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Naltrexone for treatment of impaired awareness of hypoglycemia in type 1 diabetes: A randomized clinical trial

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ABSTRACT

Aims: Impaired awareness of hypoglycemia (IAH) is a limiting factor in the treatment of type 1 diabetes (T1D) and is a challenging condition to reverse. The objective of this study was to test the hypothesis that naltrexone therapy in subjects with T1D and IAH will improve counterregulatory hormone response and recognition of hypoglycemia symptoms during hypoglycemia.
Methods: We performed a pilot randomized double blind trial of 4 weeks of naltrexone therapy (n = 10) or placebo (n = 12) given orally in subjects with T1D and IAH. Outcome measures included hypoglycemia symptom scores, counterregulatory hormone levels and thalamic activation as measured by cerebral blood flow using MRI during experimental hypoglycemia in all subjects before and after 4 weeks of intervention.
Results: After 4 weeks of therapy with naltrexone or placebo, no significant differences in response to hypoglycemia were seen in any outcomes of interest within each group.
Conclusions: In this small study, short-term treatment with naltrexone did not improve recognition of hypoglycemia symptoms or counterregulatory hormone response during experimental hypoglycemia in subjects with T1D and IAH. Whether this lack of effect is related to the small sample size or due to the dose, the advanced stage of study population or the drug itself should be the subject of future investigation.

1. Introduction

Iatrogenic hypoglycemia is a common and feared complication of insulin therapy. Recurrent exposure to iatrogenic hypoglycemia in patients with insulin treated diabetes can lead to development of impaired awareness of hypoglycemia (Cryer, 2005), a condition that is estimated to occur in 20% of patients with type 1 diabetes (Geddes, Schopman, Zammitt, & Frier, 2008). Fear of hypoglycemia can limit the ability of patients with diabetes to achieve the glycemic control shown to prevent complications of diabetes. Strict avoidance of hypoglycemia has been shown to partially restore awareness of hypoglycemia; however it is very difficult to achieve and maintain over the long term (Dagogojack, Rattarasarn, & Cryer, 1994; Fanelli, Pampanelli, Epifano, et al., 1994; Leelarathna, Little, Walkinshaw, et al., 2013). Consequently, there has been great interest in developing therapies that will prevent and/or reverse impaired awareness of hypoglycemia in diabetes.

One potential therapy to prevent or reverse impaired awareness hypoglycemia in diabetes may be opioid receptor antagonists. Endogenous opiates have been shown to modulate hormonal responses during hypoglycemia and may play a role in the development of impaired awareness of hypoglycemia (McCrimmon, 2011). Intravenous administration of naloxone, an opioid receptor antagonist, during hypoglycemia has been shown to augment the counterregulatory response to hypoglycemia in dogs (Eltayeb, Brubaker, Lickley, Cook, & Vranic, 1986) and humans (Caprio, Gerety, Tamborlane, et al., 1991). When infused during antecedent hypoglycemia, naloxone has been shown to prevent development of defective counterregulatory hormone response to subsequent hypoglycemia in healthy humans (Leu, Cui, Shamoon, & Gabriely, 2009) and in patients with type 1 diabetes (Vele, Milman, Shamoon, & Gabriely, 2011). Whether chronic administration of an opioid receptor antagonist to patients with type 1 diabetes at risk for or suffering from impaired awareness of hypoglycemia will be an effective therapy remains unknown.

How to best test potential therapies for impaired awareness of hypoglycemia in patients with diabetes has not yet been determined. Patients with the condition are likely to gain most from the

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development of a successful therapy, but it isn't clear that a drug that prevents hypoglycemia induced impairment in counterregulation will be successful in patients who already are impaired. Administration of a candidate drug to patients with type 1 diabetes who retain awareness of hypoglycemia might help us understand if the drug can prevent the development of impaired awareness, but the correct dosing regimen for chronic use must be defined. Whether the same drug can both prevent and treat impaired awareness of hypoglycemia in diabetes also remains unknown. In this report, we aim to test one approach with the intention of gaining insights that will guide the design of future trials testing drugs to prevent and treat this most challenging complication of insulin therapy in diabetes.

In this study, we examined the safety and efficacy of four weeks of oral administration of the opioid receptor antagonist naltrexone in participants with type 1 diabetes and impaired awareness of hypoglycemia defined by the Cox questionnaire (Clarke et al., 1995). The primary objective of this randomized placebo controlled trial was to test the hypotheses that naltrexone therapy in subjects with type 1 diabetes and impaired awareness of hypoglycemia will improve counterregulatory hormone responses, increase recognition of hypoglycemia symptoms, and increase brain activation during hypoglycemia in the thalamus, a region that is involved in the brain response to hypoglycemia (Mangia, Tesfaye, De Martino, et al., 2012). The secondary objective was to gain insights into whether it would be better to test patients with type 1 diabetes who do or do not have awareness of hypoglycemia in future studies of candidate drugs for the prevention and treatment of this condition. If naltrexone fails to reverse the condition in a population of diabetic subjects with impaired awareness of hypoglycemia, future efforts involving use of opioid receptor antagonist should be focused towards prevention of the development of the condition in patients with type 1 diabetes who retain awareness of hypoglycemia.

2. Materials and methods

2.1. Subjects

Otherwise healthy subjects with type 1 diabetes with HbA1C < 8% (64 mmol/mol), between 18 and 65 years of age were recruited for participation. Type 1 diabetes was defined on clinical grounds. The Cox questionnaire (Clarke et al., 1995) was used to categorize subjects with type 1 diabetes as having impaired awareness of hypoglycemia. Exclusion criteria included concomitant use of acetaminophen, aspirin or ibuprofen (all may increase risk of naltrexone induced liver dysfunction), history of liver disease, renal insufficiency, central nervous system or cardiac disease and presence of any characteristics that would preclude placement in the MRI magnet.

2.2. Study design and experimental protocol

The study was designed to assess the occurrence of hypoglycemia over one week in the free living state and responses to experimental hypoglycemia before and after a four week treatment period in which subjects were randomized to receive naltrexone for 4 weeks or an identically appearing placebo. The protocol was approved by the Institutional Review Board at the University of Minnesota.

Study participation began with a screening visit (visit 1), where subjects were educated in the use of the continuous glucose monitor and sent home with sufficient supplies to collect data for the seven days before the pre-treatment clamp study at visit 2. During this seven day period, subjects were also asked to check their blood glucose at a minimum before each of three meals and at bedtime and record any glucose reading <70 mg/dl on provided hypoglycemia log sheets. Subjects documented whether the hypoglycemia was recognized and treated by themselves or someone else and any associated symptoms they may have had. Hypoglycemia was defined as any episode of hypoglycemia that required the assistance of another to recognize/treat or any documented blood glucose < 70 mg/dl.

On the morning of the first hypoglycemia clamp study (visit 2), subjects presented to the Center for Magnetic Resonance Research after an overnight fast. After arrival, their continuous glucose monitor was removed and they were prepared for the insulin clamp study as previously described (Mangia et al., 2012). Cerebral blood flow data were collected initially during euglycemia (blood glucose 95 mg/dl) and then again during hypoglycemia (blood glucose 50 mg/dl). Samples for counterregulatory hormones were collected at baseline and every 10–15 min during hypoglycemia. Symptoms of hypoglycemia were quantified using a previously validated questionnaire (Towler, Havlin, Craft, & Cryer, 1993). Subjects were asked to score from 0 (none) to 6 (severe) on six autonomic symptoms (heart pounding, shaky/tremulous, nervous/anxious, sweaty, hungry, tingling) and six neuroglycopenic symptoms (difficulty thinking, tired/drowsy, weak, warm, faint, dizzy). At the completion of the clamp study, subjects were then sent home with their treatment assignment according to the randomization protocol.

An Investigational New Drug approval for the use of naltrexone was obtained from the Food and Drug Administration (#103409). The investigational pharmacy at the University of Minnesota ensured that the naltrexone and placebo tablets were identical in appearance and managed the randomization assignments. Assignment to naltrexone or placebo was blinded to participants and investigators until the study was completed. The dose of Naltrexone was titrated up over 10 days (25 mg daily × 5 days, then 50 mg daily × 5 days, then 50 mg twice daily × 18 days).

At 14 ± 1 days after the first episode of experimental hypoglycemia, subjects returned to provide blood for measurement of ALT, AST, CPK, and creatinine (visit 3). At visit 4 (7 days prior to the second hypoglycemia clamp study), the continuous glucose monitor was again placed and subjects were instructed to keep the hypoglycemia log for the next 7 days. On day 28 (Visit 5) a second hypoglycemia clamp and MRI study was performed. Subjects took their final dose of naltrexone/placebo on the morning of visit 5 and presented to repeat the clamp study with measurement of cerebral blood flow as described above for visit 2. The full study protocol is depicted in Fig. 1.

2.3. Laboratory analyses

Blood samples for counterregulatory hormones obtained during the hypoglycemia protocol were sent to Vanderbilt Diabetes Research and Training Center (DRTC), Hormone Assay and Analytical Services Core for analysis. Plasma epinephrine and norepinephrine were measured by high-performance liquid chromatography (Dionex, formerly ESA, Inc.). Plasma growth hormone and cortisol were measured by radioimmunoassay (Diagnostic Products Corporation, Inc.). Plasma glucagon was measured by radioimmunoassay (Modified Millipore, Merck).

2.4. Continuous glucose monitor analysis

A Dexcom Seven Plus continuous glucose monitor was provided to subjects to wear for 7 days prior to each clamp study. Subjects were blinded to the monitor's glucose readings. Cumulative exposure to hypoglycemia was determined using AUC for the glucose curve over time spent with interstitial glucose < 70 mg/dl. Subjects who were previously using a personal continuous glucose monitor and declined to use the study device were allowed to continue using their own monitor (not blinded to their glucose readings), but their AUC data were not available for analysis.

2.5. MRI acquisition and processing

MRI measurements were performed using a 3.0 T Siemens Trio scanner (Siemens, Erlangen, Germany), using imaging and processing