treatment necessitates observation—for example, an annual examination by biomicroscopy of the cornea. It might also be prudent to review retinal function (colour vision and electroretinography) in patients taking flecainide.

1 Gentzkow GD, Sullivan JY. Extracardiac adverse effects of flecainide. *Am J Cardiol* 1984;53:101-5B.

- 2 Pilger IS. Pigmentation of the cornea: a review and classification. *Ann Ophthalmol* 1983;15:1076-82.
- 3 Clement RS, MacKintosh HT. Drug induced ocular lipoidosis. *Transactions of the Ophthalmological Society of New Zealand* 1982;34:52-8.
- 4 Bron AJ. Vortex patterns of the corneal epithelium. *Transactions of the Ophthalmological Society of the United Kingdom* 1973;93:455-72.
- 5 Chew E, Gosh M, McCulloch C. Amiodarone-induced cornea verticillata. *Can J Ophthalmol* 1982;17:96-9.

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Smoking and recurrent attacks of acute intermittent porphyria

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Patients with acute porphyria often present with acute manifestations of their disease, but they may also be identified by screening programmes. Such patients who have never experienced the acute features are termed latent. Although 70% of attacks of porphyria are related to ingestion of many common drugs, usually drugs inducing hepatic microsomal enzymes, the precipitating factors in the other 30% are unclear, and may include endogenous hormones.¹ Smoking is an enzyme inducer that can affect drug metabolism, and it has been implicated in the alteration of steroid hormone metabolism.² Several of our patients had recurring acute attacks requiring repeated hospital treatment. No obvious precipitating factor was identifiable in this group, but all were addicted to smoking. We therefore considered the possibility that smoking was a precipitant of attacks in patients with acute intermittent porphyria.

Subjects, methods, and results

A questionnaire sent to 144 patients with acute intermittent porphyria asked about smoking habits, the type and quantity of tobacco products used, and whether and when the patients had stopped smoking. Questions were also asked on the effects of drugs including alcohol on their disease, whether pregnancy had been a problem in the women, and the number of attacks that patients had experienced.

Diagnosis of porphyria was based on increased urinary excretion of porphyrin precursors, 5-aminolaevulinic acid and porphobilinogen, and on decreased activity of erythrocyte porphobilinogen deaminase.¹ Responses were assessed to find the number of attacks and smoking habits when the patients had been in the age group at highest risk (15-40 years in women and 25-50 years in men). In patients who formerly smoked, the frequency of attacks was investigated only at the time they had been smoking.

In all, 93 patients (65%) replied to the questionnaire (77 women, 16 men). The mean age at response was 46 (range 27-74) years in men and 41 (range 17-72) in women.

Association between smoking and porphyria. Figures are numbers (percentages)

	Two or more attacks	Single attack	Latent porphyria
Non-smokers:	9 (20)	30 (67)	6 (13)
Men (n=5)	1 (2)	3 (7)	1 (2)
Women (n=40)	8 (18)	27 (60)	5 (11)
Smokers:	35 (73)*	6 (13)*	7 (15)
Men (n=11)	9 (19)	1 (2)	1 (2)
Women (n=38)	26 (54)*	5 (10)*	6 (13)

* $\chi^2=31.37$, $p<0.001$ compared with non-smokers.

All the smokers used cigarettes. Smoking was significantly associated with patients having had two or more acute attacks of acute intermittent porphyria (table). Of the women with multiple attacks, nine (seven smokers and two non-smokers) also had some hormonal association contemporaneous with attacks. Of 25 smokers (nine men) who drank alcohol, 12 (two men) noted an adverse effect of alcohol, whereas of 14 non-smokers (six men) nine (one man) experienced adverse effects of alcohol.

Comment

The latent and active groups of patients with acute intermittent porphyria had almost identical proportions of smokers and non-smokers, which suggests that smoking is not a primary precipitant of acute attacks. In patients with active porphyria, 44% of smokers had more than one attack whereas only 11% of non-smokers had more than one attack. This would suggest that smoking is acting with other factors that induce attacks that are thereafter enhanced by components in cigarette smoke. Confounding contributing factors would be the concurrent ingestion of alcohol or drugs, or both.¹

Smoking has been implicated in the alteration of steroid metabolism with an important anti-oestrogenic effect.² Several constituents of cigarette smoke can stimulate the activity of hepatic cytochrome P-450, and steroid hormone metabolism is affected by many inducers of these enzymes.³ Indeed, the mean oestradiol concentration and mean production rate of oestradiol are significantly greater in smoking than in non-smoking men.⁴ The composition of cigarette smoke is complex; it contains many compounds likely to induce the mono-oxygenases such as the benzo[a]pyrenes.⁵ In these circumstances it will be difficult to identify the compounds that are the strongest inducers of the haem biosynthetic pathway.

Our study suggests an association between cigarette smoking and the induction of repeated acute attacks of porphyria. Because smoking alters oestrogen metabolism it seems reasonable to postulate that this may be related to induction of the activity of the hepatic mono-oxygenases with subsequent effects on steroid hormone and porphyrin metabolism.

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- 1 Moore MR, McColl KEL, Rimington C, Goldberg A. *Disorders of porphyrin metabolism*. New York: Plenum, 1987.
- 2 Michnovicz JJ, Herschopf RJ, Naganuma H, Bradlow HL, Fishman J. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-oestrogenic effect of cigarette smoking. *N Engl J Med* 1986;315:1305-9.
- 3 Kanarkowski R, Tornatore KM, D'Ambrosio R, Gardner MJ, Jusko WJ. Pharmacokinetics of single and multiple doses of ethinyl estradiol and levonorgestrel in relationship to smoking. *Clin Pharmacol Ther* 1988;43:23-31.
- 4 Klaiber EL, Broverman DM. Dynamics of oestradiol and testosterone and seminal fluid indexes in smokers and non-smokers. *Fertil Steril* 1988;50:630-4.
- 5 Appel BR, Guirguis G, Kim I-S, et al. Benzene, benzo(a)pyrene and lead in smoke from tobacco products other than cigarettes. *Am J Public Health* 1990;80:560-4.

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