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Effect of the administration of a single dose of nateglinide on insulin secretion at two different concentrations of glucose in healthy individuals

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Abstract

Background: Nateglinide is a D-phenylalanine derivative that stimulates fast insulin secretion with a short activity span. It has been suggested that the hypoglycemic effect of nateglinide is related to the glucose concentration, an aspect that still has not been completely evaluated in human beings. **Objective:** The aim of this study is to evaluate the effect of nateglinide on the insulin secretion at two different concentrations of glucose level. **Participants and methods:** A randomized, double-blind, cross-over, placebo-controlled clinical trial with two parallel groups was carried out; each group was made up by six healthy volunteers who were submitted to a hyperglycemic–hyperinsulinemic clamp technique on two different occasions, one of them prior to the administration of 120 mg nateglinide and the other one prior to the administration of an homologated placebo. One group was submitted to and maintained at a hyperglycemia of 6.9 mmol/l above the fasting glucose level and the other group at a hyperglycemia of 4.1 mmol/l above the baseline of fasting glucose level. **Results:** In volunteers submitted to the clamp at 4.1 mmol/l above the baseline of glucose level, the insulin secretion in the early phase was 212.4±55.8 pmol/l in the placebo test versus 338.4±124.8 pmol/l in the nateglinide test ($P<.05$), whereas in the group submitted at 6.9 mmol/l over the baseline, no significant differences were observed. **Conclusion:** Nateglinide increased the early insulin secretion in healthy individuals submitted to a mild hyperglycemia, but not at high glucose concentrations.

Keywords: Nateglinide; Insulin release; Insulin secretion; Insulinotropic effect

1. Introduction

Nateglinide is a derivative of D-phenylalanine, which depolarizes the beta cell of the pancreas with the consequent entrance of calcium and insulin exocytosis. In preclinical and clinical trials, it has been proven that nateglinide restores insulin secretion, it acts quickly, and it has a short half-life (1.5 h). Another characteristic that has been observed in preclinical trials and that has not been document in human trials is the relation between the glucose level and the insulin secretion by nateglinide, such as a higher glucose concentration is related to more insulin secretion caused by the drug and vice versa, with a proper reduction of a hypoglycemic risk and better safety profile (Fujitani & Yada, 1994; Johnson & Bressler, 1997; Sato, Nishikawa, Shinkai, & Sukegawa, 1991a; Shinkai, Nishikawa, & Sato, 1989; Shinkai, Toi, & Kumashiro, 1988).

The hyperglycemic–hyperinsulinemic clamp technique permits the quantification of the function of the beta cell at a determined ambient glucose level. With this method, the glucose concentration is elevated to a blood level previously established above its baseline through a continuously adjusting infusion of dextrose, based on the estimated glucose metabolism throughout the clamp. In this condition of constant hyperglycemia, the response of the insulin by the organism has two phases, an initial secretion (early phase) in the first minutes, followed by a gradual increase in the insulin level (late phase) until the end of the clamp (DeFronzo, Tobin, & Andres, 1979; Ferrannini & Mari, 1998).

The aim of this study was to identify the effect of the administration of a single dose of nateglinide on the

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insulin secretion at two different glucose concentrations in healthy individuals.

2. Materials and methods

A randomized, double-blind, cross-over, placebo-controlled clinical trial with two parallel groups was carried out in 12 healthy volunteers. We included individuals between 18 and 40 years old with legal capacity to give their informed consent, with a body mass index (BMI) from 19 to 25 kg/m^2, stable weight during the last 3 months, glucose level between 3.9 and 6.1 mmol/l, and a blood pressure below 140/90 mm Hg. We excluded pregnant women or those with a suspected pregnancy, as well as individuals with a history of active smoke and sedentary habits during the year prior to the study and those known hypersensitivity to nateglinide, treatment with warfarine, dicumarol, sympathicomimetics, diuretics, hypolipemiants, corticoids, or with any drug, which may influence the glucose or insulin metabolism in the last 3 months prior to the study. We also excluded the individuals with a history of toxic substance abuse (including alcoholism), with coronary disease, cardiac surgery, ventricular tachycardia, ventricular fibrillation, cerebrovascular disease, hepatic disease, elevation of hepatic enzymes two times above the normal value, elevation of direct bilirubin 1.3 times above the normal superior value, creatinine level higher than 115 μmol/l, uncontrolled thyroid disease, diagnosis of Type 1 or 2 diabetes mellitus, hypertension, uric acid higher than 416 μmol/l, and blood donation or loss equivalent to 500 ml or more during the last 6 weeks. We asked all volunteers to take an isocaloric diet of 250 g of carbohydrates during the day during 3 days prior to the test, and the females participants were asked to abstain from any sexual activity and to have been in the first 8 days of their menstrual cycle.

Each patient was called on three times. During the first call, the selection criteria were evaluated and a complete physical checkup was performed. Subsequently, with the volunteer in complete rest, we proceeded to take 20 ml of venous blood for the measurement of glucose, urea, creatinine, uric acid, total cholesterol, tryglicerides, and high-density lipoprotein cholesterol (HDL). During the second call, weight, height, BMI, and vital signs were taken to all the participants. The participants were assigned at random to belong to the 4.1 or the 6.9 mmol/l group above the baseline of glucose, in the hyperglycemic–hyperinsulinemic clamp (DeFronzo et al., 1979), and to receive 120 mg of nateglinide or placebo; the first clamp was also performed. During the third call, the second hyperglycemic–hyperinsulinemic clamp was applied with the cross-over administration of nateglinide and placebo. The adverse effects were permanently recorded throughout the study.

The weight and the height were measured with the individual wearing light clothes and without shoes. The height was quantified in centimeters, with fractions rounded off to the nearest centimeter. The blood pressure was measured in the right arm after a resting period of at least 5 min and the individual sitting on a chair. The measurement was obtained by the same investigator on each occasion, using a mercury sphygmomanometer, and the diastolic blood pressure was considered with Phase V of the Korotkoff sound.

To perform the hyperglycemic–hyperinsulinemic clamp technique, a venous access in retrograde way over some of the veins of the hand was installed, through a 19 G butterfly catheter, for taking samples during the test; the hand was wrapped in a thermal mattress to achieve a local temperature higher than 40 °C to arterialize the blood. Nateglinide (120 mg) or placebo was administered orally.

A second venous access was installed on the contralateral arm with a 19 G catheter, and 30 min later, the clamp test was initiated with a 20% dextrose infusion at a previously calculated velocity based on the body weight, the basal glucose, and the glucose required throughout the test (4.1 or 6.9 mmol/l above the basal value). At the 2nd, 4th, 6th, 8th, and 10th min, 5 ml of blood was taken and, after that, every 10 min until the 120th minute for the determination of insulin. Every 5 min, we took an additional 1.5 ml blood sample for the determination of glucose to calculate the estimate of the glucose metabolism and, that way, be able to adjust the rate of dextrose infusion. At the end of the 120 min of the test, the dextrose infusion was maintained for 30 min as a precaution to avoid hypoglycemia. The individual was observed for the rest of the day through preprandial capillary glycemia and prior to going to sleep.

The serum glucose was determined by the glucose-oxidase technique (Beckman Instruments, Brea, CA, USA) with an intra- and interassay coefficient of variation below 1%. The lipid profile (total cholesterol, HDL, and tryglicerides), creatinine, and uric acid were measured by enzymatic methods. In particular, the HDL was determined after selective precipitation of the non-HDL fraction. All determinations were performed with commercially available equipment (Ortho-Clinical Diagnostics, Rochester, NY, USA) with an intra- and interassay coefficient of variation less than 3%. The concentration of insulin levels was determined with standard radioimmunoassay technique (Diagnostic Products, Los Angeles, CA, USA) with intra- and interassay coefficient of variation of 4.6% and 7.1%, respectively.

The sample size was calculated with a clinical trial formula (Jeyaseelan & Rao, 1989), with a confidence level of 95%, a statistical power of 80%, a standard deviation of the first phase of insulin secretion of 49.8 pmol/l, and an expected difference of 75.0 pmol/l, which resulted in six individuals per group. The values were reported as mean and standard deviation. Friedman, Wilcoxon sign rank and Mann–Whitney U tests were used to compare differences intragroup and between both groups, as well as chi square in the case of qualitative variables. A significance of $P<.05$ was considered.

The study was authorized by the Ethics Committee of the participating hospital and met all the requirements for