The Efficacy Of Transdermal Nicotine In Conjunction With Conventional Therapies In Active Ulcerative Colitis

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A. Statement of study and purpose rationale

The purpose of this study is to determine the efficacy of transdermal nicotine in conjunction with azulfidine and prednisone in active ulcerative colitis in inducing remission. Ulcerative colitis is an inflammatory bowel disorder that has a predilection for nonsmokers(l). Case reports indicate that smokers who quit are at increased risk for ulcerative colitis and smokers who develop the disease after quitting subsequently go into remission after resuming cigarette smoking (2). Many have postulated that it is the nicotine in cigarette smoking that is the active component involved in putting the disease into quiescence (3). Cope and Heatley have suggested that nicotine acts by altering intestinal mucous, by vasoconstricting and thus decreasing the ability of the inflammatory mediators to reach the intestine, and by altering intestinal permeability (4).

There have been a few studies to date investigating the therapeutic role of nicotine in ulcerative colitis. A controlled trial to determine the efficacy of transdermal nicotine in maintaining remission showed that nicotine was no better than placebo (5). Another study compared transdermal nicotine to oral prednisone in the treatment of active ulcerative colitis. Prednisone was found to be more efficacious in putting the disease into remission, 32% for transdermal nicotine and 58% for oral prednisone (6). A more recent randomized placebo controlled trial showed that transdermal nicotine at the highest tolerated dosages is efficacious in controlling clinical symptoms of mild to moderately active disease. Of patients treated with nicotine, 49% showed clinical improvement at 4 weeks compared with 24% of the placebo group (7). In sum, studies to date show that nicotine does not have a role as maintenance therapy but that it does have a role as therapy in patients with active disease but it is no better than conventional therapies for active disease. My hypothesis states that using nicotine as an adjunct to standard medical therapy (i.e. azulfidine and steroids) in active disease would be more efficacious than standard therapy alone in inducing remission in 6 weeks. Many patients require steroids to control flares and subsequently suffer the side effects secondary to chronic steroid use. It would be of great value to shorten the length of active disease and thus possibly reduce the length of steroid use in the treatment of this disease.

B. Description of study design and statistical analysis

a. Study design

This study will be a double blind randomized placebo controlled trial investigating the effects of transdermal nicotine in addition to steroids and azulfidine in patients with mild to moderate active ulcerative colitis. Patients will come to the general clinic research center and fill out a questionnaire about their clinical symptoms at the beginning of the study as well as at the conclusion of the study. The symptoms will then be assessed by a clinician who will determine the clinical grade, at baseline and at 6 weeks, using a scale designed by Truelove et al (8). At the

beginning of the study, all patients will have CO breath measured to confirm the absence of cigarette smoking. They will also have plasma nicotine and cotinine levels drawn at baseline and at the end of 6 weeks to confirm that the serum levels are within the therapeutic ranges previously described. Patients will undergo flexible sigmoidoscopy and rectal biopsies this same day to confirm the presence of active disease. All siginoidoscopies will be done by the same gastroenterologist who is not a member of the research team. The intestinal appearance will be graded using a scale described by Baron et al. and the histology of the rectal biopsies will be graded using a scale described by Truelove and Richards (9,10).

Only patients with a combined score (clinical, histologic and sigmoidoscopicurade) greater or equal to five will be included.

The patients will be stratified to three groups based on the combined score of the clinical, signioidoscopic: and histologic grade (See Appendix A). Thus group A would contain grades 5-7, group B grades 8,9, group C grades 10,11. The patients in each group will then be randomly assigned treatment by a computer generated randomization sequence. Patients assigned to the nicotine arm will wear an 11-ing patch for one week and then a 22 ing patch for five weeks. Patients in both arms of the study will receive prednisone 40 mg PO per day and azulfidine four grams PO qd. Once patients have a clinical response, the tapering of steroids will be left up to the discretion of the patient's gastroenterologist who will keep a strict record of the dosage of steroids used each day during the study. The patients will also keep their own record of the amount of steroids taken daily. At the end of the study, the cumulative dosage of steroids taken during the 6 weeks will be tallied up. All patches will be counted in order to test for compliance. As previously stated, patients will fill out questionnaires regarding their clinical symptoms and also have serum nicotine and cotinine levels drawn. Patients will have a repeat flexible sigmoidoscopy and rectal biopsies taken after 6 weeks of therapy and the mucosal appearance and histology will be graded in the same way previously described. Patients will be considered in clinical remission only when the combined score for clinical grade, sigmoidoscopy and histology grade is ≤2.

b. Statistical analysis

In order to achieve a power of 80%, 40 patients will be randomized to each group to show an increase from 60-85% in the number of patients in clinical remission at 6 weeks after using nicotine in conjunction with prednisone and azulfidine. The estimated amount of time to recruit this number of patients would be two years. The Fischer exact test will be use to compare the distribution of remission following 6 weeks exposure to the study. The cumulative amount of steroids used in each group will be compared by the t test.

C. Description of study procedures

Each patient will have an initial flexible siginoidoscopy and rectal biopsies taken. This will be repeated at the end of 6 weeks. The estimated time of the procedure will be about 30 minutes. There could be some local discomfort. The risks would be bowel perforation and bleeding. Standard clinical care would require this procedure this frequently. Patients will have breath carbon monoxide measured by the Bedfont MicroSmokerlyzer at the beginning of the study. No risks are involved with this procedure. Patients will also have blood drawn to have serum nicotine and cotinine levels measured at baseline and at 6 weeks. The risk of phlebotomy is minimal and would include bleeding and bruising.

D. Study drugs

The study drug is a nicotine patch that will be given in varying doses: 11-mg x one week then 22 mg for the remainder of the study. There will also be a placebo patch that will look identical to the nicotine patch. Either patch will be applied every 24 hours to the upper torso. The side effects include headaches, nausea, dizziness, flushing, and allergic contact dermatitis. There is evidence to show that it may be harmful in patients with coronary artery disease.

E. Medical devices

None

F. Study questionnaires

A questionnaire involving clinical symptoms such as abdominal pain, stool frequency and consistency, rectal bleeding, and presence of mucous will be designed and used at baseline and at the end of 6 weeks. One clinician will administer the questionnaire.

G. Description of study subjects and method of recruitment

The study subjects will include those patients with an ulcerative colitis flare that have a combined score of clinical, histologic and sigmoidoscopic grade (as previously described in the study design) greater than or equal to five. Patients with coronary artery disease, pregnant women, patients with evidence of enteric infection, current smokers and patients with any history of smoking will be excluded from the study. Given the addictiveness of nicotine, it would not be ethical to include patients in the study who have successfully quit smoking. Abstinence from cigarette smoking will be documented by CO breath monitoring. Patients will be referred by their gastroenterologists either from the GI clinic here at CPMC or from CPMC gastroenterologists in their private practice when they present with an acute flare. The gastroenterologists would determine eligibility for the study and contact a member of the research team who will then explain the nature of the study and obtain consent if the patient is interested in participating in the study. Patients will need to return the next day to GCRC on Harkness 10 to fill out the questionnaire, have CO breath measured, serum nicotine and cotinine levels drawn and to have a flexible sigmoidoscopy and rectal biopsies.

H. Confidentiality of study data

All study data will be coded and stored in a secure location which will be accessible only to investigators. All data will be reported anonymously.

I. Location of study

CPMC. Patients will be evaluated in the outpatient clinic of the Irving Center, Harkness Pavilion 10. Signioldoscopies will be performed at Presbyterian Hospital, 12th floor

J. Risks and benefits

The risks are few. There may be unpleasant side effects of nicotine such as headaches, nausea, dizziness, vomiting or contact dermatitis. Also there are risks generally involved in flexible siginoidsocopies which include perforation and bleeding. All patients with active disease would need to have this test done even if they were not enrolled in the study. The benefits would be possibly a reduction in length of disease activity and length of steroid use.

I. Alternative therapies

Alternative therapies would include 6 -mercaptop urine, methotrexate, and cyclosporin and would be available to the patient if the patient so desires.

J. Compensation

The flexible sigmoidoscopies in this study would be covered most likely under the patient's insurance. If the siginoidoscopies are not covered under their insurance it will be done for free. The clinic visits will also be free.

K. Minors and research

No subjects will be included under the age of 18.

L. Radiation and radioactive substances

No radiation or radioactive substances will be used.

M. References

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