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.

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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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