Pharmacology Biochemistry & Behavior, Vol. 40, pp. 937–940. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Changes in Urinary Catecholamine Excretion After Smoking Cessation[1]

KENNETH D. WARD,[2] ARTHUR J. GARVEY, RYAN E. BLISS

Normative Aging Study, Department of Veterans Affairs Outpatient Clinic and Harvard School of Dental Medicine, Boston, MA

DAVID SPARROW

Normative Aging Study, Department of Veterans Affairs Outpatient Clinic, Boston, MA

JAMES B. YOUNG AND LEWIS LANDSBERG

Department of Medicine, Northwestern University Medical School, Chicago, IL

Received 18 April 1991

WARD, K. D., A. J. GARVEY, R. E. BLISS, D. SPARROW, J. B. YOUNG AND L. LANDSBERG. *Changes in urinary catecholamine excretion after smoking cessation.* PHARMACOL BIOCHEM BEHAV **40**(4) 937–940, 1991.—Excretion levels of norepinephrine, epinephrine, and dopamine were assessed in 17 habitual cigarette smokers while smoking and periodically during 30 days of abstinence to determine whether a pattern of transient change existed, suggestive of sympathetic nervous system (SNS) involvement in tobacco withdrawal. Excretion of all three catecholamines declined 1 day after abstinence but did not return to precessation levels during the rest of the follow-up period. The results suggest that postcessation declines in excretion may be permanent changes caused by loss of tobacco's agonist effects, rather than transient withdrawal phenomena resulting from SNS adaptation to the stimulatory effects of tobacco.

Smoking cessation Catecholamines Tobacco Withdrawal

SEVERAL physiological changes occur after cessation of cigarette smoking by habitual smokers (6,17), including an immediate decline in urinary excretion of the catecholamines epinephrine and norepinephrine (1, 12, 19), indices of sympathetic nervous system (SNS) activity (2). It is unclear whether such declines in catecholamine excretion are permanent or transient abstinence effects (6).

This issue has implications for understanding tobacco withdrawal effects. An initial drop in catecholamine excretion after smoking cessation without further change over time could represent simply a return to a nonsmoking level of excretion due to loss of tobacco's agonist effects on the SNS. On the other hand, if excretion declines immediately after cessation and then returns toward baseline, this initial decline might represent a "rebound." Rebound refers to a temporary, homeostatic response opposite in direction to the agonist effect of a drug to which physiological adaptation has occurred. Such rebound effects are known to occur for several physiological parameters during withdrawal from narcotics and other drugs of dependence (7,11).

Data concerning changes in catecholamine excretion after smoking cessation are scarce. We know of only three published studies that have used more than a single follow-up point to examine postcessation catecholamine changes. Urinary excretion levels of norepinephrine and epinephrine have been reported to decline during 4 to 5 days of smoking cessation, with no evidence of a return toward precessation levels during these brief follow-up periods (1,12). A more recent study reported that epinephrine excretion decreased during 3 days of abstinence and then returned to precessation level by 10 days postcessation (19). Studies of postcessation changes in excretion of the catecholamine dopamine are lacking. However, one study reported no change in dopamine excretion after 24 hours of abstinence (18). The present study attempted to clarify the pattern of change in catecholamine excretion after smoking cessation by following a group of habitual smokers during 30 days of abstinence.

METHOD

Subjects were recruited for a 1-year prospective study of physiological and behavioral changes among smokers who planned

[1]Presented in part at the World Conference on Lung Health, May, 1990, Boston, MA.

[2]Requests for reprints should be addressed to Kenneth D. Ward, Normative Aging Study (151A), Department of Veterans Affairs Outpatient Clinic, 251 Causeway St., Boston, MA 02114.

to quit without formal treatment intervention. Smokers were enrolled who planned to quit "cold-turkey" and who were at least 18 years of age, smoked at least 5 cigarettes every day, were in good health and without history of adrenal, cardiovascular, or kidney disease, did not use medications other than mild analgesics or oral contraceptives, and agreed not to use nicotine gum or other tobacco products to aid in cessation.

Subjects provided a complete 24-hour urine collection on the day before their quit attempt (baseline) while smoking at their usual rate and pattern, on days 1, 3, 8, 15, 30, 45, and 60 postcessation, and monthly thereafter for the remainder of the year. Urine collection was discontinued if regular smoking was resumed. Urine was collected in 3-liter plastic containers with a preparation of hydrochloric acid, sodium metabisulfite, and mineral oil added as a preservative. Urine specimens were refrigerated after collection and were analyzed by high performance liquid chromatography with electrochemical detection according to the method of Smedes et al. (16) as modified by MacDonald and Lake (9). Intraassay coefficients of variation for urine samples (corrected for recovery) are 4–6% for E, NE, and DA; interassay coefficients of variation are 6–7% for all three catecholamines.

Smoking status was verified at each interview by expired carbon monoxide (CO) and salivary cotinine concentrations. Cut-offs for classification as abstinent were <8 ppm CO at day 1 postcessation and beyond, and <15 ng/ml cotinine at day 8 postcessation and beyond. CO was measured using an Ecolyzer Model 3000 (National Draeger Co., Pittsburgh, PA), and cotinine was assayed by radioimmunoassay according to the method of Langone et al. (8).

For the present study, catecholamine data were analyzed through day 30 postcessation for subjects abstinent continuously (i.e., no smoking whatsoever) throughout this follow-up period. One hundred twenty-six subjects made a quit attempt, and 18 were abstinent continuously for 30 days. Complete catecholamine data were available for 17 of these abstainers, of whom 4 were women. These 17 abstainers had a mean age of 43.5 years (range 26–64 years) and had smoked for a mean of 27.6 years (SD = 12.7). Mean baseline smoking rate was 21.5 cigarettes/day (SD = 16.2) and mean estimated nicotine yield was 0.8 mg/cigarette (SD = 0.4), based on U.S. government estimates (3). At baseline, mean expired CO was 24.2 ppm (SD = 11.8) and mean salivary cotinine concentration was 558.9 ng/ml (SD = 265.8).

Excretion of each catecholamine was expressed as micrograms per total 24-hour urine excretion. Across all assessment points (baseline, days 1, 3, 8, 15, and 30 postcessation), mean urine volume was 1540 ml (SD = 65). Mean urine volumes at each assessment point did not differ significantly.

Statistical analysis was guided by previous research suggesting that catecholamine excretion declines steeply within 24 hours of abstinence, levels off during the next few days (1,12), and returns toward precessation level within 10 days of abstinence (19). Two one-way analysis of variance models for repeated measures were tested for each catecholamine. One model compared mean excretion at baseline and day 1 postcessation; the second model compared excretion at days 1, 3, 8, 15, and 30 postcessation. Next, linear contrasts for repeated measures were tested on excretion of each catecholamine at days 1, 3, 8, 15, and 30 to determine whether trends existed for excretion levels to return toward baseline level following the expected initial declines at day 1 postcessation. Analyses were conducted with the general linear model procedure of the SAS statistical software package (15).

RESULTS

All 17 subjects fulfilled criteria for biochemical validation of abstinence. Mean CO levels at days 1, 3, 8, 15, and 30 were below 4 ppm. Mean cotinine concentrations at days 8, 15 and 30 were below 4 ng/ml.

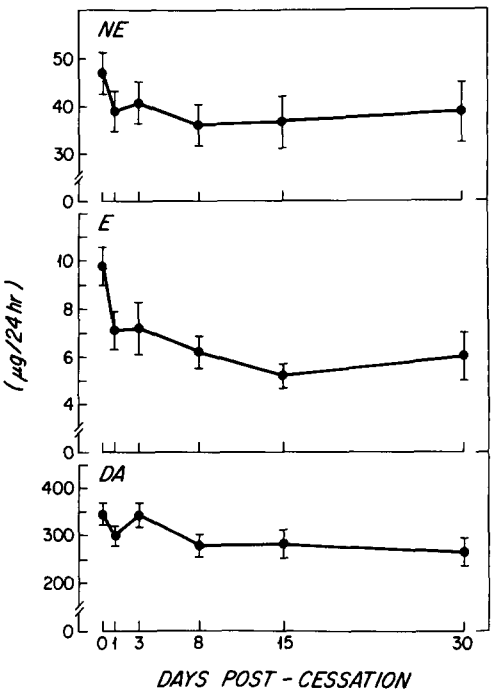

FIG. 1. Urinary excretion of catecholamines (mean ± 1 SE; n = 17) before and during 30 days of smoking abstinence. Upper panel: norepinephrine; middle panel: epinephrine; bottom panel: dopamine.

Postcessation changes in catecholamine excretion are illustrated in Fig. 1. Between baseline and day 1, excretion of norepinephrine, epinephrine, and dopamine declined by 7.9, 2.7, and 47.2 μg, respectively. These declines were statistically significant (all p values <0.01). For all three catecholamines, the steepest postcessation decline, i.e., the magnitude of decline per unit of time, occurred between baseline and day 1.

Norepinephrine excretion did not appear to change in any consistent pattern after day 1 (Fig. 1, top panel). From days 1 through 30, mean NE excretion levels did not differ significantly from each other ($p = 0.84$), and there was no significant linear trend ($p = 0.86$).

Epinephrine excretion levels remained constant at days 1 and 3, decreased through day 15, reaching a level of 5.2 μg, and then rose slightly at day 30 (Fig. 1, middle panel). However, from day 1 through day 30, mean epinephrine excretion levels did not differ significantly from each other ($p = 0.29$), and there was no significant linear trend ($p = 0.31$). A post hoc linear contrast of epinephrine excretion from day 1 through day 15 was statistically significant, $F(1,16) = 4.6$, $p = 0.05$, indicating a trend for epinephrine to continue dropping through day 15.

Dopamine excretion levels returned toward baseline between days 1 and 3, and then declined again, remaining below baseline during the rest of the follow-up period (Fig. 1, bottom panel). Mean dopamine excretion levels from day 1 through day 30 differed from each other, $F(4,64) = 2.7$, $p = 0.04$, likely due to the increase between days 1 and 3. There was no significant linear trend in excretion levels from day 1 through day 30 ($p = 0.27$).

It is possible that smokers with greater tobacco intake are more likely to exhibit rebound after cessation, due to increased physiological adaptation to nicotine. To examine this issue, the 17 abstainers were divided according to median baseline smoking rate into "low intake" (≤15 cigarettes/day) and "high intake" (>15 cigarettes/day) groups. The low intake group (n=9) had a mean smoking rate of 11.6 cigarettes per day, whereas the high intake group (n=8) had a mean rate of 32.6 cigarettes/day. Baseline catecholamine levels did not differ significantly between the groups.

For both groups, trends in excretion of the 3 catecholamines paralleled the trends observed for the entire sample of 17 subjects. Baseline to day 1 declines in excretion of norepinephrine, epinephrine, and dopamine were 6.5, 2.5, and 46.7 μg, respectively for the low intake group, and 9.5, 3.0, and 47.7 μg, respectively for the high intake group. For all 3 catecholamines, baseline to day 1 declines were significant in both groups ($p<0.05$ for all comparisons), but the declines did not differ between the groups ($p>0.48$ for all comparisons). Excretion levels of each catecholamine at days 1, 3, 8, 15, and 30 did not vary significantly for either the low intake or high intake groups. Similar results emerged when the sample was divided by baseline carbon monoxide levels instead of smoking rate. Thus smokers with greater baseline tobacco intake were not more likely to show rebound in catecholamine excretion after smoking cessation.

DISCUSSION

Urinary excretion of all three catecholamines declined 24 hours after smoking cessation and showed an overall trend to remain below the smoking level during the remainder of the 30-day follow-up period. Excretion of norepinephrine, epinephrine, and dopamine reflects different aspects of SNS functioning: urinary norepinephrine is derived mainly from sympathetic nerve terminals throughout the body, whereas urinary epinephrine is largely a product of hormonal release by the adrenal medulla. The source of urinary dopamine is not known with certainty (2). The consistency in the postcessation trends for excretion of the three catecholamines suggests that cigarette smoking has similar stimulatory effects at various levels of the SNS.

The pattern of change in epinephrine excretion was of particular interest because of previous evidence that epinephrine may return to precessation levels within 10 days of smoking abstinence (19). In the present study, however, epinephrine excretion dropped steeply during the first day after cessation and did not rise above the day 1 level during the remainder of the 30-day follow-up period. The negative linear trend observed for epinephrine excretion between day 1 and day 15 suggests that epinephrine excretion may not stabilize for at least 15 days after smoking cessation.

This study had several advantages over previous research that evaluated the effects of smoking cessation on catecholamine excretion. Subjects in the present study were abstinent entirely from nicotine throughout the follow-up period, and abstinence was validated biochemically. In previous studies subjects used nicotine gum (18,19) or did not abstain entirely from cigarettes (1,12), yet both of these factors may affect catecholamine excretion.

Other advantages of the present study were the availability of 24-hour urine samples collected at multiple follow-up points and the evaluation of three indices of SNS activity. Previous studies collected single urine voids (1, 12, 18, 19), which may not provide a reliable estimate of diurnal catecholamine excretion. One previous study found evidence of transient change in epinephrine excretion (19), but did not evaluate change in norepinephrine or dopamine. In addition, West et al. (19) found that epinephrine excretion appeared to return to baseline, but this trend was observed between only two follow-up points within 10 days of abstinence. It is unclear whether this upward trend would be consistent during longer follow-up. We were able to avoid these limitations by examining three measures of SNS activity at multiple follow-up points during 30 days of abstinence.

Our data revealed no evidence of rebound in catecholamine excretion after smoking cessation. Evidence that initial postcessation declines in excretion involve an element of rebound, i.e., a temporary "overshoot" representing homeostatic adaptation to tobacco's agonist effects, would require that excretion levels return toward baseline after an initial decline. It is possible that initial postcessation declines in catecholamine excretion do represent rebound but that no subsequent return toward baseline was evident because the SNS requires longer than 30 days after cessation to regain normal functioning. However, in a subset of subjects abstinent for 90 days (n=7; data not shown), we found no evidence that excretion of any catecholamine returned toward baseline during this longer follow-up period.

Consistent with previous studies of smoking cessation by unaided quitters [e.g., Marlatt et al. (10)], only 14% of subjects in this study maintained continuous abstinence during the 30-day follow-up period. It is possible that rebound in catecholamine excretion did not occur because subjects able to maintain abstinence for 30 days may have been less dependent smokers who exhibited little physiological adaptation to tobacco. Against this possibility, however, is that abstainers were not particularly low on dependence, based on duration of smoking (mean=27.6 years) or tobacco intake (mean baseline smoking rate=21.5 cigarettes/day, and mean estimated nicotine yield=0.8 mg/day). In addition, when these 17 abstainers were split into high and low tobacco intake groups, based on baseline smoking rate and carbon monoxide levels, there was no evidence that smokers with higher baseline tobacco intake were more likely to exhibit rebound. Thus the absence of rebound in catecholamine excretion is not likely due to a selection bias of including less dependent smokers.

A limitation of this study is the lack of a control group of smokers not undergoing abstinence. We are unable, therefore, to say definitively that the changes observed in catecholamine excretion are due to smoking cessation. However, the changes observed early after cessation are consistent with previous studies which have employed control groups. West et al. (19) and Myrsten et al. (12) reported declines in catecholamine excretion immediately after cessation, but no such changes in smokers not undergoing abstinence. Using a cross-over design, Elgerot et al. (1) found that catecholamine excretion declined when smokers were abstinent, but not during smoking. The consistency in excretion patterns by smoking status in these published studies strongly suggests that the declines in catecholamine excretion observed in the present study resulted from smoking cessation.

The sustained decrease in catecholamine excretion after smoking cessation suggests that the SNS was tonically stimulated by cigarette smoking. This decrease in SNS activity may contribute to the reduction in metabolic rate noted in smokers during abstinence (4,5) and, therefore, predispose to weight gain. The decrease in SNS activity after smoking cessation may also contribute to the reduction in cardiovascular risk noted in smokers who quit (13,14).

In conclusion, these data indicate that initial postcessation declines in catecholamine excretion are sustained for at least 30 days of abstinence. The absence of a return toward baseline for any of the catecholamines suggests that initial declines in excretion represent loss of the agonist effects of tobacco rather than transient homeostatic rebounds caused by SNS adaptation to chronic tobacco intake.

ACKNOWLEDGEMENTS

Support for this research was provided by the Medical Research Service of the Department of Veterans Affairs and by PHS Grant Number HL 39211 awarded by the National Heart, Lung, and Blood Institute.

REFERENCES

1. Elgerot, A. Psychological and physiological changes during tobacco-abstinence in habitual smokers. J. Clin. Psychol. 34:759–764; 1978.
2. Esler, M.; Jennings, G.; Lambert, G.; Meredith, I.; Horne, M.; Eisenhofer, G. Overflow of catecholamine neurotransmitters to the circulation: source, fate, and functions. Physiol. Rev. 70:963–985; 1990.
3. Federal Trade Commission. "Tar," Nicotine and carbon monoxide of the smoke of 272 varieties of domestic cigarettes. Washington, DC; 1988.
4. Glauser, S. C.; Glauser, E. M.; Reidenberg, M. M.; Rusy, B. F.; Tallarida, R. J. Metabolic changes associated with the cessation of cigarette smoking. Arch. Environ Health 20:377–381; 1970.
5. Hofstetter, A.; Schutz, Y.; Jequier, E.; Wahren, J. Increased 24-hour energy expenditure in cigarette smokers. N. Engl. J. Med. 314:79–82; 1986.
6. Hughes, J. R.; Higgins, S. T.; Hatsukami, D. Effects of abstinence from tobacco: a critical review. In: Kozlowski, L. T.; Annis, H. M.; Cappell, H. D., et al., eds. Research advances in alcohol and drug problems, vol. 10. New York: Plenum Publishing Co.; 1990.
7. Kalant, H.; LeBlanc, A. E.; Gibbins, R. J. Tolerance to, and dependence on, some nonopiate psychotropic drugs. Pharmacol. Rev. 23:135–191; 1971.
8. Langone, J. J.; Gjika, H. B.; VanVunakis, H. Nicotine and its metabolites: radioimmunoassay for nicotine and cotinine. Biochemistry 12:5025–5030; 1973.
9. MacDonald, I. A.; Lake, D. M. An improved technique for extracting catecholamines from body fluids. J. Neurosci. Methods 13:239–248; 1985.
10. Marlatt, G. A.; Curry, S.; Gordon, J. R. A longitudinal analysis of unaided smoking cessation. J. Consult. Clin. Psychol. 56:715–720; 1988.
11. Martin, W., ed. Drug addiction I and II: Handbook of experimental pharmacology, vol. 45. New York: Springer-Verlag; 1990.
12. Myrsten, A-L.; Elgerot, A.; Edgren, B. Effects of abstinence from tobacco smoking on physiological and psychological arousal levels in habitual smokers. Psychosom. Med. 39:25–38; 1977.
13. Rosenberg, L.; Kaufman, D. W.; Helmrich, S. P.; Miller, D. R.; Stolley, P. D. The risk of myocardial infarction after quitting smoking in men under 55 years of age. N. Engl. J. Med. 313:1511–1514; 1985.
14. Rosenberg, L.; Palmer, J. R.; Shapiro, S. Decline in the risk of myocardial infarction among women who stop smoking. N. Engl. J. Med. 322:213–217; 1990.
15. SAS User's Guide: Statistics, Version 5 edition. Cary, NC: SAS Institute; 1985.
16. Smedes, F.; Kraak, J. C.; Poppe, H. Simple and fast solvent extraction system for selective and quantitative isolation of adrenaline, noradrenaline, and dopamine from plasma and urine. J. Chromatogr. 231:25–39; 1982.
17. U.S. Department of Health and Human Services. The health consequences of smoking: nicotine addiction. A report of the Surgeon General. DHHS Pub. No. (CDC) 88–8406, Washington, DC: U.S. Government Printing Office; 1988.
18. West, R. J.; Jarvis, M. J.; Russell, M. A. H.; Carruthers, M. E.; Feyerabend, C. Effect of nicotine replacement on the cigarette withdrawal syndrome. Br. J. Addict. 79:215–219; 1984.
19. West, R. J.; Russell, M. A. H.; Jarvis, M. J.; Pizzey, T.; Kadam, B. Urinary adrenaline concentrations during 10 days of smoking abstinence. Psychopharmacology (Berlin) 84:141–142; 1984.