SHORT REPORTS

Should patients with inflammatory bowel disease smoke?

An observation that fewer people with ulcerative colitis smoked cigarettes than would be expected[1] has been confirmed by further studies.[2-4] The relevance of this finding is at present not clear,[5] but it has been suggested that smoking may protect against ulcerative colitis. The reports received widespread publicity, and we are often asked by patients with the disease for advice on smoking. We therefore studied smoking habits in patients with inflammatory bowel disease to ascertain whether smoking is associated with less severe disease.

Patients, methods, and results

A total of 252 consecutive outpatients with inflammatory bowel disease were interviewed and their case notes reviewed. Details were obtained of smoking habit, frequency of relapse, symptoms in remission and relapse, extent of disease, complications, and the numbers of admissions to hospital and of operations. The means of the three most recent full blood cell counts, white cell counts, erythrocyte sedimentation rates, albumin concentrations, and platelet counts were recorded. Patients were subdivided into three groups on conventional clinical grounds: 102 patients had ulcerative colitis, 96 Crohn's colitis, and 54 Crohn's disease of the small bowel. Patients with Crohn's disease in both the small bowel and the colon were included in the third group. Analysis of 172 variables for each patient was carried out with an ICL 2970 computer, using the statistical package for the social sciences (SPSS). The χ^2 test, with Yates's correction factor when appropriate, was used for all cross tabulation of coded variables. Continuous variables were analysed with a two tailed Student's t test. Probability values of less than 5% were considered to be significant.

The proportion of cigarette smokers was smaller among patients with ulcerative colitis (eight (8%)) than among those with Crohn's colitis (24 (25%); $p < 0.02$) or with small bowel Crohn's disease (28 (52%); $p < 0.0001$); the difference in the proportion of smokers between patients with Crohn's colitis and small bowel Crohn's disease was also significant ($p < 0.02$). Thirty three patients with ulcerative colitis (32%), 29 with Crohn's colitis (30%), and seven with small bowel Crohn's disease (13%) were ex-smokers. The groups were well matched for age, sex, social class, and duration of disease. The table shows clinical details of patients within groups according to current smoking habits. Smokers with Crohn's colitis tended to have relapses more often ($p < 0.028$) and more severe pain ($p < 0.007$) than non-smokers. Smokers with small bowel Crohn's disease tended to have more frequent bowel movements ($p < 0.05$), more admissions to hospital ($p < 0.05$), more operations ($p < 0.04$), and higher white cell counts ($p < 0.001$). There were relatively few smokers with ulcerative colitis which made comparison largely irrelevant in this group. Of the total of 252 patients, 13 claimed to have continuous symptoms, nine of whom were current smokers, whereas of 49 patients who had on average less than one relapse a year, only 11 smoked ($p < 0.004$).

Comment

This study confirms the low prevalence of smoking among patients with ulcerative colitis. Smokers therefore appear to have a reduced risk of developing the disease, and possibly smoking is in some way protective. We think, however, that a more attractive hypothesis is that smoking in some way influences the pathological appearances, possibly by an effect on the immune system, leading to features of Crohn's disease rather than ulcerative colitis.

It is difficult to assess the course of disease in a retrospective study, but smokers tended to do worse on most counts in each group of patients studied. Two explanations are possible: either smoking has a direct effect on the disease or patients who have more severe symptoms find psychological relief by continuing smoking. In either event, our findings together with the known health hazard of smoking lead us to conclude that, for the present, patients with inflammatory bowel disease should be advised to stop smoking.

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4 Logan R, Edmund M, Langman MJS. Is non-smoking associated with ulcerative colitis? *Gut* 1983;**24**:A499.
5 Bailas JC. Cigarettes, ulcerative colitis and inferences from uncontrolled data. *N Engl J Med* 1983;**308**:275-7.

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Liver damage from verapamil

Verapamil hydrochloride, a derivative of papaverine, is a calcium channel blocking drug used to treat angina pectoris, supraventricular tachycardia, subaortic stenosis, and hypertension. Several recent reports have suggested that verapamil may induce liver injury.[1-4] We report a case of idiosyncratic hepatic injury caused by verapamil.

Case report

The patient was a 47 year old man with an unremarkable medical and family history. One week before admission to hospital he had complained of diffuse abdominal pain, fever (38°C), arthralgias, headache, and vomiting followed by dark urine and jaundice. Hepatitis was diagnosed. Treatment for angina pectoris with dipyridamole 220 mg daily and verapamil 120 mg daily had been started three months and two weeks previously, respectively. On clinical examination on 3 February he had jaundice and diffuse abdominal pain especially in the right upper quadrant, with the liver palpable 8 cm below the costal margin. The spleen was not palpable.

Laboratory findings showed serum bilirubin concentration 128 μmol/l (7·5 mg/100 ml) (normal range 1·7-17 μmol/l (0·1-1·0 mg/100 ml)); serum

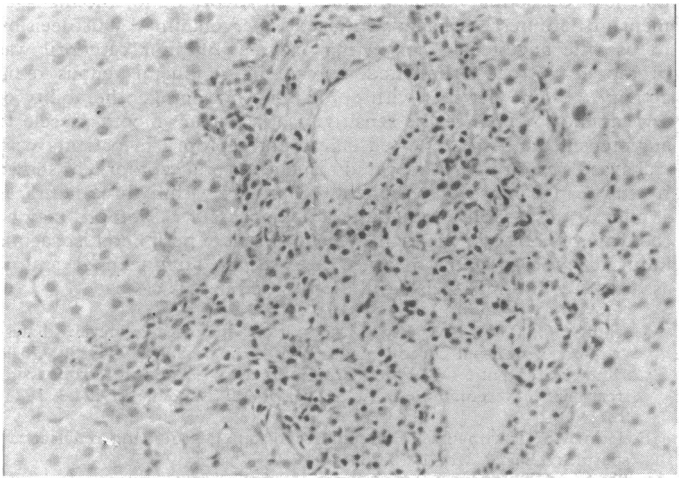
Comparison of clinical course of disease in each diagnostic group according to current smoking habit

	Ulcerative colitis		Crohn's colitis		Small bowel Crohn's disease	
	Non-smokers	Smokers	Non-smokers	Smokers	Non-smokers	Smokers
No of patients	94	8	71	24	26	28
Mean (SD) No of relapses in past year	1·9 (2·6)	2·3 (0·9)	2·5 (3·7)	3·8 (5·3) $p<0.03$	1·9 (3·5)	2·96 (3·5)
Mean (SD) No of relapses/year	1·9 (2·6)	2·2 (1·1)	2·1 (2·3)	2·9 (1·9)	3·5 (5)	4·4 (5·4)
Mean (SD) severity of pain during relapse*	5·5 (2·3)	9·0 (18) $p<0.009$	5·3 (2·3)	7·2 (2·3) $p<0.007$	6·8 (2·5)	7·0 (2·3)
Mean (SD) bowel frequency/day during relapse	7·2 (5·4)	7·0 (7·8)	6·1 (5·1)	7·3 (6·4)	5·5 (3·7)	9·8 (5·4) $p<0.05$
Mean (SD) No of hospital admissions/patient	0·6 (0·9)	0·6 (0·8)	0·76 (8)	0·98 (1)	1·0 (0·9)	1·9 (1·8) $p<0.05$
No undergoing surgery	4		7	2	9	18 $p<0.04$
Mean (SD) white cell count ($\times 10^9$/l)	7·9 (2·2)	7·8 (2·8)	9·7 (11·3)	9·7 (2·8)	7·5 (1·9)	9·7 (2·2) $p<0.001$
Mean (SD) erythrocyte sedimentation rate (mm in first h)	16 (15)	13 (21)	20 (8)	24 (11)	18 (15)	27 (21)

*Measured on linear analogue scale of 0-10.

glutamic pyruvic transaminase activity 145 IU/l (normal range 1-40 IU/l); alkaline phosphatase activity 170 IU/l (normal range 29-48 IU/l); γ glutamyl transferase activity 568 IU/l (normal range 6-28 IU/l); and 17% eosinophils in peripheral blood. Markers for hepatitis A and B viruses, Epstein-Barr virus, and cytomegalovirus and autoantibodies were not found in the serum. A bile culture and tests for rheumatoid arthritis and lupus erythematosus yielded negative results. Ultrasonography of the liver confirmed hepatomegaly with no dilatation of the bile ducts. On 14 February blood tests showed serum glutamic pyruvic transaminase activity 108 IU/l; serum bilirubin concentration 21 μmol/l (1·2 mg/100 ml); alkaline phosphatase activity 175 IU/l; glutamyl transferase activity 419 IU/l; and eosinophils in the peripheral blood 9%. Laboratory findings on 26 February showed serum glutamic pyruvic transaminase activity 83 IU/l; serum bilirubin concentration 10 μmol/l (0·6 mg/100 ml); alkaline phosphatase activity 70 IU/l; γ glutamyl transferase activity 68 IU/l; and 2% eosinophils in peripheral blood. A percutaneous liver biopsy performed on the same day showed mixed inflammatory cells with infiltrates rich in eosinophils occupying the portal tracts; moderate cholestasis and slight increase in lipocytes were also noted. The lobular structure was normal (figure).

At the beginning of March he seemed well; all his symptoms had resolved and the liver was smaller. All laboratory findings were within normal limits.



Portal tract containing infiltrate of mixed inflammatory cells rich in eosinophils. Haematoxylin and eosin ×250.

Comment

In 1969 Ronnov-Jessen and Tjernlund first reported hepatic injury due to treatment with papaverine; their data suggested a hypersensitivity reaction.[2] A similar mechanism might therefore be expected with the papaverine derivative verapamil. Recently three cases of hepatotoxicity possibly induced by verapamil were described.[1 3 4] An allergic mechanism was supposed in all of them, but no histological study was performed. In our patient the absence of demonstrable viral infection, autoimmune disease, and intake of other toxic drugs supports the view that a syndrome similar to hepatitis can be caused by verapamil. An allergic pathogenesis is even more strongly indicated in this than in previous cases: the clinical picture, the interval (two weeks) between the start of treatment with verapamil and onset of symptoms, and the eosinophilia strongly suggest a hypersensitivity reaction. Furthermore, histological appearances in our patient were those typically described in idiosyncratic hepatic injury related to hypersensitivity[5] and were similar to those found by Ronnov-Jessen and Tjernlund in two of four cases of hepatotoxicity induced by papaverine.[2]

So far only a limited number of cases have been documented histologically, but the possibility that papaverine and its derivatives may cause hepatitis should be kept in mind if new cases with a similar histological picture are described. Physicians should be made aware that treatment with verapamil may occasionally provoke hepatic injury, and liver function tests should be monitored carefully in patients being treated with verapamil.

[1] Nash DT, Feer TD. Hepatic injury possibly induced by verapamil. *JAMA* 1983;**249**:395-6.

[2] Ronnov-Jessen V, Tjernlund A. Hepatotoxicity due to treatment with papaverine. *N Engl J Med* 1969;**281**:1333-5.

[3] Brodsky SJ, Cutler SS, Weiner DA, Klein MD. Hepatotoxicity due to treatment with verapamil. *Ann Intern Med* 1981;**94**:490-1.

[4] Stern EH, Pitchon R, King BD, Wiener I. Possible hepatitis from verapamil. *N Engl J Med* 1982;**306**:612.

[5] Zimmerman HJ, Ishak KG. Hepatic injury due to drugs and toxins. In: MacSween RNM, Anthony PP, Shever PJ, eds. *Pathology of the liver*. Edinburgh: Churchill Livingstone, 1979:335-86.

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Cardiac arrest after reversal of effects of opiates with naloxone

Naloxone reverses respiratory depression after both anaesthesia and overdosage of narcotics and is also recommended in suspected opiate coma. Cardiovascular problems have developed after anaesthesia in patients given naloxone to reverse the effects of opiates.[1] We report on a patient addicted to narcotics who suffered ventricular fibrillation on four occasions after treatment with naloxone.

Case report

A 45 year old man presented with vomiting. He had drunk a bottle of spirits daily for over 10 years and had been admitted to hospital several times previously for conditions related to his alcoholic intake. We later learnt that he had also been taking up to 10 mg diamorphine daily for eight years. He showed signs of chronic liver disease, but pulse rate, respiration, blood pressure, a chest radiograph, and an electrocardiogram were normal. Liver function tests showed a pattern similar to that seen in hepatitis, and blood glucose concentration was 31 mmol/l (560 mg/100 ml). He was given an insulin infusion (3 U/hour), parenteral B vitamins, vitamin K, and chlormethiazole titrated to his withdrawal symptoms.

After 24 hours his condition was stable. Unknown to us, he then injected himself with diamorphine. Five hours later he became drowsy and then unrousable. A used syringe was near his hand, and an empty ampoule of diamorphine was found in his clothing. His wife, a fellow addict, later admitted to having smuggled these in. He was given two doses of naloxone 0·4 mg intravenously three minutes apart. Ventricular fibrillation was noted on the monitor three minutes later and responded to cardioversion. Blood glucose concentration was 11 mmol/l (198 mg/100 ml) and plasma potassium concentration 3·1 mmol(mEq)/l. He recovered consciousness but then relapsed into coma. He was intubated, and five minutes after two further doses of naloxone 0·4 mg intravenously he had another episode of ventricular fibrillation. He was defibrillated and given antiarrhythmic drugs. He recovered fully and discharged himself 10 days later.

Eight months later he was readmitted with symptoms of alcohol withdrawal. Signs, liver function, radiographic and electrocardiographic appearances, and treatment were as previously. He again surreptitiously injected himself with diamorphine and became comatose. Two doses of naloxone 0·4 mg intravenously were followed by one intramuscularly. His degree of consciousness improved, but after 30 minutes ventricular fibrillation supervened, necessitating defibrillation and infusion of lignocaine. Naloxone 0·4 mg was again administered intramuscularly, but ventricular fibrillation recurred 50 minutes later. Cardioversion and antiarrhythmic drugs maintained a stable cardiac output, but he died from hepatic and renal failure one week later. Postmortem examination showed hepatic cirrhosis and alcoholic cardiomyopathy.

Comment

Ventricular fibrillation has been reported after reversal of narcotic poisoning with nalorphine in a young woman presenting in casualty.[2] More recently seven cases of adverse cardiac effects after administration of naloxone during or after anaesthesia with opiates and nitrous oxide have been reviewed[1]; five patients had pre-existing cardiac disease, and the two others were fit young women. They showed either a rapid and substantial rise in blood pressure associated with atrial tachycardia and followed by cardiac decompensation, or ventricular fibrillation. In normal subjects anaesthetised with morphine and nitrous oxide,[3] and in patients addicted to narcotics, pulse rate and blood pressure increase appreciably after reversal of the effects