form of treatment on cardiovascular morbidity and mortality. Although disappointing, this is not altogether surprising in view of the overwhelming preponderance of the blood pressure level as the major risk factor for cardiovascular morbidity and mortality in this group. Some workers have found that the blood pressure is a more significant risk factor for arterial disease among established diabetics than among non-diabetics.[15] Possibly hypotensive treatment should therefore be more readily used in people who also have glucose intolerance or diabetes. The only other conventional risk factor which also had some predictive power in borderline diabetics was the plasma cholesterol concentration. The implication of this finding is that diets aimed at lowering plasma cholesterol might be more appropriate than simply low-carbohydrate or low-calorie diets, as we have discussed more fully elsewhere.[2]

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Copies of the unpublished tables can be obtained from Dr R J Jarrett, Unit for Metabolic Medicine, Department of Medicine, Guy's Hospital Medical School, London Bridge, London SE1 9RT.

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SIDE EFFECTS

Perforation of chronic peptic ulcers after cimetidine

The H_2 receptor antagonist cimetidine has been marketed in Britain since November 1976 (as Tagamet). It has been generally acclaimed for its success in treating peptic ulceration, and there have been few reported side effects. We report here three cases of perforation of chronic peptic ulcers in which abrupt cessation of treatment with cimetidine may have precipitated the perforation.

Case 1

A 59-year-old man who had had symptoms of peptic ulcer for 25 years was admitted on 10 January 1977 with a perforated duodenal ulcer. He had not been investigated previously for his dyspepsia. Five days before his admission he had completed a six-week course of cimetidine, 200 mg thrice daily plus 400 mg at night (200 tablets), which had completely relieved his symptoms. At laparotomy a large perforation of a chronic duodenal ulcer with gross contamination of the peritoneal cavity was found and simple closure of the perforation was carried out.

Case 2

A 43-year-old man with a five-year history of symptoms of peptic ulcer was admitted on 13 June 1977 with a perforated gastric ulcer. A barium meal examination in 1973 had confirmed prepyloric ulceration. Ten days before admission he had completed a four-week course of cimetidine, 200 mg thrice daily plus 400 mg at night (140 tablets), which gave no symptomatic relief. Laparotomy showed that a 3-cm prepyloric ulcer crater had perforated with gross contamination of the peritoneal cavity. Simple closure of the perforation after biopsy was carried out. Biopsy confirmed a benign gastric ulcer.

Case 3

A 43-year-old woman who had had symptoms of peptic ulcer for 12 years was admitted on 13 June 1977 with a perforated duodenal ulcer. A barium meal examination in 1965 had shown deformity of the duodenal cap. Ten days before admission she had completed a six-week course of cimetidine, 200 mg thrice daily plus 400 mg at night (200 tablets), which had given complete relief of her symptoms. At laparotomy moderate contamination of the peritoneal cavity from a perforated duodenal ulcer was found, and a truncal vagotomy and pyloroplasty were carried out.

Comment

During the six months from December 1976 to June 1977 17 patients with perforated peptic ulcers (14 duodenal ulcers and three gastric ulcers) required laparotomy in this district hospital group. In the three patients described here acute perforation of a chronic ulcer had occurred within two weeks of an abrupt cessation of cimetidine treatment. This complication has not been described.

In reviewing published work on H_2 receptor antagonists we found one further case of perforation of a duodenal ulcer occurring six days after stopping metiamide,[1] the predecessor of cimetidine. In this case the patient had been given a one-month course of metiamide followed by 400 mg at night as a maintenance dose for eight months. The perforation occurred six days after the maintenance dose was stopped, and the patient died.

There are two disturbing features to highlight in our three cases. Firstly, all three patients were prescribed cimetidine by their general practitioners and had no pretreatment investigation and no subsequent investigation planned to confirm ulcer healing. The possibility of treating a gastric cancer was therefore not excluded, and cimetidine can produce symptomatic relief in gastric cancer.[2] Secondly, in all three patients the large size of the perforation resulted in moderate to gross contamination of the peritoneal cavity, which precluded definitive ulcer surgery in two of the patients.

The perforations may have occurred because of rebound hyperacidity after cimetidine had been stopped, but there is no consistent evidence of a "rebound" rise in gastric acid secretion in the studies so far carried out.[3 4] Alternatively, the partially healed chronic ulcer which has responded to cimetidine may be less resistant to perforation when exposed to the normal acid concentrations after cimetidine has been stopped.

Conclusion—As a result of this experience we recommend that the treatment of a chronic peptic ulcer with cimetidine should be conducted as follows. An initial course, consisting of 200 mg thrice daily plus 400 mg at night, should last at least six weeks and be followed immediately by a maintenance course of 400 mg at night for three months or until ulcer healing has been shown on endoscopy. This treatment regimen should be considered even if there is no sympto-

matic response to the initial course (see case 2). Such a course should prevent perforation, and this maintenance dose regimen has also been shown to reduce the recurrence rate of the ulcers.[1 5]

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Queen Elizabeth Hospital, Sheriff Hill, Gateshead NE9 6SX
W A WALLACE, MB, CHB, surgical registrar
C M E ORR, MB, CHB, surgical registrar
A R BEARN, FRCS, consultant surgeon

Acne induced by PUVA treatment

Recently there has been a rapid development in the world-wide use of oral and topical methoxsalen (8-methoxypsoralen; 8-MOP) with long-wave ultraviolet light (UVA) for treating patients with psoriasis. This form of photochemotherapy is known as PUVA treatment, and is effective in clearing and maintaining a remission of psoriasis in most patients treated.[1-3] It is currently being evaluated at various centres in the UK to define the indications for its use and to determine the short- and long-term side effects. Acute side effects such as erythema, nausea, pruritus, and dizziness, though rare, are well recognised.[4] We report a hitherto unrecognised side effect of PUVA treatment: the development of an acneiform eruption in one of our patients.

Case report

The patient, a 37-year-old man with extensive psoriasis for over 30 years, was started on PUVA treatment in April 1977. He was treated initially three or four times weekly, taking by mouth 40 mg methoxsalen two hours before being irradiated by arrays of high-intensity UVA fluorescent tubes arranged in two modules (Dermatron-48). The irradiance as measured at skin surface varied from 3-6 mW/cm^2. The treatment dose was gradually increased by 0·5 J/cm^2 twice weekly from an initial dose of 2·0 J/cm^2. After six weeks (20 treatments) his psoriasis was clearing, but he developed an acneiform eruption on the chest and back that consisted mainly of small, red, dome-shaped papules and a few comedones and pustules. He had never had acne vulgaris and there was no history of exposure to industrial oils. Treatment with topical corticosteroids had been discontinued in January 1977.

A biopsy specimen of a papular lesion showed a dilated pilosebaceous follicle filled with inflammatory debris and keratin. At one point the follicular epithelium was necrotic and ruptured with a sparse surrounding dermal infiltrate. We considered that his acneiform eruption was induced by the PUVA treatment. We did not discontinue treatment because the patient regarded the eruption as much less of a problem than his psoriasis. By the end of July (34 treatments) his psoriasis had almost completely cleared apart from a few residual plaques on the elbows and lower legs. His acneiform eruption on the chest, upper back, and deltoid regions persisted.

Comment

Acneiform eruptions may occur after prolonged periods of sunbathing. In 1972, Hjorth *et al*[5] described 40 patients who developed an acneiform eruption which they termed "acne aestivalis," and because it often followed a Mediterranean holiday in the sun, "Majorca acne." Studies on a case of acne aestivalis[6] have not helped in disclosing its cause, though the histopathological findings resembled those in cases of steroid acne[7]—namely, necrosis of a segment of the follicular lining with a sparse neutrophil infiltrate. Histological evidence of this type of monomorphic acne was found in the biopsy specimen taken from our patient. The papular lesions he developed were like those described in acne aestivalis,[5 6] but he also had pustules and comedones such as occur in the sun-aggravated common acne.

Though acne usually improves during the summer with exposure to sunshine, it may be aggravated in some patients,[8] particularly in a hot and humid climate. It is probably related to excessive sweating.[8 9] Patients undergoing PUVA treatment are usually irradiated in enclosed cabinets and cubicles in rather confined areas. Despite powerful extractor fans and fans incorporated in the cabinets and modules used, the temperature and humidity in these units are often high, and some patients sweat profusely. We consider that these factors including the UVA light contributed to the development of the acneiform eruption in our patient, and would be interested to know if others have seen this side effect of PUVA treatment.

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Rupert Hallam Department of Dermatology, Hallamshire Hospital, Sheffield S10 2JF
C JONES, MB, MRCP, registrar in dermatology
S S BLEEHEN, MB, FRCP, consultant dermatologist

Disopyramide and warfarin interaction

Disopyramide is an antiarrhythmic compound, with activity against supraventricular and ventricular dysrhythmias.[1 2] Recent work has suggested that it may be particularly useful in ectopic atrial tachycardia.[3] We describe here an interaction between disopyramide and warfarin that may be of clinical importance.

Case report

A 58-year-old marine engineer, who had previously enjoyed good health, was admitted to the coronary care unit on 9 May 1977 suffering from an acute anteroseptal cardiac infarction. Complications included left ventricular failure on presentation and an episode of atrial tachycardia at 12 hours. The latter was immediately treated with an intravenous bolus dose of disopyramide phosphate (1·5 mg/kg body weight), with a rapid and sustained reversion to sinus rhythm. The patient was digitalised and started on a maintenance regimen of disopyramide base administered by mouth (100 mg every six hours). The policy of the coronary care unit is to use prophylactic intravenous heparin in the absence of contraindications. Heparin was administered for 48 hours, after which it was replaced by oral anticoagulation with warfarin.

The patient's further recovery was uneventful and he was eventually discharged after two weeks in hospital on the following treatment: digoxin 0·25 mg/day, frusemide 80 mg/day, potassium supplements, warfarin 3 mg/day, and disopyramide base 100 mg every six hours.

Four weeks later he returned because of general malaise and was found to be hypotensive (80/60 mm Hg). The disopyramide was discontinued in view of its potential negative inotropic effect. There was a good clinical response over 24 hours. Over the next few days we noticed that his previously stable prothrombin time fell considerably, requiring incremental doses of warfarin (see table). At no time was there any evidence of hepatic or renal dysfunction in this patient.

Comment

We are unaware of any reported interaction between disopyramide and warfarin in vivo. There is, however, some suggestion of an in-vitro synergism in animal studies (personal communication, Searle Laboratories). The mechanism is unknown but unlikely to be due to displacement of warfarin by disopyramide from plasma protein binding sites, as disopyramide is only 27% protein bound.[4] Coumarin metabolism occurs in hepatic microsomal mixed function oxidase systems,[5] and the apparent interaction between disopyramide and