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Лантус, первый беспиковый аналог базального инсулина – 10-летний опыт применения у детей и подростков

Кураева Т.Л.

ФГБУ Эндокринологический научный центр, Москва
(директор – академик РАН И.И. Дедов)

Обзор посвящен анализу данных литературы, включая собственные данные, по результатам клинических исследований эффективности и безопасности применения инсулина гларгин (Лантус®) у детей и подростков, а также особенностям управления диабетом 1 типа у данной возрастной категории пациентов, в том числе проблеме снижения частоты гипогликемий при сохранении адекватного гликемического контроля. Рассмотрены также отдельные проблемы в управлении диабетом у детей и подростков, такие как роль гликемического контроля в развитии сосудистых осложнений, гипогликемии, вариабельность гликемии. Представленные данные свидетельствуют о высокой эффективности инсулина Лантус в отношении компенсации сахарного диабета, включая снижение частоты гипогликемий и вариабельности гликемического профиля, о безопасности его применения у детей и подростков, включая детей первых лет жизни, о повышении качества жизни пациентов и их родителей.
Ключевые слова: *сахарный диабет 1 типа; дети и подростки; инсулин гларгин (Лантус); гликемический контроль; безопасность*

Lantus, the first peakless basal insulin analogue: 10 years of clinical experience in children and adolescents

Kuraeva T.L.
Endocrinology Research Centre, Moscow, Russian Federation

This review analyses existing literature, including authors' own data, describing the results of clinical trials which assess safety and efficacy of insulin Glargine (Lantus®) in children and adolescents, as well as peculiar features of T1D management in this age group, including the challenge of reducing the rate of hypoglycemia while maintaining adequate glycemic control. The article also discusses various issues in T1D management in children and adolescents, including the role of glycemic control in development of vascular complications, hypoglycemia and the variability of glycemia. The data confirm the high efficacy of Lantus insulin in respect to metabolic control, including the decrease in the incidence of hypoglycemia and in variability of glycemic profile, the safety of its clinical use in treatment of children, including young children, and adolescents, as well as its ability to improve the quality of life for patients and their parents.
Keywords: *T1D; children and adolescents; insulin Glargine; glycemic control; safety.*

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The treatment of diabetes mellitus (DM) in children and adolescents presents a number of serious challenges. In the ideal situation, the optimal glycaemic control involves the administration of insulin in a regimen that is acceptable to a child and his/her family and the results in achieving target levels of carbohydrate metabolism without the onset of hypoglycaemia. Compared to adult patients, the paediatric population has some specific issues, such as difficulties in planning a dietary regimen due to the variability in appetite, difficulties in forecasting physical activity, hormonal changes during puberty, the 'risky behaviour' of adolescents, and so on. Obviously, to achieve optimal metabolic control, the insulin therapy regimen must be adapted to a child's personality and to his family. More than 15 years of clinical experience with insulin analogues has demonstrated the efficacy and safety of their use in paediatric practice. Basal analogues occupy a special place as the selection of an adequate profile of basal insulinaemia allows for the closest approximation of target levels of carbohydrate metabolism without increasing the risk of hypoglycaemia. Insulin glargine (Lantus®) is the first peakless basal analogue, and more than 10 years of its clinical use in the treatment of DM patients worldwide has proven its high efficacy.

Over the last six decades since insulin was introduced in clinical practice in 1922, researchers have been improving the quality of insulin preparations that are isolated from animal pancreases. However, it was only in 1964 that Panavotis and Katsoyan succeeded in using DNA recombinant techniques to synthesise human insulin, which currently occupy an important place in DM treatment in all developed countries. The availability of human insulin reduced its immunogenicity and changed the absorption rate. Along with the development of the basal-bolus insulin regimen and the improvement of self-control methods, it has become possible to improve the carbohydrate metabolism status in many patients. The availability of efficient short- and long-acting insulin has revolutionised the treatment of diabetes and increased the life expectancy of patients [1, 2]. Nevertheless, the risk of delayed vascular complications still persists, albeit to a lesser extent.

THE ROLE OF GLYCAEMIC CONTROL IN THE DEVELOPMENT OF VASCULAR COMPLICATIONS

A number of research projects conducted to date have irrefutably proven the importance of glycaemic control for the prevention of specific vascular complications. The Diabetes Control and Complications Trial (DCCT), conducted in 1982–1989, is rightfully considered the most important trial for diabetes. This randomised study of the control of diabetes and its complications compared two groups of patients, those who received conventional insulin therapy (1 or 2 injections per day) and those who received intensive therapy (multiple injections per day or continuous subcutaneous insulin infusion) [3]. A total of 1,441 patients with type 1 diabetes mellitus (T1DM) were enrolled in the study, including a subgroup of 195 adolescents (13–17 years old). A total of 125 diabetic adolescents had no retinopathy, while 70 had moderate retinopathy. After 6.5 years, the level of glycosylated haemoglobin (HbAlc) in adolescents in the intensive therapy group was lower (8.1% vs. 9.8% in the control group, $p < 0.001$) and the reported decrease in the risk of retinopathy was 53%. At the same time, the group with retinopathy had a 70% decrease in the progression of retinopathy as well as a 55% decrease in the risk of microalbuminuria. However, a significant increase in the risk of severe hypoglycaemia and body mass index in the intensive therapy group suggests that these are adverse effects of intensive therapy [4].

At the end of the DCCT study, all of the patients were encouraged to switch to the intensive insulin therapy regimen with follow-up within the framework of the Epidemiology of Diabetes Interventions and Complications Research (EDIC) study. Four years later, the HbA_{1c} levels in the adolescent cohort were comparable between the two groups; however, the risk of retinopathy progression remained lower in the group that initially received intensive treatment [5]. This phenomenon has subsequently been named "metabolic memory". The results of the DCCT study demonstrated the importance of good glycaemic control for reducing the risk of complications and for the continued efficacy in the prevention of complications during the period of improved control.

Despite the awareness of the importance of maintaining good glycaemic control, the HbA_{1c} levels in children and adolescents are usually unsatisfactory. A multi-centre international study of paediatric diabetes centres in 17 countries found that the mean HbA_{1c} level was 8.6% [6], which is significantly higher than the best value recommended in the International Society for Paediatric and Adolescent Diabetes (ISPAD) Consensus [7]. The results of a large-scale epidemiological study of 1,532 children and adolescents in various regions of Russia (2002–2005) found that the mean HbA_{1c} level was 9.8%. However, it ranged from 8.3 to 8.6% in Moscow and other large cities [8, 9], which may indicate that the distance from the major centres plays a role in the quality of metabolic control.

Adolescence is almost always associated with deterioration of glycaemic control, which may be caused not only by psychological factors and noncompliance but also by the activation of counterregulatory hormones, such as growth hormone and sex steroids, which, in turn and irrespective of the glycaemic control status, may also contribute to the development of complications [10].

HYPOGLYCAEMIA

Hypoglycaemia is a common problem in children with T1DM and encompasses a broad range of manifestations, ranging from common mild effects to rare episodes of severe hypoglycaemia, which may lead to loss of consciousness. Severe hypoglycaemia is an obstacle to the implementation

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of tight glycaemic control in adolescents with diabetes. The parents' fear of hypoglycaemia, especially the nocturnal type, can make them reluctant to carry out insulin therapy [11]. Hypoglycaemia is one of the major limiting factors in achieving normoglycaemia. Initially, the intensive DM therapy led to a pronounced increase in the rate of hypoglycaemia in adolescents [12]. The DCCT study showed that every reduction in the HbAlc level by 10% was associated with a 43% reduction in the risk of retinopathy progression and with an 18% increase in the risk of severe hypoglycaemia, up to the onset of coma. Increased clinical experience with intensive therapy and the introduction of insulin analogues have greatly reduced the incidence of severe hypoglycaemia.

One of the causes of severe hypoglycaemia is the lack of signs of impending hypoglycaemia due to impairment in the autonomous regulation. Adolescents with T1DM are not always informed about possible disruptions in counterregulatory mechanisms in response to hypoglycaemia. Nocturnal hypoglycaemia is especially dangerous. A hypoglycaemia assessment study of 28 patients younger than 12, which continued for 3 days, showed that 78% and 43% of patients experienced hypoglycaemia at least one or two and more nights, respectively [13]. Pronounced hypoglycaemia may be associated with hypopotassaemia and QT prolongation in adults. There are reports of spontaneous nocturnal hypoglycaemia in combination with QT prolongation in children and adolescents [14]. Physical activity levels may play an important role in their development and in the corresponding changes in the heart function [15]. Although it is still unclear to what extent severe nocturnal hypoglycaemia is responsible for rare cases of the "dead-in-bed" syndrome in adolescents [16], the maintenance of a non-hazardous level of glycaemia at night is one of the most important targets in the selection of an adequate insulin therapy in paediatric practice. Repeated hypoglycaemic episodes have a varied impact on cognitive function. In the short term, hypoglycaemia largely affects the mood; however, in the long term, severe hypoglycaemia is associated with a decline in cognitive abilities. These disorders are the most pronounced in children who experience hypoglycaemia before age of 5 [17].

GLYCAEMIA VARIABILITY

Cox et al. [18] showed that pronounced variability in the blood glucose level precedes the onset of severe hypoglycaemia in patients. Therefore, the authors suggest that a decrease in blood glucose fluctuations may reduce the risk of severe hypoglycaemia. Several studies have shown that glycaemic variation may also play an independent role in the development of diabetic complications [19, 20]. Elevated glycaemic variability, irrespective of the mean blood glucose and HbA_{1c} levels, is thought to contribute to the development of vascular complications [21]. This suggests that the variability of the blood glucose level is an independent risk factor and, in combination with the HbA_{1c} level, it is an important indicator of glycaemic control and the risk of developing delayed complications [22].

REGULATION OF CARBOHYDRATE METABOLISM

In healthy humans, insulin secretion throughout the day is carried out in two modes. Between meals, insulin is released at a relatively constant basal rate that is sufficient to limit the rate of hepatic glucose production, conforming to the rate of glucose absorption in tissues. However, the basic insulin requirement varies throughout the day; it is minimal one hour after midnight, which is followed by an increase towards the end of the night (the dawn phenomenon) that is caused by the metabolic activity of growth hormone. This phenomenon is particularly pronounced at puberty. Young children often have a higher insulin requirement around midnight with a subsequent decrease towards the morning (the so-called inverse dawn phenomenon). In some cases, an increase in the basic insulin requirement is observed around dinnertime (the dusk phenomenon). It has been impossible to address all of these differences in the basic insulin requirement with the administration of NPH insulin, which has a maximum peak of activity 5–6 hrs after administration, followed by a decrease to the minimum after 15 hrs, even if it is administered 2–3 times. The insulin secretion rate rapidly increases after a meal, which further suppresses hepatic glucose production and increases glucose uptake in insulin-sensitive tissues. This effect is followed by the restoration of normal blood glucose levels. In patients with diabetes, the mechanism of hyperglycaemia between meals is associated with the failure to inhibit hepatic glucose production, which is caused by inadequate levels of insulin in the liver and hepatic insulin resistance from glucose toxicity. ***The main strategy of DM therapy should be to recover normal blood glucose levels with adequate levels of insulin to limit the enhanced hepatic glucose production both between and after meals.***

Disruption in the carbohydrate metabolism regulatory mechanisms in patients with DM increases both basal and postprandial glycaemia. Because the level of glycated haemoglobin depends on both basal and postprandial glycaemia, it emphasises ***the importance of achieving carbohydrate metabolism compensation in DM patients who would provide normal levels of glycated haemoglobin and only small fluctuations in the blood glucose levels throughout the day.*** This extremely important issue has largely been resolved with the introduction of insulin analogues.

One reason for the insufficient efficiency of T1DM therapies is the discrepancy between the pharmacokinetics of exogenously administered human insulin and the physiological profile of insulinaemia in a healthy body. The lower absorption and excretion rate of rapid-acting insulin is markedly different from the physiological postprandial insulinaemia, while the presence of peaks of long-acting NPH insulin does not allow for a smooth basal insulinaemia even for a multiple dosage administration regimen. The

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closest approximation of the physiological profile of insulinaemia is the best way to achieve proper metabolic control.

Fast analogues (lispro, aspart and glulisine) reach the peak maximum concentration close to the time rate of food intake, which is followed by a rapid decline that adequately reduces the postprandial hyperglycaemia while reducing the risk of hypoglycaemia in the later hours. Long-acting insulin analogues glargine (Lantus®, Sanofi) and detemir (Levemir®, NovoNordisk), which were later named basal insulins, have been developed to improve the profile of basal insulinaemia.

Lantus® (insulin glargine) is the first peakless insulin analogue with a 24-hour period of activity. Lantus® was registered by the European Agency for the Evaluation of Medicinal Products in 2000, in the United States in 2001, and in Russia in 2003. The use of Lantus in children and adolescents older than 6 has been approved in Russia since March 2003 and in children older than 2 since February 2013

Insulin glargine differs from human insulin by three amino acid residues, the presence of glycine instead of asparagine at position A21 and two arginine residues attached to the carboxyl terminus of the B chain at positions B31 and B32. These structural changes shift the isoelectric point of the molecule towards neutral values (from pH 5.4 to 7.0). Therefore, insulin is more soluble in the acidic environment in vitro, but it becomes insoluble at a neutral pH in the subcutaneous tissue. The formation of microprecipitates at the injection site slows down the delivery of insulin glargine to the bloodstream. Replacement of asparagine with glycine at position A21 makes the hexamer insulin structure more stable. Due to these changes, insulin glargine is slowly absorbed from the subcutaneous tissue, has a long-lasting effect and has a predictable, smooth (peakless) profile of action [23].

Lantus® can be administered at any time of day. It is preferable that adolescents administer it in the evening because of their dawn phenomenon. The initial dose is set to 80% of the total daily dose of intermediate-acting insulin. Further dose titration is conducted based on the fasting blood glucose levels and at night time, taking into account the blood glucose level at bedtime. The glycaemic levels after breakfast, in the afternoon and in the evening are regulated by super short-acting or short-acting insulin. Treatment with Lantus® insulin prevents the need for additional injections of short-acting insulin early in the morning in most adolescents with the dawn phenomenon; it also reduces the lability of the course of DM in many patients.

Results of the Lantus® efficacy and safety clinical studies in paediatric patients

Many publications dedicated to clinical trials of insulin glargine in adult DM patients report the benefits of using this insulin, such as the reduction in the morning fasting glucose level and lower hypoglycaemia rates. Some studies have also demonstrated an effect on the HbA_{1c} levels that is comparable to that of the NPH treatment, while other studies report it has a reliable decrease if insulin glargine is used.

Several large-scale international randomised trials have been conducted to register Lantus® for paediatric use. The data on the pharmacodynamics of Lantus® insulin in adolescents confirmed its 24-hour period of activity and its ability to maintain stable blood glucose values during the night, which matches the profile of its activity in adults. A significant decrease in fasting glucose levels and a reduction in the incidence of hypoglycaemia, especially pronounced at night, have been confirmed. Many studies have also reported a significant reduction in the HbA_{1c} levels.

The study "Comparison of the efficacy and safety of insulin glargine in children and adolescents with type 1 diabetes when administered once a day at bedtime compared with NPH insulin administered once or twice a day over 24 weeks of therapy" [24] was conducted in 30 centres in 12 countries. It included 349 children aged between 5 and 16. After the registration, the study was continued to collect data on the long-term safety of Lantus. Thus, the duration of treatment with insulin glargine in the study was 3 years. The study involved children with a DM duration of more than 1 year and HbA_{1c} levels up to 12%. The patients received injections of short-acting insulin before each meal in addition to basal insulin. Changes in the insulin dose over the study period were essentially the same in children as the dose titration in adult T1DM patients. The total change in the insulin dosage was very small and amounted to 4 IU in the NPH group at the end of the study compared to 2 IU in the insulin glargine group. The basal insulin dose in the Lantus® group remained unchanged in contrast to the NPH group, where it increased by the end of treatment. Short-acting insulin doses were increased in both groups. The magnitude of changes in the insulin doses during the study was related to the initial dose and the baseline frequency of basal insulin administration in the children included in the study. Children who received NPH two or more times per day at baseline had more pronounced changes in their total dose of insulin. It should be noted that following the recommendations of the study protocol, in the initial period of the study, the dose of basal insulin was reduced by 20% in the group of children treated with Lantus® who were enrolled in the study with two or more NPH injections, while the short-acting insulin dose was increased. The results of the study demonstrate that Lantus® provides as effective glycaemic control as NPH insulin as well as protects children against nocturnal hypoglycaemia. By the end of the study, no statistically significant difference in the reduction in the HbA_{1c} level was observed in children and adolescents compared to the NPH insulin group. Meanwhile, children in the Lantus® group had a significantly greater decrease in their fasting blood glucose levels compared with the NPH group and adolescents as well as a lower mean daily blood glucose level. Daily monitoring showed that adolescents who received Lantus® had more stable and peakless

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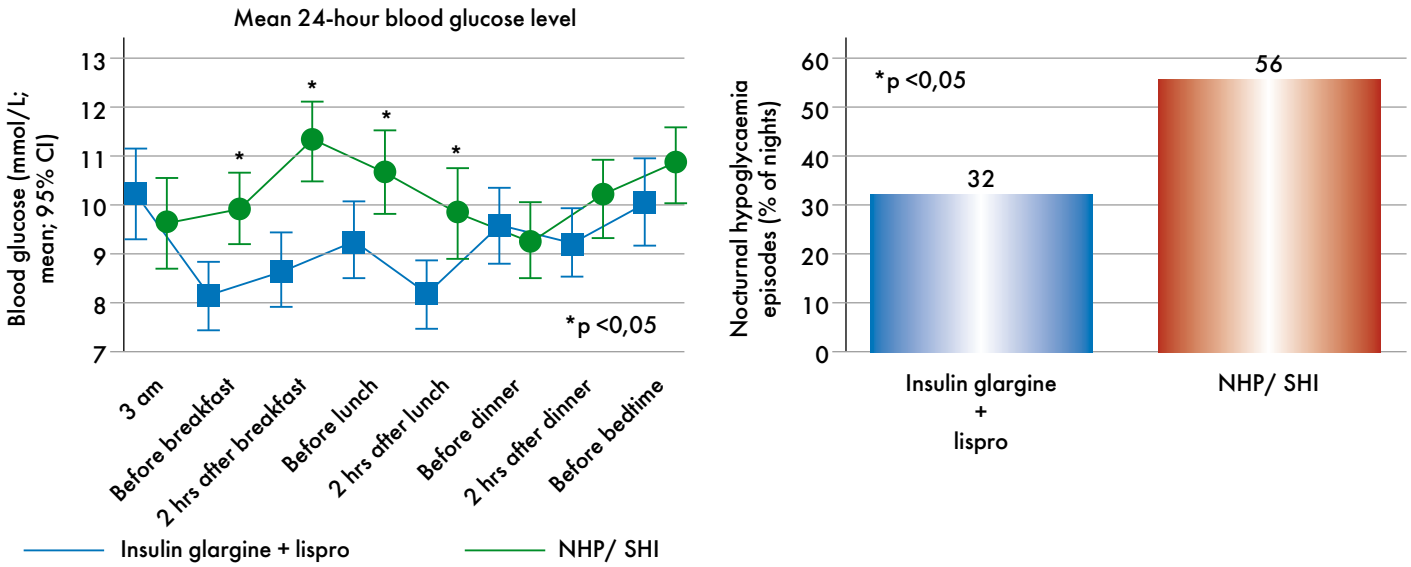

Fig. 1. Changes in the blood glucose level and the dynamics of nocturnal hypoglycaemia.

blood glucose levels at night. With the lower fasting blood glucose level achieved using Lantus® insulin, there was a tendency towards decreasing the incidence of nocturnal hypoglycaemia, especially in children under 11 years of age. With the same level of glycaemic control in adolescents (12–18 years old), the number of episodes of nocturnal hypoglycaemia was lower in the Lantus® group compared with the NPH group.

No adverse events, serious adverse events related to the study drug, allergic reactions or changes at the injection site were recorded during the assessment of Lantus® safety in children and adolescents. By the end of treatment, children who received Lantus® had a lower mean titre of antibodies against insulin glargine and human insulin, while the titre in the group receiving NPH insulin increased. The difference in the titre changes between the two treatment groups was statistically significant.

A number of other studies have also demonstrated that insulin glargine is as effective as NPH insulin, while it simultaneously reduces the rate of asymptomatic nocturnal hypoglycaemia and the level of morning glycaemia. Replacement of insulin isophane with insulin glargine in combination with fast-acting analogues reduced the frequency of nocturnal hypoglycaemia in children and adolescents [25] (Fig. 1).

In the study involving 349 children and adolescents who received insulin glargine, the fasting glucose level was lower than that in the group receiving insulin isophane, but no differences were observed for the HbA_{1c} level. There was also a tendency towards a reduction in the incidence of severe nocturnal hypoglycaemia if insulin glargine was used [26].

An open-label, randomised, controlled study involving 175 T1DM patients between 9 and 17 years of age compared the parallel groups of insulin glargine therapy administered once a day and NPH /Lente therapy administered twice a day in the multiple injection regimen. It assessed changes in the HbA_{1c} level, the incidence rates of hypoglycaemia and adverse events. The changes in the HbA_{1c} level on week 24 were comparable in the two groups with insulin glargine (n = 76) -0.25 ± 0.14% and NPH / Lente (n = 81) -0.05 ± 0.13% (p = 0.1725). Nevertheless, the analysis of covariance adjusted for the baseline HbA_{1c} values showed that the decrease in the HbA_{1c} level was significantly more pronounced in patients treated with insulin glargine who had higher baseline values of HbA_{1c} (>8.8%). No differences were observed for the HbA_{1c} level <7.5%. There were no differences in either the rates of severe hypoglycaemia development (p = 0.1814) or in the incidence of blood glucose levels of 2.8 mmol/L (p = 0.82) or <2 mmol/L (p = 0.32). The authors concluded that insulin glargine displays good tolerability when used in a multiple injection regimen in T1DM adolescents and has a higher efficacy than NPH / Lente in individuals with elevated HbA_{1c} (>8.8%) [27].

We have conducted several studies on the efficacy and safety of Lantus® in paediatric practice in Russia. The first study was conducted in 2003 [28], which was a 24-week, open-label, non-randomised, controlled study involved 49 T1DM patients aged 6–18 with a diabetes duration of at least 6 months and HbA_{1c} levels <12%.

Following the study protocol, children receiving long-acting insulin in one injection regimen were prescribed the same dose of Lantus®. For children on the two or more injection regimen, the initial dose was 70–80% of the total daily dose of intermediate-acting insulin. Lantus® was administered once at 9–11 pm. Lantus® dose titration was performed every 2–3 days and the dose was changed by 1–2 IU depending on the level of fasting glycaemia and with allowance for glycaemic values before bedtime. Dose titration of acting insulin was performed simultaneously.

Hypoglycaemia

There were no severe hypoglycaemic episodes in patients in the analysed group over the entire study period. A total of 38 cases of nocturnal hypoglycaemia were recorded (with a median value of 2.95 mmol/L). Within the first month, there were 10 cases of nocturnal hypoglycaemia (including repeated episodes in the same patient) within the last

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Table 1

Dynamics of the blood glucose levels (M ± m).			
Glycaemia, mmol/L	Baseline	After 3 months	After 6 months
Pre-prandial	9,7±2,7	8,6±3,0	8,4±2,8
Nocturnal	9,1±2,4	8,8±2,4	8,7±2,5
Daytime	8,7±2,9	8,5±3,2	8,4±3,0
At 6 am	10,9±4,2	8,4±2,8*	8,8±3,1*
Before breakfast	7,3±3,2	5,8±3,3	5,8±3,2
2 hrs after breakfast	9,3±2,7	9,0±2,9	8,0±2,6
Before lunch	8,7±3,4	8,7±3,4	8,7±2,9
2 hrs after lunch	8,0±3,0	8,3±3,2	7,5±2,6
Before dinner	9,8±3,5	8,8±3,1	8,9±2,6
At 10 pm	9,5±3,2	9,0±2,9	8,8±3,0
At 3 am	9,2±2,9	9,0±3,2	8,5±2,5

* (p≥0,003)

month of follow-up (5 cases). All nocturnal hypoglycaemic episodes occurred in patients during the insulin titration period, in cases for which additional short-acting insulin injections were required to correct hyperglycaemia or in cases with additional food intake. Six cases of documented ***asymptomatic hypoglycaemia*** were reported over the entire study period. Overall, over the 24 weeks of the study, mild clinical and asymptomatic hypoglycaemic episodes were observed in 26 patients (78%). The onset of hypoglycaemic episodes was associated with impairment in the patients' diets, foot intake regimens and inadequate short-acting insulin doses rather than with the administration of Lantus®.

Changes in the level of anti-insulin antibodies (AIA)

Twenty-seven patients had a negative antibody titre both at the baseline and after 6 months. A decrease in the antibody levels from 28 to 21 IU was observed in 12 examined patients.

Changes in the HbA_{1c} levels

The baseline level of the HbA_{1c} was 9.1 ± 1.5%. After 3 months, the level was 9.3 ± 1.8% (the second and the third months of the study were July and August when most of the patients were on summer vacation and had a lower quality and frequency of self-control and insufficient insulin dose adjustment). By the end of the study period (6 months), there was a statistically significant decrease in this indicator to 8.4 ± 1.5% (p <0.05) compared with the baseline data. The proportion of patients with a satisfactory degree of carbohydrate metabolism compensation (HbA_{1c} < 7.5%) increased from 18.4% to 32.7% and the number of patients with extremely poor values of glycated haemoglobin (HbA_{1c} > 10.0%) decreased twofold.

Six months after the study ended, the HbA_{1c} level increased to 8.8%, but it did not reach the baseline value. An analysis of the HbA_{1c} levels in the two groups of children (those with HbA_{1c} level ≤ 8% and those with levels HbA_{1c} > 8%) revealed no changes in this parameter in the first group and a significant decrease from 10.1 ± 1.08% to 8.7 ± 1.47% (p = 0.0004) in the second group.

A comparison of the mean blood glucose levels throughout the day (recorded at baseline and after 3 and 6 months) is shown in Table 1

The downward trend in the blood glucose levels was observed in all measurements. A statistically significant reduction in the blood glucose level in patients who received Lantus® therapy was recorded at 6 am. After 6 months of Lantus® treatment, only 2 patients (compared to 11 at baseline) needed an additional injection of short-acting insulin at 6 am.

The benefit of a single injection of insulin glargine was highly appreciated by children in all age groups, while one of the benefits of switching to Lantus® for adolescents was the possibility of forgoing an additional injection of short-acting insulin at 6 am, shifting breakfast to a later time (allowing for more sleep). A constant feeling of anxiety and being psychologically ready for a possible onset of nocturnal hypoglycaemia were almost entirely eliminated. After the end of the 6-month study, all patients continued Lantus® treatment.

The second study focused on the effectiveness of insulin Lantus® in clinical practice [29]. In contrast to the previous study, the clinical protocol of which pre-specified the tight

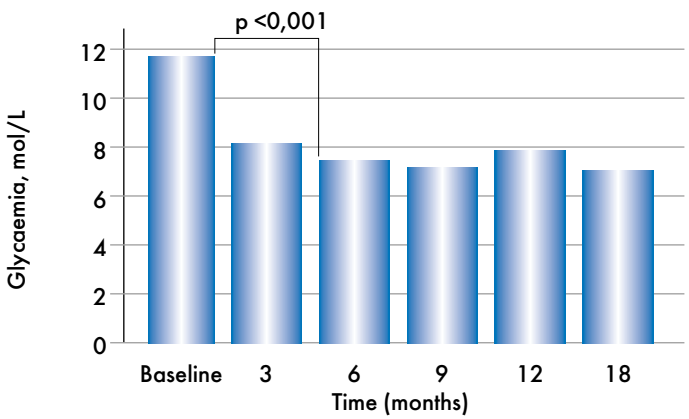


Fig. 2. Dynamics of the fasting glucose levels in children and adolescents with T1DM undergoing Lantus therapy in daily clinical practice.

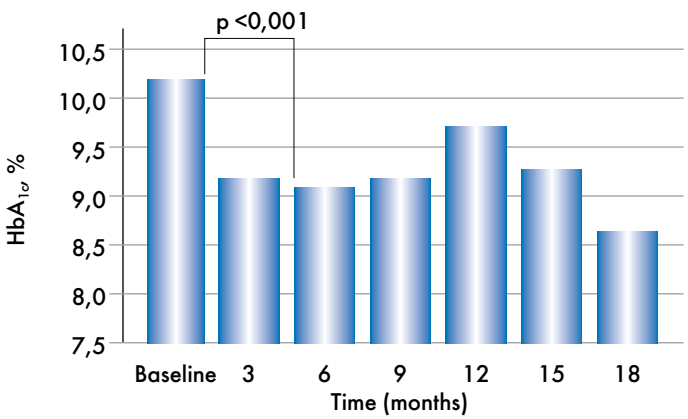
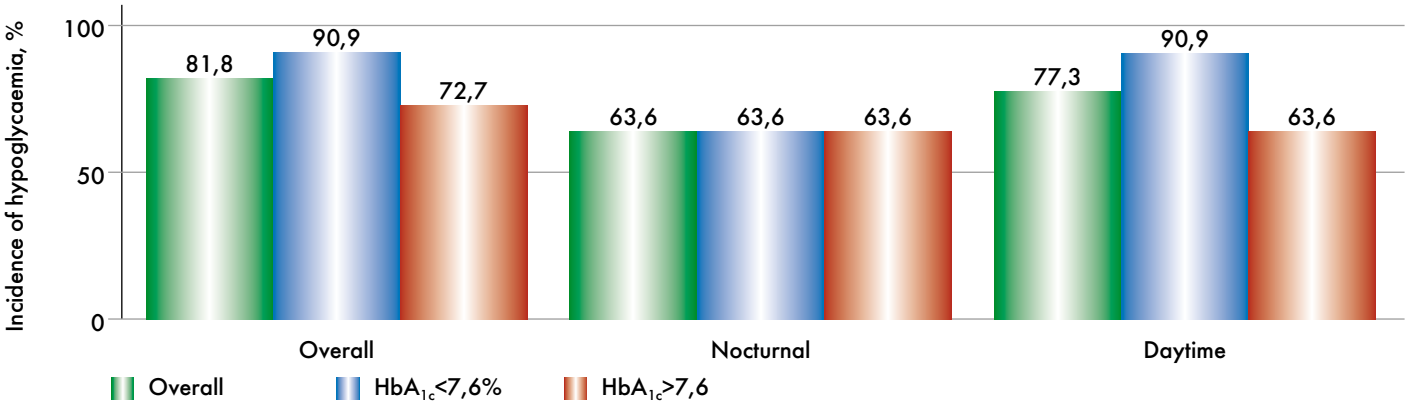


Fig. 3. Dynamics of the HbA_{1c} levels in children and adolescents with T1DM undergoing Lantus therapy in daily clinical practice.



The groups with DM compensation showed a higher incidence of daytime hypoglycaemia compared with the subcompensated DM group. The incidence of nocturnal hypoglycaemia was the same for the two groups.

Fig. 4. CGMS monitoring of the incidence of hypoglycaemia in patients receiving insulin Lantus® according to the HbA_{1c} levels.

monitoring of the patients, this study was retrospective and showed the impact of Lantus® therapy on carbohydrate metabolism in real-life clinical conditions. The study included 165 patients, aged 5–18, who were transferred to Lantus® at the Endocrinology Research Centre (Russian Academy of Medical Sciences). The fasting glucose and HbA_{1c} levels were evaluated at the re-admission of the patients, who often had deterioration of carbohydrate metabolism indicators. A significant reduction in the fasting glucose levels, almost reaching the target values, was recorded over the entire observation period (Fig. 2). There was a pronounced reduction in the HbA_{1c} level was significant at 6 months, with an increase towards the maximum at 12 months (Fig. 3). The insulin dose titration performed at that period, mostly at the expense of the dietary insulin, led to an even more significant reduction in glycated haemoglobin after 1.5 years of therapy.

It is noteworthy that we obtained these results while analysing the data on children and adolescents who switched to Lantus therapy in daily clinical practice, as the conditions of clinical trials are not always identical to the real-life scenario.

Patients and their parents also reported that an additional advantage of Lantus® insulin was the easier management of diabetes at home and correction of glycaemia during the day with the lack of numerous additional injections of short-acting insulin. There was also a decrease in the incidence of impaired counterregulation or even its complete disappearance in many patients.

Another one of our studies focused on the frequency of hypoglycaemia when using insulin glargine in combination with insulin aspart, depending on the degree of carbohydrate

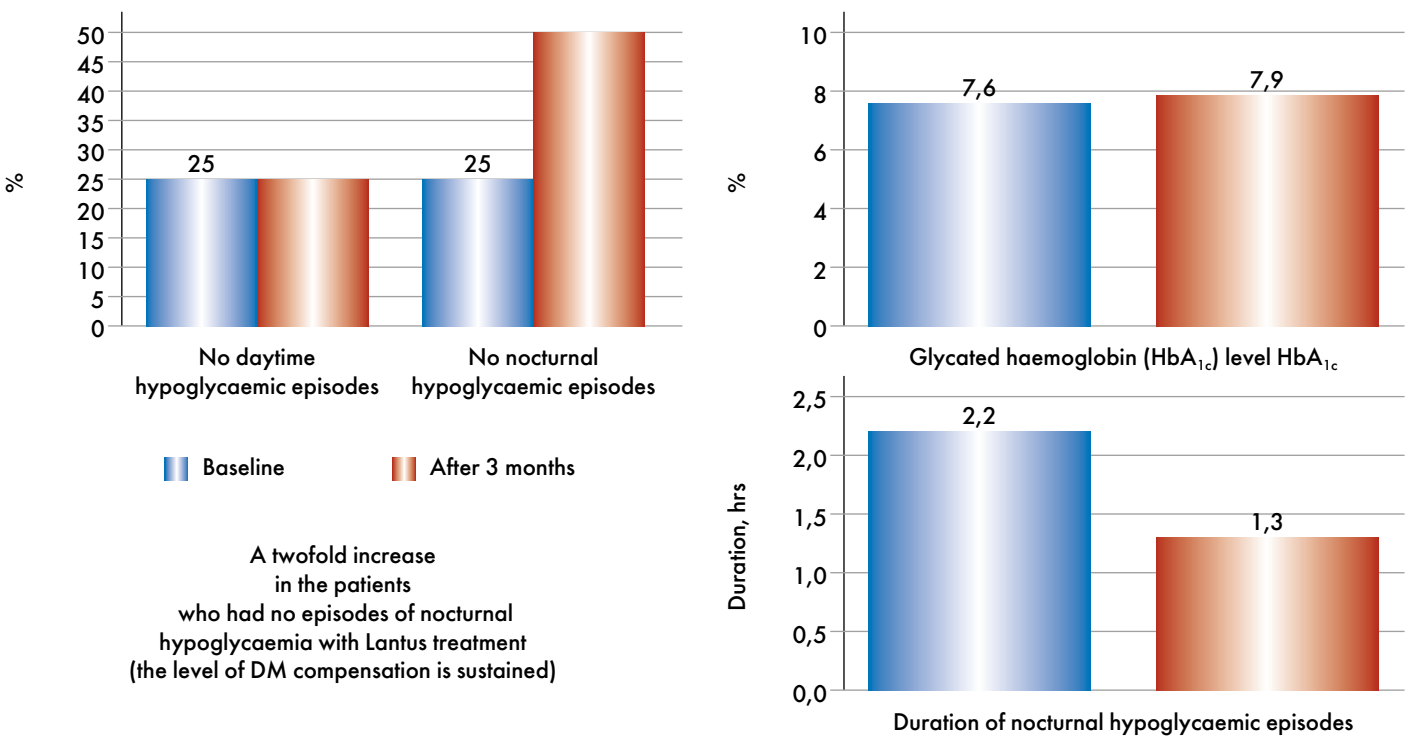


Fig. 5. Dynamics of the HbA_{1c} levels and hypoglycaemic episodes after 3 months of adjustment of insulin therapy (CGMS).

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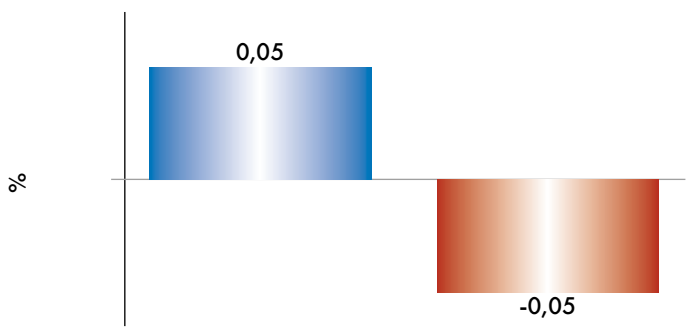
metabolism compensation under control conditions of the Continuous Glucose Monitoring System (CGMS) [30]. The study included 22 T1DM patients, aged 6–17 years (mean age, 13.1 ± 3.4), and a HbA_{1c} level of 5.8–8.9% (7.5 ± 0.9%). The patients were divided into two groups of 11 each with no significant differences in the age and diabetes duration. Group 1 had HbA_{1c} < 7.6% and Group 2 had HbA_{1c} >7.6%. Glycaemic monitoring was carried out for 72 hrs. Hypoglycaemia was defined as glucose <4 mmol/L. The results of this study demonstrated that only 18% of the examined patients had a lack of hypoglycaemia during the 72 hrs of CGMS monitoring, while only 36.4% had no nocturnal hypoglycaemia. There were no differences in the incidence of nocturnal hypoglycaemia between the two groups (63.6%) (Fig. 4). A total of 96.4% of nocturnal hypoglycaemic episodes and 74.6% of the daytime ones were asymptomatic. Of the patients with hypoglycaemia, the frequency was 4.7 hypoglycaemic episodes/72 hrs/patient (daytime – 3.5, nocturnal – 2.0). The average duration of the nocturnal hypoglycaemic episodes was 2.4 ± 2.7 hrs and that of the daytime ones was 0.9 ± 1.0 hrs without the onset of severe hypoglycaemia.

The adjustment of insulin therapy reduced the incidence of nocturnal hypoglycaemic episodes by 50%, while simultaneously decreasing their duration without a reliable increase in the HbA_{1c} level (Fig. 5).

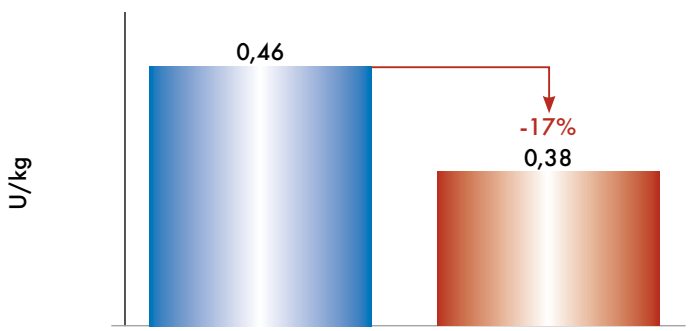
The study showed that Lantus® insulin therapy in patients with good metabolic compensation results in the same incidence of nocturnal hypoglycaemia as that observed for the group with carbohydrate metabolism subcompensation. The duration of nocturnal hypoglycaemia was significant, which is in agreement with the smooth profile of Lantus insulin activity. Nearly all hypoglycaemic episodes were asymptomatic, which can be associated with a sufficiently smooth profile of glycaemia at that time as well as with poor sensitivity to low glucose concentrations while asleep. These data confirm the need for better control of nocturnal glycaemia in T1DM patients. Remarkably, the adjustment of insulin therapy can be used to reduce the frequency of hypoglycaemia without affecting the glycated haemoglobin levels.

The clinical experience of using insulin glargine in children younger than 5 is very limited. Goonetilleke et al. [31] followed up two children younger than 2 years of age who demonstrated excellent responses to treatment with insulin glargine. In a retrospective study by Hathout, Fujishige, Geach et al. [32], a switch from NPH insulin to insulin glargine in children (including those of pre-school age) and adolescents (n = 72) significantly reduced the HbA_{1c} levels (on average from 9.5 to 8.6%) and the incidence of hypoglycaemia after 9 months without increasing the body mass index. A prospective study of 80 patients aged 2–19 showed a decrease in the fasting glucose levels as well as in the HbA_{1c} level from 7.63 to 7.14% in the overall group and from 7.54 to 6.96% in 14 preschool children, without increasing the incidence of hypoglycaemia six months after switching from NPH insulin to insulin glargine [33]. Preschool-aged children with positive results were also included in the analysis. However, the studies were conducted for a small cohort of preschool-aged children and lacked control groups.

The most significant multinational open-label randomised study of preschool-aged children (PRESCHOOL) was conducted at 61 clinical centres in 16 countries, including Russia. The study included 125 children aged 1–6 [34]. The follow-up period was 24 weeks. The PRESCHOOL study used the CGMS to assess hypoglycaemia, glycaemic control and variability in young children who received insulin glargine or NPH as basal insulin. This was the first study conducted in this population of children that assessed the data using the CGMS, and it was one of the largest-scale studies conducted in this age group alone. The comparable control of the HbA_{1c} level was observed at a lower daily dose of insulin received once a day compared with NPH administered twice a day (Figs. 6 and 7). There was a lower incidence of hypoglycaemia, both overall and nocturnal, as well as lower blood glucose levels throughout the day when using insulin glargine compared with NPH. These data confirmed the safety of using Lantus® insulin in young children with respect to the risk of hypoglycaemia as well as its sufficient efficacy with respect to carbohydrate metabolism compensation. Based on the results of this study, insulin glargine was approved for use in



NPH insulin therapy (1 or 2 times per day, n = 64)
Lantus® insulin therapy (1 per day, n = 61)
95% CI -0,093 (-0,39–0,21).
Fig. 6. Changes in the HbA_{1c} levels



NPH insulin therapy (1 or 2 times per day, n = 64)
Lantus® insulin therapy (once per day, n = 61)
p value is not assessed
Fig. 7. Mean daily insulin dose, U/kg

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children aged 2 years and older.

The assessment of glycaemic variability is becoming one of the key factors in evaluating the efficiency of insulin analogues. White, Chase, Abslanian and Tamborlane [35] conducted a large-scale, randomised clinical trial of T1DM adolescents and compared two approaches to intensive insulin therapy, a single injection of insulin glargine (n = 45) as basal therapy or two injections of NPH / Lente insulin (n = 45) as basal therapy with the additional use of lispro as bolus insulin. The analysis of the glycaemic variability was based on the data from long-term monitoring of glycaemia using the CGMS. A reliable decrease in the glucose variability was confirmed both in terms of the average SD value of the CGMS-measured glucose level (weeks 12 and 24 of the study) and in terms of the mean amplitude of the glycaemic fluctuations in week 24. The reduction in glycaemic variability may have important clinical implications in reducing the risk of hypoglycaemia and vascular complications [36]. Therefore, the reduction in the variability in the glycaemic profile when switching to Lantus® insulin is an extremely important factor, even in the cases when no HbA_{1c} level changes were achieved.

CONCLUSION

The introduction of human insulin analogues, which are currently widely used in clinical practice for children and adolescents, was a revolutionary breakthrough in the treatment options for T1DM patients and in preventing diabetes complications. The results of large-scale re-screening epidemiological studies in Russia have demonstrated that an increase in the use of insulin analogues in Russia to 95% was accompanied by a reduction in the HbA_{1c} levels in many regions as well as by a two to threefold reduction in the prevalence of specific diabetic complications, even in regions that lacked significant changes in the HbA_{1c} levels. The reduction in the glycaemic variability observed for therapy with insulin analogues may be one of the reasons for these findings (E.A. Andrianov, personal communication).

More than 10 years of clinical experience with Lantus® in paediatric diabetology has confirmed its high efficacy with respect to metabolic control, including a reduction in the incidence of hypoglycaemia and the glycaemic variability profile and its safety for children and adolescents (including young children) as well as its ability to improve the quality of life for patients and their parents. Along with other insulin analogues, it significantly improves metabolic control and reduces the risk of vascular complications.

DISCLOSURE INFORMATION

The author declares a lack of explicit and potential conflicts of interest related to the publication of this manuscript.

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INFORMATION ABOUT THE AUTHORS

Tamara L. Kuraeva — MD, PhD, Professor, Head of the Diabetes Department, Paediatric Endocrinology Institute, Endocrinology Research Centre, 11, Dmitriya Ul'yanova street, Moscow, Russian Federation, 117036
E-mail: andrew-135@yandex.ru

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