed to this therapy that when our study group was about to disband because of the loss of the lead investigator we found a replacement and then we negotiated directly with the hospital to continue supporting the study. Nothing was going to deprive us of this wonderful treatment!

The 1990s were hard years but they ended on a note of enthusiastic optimism and by 2001 the technology had been much improved: pump battery life was extended to eight years, infections had become rare, and procedures had been developed to keep catheters working. On the international stage, a professional medical association dedicated to the implantable insulin pump, EVA-DIAC (a), was formed in France and throughout the world numerous research studies were carried out and significant amounts of data collected. In the early part of the new century, the implantable insulin pump had validated the safety, efficacy and importance of peritoneal insulin delivery. The pump was ready for the next-generation design conversion that was much needed to take advantage of the latest technological developments – ten years is a near eternity in technology development and by the end of that period it was possible to design a smaller and far superior pump. It would be critically important that a new design replace antiquated parts that were no longer available. 500 patients would be need-

As we mentioned, the first decade that had been hard on us, also served an unexpected but very productive purpose. At times, when a technical problem would deprive us of working pumps, we would have to rely upon subcutaneous insulin temporarily until regaining our implantable pumps. This gave us the opportunity to observe the dramatic contrast in how we felt, physically and mentally, and how we were able to function in daily life when we had working pumps and when we did not. The difference was nearly unbelievable. When our implantable pumps were working, our ability to function was so enhanced that we often stated that we almost felt like we were no longer diabetic. When the implantable pumps were not working, we felt just as we had before 1992 - except that now we knew that there was something better - and we badly missed it.

Prior to receiving our first implantable pumps, we had lived successfully with diabetes for years and during that time we had no idea that we did not feel all that well nor did we consciously realize that so much of our energy, time and attention were being consumed by our diabetes. In the late 1990s, our group of ten implantable pump study subjects was asked to meet with a psychologist and to bring our significant others along. The psychologist began by asking our partners if there was a difference living with us while we were on the implantable pump as compared to when we were on subcutaneous insulin. The response was shocking - the unanimous and enthusiastic answer from those closest to us was that while we were on the implantable pump we were more enjoyable to be around and much easier to live with! We had never thought about it before, but this comment helped us to become aware of just how much diabetes drains ones energy. This, combined with fighting recurring hypoglycemia (or alternatively accepting constantly high blood sugars) makes it more difficult to consistently be the even tempered and considerate person one would like to be.

In 2001, MiniMed was sold to Medtronic. Initially we were worried that the change would negatively impact the pump project and in some ways it did. The study seemed to drift and lose focus from what we could observe and then, in early 2007, Medtronic announced that the implantable insulin pump study was being cancelled and that we were expected to have our pumps explanted by June of that year - we were devastated. Initially, not only the U.S. was slated for cancellation, but also Europe where the pump and insulin had been approved for general use. For years, we had been told repeatedly that FDA approval was right around the corner. Then, in 2007, we read a report by Saudek (1) stating that as of 2006 no FDA pre-market approval submission had been made for the implantable pump – a disturbing revelation.

Fortunately and for a variety of reasons (including a very strong protest by the European physicians), Europe was given a reprieve from this termination and availability of the implantable pump continued in Europe. After a period of reflection, we decided to contact one of the prominent French research physicians whom we had met years earlier at a scientific meeting focusing on implantable insulin pumps. We asked him if he would take us on as patients. He graciously agreed and for the past four years we have been traveling to Montpellier, France. This requires that we fly to Europe at least every three months just for pump refills – a twenty minute procedure. After a couple of years of this we were asked and gladly agreed to help two other U.S. patients to make the transition to France and our group of American pump expatriates doubled in size.

In about 2005, the insulin manufacturer Sanofi Aventis (b) had developed a new,

(a). Evaluation dans le Diabète du Traitement par Implants Actifs (Rough translation = Assessment in Diabetes Treatment by Active Implants).
human recombinant, insulin that was slated to replace the older, semi-synthetic human insulin that was being retired. We were test subjects in the trials for this new insulin and as far as we could tell it worked well. When news of the worldwide cancellation of the pump was announced however, Sanofi discontinued production of the new insulin and disassembled the production line (the only use of this specialized insulin was for the implantable pump). As a result, when termination of the project was reversed for Europe the only insulin available were residual stocks of the left-over 1997 type semi-synthetic human insulin. This has been the world’s only source of implantable pump insulin for the past four years and it will eventually run out. Fortunately, Sanofi agreed to revitalize its production capabilities and the newest human recombinant insulin is once again available and in late-stage testing in France. If all goes as well as is expected, it will be commercially available by next spring. We are control subjects in the study for this new insulin.

Quite recently (in 2011), the French were informed by Medtronic that only a very limited number of pumps could be built from the dwindling inventory of specialized parts. Apparently, there are parts for fewer than 200 pumps and that is assuming 100% efficiency in converting these parts into pumps – not a likely scenario. Our understanding is that unless identical replacement parts are found (unlikely) or vendor can be identified who will precisely replicate all of the missing parts (again unlikely) this problem will require a concerted effort on the part of Medtronic to either redesign the current pump to accept components that are available or alternatively, design a new pump. From our point of view, the current situation is not tolerable and we are looking for any solution that will insure that this technology does not disappear. We would welcome a decision by Medtronic to seriously dedicate the necessary resources to this task and encourage them to do so. Time is running out.

Stay tuned and check our web site for updates www.theiipump.com

Why do we think the implantable insulin pump works so well?

It is quite clear that we are strong proponents of the implantable insulin pump. There is no question in our minds that it is, by far, the best way to treat type 1 diabetes. We were (and still are) certain about this, but we also felt that our personal experience alone was not enough - we wanted to know why we felt so well. Was there a theoretical basis as to why peritoneal insulin should work better than subcutaneous and if so, was there supporting experimental evidence? We think the answer to these questions is yes and with the caveat that we are not medical professionals the following is some of what we have learned from twenty years thinking about this topic and scouring the medical literature. In our opinion, the evidence unambiguously supports our experience.

Theory and our experience do agree - at least from a patient's perspective

We were thrust into a new reality on the day we got our implantable insulin pumps and because of how dramatically our lives were changed for the better we had a need to understand this new reality. This required us to dig a lot deeper than patients usually do. To begin, there are several key physiological concepts that we had to get our arms around in order to make sense of what we were experiencing. The foundation of the efficacy of the implantable insulin pump seems to reside in the fact that in normal (i.e., in this case, non-diabetic) people the liver plays a central role in maintaining optimal and constant blood sugar levels and it commands a remarkably privileged status in relationship to the pancreas and access to insulin.

• The liver keeps a lot of the insulin for itself: the liver captures at least half, and often a lot more of the insulin it receives from the portal vein. The rest of the body only gets its insulin from the blood leaving the liver after the liver has taken its large share. As a result, all of the other body tissues normally see considerably less insulin than does the liver.

• The difference, pound for pound, is huge: the liver represents approximately 5% of a person’s total body weight – and uses over half of the insulin. This means that, on average, the liver cells are using at least twenty times more insulin than any of the other cells in the body.

This normal process of insulin delivery to the liver and the liver’s remarkably high use of insulin contribute to creating what is known as a Positive Portal Peripheral Insulin Gradient in the normal, non-diabetic person. In other words, the blood entering the liver from the portal vein has a greater concentration of insulin than the blood in the rest of the body (peripheral). This state is preserved as insulin secreted from the pancreas increases or decreases throughout the day and night and changes in blood sugar levels are taken in stride:

1. As Blood Sugars Rise: in the non-diabetic, insulin arriving from the pancreas acts as a messenger to the liver. As blood sugars rise (from meals for example) insulin released from the pancreas is increased and this rising insulin concentration is a signal for the liver to:

a. Slow down or stop the breakdown of liver glycogen and the resulting release of glucose into the blood stream (glycogenolysis). You don’t need more sugar in your blood if blood sugar is rising.

(b). Hoechst had earlier changed its name to Aventis and then merged with the French firm Sanofi.
b. Slow down or stop the formation of brand new glucose from other substrates (gluconeogenesis) such as protein.

c. Increase the storage of incoming glucose as liver glycogen. You have extra sugar so the smart thing is to store it for later use.

2. As Blood Sugars Drop: Again, in the normal, non-diabetic person, (as in fasting or exercise for example) the pancreas of the non-diabetic decrease the amount of insulin being released to the liver. This is a signal for the liver to:

a. Start or increase the rate of liver glycogen breakdown into glucose and to release this glucose into the blood stream. You need glucose so the liver goes about providing it.

b. Start or increase the rate of new glucose formation from substrates such as protein.

c. Stop or diminish the storage of glucose as liver glycogen.

In the case of type 1 diabetes, this beautiful control system is seriously disrupted by type 1 diabetes and the liver is critically hampered in performing its blood glucose control functions. This leads to the following sub-optimal scenarios:

1. Insulin delivered subcutaneously starts its journey under the skin and the liver is at the back of the line: following a subcutaneous injection of insulin (or constant subcutaneous infusion from an external pump) insulin is first absorbed into the peripheral circulation. By the time the blood gets to the portal vein there is far less insulin available to the liver and the normal pattern of delivery is lost. The subcutaneous insulin-treated type 1 diabetic is chronically and unnaturally in the state of a Negative Portal Peripheral Insulin Gradient with peripheral blood insulin levels higher than those arriving at the liver – the reverse of normal physiology.

2. Rising blood sugars: As blood sugars rise and we (type 1 diabetics) respond by injecting more insulin under the skin the liver does not see the added insulin right away and when it does the insulin is less concentrated due to dilution in the blood and due to the peripheral tissues taking it first. As a result, the liver is not getting the intensity signal or the type of signaling it needs to respond optimally. In order to get more insulin (but still less than optimal amounts) to the liver, peripheral tissues would have to be over-saturated with insulin and this is the cause of the peripheral hyper-insulinemia (excessively high insulin levels) seen in diabetics treated with subcutaneous insulin. The amount AND timing AND pattern of insulin are all critical to optimal liver functioning and no matter how carefully we manipulate the subcutaneous delivery of insulin we cannot get close to what the liver needs in this regard.

- Dropping blood sugars: as blood sugars drop and we respond by decreasing the insulin going under the skin (in the case of an external pump, turning down the basal or turning it off), there is a greatly extended time lag where the liver does not notice a change in insulin arrival and so does not respond by releasing glucose as we would like. In addition, the peripheral tissues are over-saturated with insulin and will continue to take up glucose when it would be better if they did not.

So, this is the core issue of interest in the insulin treatment of type 1 diabetics: Normally, all of the insulin produced by the pancreas is sent directly to the portal vein of the liver and the liver keeps the majority of that insulin for its own use. Experimental evidence strongly suggests that this arrangement is required in order to maintain an optimal blood sugar and that achieving preferential delivery of insulin to the liver in the treatment of type 1 diabetes produces superior therapeutic results. If we could prove that insulin delivered to the peritoneum did in fact end up in the portal circulation of the liver (as the anatomy would suggest it should) we would have a foundation for understanding why the implantable insulin pump works so well. Fortunately, we do have our proof. A paper published by Selam, et al in 1990 (2) demonstrated that virtually all of the insulin delivered to the peritoneum did in fact arrive at the liver – insulin delivered to the peritoneum is the path to a Positive Portal Peripheral Insulin Gradient for an insulin treated diabetic! In effect, the implantable insulin pump is delivering insulin in a way that mimics normal physiology and that could never be duplicated by subcutaneous delivery. No matter how elaborate we make external pumps and control algorithms and no matter how creatively we modify insulin we will never get close to mimicking nature in this way with subcutaneous insulin. Currently, and for the foreseeable future, the most promising way we have to approach this normal state is the implantable insulin pump delivering insulin to the peritoneum.

Now that we know that insulin from our implantable pumps was getting to our livers we next needed to know what evidence is there was that this actually makes a difference? Fortunately, there is an extensive and varied body of relevant research focusing on this question and one old but excellent example is the report of a clever experiment first reported in 1967 at the 36th Annual Meeting of the American Diabetes Association. The full write up of the experiment (3)did not appear until late in 1979.

The authors tell of a colony of rats that had been made diabetic by the selective chemical destruction of their beta cells. As expected, these rats developed severe symptoms of diabetes:

- Very high blood sugar levels (in the 500 mg/dl range)
- Excessive urine production in the range of 80 ml. per day (on the order of 1/3rd of their body weight)
• Excessive urine glucose excretion (8 grams per day)

The authors next transplanted fetal pancreases from genetically matched donors (therefore no need for immune suppression). The fetal pancreases were placed under the capsule covering the kidneys – this placement guaranteed that the insulin produced would be delivered to the peripheral circulation (as when insulin is injected subcutaneously). Symptoms improved partially but did not disappear. Next, they performed a surgical procedure that caused the insulin from the transplanted pancreases to flow directly to the liver – with dramatic results: over the following days, all of the diabetes symptoms completely disappeared. Blood sugars were normal, urine production was normal and there was no glucose excreted in the urine.

Insulin routed to the peripheral circulation helped a bit but when it was rerouted to the liver it completely reversed the diabetes. The authors conclude with the following insightful statement (bold emphasis is ours):

“These observations emphasize the important role of the hepatic portal circulation for delivery of insulin to the liver and the key role of the liver in control of the blood sugar. It is not now possible to replace insulin in human beings with insulin-deficient diabetes by this route and insulin injections may result in chronic exposure of peripheral tissues to excess insulin. In considering alternative methods for replacement of insulin in diabetic patients such as transplantation or artificial devices, attention to the site of insulin delivery is important.”

If you would like to read about a lot more research pertinent to the implantable insulin pump check out the Research section of our web site. There, you will find abstracts of several relevant and interesting experiments. We will add new material regularly.

**Conclusion: if the only tool you have...**

There is a famous saying attributed to the psychologist Abraham Maslow: "It is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail”. This saying highlights our natural human tendency to favor and stick with the known and familiar solution even to the exclusion of potentially more effective but unfamiliar options. In the 1920s insulin was a bona fide miracle. Parents lived in fear of a child’s increased thirst and urination and drastic weight loss -signs that might mark the beginning of a year of cruel starvation and ketosis inevitably ending in death. That all miraculously changed with the first injection of insulin. How natural to stick with a winning strategy even as the limitations of that strategy became known and our advanced technological capabilities have made a far superior solution possible. How natural to try to improve on the “hammer” and not realize that there is a better tool waiting to be brought to the task.

In 1980, when the very first implantable insulin pumps were implanted in diabetic patients, our technological capabilities were not quite up to the task of implementing this brilliant idea. Today, technology is not the limiting factor. Our will and money are all that are stopping us from achieving this amazing improvement in diabetes treatment.

Considerable expenditures of time, creativity, capital and the sacrifices of hundreds of experimental subjects were needed to transform the ideas of the 1970s into the current version of the implantable insulin pump. Numerous companies such as Siemens, Infusaid, Shiley, Metal Bellows and others contributed to the effort and in the end, MiniMed emerged with the most successful and the only surviving candidate for a commercial product. Medtronic took over this technology in 2001 and the components and design of today’s implantable insulin pump remain essentially unchanged from that time. The effort required to develop a far superior and technologically current implantable insulin pump is minimal in comparison to the historical investments in this technology and is almost negligible in comparison to the vast investments that have been and continue to be made in an attempt to refine methods of subcutaneous delivery of insulin – a strategy that lacks the physiological integrity of the implantable insulin pump. Finally, current treatment options for type 1 diabetics, as wonderful as they are, do not adequately address the needs of the vast majority of type 1 patients. We only need to look at the devastating human and economic costs that continue to mount. It is time for a better way to treat type 1 diabetes.

We intend to do whatever we can to salvage the future of the implantable insulin pump - check in with our web site www.theiipump.com in the coming months - we will be posting progress reports.

In closing we should mention that, as type 1 diabetics, we are naturally focused on the role of peritoneal insulin in type 1 diabetes – there is also a case to be made for the superiority of this technology for insulin-requiring type 2 diabetics. Perhaps another time for this topic....

**References**

NovoLog®: no other rapid-acting insulin is part of so many lives1,2

NovoLog® is proven effective across a broad range of patients

- Adults with type 1 diabetes
- Adults with type 2 diabetes
- Children and adolescents with type 1 diabetes
- Pump users (adults and children/adolescents)
- Geriatric patients (aged ≥65 years)
- Pregnant women (Category B)

Currently available for more than 95% of managed care patients nationwide*

Visit NovoMedLink.com/Products/NovoLog for more information about NovoLog® and the educational and support programs available for you and your patients.

Indications and usage

- NovoLog® is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus

Important safety information

- NovoLog® is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog® or one of its excipients
- NovoLog® has a more rapid onset and shorter duration of action than regular human insulin. An injection of NovoLog® should be immediately followed by a meal within 5 to 10 minutes. Because of the short duration of action of NovoLog®, a longer-acting insulin also should be used in patients with type 1 diabetes and may be needed in patients with type 2 diabetes. When used in an external subcutaneous insulin infusion pump, NovoLog® should not be mixed with any other insulin or diluent. Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulins
- Any change of insulin dose should be made cautiously and only under medical supervision. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy. As with all insulin preparations, the time course of action of NovoLog® may vary in different individuals or at different times in the same individual and is dependent on many conditions, including injection site, local blood supply, temperature, and level of physical activity

- Needles and NovoLog® FlexPen® must not be shared
- NovoLog® has not been studied in children with type 2 diabetes or in children with type 1 diabetes under the age of 2
- Severe, life-threatening generalized allergy, including anaphylactic reaction, may occur with any insulin product, including NovoLog®. Adverse reactions observed with NovoLog® include hypoglycemia, allergic reactions, local injection site reactions, lipodystrophy, rash, and pruritus. Insulin, particularly when given intravenously or in settings of poor glycemic control, may cause hypokalemia. Like all insulins, NovoLog® requirements may be reduced in patients with renal impairment or hepatic impairment
- All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy

Please see brief summary of prescribing information on adjacent page.

*Intended as a guide. Lower acquisition costs alone do not necessarily reflect a cost advantage in the outcome of the condition treated because there are other variables that affect relative costs. Formulary status is subject to change.

Needles are sold separately and may require a prescription in some states.

References: 1. IMS Health Inc. IMS National Sales Perspectives (12 months ending October 2009)
2. IMS Health Inc. IMS MIDAS (MAT2Q09). B. Data on file. Access Point, Q3 2009

FlexPen® and NovoLog® are registered trademarks of Novo Nordisk A/S.
© 2010 Novo Nordisk
142057 August 2010

NovoLog®
insulin aspart (rDNA origin) injection
Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog® [see Warnings and Precautions]. NovoLog® should not be exposed to temperatures greater than 57°C (134.6°F). NovoLog® that will be used in a pump should not be mixed with other insulin or with a diluent [See Warnings and Precautions].

ADVERSE REACTIONS: Clinical Trial Experience: Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those reported in another clinical trial, and may not reflect the rates observed in practice. Hypoglycemia: Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog® [see Warnings and Precautions].

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (Adverse events with frequency ≥ 5% and occurring more frequently with NovoLog® compared to conventional insulin)

<table>
<thead>
<tr>
<th></th>
<th>NovoLog® + NPH</th>
<th>Human Regular Insulin + NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=596</td>
<td>N=286</td>
</tr>
<tr>
<td>Preferred Term</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Hypoglycemia*</td>
<td>448 (75%)</td>
<td>205 (72%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>7 (1%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 (7%)</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28 (5%)</td>
<td>9 (3%)</td>
</tr>
</tbody>
</table>

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL.

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (except for hypoglycemia, adverse events with frequency ≥ 5% and occurring more frequently with NovoLog® compared to human regular insulin are listed)

<table>
<thead>
<tr>
<th></th>
<th>NovoLog® + NPH</th>
<th>Human Regular Insulin + NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=91</td>
<td>N=91</td>
</tr>
<tr>
<td>Preferred Term</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>25 (27%)</td>
<td>33 (36%)</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>10 (11%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Onychomasis</td>
<td>9 (9%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td>8 (8%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5 (5%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Skin disorder</td>
<td>5 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5 (5%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

*Hypokalemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms.

Postmarketing Data: The following additional adverse reactions have been identified during postapproval use of NovoLog®. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Medication errors in which other insulins have been accidentally substituted for NovoLog® have been identified during postapproval use.

OVERDOSAGE: Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

More detailed information is available on request.

Date of Issue: March 17, 2010

Version 17

Manufactured by Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

For information about NovoLog® contact: Novo Nordisk Inc., Princeton, New Jersey 08540 1-800-727-6500 www.novonordisk-us.com

FlexPen® and NovoLog® are registered trademarks of Novo Nordisk A/S.

NovoLog® is covered by US Patent Nos. 5,518,913, 5,866,538, and other patents pending. FlexPen® is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,004, and other patents pending.

© 2010 Novo Nordisk

134600-R3 8/10