For further details on the treatment of insulin-induced hypoglycaemia, see p.447.

Diabetic ketoacidosis is caused by an absolute or relative lack of insulin and commonly occurs after noncompliance or failure to adjust insulin dosage in the presence of factors such as infection that increase insulin requirements (see Precautions for Insulin, p.447). Failure of an insulin pump can be a cause.[5] Also pregnant diabetic women are more prone to development of diabetic ketoacidosis.

Diabetic ketoacidosis is characterised by hyperglycaemia, hyperketonaemia, and acidaemia, with subsequent dehydration and electrolyte abnormalities. Onset may be rapid, or insidious over many days. Initial presenting symptoms such as thirst, polyuria, fatigue, and weight loss are those of any newly presenting type 1 diabetic; they then progress to nausea, vomiting, abdominal pain, and impaired consciousness or coma, and, if untreated, death.[5,6]

Diabetic ketoacidosis is a medical emergency and should be treated immediately with fluid replacement and insulin.[5-8] Fluid requirements depend on the needs of the individual; overvigorous fluid replacement without severe dehydration carries the risk of precipitating cerebral oedema.[6-8]

Soluble insulin should also be given immediately. Large doses were formerly thought necessary, but lower dose regimens accompanied by adequate hydration have since been shown to be preferable.[5] Insulin resistance in diabetic ketoacidosis is generally exacerbated by hyperosmolarity and other confounding factors, and insulin therapy is therefore most effective when preceded or accompanied by adequate fluid and electrolyte replacement.[5] In the UK, the *BNF* considers that insulin should preferably be given by intravenous infusion, with the intramuscular route used if facilities for intravenous infusion are not available. However, in the USA some consider that an intravenous bolus followed by subcutaneous injection may be appropriate in certain patients.[5] Intramuscular or subcutaneous injection are not appropriate in patients with hypovolaemic shock, due to poor tissue perfusion.[5] Where the response to insulin is inadequate the intravenous route is generally required[5] and the rate of infusion may be doubled on an hourly basis until an appropriate response is seen. A case report has suggested that mecasermin may be useful if there is insulin resistance.[9]

When the blood-glucose concentration has fallen to about 12.5 mmol/litre the dose of insulin may be reduced by about half and glucose given intravenously,[5] usually in a strength of 5% with saline although in rare cases a glucose strength of 10% may be necessary.[5] The use of glucose enables insulin to be continued in order to clear ketone bodies without inducing hypoglycaemia. Once glucose concentrations have been controlled and acidosis has completely cleared, subcutaneous injections of insulin can begin;[6] but intravenous insulin should not be stopped until subcutaneous dosage has begun.

Total body stores of potassium are depleted in patients with diabetic ketoacidosis. Insulin deficiency appears to be the main initiating factor for hyperkalaemia in diabetic ketoacidosis.[10] Although patients may present with raised, normal, or decreased serum-potassium concentrations, the concentrations will start to fall with the correction of acidosis. Potassium is added to the infusion fluid after initial fluid expansion and once insulin therapy has begun.[5] In hyperkalaemic patients, potassium is given once serum concentrations have fallen to within normal limits.[5,6] In the rare patient presenting with hypokalaemia potassium replacement should be begun before insulin therapy and the latter withheld until potassium concentrations have risen to normal values.[5]

Intravenous bicarbonate is now generally reserved for patients with severe acidaemia; a common practice[5,6] is to give isotonic bicarbonate to those with a pH of less than 7.0 with the aim of raising the pH to 7.1.

Phosphate concentrations are affected in a similar manner to potassium concentrations in the ketoacidotic state, but there is less agreement on the need for routine doses of phosphate. Phosphate concentrations should be monitored and phosphate given if clinically significant hypophosphataemia occurs.[5,6]

The precipitating cause of diabetic ketoacidosis should also be identified and managed appropriately.

Hyperosmolar hyperglycaemic state or hyperosmolar hyperglycaemic nonketotic coma (HONK) occurs mainly in elderly patients with type 2 diabetes and though much less common than diabetic ketoacidosis it carries a higher mortality. Patients may present in coma with severe hyperglycaemia but with minimal ketosis; dehydration and renal impairment are common.[5] Treatment is similar to that of diabetic ketoacidosis (see above), although potassium requirements are lower and large amounts of fluid and less insulin may be required; some suggest the use of hypotonic fluid if necessary.[11] There is an increased likelihood of thrombotic events, so prophylactic anticoagulation should be considered.

1. Cranston I, *et al.* Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. *Lancet* 1994; **344:** 283–7.
2. Boyle PJ, *et al.* Brain glucose uptake and unawareness of hypoglycemia in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 1995; **333:** 1726–31.
3. Debrah K, *et al.* Effect of caffeine on recognition of and physiological responses to hypoglycaemia in insulin-dependent diabetes. *Lancet* 1996; **347:** 19–24.
4. Watson JM, *et al.* Influence of caffeine on the frequency and perception of hypoglycemia in free-living patients with type 1 diabetes. *Diabetes Care* 2000; **23:** 455–9.
5. Kitabchi AE, *et al.* Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001; **24:** 131–53.
6. Lebovitz HE. Diabetic ketoacidosis. *Lancet* 1995; **345:** 767–72.
7. Adrogué HJ, *et al.* Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis: use in patients without extreme volume deficit. *JAMA* 1989; **262:** 2108–13.
8. Johnston C. Fluid replacement in diabetic ketoacidosis. *BMJ* 1992; **305:** 522.
9. Usala A-L, *et al.* Brief report: treatment of insulin-resistant diabetic ketoacidosis with insulin-like growth factor I in an adolescent with insulin-dependent diabetes. *N Engl J Med* 1992; **327:** 853–7.
10. Anonymous. Hyperkalaemia in diabetic ketoacidosis. *Lancet* 1986; **ii:** 845–6.
11. Wright AD. Diabetic emergencies in adults. *Prescribers' J* 1989; **29:** 147–54.

Acarbose *(BAN, USAN, rINN)*

Acarbosa; Acarbosum; Akarboosi; Akarbos; Akarbosa; Akarboz; Akarbozė; Bay-g-5421. *O*-{4-Amino-4,6-dideoxy-*N*-[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-hydroxymethylcyclohex-2-enyl]-α-D-glucopyranosyl}-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucopyranose.

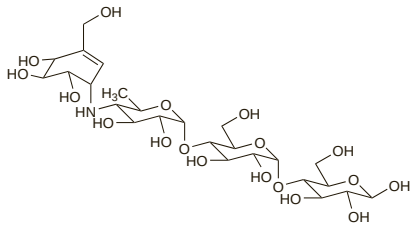
Акарбоза

$C_{25}H_{43}NO_{18}$ = 645.6.

CAS — 56180-94-0.

ATC — A10BF01.

ATC Vet — QA10BF01.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Acarbose). A white or yellowish, amorphous, hygroscopic powder. Very soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 31 (Acarbose). Produced by certain strains of *Actinoplanes utahensis*. Store in airtight containers.

Adverse Effects

Acarbose often causes gastrointestinal disturbances, particularly flatulence due to bacterial action on nonabsorbed carbohydrate in the colon. Abdominal distension, diarrhoea, and pain may occur. Ileus has been rarely reported. A decrease in dosage and improved dietary habits may reduce these adverse effects. Hepatotoxicity may occur and may necessitate a reduction in dosage or withdrawal of the drug. Skin reactions have occurred rarely. Very rarely oedema has been reported.

Incidence of adverse effects. The manufacturers reported that adverse effects of acarbose were rarer in a postmarketing surveillance study than in previous clinical trials;[1] this was held to represent better tailoring of individual doses to patient tolerability.

1. Spengler M, Cagatay M. The use of acarbose in the primary-care setting: evaluation of efficacy and tolerability of acarbose by postmarketing surveillance study. *Clin Invest Med* 1995; **18:** 325–31.

Effects on the liver. Hepatocellular liver damage, with jaundice and elevated serum aminotransferases, have been reported in patients receiving acarbose.[1-3] Symptoms resolved on stopping the drug.

1. Andrade RJ, *et al.* Hepatic injury caused by acarbose. *Ann Intern Med* 1996; **124:** 931.
2. Carrascosa M, *et al.* Acarbose-induced acute severe hepatotoxicity. *Lancet* 1997; **349:** 698–9.
3. Fujimoto Y, *et al.* Acarbose-induced hepatic injury. *Lancet* 1998; **351:** 340.

Effects on the skin. Generalised erythema multiforme and eosinophilia occurred in a male diabetic patient 13 days after starting acarbose.[1] The hypersensitivity reaction was confirmed by rechallenge.

1. Kono T, *et al.* Acarbose-induced generalised erythema multiforme. *Lancet* 1999; **354:** 396–7.

Precautions

Acarbose is contra-indicated in inflammatory bowel disease, particularly where there is associated ulceration, and in gastrointestinal obstruction or patients predisposed to it. It should be avoided in patients with chronic intestinal diseases that significantly affect digestion or absorption, and in conditions which may deteriorate as a result of increased gas formation, such as hernia.

Acarbose is also contra-indicated in patients with hepatic impairment and liver enzyme values should be monitored, particularly at high doses.

If hypoglycaemia should develop in a patient receiving acarbose it needs to be treated with glucose, since the action of acarbose inhibits the hydrolysis of disaccharides.

Breast feeding. In the absence of evidence, licensed product information recommends that acarbose should be avoided during breast feeding.

Interactions

Acarbose may enhance the effects of other antidiabetics, including insulin, and a reduction in their dosage may be needed. Use with gastrointestinal adsorbents and digestive enzyme preparations can diminish the effects of acarbose and should be avoided. Neomycin and colestyramine may enhance the effects of acarbose and a reduction in its dosage may be required. Acarbose may inhibit the absorption of digoxin (see Antidiabetics, under Interactions of Digoxin, p.1261).

Pharmacokinetics

After ingestion of acarbose, the majority of active unchanged drug remains in the lumen of the gastrointestinal tract to exert its pharmacological activity and is metabolised by intestinal enzymes and by the microbial flora. Ultimately about 35% of a dose is absorbed in the form of metabolites. Acarbose is excreted in the urine and faeces.

Uses and Administration

Acarbose is an inhibitor of alpha glucosidases, especially sucrase. This slows the digestion and absorption of carbohydrates in the small intestine and hence reduces the increase in blood-glucose concentrations after a carbohydrate load. It is given in the treatment of type 2 diabetes mellitus (p.431) either alone or with a sulfonylurea, biguanide, or insulin. Acarbose treatment may be started with a low oral dose of 25 or 50 mg daily to minimise gastrointestinal disturbance. It is then gradually increased to a usual dose of 25 or 50 mg three times daily, immediately before food. Doses up to 100 to 200 mg three times daily may be given if necessary. Some benefit has also been found when acarbose is used to supplement insulin therapy in type 1 diabetes mellitus.

Acarbose has also been studied for the treatment of reactive hypoglycaemia, the dumping syndrome, and certain types of hyperlipoproteinaemia.

◊ References.

1. Chiasson J-L, *et al.* The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus: a multicenter controlled clinical trial. *Ann Intern Med* 1994; **121:** 928–35.

2. Coniff RF, *et al.* Multicenter, placebo-controlled trial comparing acarbose (BAY g 5421) with placebo, tolbutamide, and tolbutamide-plus-acarbose in non-insulin-dependent diabetes mellitus. *Am J Med* 1995; **98:** 443–51.
3. Spengler M, Cagatay M. The use of acarbose in the primary-care setting: evaluation of efficacy and tolerability of acarbose by postmarketing surveillance study. *Clin Invest Med* 1995; **18:** 325–31.
4. Salvatore T, Giugliano D. Pharmacokinetic-pharmacodynamic relationships of acarbose. *Clin Pharmacokinet* 1996; **30:** 94–106.
5. Anonymous. Acarbose for diabetes mellitus. *Med Lett Drugs Ther* 1996; **38:** 9–10.
6. Hoffman J, Spengler M. Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II study. *Am J Med* 1997; **103:** 483–90.
7. Hollander P, *et al.* Acarbose in the treatment of type I diabetes. *Diabetes Care* 1997; **20:** 248–53.
8. Buse J, *et al.* The PROTECT study: final results of a large multicenter postmarketing study in patients with type 2 diabetes. *Clin Ther* 1998; **20:** 257–69.
9. Holman RR, *et al.* A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (UK Prospective Diabetes Study 44). *Diabetes Care* 1999; **22:** 960–4.
10. Riccardi G, *et al.* Efficacy and safety of acarbose in the treatment of type 1 diabetes mellitus: a placebo-controlled, double-blind, multicentre study. *Diabet Med* 1999; **16:** 228–32.
11. Chiasson J-L, *et al.* Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359:** 2072–7.

Impaired glucose tolerance. A prospective study of patients with impaired glucose tolerance concluded that acarbose significantly reduced the incidence of cardiovascular disease and hypertension.[1]

1. Chiasson J-L, *et al.* Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003; **290:** 486–94.

Preparations

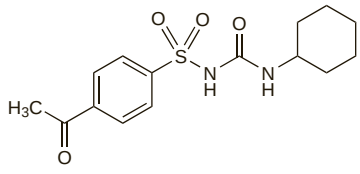
Proprietary Preparations (details are given in Part 3)
Arg.: Glucobay; ***Austral.:*** Glucobay; ***Austria:*** Glucobay; ***Belg.:*** Glucobay; ***Braz.:*** Aglucose; Glucobay; ***Canad.:*** Prandase; ***Chile:*** Glucobay; ***Cz.:*** Glucobay; ***Denm.:*** Glucobay; ***Fr.:*** Glucor; ***Ger.:*** Glucobay; ***Gr.:*** Glucobay; ***Hong Kong:*** Glucobay; ***Hung.:*** Glucobay; ***India:*** Acarbay; Asucrose; Glubose; Glucar; Glucobay; ***Indon.:*** Glucobay; ***Irl.:*** Glucobay; ***Israel:*** Prandase; ***Ital.:*** Glicobase; Glucobay; ***Malaysia:*** Dibose; Glucar; Glucobay; Precose; ***Mex.:*** Glucobay; Incardel; Sincrosa; ***Neth.:*** Glucobay; ***Norw.:*** Glucobay; ***NZ:*** Glucobay; ***Philipp.:*** Glucobay; Gluconase; ***Pol.:*** Glucobay; ***Port.:*** Glucobay; ***Rus.:*** Glucobay (Глюкобай); ***S.Afr.:*** Glucobay; ***Singapore:*** Glucobay; ***Spain:*** Glucobay; Glumida; ***Swed.:*** Glucobay; ***Switz.:*** Glucobay; ***Thai.:*** Glucobay; ***Turk.:*** Glucobay; Glynose; ***UK:*** Glucobay; ***USA:*** Precose; ***Venez.:*** Glucobay.

Acetohexamide *(BAN, USAN, rINN)*

Acetohexamid; Acetohexamida; Acétohexamide; Acetohexamidum; Asetoheksamidi; Compound 33006. 1-(4-Acetylbenzenesulphonyl)-3-cyclohexylurea.

Ацетогексамид

$C_{15}H_{20}N_2O_4S$ = 324.4.
CAS — 968-81-0.
ATC — A10BB31.
ATC Vet — QA10BB31.



Pharmacopoeias. In *Jpn* and *US*.
USP 31 (Acetohexamide). A white, practically odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 230 of alcohol and 1 in 210 of chloroform; soluble in pyridine and in dilute solutions of alkali hydroxides.

Profile
Acetohexamide is a sulfonylurea antidiabetic (p.460). Its duration of action is 12 hours or more. It has been given orally in the treatment of type 2 diabetes mellitus (p.431) in a usual initial dose of 250 mg daily before breakfast. The daily dose may then be increased by 250 to 500 mg at intervals of 5 to 7 days, to a maintenance dose of up to 1.5 g daily; increasing the dose above 1.5 g does not usually lead to further benefit. Doses in excess of 1 g daily may be taken in 2 divided doses, before the morning and evening meals.

Preparations
USP 31: Acetohexamide Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Dymelor†.

Biguanide Antidiabetics

Antidiabéticos biguanídicos.

Adverse Effects
Gastrointestinal adverse effects including anorexia, nausea, vomiting, and diarrhoea may occur with biguanides; patients may experience taste disturbance and there may be weight loss. Absorption of various substances including vitamin B_{12} may be impaired. Skin reactions have been reported rarely.

Hypoglycaemia is rare with a biguanide given alone, although it may occur if other contributing factors or drugs are present.

Lactic acidosis, sometimes fatal, has occurred with biguanides, primarily with phenformin. When it has occurred with metformin most cases have been in patients whose condition contra-indicated the use of the drug, particularly those with renal impairment.

Phenformin has been implicated in the controversial reports of excessive cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p.461).

◊ Reviews.

1. Paterson KR, *et al.* Undesired effects of biguanide therapy. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 173–82.
2. Howlett HCS, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. *Drug Safety* 1999; **20:** 489–503.

Effects on the blood. Megaloblastic anaemia has occurred with biguanide therapy (see Malabsorption, under Effects on the Gastrointestinal Tract, below). A few cases of metformin-induced haemolysis resulting in hyperbilirubinaemia and jaundice have also been described.[1,2]

1. Lin K-D, *et al.* Metformin-induced hemolysis with jaundice. *N Engl J Med* 1998; **339:** 1860–1.
2. Meir A, *et al.* Metformin-induced hemolytic anemia in a patient with glucose-6-phosphate dehydrogenase deficiency. *Diabetes Care* 2003; **26:** 956–7.

Effects on the gastrointestinal tract. ***DIARRHOEA.*** In a retrospective survey,[1] 30 of 265 diabetic patients reported diarrhoea or alternating diarrhoea and constipation, comprising: 11 of 54 taking metformin; 9 of 45 taking metformin with a sulfonylurea; 3 of 53 taking a sulfonylurea only; 5 of 78 on insulin therapy; 2 of 35 on diet alone. Among 150 nondiabetic controls 12 reported diarrhoea. Chronic diarrhoea described as watery, often explosive, and frequently causing faecal incontinence, has been reported as an adverse effect of late onset in patients receiving metformin. Some patients had been on stable metformin therapy for several years before the onset of diarrhoea. Symptoms ceased upon withdrawal of metformin, and recurred in cases of rechallenge.[2,3]

1. Dandona P, *et al.* Diarrhea and metformin in a diabetic clinic. *Diabetes Care* 1983; **6:** 472–4.
2. Raju B, *et al.* Metformin and late gastrointestinal complications. *Am J Med* 2000; **109:** 260–1.
3. Foss MT, Clement KD. Metformin as a cause of late-onset chronic diarrhea. *Pharmacotherapy* 2001; **21:** 1422–4.

MALABSORPTION. Megaloblastic anaemia due to vitamin B_{12} malabsorption in a 58-year-old woman was associated with long-term treatment with metformin.[1]

In a survey of diabetic patients receiving biguanide therapy,[2] malabsorption of vitamin B_{12} was observed in 14 of 46 diabetics taking metformin or phenformin; metformin was more commonly to blame. Withdrawal of the drug resulted in normal absorption in only 7 of the 14. In a series of 10 patients[3] with vitamin B_{12} deficiency associated with metformin, vitamin B_{12} concentrations and blood count abnormalities were reported to have been corrected within 3 months of starting treatment with intramuscular or oral cyanocobalamin; 2 patients were transferred to treatment with other antidiabetic agents.

1. Callaghan TS, *et al.* Megaloblastic anaemia due to vitamin B malabsorption associated with long-term metformin treatment. *BMJ* 1980; **280:** 1214–15.
2. Adams JF, *et al.* Malabsorption of vitamin B and intrinsic factor secretion during biguanide therapy. *Diabetologia* 1983; **24:** 16–18.
3. Andrès E, *et al.* Metformin-associated vitamin B deficiency. *Arch Intern Med* 2002; **162:** 2251–2.

Effects on the liver. Severe cholestatic hepatitis attributed to metformin has been reported.[1]

1. Babich MM, *et al.* Metformin-induced acute hepatitis. *Am J Med* 1998; **104:** 490–2.

Effects on the pancreas. Acute pancreatitis is more commonly associated with phenformin.[1,2] However, there have also been a few cases of pancreatitis associated with metformin, in which renal failure may have precipitated metformin toxicity.[3,4]

1. Wilde H. Pancreatitis and phenformin. *Ann Intern Med* 1972; **77:** 324.
2. Chase HS, Mogan GR. Phenformin-associated pancreatitis. *Ann Intern Med* 1977; **87:** 314–15.
3. Mallick S. Metformin induced acute pancreatitis precipitated by renal failure. *Postgrad Med J* 2004; **80:** 239–40.
4. Fimognari FL, *et al.* Metformin-induced pancreatitis: a possible adverse drug effect during acute renal failure. *Diabetes Care* 2006; **29:** 1183.

Hypersensitivity. Vasculitis and pneumonitis in a 59-year-old woman was associated with use of metformin.[1] Symptoms improved on withdrawal of metformin, but reappeared on its reintroduction. Cutaneous vasculitis in a 33-year-old woman also resolved on withdrawal of metformin and recurred with its reintroduction.[2]

1. Klapholz L, *et al.* Leucocytoclastic vasculitis and pneumonitis induced by metformin. *BMJ* 1986; **293:** 483.
2. Salem CB, *et al.* Rare case of metformin-induced leukocytoclastic vasculitis. *Ann Pharmacother* 2006; **40:** 1685–7.

Hypoglycaemia. UK licensed product information for metformin states that hypoglycaemia does not occur with metformin alone, even in overdosage, although it may occur if given with alcohol or other hypoglycaemics. Interim results from the UK Prospective Diabetes Study,[1] however, indicate that metformin therapy was associated with fewer hypoglycaemic episodes than sulfonylurea or insulin treatment, but more than with diet alone. One or more hypoglycaemic episodes were reported in 6% of the patients receiving the biguanide in this study, although only 1 patient had a severe episode.

1. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for 3 years. *BMJ* 1995; **310:** 83–8.

Lactic acidosis. There is a small but definite risk of lactic acidosis associated with use of biguanide antidiabetics. Most early reports involved phenformin, which was consequently removed from the market in many countries although cases of phenformin-associated lactic acidosis still occur.[1-3] There has therefore been concern about the risks of lactic acidosis with metformin, which is still in wide use. However, lactic acidosis with metformin appears to be much less common: a review suggested that the incidence was of the order of 3 cases per 100 000 patient years, which was 20 times less frequent than with phenformin.[4] This concurs with the findings of the FDA after the introduction of metformin to the US market: in the year after the marketing of metformin in the USA, the FDA had received reports of metformin-associated lactic acidosis in 66 patients,[5] the diagnosis being confirmed in 47. This represented a rate of about 5 cases per 100 000. Most patients who do develop lactic acidosis with metformin have one or more precipitating risk factors such as renal impairment, congestive heart failure, or other conditions predisposing to hypoxaemia or acute renal failure, including septicaemia, acute hepatic decompensation, alcohol abuse, acute myocardial infarction, and shock.[4] A systematic review,[6] which considered results comprising nearly 48 000 patient years of treatment with metformin, concluded that provided metformin was prescribed taking into account the proper contra-indications, there was no evidence of an increased risk of lactic acidosis. Nonetheless, there have been a few reports of lactic acidosis developing in metformin-treated patients without apparent risk factors.[4]

1. Rosand J, *et al.* Fatal phenformin-associated lactic acidosis. *Ann Intern Med* 1997; **127:** 170.
2. Enia G, *et al.* Lactic acidosis induced by phenformin is still a public health problem in Italy. *BMJ* 1997; **315:** 1466–7.
3. Kwong SC, Brubacher J. Phenformin and lactic acidosis: a case report and review. *J Emerg Med* 1998; **16:** 881–6.
4. Chan NN, *et al.* Metformin-associated lactic acidosis: a rare or very rare clinical entity? *Diabet Med* 1999; **16:** 273–81.
5. Misbin RI, *et al.* Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998; **338:** 265–6.
6. Salpeter S, *et al.* Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 02/05/06).

Treatment of Adverse Effects
Acute poisoning with biguanides may lead to the development of lactic acidosis (see Metabolic Acidosis, p.1667) and calls for intensive supportive therapy. Glucose or glucagon may be required for hypoglycaemia, the general management of which is outlined in Insulin, p.447.

Precautions
Biguanides are inappropriate for patients with diabetic coma and ketoacidosis, or for those with severe infection, trauma, or other severe conditions where the biguanide is unlikely to control the hyperglycaemia; insulin should be used in such situations. Biguanides should not be given to patients with even mild renal impairment, as it may predispose patients to lactic acidosis, and renal function should be monitored throughout therapy. Dehydration may contribute to renal impairment. Conditions associated with hypoxia, such as