

The mode of action of metformin may be linked to an increase of insulin sensitivity. It does not stimulate insulin release but does require the presence of insulin to exert its hypoglycaemic effect. Possible mechanisms of action include inhibition of gluconeogenesis in the liver, delay in glucose absorption from the gastrointestinal tract and an increase in peripheral uptake of glucose.

Metformin has an antiketogenic activity which is comparable, though somewhat inferior, to insulin itself.

Metformin lowers both basal and post-prandial blood glucose in diabetic patients but does not cause hypoglycaemia in either diabetics or normal individuals.

Clinical trials

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed the following:

- a significant reduction of the absolute risk of any diabetes related complication in the metformin group (29.8 events/1,000 patient years) versus diet alone (43.3 events/1,000 patient years), $p = 0.0023$, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1,000 patient years), $p = 0.0034$;
- a significant reduction of the absolute risk of diabetes related mortality: metformin 7.5 events/ 1,000 patient years, diet alone 12.7 events/1,000 patient years, $p = 0.017$;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient years versus diet alone 20.6 events/1,000 patient years ($p = 0.011$), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1,000 patient years ($p = 0.021$);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient years, diet alone 18 events/1,000 patient years ($p = 0.01$).

For metformin used as second line therapy, in combination with a sulfonylurea, benefit regarding clinical outcome has not been shown.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

Pharmacokinetics

Absorption: After oral administration, metformin hydrochloride is absorbed along the entire gastrointestinal mucosa. Studies using single oral doses of metformin tablets indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an

increase in elimination. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are nonlinear.

At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations are reached in 24 to 48 hours and are generally less than 1 µg/mL. During controlled clinical trials, maximum metformin plasma levels did not generally exceed 5 µg/mL, even at maximum doses.

Distribution: Metformin is not bound to plasma proteins.

Metabolism: Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism.

Excretion: In patients with decreased renal function (based on measured creatinine clearance), the plasma half-life of metformin is prolonged and renal clearance is decreased in proportion to the decrease in creatinine clearance, e.g. if creatinine clearance is 10 to 30 mL/min, renal clearance is reduced to 20% of normal.

Indications

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

Metformin may be used as initial treatment or in sulfonylurea failures either alone or in combination with a sulfonylurea and other oral agents.

Adjuvant therapy in insulin dependent diabetes especially if overweight.

Dosage and Administration

Life threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and high doses of metformin above 2 g per day.

It is important that the tablets are taken in divided doses with meals.

Initially 500 mg should be taken once or twice a day and, if necessary, increased over a few weeks up to 1 g three times per day. The dose should be titrated with gradual dose increments until the desired effect is obtained. 500 mg three times a day is often sufficient to obtain diabetic control. If necessary, the dose can be increased to 1 g three times daily, which is the maximum recommended daily dose. Control may be attained within a few days but occasionally requires up to two weeks. Once control has been obtained, the dosage should be reviewed and reduced to the lowest maintenance level consistent with good diabetic control.

The 250 mg tablet should be used only for the purpose of dose titration. There are no clinical data to support a minimum effective dose lower than 500 mg. If dose titration has been achieved with one tablet strength, then the patient's response should be reassessed if a different strength or dose schedule is commenced.

Metformin dosage should be frequently reviewed in patients stabilised on metformin, especially if they develop an illness, as they may tolerate the drug less well, particularly if the illness is accompanied by a decrease in renal function. If necessary, metformin should be ceased for a few days during an illness and then restarted at low dosage, as for initial therapy.

The action of Arrow - Metformin is progressive and no final assessment of the patient's real response should be made before the 21st day of treatment; blood sugar estimations are recommended during the initial 15 days of stabilisation. Metformin will not produce a hypoglycaemic state when used alone, however, it increases insulin effectiveness.

Arrow - Metformin therapy with a sulphonylurea or insulin should be monitored by blood-sugar readings because combined therapy may cause hypoglycaemia. If it is decided to stabilise diabetic patients with metformin and insulin therapy, it is recommended that this is carried out in hospital because of the possibility of hypoglycaemia until the correct ratio of the two medicines is determined.

Elderly

The initial and maintenance dosing of metformin should be conservative in elderly patients, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly patients should not be titrated to the maximum dose of metformin.

Debilitated or malnourished patients

The dosing should be conservative and based on a careful assessment of renal function.

Children

Arrow - Metformin is not recommended for use in children.

Contraindications

Arrow - Metformin is contraindicated in the following conditions:

- Juvenile diabetes mellitus that is uncomplicated and well regulated on insulin
- Diabetes mellitus regulated by diet alone
- During or immediately following surgery where insulin is essential

- Hypersensitivity to metformin hydrochloride and other biguanides, or to any of the excipients
- Diabetic ketoacidosis, diabetic precoma
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/minute)
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see **Warnings and Precautions**)
- Acute or chronic disease which may cause tissue hypoxia such as cardiac failure, recent myocardial infarction, respiratory failure, pulmonary embolism, shock, acute significant blood loss, sepsis, gangrene, pancreatitis
- Severe hepatic insufficiency, acute alcohol intoxication, alcoholism
- History of lactic acidosis
- Lactation.

Warnings and Precautions

Lactic acidosis is a rare but serious metabolic complication which can occur due to metformin accumulation during treatment. When it occurs, it is fatal in approximately 50% of cases. Lactic acidosis is a medical emergency and must be treated in hospital immediately. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.

The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases per 1,000 patient years, with approximately 0.015 fatal cases per 1,000 patient years). The onset is often subtle and accompanied by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. Lactic acidosis may also occur in association with a number of pathophysiological conditions, including diabetes mellitus, and when there is significant tissue hypoperfusion and hypoxaemia. Lactic acidosis is characterised by acidosis (decreased blood pH), elevated lactate levels with increased lactate/pyruvate ratio and electrolyte disturbances with an increased anion gap.

Heart failure: Type 2 diabetic patients with heart failure are at an increased risk of hypoperfusion and possible renal insufficiency. Renal insufficiency is a risk factor for systemic accumulation of metformin and consequently lactic acidosis. Careful monitoring of renal function is recommended when metformin is used in patients with cardiac failure. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 µg/mL are generally found (see **Pharmacokinetics**). Underlying renal

disease, or a deterioration in renal function, result in reduced clearance of metformin and drug accumulation and are therefore major risk factors in lactic acidosis. The risk of lactic acidosis may therefore be significantly decreased by regular monitoring of renal function in patients taking metformin and by the use of the minimum effective dose of metformin. In addition, metformin therapy should be temporarily stopped in the presence of any condition associated with hypoxaemia or dehydration, in patients suffering from serious infections or trauma (particularly if gastrointestinal disturbances are noted or acidosis is suspected) and in those undergoing surgery.

Radiological studies involving the use of intravascular iodinated contrast materials (for example intravenous urogram, intravenous cholangiography, angiography, any computed tomography scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, metformin should be stopped at least 48 hours prior to, during and for 2 days after the radiological studies. For an emergency procedure, metformin should be stopped on admission. Metformin should be reinstated only after renal function has been re-evaluated and found to be normal.

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should therefore be warned against excessive alcohol intake, acute or chronic, while taking metformin.

Periodic assessment of renal, hepatic and cardiovascular function is recommended during prolonged periods of treatment with metformin.

Patients receiving continuous metformin therapy should have an annual estimation of vitamin B₁₂ levels because of reports of decreased vitamin B₁₂ absorption.

Carcinogenicity, mutagenicity, impairment of fertility

Long term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately two to three times the recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumourigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

No evidence of a mutagenic potential of metformin was found in the Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in vivo* micronuclei test (mouse bone marrow).

Fertility of male or female rats was unaffected by metformin administration at doses up to 600 mg/kg/day, or approximately twice the maximum recommended human daily dose on a body surface area basis.

Use in pregnancy (Category C)

Oral hypoglycaemics may enter the foetal circulation and cause neonatal hypoglycaemia. Since it is important to achieve strict normoglycaemia during pregnancy, metformin should be replaced by insulin.

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of foetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, any decision to use this drug should be balanced against the benefits and risks. The safety of metformin in pregnant women has not been established.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Use in lactation

Studies in lactating rats show that metformin is excreted in milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers, but caution should be exercised in such patients, and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in children

Arrow - Metformin is not recommended for use in children, except those with insulin resistant diabetes who are being treated in hospital.

Use in the elderly

The risk of lactic acidosis in association with metformin is increased in elderly patients on long-term therapy due to the physiological alteration of the renal function and the possible accumulation of metformin. Metformin may be used in the elderly when the issues raised under **Contraindications** and **Warning and Precautions** have been taken into consideration, the dosage is frequently reviewed and the renal function is closely monitored.

Adverse Effects

Gastrointestinal

Very common: Mild gastrointestinal symptoms (such as diarrhoea, nausea, vomiting) are the most frequent reactions to metformin (> 1/10), especially during the initial treatment period. These symptoms are generally transient and resolve spontaneously during continued treatment.

Gastrointestinal side effects can possibly be avoided if Arrow - Metformin is taken with meals and if the dose is increased slowly. Occasionally, a

temporary dose reduction can be considered. Occurrence of gastrointestinal symptoms, once a patient is stabilised on any dose of metformin, could be due to lactic acidosis or other serious disease.

Systemic and/or metabolic

Very rare. Lactic acidosis (see **Warnings and Precautions**) is a very rare (< 1/10,000) but serious metabolic complication that can occur due to metformin accumulation during treatment.

The onset of lactic acidosis is often subtle and accompanied only by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's doctor must be aware of the possible importance of such symptoms and the patient should be instructed to notify the doctor immediately if they occur. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Lactic acidosis is a medical emergency that must be treated in hospital. In a patient with lactic acidosis who is taking Arrow - Metformin, the drug should be discontinued immediately and general supportive measures should be instituted promptly.

Dermatological

Mild erythema has been reported in some hypersensitive individuals but the incidence is very rare (< 1/10,000).

Haematological

A decrease of vitamin B₁₂ absorption with a decrease in serum levels has been observed in patients treated long-term with metformin and appears to be generally without clinical significance (< 1/10,000). Therefore, serum B₁₂ levels should be appropriately monitored and periodic parenteral B₁₂ supplementation considered.

Others

Metallic taste (3%) is common.

Interactions

Pharmacokinetic interactions

Cimetidine: Reduced clearance of metformin has been reported during cimetidine therapy, so a dose reduction should be considered.

Anticoagulants: Metformin increases the elimination rate of vitamin K antagonists. Consequently, the prothrombin time should be closely monitored in patients in whom metformin and vitamin K antagonists are being

coadministered. Cessation of metformin in patients receiving vitamin K antagonists can cause marked increases in the prothrombin time.

Nifedipine: A single dose, metformin/nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of metformin and nifedipine increased plasma metformin C_{max} and AUC by 20 and 9%, respectively, and increased the amount of metformin excreted in the urine. T_{max} and half-life of metformin were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on the pharmacokinetics of nifedipine.

Pharmacodynamic interactions

Sulfonylureas and repaglinide: During concomitant therapy with sulfonylureas and repaglinide, blood glucose should be monitored because combined therapy may cause hypoglycaemia.

Beta-blockers: Coadministration of metformin and beta-blockers may result in a potentiation of the hypoglycaemic action. In addition, some of the premonitory signs of hypoglycaemia, in particular tachycardia, may be masked. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent.

ACE inhibitors: Coadministration of metformin and ACE inhibitors may result in a potentiation of the hypoglycaemic action. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent

Calcium channel blockers: Calcium channel blockers may affect glucose control in diabetic patients; regular monitoring of glycaemic control is recommended.

Thyroid products: Thyroid products tend to produce hyperglycaemia and may therefore lead to loss of control.

Corticosteroids: Corticosteroids tend to produce hyperglycaemia and may lead to loss of control.

Alcohol: Alcohol decreases blood glucose concentration by inhibiting hepatic glucose output, thus increasing the risk of hypoglycaemia and can also mask its warning symptoms. The CNS depressant effects of alcohol plus hypoglycaemia can make driving or the operation of dangerous machinery much more hazardous. Excessive consumption of alcohol while on metformin may result in elevation of blood lactate.

Thiazide diuretics: Thiazide therapy may impair glucose tolerance. Dosage adjustment of metformin may be required.

Iodinated contrast media: Arrow - Metformin should be temporarily withheld in patients undergoing radiological studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see **Warnings and Precautions**).

Laboratory tests: No information is available.

Overdosage

Symptoms

Hypoglycaemia has not been seen with ingestion of up to 85 g of metformin alone, although lactic acidosis has occurred in such circumstances. The onset of lactic acidosis is often subtle and accompanied only by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Treatment

Lactic acidosis should be suspected in diabetic metformin treated patients with overdose. Lactic acidosis is diagnosed and monitored by measurement of serum electrolytes, arterial pH and pCO₂ and arterial lactate plasma level.

The aim of treatment is to manage any underlying disorder and in some cases this will be sufficient to enable the body's homeostatic mechanism to correct the acid-base imbalance. The advantages of more active treatment of the acidosis must be balanced against the risks, including over alkalinisation with sodium bicarbonate. Because metformin hydrochloride is dialysable (with a clearance of up to 170 mL/min under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Pharmaceutical Precautions

Storage

Store below 30 °C

Shelf life

36 months

Medicine Classification

Prescription only medicine

Package Quantities

Arrow - Metformin 250 mg tablet: each pack contains 100 tablets

Arrow - Metformin 500 mg tablet: each pack contains 100 and 500 tablets

Arrow - Metformin 850 mg tablet: each pack contains 60 tablets

Arrow - Metformin 1000 mg tablet: each pack contains 90 tablets.

Further Information

Nil

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