acute heart failure, recent myocardial infarction, or shock, may increase the risk of lactic acidosis. Other conditions that may also predispose to lactic acidosis in a patient taking a biguanide include excessive alcohol intake and hepatic impairment. Biguanides should be temporarily stopped for examinations using contrast media (see under Interactions, below).

Insulin is preferred for the treatment of diabetes in pregnancy.

Owing to the possibility of decreased vitamin B_{12} absorption, annual monitoring of vitamin B_{12} concentrations is advisable during long-term treatment.

Driving. In the UK, patients with diabetes mellitus treated with insulin or oral hypoglycaemics are required to notify their condition to the Driver and Vehicle Licensing Agency, who then assess their fitness to drive. Patients treated with oral hypoglycaemics are generally allowed to retain standard driving licences; those treated with insulin receive restricted licences which must be renewed (with appropriate checks) every 1 to 3 years. Patients should be warned of the dangers of hypoglycaemic attacks while driving, and should be counselled in appropriate management of the situation (stopping driving as soon as it is safe to do so, taking carbohydrate immediately, and quitting the driving seat and removing the ignition key from the car) should such an event occur. Patients who have lost hypoglycaemic awareness, or have frequent hypoglycaemic episodes, should not drive. In addition, eyesight must be adequate (field of vision of at least 120°) for a licence to be valid. Patients treated with diet or oral hypoglycaemics are normally allowed to hold vocational driving licences for heavy goods vehicles or passenger carrying vehicles; those treated with insulin may not drive such vehicles, and are restricted in driving some other vehicles such as small lorries and minibuses.

References.

1. British Diabetic Association (Diabetes UK). Information sheet: driving and diabetes: May 2008. Available at: http://www.diabetes.org.uk/Documents/catalogue/driving_and_diabetes-may_08.pdf (accessed 20/08/08)
2. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

Interactions

Use of a biguanide with other drugs that lower blood-glucose concentrations increases the risk of hypoglycaemia, while drugs that increase blood glucose may reduce the effect of biguanide therapy.

In general fewer drug interactions have been reported with biguanides than with sulfonylureas. Alcohol may increase the risk of lactic acidosis as well as of hypoglycaemia. Care should be taken if biguanides are given with drugs that may impair renal function.

Anticoagulants. For the effect of metformin on *phenprocoumon* activity, see Antidiabetics, p.1428.

Antivirals. Fatal lactic acidosis has been reported[1] in a patient given metformin with *didanosine*, *stavudine*, and *tenofovir*.

1. Worth L, *et al*. A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Cimetidine. Cimetidine increased plasma-metformin concentrations in 7 healthy subjects.[1] The renal clearance of metformin was reduced; competition for proximal tubular secretion was considered responsible. A reduction in metformin dosage may be required in patients taking metformin and cimetidine, in order to reduce the risk of lactic acidosis.

1. Somogyi A, *et al*. Reduction of metformin renal tubular secretion by cimetidine in man. *Br J Clin Pharmacol* 1987; **23:** 545–51.

Contrast media. Biguanides should be temporarily stopped for examinations using iodinated contrast media and withheld after the examination until normal renal function is confirmed, because of the risk of contrast media-induced renal impairment leading to biguanide toxicity and associated lactic acidosis. Licensed product information for some contrast media preparations warns that biguanides should be temporarily stopped 48 hours before the examination, and withheld for at least 48 hours after and until normal renal function is confirmed.

A number of guidelines on the use of iodinated contrast media give advice for the management of patients taking metformin. Some suggest that, in general, metformin can be stopped at the time of the examination.[1,2] Others are more detailed, suggesting that if serum-creatinine is normal metformin may be stopped at the time of the examination, but that if it is raised metformin should be stopped 48 hours before giving the contrast medium.[3,4] They all agree that metformin should be withheld for 48 hours after the examination and until normal renal function is confirmed, although one suggests that no special precaution is needed for patients with normal serum-creatinine who are to be given a low volume of iodinated contrast medium (up to 100 mL).[3]

1. Committee on Drugs and Contrast Media, Commission on General and Pediatric Radiology of the American College of Radiology. Manual on contrast media, 5th ed. Available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx (accessed 26/06/07)
2. Benko A, *et al*. Canadian Association of Radiologists: consensus guidelines for the prevention of contrast-induced nephropathy. *Can Assoc Radiol J* 2007; **58:** 79–87. Correction available at: http://www.car.ca/Files%5CNephropathy.pdf (accessed 20/08/08) [correct version]
3. Board of the Faculty of Clinical Radiology; The Royal College of Radiologists. Standards for iodinated intravascular contrast agent administration to adult patients (issued November 2005). Available at: http://www.rcr.ac.uk/docs/radiology/pdf/IVcontrastPrintFinal.pdf (accessed 26/06/07)
4. European Society of Urogenital Radiology. ESUR guidelines on contrast media (version 6.0, issued February 2007). Available at: http://www.esur.org/fileadmin/Guidelines/ESUR_2007_Guideline_6_Kern_Ubersicht.pdf (accessed 26/06/07)

Ketotifen. Platelet counts in 10 diabetic patients receiving biguanides fell (markedly in 3 patients) when they were also given ketotifen.[1] Counts returned to normal a few days after the end of ketotifen therapy. However, the investigators did not consider the effect clinically significant.

1. Doleček R. Ketotifen in the treatment of diabetics with various allergic conditions. *Pharmatherapeutica* 1981; **2:** 568–74.

Sulfonylureas. For reference to an apparent increase in mortality with an intensive regimen of metformin plus a sulfonylurea, see p.462.

Uses and Administration

The biguanide antidiabetics are a class of oral antidiabetic drugs used in the treatment of type 2 diabetes mellitus (p.431). They are given to supplement treatment by diet modification when such modification has not proved effective on its own. In addition, because biguanides are not associated with weight gain they are preferred in obese patients. Although sulfonylureas (p.460) may be preferred in non-obese patients, a biguanide is often added or given instead to patients who are not responding to a sulfonylurea.

The mode of action of biguanides is not clear. They do not stimulate insulin release but require that some insulin be present in order to exert their antidiabetic effect. Possible mechanisms of action include delay in the absorption of glucose from the gastrointestinal tract, an increase in insulin sensitivity and glucose uptake into cells, and inhibition of hepatic gluconeogenesis. Biguanides do not usually lower blood-glucose concentrations in non-diabetic subjects.

Hyperlipidaemias. The effect of biguanides on lipid metabolism is unclear, although some studies have shown a beneficial effect on serum-lipid profiles in both obese and lean patients with type 2 diabetes, hypertension, and/or hyperlipidaemia.[1] Reductions in concentrations of total cholesterol, low-density and very low-density-lipoprotein cholesterol have been reported, as well as modest increases in high-density-lipoprotein cholesterol. Some studies have also reported a reduction in serum-triglyceride levels. Such effects may be beneficial in the long-term treatment of type 2 diabetes mellitus with concomitant lipid disorders.

1. Dunn CJ, Peters DH. Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995; **49:** 721–49.

Polycystic ovary syndrome. For discussion of the potential of metformin in polycystic ovary syndrome, see p.454.

Preparations

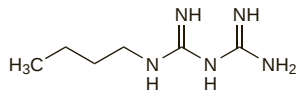
Proprietary Preparations (details are given in Part 3)
Mex.: Azucaps†.
Multi-ingredient: ***Mex.:*** Glinorboral.

Buformin *(USAN, pINN)*

Buformina; Buformine; Buforminum; DBV; W-37. 1-Butylbiguanide.

Буформин

$C_6H_{15}N_5$ = 157.2.
CAS — 692-13-7 (buformin); 1190-53-0 (buformin hydrochloride).
ATC — A10BA03.
ATC Vet — QA10BA03.



Profile

Buformin is a biguanide antidiabetic (p.437). It has been given orally in the treatment of type 2 diabetes mellitus (p.431) in doses of up to 300 mg daily. Buformin is also used as the hydrochloride.

Preparations

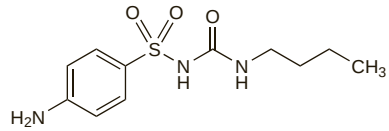
Proprietary Preparations (details are given in Part 3)
Cz.: Adebit†; Silubin†; ***Hung.:*** Adebit; ***Spain:*** Silubin†; ***Switz.:*** Silubin†.

Carbutamide *(BAN, rINN)*

BZ-55; Ca-1022; Carbutamida; Carbutamidum; Glybutamide; Karbutamid; Karbutamidi; U-6987. 1-Butyl-3-sulphanilylurea.

Карбутамид

$C_{11}H_{17}N_3O_3S$ = 271.3.
CAS — 339-43-5.
ATC — A10BB06.
ATC Vet — QA10BB06.



Profile

Carbutamide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) in single daily doses of 0.5 to 1 g, but is more toxic than chlorpropamide.

Preparations

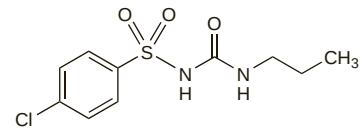
Proprietary Preparations (details are given in Part 3)
Fr.: Glucidoral.

Chlorpropamide *(BAN, rINN)*

Chloropropamid; Chlorpropamid; Chlorpropamidas; Chlorrpropamidum; Clorpropamida; Klooripropamidi; Klórpropamid; Klorpropamid. 1-(4-Chlorobenzenesulphonyl)-3-propylurea.

Хлорпропамид

$C_{10}H_{13}ClN_2O_3S$ = 276.7.
CAS — 94-20-2.
ATC — A10BB02.
ATC Vet — QA10BB02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Chlorpropamide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.
USP 31 (Chlorpropamide). A white crystalline powder having a slight odour. Practically insoluble in water; soluble in alcohol; sparingly soluble in chloroform.

Adverse Effects and Treatment

As for sulfonylureas in general, p.460.

Chlorpropamide may be more likely than other sulfonylureas to induce a syndrome of inappropriate secretion of antidiuretic hormone characterised by water retention, hyponatraemia, and CNS effects. Patients receiving chlorpropamide may develop facial flushing after drinking alcohol.

Precautions

As for sulfonylureas in general, p.461.

Chlorpropamide should be avoided in the elderly and in renal or hepatic impairment because its long half-life increases the risk of hypoglycaemia. The antidiuretic effect of chlorpropamide may cause problems in patients with conditions associated with fluid retention.

Fasting. For the view that although some sulfonylurea antidiabetics may be able to be used with caution in fasting Muslim patients during Ramadan, chlorpropamide is contra-indicated, see under Precautions of Insulin, p.448.