Can J Diabetes 39 (2015) 296–301

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Replacing Insulin Glargine with Neutral Protamine Hagedorn (NPH) Insulin in a Subpopulation of Study Subjects in the Action to Control Cardiovascular Risk in Diabetes (ACCORD): Effects on Blood Glucose Levels, Hypoglycemia and Patient Satisfaction

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ARTICLE INFO

Article history:
Received 2 July 2014
Received in revised form
18 November 2014
Accepted 9 December 2014

Keywords:
A1C
blood glucose
glargine insulin
hypoglycemia
NPH insulin
patient satisfaction

ABSTRACT

Objective: To ensure patient safety when replacing insulin glargine (IG) with neutral protamine Hagedorn (NPH) insulin and to determine differences in blood glucose control, frequency of hypoglycemia, insulin dosing, health resource utilization and quality of life between users of IG and NPH insulin.
Methods: A single-site, open-label, randomized, 6-month comparative study of 66 patients from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Randomization was 1:1 to receive IG or NPH insulin. Data regarding blood glucose control, insulin dosage adjustment and recording of hypoglycemia episodes were obtained through telephone calls; office visits were conducted to measure weight, glycated hemoglobin, fasting plasma glucose and blood glucose profile. The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was used to measure patients' satisfaction with their diabetes treatment.
Results: Rates of symptomatic hypoglycemia did not differ significantly between groups: 37.5±2.2 for the IG group and 31.1±2.1 for the NPH group. However, patients treated with NPH insulin had higher frequencies of severe hypoglycemia (6.1±0.9) compared with 2.7±0.6 for the IG group. A significant difference in changes in glycated hemoglobin (A1C) was observed between the groups: the mean ± standard error A1C decreases from baseline were −0.34%±0.11 for the IG group, vs −0.01%±0.10 for the NPH insulin group. The data obtained from the DTSQ showed greater treatment satisfaction in the IG group compared with the NPH insulin group.
Conclusions: Switching from IG to NPH insulin resulted in more than double the rate of severe hypoglycemias and led to decreased metabolic control. Greater treatment satisfaction was observed with IG, compared with NPH insulin, as measured by change from baseline in the DTSQ scores.

Mots clés :
A1c
glycémie
insuline glargine
hypoglycémie
insuline NPH
satisfaction des patients

RÉSUMÉ

Objectif : Assurer la sécurité des patients lors du remplacement de l'insuline glargine (IG) par l'insuline NPH (Neutral Protamin Hagedorn) et déterminer les différences dans la régulation de la glycémie, la fréquence de l'hypoglycémie, les doses d'insuline, l'utilisation des ressources en santé et la qualité de vie entre les utilisateurs d'IG et les utilisateurs d'insuline NPH.
Méthodes : L'étude clinique aléatoire, ouverte et unicentrique de 6 mois comptait 66 patients de l'essai ACCORD (Action to Control Cardiovascular Risk in Diabetes). La hasardisation pour recevoir l'IG ou l'insuline NPH était de 1:1. Les données concernant la régulation de la glycémie, l'ajustement des doses d'insuline et l'enregistrement des épisodes d'hypoglycémie étaient obtenues lors d'appels téléphoniques; des visites en cabine étaient réalisées pour mesurer le poids, l'hémoglobine glyquée (A1c), le profil de la glycémie veineuse à jeun et de la glycémie. Le questionnaire DTSQ (Diabetes Treatment

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1499-2671/$ – see front matter © 2015 Canadian Diabetes Association
http://dx.doi.org/10.1016/j.jcjd.2014.12.008

Satisfaction Questionnaire) a été utilisé pour mesurer la satisfaction des patients concernant leur traitement du diabète.

Résultats : Les taux d'hypoglycémie symptomatique ne différaient pas significativement entre les groupes: 37,5 ± 2,2 pour le groupe recevant l'IG et 31,1 ± 2,1 pour le groupe recevant l'insuline NPH. Cependant, les patients traités par l'insuline NPH avaient des épisodes d'hypoglycémie grave plus fréquents (6,1 ± 0,9) par rapport aux patients du groupe recevant l'IG (2,7 ± 0,6). Une différence significative de l'A1c était observée entre les groupes: les diminutions moyennes ± l'erreur type de l'A1c par rapport aux valeurs initiales étaient de −0,34 % ± 0,11 pour le groupe recevant l'IG et de −0,01 % ± 0,10 pour le groupe recevant l'insuline NPH. Les données obtenues du DTSQ montraient une plus grande satisfaction à l'égard du traitement dans le groupe recevant l'IG que dans le groupe recevant l'insuline NPH.

Conclusions : La substitution de l'IG à l'insuline NPH entraînait plus que le double du taux d'hypoglycémie grave et menait à la diminution de la régulation du métabolisme. La satisfaction à l'égard du traitement était plus grande chez ceux qui prenaient de l'IG par rapport à ceux qui prenaient l'insuline NPH, et ce, par rapport aux valeurs initiales des scores du DTSQ.

Introduction

Individuals with longstanding type 2 diabetes experience an increase in blood glucose levels due to the progressive dysfunction of beta cells through the advancement of the disease. As a result, it becomes more difficult to reach blood glucose target levels as the disease progresses (1). It has been suggested that newly diagnosed individuals with type 2 diabetes treat their condition through lifestyle changes (i.e. nutrition and physical activity). However, if these changes do not lead to a decrease in glycated hemoglobin (A1C) levels within 2 to 3 months, then antihyperglycemic agents and/or insulin treatment must be initiated (2). The goal of insulin therapy is to mimic the normal physiologic secretion of insulin (3).

Numerous types of insulin are available, each of which has a different action profile. Insulin glargine (IG) and detemir are long-acting insulin analogues that provide patients with optimal glycemic control and a reduced risk for hypoglycemia (3). IG has a smooth action profile with no pronounced peaks; conversely, neutral protamine Hagedorn (NPH) insulin has a peak of insulin concentration approximately 4 hours after injection (4). Because of its action profile, NPH insulin results in an increased frequency of nocturnal hypoglycemia as compared with insulin glargine (5).

Hypoglycemic events are significant because they may result in neurogenic symptoms (e.g. nausea, anxiety) and neuroglycopenic symptoms (e.g. confusion, dizziness) (6).

Because insulin glargine and NPH insulin have such different action profiles they, in turn, have varying effects on individuals' blood glucose levels. Three regulatory trials in patients with type 2 diabetes who are taking insulin have demonstrated the safest dosage transfer from NPH insulin to insulin glargine; however, until now, no clinical study had been performed to determine the appropriate transfer dosage from insulin glargine to NPH insulin.

The Action to Control Cardiovascular Disease (ACCORD) trial began in North America in 2000 (7). During the trial, most patients were treated with insulin glargine or insulin detemir. At the conclusion of the trial, all participants were provided with 3-month supplies of the study's medication and discharged to either their primary care physicians or their endocrinologists for their diabetes management.

In the province of Manitoba, insulin glargine is available only through private medical insurance coverage or provincial exception drug status (EDS) application (8). In order to qualify for provincial coverage, people with diabetes must have experienced hypoglycemia while on NPH insulin. ACCORD patients represent an interesting challenge in this regard because the majority of them have never received NPH insulin and are, therefore, ineligible to apply for EDS coverage.

The concern regarding lack of access to insulin glargine is twofold. First, many ACCORD patients have returned to their primary care providers for diabetes management and are, thus, without the close monitoring and expertise of the ACCORD study site's healthcare team. Their primary care providers are left to determine how to switch patients to NPH insulin with virtually no guidance. Second, without intensive monitoring regarding their insulin dosages, these patients may be at increased risk for hypoglycemia. Hypoglycemia should be avoided in patients who are at high risk for cardiovascular disease; it has been shown that severe hypoglycemia in these individuals leads to an increased risk for vascular events and death (9).

The goal of this study was to ensure patient safety (particularly with respect to hypoglycemia and severe hypoglycemia) when insulin glargine was replaced by NPH insulin. The study also sought to determine the differences in blood glucose control, frequency of hypoglycemia, insulin dosing, health resource utilization and quality of life in the groups.

Methods

Study design and sample population

The trial was a single-site, open-label, randomized, 6-month comparative study. The sample population consisted of 66 ACCORD patients from the Winnipeg ACCORD trial centre. Patients were randomized 1:1 to receive either insulin glargine or NPH insulin. Randomization was completed at site levels after screening visits occurred. An independent source randomly prepared envelopes containing assignments of either insulin glargine or NPH insulin. These envelopes were then distributed to the participants in a consecutive fashion. All participants provided written informed consent prior to their entry into the study.

Inclusion criteria

The study population consisted of ACCORD patients who were receiving basal insulin therapy with a long-acting insulin analogue. In order to be considered for the study, the patients must have been ineligible for financial reimbursement for the drug (provincial or private) or unable to afford to pay for insulin glargine. Subjects were not permitted to participate in any clinical trial other than the ACCORD extension trial (for observation only). Patients who required any type of medical treatment that would preclude their safe participation in the study were excluded at the discretion of the investigator.

Procedures

The majority of subjects entering the study were taking once-daily insulin glargine. The investigator determined insulin