A 4-week Pilot Study With the Cannabinoid Receptor Agonist Dronabinol and Its Effect on Metabolic Parameters in a Randomized Trial

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ABSTRACT

Purpose: Dronabinol (synthetic Δ^9- tetrahydrocannabinol) is used in patients with nausea and vomiting from chemotherapy and in AIDS patients for appetite stimulation. Recently, dronabinol was used to successfully treat visceral hypersensitivity causing noncardiac chest pain. With widening uses of this medication, we aim to explore its effects on metabolic parameters in long-term dosing and hypothesize that it will not affect major metabolic parameters.

Methods: A double-blind, placebo-controlled, 28-day trial was performed with patients 18 to 75 years old without cardiac disease. Patients had at least 2 weekly episodes of chest pain for the last 3 months and evidence of esophageal hypersensitivity after balloon distention testing. Prior use of pain medication, psychiatric diagnosis, or significant medical comorbidities precluded inclusion in the study. Patients were randomized to receive 5 mg dronabinol or placebo twice daily with metabolic parameters examined before and after the use of medication.

Findings: Thirteen patients completed the study (7 with dronabinol [6 women and 1 man] and 6 with placebo [5 women and 1 man]). None of the measured values, including body mass index, HDL, triglycerides, calculated LDL, high-sensitivity C-reactive protein, glucose, insulin, leptin, aspartate aminotransferase, alanine aminotransferase, LDH, or non-HDL, differed significantly in either group before or after treatment. In general, treatment with dronabinol coincided with favorable trends in some parameters, although these trends were not statistically significant.

Implications: Dronabinol administration does not significantly affect basic metabolic components after a period of 28 days. The implications of these findings are important because dronabinol may be able to be used in patients with metabolic disorders. The favorable trends observed here warrant further exploration into its long-term effects. ClinicalTrials.gov identifier: NCT01598207. (*Clin Ther.* 2015;37:2267–2274)

Key words: cannabinoid receptors, CB_1 agonist, metabolic parameters, noncardiac chest pain.

INTRODUCTION

Dronabinol, Δ^9- tetrahydrocannabinol (THC), is a cannabinoid receptor agonist active at both cannabinoid receptors, CB_1 and CB_2, that has a slightly greater affinity for CB_1.[1,2] CB_1 and CB_2 receptors are found throughout the body, including the brain and gastrointestinal tract.[3–6] The effects of dronabinol on these receptors are systematically multifactorial. In particular, within the gastrointestinal tract, they decrease visceral hypersensitivity, nausea, and vomiting, delay gastric emptying, and increase appetite.[7–12]

Early studies found favorable metabolic changes by initiating a blockade of CB_1 receptor signaling and many studies have sought to explore this association. A study that used a rat model to investigate the interplay among CB_1 receptors, ghrelin, and the CB_1 receptor antagonist, rimonabant, in the short term or during a week, found that CB_1 receptors play a role in

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ghrelin levels secreted from neuroendocrine cells located in the stomach.[13] However, the association between CB_1 receptors and ghrelin was found to require an intact vagus nerve emphasizing the complex role of the endocannabinoid system as a mediator of neurologic and gastrointestinal functions including food intake.[13]

Studies have explored the effect of CB_1 blockade on metabolic parameters. Merroun et al[14] administered a CB_1 blocker (AM251) at a dose of 3 mg/kg IP for 21 days and found a reduction in the levels of glucose, leptin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase, bilirubin, LDL, triglycerides, and overall cholesterol. In addition, an increase in HDL was noted.[14] Increasing HDL through CB_1 antagonists was also reported and linked to a gene variant of the *CNR1* gene.[15] Additional studies have found that CB_1 antagonists lowered triglycerides and insulin levels as well as augmented HDL levels without affecting total cholesterol or LDL levels.[16] Another recent study reported that rimonabant at 10 mg/kg daily for 28 days decreased leptin and insulin levels with no change in glucose concentration.[17]

Dronabinol may be used for nausea and vomiting in patients with cancer and in patients with anorexia due to AIDS.[18] Recently, dronabinol was found to decrease visceral sensitivity in patients with noncardiac chest pain.[7] With the potential for widened uses of dronabinol, and hypothetically other cannabinoid receptor agonists, it is important to understand how it may affect other metabolic parameters. Given the high prevalence of patients with hyperlipidemia, diabetes, and obesity, understanding the effect of dronabinol on these patients will allow for improved care without unintended sequelae of worsening chronic medical conditions.[19]

However, most of these studies looked at very short periods. To our knowledge, such examination with a specific agent for a prolonged period has not been performed to look at each of the metabolic parameters we have examined here. The aim of our study was to evaluate the effects of dronabinol on measures of body mass index (BMI), weight, total cholesterol, HDL, triglycerides, high-sensitivity C-reactive protein (HS-CRP), glucose, insulin, leptin, AST, ALT, and LDH for a duration of 28 days in patients with noncardiac chest pain in a placebo-controlled, double-blind, parallel study. We hypothesize that a short duration will not result in significant changes in metabolic parameters.

MATERIALS AND METHODS

Selection of Patients

Patients with NCCP referred to our tertiary care center between April 1, 2011 and January 31, 2014 were recruited to the study. All patients underwent cardiac evaluation that excluded a cardiac source for chest pain and, in many instances, after various empirical therapies had proven ineffective. Patients aged 18 to 75 years were included if they fulfilled diagnostic criteria of at least 2 weekly episodes of chest pain for the last 3 months with normal cardiac evaluation results (stress test with or without normal coronary angiogram). Patients had normal results on upper gastrointestinal endoscopy and 24-hour pH studies. All participants had abnormal balloon distention test results. Patients were excluded if they had a history of requiring narcotics, pain medications, substance abuse, Barrett esophagus, or peptic stricture on endoscopy. In addition, patients who had significant comorbid illnesses, such as cardiac, pulmonary, renal, or hepatic disease, or those with diabetes, neuropathy, history of peptic ulcer disease, or seizures were excluded from the study. Patients with a history of psychiatric disorders or under treatment with psychotropic drugs were excluded. All patients gave written informed consent approved by the University of Iowa Human Subjects Institutional Review Board. A total of 19 patients with functional chest pain and esophageal hypersensitivity were invited to enroll.

Drug Dosing, Duration, and Clinical Evaluation

This study consisted of a baseline screening period and a 4-week treatment period. Subsequently, patients were randomized to receive oral capsules of 5 mg dronabinol or placebo BID for 4 weeks after meals. The pharmacist who prepared medications randomized patients in a 1:1 manner but had no contact with them and was not involved in any of the research meetings. Both researchers and patients were blinded to treatment groups. The BMI, weight, total cholesterol, HDL, triglycerides, HS-CRP, glucose, insulin, leptin, AST, ALT, and LDH were obtained before and after study. Venous blood samples were collected at 9 am after an overnight fast both before and after the collection periods. Insulin resistance and β-cell function