Original article

Assessment of hypoglycaemia during basal insulin therapy: Temporal distribution and risk of events using a predefined or an expanded definition of nocturnal events

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A R T I C L E   I N F O

A B S T R A C T

Aim. – To describe in type 2 diabetes the 24-hour distribution of hypoglycaemia and compare the frequency of nocturnal events based on a predefined nocturnal window or an expanded interval, using illustrative data for two insulin glargine formulations.

Methods. – Temporal distribution of hypoglycaemic events was assessed descriptively and by profile using participant-level data from three randomized trials comparing insulin glargine 300 U/mL (Gla-300) and 100 U/mL (Gla-100). Risk of hypoglycaemia and annualized event rates were compared for the predefined nocturnal interval (00:00 to 05:59 h) and an expanded window (22:00 h to the pre-breakfast glucose measurement).

Results. – Confirmed ($\leq$ 3.9 mmol/L [$\leq$ 70 mg/dL]) or severe hypoglycaemic events were reported most frequently between 06:00 and 10:00 h with both insulins. Nearly threefold more events were identified using the expanded nocturnal interval. Risk of $\geq$ 1 nocturnal event was 25% lower with Gla-300 than Gla-100 with the predefined, and 16% lower with the expanded interval; annualized event rates were 31% and 24% lower with the predefined and expanded window, respectively. The between-insulin difference in number of nocturnal events depended markedly on the chosen nocturnal interval (556 vs. 1145 fewer events with Gla-300 using the predefined vs. expanded interval).

Conclusions. – The predefined 00:00–05:59 h nocturnal interval excluded many hypoglycaemic events occurring during the actual overnight interval. While Gla-300 reduced hypoglycaemic events versus Gla-100 (regardless of the interval considered), the results obtained using the expanded window better reflect the clinical experience of people treated with basal insulin.

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Introduction

Hypoglycaemia is a leading barrier to attaining glycaemic goals with insulin therapy [1]. Nocturnal hypoglycaemia may be particularly alarming to individuals with diabetes and providers, and disruptive to medical management [2–4]. Recent clinical trials investigating the use of new long-acting insulin preparations in type 2 diabetes (T2DM) have examined the frequency of nocturnal hypoglycaemia to determine whether this unwanted effect is reduced with the newer products. Nocturnal hypoglycaemia has usually been defined as occurring between 00:00 and 05:59 h, to limit the inclusion of hypoglycaemia potentially related to mealtime insulin taken after wakening. However, this 6-hour window may not include all events occurring during the period between waking and breakfast, during which fasting continues and glucose is still regulated by basal insulin; it also does not include the period between an evening injection of basal insulin and midnight. Thus, many events of hypoglycaemia related to basal insulin during the night will be ignored when assessing differences between insulins.

Here we report the temporal (24-hour) distribution of hypoglycaemic events using participant-level data available from three trials of insulin glargine (EDITION 1–3) in T2DM [5–7]. In addition to the number and timing of hypoglycaemic events, the times of evening insulin injections and of pre-breakfast self-measured glucose tests were routinely collected in the EDITION trials, and assessments were made of the incidence and rate of hypoglycaemia meeting the primary hypoglycaemia definition and an alternative definition of < 3.0 mmol/L (< 54 mg/dL). Using this information, we examined the effect of including events occurring in a wider nocturnal window, defined as the interval between 22:00 h and the pre-breakfast glucose test for each participant, as compared with the 00:00–05.59 h interval that was predefined as "nocturnal" in these trials. Because the trials were randomized comparisons of treatment with insulin glargine 300 U/mL (Gla-300) or insulin glargine 100 U/mL (Gla-100), our analysis allowed evaluation of the effect of the nocturnal interval chosen on the observed differences between these insulins.

Materials and methods

Data sources and participants

EDITION 1, 2, and 3 were multicentre, randomized, open-label, two-arm, parallel-group, phase 3a trials (NCT01499082, NCT01499095, NCT01676220) of similar designs that have been described previously [5–7]. In EDITION 1, participants had previously followed a regimen of basal insulin therapy with either Gla-100 or neutral protamine Hagedorn (NPH) insulin (≥ 42 U/day), together with mealtime insulin therapy, with or without metformin, for at least 1 year. In EDITION 2, participants had used basal insulin (Gla-100 or NPH insulin; ≥ 42 U/day) for more than 6 months, combined with oral anti-hyperglycaemic drugs (OADs) within the previous 4 weeks. Participants in EDITION 3 were insulin-naïve and were required to have used OADs for at least 6 months before screening. In addition, sulfonylureas were to be discontinued in EDITION 2 (2 months prior to screening) and in EDITION 3 (at baseline). All participants provided written, informed consent. All three protocols were approved by the appropriate ethics committees and the trials were conducted according to Good Clinical Practice and the principles of the Declaration of Helsinki.

After a 2-week screening phase, each trial included a 6-month main on-treatment period; data from this are included in the present analysis. No participants were < 18 years of age or had glycated haemoglobin (HbA$_{1c}$) < 7.0% (53 mmol/mol), or > 10.0% (86 mmol/mol) for EDITION 1 and 2, and > 11.0% (97 mmol/mol) for EDITION 3. Further details of inclusion and exclusion criteria have been reported previously [5–7] and are summarized in Table S1 (see supplementary materials associated with this article online).

Therapy

Participants were randomized (1:1) to receive once-daily subcutaneous injections of either Gla-300 or Gla-100 (both Sanofi, Paris France) as described previously (6–8). The basal insulin injection was administered in the evening from before dinner to bedtime, and at the same time for everyone during the 6 months of randomized therapy. Basal insulin injection time was recorded by all participants. Basal insulin dosage was adjusted seeking a fasting, pre-breakfast, self-monitored plasma glucose (SMPG) target of 4.4–5.6 mmol/L (80–100 mg/dL), using specific titration algorithms [5–7].

Outcomes

The pre-specified hypoglycaemia endpoints were the same for each trial [5–7]. Briefly, all hypoglycaemic events were categorized according to the American Diabetes Association definitions [8]:

- severe hypoglycaemia (an event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions);
- documented symptomatic hypoglycaemia (an event during which typical symptoms of hypoglycaemia are confirmed by an SMPG measurement of ≤ 3.9 mmol/L [≤ 70 mg/dL]);
- and asymptomatic hypoglycaemia identified by an SMPG measurement of ≤ 3.9 mmol/L (≤ 70 mg/dL).

The main analysis of hypoglycaemic events used the combination of the confirmed (with or without symptoms) and severe categories. Hypoglycaemic events with a plasma glucose measurement of < 3.0 mmol/L (< 54 mg/dL) were also analysed and reported.

Data analysis and statistics

All analyses included all participants randomized and exposed to ≥ 1 dose of trial drug. In each trial's protocol, hypoglycaemic events recorded between 00:00 h and 05:59 h were defined as nocturnal events ("predefined definition"). In the current post hoc analysis, an expanded window of nocturnal hypoglycaemia was defined using a fixed start time (22:00 h), and a pre-breakfast time defined for everyone by the median value of all pre-breakfast times collected on pre-breakfast, 4- or 8-point SMPG ("expanded definition").

Hypoglycaemic events were reported as the number and percentages of participants having ≥ 1 hypoglycaemic event over 6 months, the total number of events, and the annualized rate of events (events per participant-year). Relative risk for participants to have ≥ 1 hypoglycaemic event was estimated using the Cochran–Mantel–Haenszel method. The rates of hypoglycaemia were analysed using an over-dispersed Poisson regression model with treatment and randomization strata of screening HbA$_{1c}$ (< 8.0 and ≥ 8.0% [< 64 and ≥ 64 mmol/moL]) and trial as fixed effects, and logarithm of the duration of the treatment period as offset.

Although the EDITION 1, 2, and 3 studies were conducted in different populations, the consistent study designs and endpoints allowed a pooled analysis to be performed. The main analysis used pooled patient-level data from the EDITION 1, 2, and 3 studies (EDITION 1 + 2 + 3). In addition, to examine the data without the potentially confounding effect of the mealtime insulin used in EDITION 1, pooled patient-level data from the EDITION 2 and 3 studies (EDITION 2 + 3) were included in a secondary analysis. Data from each individual trial are also given as supportive information.

Results

Study population

Taken together, the EDITION 1, 2, and 3 trials randomized 2496 participants of whom 2488 were treated with study insulin and are included here. Baseline characteristics of participants in the pooled populations are provided in Table 1; those for participants in each trial have been previously reported [5–7] and are provided in Table S2 (see supplementary materials associated with this article online). Important differences between the trial populations are evident. Notably, participants in EDITION 1 (who were all users of basal and mealtime insulin) were approximately 2 years older on average and had ~3–6 years longer duration of diabetes than those in EDITION 2 and 3. Participants in EDITION 1 had also used insulin for longer than those in EDITION 2.