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EDITORIAL COMMENT

Snuff, Nicotine and Cardiovascular Disease: Implications for Tobacco Control*

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Cigarette smoking is a major risk factor for coronary as well as peripheral vascular disease and stroke. The general mechanisms by which cigarette smoking accelerates atherosclerosis and causes acute cardiovascular events are believed to include adverse effects on lipids, endothelial damage or dysfunction, hemodynamic stress, oxidant injury, neutrophil activation, enhanced thrombosis and increased fibrinogen and blood viscosity (1). Although there are several thousand potentially toxic chemicals in cigarette smoke, there has been persistent concern that nicotine has direct injurious effects on the cardiovascular system. Many smokers who are trying to quit, as well as their physicians, are afraid of the potential toxicity of nicotine. This fear results in physicians failing to prescribe nicotine and patients not using or using too little nicotine to optimally aid smoking cessation. Several lines of evidence indicate that nicotine is not a direct cause of tobacco-related cardiovascular disease (other than by sustaining tobacco addiction, of course).

One line of evidence includes epidemiologic studies of the health consequences of smokeless tobacco use, where there is systemic absorption of nicotine but no absorption of other combustion products. The daily level of exposure to nicotine from smokeless tobacco has been shown to be similar to that from cigarette smoking (2,3). It must be noted, however, that with cigarette smoking nicotine is delivered intermittently into the pulmonary circulation, resulting in transiently high levels of nicotine in arterial blood, exceeding manyfold those levels seen in blood when nicotine is dosed gradually from smokeless tobacco or pipe smoking (4). Rapid delivery of nicotine through cigarette smoke is expected to produce more deleterious effects on the arterial circulation than nicotine absorbed more slowly through the buccal mucosa, as is the case with the use of snuff. For this reason, safety data from smokeless tobacco studies cannot entirely exclude a contribution of nicotine from cigarette smoking to cardiovascular disease.

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Huhtasaari et al. (5,6) have published two case-control studies of myocardial infarction among residents of northern Sweden who participated in the World Health Organization MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) Project. The second study, published in this issue of the *Journal*, included 687 men, 25 to 64 years old, who presented with their first acute myocardial infarction or sudden death, studied between 1991 and 1993 (5). These patients were compared with age-matched and place-of-living–matched control subjects. The earlier study involved 585 men, 35 to 64 years old, with acute myocardial infarction, compared with randomly selected control subjects, studied between 1989 and 1991 (6). Neither study found evidence of an increased risk of myocardial infarction or sudden death in regular snuff users, although both studies confirmed the known effect of cigarette smoking to increase the risk of myocardial infarction. In contrast, a prospective cohort study involving construction workers from all of Sweden has reported that regular snuff use incurs a significant increased risk of mortality from ischemic heart disease (7). Data on tobacco use in this cohort study were collected during a medical examination between 1971 and 1974, with follow-up for cause-specific mortality between 1974 and 1985. It is unclear why the results of the case-control and prospective studies differ. In comparing the studies, it was found that the study groups were different, the prevalence of snuff use in the groups was different, the years during which the studies were conducted were different, the tobacco use exposure over the course of the risk years before the event may have been different and the methods for ascertaining end points were different. Perhaps one or more of these differences may explain the discrepant results.

In support of the conclusions of the case-control studies indicating that the use of snuff is not associated with increased cardiovascular risk, are experimental studies of the physiologic effects of smokeless tobacco and transdermal nicotine. The later studies specifically address the question of whether nicotine contributes to thrombosis, which is an important, if not the most important, mechanism for smoking-induced acute cardiovascular events. The marker of the prothrombotic effect was urinary excretion of a metabolite of thromboxane A_2, which is an indication of in vivo platelet activation. Snuff users and cigarette smokers with similar blood levels of cotinine, a biomarker for nicotine intake, showed no difference in urinary excretion of thromboxane A_2 metabolites as compared with snuff users and those who do not use tobacco at all, whereas smokers

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had increased levels of thromboxane A_2 metabolite excretion (2). Similar results using thromboxane A_2 metabolite excretion were found in a crossover study comparing smokers when they were smoking cigarettes, using transdermal nicotine or placebo patch (8).

Studies of nicotine medication to aid smoking cessation also support the proposition that nicotine does not substantially contribute to acute cardiovascular events. Two prospective studies involving treatment of patients with known cardiovascular disease with transdermal nicotine have been published (9,10). Neither found evidence that transdermal nicotine increased the risk of acute cardiovascular events as compared with placebo treatment. In addition, the Health Lung study involved treating >3,000 middle-aged smokers with chronic obstructive pulmonary disease with nicotine gum (11). Over five years, nicotine gum users were found to have lower hospital admission rates for cardiovascular disease as compared with those who quit smoking without using nicotine gum, and in both cases they had lower rates as compared with individuals who continued to smoke with or without using gum. Finally, an experimental study showed that patients with severe coronary artery disease treated with transdermal nicotine, which suppressed but did not eliminate smoking, resulted in a substantial reduction in the exercise-induced myocardial perfusion defect size studied by quantitative thalium-201 single-photon emission computed tomography (12). Improved perfusion was noted despite a twofold increase in nicotine levels while using patches and smoking at the same time, as compared with the baseline smoking alone condition. It is likely that the improved perfusion was due to reduced exposure to carbon monoxide and other combustion products.

Overall, the epidemiologic and experimental data suggest that nicotine absorbed from smokeless tobacco, nicotine gum or transdermal nicotine is not a significant risk factor for accelerating coronary artery disease or causing acute cardiovascular events.

What are the implications of these studies for tobacco control? One obvious question is whether snuff use has been exonerated as a health concern. The answer is clearly no. It should be noted that in Sweden nearly all smokeless tobacco use is moist snuff, but in the U.S. both snuff and chewing tobacco are used. All forms of smokeless tobacco have the potential to cause oral cancer and other oral diseases, and possibly some nonoral cancers (13). Oral cancer may be a more significant problem with users of U.S. snuff as compared with Swedish snuff because of higher nitrosamine levels in U.S. snuff (14). Smokeless tobacco, especially chewing tobacco, contains considerable sodium (as part of an alkaline buffer to facilitate nicotine absorption). In one study, individuals who chewed tobacco had an excess sodium intake of 40 mEq/day, as compared with the same individuals not chewing tobacco (3). Such a sodium load could aggravate hypertension, congestive heart failure or other edematous states. Finally, in the U.S. perhaps the most serious concern about smokeless tobacco use is that in adolescents snuff use facilitates the development of nicotine addiction and predisposes adolescents to becoming adult cigarette smokers (15).

A second tobacco control issue is the use of nicotine medication to aid smoking cessation and for harm reduction. The data described previously, as well as other research, indicate that medicinal nicotine is always safer than cigarette smoking. Thus, the use of nicotine to aid smoking cessation is warranted even in patients with active cardiovascular disease. The harm reduction concept includes the use of medications for long periods to reduce or eliminate smoking (16). The anticipated result would be a reduction in smoking-related disease. This approach is similar to the use of methadone maintenance to treat heroin addiction. Harm reduction would be targeted at those smokers who are unable to quit smoking but who would like to reduce the health risks incurred by smoking cigarettes. There has been some concern about enhanced toxicity from using nicotine products and smoking at the same time. However, a recent study from my laboratory involving individuals who used up to three nicotine patches (63 mg) per day (the usual patch dose is 15 to 21 mg/day), combined with ad libitum cigarette smoking, showed no greater cardiovascular effect of the combination as compared with cigarette smoking or transdermal nicotine use alone (17). Thus, the available data suggest that the risk of long-term nicotine exposure is low, and the use of nicotine as a harm reduction strategy is a reasonable idea. Clinical trials of long-term nicotine therapy for harm reduction are clearly warranted.

Another harm reduction approach is the promotion of potentially less hazardous cigarette-like delivery devices. Two such products, the R.J. Reynolds Eclipse and the Phillip Morris Accord, are being test-marketed in the United States at this time. Both devices heat rather than burn tobacco. The resultant smoke contains nicotine as well as carbon monoxide, producing blood levels similar to those derived from cigarette smoking (18). However, this smoke contains much lower levels of oxidant gases, polynuclear aromatic hydrocarbons and other combustion products. As regulators of public health, policymakers consider whether or not to support the use of such products, which includes assessment of the relative safety of nicotine in the absence of most of the oxidant gases and carcinogens. The available data suggest that nicotine alone is reasonably safe, with the caveat mentioned earlier that there may be differences in effects between more rapidly and more slowly absorbed nicotine. The hazards of carbon monoxide remain an obvious concern. However, on balance, it seems worthwhile to pursue further safety studies with these types of nicotine delivery devices as a potential alternative to smoking in those who cannot otherwise quit.

Finally, nicotine has also been proposed as a medication for treatment of conditions such as ulcerative colitis, Alzheimer's disease, Tourette's syndrome and possibly attention deficit disorder and affective disorders. The same safety

considerations apply for nicotine therapy for medical diseases as discussed for harm reduction.

In conclusion, nicotine is harmful primarily because it sustains tobacco use. Tobacco use is harmful owing to toxic combustion products, nicotine-derived nitrosamines and various other tobacco additives. All tobacco use should be discouraged. Nicotine itself may be potentially harmful in certain individuals, with particular concern in pregnancy and possibly in patients with acute cardiovascular disease (1). However, nicotine is always less hazardous than using tobacco. The Huhtasaari study and others reviewed in this editorial comment support 1) the safety of using nicotine for smoking cessation, even in patients with active cardiovascular disease; 2) its use for harm reduction among recalcitrant smokers; 3) further study of cigarette-like nicotine delivery devices; and 4) the safety of conducting trials of nicotine as a medication for medical diseases.

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REFERENCES

1. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J Am Coll Cardiol 1997;29:1422–31.
2. Wennmalm A, Benthin G, Granström EF, Persson L, Peterson A, Winell S. Relation between tobacco use and urinary excretion of thromboxane A_2 and prostacyclin metabolites in young men. Circulation 1991;83:1698–704.
3. Benowitz NL, Jacob P III, Yu L. Daily use of smokeless tobacco: systemic effects. Ann Intern Med 1989;111:112–6.
4. Henningfield JE, Stapleton JM, Benowitz NL, Grayson RF, London ED. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. Drug Alcohol Depend 1993;33:23–9.
5. Huhtasaari F, Lundberg V, Eliasson M, Janlert U, Asplund K. Smokeless tobacco as a possible risk factor for myocardial infarction: a population-based study in middle-aged men. J Am Coll Cardiol 1999;34:1784–90.
6. Huhtasaari F, Asplund K, Lundberg V, Stegmayr B, Wester PO. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? BMJ 1992;305:1252–6.
7. Bolinder G, Alfredsson L, Englund A, deFaire U. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. Am J Public Health 1994;84:399–404.
8. Benowitz NL, Fitzgerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. J Am Coll Cardiol 1993;22:1159–67.
9. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Nicotine replacement therapy for patients with coronary artery disease. Arch Intern Med 1994;154:989–95.
10. Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N Engl J Med 1996;335:1792–8.
11. Murray RP, Bailey WC, Daniels K, et al. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. Chest 1996;109:438–45.
12. Mahmarian JJ, Moye LA, Nasser GA, et al. Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischemia. J Am Coll Cardiol 1997;30:125–30.
13. Winn DM. Epidemiology of cancer and other systemic effects associated with the use of smokeless tobacco. Adv Dent Res 1997;11:313–21.
14. Hoffmann D, Djordjevic MV, Fan J, Zang E, Glynn T, Connolly GN. Five leading U.S. commercial brands of moist snuff in 1994: assessment of carcinogenic N-nitrosamines. J Natl Cancer Inst 1995;87:1862–9.
15. Hu FB, Hedeker D, Flay BR, Sussman S, Day LE, Siddiqui O. The patterns and predictors of smokeless tobacco onset among urban public school teenagers. Am J Prev Med 1996;12:22–8.
16. Henningfield JE. Introduction to tobacco harm reduction as a complementary strategy to smoking cessation. Tob Control 1995;4 Suppl 2:S25–8.
17. Zevin S, Jacob P III, Benowitz NL. Dose-related cardiovascular and endocrine effects of transdermal nicotine. Clin Pharmacol Ther 1998;64:87–95.
18. Benowitz NL, Jacob P III, Slade J, Yu L. Nicotine content of the Eclipse nicotine delivery device (letter). Am J Public Health 1997;87:1865–6.