High dose transdermal nicotine therapy for heavy smokers: safety, tolerability and measurement of nicotine and cotinine levels

Abstract

Transdermal nicotine has been shown to relieve nicotine withdrawal and to double smoking cessation rates compared to placebo in clinical trials. A 21 or 22 mg/day dose provides a steady state serum nicotine that is less than obtained from smoking. Limited information is available about higher nicotine patch doses. To define better the optimal dosing of nicotine patch therapy, we undertook an open-label study to determine the safety and tolerability of 44 mg/day dose for smoking cessation in subjects smoking ≥ 20 cigarettes per day. Forty smokers received 44 mg/day of transdermal nicotine for 4 weeks followed by 4 weeks of 22 mg/day. Of the 40 subjects enrolled, 38 (95%) completed the 4 weeks of 44 mg patch therapy and 36 (90%) completed the entire 8 weeks of patch therapy. Non-smokers at week 4 had a mean serum nicotine level of 23.4 ± 11.7 ng/ml and cotinine of 152.2 ± 87.3 ng/ml. Percent replacement was calculated by dividing the steady state level at week 4 by the baseline level while the subjects were smoking their usual number of cigarettes. Percent nicotine replacement for non-smokers at week 4 (while on 44 mg nicotine patch) averaged 158% ± 108.4%, and for cotinine was 112.0 ± 73.8. For nicotine, 33% of non-smokers at week 4 had ≤ 100% nicotine replacement and for cotinine 63% ≤ 100% replacement. Biochemically confirmed point prevalence smoking cessation rates were 65% and 55% at weeks 4 and 8 of patch therapy, respectively, and self-reported smoking cessation at 3 months was 50%. The most common effect was skin irritation at the patch site. A single subject was admitted for myocardial infarction following step-down from 44 to 22 mg of replacement nicotine. The subject was not smoking and the adverse event was deemed to be not related to the patch therapy. Sleep complaints were reported in 33% of subjects during the 44 mg phase. Other complaints were infrequent. We conclude that 44 mg per 24-h nicotine patch therapy in heavy smokers is safe, tolerable, and without significant adverse events.

Key words

High dose transdermal nicotine therapy · Smoking cessation

Introduction

Transdermal nicotine patch therapy has been shown in multiple studies to increase smoking cessation rates and to decrease withdrawal symptoms (Abelin et al. 1989; Hurt et al. 1990, 1994; Tonnesen et al. 1991; Transdermal Nicotine Study Group 1991; Sachs et al. 1993; Fiore et al. 1992, 1994). Short-term efficacy has ranged from a low of 18% at 3 weeks (Rose et al. 1990) to a high of 77% at 6 weeks (Hurt et al. 1990; Buchkremer et al. 1991) with most studies showing end-of-treatment abstinence rates of 40–60% after 6–12 weeks of therapy (Daughton et al. 1991; Tonnesen et al. 1991; Transdermal Nicotine Study Group 1991). Approximately half of smokers assigned to active patch fail to achieve abstinence during treatment.

Presently heavier smokers (≥ 20 cigarettes per day) are usually prescribed a 21 or 22 mg daily dose of nicotine replacement. However, this dose provides a steady state venous serum nicotine that is substantially less than levels obtained from smoking (Hurt et al. 1993). Only 33% of abstinent subjects on a daily 22 mg nicotine active patch had complete venous nicotine
We have shown that higher end-of-treatment stop rates number of cigarettes (Hurt et al. 1994). This indicates patch groups had a higher cessation rate than placebo.

nicotine patch therapy. In one multi-site study, smoking cessation outcome was related to dosing with the nicotine patch where the 21 mg patch was found to be more effective than 14 mg of daily nicotine (Transdermal Nicotine Study Group 1991). Both active patch groups had a higher cessation rate than placebo. We have shown that higher end-of-treatment stop rates are found in subjects on a 22 mg active patch who had lower serum nicotine levels while smoking their usual number of cigarettes (Hurt et al. 1994). This indicates the improbability that a single dose of transdermal nicotine will be adequate for all smokers and that higher doses may be important in initiating abstinence.

There have been few studies of dosages beyond 21 or 22 mg nicotine per day. In order better to define the optimal dosing of nicotine patch therapy, the present study was undertaken to determine the safety and tolerability of 44 mg per day of transdermal nicotine when used as an aid for smoking cessation in subjects smoking ≥20 cigarettes per day. Venous nicotine and cotinine levels were obtained for each subject under each treatment condition. This study was approved by the Mayo Institutional Review Board.

Materials and methods

A total of 40 smokers seeking smoking cessation were enrolled at Mayo Clinic Jacksonville in this open label, outpatient, 8-week study. Potential participants responding to a news release and screened for inclusion by telephone. Those who passed this screen were invited to an information session and to have a physical examination prior to entry into the study. All subjects gave informed consent prior to participation. Subjects were instructed not to change their smoking behavior before their prescreening venipuncture. Inclusion criteria were: the subjects were in good health as verified by a physician, age 20–65 years, and smoked ≥20 cigarettes per day for the past year. Exclusion criteria were: a recent history of significant cardiovascular disease, current substance abuse as determined by clinical history and a self-administered alcoholism screening test (SAAST) (Hurt et al. 1980), current psychiatric disorder, severe skin allergies, at risk for pregnancy, and present use of tobacco products other than cigarettes or having ever received transdermal nicotine patch therapy. Subjects currently (within past 30 days) using medications that might have an effect on smoking cessation (clonidine, buspirone, doxepin, and fluoxetine) were also excluded.

A physician investigator assisted each subject in setting a stop date. Each subject was provided the National Cancer Institute (NCI) self-help booklet, "Clearing the Air". All subjects were assigned to a 44 mg dose (two 22 mg nicotine patches) of transdermal nicotine per day for 4 weeks followed by 4 weeks of 22 mg per day. The subjects were instructed to change patches and rotate sites daily.

Smoking status based on the subjects' self-report in their daily diary was reviewed at weekly visits with a study nurse. The diary also contained the Hughes-Hatsukami Withdrawal Questionnaire (Hughes and Hatsukami 1986). Self-reported abstinence was considered confirmed if the expired CO level was ≤8 ppm at the weekly visit. Brief counseling was provided by the nurse to each subject during these 30-min visits, and subjects who had not achieved abstinence from cigarettes were encouraged to set a new stop date. Serum nicotine and cotinine levels were determined at prescreening, week 4 and week 8 of patch therapy. Information about adverse events was by non-specific or general questions from the nurse.

Results

Table 1 shows the demographic information on all 40 study subjects. As can be seen in this table, the subjects were heavy smokers with a mean smoking rate of 32.4 cigarettes per day, a mean of 28.8 years of smoking, and a mean Fagerstrom score of 7.3 (Fagerstrom 1978). Of the 40 subjects enrolled, 38 (95%) completed the 4 weeks of 44 mg patch therapy and 36 (90%) completed the entire 8 weeks of patch therapy. The four subjects who dropped out of the study did so for non-patch-related reasons (i.e., one heart attack and three noncompliance). The remainder of the subjects wore the patches as prescribed.

Table 2 summarizes the serum nicotine levels at prescreening (while smoking and before receiving patch therapy) and the levels at week 4 and week 8 for the overall group, those who reported smoking, and those who were biochemically confirmed not to be smoking. Subjects who reported not smoking who were not biochemically confirmed were counted as smokers. Subjects who did not self-report smoking status are included only in the overall statistics. Also displayed is the percent replacement for week 4 and week 8 which expresses the week 4 or 8 nicotine level as a percentage of the prescreening level. At the bottom of Table 2 are categorical presentations of these findings. Table 3 is a similar display for serum cotinine. Blood samples were collected and analyzed for all but four subjects.

Change in the mean withdrawal score from baseline was determined from the Hughes-Hatsukami Questionnaire reported by subjects in their daily diaries. The following symptoms are included in the questionnaire: anger, anxiety, awakening, concentration, depression, hunger, impatience, and desire to smoke. Subjects rated these items as none (0), slight (1), mild (2), moderate (3), or severe (4). At baseline, while smoking their usual number of cigarettes, the mean score ± SD was 0.73 ± 0.30 for all 40 subjects. Apart from the first 2 days on patch therapy, the change in mean withdrawal scores was on average quite minimal.

The most common adverse event reported by the study subjects was skin irritation at the patch site. The reactions were graded as erythema only, erythema with edema, erythema with vesicles, and bullae/erosions. The percentage of subjects reporting as their worst skin reaction was 15.0, 5.0, and 2.5% in the above