Testing Nicotine Gum for Ulcerative Colitis Patients
Experience with Single-Patient Trials

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Epidemiologic studies have documented an association between nonsmoking and ulcerative colitis and case reports have demonstrated that symptoms improve with smoking and worsen with removal of a nicotine source. A double-blind randomized crossover trial for individual ulcerative colitis patients (single-patient trial, or N of 1 clinical trial) was designed to study the safety, patient acceptance, and the effectiveness of nicotine gum in improving patient symptoms and proctoscopic appearance of involved colon. Seven nonsmoking patients chewed up to 10 squares/day (20 mg) of nicotine gum or placebo gum for two weeks. Therapy was crossed-over every two weeks over the eight-week trial. Effectiveness was judged from comparisons between nicotine-gum and placebo-gum periods of patient self-reported symptoms at the conclusion of each two-week period using visual analog scales and proctoscopic appearance using ordered categorical scales. Three of seven patients, all three of whom were former smokers, demonstrated sufficient improvement without adverse effects to warrant institution of nicotine gum into their drug treatment regimens. Three patients demonstrated an uncertain response, despite tolerating the drug, and have not had nicotine gum added to their regimens. One patient could not tolerate the medication and was withdrawn from the study. No serious side effects were noted. We conclude that a randomized trial for an individual patient is a useful method for evaluating treatment regimens for ulcerative colitis and that nicotine gum may be effective therapy for individual patients with ulcerative colitis who demonstrate an objective response with few adverse effects.

KEY WORDS: nicotine gum; ulcerative colitis; single-patient trials.

Several epidemiologic studies have documented an association between nonsmoking and ulcerative colitis (1-12). In these studies ulcerative colitis patients have been compared to hospital controls (Crohn's disease, irritable bowel syndrome, fracture clinic), or community controls (health care registries, Mormons). There have been methodologic criticisms of several studies (13-15), but the consistency of the observation lends credence to the overall result. Ulcerative colitis patients are less likely to be current smokers, are less likely to have ever smoked, and are less likely to have been exposed to tobacco before disease onset. The opposite effect is seen in Crohn's disease where patients are more likely to smoke than controls (4, 5, 7, 16, 17).

There have been interesting reports of individual patients whose symptoms of ulcerative colitis have
improved with institution or resumption of smoking, or with institution of nicotine-containing chewing gum (18–21). Disease activity has been known to flare when a nicotine source was removed and to improve when it was reinstituted. For some ulcerative colitis patients, nicotine may be an additional therapeutic maneuver.

This study was aimed at evaluating possible effectiveness, safety, and tolerance of nicotine chewing gum for therapy of individual patients with mildly to moderately active ulcerative colitis. The study design was that of a series of randomized clinical trials for individual patients (single-patient trial, or N of 1 clinical trial (22, 23).

MATERIALS AND METHODS

Study Design. The study was designed to test the efficacy, short-term safety, and patient acceptance of nicotine chewing gum in individual patients. Nonsmokers with ulcerative colitis willing to participate were randomized to receive nicotine gum or placebo gum for a two-week interval in a double-blind fashion. A two-week treatment period was chosen since it was felt to be the maximum length of time that a patient would tolerate continuing symptoms of ulcerative colitis during placebo therapy or during ineffective nicotine-gum therapy. Therapy was crossed over every two weeks for the duration of the eight-week study, and patients were assessed for symptomatic and proctoscopic response. It was not felt that a washout period was necessary since evaluation was done at the end of each two-week period, long after the effect of nicotine gum had worn off. The study was approved by the University of Chicago Clinical Investigation Committee.

Patients. Currently nonsmoking patients older than 18 years of age with mildly to moderately active ulcerative colitis as documented by typical symptoms of hematochezia and diarrhea, negative stool cultures, and typical proctoscopic findings such as superficial ulcerations, distorted mucosal vascular pattern, granularity, and exudate were eligible for the study. Mildly to moderately active disease was defined as disease not requiring blood transfusion, hospital admission, or imminent surgery. Patients were clinically stable and on a stable dose of corticosteroids and/or sulfasalazine for two weeks prior to entry.

Patients with a known adverse reaction to nicotine; a history of coronary artery disease, angina pectoris, myocardial infarction, atrial fibrillation, peptic ulcer disease; dentures; or women who were pregnant or attempting to conceive were excluded from the study. Any patient with acute or unstable concomitant illness that may have interfered with evaluation of the effects of therapy on symptoms were excluded. A previous smoking habit was not a reason for exclusion.

Patients were withdrawn from the study for deterioration of symptoms or signs, or for mucosal appearance to the point where the patient’s physician felt it was unsafe to continue. Patients were withdrawn for failure to refrain from smoking, or for intolerance to or allergy from therapy.

Therapy. After informed consent was obtained, patients were randomly allocated, using a random number table, to receive nicotine gum or placebo gum. Nicotine gum was supplied by the Merrell Dow Pharmaceutical Co. as Nicorette. Each piece of chewing gum contained 2 mg of nicotine. The placebo gum, also supplied by Merrell Dow, was identical to the active drug in appearance and taste. It consisted of chewing gum containing 1 mg of nicotine with reduced biologic availability due to the lack of an alkaline buffer.

Therapy was administered in a double-blind fashion and the code was not broken until a patient completed or was withdrawn from the study. At the end of each two-week period, therapy was crossed-over until completion of the eight-week protocol or patient withdrawal.

Patients were advised to begin with two squares per day and to titrate the dose to symptoms of the disease or to side effects up to a maximum of 20 mg/day (10 squares/day). Patients were asked to record the number of squares chewed in a day. They were advised to take 15 chews, wait 1 min, then take 15 more chews. They were then advised to chew slowly and intermittently for 30 min. If symptoms of intolerance developed, they were asked to chew more slowly or to contact the physician for possible withdrawal from the study.

It was requested that any medication used for the treatment of ulcerative colitis (ie, prednisone or sulfasalazine) remain at stable doses for the duration of the study. If the patient’s physician determined that a dose change was indicated, patients were to be withdrawn from the study.

Evaluation. During the course of the study, the patient was evaluated every two weeks for symptomatic response, proctoscopic appearance, and any adverse reactions.

Symptomatic response was judged from a series of visual analog scales with each variable ranging between zero and 100 based on anchoring words. For consistency of bowel movements, zero was “formed” and 100 was “watery”; for hematochezia, zero was “never” and 100 was “always”; for abdominal pain, zero was “absent” and 100 was “severe”; and for general sense of well being, zero was “completely better” and 100 was “much worse.” Number of bowel movements per day was quantified.

All proctoscopic evaluations were performed by a single investigator (B.A.L.) without knowledge of the patient’s treatment, symptomatic response, or previous proctoscopic examinations. At each proctoscopy, four categories were graded with ordered categorical scales. The findings and categories were: friability (0, none to cotton swabbing; 1, pinpoint hemorrhagic spots with swabbing; 2, oozing blood with cotton swabbing; 3, spontaneous bleeding without cotton swabbing); mucosal surface texture (0, glistening or “frosted glass”; 1, fine granularity with small, shallow ulcerations; 2, coarse granularity with extensive ulcerations; 3, course pitting and denuded areas); edema (0, normal vascular pattern and valves distinct; 1, vessels occasionally visible and valves indistinct; 2, no superficial vessels visible and...