from a mean of 11.6 (median 4) in 1988 to 15.6 (5) in 1989 ($T=3.83$, $p<0.001$). The numbers of partners in the month before interview also significantly increased from a mean of 2.1 (median 1) to 2.2 (1) ($T=2.03$, $p<0.05$).

More importantly from the point of view of HIV transmission the mean number of penetrative sexual partners in the previous year rose from 2.2 (median 1) to 2.5 (1) and in the previous month from 0.5 (0) to 0.6 (0), though neither increase was significant. The proportion of partners with whom anal penetration occurred was, however, significantly lower for the monthly estimates (0.37 compared with 0.52; $T=17.12$, $p<0.001$) and for the previous year (0.31 compared with 0.34; $T=21.63$, $p<0.001$).

Comment

The proportion of men in the cohort engaging in anal intercourse increased between 1988 and 1989. Anal intercourse seemed to be an infrequent occurrence

for a comparatively large number of them and not restricted to a small group who had yet to adopt or who had abandoned practising safer sex.

Although men had anal intercourse with a smaller proportion of their sexual partners, the number of partners increased, thus increasing the number of risk encounters. These findings lead us to predict a rise in HIV infections and marker diseases such as rectal gonorrhoea.

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(Accepted 12 November 1990)

Department of
Ophthalmology, Aarhus
Kommunehospital,
DK-8000 Aarhus C,
Denmark
Hans Ulrik Møller, research
fellow

Department of Internal
Medicine, Division of
Cardiology, Aarhus
Amtssygehus, DK-8000
Aarhus C, Denmark
Kristian Thygesen,
consultant cardiologist

Department of
Ophthalmology,
Diaconessenhuis, 2334 CK
Leiden, The Netherlands
Pieter Jan Kruit, consultant
ophthalmologist

Correspondence to:
Dr Møller.

BMJ 1991;302:506-7

Corneal deposits associated with flecainide

Hans Ulrik Møller, Kristian Thygesen,
Pieter Jan Kruit

Flecainide is a potent antiarrhythmic drug (class IC) for the treatment of ventricular and supraventricular tachycardias. Recently, proarrhythmogenic events and sudden death, in addition to milder side effects, have been reported.¹ Corneal deposits caused by various drugs have been well documented.² We report two cases of corneal deposits associated with flecainide treatment.

Case reports

CASE 1

A 46 year old Danish man started treatment with flecainide 200-300 mg daily in February 1988 for recurrent atrial fibrillation. Six months later he developed photophobia and blurring of and glaring in his vision. Successful concomitant digoxin treatment was started in November 1988 because of relapse of the

atrial fibrillation. In May 1989 his visual acuity with correction by spectacles was 0.8 in the right eye and 0.7 in the left. Biomicroscopy with a slit lamp showed a greyish, superficial configuration of close narrow lines. The centre of the whorl was situated below the centre of the cornea and contained a sharply demarcated rounded area (1 mm²) of epithelium with a normal appearance (figure).

Flecainide treatment was discontinued. To relieve symptoms quickly and to establish a diagnosis both eyes were operated on under local anaesthesia. The opacities were easily abraded, and after a few weeks visual acuity was 1.0 in the right eye and 0.9 in the left and the blurring and glare had disappeared. The abraded epithelium was examined by means of high pressure liquid chromatography by Med-Lab AS, Copenhagen, which said that the specimen contained a substance that had the same appearance chromatographically as flecainide and was likely to be flecainide combined, for example, with peptides.

CASE 2

A 72 year old Dutch man was treated with flecainide 100-200 mg daily in November 1987 for atrial fibrillation. After four months his visual acuity was 0.5 in the right eye and 0.6 in the left with correction by spectacles. Slit lamp examination gave similar results to those in case 1. Treatment with flecainide was discontinued; after three months vision returned to 1.0 in both eyes.

Comment

Visual disturbance has been described in 28% of patients receiving flecainide.¹ The condition was speculatively thought to be an effect of flecainide on the ciliary muscle, although no slit lamp examinations were carried out.

The chemical structure of flecainide gives it amphipathic cationic properties similar to those of chloroquine and amiodarone, which may permit the formation of drug-lipid complexes that manifest as drug induced lipidosis of the cornea.³

The distribution of the corneal pigment is due to epithelial cell slide.⁴ The clear area in the figure is atypical of entities with corneal pigmentation and cannot be explained.

That the opacities were situated comparatively superficially is noteworthy. Deposits deeper in the corneal stroma have, however, been found in corneal amiodarone lipidosis,⁵ thus implying that prolonged

Slit lamp photograph of corneal deposits of flecainide in case 1. Arrow shows clear zone at centre of whorl. Insert shows that dust like deposits are in vortical configuration

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.

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(Accepted 17 October 1990)

Smoking and recurrent attacks of acute intermittent porphyria

Gregory Y H Lip, Kenneth E L McColl, Abraham Goldberg, Michael R Moore

University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow G11 6NT

Gregory Y H Lip, MB, research fellow
Kenneth E L McColl, MD, senior lecturer
Sir Abraham Goldberg, FRCP, regius professor of the practice of medicine (now retired)
Michael R Moore, DSC, reader in medicine

Correspondence to: Dr Moore.

BMJ 1991;302:507

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.

We thank Mrs Anne Cook for expert technical assistance and Dr Gordon Murray for statistical advice.

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(Accepted 27 November 1990)