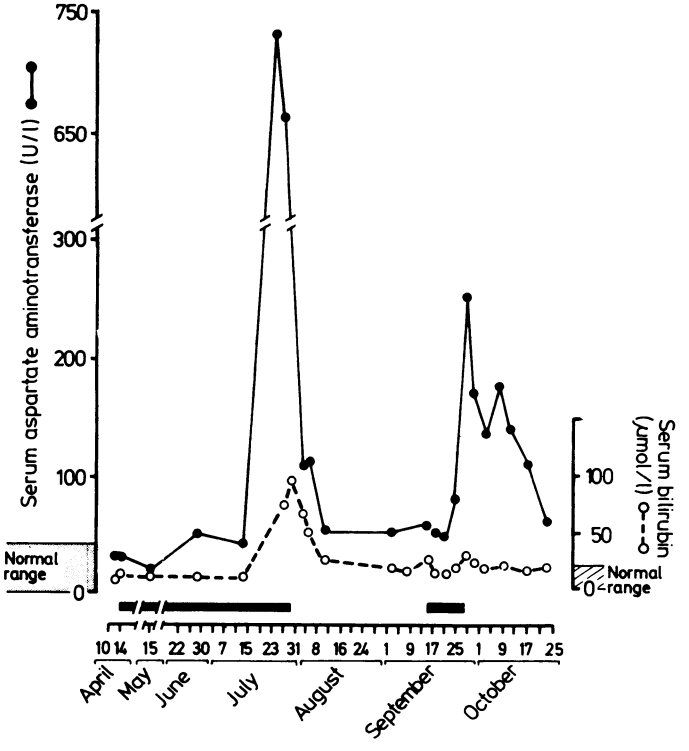
Tamoxifen and liver damage

Tamoxifen in the treatment of metastatic carcinoma of the breast is usually well tolerated with few side effects.[1 2] We report on a patient in whom tamoxifen was associated with deterioration of liver function.

Case report

A 75 year old woman, who had undergone radical mastectomy in 1978 for breast carcinoma, developed bony metastases by April 1982 and was treated with tamoxifen 10 mg twice daily. Ten weeks later she developed nausea, vomiting, and hip pain due to progressive skeletal disease. Serum liver enzyme activities, serum calcium concentrations, and a liver scan were all normal. Prednisolone 5 mg twice daily was added to her treatment, but, despite regular antiemetics, nausea and vomiting persisted. Serum bilirubin concentration and aspartate aminotransferase activity continued to rise (figure). All drugs except diamorphine and prednisolone were stopped on 29 July, and aspartate aminotransferase activity and bilirubin concentration fell for two weeks (figure). Serological tests for hepatitis A and B proved negative, and an ultrasound scan of the liver was normal. A liver biopsy carried out 11 days after tamoxifen was stopped showed slightly swollen hepatocytes, cholestasis, prominent Kupffer's cells filled with pigment, and an inflammatory portal lesion with minimal duct changes.



Serum aspartate aminotransferase activity and bilirubin concentration. Horizontal bars indicate treatment with tamoxifen 10 mg twice daily.
Conversion: SI to traditional units—Bilirubin: 1 μmol/l ≈ 0·05 mg/100 ml.

During the next two months she remained well and measurements of aspartate aminotransferase and bilirubin continued in the upper normal range. She was readmitted in September for challenge with tamoxifen. After nine days of treatment aspartate aminotransferase activity had risen from a mean of 54 U/l before treatment to 79 U/l and nausea and vomiting had returned. Tamoxifen was stopped after 12 days, and 24 hours later aspartate aminotransferase activity had risen to 258 U/l and bilirubin concentration to 31 μmol/l (1·8 mg/100 ml). Activity of alkaline phosphatase was raised throughout this period, which was consistent with metastatic bone disease. During the succeeding month the aspartate aminotransferase activity and bilirubin concentration fell towards normal, but she developed cerebral metastases and died on 9 November.

At necropsy the liver was small (823 g) and contained deposits of metastatic tumour, which were confirmed histologically. These measured up to 1·5 cm in diameter and were scattered throughout both lobes. No evidence was found of bile duct obstruction or gall stones.

Comment

One previous case has been reported in which tamoxifen was associated with cholestatic jaundice, but the patient refused liver biopsy and rechallenge with tamoxifen.[3] We have observed two other patients with metastatic breast cancer in whom tamoxifen was suspected of causing impairment of liver function but in whom further investigations were not feasible. Imperial Chemical Industries, who manufacture tamoxifen, and the Committee on Safety of Medicines have not received any other reports of liver dysfunction.

Liver biopsy showed cholestasis, which is one of the most common signs of drug induced liver damage. Histologically, it is difficult to distinguish drug induced cholestasis from mechanical biliary obstruction; thus identification must depend largely on exclusion of possible causes of obstruction.

Our patient might have had hepatic metastases that were not detectable by the initial liver scan. In addition, she was taking other drugs (analgesics and steroids) that might have damaged the liver. There was, however, a close temporal relation between administration of tamoxifen and liver damage as indicated by a rise in activity of aspartate aminotransferase when the drug was started and a fall in activity when the drug was stopped. This relation was confirmed on rechallenge with tamoxifen, when enzyme activity again rose.

Liver damage attributable to tamoxifen appears to be extremely rare. We have observed it with certainty in only one of the 873 patients we have treated over the past 10 years, an incidence of only 0·1%. This toxic effect does not detract from the value of tamoxifen in the management of metastatic breast cancer, but it may have relevance if tamoxifen becomes widely used as adjuvant treatment after mastectomy.

We thank Professor P J Scheuer for helpful comments on the liver biopsy specimens.

[1] Ward HWC. Anti-oestrogen therapy for breast cancer: a trial of tamoxifen at two dose levels. *Br Med J* 1973;i:13-4.
[2] Patterson JS, Baum M. Safety of tamoxifen. *Lancet* 1978;i:105.
[3] Agrawal BL, Zelkowitz L. Bone 'flare', hypercalcaemia and jaundice after tamoxifen therapy. *Ann Intern Med* 1981;**141**:1240.

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Severe peripheral ischaemia during concomitant use of beta blockers and ergot alkaloids

Certain drugs may adversely affect perfusion through peripheral tissue. Ergot alkaloids, for instance, cause arterial vasoconstriction, which may give rise to ischaemia leading to gangrene of the toes and fingertips.[1] β Blockers may diminish blood flow to striated muscle by inhibiting β_2 mediated vasodilatation, by causing β_1 mediated depression of cardiac output, and possibly through cerebral mechanisms. Clinical signs of this condition may be cold fingers and toes and even peripheral gangrene.[2] β Blockers used in conjunction with ergot derivatives may have a synergistic effect on perfusion through peripheral tissue, which could be hazardous. We report two cases in which this interaction may have occurred.

Case reports

CASE 1

A 21 year old policeman was admitted to hospital with progressive severe pain in his legs and feet of one week's duration. He had suffered from migraine for 10 years and had been taking methysergide (3 mg) and propranolol (120 mg) daily for two weeks. On examination his feet were pale, cold, and poorly perfused and only the femoral pulses were palpable in his legs.

Aortography disclosed extreme bilateral narrowing of the superficial femoral arteries consistent with severe spasm. Intravenous infusions of 10% dextran 40 in saline (Rheomacrodex) and heparin (500 units/hour) and a lumbar epidural block with 1% lignocaine failed to afford any improvement.

Infusion of isoprenaline (1-2 μg/min) the next day resulted in mild improvement. Nevertheless, both feet gradually became gangrenous, and bilateral below knee amputations were performed six days after admission.

CASE 2

A 28 year old housewife was admitted complaining of excrutiating pain in her feet. On examination her feet were pale and cold. Her hands were also cold but of normal colour. Her carotid, axillary, and femoral pulses were the only palpable peripheral pulses. She had suffered from migraine and duodenal ulceration for some years and had taken numerous drugs including propoxyphene, benzodiazepine derivatives, diclofenac, cimetidine, chlordiazepoxide, raubasine, sucralfate, ergotamine tartrate, and oxprenolol. The precise dosages and duration of these treatments could not be established, but we ascertained that she had been taking oxprenolol and ergotamine tartrate tablets for a considerable time before admission. Arteriography showed severe spasm of most parts of the femoral arteries, the distal parts of the brachial arteries, and the radial arteries.

Intravenous infusion of heparin (500 units/hour) and dopamine (150-300 μg/min) resulted in moderate improvement in the circulation except in the left foot, which remained painful and developed a mottled appearance. A cannula was placed in the left femoral artery, and nitroglycerin (1 mg/hour) and heparin (500 units/hour) were infused. This caused a dramatic improvement. After 24 hours the peripheral pulses were palpable and the cannula was removed. Intravenous treatment was reduced over the next two days, and she made a satisfactory recovery.

Comment

Both β blockers and ergot alkaloids are commonly recommended for the management of migraine.[3 4] We believe that these drugs may interact to have an adverse effect on peripheral arterial perfusion, though we have not found any other reports of such an interaction. Our cases represent two instances in which this type of interaction may have occurred and suggest that care should be taken when prescribing these drugs for migraine. Particular care should be taken to exclude pre-existing impairment of perfusion through the peripheral arteries.

Cases such as those reported here are difficult to manage, but the response of the patient in case 2 suggests that direct intra-arterial infusion of nitroglycerin and heparin may be of value.

[1] Cameron EA, French EB. St Anthony's fire rekindled: gangrene due to therapeutic dose of ergotamine. *Br Med J* 1960;ii:28-30.
[2] Vale JA, Jefferys DB. Peripheral gangrene complicating beta-blockade. *Lancet* 1978;i:1216.
[3] Anonymous. Treatment of migraine. [Editorial.] *Lancet* 1982;i:1338-40.
[4] Blau JN. A plain man's guide to the management of migraine. *Br Med J* 1982;**284**:1095-7.

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Metformin and glibenclamide: comparative risks

Oral hypoglycaemic agents are used widely in the management of non-insulin dependent diabetes mellitus. There are many sulphonylurea preparations available, of which glibenclamide is the most commonly prescribed in the United Kingdom. Among biguanides phenformin was withdrawn in the UK in 1982 because of the risk of "spontaneous" lactic acidosis and metformin is now the biguanide of choice. It is often stated that the sulphonylureas are safer because the risk of patients developing, and possibly dying from, hypoglycaemia is much less than that of developing lactic acidosis associated with metformin. This study was designed to compare mortality risks for these two conditions.

Methods and results

I reviewed a report of glibenclamide induced hypoglycaemia in Sweden between 1972 and mid-1981[1] and two reports of metformin associated lactic acidosis.[2 3] The Swedish Adverse Drug Reaction Advisory Committee provided details of further cases of metformin associated lactic acidosis and gave figures on sales (expressed in "patient years") of glibenclamide and metformin in the same period, which enabled the relative risks of mortality to be calculated.

Glibenclamide associated hypoglycaemia and metformin associated lactic acidosis in Sweden, 1972 to mid 1981

Drug	No of reports	No of deaths	Use* (patient years)	Mortality risk per 1000 patients years
Glibenclamide	57	10	300 645	0·0332
Metformin	7	2	83 482	0·0240

*Average daily doses: 10 mg glibenclamide, 1·5 g metformin.

In 57 patients (mean age 75) with hypoglycaemia induced by glibenclamide (mean daily dose 10 mg), hypoglycaemia was protracted (12-72 hours) in 24. Ten died, some receiving only 2·5-5 mg daily.[1] In the published reports of metformin associated lactic acidosis the two patients were elderly (84 and 82) and had impaired renal function; one also had bronchopneumonia and cardiac failure,[2] and the other, who died, had cardiac failure.[3] Five further cases (one resulting in death) were reported to the Swedish Adverse Drug Reactions Advisory Committee. The table shows that the difference in risk of mortality/1000 patient years between glibenclamide and metformin was not significant. The incidence of glibenclamide induced hypoglycaemia, however, was significantly greater than that of metformin associated lactic acidosis (2 $p=0·036$; standard error of differences between proportions).

Comment

This study shows similar mortality risks for hypoglycaemia induced by glibenclamide and lactic acidosis associated with metformin, but the incidence of hypoglycaemia with glibenclamide was greater than that of lactic acidosis associated with metformin. Similar comparative mortality data for sulphonylurea induced hypoglycaemia (0·02/1000 patient years) and metformin associated lactic acidosis (0·024/1000 patient years) are available from Switzerland.[4] No reports of lactic acidosis associated with metformin have been published in the UK despite its use for 330 000 patient years in 1972-82. Similarly, since the introduction of metformin in Canada in 1972, this drug has been used for 56 000 patient years without a single documented case of lactic acidosis.[5] This has been due to clinicians' strict observance of the prescribing information by excluding patients with renal or hepatic impairment and by remaining alert to any intercurrent acute illness likely to cause hypoxia and increased production of lactate or conditions in which renal or hepatic failure may occur.

From the recent study of glibenclamide in Sweden it has become clear that equal caution is required in the use of sulphonylureas. Careful assessment of cardiovascular, renal, and hepatic status is required, especially in patients over 70. In addition, patients should be warned against restricted carbohydrate intake at times of anorexia, and care should be taken when potentiating drugs such as salicylates, warfarin, or co-trimoxazole are given.

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[1] Asplund K, Wiholm BE, Lithner F. Glibenclamide-associated hypoglycaemia: a report on 57 cases. *Diabetologia* 1983;**24**:412-7.
[2] Anonymous. Socialstyrelsens läkemedelsavdelning, biverkningsnämnden: rapport om ett fall av mjölksyraacidos (laktatacidosis). Uppsala: The National Board of Health and Welfare, Sweden, 1977.
[3] Hermann LS, Magnusson S, Möller B, Casey C, Tucker GT, Woods HF. Lactic acidosis during metformin treatment in an elderly diabetic patient with impaired renal function. *Acta Med Scand* 1981;**209**:519-20.
[4] Berger W. Present status of biguanides. *Pharma-Kritik* 1979;**1**:9-12.
[5] Lucis OJ. The status of metformin in Canada. *Can Med Assoc J* 1983;**128**:24-6.

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