Original Contributions

Cardiovascular Effects of Transdermal Nicotine in Mildly Hypertensive Smokers

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Smoking potentiates the enhanced cardiovascular risk of hypertensive patients. Although nicotine replacement therapy is safe when used by healthy individuals to quit smoking, there is no evidence that nicotine replacement therapy is safe in hypertensive smokers. In this crossover, single-blinded, placebo-controlled study, we compared for 4 h the acute effects of transdermal nicotine on the mean arterial pressure (MAP) and heart rate (HR) of mildly hypertensive smokers treated with hydrochlorothiazide with the responses in normotensive smokers and non-smokers monitored with Finapres and ambulatory blood pressure systems. The plasma concentrations of thromboxane B2 (TXB2, the stable breakdown product of TXA2) were also measured by ELISA to assess whether transdermal nicotine acutely affects TXA2 production. The use of 21-mg nicotine patches increased the MAP and HR in nonsmokers (from 94 ± 4 mm Hg and 69 ± 3 beats/min to 117 ± 7 mm Hg and 83 ± 3 beats/min, respectively; \( P < .05 \)) as well as the MAP in normotensive smokers (from 83 ± 4 to 106 ± 7 mm Hg; \( P < .05 \)). However, MAP and HR remained unaltered in hypertensive smokers after transdermal nicotine. Higher basal TXB2 levels were observed in hypertensive smokers compared with normotensive smokers and nonsmokers (2019 ± 402 v 670 ± 167 and 556 ± 68 pg/mL, respectively; \( P < .05 \)). Transdermal nicotine increased the TXB2 levels only in nonsmokers (\( P < .05 \)). These data indicate that the use of transdermal nicotine in mildly hypertensive smokers is probably safe. Further studies involving other classes of hypertensive patients are warranted. Am J Hypertens 2001;14:610–614 © 2001 American Journal of Hypertension, Ltd.

Key Words: Nicotine, arterial hypertension, smoking, thromboxane, blood pressure.

Smoking is an important factor for cardiovascular morbidity and mortality and is associated with an increased risk of peripheral arterial disease, coronary heart disease, and sudden death.1 Several studies have demonstrated that smoking may cause endothelial injury leading to an impairment of endothelial function2 and accelerated atherogenesis.3 Cardiovascular morbidity and mortality are also potentiated when smoking and hypertension are associated.1

Nicotine is the main compound responsible for the addictiveness of tobacco. Nicotine replacement therapy (NRT) using chewing gum, nasal sprays, buccal inhalers, and transdermal patches is partially effective when used as a part of a strategy for smoking cessation.4 However, there is concern regarding the efficacy and the prevention of relapse after NRT, with higher doses of nicotine increasing the smoking cessation rates.5–7 Although other medications and a combination of two or more methods for providing nicotine have been proposed,8 nicotine by itself has been the mainstay of pharmacotherapy for tobacco addiction.9

Although NRT is apparently safe in healthy individuals,10 the same may not be true in patients with cardiovascular disease. A previous study found no exacerbation of ischemic heart disease with the use of nicotine patches,11 but two cases of myocardial infarction were reported in patients using 21-mg nicotine patches.12,13 In another study with hypertensive smokers, 1 patient of 10 with angiographically proven coronary artery disease reportedly developed an increase in systolic blood pressure to 180 mm Hg during nicotine patch use.14

In this study, we examined the acute effects of transdermal 21-mg nicotine patches on the arterial pressure and heart rate of hypertensive smokers. We also measured the
plasma concentrations of thromboxane B2 (TXB₂, the stable breakdown product of TXA₂) to assess whether transdermal nicotine acutely affects the production in vivo of TXA₂, a potent vasoconstrictor with platelet-aggregating actions that is involved in a number of cardiovascular conditions. Increased urinary excretion of TXB₂ has been described in healthy men after cigarette smoking, but it is not known whether NRT affects TXA₂ production in hypertensive smokers.

**Methods**

**Subjects**

This study was approved by this institution’s Ethics Committee and each subject provided written informed consent. Three groups of subjects were studied (n = 9 to 10/group): normal healthy nonsmokers volunteers (control group), normotensive smokers, and mildly hypertensive smokers who were on hydrochlorothiazide (25 mg/day) as antihypertensive pharmacotherapy. Nonsmokers and normotensive smokers were recruited from the general public, whereas hypertensive smokers were recruited from our hospital clinic. The volunteers provided a complete health history and underwent a physical examination, an electrocardiogram and laboratory analysis to exclude individuals with dyslipidemia, diabetes mellitus, and evidence of hepatic, renal, or hematologic dysfunction.

**Study Protocol**

The study had a placebo-controlled, crossover, single-blinded design. The subjects were admitted to the university hospital on two different days for a 4-h study. Smokers were asked to maintain the number of cigarettes usually consumed before the study period. Expired carbon monoxide (COexpired) was determined using a CO monitor (Bedfont Scientific Limited, Rochester, UK) immediately before the study. An indwelling venous catheter was inserted for blood sample collection and the subjects remained supine thereafter. Subjects were randomized to treatment with either transdermal 21-mg nicotine patch (Nicoderm; Alza, Palo Alto, CA) or placebo after they had remained supine for at least 30 min.

**Noninvasive Blood Pressure Monitoring**

Beat-to-beat, noninvasive finger mean arterial pressure (MAP) and heart rate (HR) were monitored with a Finapres 2300 device (Ohmeda, Englewood, CO). Briefly, this device, which is based on the arterial volume clamp method, measures blood pressure through a small finger cuff wrapped around the middle finger of the hand. The MAP and HR values were recorded every 10 sec throughout the study period. The average values recorded during 5 min around predetermined time points were used to compare the MAP and HR results. Simultaneously, an ambulatory blood pressure system (SpaceLabs Medical, Inc., Redmond, WA) was used to check the Finapres measurements every 5 min.

**Measurement of Plasma TXB₂**

Venous blood samples (10 to 15 mL) were collected into tubes containing EDTA at baseline and 30 min, 1 h, and 4 h after the nicotine (or placebo) patch administration. The plasma was separated by centrifugation and stored at −20°C until assayed. Plasma samples were extracted using C18 reverse-phase cartridges (Waters Co., Milford, MA) and the TXB₂ levels were determined using a commercial enzyme immunoassay (Cayman Chemical Co., Ann Arbor, MI).

**Statistical Analysis**

The results were expressed as means ± SEM. Baseline MAP, HR, and TXB₂ levels were compared using one-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls’s test. The changes in MAP, HR, and TXB₂ levels from baseline values within each group were analyzed using one-way analysis of variance (ANOVA) for repeated measures followed by Dunnet’s test. A probability value < .05 was considered the minimum level for statistical significance.

**Results**

**Characteristics of the Study Groups**

Table 1 summarizes the basic characteristics of the study subjects. There was no significant difference in the age,
weight, years of tobacco use, number of cigarettes/day, and Fagerström score between normotensive and hypertensive smokers. These results were derived from a questionnaire generally used to assess addiction to smoking.

**Arterial Blood Pressure Recordings**

Data from the Finapres system showed similar changes as compared with those from the ambulatory blood pressure system and were used for the analysis of MAP and HR responses. Hypertensive smokers had higher baseline MAP values compared with normotensive smokers ($P < .05$), but there were no differences in the baseline HR values (Fig. 1). The use of a placebo patch did not change the MAP and HR in the three experimental groups (Fig. 1). In the control group, the MAP and HR increased 30 to 60 min after initiating the use of the patch (Fig. 1). This increase in MAP and HR was accompanied by nausea, lightheadedness, mild headache, and sweating in most control subjects, thus precluding the experiments from continuing for much more than 1 to 1.5 h in this group. Curiously, the MAP increased ($P < .05$) after the use of transdermal nicotine for 2 h in normotensive smokers, whereas there were no changes in the MAP values in hypertensive smokers after use of the nicotine patch for 4 h (Fig. 1). Although transdermal nicotine had different effects on the MAP of the two groups of smokers, there were no effects on the HR in either group (Fig. 1).

**Plasma TXB$_2$ Levels**

Hypertensive smokers had higher ($P < .05$) basal TXB$_2$ levels compared with the controls and normotensive smokers (Fig. 2). Treatment with the placebo patch did not alter the plasma TXB$_2$ levels in the three experimental groups (Fig. 2). The use of transdermal nicotine for 1 h increased ($P < .05$) the TXB$_2$ concentrations only in the control group; no changes were observed in either group of smokers throughout the study period (Fig. 2).

**Discussion**

The use of 21-mg nicotine patches in this study did not increase the MAP and HR in mildly hypertensive smokers on hydrochlorothiazide pharmacotherapy, but did increase the MAP in normotensive light smokers. In addition, transdermal nicotine did not change the circulating levels of TXB$_2$ in normotensive and hypertensive smokers, although hypertensive smokers had higher plasma concentrations of this eicosanoid than normotensive smokers.
In addition to oxidant gases from smoke, nicotine apparently has an important role in the cardiovascular effects of smoking because it interacts with the endothelium\(^{19}\) to decrease endothelium-dependent vasodilatation\(^{20}\) and thus, may contribute to the atherosclerosis associated with smoking.\(^{21}\) Notably, smoking cessation reverses smoking-induced endothelial dysfunction\(^{3}\) and this fact may underlie the dramatic reduction in the risk of cardiovascular mortality after quitting smoking.

The increased MAP and HR observed in nonsmokers resulted from the sympathomimetic actions of nicotine\(^{22}\) and these effects have raised concerns regarding the safety of nicotine use, especially in patients with cardiovascular diseases.\(^{11,23}\) As part of its complex cardiovascular effects, nicotine increases the HR and MAP by stimulating the central nervous system and autonomic ganglia, and by eliciting the release of noradrenaline from sympathetic nerve endings and the discharge of adrenaline from the adrenal medulla.\(^{24}\)

The safety of high-dose transdermal nicotine has been evaluated in a study with healthy men focused on the dose-related effects in healthy men.\(^{10}\) No significant changes in the heart rate or blood pressure were observed with increasing doses of nicotine (up to 63 mg/day) or with combined transdermal nicotine and smoking compared with nicotine alone, suggesting that the treatment of heavy smokers with high-dose transdermal nicotine is safe.\(^{10}\) In line with these findings, nicotine patches produced only minor disturbances of autonomic regulation.\(^{25}\) However, these studies involved only healthy smokers and no previous study has really provided evidence that NRT is safe in hypertensive smokers.\(^{26}\)

The increased levels of TXB\(_2\) in hypertensive smokers compared with normotensive smokers or nonsmokers may reflect an increased platelet activation\(^{16}\) in this group. Because platelet activation is an initiating event for intimal hyperplasia,\(^{27}\) this finding may help explain the augmented cardiovascular risk in hypertensive smokers. Together, the stable MAP, HR, and plasma levels of TXB\(_2\) in hypertensive smokers after the use of transdermal nicotine strongly suggest that NRT does not further increase their cardiovascular risk. Specifically, the TXB\(_2\) levels remained stable in normotensive smokers after nicotine patch exposure, a similar response to that observed in hypertensive smokers. The unaltered TXB\(_2\) levels in normotensive smokers suggest that exposure to transdermal nicotine does not adversely affect platelets in this group. This finding agrees with a previous study demonstrating unaltered urinary excretion of TXB\(_2\) in healthy smokers treated with 21-mg nicotine patches, although the excretion of TXB\(_2\) increased in the same individuals after smoking.\(^{16}\)

Smokers have enhanced TXB\(_2\) formation.\(^{28}\) In this study, the similarities between normotensive smokers and nonsmokers included comparable basal TBX\(_2\) levels and increased MAP values after the use of transdermal nicotine. These similarities, which differ from those previously reported,\(^{28}\) may have occurred as a result of the relatively small number of cigarettes smoked per day by normotensive smokers.

An intravenous infusion of nicotine for 30 min in healthy nonsmokers was not accompanied by a significant release of TXA\(_2\).\(^{29}\) In agreement with this finding, we observed stable TXB\(_2\) levels in nonsmokers 30 min after the nicotine patch was applied. However, the TXB\(_2\) levels increased significantly after 1 h of nicotine patch use. This response may reflect the gradual increase in serum nicotine levels when patches are used.\(^{30}\) Also, we do not know to which extent some turbulence during blood drawing might have affected platelets and measured TXB\(_2\) levels.

Although these findings must be confirmed by further studies, they strongly suggest that light smokers tend to present cardiovascular responses to transdermal nicotine that parallel those of nonsmokers, thereby making light smokers prone to increases in MAP associated with NRT. On the other hand, possible nicotine receptor down-regulation could explain the absence of an increase in blood pressure in hypertensive smokers.

Some relevant aspects need to be commented on when analyzing these results. First, the effects of NRT were studied for only 4 h mainly because prolonged measurement of MAP with Finapres leads to discomfort. Thus, the...
cardiovascular effects of transdermal nicotine were not evaluated when the rate of nicotine absorption is maximal, normally 6 to 12 h after the patch is applied. In addition, the effects of nicotine on blood pressure may not be sustained because of the development of tolerance. Second, the hypertensive smokers were on hydrochlorothiazide pharmacotherapy for hypertension and NRT may interact differently with other antihypertensive agents. Third, the responses to transdermal nicotine found in mildly hypertensive smokers may not be the same as those found in moderate/severe hypertensive smokers or in heavy smokers. Finally, a venous catheter was kept in place for 4 h for blood sampling and plasma TXB₂ levels determination. Although the presence of the catheter itself can activate platelets and affect TXB₂ concentrations, this effect was probably minimized by the volume of sample that was drawn (10 to 15 mL) in this study.

Despite these limitations, our results indicate that transdermal nicotine is safe for short-term exposure in mildly hypertensive smokers. Further studies involving other classes of hypertensive patients are warranted to extend these conclusions.

Acknowledgments

The authors thank Joaquim Francisco do Prado for technical support and Dr. Stephen Hyslop for reviewing the manuscript.

References