Abstract—The purpose of this study was to compare circadian blood pressure and heart rate patterns and other cardiovascular effects of nicotine delivered rapidly (via nasal spray, NNS), slowly (transdermal nicotine, TDN), by cigarette smoking (rapid delivery of nicotine plus other smoke toxins), and placebo NNS. Twelve healthy cigarette smokers were studied on a research ward when they smoked cigarettes (16 per day) or used TDN (15 mg/16 h), NNS (24 1-mg doses per day), or placebo NNS, each for 5 days. There were no significant differences in systolic blood pressure, but diastolic blood pressure was slightly increased during cigarette smoking. Plasma epinephrine, β-thromboglobulin, and fibrinogen levels were higher during cigarette smoking than with TDN. For most measurements, NNS values were intermediate between and not significantly different from those of cigarette smoking and TDN. We conclude that, at recommended doses, TDN and NNS have fewer effects on biomarkers of cardiovascular risk than does cigarette smoking. (Hypertension. 2002;39:1107-1112.)

Key Words: smoking ■ cardiovascular diseases ■ risk factors ■ catecholamines

Nicotine replacement therapy is the most widely used pharmacotherapy to aid smoking cessation. Currently available nicotine therapies include nicotine gum, patches, nasal spray, inhalers, and lozenges. Nicotine nasal spray differs from other commonly marketed medications in that nicotine is absorbed fairly rapidly from the nose and produces psychological effects that resemble those of cigarette smoking.1

The safety of transdermal nicotine has been demonstrated in studies comparing the incidence of cardiovascular events while using transdermal nicotine versus using placebo patches to aid smoking cessation in patients with cardiac disease.2 A study of nicotine nasal spray in addition to cigarette smoking compared with cigarette smoking alone showed that the myocardial oxygen demand was not increased by adding the spray.3 Still, there has been some concern that nicotine replacement therapy is hazardous for people with underlying cardiovascular disease.

The mechanisms by which cigarette smoking is likely to contribute to acute vascular events include the following: (1) induction of a hypercoagulable state, (2) increased myocardial work, (3) carbon monoxide–mediated reduction in the oxygen-carrying capacity of the blood, (4) induction of endothelial dysfunction, (5) coronary vasoconstriction, and (6) catecholamine release.4 There are many toxins in cigarette smoke other than nicotine (for example, carbon monoxide and oxidant gases) that might contribute to the cardiovascular toxicity.

Cigarette smoking and nicotine nasal spray deliver nicotine as intermittent doses,1 whereas transdermal nicotine delivery systems deliver nicotine in a more steady fashion. Previous studies have indicated that the magnitude of the acute cardiovascular and subjective responses to intravenously administered nicotine is greater when administered rapidly rather than slowly.5 This is believed to result from higher concentrations of nicotine in the arterial blood and less time for development of tolerance, because of the rapid increase of nicotine levels in the brain.

The mechanism of blood pressure and heart rate elevation by nicotine is believed to be via activation of the sympathetic nervous system with release of norepinephrine and epinephrine.6 Cigarette smoking results in sympathetic neural arousal that lasts for 24 hours of the day.7 Circadian fluctuations in sympathetic neural activity may have implications for the development of acute cardiovascular events. Acute cardiovascular events are known to have a peak incidence between 6 and 10 AM.8,9 This is the time when blood pressure and catecholamine levels, associated with awakening and exercise, increase.10,11 It is postulated that the extent of change in blood pressure from night to day is an important determinant of myocardial ischemia and, therefore, of the likelihood of acute cardiovascular events.12 Thus, drugs that affect the circadian pattern of blood pressure and heart rate and sympathetic nervous system arousal might influence cardiovascular risk.
To better understand the cardiovascular pharmacology of nicotine and to evaluate the safety of different nicotine replacement medications, we conducted a study of circadian blood pressure and heart rate patterns in smokers while smoking cigarettes or using either transdermal nicotine, nicotine nasal spray, or placebo nasal spray. We also examined the impact of these treatments on several biomarkers of cardiovascular risk, including catecholamine excretion, hemostatic factors, plasma renin, and steroid levels.

Methods

Subjects
The subjects were 12 healthy men aged 25 to 57 years (mean age, 38 years), who smoked an average of 27 cigarettes per day (range, 18 to 50) and had smoked for an average of 23 years (range, 9 to 35). Written informed consent was obtained from each subject, and the study was approved by the University of California, San Francisco, Committee on Human Research.

Experimental Protocol
This study was designed to compare the pharmacokinetics and cardiovascular effects of cigarette smoking, transdermal nicotine, and nicotine nasal spray. The results of the pharmacokinetic aspects of this study have been published previously. Subjects were admitted to the Clinical Research Center for 21 days. They were studied in 4 consecutive treatment blocks, each of 5 days duration. The treatments were (1) cigarette smoking, 16 cigarettes per day spaced at regular intervals over 16 hours; (2) transdermal nicotine patches labeled as delivering 15 mg over 16 hours; (3) nicotine nasal spray containing 1 mg (2 sprays) dosed 24 times a day at 40-minute intervals for 16 hours; and (4) placebo nasal spray doses on the same schedule as the active nicotine nasal spray. The sequence of cigarette smoking and the 2 nicotine-containing medications was balanced using Latin squares. The placebo nasal spray was always administered last to avoid the possibility of nicotine intoxication during the study. This is because nicotine intoxication might occur in subjects who have lost their tolerance to the noxious effects of nicotine during placebo treatment when they are re-exposed to nicotine in a subsequent treatment.

Five days duration for each treatment was decided on as the time needed to reach a steady state with respect to the pharmacokinetics of nicotine and metabolites. Cardiovascular and hormonal responses to nicotine occur rapidly after exposure. Inflammatory and platelet markers have been shown in a prior study to diminish significantly within 5 days of smoking cessation. For these reasons and considering the balanced order of the treatment conditions, carryover effects from one condition to the next were not expected to bias the outcomes.

On days 3 and 4 of each treatment block, blood pressure and heart rate were recorded every 15 minutes for 24 hours using an Accutrace II ABP heart rate monitor (SunTech Medical Instruments) ambulatory blood pressure system. On days 3, 4, and 5, urine was collected over 24 hours for measurement of catecholamines. On day 4, venous blood samples were collected at 8 AM and 12 noon following overnight fasting for measurement of white blood cell count, platelet count, fibrinogen, and the platelet α granule factors: platelet factor 4 and β-thromboglobulin. On day 5, circadian blood sampling over 24 hours was obtained from an indwelling catheter at 4-hour intervals for measurement of plasma nicotine, cotinine, and blood carboxyhemoglobin concentrations. Samples were drawn midway between cigarette or nasal spray doses. In addition, on day 5 a postural renin and steroid study was performed, measuring plasma renin activity, aldosterone, and cortisol in blood samples collected while supine, during overnight sleep (7 AM), and after 2 hours in an upright posture (sitting or standing) (9 AM).

Analytical Chemistry
Plasma concentration of nicotine and cotinine were measured by gas chromatography with nitrogen-phosphorus detection as described elsewhere. Plasma and urinary catecholamines were assayed by high performance liquid chromatography using an electrochemical detector. Plasma fibrinogen was measured using a fibrometer (BBL Fibrofibrinogen Model 7). Platelet factor 4 and β-thromboglobulin were measured by radioimmunoassay using commercial kits.

Data Analysis
Ambulatory blood pressure and heart rate data were analyzed as mean 24-hour values, mean daytime values (7 AM to 10 PM, inclusive), mean nighttime values (11 PM to 6 AM, inclusive), day/night differences, and percentage day/night difference. These data were also analyzed in 6-hour blocks as follows: (1) 7 AM to 12 noon, inclusive; (2) 1:00 PM to 6:00 PM, inclusive; (3) 7 PM to 12 midnight, inclusive; and (4) 1:00 AM to 6:00 AM, inclusive.

In several subjects, portions of the data were lost for technical reasons. These data included some ambulatory blood pressure recordings and hemostatic and/or hormone measurements. Statistical analyses were performed comparing within-subject values for subjects who had complete data available for that measurement in all treatment conditions. For this reason, the number of subjects noted in the analyses for some outcome measures may be less than 12. The power of the study was computed based on detecting a difference of 25% comparing one condition to the other 2 conditions, where α=0.05. For responses with a coefficient of variation of 10% (such as systolic blood pressure, heart rate, or fibrinogen), the power for n=12 is 99%. Considering possible missing data, an n of 6 would provide 80% power. For responses with a coefficient of variation of 25% (such as β-thromboglobulin), the power with n=12 equals 60%.

No adjustments were made for multiple comparisons. Adjustments are needed when testing a number of independent responses to keep the overall Type 1 error less than 5%. However, many of the various responses that we measured are not independent, but rather reflect the same physiological processes (for example, changes in heart rate, blood pressure, and epinephrine levels).

Results

Nicotine and Cotinine Levels
Mean steady state plasma concentrations of nicotine and cotinine during the fifth day of administration of the different nicotine treatments are shown in the Figure. The daytime (12 noon to 12 midnight) average nicotine concentration was higher for cigarette smoking (16.3 ng/mL) than for nicotine nasal spray (10.5 ng/mL) and transdermal nicotine (9.2 ng/mL). The corresponding data for average plasma cotinine concentrations were 301, 170, and 154 ng/mL, respectively.

Blood Pressure
Mean blood pressure and heart rate measurements during the 4 treatments at various times of the day are shown in Table 1. For the systolic blood pressure, there were no significant overall treatment effects on the 24-hour average, daytime, or nighttime values, in comparing the 3 nicotine exposure conditions. However, the daytime and day-nighttime differences were higher for the nicotine treatments compared with
placebo. The 1 AM to 6 AM interval differed from the other time intervals.

The mean 24-hour value for diastolic blood pressure was significantly higher for smoking compared with transdermal nicotine. The effect of the nicotine nasal spray was intermediate between and not significantly different from that of smoking and transdermal nicotine.

**Heart Rate**

The 24-hour average heart rate for cigarette smoking was significantly higher than for transdermal nicotine. The effect of the nicotine nasal spray was between that of smoking and transdermal nicotine. Daytime values for cigarette smoking significantly exceeded those for transdermal nicotine and again the effect of the nicotine nasal spray was intermediate, the latter difference not significant from other conditions. Daytime and 24-hour averages during the placebo treatment were lower than for the nicotine treatments (not tested statistically).

**Catecholamine, Renin, and Steroid Measurement**

Urine levels of norepinephrine, epinephrine, and dopamine were not significantly different following administration of the 3 nicotine treatments. In plasma, the epinephrine level during cigarette smoking (25 ± 10 [SD] pg/mL) was significantly higher than after treatment with transdermal nicotine (16 ± 6 pg/mL). Plasma epinephrine during nicotine nasal spray was intermediate (22 ± 11 pg/mL), and the placebo treatment was similar to transdermal nicotine. For plasma norepinephrine, no significant differences between the nicotine treatments were seen. There were no significant condition differences for cortisol, aldosterone, or renin activity.

**Hemostatic Measurements**

Several different parameters of importance to blood coagulation, including platelet factor 4, β-thromboglobulin, fibrinogen, white blood cell counts, and platelet counts were measured in this study (Table 2). The level of platelet factor 4 was similar for the 4 treatments. For β-thromboglobulin, significantly higher levels were found during cigarette smoking compared with transdermal nicotine and nicotine nasal spray. Significantly higher concentrations of fibrinogen were found for cigarette smoking compared with transdermal nicotine. The platelet count was significantly higher for cigarette smoking than for nicotine nasal spray. There were no treatment differences for white blood cell count.

**Discussion**

This study was designed to investigate and compare the cardiovascular, hemostatic, and hormonal effects of nicotine nasal spray, which delivers nicotine in a fairly rapid manner, with those of transdermal nicotine, which provides for a slow absorption of nicotine, and with those of cigarette smoking, which has a rapid absorption and delivers potential cardiovascular toxins other than nicotine as well.

**TABLE 1. Cardiovascular Responses to Nicotine Nasal Spray, Nicotine Patch, Cigarette Smoking, and Placebo Nasal Spray**

<table>
<thead>
<tr>
<th></th>
<th>Systolic Blood Pressure (mm Hg)</th>
<th>Diastolic Blood Pressure (mm Hg)</th>
<th>Heart Rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Transdermal Nicotine Patch</td>
<td>Nic Spray</td>
</tr>
<tr>
<td>Mean, 24 h</td>
<td>113 ± 10</td>
<td>114 ± 10</td>
<td>115 ± 11</td>
</tr>
<tr>
<td>Mean, daytime (7 AM–10 AM)</td>
<td>116 ± 9</td>
<td>120 ± 11*</td>
<td>121 ± 12*</td>
</tr>
<tr>
<td>Mean, nighttime (11 PM–6 AM)</td>
<td>107 ± 13</td>
<td>103 ± 10</td>
<td>104 ± 11</td>
</tr>
<tr>
<td>Mean, day–night</td>
<td>10 ± 6</td>
<td>18 ± 6</td>
<td>14 ± 6</td>
</tr>
<tr>
<td>Mean, % day–night</td>
<td>8.8 ± 5.2</td>
<td>14.5 ± 5</td>
<td>12.5 ± 5</td>
</tr>
<tr>
<td>Mean, 7 AM–12 noon</td>
<td>114 ± 10</td>
<td>119 ± 11‡</td>
<td>122 ± 16†,§</td>
</tr>
<tr>
<td>Mean, 1 AM–6 AM</td>
<td>117 ± 9</td>
<td>120 ± 12‡</td>
<td>119 ± 9‡</td>
</tr>
<tr>
<td>Mean, 7 AM–12 midnight</td>
<td>116 ± 11</td>
<td>117 ± 10‡</td>
<td>113 ± 10‡</td>
</tr>
<tr>
<td>Mean, 1 AM–6 AM</td>
<td>105 ± 15</td>
<td>101 ± 11</td>
<td>104 ± 12</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD; n = 10, placebo; n = 9, transdermal; n = 9, nicotine nasal spray; n = 9, cigarette smoking; the placebo treatment was not included in the statistical analysis.

*Significantly higher than for nicotine patch.
†Significantly higher than during 1 AM–6 AM time interval.
‡Significantly higher than during 7 PM–12 Midnight time interval.
The present study confirmed previously published reports that heart rate is increased throughout the day while smoking compared with while not smoking.7,16,17 We also found that the use of nicotine nasal spray tends to increase heart rate compared with transdermal nicotine and placebo conditions. These differences were found only during daytime; nighttime heart rates were similar for all conditions.

In most studies, office or clinic blood pressure has been found to be lower in smokers than in nonsmokers.18–21 However, when measured via an indwelling arterial catheter or with automatic noninvasive blood pressure monitoring, smoking a cigarette transiently increased blood pressure at any time throughout the day.22,23 Several studies of noninvasive ambulatory blood pressure in smokers compared with nonsmokers have shown either no difference or slightly higher or lower 24-hour blood pressure profiles, when smoking compared with when not smoking.16,24–26 In the present study, no significant differences in systolic blood pressure were observed, but a small increase in diastolic blood pressure was seen when smoking compared with when not smoking or while using transdermal patches. No increase in blood pressure was seen comparing nicotine nasal spray or transdermal nicotine with placebo conditions. Importantly, the overall effects on the heart rate and blood pressure of nicotine nasal spray or transdermal nicotine were similar to or less than those of cigarette smoking.

Individuals with coronary heart disease are known to be at highest risk for acute ischemic events and arrhythmias in the morning.8,9 Likely mechanisms include enhanced coagulability and the increase of sympathetic nervous system activity associated with wakening and early morning activity.10 As observed by others, the present study showed that daytime blood pressure was greater than nighttime blood pressure following cigarette smoking or use of a nicotine nasal spray, transdermal nicotine, or placebo, but no differences in the circadian pattern between treatments were observed. The day–nighttime difference tended to be higher for cigarette smoking and use of nicotine nasal spray—during both of which nicotine is rapidly absorbed—than for placebo. Greater night–day heart rate differences could have implications for more early morning ischemic stress.

The average concentration of nicotine following smoking was higher (16.3 ng/mL) than those following nicotine nasal spray (10.5 ng/mL) and transdermal nicotine (9.2 ng/mL). The study was designed to achieve similar plasma levels administered after the different treatments. The intended systemic dose for the 3 nicotine treatments was 1 mg nicotine per hour. However, the mean systemic doses, as presented elsewhere, were 22, 13, and 13 mg of nicotine for cigarette smoking, nicotine nasal spray, and transdermal nicotine, respectively.13 Thus, more than the typical 1 mg of nicotine per cigarette was extracted from cigarettes in this study. Because the plasma concentration of nicotine was substantially higher after smoking than after use of the nicotine nasal spray, it cannot be concluded whether the greater cardiovascular effect of cigarette smoking that we observed was due to components of cigarette smoke other than nicotine or to the higher exposure to nicotine. On the other hand, previous studies have shown that the dose–response relationship, with regard to cardiovascular parameters of nicotine, is flat.7,30 The flat dose–response is thought to reflect the development of tolerance.

Release of catecholamines is a mechanism by which nicotine could activate platelets.31 In the present study, an increase in β-thromboglobulin could be shown only during cigarette smoking. Previous studies have suggested that components other than nicotine in cigarette smoke are responsible for the platelet activation seen in cigarette smokers.14

Cigarette smoking is known to activate the sympathoadrenal system, increasing heart rate, blood pressure, and circulating levels of catecholamines and corticosteroids.6 Plasma cortisol is increased acutely by cigarette smoking.5 Some studies indicate an effect on cortisol excretion during regular smoking, whereas others do not report such differences.7,52 In the present study, there was no significant increase in plasma cortisol levels in comparing smoking, nicotine replacement therapy, and placebo.

The renin–angiotensin system plays a key role in blood volume and blood pressure regulation, as well as in affecting myocardial structure and function. No differences in the renin levels between the different treatments were found in this study. Nicotine, cotinine, and anabasine (a minor tobacco alkaloid) have been reported to inhibit aldosterone synthesis in the adrenal cells of rats, with cotinine being the most potent inhibitor.33 A previous study showed decreased excretion of aldosterone when smoking compared with using transdermal

### TABLE 2. Homostatic Factors During Cigarette Smoking, Nicotine Nasal Spray, Nicotine Patch, and Placebo Nasal Spray

<table>
<thead>
<tr>
<th>Factor</th>
<th>Placebo 8 AM</th>
<th>Placebo 12 noon</th>
<th>Transdermal Nicotine 8 AM</th>
<th>Transdermal Nicotine 12 noon</th>
<th>Nicotine Nasal Spray 8 AM</th>
<th>Nicotine Nasal Spray 12 noon</th>
<th>Cigarette Smoking 8 AM</th>
<th>Cigarette Smoking 12 noon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet factor, ng/mL (n=8)</td>
<td>4.3±1.9</td>
<td>3.2±1.5</td>
<td>4.3±1.4</td>
<td>3.5±1.2</td>
<td>4.8±1.6</td>
<td>4.0±1.5</td>
<td>5.1±1.5</td>
<td>3.8±1.1</td>
</tr>
<tr>
<td>β-thromboglobulin, ng/mL (n=8)</td>
<td>25±6</td>
<td>23±5</td>
<td>25±6</td>
<td>22±5</td>
<td>26±7</td>
<td>23±4</td>
<td>30±7†‡</td>
<td>24±6</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL (n=12)</td>
<td>270±19</td>
<td>278±21</td>
<td>289±26</td>
<td>291±23</td>
<td>293±34</td>
<td>293±33</td>
<td>314±37†</td>
<td>320±35†</td>
</tr>
<tr>
<td>White blood cell count, 10³/µL (n=10)</td>
<td>5.1±0.9</td>
<td>5.4±0.9</td>
<td>5.3±0.9</td>
<td>5.9±2.0</td>
<td>5.2±1.0</td>
<td>5.9±1.2</td>
<td>5.8±0.9</td>
<td>6.1±2.0</td>
</tr>
<tr>
<td>Platelet count, 10³/µL (n=10)</td>
<td>199±34</td>
<td>202±33</td>
<td>202±22</td>
<td>199±23</td>
<td>197±25</td>
<td>193±29</td>
<td>203±21</td>
<td>211±23†</td>
</tr>
</tbody>
</table>

*Significantly different from transdermal nicotine.
†Significantly different from nicotine nasal spray.
‡Significant differences, 8 AM and 12 Noon.
nicotine.\(^3^0\) However, no decrease in plasma aldosterone levels after treatment with nicotine was observed in this study.

Fibrinogen is an important component of the coagulation system. It is involved in the production of fibrin, which is a cofactor for platelet aggregation, and it increases blood viscosity. Cigarette smokers have higher fibrinogen levels than those of nonsmokers,\(^3^4\) and fibrinogen levels have been shown to be positively correlated with the risk of coronary heart disease.\(^3^5\) Our study showed that fibrinogen levels were higher after cigarette smoking than after treatment with transdermal nicotine. This is in agreement with 2 previous studies that showed that fibrinogen levels were similar in nicotine and placebo patch treatment.\(^1^4,3^6\)

In conclusion, transdermal nicotine, which is absorbed slowly, had less effect in healthy smokers on biomarkers of cardiovascular risk such as heart rate, blood pressure, concentrations of catecholamines, \(\beta\)-thromboglobulin, and fibrinogen compared with cigarette smoking. Nicotine nasal spray, which results in a rapid absorption of nicotine, but not as rapid as that from cigarette smoking, had, on average, a similar or lesser effect on heart rate, blood pressure, catecholamine excretion, and fibrinogen levels compared with cigarette smoking. Nicotine nasal spray had a significantly smaller effect on platelet activation, as indicated by \(\beta\)-thromboglobulin concentration, than did cigarette smoking.

**Perspectives**

Because nicotine nasal spray is absorbed more rapidly than other nicotine medications, there has been concern that it might be associated with a greater potential for cardiovascular risk than other nicotine medications. Our study does suggest that the hemodynamic effects of nicotine nasal spray are greater than those of transdermal nicotine (although the differences were not significant). But, most importantly, our study shows that, in healthy smokers, both transdermal nicotine and nicotine nasal spray used at recommended dosage rates have less of an impact than cigarettes on biomarkers of cardiovascular disease. It is likely that the potential benefits of nicotine nasal spray in promoting smoking cessation far outweigh its risk for smokers. However, further studies are needed of smokers who have hypertension and/or other cardiovascular diseases.

**Acknowledgments**

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Cardiovascular Effects of Nasal and Transdermal Nicotine and Cigarette Smoking
Neal L. Benowitz, Anna Hansson and Peyton Jacob III

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