

an injection meal interval. Rapid-acting insulin analogs (RAIA) were developed some 15-20 years ago to improve the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the prandial insulin formulation; i.e. to achieve a more rapid absorption / metabolic action and a shorter duration of action than regular insulin (therefore these insulin formulations sometimes are also called short-acting insulin analogues). Sometimes RAIAs are also called short-acting insulin analogs to highlight that they also have a shorter duration of action compared to regular insulin. Subsequently, a number of meal related studies were performed to demonstrate/prove that RAIAs allow a more effective control of postprandial glucose excursions. The three RAIAs that are on the market do not differ in their PK/PD properties very much. However, it was reported that in a given patient group (obese subjects) one of the three RAIAs (glulisine/Apidra) has advantages.

Despite the considerable step forward made with the invention with RAIAs, one has to acknowledge that the currently available RAIAs are not able to mimic the physiological post-meal insulin secretion pattern to a full extent. For example, a recent publication about the optimal application-meal interval in patients using continuous subcutaneous insulin infusion (CSII) showed that even with RAIAs an interval of 20 min is helpful to optimize postprandial glycemic excursions in a meal study with a standardized meal.

Thus, an even faster onset of action is warranted to achieve an even tighter postprandial glucose control.

Historically, a number of other approaches were studied to improve

the rate of absorption of regular human insulin from the SC insulin depot by more “mechanical” measures: application of ultrasound, addition of Trayslol, usage of a sprinkler needle etc. However, after the invention of RAIAs practically all these developments were stopped for quite a while. Clearly, the insulin manufacturers were not too much interested in developing competing approaches (the major advantage of RAIAs for them is the good patentability); at the same time, the hope/understanding was that RAIAs have solved this issue: we are able to cover each and every meal in an optimal manner by using these.

Insulin and optimizing the PK/PD properties of insulin was not a hot topic in the last 10 years. At scientific congresses the number of symposia, oral presentations and poster dealing with insulin formulations etc. were relatively small (despite the fact that the insulin manufacturers have intensified their internal insulin research activities). As a result of this “silence”, many diabetologists believe that optimal coverage of prandial and basal insulin requirements is possible by using rapid-acting and long-acting insulin analogs in a smart manner. This belief was supported by the massive marketing campaigns of the insulin manufacturers. If in daily practice the patients disprove this belief, one tends to say, the patients are not smart enough.

More recently, a number of attempts showed up, that are aiming to develop an prandial insulin with a more rapid onset of insulin action after administration: “Ultrafast” insulins (UFIs). The idea for this name is clearly to differentiate them from the RAIAs but also to highlight the aim: to mimic the physiological situation with a rapid release of insulin when a

meal is ingested. The improved time-action profile should help to more rapidly shut off the hepatic glucose production (the liver is sensitive to the gradient with which the insulin concentration in blood changes).

The “technology” used for the different attempts differ widely:

- Oral insulin: Like with RAIAs the molecular structure of insulin molecule is modified (a chain is conjugated to the insulin) to achieve an insulin molecule that is rapidly absorbed in reasonable quantities after oral administration (IN-105; Biocon, India),
- Technical approach: Heating the local skin area above the insulin depot is supposed to increase the local blood flow in the subcutaneous tissue which led to an increased insulin absorption/action (InsuLine, Israel),
- Compartmental approach: Injecting or infusing the insulin by means of short insulin needles (“microneedles”) into the dermis instead of the subcutaneous tissue also led to improved PK/PD properties (Becton Dickinson),
- Insulin monomers: Mixing regular human insulin with GRAS substances reduces insulin self-assembly to hexamers (Linjeta; Biode, USA),
- Subcutaneous space: Reduction of diffusion barriers in the SC tissue by locally applying an enzyme (hyaluronidase) that digest these (Halozyme, USA),
- Inhaled insulin: Mixing insulin molecules with a substances that support rapid absorption after application of fine particles to the deep lung (Afrezza/Technospheres; MannKind, USA).

Most probably, this list is not complete and other attempts exist; clearly the large insulin manufacturers (Novo

Nordisk has indicated that they are working on this topic without disclosing details) will also work on improved RAIAs as their patents on the currently available ones will expire sooner than later. They have to fear that generic RAIAs will take over a considerable part of this market once this happens.

Our level of understanding about the science behind these developments differ, in some case a wealth of studies is available, also good review articles about the principle, in other cases there is room for improvement. Clearly, it is not only the time-action profile that is of relevance to make one or the other approach successful, many more aspects, also regulatory and economical one, have to be considered. Among other the reproducibility of the insulin effect after application is also of relevance to optimize postprandial metabolic control. Interestingly enough, the number of respective studies is quite small. For example, no study was performed that far which would have studied the reproducibility of insulin bolus application with CSII. An aspect that is also of high relevance for the development of a practically applicable artificial pancreas.

One thing is relatively simple to answer: Which is the best approach? Or in other words: with which approach the best optimization of

postprandial metabolic control can be achieved. What we need for that are well designed and executed meal studies. They will prove if UFIs are of true benefit or not. To perform such studies might sound trivial at first glance, however, in reality they are difficult to perform. It requires a good deal of experience to achieve meaningful outcome (citations). Unfortunately, most meal studies published that far do not fulfil these expectations, e.g., they have not paid enough attention to the preprandial situation. Without comparable (= identical) glucose/insulin levels in the last hour(s) prior to the intervention (= ingestion of the meal/insulin application), no meaningful comparison of the results obtained on different study days is possible. With the UFIs presented above some meal related studies fulfilling these requirements have been performed demonstrating their benefits also in comparison to RAIAs.

In summary, with the invention of “ultrafast insulin” (further) optimization of postprandial metabolic control can be assumed to be possible. How long it will take until one of the different UFIs that are in clinical developments will become available as a product is difficult to say; at least for two the necessary documents have been submitted to the regulatory authorities (MannKind, Biondi), others are more or less advanced in

the development process and can also become available within the next few years. We have to acknowledge that good progress has been made with UFIs in the last years and that most probably the “portfolio” to cover prandial insulin requirements better than this was possible until now will become bigger quite soon. To which extent this can be converted into improved long-term metabolic control (= reduced glycosylated hemoglobin) remains to be seen. It is also not clear right now what the market uptake of the different attempts will be, many factors like costs, safety, patient preferences (practicability, handling efforts) etc. will have a major impact on that. Let’s hope that it is at the end not only the better marketing campaign that brings one of the UFIs into the forefront, but that the one which allows to optimize postprandial metabolic control the most will win.

Conflict of interest

The author is consultant for a number of companies that develop novel diagnostic and therapeutic options for diabetes treatment.

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Transition to Insulin Pump Therapy: What are the Experiences of Children with Type 1 Diabetes, Adolescents with Type 1 Diabetes and their Parents?

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Insulin pump therapy is an alternative to injections to manage type 1 diabetes in children and adolescents. Benefits of insulin pump therapy include less hypoglycaemia, fewer injections, and flexible sleeping and eating patterns. Disadvantages of insulin pump therapy include an increased risk of ketoacidosis, more frequent blood glucose monitoring, being attached to an external device, and the risk of infection (Rodgers, 2008). The most common reasons for initiating insulin pump therapy are to improve glycaemic control, fewer fluctuations in blood glucose levels, an alternative to insulin injections, and increased flexibility in daily living.

Few data are available concerning the factors that predict which children will benefit from insulin pump therapy (Maniatis, Toig, Klingensmith, Fay-Itzkowitz, & Chase, 2001). Cogan et al. (2002) and Sullivan-Bolyai et al. (2004) found that parents, who could recall the diagnosis of diabetes, achieved better glycaemic control when their child or adolescent commenced insulin pump therapy. Commencing insulin pump therapy is also accompanied by a sense of excitement, which is associated with the possibility of greater flexibility and improved quality of life (Cogan et al., 2002).

Most parents felt comfortable using the pump after two to three months (Sullivan-Bolyai et al., 2004). Parents and children were equally well prepared for the transition to insulin pump therapy and using the pump was rated from easy to very easy (Mednick, Cogan & Streisand, 2004). Parents and children

said there was more flexibility and they had fewer worries about caring for their diabetes, there was improved glycaemic control and children were better able to manage their diabetes.

Parents are not always adequately prepared for the challenges of using an insulin pump (Low, Massa, Lehman, & Olsham, 2005). Adolescents and families who anticipated that insulin pump therapy would improve glycaemic control and increase flexibility did better than those with unrealistic expectations (Low et al., 2005). Parents had more difficulties adjusting to insulin pump therapy if they were not prepared for the demands of checking blood glucose levels frequently, including overnight, site changes, programming and pump problem solving (Low et al., 2005). Inserting the infusion cannula was a challenge for most children (Mednick et al., 2004; Hanas, 2002). Insertion sites and mechanics of pumping can present challenges for families. Adolescents are often more comfortable with pump technology than parents but rely on parents for assistance with set changes and programming (Low et al., 2005).

Managing young children can be difficult because insulin absorption is unpredictable due to their erratic eating patterns and activity levels, increased sensitivity to small amounts of insulin, parental fear of hypoglycaemia and the difficulty of treating hypoglycaemia when the child refuses to eat or drink (Fox et al., 2005). Fear of hypoglycaemia is known to be a major concern for people with type 1 diabetes (Barnard & Skinner, 2007). Hypoglycaemia often poses a barrier to good diabetes control

(Phillip, Battelino, Rodriguez, Danne, & Kaufman, 2007). Parents and adolescents who fear hypoglycaemia tend to maintain higher blood glucose levels (Juliussen, Graue, Wentzel-Larsen, & Sovik, 2006). Parents were less concerned about hypoglycaemia, when using an insulin pump if meals or snacks were delayed, high blood glucose levels could be corrected easily, and there was more choice and flexibility with food (Klingensmith, Temple-Trujillo, & Johnson, 2001).

Because only rapid acting insulin is used in the pump, there is a greater risk of diabetic ketoacidosis (DKA) occurring compared with children on insulin injections (Bode, Tamborlane, & Davidson, 2002). Unexplained high blood glucose levels can indicate a problem with insulin delivery such as an occlusion with the infusion set (Boland, Ahern, & Grey, 1998). The pump may not detect an interruption in insulin delivery for several hours resulting in higher blood glucose levels and ketones (Torrance, Franklin, & Greene, 2003). Bode et al. (2002) observed fewer episodes of DKA in adolescents and adults using insulin pump therapy. Likewise, Hanas & Adolfsson (2006) found that recurrent admissions for DKA were reduced when using insulin pump therapy.

The appropriate adjustment of the insulin pump during exercise among children and adolescents is not yet clear (Admon et al., 2005; Low et al., 2005). Trial and error remains the principal method of regulating blood glucose levels during exercise (The Diabetes Research in Children Network Study, 2006). Children often participate in

unplanned physical activity. Admon et al. (2005) found that hypoglycaemia during exercise could be prevented only when the meal bolus was reduced by 50% and basal insulin discontinued during exercise. Reducing the meal bolus requires planning the activity. Reducing the basal insulin rate by 25% during the hours following exercise reduced late hypoglycaemia. A bedtime snack was also recommended to prevent hypoglycaemia.

Low et al. (2005) reported concerns relating to checking blood glucose levels, bolusing, and pump management while at school. Education and training for school personnel was one of the most frequent concerns mentioned (Low et al., 2005). Older primary school aged children may be able to program the pump themselves but are cognitively unable to troubleshoot when problems occur (Klingensmith et al., 2001). School nurses are initially scared when they encounter insulin pump therapy due to a lack of education and experience (Darby, 2006).

Rather than encouraging full independence, a continued child/parent relationship should be maintained while insulin pump therapy is initiated. Giving children and adolescents full responsibility too soon often leads to reduced adherence to the diabetes management regimen. When adolescents transitioned to insulin pump therapy parental involvement stayed the same or decreased (Mednick et al., 2004).

Quality of life issues are extremely important because they may be significant in predicting an individual's capacity to manage their disease and maintain long-term health and well being. Some psychosocial factors including health related beliefs, social support, coping style, and personality type might have a significant effect on quality of life. Although several studies into insulin pump therapy have been conducted few address the psychosocial aspects or quality of life issues in the paediatric population (Fox et al., 2005). Fox et al. (2005) concluded that insulin pump therapy is safe and well tolerated in young children, and enhances their qual-

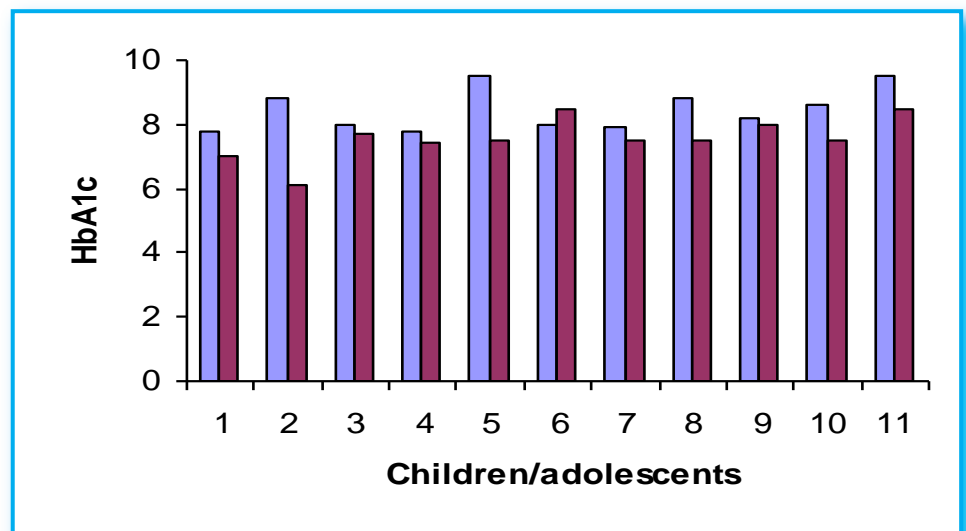


Figure 1: *HbA1c before and after insulin pump therapy.*

ity of life, although it may not improve glycaemic control. Likewise, Hanas and Adolfsson (2006) suggested quality of life issues are becoming increasingly important when deciding to use insulin pump therapy to manage diabetes. This research study aimed to add to the existing research on insulin pump therapy.

Methods

Participants

A convenience sample of 11 families including children with type 1 diabetes, adolescents with type 1 diabetes and their parents making the transition to insulin pump therapy at the Mater Children's Hospital in Brisbane from October, 2008 to January, 2009 participated in the study. The study participants were aged 3-16 years of age (mean = 10.5 years), living in Brisbane (n = 11 families which included 11 parents and 12 children and adolescents). There were no single parent families in this study. Of the 12 children and adolescents included in the study there were six females and six males. Duration of diabetes ranged from nine months to 10 years (mean = 4 years).

Materials

A questionnaire and pre pump interview guides were developed for this study. The interview was developed to gain information regarding the meaning of diabetes. The questionnaire was the

same for parents, children and adolescents, however the interview guides differed. Another questionnaire and interview guides were developed to be used three months after making the transition to insulin pump therapy. Again, the questionnaire was the same for parents, children, and adolescents. Interview guides were developed for this study to gain an understanding of the experience of families making the transition to insulin pump therapy. The interview guide for parents differed from the interview guide for children and adolescents.

Procedure

Participants, including parents, school-aged children, and adolescents were interviewed and filled in a questionnaire before commencing insulin pump therapy. The families were given diaries to record information about the transition to insulin pump therapy. Families were interviewed and filled in a questionnaire again approximately three months after making the transition to insulin pump therapy.

Results

NVivo version 8 was used to conduct a thematic content analysis to identify, analyse and report emerging patterns and themes from the interviews and diaries. Themes included freedom, constancy, worries/concerns, hypoglycaemia, long term health, starting over,

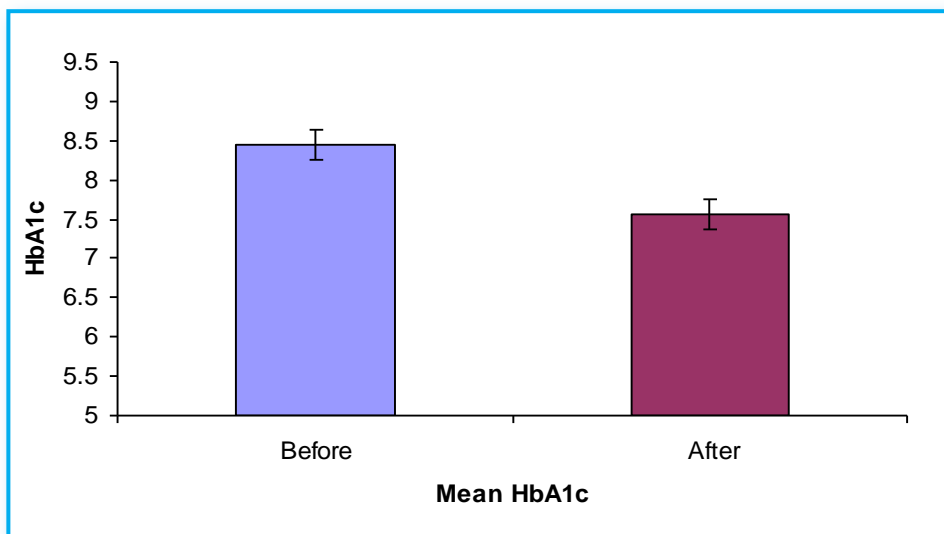


Figure 2: Mean HbA1c before and after insulin pump therapy.

effort, fewer needles, better blood glucose levels, being attached, and feeling normal. SPSS 11.0 student version was used to conduct a descriptive analysis of the questionnaires to compare differences between families before starting insulin pump therapy and again three months after starting the insulin pump.

The meaning of diabetes describes the impact of diabetes on the lives of children and adolescents with type 1 diabetes and their parents. Some children and adolescents said that diabetes made no difference or had minimal impact on their lives. It meant having injections, doing finger pricks, a lack of freedom regarding food choices, and extra attention. One of the biggest adjustments children and adolescents had to make since being diagnosed with diabetes was freedom regarding food choices, and amounts of food they liked to eat. They also had to eat at set times, whether they wanted to or not; often food was refused to prevent high blood glucose levels or to avoid having another needle.

Parents had more worries since their child or adolescent was diagnosed with diabetes. Mothers worried more, were sadder, and more protective. Mothers were more worried about hypoglycaemia, particularly at night time than were fathers or children and adolescents. Mothers also said there was a lack of freedom regarding timing of meals and food choices, and constantly checking on their child or adolescent. Fathers also

had more worries, were more planned and organised, felt they had more responsibility, and were constantly aware of diabetes.

Fathers, children, and adolescents were more concerned about hyperglycaemia. The long term health of children and adolescents represented a major concern for parents because they worried about the complications of diabetes. Long term health remained a major concern for parents following transition to an insulin pump.

Transition to insulin pump therapy represented a new beginning in the management of diabetes. Mothers said that making the transition to insulin pump therapy was like starting over. Children and adolescents felt excited yet nervous about starting on the pump. Starting on an insulin pump meant less stress for parents although some mothers were stressed initially while becoming accustomed to the pump.

Most parents took approximately two months to become accustomed to the pump. All but one mother were satisfied or very satisfied with the pump. Most parents, children, and adolescents said the transition to insulin pump therapy was not difficult, or slightly difficult. One mother said the transition was very difficult. Parents, children and adolescents were slightly prepared or well prepared for the transition to insulin pump therapy; one mother and one father were not prepared.

Benefits of the pump included fewer needles, freedom, and better glycaemic control. Disadvantages included being attached, the pump not working, taking the pump off for sport, resetting, and problems with the cannula, and sites, and getting used to the pump. Parents, children, and adolescents talked about having better, more stable blood glucose levels. Some parents reported that the behaviour of their child or adolescent had improved because there were fewer fluctuations in blood glucose levels. Parents also observed a change in emotions.

Prior to the pump start parents and children said the pump would make life easier. Parents and children/adolescents had differing opinions regarding effort needed to use the pump. Children and adolescents said the pump was easier because all they had to do was press a few buttons rather than having a needle. Parents found the night time monitoring particularly difficult because sleep interruption caused exhaustion.

For children/adolescents getting the pump represented getting their freedom back; freedom from needles, and freedom in terms of food, being able to eat when they wanted and more choice in the foods they could eat. Parents also said freedom was a benefit of insulin pump therapy. Freedom also meant being able to sleep in.

Both parents and children said that being attached to a machine was a disadvantage. Despite being attached to a machine most children/adolescents felt more normal after getting a pump. They talked about not feeling normal before getting the pump. Parents also used the term 'normal' in their conversations. One adolescent stopped using the pump after six weeks because she did not feel normal being attached to a machine. She was happier using pens to manage her diabetes.

For children and adolescents the hardest things to get used to when starting the pump were cannula changes, carbohydrate counting, and remembering to bolus. Children and adolescents who did not forget to bolus said it had become a habit. Parents also reminded them to

bolus. Children and adolescents reported that programming the pump was easy. For parents, adjusting the basal and bolus rates was more difficult. Changing the cannula, programming the pump, carbohydrate counting, learning the new language, remembering to change the site every three days, and trusting the pump also represented a challenge for parents. Parents found dosing the insulin was easy. Hyperglycaemia and ketones occurred more frequently since starting the pump however families were more likely to check for ketones.

Most children and adolescents took the pump off for sport and often this was all they needed to prevent hypoglycaemia following exercise. Children and adolescents who were doing a lot of exercise also set a temporary basal rate afterwards to prevent hypoglycaemia.

Children from eight years of age bolused for meals at school, without assistance. Parents wrote the carbohydrate amount on stickers which they put on the food in the school lunch box. Older children and adolescents kept their blood glucose meter and hypo kit in their school bag and did their blood glucose levels where their school bag was or wherever they were. One child did the blood glucose level in the classroom and one at the school office. Children and adolescents who gave injections at school did them wherever they were. There was not anywhere they could go to do their injection unless they went to the toilets or the office. Using the pump was easier than having injections at school.

Of the 11 children and adolescents still using the pump, 10 children/adolescents had lower HbA1c's three months after starting the pump (mean HbA1c 7.6%, SD .67) compared to before the pump (mean HbA1c 8.4%, SD .64). Only one child had a higher HbA1c three months after starting the pump. This was because he forgot to bolus for food and forgot to put his pump back on after removing it for swimming. HbA1c readings for children/adolescents before and after starting the pump are illustrated in figure 1. Figure 2 illustrates mean HbA1c before and after starting the pump.

Discussion

While most children and adolescents wanted the pump to avoid needles, parents wanted the pump to allow freedom and flexibility. Low et al. (2005) also reported that adolescents wanted a pump to avoid needles. Improved glycaemic control was not the most common reason for wanting the pump despite long term health being the main concern for parents. Over time, some families seem to neglect trying to improve metabolic control in favour of improved lifestyle factors. These findings are consistent with Mednick et al (2004) who found that better lifestyle and quality of life was more important than improved metabolic control. Previous research (Sullivan-Bolyai et al., 2004; Maniatis et al., 2001) also found that a combination of improved metabolic control and easier lifestyle were the main reasons for making the transition to insulin pump therapy. There are conflicting reports about how difficult the transition to insulin pump therapy is. Mednick et al. (2004) reported that families found the transition easy. Sullivan-Bolyai et al. (2004) reported that all parents emphasised that insulin pump therapy required work. Similar results were found with the present study. Most parents, children, and adolescents reported being slightly or well prepared for insulin pump therapy and were satisfied or very satisfied with insulin pump therapy. Only one mother was not happy. Results from Mednick et al. (2004) were slightly more positive and found that parents and children were extremely satisfied and well prepared for insulin pump therapy. Low et al. (2005) also found that families had high levels of satisfaction with the pump.

Children and adolescents said set changes, remembering to bolus, and carbohydrate counting was harder to become accustomed to although most of it was easy. For mothers the most difficult tasks were adjusting insulin doses, set changes and programming the pump. Previous research (Low et al., 2005) suggested that adolescents were more

comfortable with pump technology than were parents. Sullivan-Bolyai (2004) also identified that parents and children found learning to insert the cannula was difficult. When children have difficulties inserting the set they are more likely to prolong changing the set, leaving the old set in longer than the recommended three days resulting in higher blood glucose levels thus compromising metabolic control.

Burdick et al. (2004) revealed that missed meal boluses were the main reason for suboptimal metabolic control when using the pump. Forgetting to bolus four times per week represented a 1% increase in HbA1c. One third of children and adolescents in the present study said remembering to bolus was one of the more difficult things to get used to and half of the children and adolescents reported forgetting to bolus. Children and adolescents who did not previously have an injection at lunch time were more likely to forget to bolus. The pump allowed flexible eating times and amounts of food which could be eaten allowing children and adolescents to eat when they were hungry. Parents were often restrictive in food choices and amounts of food their child or adolescent was allowed to eat because they are worried that high blood glucose levels would occur. The pump also allowed for more flexible sleeping patterns.

In the beginning, parents needed to monitor blood glucose levels more frequently, including overnight leading to disruptive sleeping patterns for parents and some children/adolescents. Night time monitoring of blood glucose levels was difficult because of subsequent sleep deprivation. Parents, especially those of the younger children continued to monitor blood glucose levels and were still doing overnight blood glucose levels when interviewed at three months.

Insulin pump therapy made it easier for parents to manage sport. The Diabetes Research in Children Network Study (2006) suggested trial and error is the principal method of managing blood glucose levels during exercise. Considering there are no guidelines, it

might be expected that families have some trouble managing sport. The families in this study did not have any major concerns working out whether the child/adolescent should have less insulin, more food or a combination of less insulin and more food for sport.

Children/adolescents from eight years of age looked after the pump at school without supervision. Day care and schools need to take on more responsibility for younger children. An eight year old child can program a high blood glucose level into the pump and bolus for food if the food is labelled with the carbohydrate content, however they are not able to problem solve if the blood glucose levels are high. School personnel often are not adequately prepared to manage an insulin pump.

The adolescents in this study became more independent when they transitioned to insulin pump therapy. Parents were available for support if required but adolescents took on more responsibility for diabetes management. Williams et al. (2004) suggest that a child/parent relationship be maintained while insulin pump therapy is initiated. To encourage adolescents and older children to use the pump appropriately, they need continued support from parents.

It is apparent that some mothers purposely run blood glucose levels high to avoid hypoglycaemia. Two mothers in the present study admitted to this and other mothers were worried about hypoglycaemia, particularly at night. Fear of hypoglycaemia is a deterrent to good glycaemic control (Phillip, Battelino, Rodriguez, Danne, & Kaufman, 2007). Parents in the present study were a little less concerned about hypoglycaemia after starting the pump.

A small number of participants were recruited for this study from one hospital in Brisbane and may not be representative of the whole population. This research could be extended by including participants from several hospitals. Further research may also clarify if not feeling normal results in discontinuation of insulin pump therapy.

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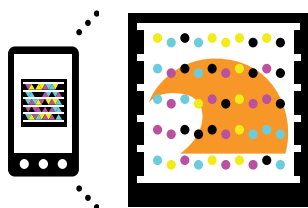
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- NovoLog[®] is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog[®] or one of its excipients
- NovoLog[®] has a more rapid onset and shorter duration of action than regular human insulin. An injection of NovoLog[®] 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 (MATQ209). 3. Data on file. Access Point, Q3 2009.

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August 2010



NovoLog[®]
insulin aspart (rDNA origin) injection

NovoLog® (insulin aspart [rDNA origin] injection)

Rx only

BRIEF SUMMARY. Please consult package insert for full prescribing information.

INDICATIONS AND USAGE: Treatment of Diabetes Mellitus: NovoLog® is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

CONTRAINDICATIONS: NovoLog® is contraindicated during episodes of hypoglycemia and in patients with hypersensitivity to NovoLog® or one of its excipients.

WARNINGS AND PRECAUTIONS: Administration: NovoLog® has a more rapid onset of action and a shorter duration of activity than regular human insulin. An injection of NovoLog® should immediately be followed by a meal within 5-10 minutes. Because of NovoLog®'s short duration of action, a longer acting insulin should also be used in patients with type 1 diabetes and may also be needed in patients with type 2 diabetes. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy. Any change of insulin dose should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin strength may result in the need for a change in dosage. As with all insulin preparations, the time course of NovoLog® action may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, temperature, and physical activity. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages. Insulin requirements may be altered during illness, emotional disturbances, or other stresses. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure. **Needles and NovoLog® FlexPen® must not be shared.** **Hypoglycemia:** Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog®. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with NovoLog®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., patients who are fasting or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia. Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring more close monitoring for hypoglycemia. **Hypokalemia:** All insulin products, including NovoLog®, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, and patients receiving intravenously administered insulin). **Renal Impairment:** As with other insulins, the dose requirements for NovoLog® may be reduced in patients with renal impairment. **Hepatic Impairment:** As with other insulins, the dose requirements for NovoLog® may be reduced in patients with hepatic impairment. **Hypersensitivity and Allergic Reactions: Local Reactions** - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of NovoLog® injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog®. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in NovoLog®. **Systemic Reactions** - Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin product, including NovoLog®. Anaphylactic reactions with NovoLog® have been reported post-approval. Generalized allergy to insulin may also cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis. In controlled clinical trials, allergic reactions were reported in 3 of 735 patients (0.4%) treated with regular human insulin and 10 of 1394 patients (0.7%) treated with NovoLog®. In controlled and uncontrolled clinical trials, 3 of 2341 (0.1%) NovoLog®-treated patients discontinued due to allergic reactions. **Antibody Production:** Increases in anti-insulin antibody titers that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog®. Increases in anti-insulin antibodies are observed more frequently with NovoLog® than with regular human insulin. Data from a 12-month controlled trial in patients with type 1 diabetes suggest that the increase in these antibodies is transient, and the differences in antibody levels between the regular human insulin and insulin aspart treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. These antibodies do not appear to cause deterioration in glycemic control or necessitate increases in insulin dose. **Mixing of Insulins:** Mixing NovoLog® with NPH human insulin immediately before injection attenuates the peak concentration of NovoLog®, without significantly affecting the time to peak concentration or total bioavailability of NovoLog®. If NovoLog® is mixed with NPH human insulin, NovoLog® should be drawn into the syringe first, and the mixture should be injected immediately after mixing. The efficacy and safety of mixing NovoLog® with insulin preparations produced by other manufacturers have not been studied. Insulin mixtures should not be administered intravenously. **Continuous Subcutaneous Insulin Infusion by External Pump: When used in an external subcutaneous insulin infusion pump, NovoLog® should not be mixed with any other insulin or diluent.** When using NovoLog® in an external insulin pump, the NovoLog®-specific information should be followed (e.g., in-use time, frequency of changing infusion sets) because NovoLog®-specific information may differ from general pump manual instructions. Pump or infusion set malfunctions or insulin degradation can lead to a rapid onset of hyperglycemia and ketosis because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly

absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required [see *Warnings and Precautions*]. NovoLog® should not be exposed to temperatures greater than 37°C (98.6°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 rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice. **Hypoglycemia:** Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog® [see *Warnings and Precautions*]. **Insulin initiation and glucose control intensification:** Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy. **Lipodystrophy:** Long-term use of insulin, including NovoLog®, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. **Weight gain:** Weight gain can occur with some insulin therapies, including NovoLog®, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. **Peripheral Edema:** Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. **Frequencies of adverse drug reactions:** The frequencies of adverse drug reactions during NovoLog® clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

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 human regular insulin are listed)

Preferred Term	NovoLog® + NPH N= 596		Human Regular Insulin + NPH N= 286	
	N	(%)	N	(%)
Hypoglycemia*	448	75%	205	72%
Headache	70	12%	28	10%
Injury accidental	65	11%	29	10%
Nausea	43	7%	13	5%
Diarrhea	28	5%	9	3%

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

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)

	NovoLog® + NPH N= 91		Human Regular Insulin + NPH N= 91	
	N	(%)	N	(%)
Hypoglycemia*	25	27%	33	36%
Hyporeflexia	10	11%	6	7%
Onychomycosis	9	10%	5	5%
Sensory disturbance	8	9%	6	7%
Urinary tract infection	7	8%	6	7%
Chest pain	5	5%	3	3%
Headache	5	5%	3	3%
Skin disorder	5	5%	2	2%
Abdominal pain	5	5%	1	1%
Sinusitis	5	5%	1	1%

*Hypoglycemia 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.

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Version 17

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

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

NovoLog® is covered by US Patent Nos. 5,618,913, 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.

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NovoLog®
insulin aspart (rDNA origin) injection