Youth insulin treatment and severe hypoglycemia risk. Medico-legal implications.

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Abstract: Tight control of insulin treatment results, in terms of hypo- or hyper-glycemia, is difficult to maintain in small children, because hypoglycemia may impair normal brain development which is not complete. Because pre-adolescents appear to be relatively protected from micro-vascular complications, the need for tight control might be less than in post-pubertal subjects. The danger of hypoglycemia is greater in infants and children because food intake, activity and adherence to treatment schedules are less predictable than in adults. Initially, we noticed an association between: increased number of injection, tight control and the occurrence of hypoglycemia. We assess the effects of intensive, flexible insulin treatment with insulin analogues, after 3 months and 12 months, by measuring different parameters, including HbA1c and the number of severe hypoglycemic events (80 patients were enrolled.). After one year of intensive treatment with analogues of insulin, the number of severe hypoglycemic events decreased, combined with an intensified education. Because hypoglycemia is commonly seen in situations of medication error, homicide attempt and suicide attempt, sudden death, traffic accidents, strange behavior or aggressive status, memories black-outs etc., all incidents with great significance for forensic medicine, demonstration of it becomes a relevant objective. Physicians of children with diabetes should be aware of these consequences and a clinical judgment will be required in treatment options decision making.

Key words: diabetes, hypoglycemia, intensive insulin treatment, forensic aspects of hypoglycemia

The Diabetes Control and complication Trial (DCCT) and other similar studies attest to the importance of glicemic control in prevention of eye, kidneys and nervous system complications in patients with diabetes [1]. According to the DCCT, a dramatic decrease in HbA1c was achieved in the first year of introduction of intensive insulin therapy, especially in adolescents and adults [1].

A shortcoming of the treatment with multiple injections was the multiplication of hypoglycemic episodes, particularly severe hypoglycemia. It is assumed that a very strict glicemic control led in time to the emergence of asymptomatic hypoglycemia, associated with increased severe hypoglycemia in the absence of warning signals from a body adapted to increasingly smaller glicemic values this event being evoked by many researchers [2, 3]. Intensive insulin treatment is clearly associated with increased risk of mild and moderate hypoglycemia; hypoglycemia (mild) is by far the most common metabolic complication of insulin treatment.

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The treatment with insulin analogues (lis/asp + glargine) causes a physiological replacement of insulin requirements, both the pre-prandial needs (short duration of action) and the basal insulinemia (long-acting, no "peak") [4]. Also DCCT demonstrated that the intensive insulin treatment with multiple injections leads to "dramatic" decrease in the risk of microvascular complications and their rate of progression, compared to the conventional treatment with 2 or 3 injections per day [1].

Objectives

To identify the optimal management of child and adolescent insulin-dependent diabetes mellitus, from a comparison between insulin treatment prior to introduction into the treatment of insulin analogues, to highlight the efficiency of the latter.

Wishing to improve the glycemic control at this age group, we assessed the effectiveness of combining the 2 types of insulin analogues (insulin lispro / insulin glargine plus aspartame) versus therapy with insulin lispro / insulin plus aspartame semilent (NPH / Insulatard) in children and adolescents with insulin-dependent diabetes mellitus (type 1).

In theory, the combination of insulin analogues with ultrarapid action administered pre-prandial (either lispro or aspartame) with a "basal" analogue insulin should lead to improved insulin substitution to reduce the frequency of hypoglycemia. We wanted to check this assumption in practice, considering the medico-legal implications the optimal administration of insulin has to a body in the process of growth and development.

Material and method

The study was conducted over a period of 2 years (June 2003 - May 2005) and consisted of switching to treatment with insulin glargine for 80 patients previously treated with semilente insulin in various combinations with insulin analogues (lispro or aspartame). This study was a prospective one, where (2003-2005) the development of reference parameters: age, sex, age at onset, duration of diabetes, HbA1c in the dynamic, total dose insulin dose basal insulin, insulin dose pre-diet, the rate of severe hypoglycemia have been noted trimestrial over a period of 2 years, expressed in number of events / 100 patients / year.

Children and adolescents who entered this study were from the Constanța Diabetes Center and were aged between 7.1 and 17.8 years. Before entering the study all patients followed some courses in the education center in the training room for type 1 diabetes, in order to refresh their knowledge on insulin-dependent diabetes mellitus, the amount of carbohydrates, the breakdown tables, units of insulin adjustment according to the results of glycemic self-control, how to perform glycemic self-control and insulin injections.

Table 1 - General characteristics of patients entering the study after 3 months of treatment.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ITT* (lis/asp + semilent)</th>
<th>TII flexible (lis/asp + glargine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (N = 80)</td>
<td>HbA1c &lt;8% (N = 41)</td>
</tr>
<tr>
<td>Medium age (years)</td>
<td>14.7 ± 1.9</td>
<td>15.2 ± 2.2</td>
</tr>
<tr>
<td>Girls, %</td>
<td>67.5</td>
<td>61.9</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>8.5 ± 3.5</td>
<td>9.2 ± 3.1</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>6.2 ± 3.1</td>
<td>5.9 ± 2.8</td>
</tr>
</tbody>
</table>

*ITT=intensive insulin treatment
Data represent mean ± SD. HbA1c <8.0%, and more "target" 8.0%.

Emphasis was placed on the premises of a better acceptability of the new treatment (flexibility), on the fact that treatment is always adapted to changing needs of children and not
vice versa (i.e. the life of a child with diabetes should not be influenced negatively by the disease and treatment, as unfortunately happens more often than not). Out of the 80 children over the age of 7 years (7-18 years), one received treatment with insulin pump, MiniMed, Medtronic and was excluded from the lot.

There are no differences between the 2 groups analyzed, because all children previously treated with a combination of Lis / aspartame + NPH (insulin semilenta) were replaced by type NPH insulin to insulin Glargine (Lantus). What is remarkable, analysis of table 2, is that patients entering the study were evaluated with respect to HbA1c, insulin dose and rate of major hypoglycemic events.

**Results**

We found that in batch ITT Lis / asp + NPH there is a higher rate of severe hypoglycaemia before using analogues with fast action. Thus the rate of severe hypoglycemia overall was 20.6, higher for those with optimal control glicemic by 23.6 and 17.4 in those with HbA1c above "target".

Dropping rate hypoglycemic events in this category is determined by a rigorous education of children and families made a date with the increasing number of injections. This was associated with a reduction in HbA1c values.

**Table 2 Characteristics after 1 year of treatment**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TII (lis/asp + semilenta)</th>
<th>TII flexible (lis/asp+glargine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients (N = 80)</td>
<td>HbA1c Above target (N = 39)</td>
</tr>
<tr>
<td>Pre-U/kg</td>
<td>0.97 ± 0.2</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Post-U/kg</td>
<td>0.91 ± 0.2</td>
<td>0.94 ± 0.2</td>
</tr>
<tr>
<td>Prebolus: basal</td>
<td>1.0 ± 0.4</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>Postbolus: basal</td>
<td>1.32 ± 0.3*</td>
<td>1.37 ± 0.5*</td>
</tr>
<tr>
<td>Pre-HbA1c%,</td>
<td>8.4 ± 1.0</td>
<td>8.0 ± 1.1</td>
</tr>
<tr>
<td>Post-HbA1c%,</td>
<td>7.8 ± 0.8</td>
<td>7.2 ± 0.6</td>
</tr>
<tr>
<td>Pre-HS*</td>
<td>20.6</td>
<td>23.6</td>
</tr>
<tr>
<td>Post-HS*</td>
<td>8.2*</td>
<td>8.6*</td>
</tr>
</tbody>
</table>

Data are mean ± SD. HbA1c <8.0% over "target" 8.0%.

ITT pre-post  ♦ P < .005, ♠P < .03, ♦ P < .05, P < .002; ♥P < .008.

Pre-F-IIT versus post-F-IIT: ♦P < .005, ♦ P < .03, ♠P < .05.

The rate of severe hypoglycemia (HS) was expressed in number of events per 100 patient-years.

Also from the Table 2 analysis results that after the introduction of flexible intensive insulin therapy with insulin analogues the rate of severe hypoglycemia increased from an initial value of 18.8 events per 100 patients-years, both overall and by groups established according to the HbA1c to 14.2 events per 100 patients-years for those with optimal HbA1c and 22.9 events per 100 patients-year, the event is possible and quoted in the literature.

The measures of monitoring glicemic levels and discussions doctor-patient-parent were intensified. The mechanism of action of these modern insulins was explained in detail and we tried to make families more responsible about the importance of careful monitoring the treatment with insulin at home.

Most hypoglycemic events were related to a delay between the administration of insulin and consumption of carbohydrates.
After 1 year of implementation of intensive insulin flexible treatment, there is a reduction in major hypoglycemic events per group at 7.7.

The treatment with insulin analogues (lis/asp glargine +) causes a physiological replacement of insulin requirements, both of the pre-prandial needs (short duration of action) and of the basal insulinemia (long-acting, no "peak") [4]. This replacement and frequent determinations of blood glucose, permanent adjustment of the dose of insulin at the time of day to the amount of carbohydrate, to the glicemic values, the physical effort that is conducted or that follows have clearly contributed to a proper metabolic control, with a hypoglycemic episodes decreased rate.

Establishment of strict equivalence between carbohydrates and blood glucose and insulin as well as education lessons has increased the involvement of children and parents in self-management of diabetes at home. Motivating children and parents to the new treatment, not only improved metabolic control, but also increased adherence to multiple therapy.

Half of children and adolescents treated flexibly had adequate blood glucose, with an HbA1c <8%. 50% of patients treated flexibly have failed HbA1c decrease by 1% after 1 year of treatment, explainable as follows:
- omission of injections administration of insulin analogue with rapid ingestion of carbohydrate in meals or snacks
- administration of insufficient amounts of insulin quickly.

We observed high values of HbA1c, particularly in the age group over 13 years, and the preschoolers. Children usually require a greater number of injections per day, combination of fast and semilente insulin before meals and at bedtime for an optimal glicemic control. Conventional insulin treatment fails to "meet" their needs, fix doses of insulin recommended at the discharge from hospital contributing to higher values of HbA1c. Rather vague distribution of carbohydrates, in particular the establishments of rigid values of 200 g or 250 g of carbohydrates per day, too big or too small snacks, all have contributed to the failure of a good or even satisfactory control, with predictable consequences.

Following study completion, we found, on one hand, increased HbA1c values and, on the other hand, the incidence of very high initial hypoglycemia.

13-18 years age group had the highest HbA1c, a possible explanation being an increase in insulin-resistance, the type of nutrition and psycho-social changes, so characteristic in this category.

5-12 years age group had a low average of HbA1c perhaps because the insulin-resistance does not manifest yet in this category of children and by the much more influence and control that parents have.

HbA1c decreased in all age groups, with an increase, however, of the hypoglycemic episodes initially. After the introduction of insulin analogues, the glicemic improved further, and severe hypoglycemic episodes decreased.

**Discussions**

Studying the patients previously treated "conventionally" with 2-3 injections of insulin a day, we discovered an impressive number (20!) of major hypoglycaemic events (convulsions, coma) in a girl with onset of diabetes at 1 year and 9 months, during the first 2 years after treatment with insulin. Monitored over time, she presented an alteration of cognitive function, hiperkinetic behavior, late language installation. Another case was that of a young boy CD, diagnosed with diabetes at the preschool age, in the conventional treatment, with repeated severe hypoglycaemic episodes, resulting in time with secondary epilepsy, died eventually after such convulsivant episode, at the age of 18.

The aspect described above is particularly important in children because optimal development depends on the low rate of severe hypoglycaemic episodes that can cause death [5] and the speciality literature highlights the adverse effects that intensive treatment with insulin for children and adolescents with diabetes may have [5]. It is known that pediatric patients diagnosed with type 1 diabetes do not have adequate skills to control the optimal diabetes, so an adult
participation is essential. Permanent support of family becomes an essential part in the management of children and adolescents with diabetes, along with treatment, exercise, nutrition and education.

Hypoglycemia involving a serum glucose of 40 mg/dl or less may lead to death from hypoglycemic coma. Hypoglycemia may be a factor in sudden or unexpected deaths investigated by a medical examiner. Some criteria for insulin mediation of hypoglycemia was proposed: plasma insulin $\geq 18$ pmol (ICMA immunochemiluminometric assay), C-peptide $\geq 200$ pmol/L (ICMA), proinsulin $\geq 5$ pmol/L (ICMA), $\geq$OH butyrate, $\leq 2.7$ mmol/L and generous (1.4 mmol/L) response of plasma glucose to IV glucagon administered when the patient is hypoglycemic. Sulfonylureas, meglitinides and insulin antibodies should be sought in the plasma of any hypoglycemic patient [9]. The postmortem HbA1c value serves as a definitive indicator of prolonged hyperglycemia. Some studies suggest that vitreous glucose alone should be used to diagnose hyperglycemia postmortem and that the limit of 10 mmol/L (180 mg/l) should have a good specificity for diabetic coma, which theoretically would equal an original blood glucose value of about 26 mmol/L (473 mg/l) [8].

From the point of view of clinical legal medicine, hypoglycemia may reach forensic relevance concerning about the following aspects: the psychophysical ability of running a car and with respect to a possible imputability, confusion of symptomatology with alcoholisation, aggressive behaviour – auto or hetero aggressivity – including suicide attempt by insulin overdose or associates with hypoglucemiant drugs, black out episodes, possible consequences generated by intensive and difficult to manage treatment (acute ones like hypoglycemia, or with long term impact – growing problem e.g.).

Many studies show the modest or absent role of glucose levels postmortem in the diagnostic of hypoglycemia. The reasons could be, on the one hand, release of glucose from cells after death (due of decrease - disappearance of selective permeability), adrenergic influences and, in consequence, high level of glucose in traumatic agonal stage, and, on the other hand, consume of glucose by cells in postvital phenomena- surviving cells, consuming of glucides by germs, in rapid multiplication in postmortem tissue. Thus, normal or elevated levels of glucose in postmortem blood could appear even in an overdose from insulin.

The vitreous is of no help either, because abnormally low values of glucose in the vitreous have no significance. Only elevated levels of glucose are of any significance. If the increase in concentration of insulin in the blood is caused by endogenous production by either the pancreas or a tumor, then the concentration of C-peptide should theoretically be elevated.

Thus, if one finds high insulin and high C-peptide, one assumes that the insulin is endogenous. If, however, one sees high concentrations of insulin and normal or depressed concentrations of C-peptide, then one would conclude that the insulin is of exogenous origin, that is, it was administered.

Unfortunately, the expected response of C-peptide is not absolute. In addition, C-peptide is very unstable and analysis for it in postmortem blood is not satisfactory [7]. Therefore, vitreous fluid has been used as a substitute in forensic practice, since it has a very low cell count. It has been repeatedly reported that the sum value of vitreous glucose and lactate should be used to estimate the original antemortem blood glucose level, based on the assumption that pre-existing glucose is gradually converted to lactate under anaerobic conditions during agonal phase and the early postmortem period.

Conclusions

1. Patients treated with insulin glargine and fast analogues (lispro / aspartame) did not show statistically significant increases in body weight, other than those anticipated statistically for the nondiabetic "counterparts" of the same age, gender, background.

2. In the present study, the rate of severe hypoglycemia decreased significantly at the end of the study. Cases of severe hypoglycemia are listed above.

3. The amount of administered lente insulin was limited at a value of approximately 50% of the total dose of insulin. At the lot of children receiving intensive insulin previously, there was an
average of insulin semilente of about 40%, 60% of the total dose being attributed to rapid insulin. In addition, this lot has faced an increased rate of mild and moderate hypoglycemic episodes.

4. In patients treated with lis/asp glargine + was not found any association between the low BMI and hypoglycemia and/or duration of diabetes.

5. HbA1c was improved significantly (> 1%) to 45% of patients treated flexibly, i.e. to 35 children within 1 year.

6. Low compliance to treatment, explain metabolic unbalance (hypo-, hyper-blood glucose). Thus, the refuse to check glicemia 4 times a day, the maladjustment of the insulin dose to the glicemic values, to food, the physical effort, noninvolvement of the child’s family and of the society in supporting and guiding the child’s suffering from diabetes, school unattendance (children feel 'different' and thus refuse to administer insulin at school, or to determine glicemia in public) may affect the results of treatment and may have medico-legal implications. A shortcome of treatment with multiple injections was the initial multiplication of hypoglycemic episodes.

Close collaboration between teacher, class master, teacher or parents and children is very important, but it is inconsistent. Lack of multidisciplinary teams involved in ensuring the development of better patient results leads in some centers to the lack of performance of doctors and patients in obtaining optimal glicemic control, and these teams should include: physicians, nurses, nutritionists, psychologists, teachers and kinetotherapists. Therefore, physicians who prescribe insulin should be particularly judicious to discuss with the patient and family the possibility of occurrence of severe hypoglycemia in the case of a tight metabolic control, or in the case of an unadapted dose of insulin to the self-controlled glicemic levels.

7. Hypoglycemia is probably the most common acute problem suffered by patients with diabetes. It is also a serious medical emergency with a potentially fatal outcome and the most common reason for patients with diabetes to present to the emergency room.

8. Forensic evaluation of this kind of patients has to include, for a properly explanation of causal chains that involves diabetes mellitus and his specific treatment, a large spectrum of interdisciplinary exams: biological, electro-physiological determination, neurological and psychiatric. Sudden deaths or clinical legal medicine evaluations in particular case are aspects that are not usually included in differential diagnostic. Because of difficulty to perfome and lack of specificity of the available tests, it is important to discriminate results and evaluate these from the point of view of pathology (diabetes mellitus), treatment and possible complications, including death or other situation with penal implications.

References

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