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Original article

Effect of insulin analogues on frequency of non-severe hypoglycaemia in patients with type 1 diabetes prone to severe hypoglycaemia: The HypoAna trial

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Abstract

Aim. – Insulin analogues reduce the risk of hypoglycaemia compared with human insulin in patients with type 1 diabetes (T1D) and minor hypoglycaemia problems. The HypoAna trial showed that, in patients with recurrent severe hypoglycaemia, treatment based on insulin analogues reduces the risk of severe hypoglycaemia. The present study aims to assess whether this also applies to non-severe hypoglycaemia events during the day and at night.

Methods. – This 2-year investigator-initiated multicentre, prospective, randomized, open, blinded endpoint (PROBE) trial involved patients with T1D and at least two episodes of severe hypoglycaemia during the previous year. Using a balanced crossover design, patients were randomized to basal–bolus therapy based on analogue (detemir/aspart) or human (NPH/regular) insulins. A total of 114 participants were included. Endpoints were the number of severe hypoglycaemic events and non-severe events, including documented symptomatic and asymptomatic episodes occurring during the day and at night (ClinicalTrials.gov number: NCT00346996).

Results. – Analogue-based treatment resulted in a 6% (2–10%; $P = 0.0025$) overall relative risk reduction of non-severe hypoglycaemia. This was due to a 39% (32–46%; $P < 0.0001$) reduction of non-severe nocturnal hypoglycaemia, seen for both symptomatic (48% [36–57%]; $P < 0.0001$) and asymptomatic (28% [14–39%]; $P = 0.0004$) nocturnal hypoglycaemia episodes. No clinically significant differences in hypoglycaemia occurrence were observed between the insulin regimens during the day. The time needed to treat one patient with insulin analogues to avoid one episode (TNT1) of non-severe nocturnal hypoglycaemia was approximately 3 months.

Abbreviations: ARR, Absolute risk reduction; ADA, American Diabetes Association; CGM, Continuous glucose monitoring; GCP, Good clinical practice; NPH, Neutral protamine Hagedorn; PROBE, Prospective, randomized, open, blinded endpoint; RRR, Relative risk reduction; SMBG, Self-monitored blood glucose; TNT1, Time needed to treat 1 patient to prevent 1 episode (of hypoglycaemia).

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[1] J.S. Christiansen is credited posthumously as he passed away Dec. 16th 2015.

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Conclusion. – In T1D patients prone to severe hypoglycaemia, treatment with analogue insulin reduced the risk of non-severe nocturnal hypoglycaemia compared with human insulin.

Keywords: Insulin analogues; Nocturnal hypoglycaemia; Non-severe hypoglycaemia; Randomized controlled trial; The HypoAna trial; Type 1 diabetes

1. Introduction

Hypoglycaemia is the main side-effect of insulin replacement therapy in type 1 diabetes (T1D). Severe hypoglycaemia, when patients have to rely on treatment assistance from others, is a threat with potentially serious morbidity that generates as much worry as the fear of developing serious late diabetes complications [1,2]. While daytime episodes of symptomatic hypoglycaemia may result in discomfort and disruption of daily activities, nocturnal hypoglycaemic events may involve fear of dying during the night, and may induce inappropriate corrective actions at bedtime to prevent future episodes, thereby jeopardizing glycaemic control [3]. Even asymptomatic (silent) hypoglycaemia can have adverse consequences by contributing to the development of hypoglycaemia-associated autonomic failure and impaired hypoglycaemia awareness, leading to an increased risk of severe hypoglycaemia [4–7]. Thus, the reduction of hypoglycaemia episodes, symptomatic as well as asymptomatic, is important.

Approximately, 20% of the T1D patient population suffers from recurrent severe hypoglycaemia, defined as two or more episodes of severe hypoglycaemia per year [1,3]. These high-risk patients are characterized by impaired hypoglycaemia awareness, frequent asymptomatic hypoglycaemia and fluctuating glucose levels, and have the greatest potential to benefit from near-physiological insulin replacement [4,8]. However, the effect of insulin analogues in such patients has not been previously addressed, as they are usually excluded from trials for safety reasons.

The HypoAna trial aimed to elucidate whether all-analogue-insulin therapy (insulin aspart and insulin detemir) in comparison to all-human-insulin therapy can reduce the rate of hypoglycaemia events in high-risk T1D patients. A previous report found a clinically significantly reduced rate of severe hypoglycaemia with analogue insulin treatment [9]. The present analysis aimed to determine whether this effect also applies to non-severe hypoglycaemia (symptomatic and asymptomatic) episodes during the day and at night.

2. Materials and methods

2.1. Study design

The HypoAna trial is a Danish investigator-initiated controlled multicentre crossover study with a PROBE (prospective, randomized, open, blinded endpoint) design. The design and insulin treatment protocol have been described in detail elsewhere [9–11]. The study investigated the effect of insulin analogues vs human insulin on the frequency of hypoglycaemic events – primarily, severe hypoglycaemia and, secondarily, non-severe hypoglycaemia (symptomatic and asymptomatic). Each treatment period lasted 12 months, comprising a 3-month run-in/crossover period followed by a 9-month maintenance period. Patients were block-randomized to start treatment with basal–bolus therapy (in general, four- or five-dose basal–bolus regimens) with insulin detemir (Levemir®) and insulin aspart (Novorapid®) or human NPH (neutral protamine Hagedorn) insulin (Insulatard®) and human regular insulin (Actrapid®). The goal was to maintain baseline glycaemic control in both treatment arms, as the patients at high risk of severe hypoglycaemia were expected to present their best obtainable glycaemic control at the time of inclusion. Insulin doses were adjusted according to the individual patient's need at the discretion of their physicians.

The study was approved by the Danish National Committee on Biomedical Research Ethics (#H-KA-20070008) and conducted in accordance with the Helsinki Declaration. It was also approved by the Danish Medicines Agency (#2612-3397) and conducted according to good clinical practice (GCP) standards, as monitored by the Danish agency for GCP. The trial was registered at www.clinicaltrials.gov (#NCT00346996). All participants gave their written informed consent.

2.2. Subjects

All adult (> 18 years of age) patients with T1D attending the outpatients clinics at six Danish hospitals and one diabetes centre during 2006–2007 were screened by a questionnaire on hypoglycaemia to identify candidates (those having two or more self-reported episodes of severe hypoglycaemia during the previous year) for participation in the HypoAna trial. A total of 3861 patients completed the questionnaire [1], and a total of 159 subjects were included in the study after fulfilling both inclusion and exclusion criteria, as reported elsewhere [9–11]. A predetermined cutoff point of 18 months, including at least 3 months of the second maintenance period, was set for inclusion in the per-protocol analysis [10], which comprised 114 participants.

All study participants were characterized by a mean ± SD age of 54.1 ± 13.0 years, long duration of diabetes (30.0 ± 12.9 years), a reasonable level of glycaemic control (HbA_{1c} 64 ± 11 mmol/mol [8.0 ± 1.1%]), high prevalence of reduced or absent hypoglycaemia awareness (total of 94%) and a mean rate of severe hypoglycaemia events in the preceding year of 5.4 ± 5.2 episodes/patient-year (Table 1). At baseline, the included subjects did not differ from the screened population