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Nicotine percentage replacement among smokeless tobacco users with nicotine patch

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Abstract

To obtain preliminary evidence on the safety and efficacy of high dose nicotine patch therapy among smokeless tobacco (ST) users who consume ≥3 cans of ST per week, we conducted a randomized, placebo-controlled clinical trial with 42 ST users randomized to nicotine patch doses of 21, 42, and 63 mg/day or placebo. Serum nicotine concentrations were measured during *ad libitum* ST use and nicotine replacement therapy, and percentages of nicotine replacement were calculated. We observed substantial inter-subject variability in nicotine concentrations with *ad lib* ST use. The mean percentage replacement of *ad lib* ST use serum nicotine concentrations approximated 100% with the 42 mg/day patch dose (mean ± S.D., 98.4% ± 45%). Dosing with the 21 mg/day nicotine patch was associated with mean "under-replacement" (53.2% ± 17.1%), and the 63 mg/day nicotine was associated with mean "over-replacement" (159.2% ± 121.9%). We observed symptoms of nausea consistent with nicotine toxicity in two subjects in the 63 mg/day group while no subjects in the 42 mg/day reported these symptoms. We conclude that the use of 42 mg/day nicotine patch therapy is safe and should be considered as initial therapy in the clinical setting among ST users who use ≥3 cans/week.

Keywords: Smokeless tobacco; Tobacco use cessation; Tobacco alkaloid; Nicotine; Administration; Cutaneous; Randomized clinical trial

1. Introduction

Smokeless tobacco (ST) produced in the United States is estimated to be the greatest exogenous source of human exposure to carcinogenic nitrosamines (National Toxicology Program, 2006). ST use has been reported to be associated with active periodontal disease (Fisher et al., 2005) and death from cardiovascular disease, cerebrovascular disease and cancer (Henley et al., 2005). However, the risks associated with ST may vary depending upon the type of ST used, such as snuff and chewing tobacco in the United States, snus in Sweden, and other oral tobacco preparations in India and Africa (Critchley and Unal, 2003; Foulds et al., 2003). A need for efficacious interventions exists as 64% of ST users in the US report the desire to quit (Severson, 1992).

Previous research with cigarette smokers has suggested that moderate and heavy smokers experience nicotine "under-replacement" with standard dose nicotine patch therapy (up to 22 mg/day) (Lawson et al., 1998). Nicotine "under-replacement" with standard dose nicotine patch therapy may also occur among ST users. Clinical trials assessing the efficacy of the nicotine patch for ST users in doses of 15 mg/day (Howard-Pitney et al., 1999) and 21 mg/day (Hatsukami et al., 2000) have failed to increase long-term (≥6 months) tobacco abstinence rates in ST users despite the fact that it has been shown to decrease craving and nicotine withdrawal symptoms. "Under-replacement" of serum nicotine concentrations among ST users receiving standard doses of nicotine patches may explain the disappointing treatment efficacy results.

We conducted a randomized, double-blinded placebo-controlled clinical trial in order to obtain preliminary evidence of safety and efficacy of higher dose nicotine patch therapy among ST users consuming ≥3 cans (1 can equals ∼ 34 g of moist ground tobacco) per week. We randomized 42 ST users to nicotine patch doses of 21, 42, or 63 mg/day or placebo. We evaluated whether standard dose nicotine patch therapy resulted in "under-replacement" of serum nicotine concentrations and if higher doses of nicotine patches would increase the percentage replacement of serum nicotine concentrations. The overall

Abbreviations: ST, smokeless tobacco; NRT, nicotine replacement therapy

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study design and findings from the efficacy analyses have been reported (Ebbert et al., in press). In the current report we present the serum nicotine concentrations and percentage replacement achieved with varying doses of nicotine patch therapy among ST users.

2. Methods

2.1. Participants

The Mayo Foundation Institutional Review Board (IRB) and the US Food and Drug Administration reviewed and approved the study protocol prior to recruitment and enrollment. Subjects were recruited from the community surrounding the Mayo Clinic in Rochester, MN between November 2003 and October 2004. Individuals interested in stopping ST were recruited through press releases and local advertisements.

Eligible subjects were required to be ≥18 years of age, in good general health, have used ST daily for the past year, and be using ≥3 cans/pouches per week at the time of enrollment. The cutoff of at least 3 cans/pouches per week was selected to ensure subject safety considering that the use of nicotine patch doses up to 63 mg/day in ST users had only been previously reported in a case series (Ebbert et al., 2004b).

2.2. Procedures

Details of the study have been previously reported (Ebbert et al., in press). This study was divided into three phases: an outpatient preadmission phase (phase I), an inpatient General Clinical Research Center (GCRC) phase (phase II), and an outpatient treatment and follow-up phase (phase III). We are reporting the serum nicotine data and patient experience during the inpatient phase (phase II).

Phase II consisted of a 3-day hospital stay at the Mayo GCRC. The purpose of this phase was to ensure subject safety and to allow close monitoring. Patients were admitted the evening before GCRC day #1.

On GCRC day #1, subjects used ST *ad libitum* and blood was drawn for serum tobacco alkaloids at 0800 and 1600 h. On GCRC day #2, subjects were randomly assigned to 1 of 4 groups in a blinded fashion to nicotine patch doses of 21, 42, or 63 mg/day or placebo. Each subject wore three patches simultaneously allowing for blinded removal of nicotine patches if nicotine toxicity developed. We used a nicotine toxicity questionnaire used in previous trials (Dale et al., 1995) modified for ST users collected every evening on an electronic diary. Subjects experiencing symptoms of severe nicotine toxicity removed patches which were replaced later if tolerated.

On GCRC days #2 and #3, blood samples were obtained before patch application which occurred at 0800 h. A blood sample was also obtained at 1600 h. Patients were dismissed after the afternoon blood draw on GCRC day #3. Tobacco alkaloid concentrations in blood serum were quantified using tandem mass spectrometry (Moyer et al., 2002).

2.3. Statistical analysis

Serum nicotine concentrations obtained at 1600 h during *ad lib* ST use on GCRC day #1 were used as the denominator for the calculation of percentage replacement. This timing is based upon the half-life of nicotine (2 h) and the observations that steady-state serum nicotine concentrations are achieved by this time of day in regular tobacco ST users (Benowitz et al., 1989).

The serum nicotine concentrations obtained during nicotine patch use at 1600 h on GCRC day #3 were used to represent steady-state concentrations for the given patch dose. The 1600 h time point was selected based upon the pharmacokinetics of the nicotine patch and observations that peak serum nicotine concentrations are generally achieved within 9 h with repeated patch administration, although substantial inter-individual variability exists (Gupta et al., 1995).

We used the serum nicotine concentrations rather than cotinine to calculate percentage replacement based upon our previous work suggesting that cotinine concentrations correlate with the frequency of swallowing tobacco juice in ST users and, therefore, should not be used when guiding treatment decisions such as nicotine replacement therapy (Ebbert et al., 2004a). Percentage nicotine replacement with the nicotine patch is a percentage determined by calculating the ratio of the serum nicotine concentrations achieved with the nicotine patch and the concentration observed with *ad lib* ST use (serum nicotine concentrations on nicotine patch/serum nicotine concentration with *ad lib* ST use × 100%) Data are summarized separately for each patch dose using mean ± S.D. and median (25th, 75th percentile).

3. Results

3.1. Subjects

All of the 42 enrolled subjects were male with a mean age (±S.D.) of 35.7 ± 7.5 (range 20–56) years who used an average of 5.9 ± 2.9 cans/week for 17.0 ± 7.3 years. All subjects used snuff (loose, moist ground tobacco) at an average rate of 12.5 ± 7.3 dips per day which they kept in their mouths for an average of 52.1 ± 33.1 min. The mean body mass index (BMI) was 30.4 (S.D. 5.2; median 31.1; range 19.9–41). Eighty-three percent ($N = 35$) had made one or more serious quit attempts prior to study entry. Forty-one were Caucasian, one was of Asian descent, and 76% were married.

3.2. Serum nicotine and cotinine concentrations

Serum nicotine concentrations measured at 0800 h during *ad lib* ST use during GCRC day #1were lower compared to those measured at 1600 (paired t-test, $p < 0.001$). Serum nicotine concentrations in the morning (0800 h) had a mean ± S.D. of 22.3 ± 16.2 ng/mL (median 20.5, range 2.6–80.0, $N = 42$) and in the evening (1600 h) 37.9 ± 17.6 ng/mL (median 37.0, range 8.1–95.0, $N = 40$).

During the nicotine patch phase (GCRC days #2 and #3), serum nicotine concentrations were correlated with patch dose, with higher nicotine patch dose associated with higher median serum nicotine concentration (Fig. 1).

3.3. Percentage replacement by nicotine patch dose

Nicotine concentrations measured during *ad lib* ST use were comparable across the three dose groups (Table 1). The mean

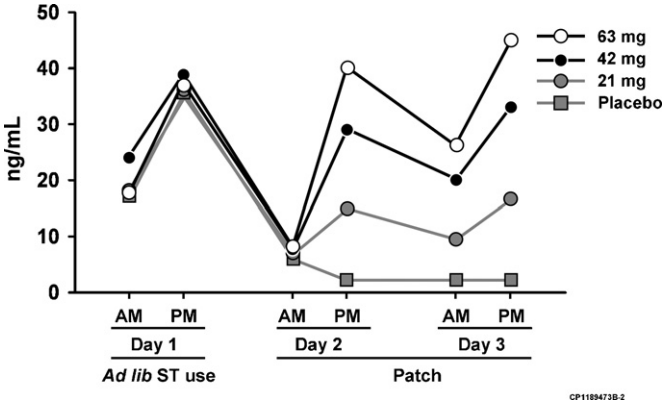

Fig. 1. Median serum nicotine concentrations by nicotine patch dose among 42 ST users in a phase II pilot study of high dose nicotine patch therapy.