Nicotine and gastrointestinal disease

Nicotine is currently under investigation to determine whether it has a therapeutic role in the treatment of ulcerative colitis. This is because of strong epidemiological evidence that ulcerative colitis is predominantly a disease of non-smokers. The suggestion that smoking may protect against a disease rather than promote it, raises a number of emotive issues; however, the possibility that nicotine may be of some benefit in certain diseases should come as no surprise. Since its introduction to Europe in the 16th century, tobacco has been used as a ‘panacea’ for various ailments. It was suggested as a cure for aches and pains, deafness, chest disease, ‘torments of the guts’, dropsy, and bites of mad dogs. It was thought to strengthen the memory, relieve hunger and thirst, take away weariness and ‘make one cheerful of one’s work’. The Navy used tobacco enemas to resuscitate the nearly drowned, Walter Cogan (1775), remarked that ‘the injection of tobacco fumes into the intestine has been universally considered amongst the most efficacious applications … It is not only the admission of a kindly warmth into the internal parts of the body, which in all cases must prove advantageous, but its stimulus connected with this warmth seems admirably adapted to excite irritability and restore the suspended or languid peristaltic motion of the intestines’.1 Simone Tissot (1780), suggested it as treatment for intestinal obstruction from whatever cause2 and Sir Astley Cooper (1804), described the use of liquid tobacco enemas in reducing abdominal hernias. Others saw things differently, smokers were condemned by James I (1604), excommunicated by Pope Urban VIII, and decapitated by Alexis I (1655). Criticism of smoking and tobacco continues today. Nicotine’s tarnished image is by association with smoking and may not be entirely justified. It is only one of over 4000 compounds in tobacco, and although the best known and pharmacologically most active, is unlikely to be responsible for all the effects of smoking. Nicotine has many physiological and pharmacological actions. Its receptors are distributed ubiquitously and stimulation may affect the central, peripheral and autonomic nervous systems, in addition to the immune, inflammatory or neuroendocrine pathways. Its varied effects are unpredictable, and depend on the dose, mode of administration and resting ‘tone’ of the system in question.

There is little information about the effect of nicotine itself on the gastrointestinal tract in man. Most observations are with smoking and therefore by implication involve nicotine. The effect of smoking on weight is perhaps the best recognized, and accounts for a reduction of 10% between smokers and non-smokers, probably as a result of decreased calorie intake and increased energy expenditure.3 Previously, most interest in smoking and nicotine focused on peptic ulcer disease, the associations of which are summarized in the Surgeon Generals Report of 1979.4 Patients with peptic ulcer disease, both gastric and duodenal, smoke more. There is an increased prevalence of peptic ulcer amongst smokers, related to the number smoked. In addition, smoking delays healing and is associated with an increased mortality in those with ulcer disease. Mechanisms involved probably relate to the mucus bicarbonate barrier in the stomach. Smoking and possibly nicotine decrease bicarbonate secretion, which is related to endogenous prostaglandins in the mucosa; they may also increase acid secretion and bile acid reflux and so disrupt the barrier.5 Smoking increases reflux oesophagitis, probably by decreasing lower oesophageal sphincter pressure,6 and increasing bile acid reflux. This is partly due to nicotine, since the number of episodes of acid reflux is increased in subjects given transdermal nicotine compared with placebo patches.7

The detrimental effects of smoking on health are well established; the effects of nicotine are not. More recently the focus of attention has turned toward the unusual relationship between smoking, nicotine and ulcerative colitis. Our initial observation in 1982, that ulcerative colitis was largely a disease of non-smokers was a chance finding from a nutritional study in which smoking habits were considered.8 Only 8% of 230 patients with colitis were current smokers, compared with 44% of matched controls. There are now over 15 case-control studies of hospital- and community-based populations in different countries
which have consistently identified the association. In a meta-analysis of data from nine suitable studies of ulcerative colitis, Calkins showed a remarkably consistent association of smoking with ulcerative colitis in terms of direction. The risk of developing the disease was reduced in current smokers and increased in non-smokers with the greatest risk in ex-smokers; the Surgeon General's criteria for causality were fulfilled, suggesting a causal relationship. Additional support for the association has come from sources other than case-control studies. In addition, a recent study identified a negative association between smoking status and the subsequent development of pouchitis in patients who had received a restorative ileal pouch for ulcerative colitis. The time patients stop smoking in relation to the onset of colitis, has been of particular interest; over two-thirds of patients who are ex-smokers develop their disease soon after quitting, and one must question whether smoking may have a favourable effect on active disease and perhaps maintain clinical remission. It would be neither practical or ethical to consider trials in which patients were asked to start and stop smoking in studies to resolve these questions. However, there is some evidence to suggest it may have an effect on the disease. Rudra et al. questioned 30 intermittent smokers about their observations; half of them thought their colitis symptoms improved over a period of 6 weeks whilst smoking 20 cigarettes daily.

The strong negative association between smoking and colitis has led to a search for the active ingredient responsible for the relationship. Initial studies with nicotine gum were inconclusive and uncontrolled, but with the introduction of transdermal nicotine it became possible to examine nicotine in controlled trials. In the first, 72 patients with active left-sided disease were treated with either transdermal nicotine patches or placebo for 6 weeks. Patients continued their usual medication, and incremental doses of nicotine were given; most patients tolerated 15–25 mg/24 h. Seventeen of 35 patients in the nicotine group had complete remissions, compared with only nine in the placebo group. The serum levels of nicotine and cotinine were only a third of the values for smokers of 20 cigarettes a day. Side-effects were more common in the nicotine group, and were more frequent in lifelong non-smokers than in ex-smokers—the most common were nausea, light-headedness, headache and sleep disturbance. In a second study, transdermal nicotine alone was compared with 15 mg of prednisolone daily in active disease. There was no significant difference between the outcome in both treatment groups, but the trend of improvement suggested prednisolone to be superior to nicotine. In a third study, transdermal nicotine was shown to be no better than placebo when given alone as maintenance therapy for 6 months. From available evidence, nicotine appears of some benefit in active disease but not as maintenance therapy—a situation analogous to steroids. Its effect on colitis is less than might be expected from the epidemiological data. However, the serum nicotine levels in all the studies were lower than in smokers and less than expected on 15 mg/day of transdermal nicotine, which may reflect poor compliance. In addition, plateau serum nicotine profiles produced by transdermal nicotine are quite different from the peaks observed in smokers; these peaks are probably associated with various metabolic changes seen in cigarette smokers, including platelet activation, and addiction. In order to reproduce the effect of smoking on colitis one may have to mimic the serum nicotine profile of smokers with the unacceptable consequence of promoting addiction. An alternative approach would be to apply nicotine topically to the colonic mucosa, either by enema or with delayed release oral formulations. Since 60% of nicotine is converted to its major metabolite cotinine on ‘first pass’ through the liver, systemic levels of nicotine, with associated side-effects, would be much lower and tissue levels at the inflammatory site much higher. Benefit from such an approach would depend on whether nicotine has a topical effect on ulcerative colitis.

Although it would seem plausible that nicotine is the active ingredient in smoking responsible for the clinical effect in ulcerative colitis, the mechanism of action remains elusive. Despite the most intense scrutiny, the cause of colitis remains unknown, which leaves much opportunity for speculation. Some effects of nicotine could be relevant to the inflammation which occurs in ulcerative colitis. Smoking influences cellular immunity and there is a suggestion that heavy smokers may have reduced levels of IgA in both saliva and intestinal secretion. It reduces the levels of some mucosal eicosanoids including prostaglandins in man, whilst infusions of nicotine in animals may change tissue levels of eicosanoids and the thickness of adherent surface mucus in the rectum. Smoking reduces blood flow in the rectum and decreases gut permeability. Whether any of these mechanisms are relevant to its effect in ulcerative colitis remains purely speculative. Elucidation of the mechanisms involved may give a clearer insight into the pathophysiology of the disease.

Crohn's disease, a closely related inflammatory bowel condition may involve any part of the gastrointestinal tract, particularly the terminal ileum and those patients with disease limited to the rectum and colon often resemble patients with colitis. The epide-
miological findings identify an increased number of smokers compared with matched controls, and smoking appears to have an adverse effect on the course of the disease. These relationships with smoking are opposite to those in ulcerative colitis, and to avoid confusion every effort should be made to make this statement clearly to both the medical profession and patients. Since smoking is bad for Crohn's disease but may help ulcerative colitis, those with Crohn's should be strongly dissuaded from smoking. Those with colitis who improve while smoking but deteriorate when they quit will make their own decisions about smoking, but will need to know the facts. No-one, however, should be encouraged to smoke!

Patients with active ulcerative colitis may benefit from transdermal nicotine but further clinical trials with different delivery mechanisms and doses are required to explore the therapeutic potential. Should further trials confirm a therapeutic role for nicotine in colitis, its use may be limited by side-effects in some patients, particularly in lifelong non-smokers. Other clinical areas where nicotine is under investigation and may be of value include Parkinson's disease, Alzheimer's and Tourette's syndrome; clinical trials in these areas may encounter the same difficulties as in ulcerative colitis. Centuries have passed since nicotine was first used as a therapy and yet the drug still receives a mixed reception. Its association with tobacco smoking ensures it continues to receive a bad press, however, the drug in a more presentable form may yet find acceptance and respectability, and regain its role as a therapeutic agent.

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References


