Biguanides and lactic acidosis in diabetics

For nearly 20 years maturity-onset diabetics not requiring insulin have been treated with biguanides—in Britain phenformin and metformin. These drugs lower the blood glucose concentration by reducing glucose absorption, increasing glycolysis, and decreasing gluconeogenesis from alanine, pyruvate, and lactate.[1] Inevitably, therefore, they cause a rise in the blood lactate concentration, which is greater in patients treated with phenformin than with metformin, though it rarely exceeds 2 mM (normal range 0·4-1·3 mM).[2] Both drugs are excreted by the kidney[3 4] and hence renal impairment increases the blood concentrations of both the drug and lactate. Phenformin is also metabolised,[4] and hepatic disease and also alcohol consumption[5] are apt to increase the hyperlactataemia. Fatal lactic acidosis has been reported in patients taking phenformin[1 6 7] and, very rarely, metformin.[1 8]

Phenformin appears to be particularly hazardous. Nearly 200 cases of lactic acidosis associated with phenformin have been reported but only 14 associated with metformin. In France, where metformin accounts for about three-quarters of the biguanide drugs used, lactic acidosis is rare and renal failure has been present in almost all cases. Lactic acidosis due to phenformin has generally occurred in patients with serious underlying disease, notably renal failure—the commonest condition—and cardiac failure; but in some cases there has been no obvious explanation other than the use of the drug. It is particularly disturbing that lactic acidosis has occurred unpredictably in patients without any predisposing cause, sometimes soon after starting phenformin treatment or increasing the dose.[6 7] Indeed, Cohen and Woods[9] recorded that roughly three-quarters of reported cases occurred within two months of starting treatment.

As the mortality rate of lactic acidosis is high (50-60% or more) prompt diagnosis and treatment are essential. It should be suspected in patients with a metabolic acidosis that cannot be accounted for by either chronic renal failure or ketoacidosis (a negative response to the plasma Ketostix test helps to exclude the latter). Blood lactate concentrations are usually greater than 5 mM. There are no specific clinical features of lactic acidosis, which may occur with or without clinical "shock" (types A and B respectively).[9] Drowsiness or coma, hyperventilation, vomiting, and abdominal pain are all non-specific features of a metabolic acidosis. Treatment is by reversal of hypoxia and circulatory collapse; infusion of alkali[1 9] (150-2500 mmol of sodium bicarbonate may be needed); and—in the most seriously ill or those who fail to respond to these measures—peritoneal dialysis, or, better still, haemodialysis to alleviate sodium overloading and probably hasten disposal of the drug. The value of the routine use of insulin and glucose is controversial,[1] but in diabetics the former is usually required to combat the hyperketonaemia (mainly from 3-hydroxybutyrate) which contributes to the acidosis.[10] Glucose is also necessary if blood glucose concentrations are normal or low. Dichloroacetate, which activates pyruvate dehydrogenase, has been used to reverse lactic acidosis experimentally, but is not yet available for clinical use.[11]

Aware of the increasing recognition of its hazard, the Committee on Safety of Medicines has recently issued a warning suggesting that the use of phenformin should be restricted. Several other countries, including the USA, have taken similar action. The manufacturers themselves have issued guidelines to the use of phenformin, which should apply also to metformin. Biguanides should be avoided in patients with renal disease, cardiac failure, or hepatic impairment; and the dose of the drug should be kept to a minimum, not exceeding 100 mg a day of phenformin, and usually less than 2 g of metformin. These drugs must always be withdrawn when patients have serious intercurrent illnesses, especially myocardial infarction and other conditions likely to cause hypotensive shock. In these crises hyperglycaemia should always be controlled with insulin. Despite these numerous restrictions, however, there is still a place for biguanide treatment after rigorous dieting and sulphonylureas have failed—and in the most obese patients a biguanide may be used alone.

Lactic acidosis is rare, and there is no need for the doctor hurriedly to withdraw phenformin from every patient. Metformin, however, is now the biguanide of choice.

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Surgical treatment of hiatus hernia

The appearance of yet another surgical procedure for sliding hiatus hernia[1] prompts us to take stock of the management of this common condition. There are three separate issues: are the patient's symptoms certainly due to sliding hiatus hernia; have all possible conservative measures been tried; and, if operation is necessary, which of the many techniques should be used?

Many patients with anatomical defects of the hiatus remain totally free of symptoms throughout life. The discovery of such a defect during a barium swallow or a barium meal examination may therefore be fortuitous, for the defect is not necessarily causing the patient's symptoms: peptic ulcer, cholecystitis, spastic colon, and other common disorders give rise to similar symptoms. The main symptoms arising directly from sliding hiatus hernia are due to oesophageal reflux—giving heartburn, a feeling of regurgitation towards or into the mouth, and a bloated, burning sensation in the epigastrium and retrosternal area; these are usually aggravated by bending, lying flat, and physical exertion or any external force that increases intra-abdominal pressure. The patient's typical symptoms can be reproduced by one of various tests in which hydrochloric acid is introduced into the oesophagus. These are not, however, infallible, and each produces both false-positive and false-negative results.

If symptoms do seem to be caused by oesophageal reflux associated with a sliding hiatus hernia there should first be a period of conservative management—provided that no