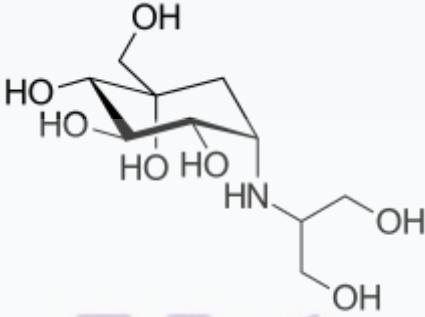


Voglibose

Voglibose	
	
 Clinical data	
AHFS/Drugs.com	Voglibose 0.2 mg + 0.3mg + Metformin 500mg (SR) Tablets
ATC code	A10BF03 (WHO)
Identifiers	
IUPAC name [show]	
CAS Number	83480-29-9 ✓
PubChem CID	444020
DrugBank	DB04878 ✓
ChemSpider	392046 ✓
UNII	S77P977AG8
KEGG	D01665 ✓
ChEMBL	CHEMBL476960 ✓
Chemical and physical data	
Formula	C ₁₀ H ₂₁ NO ₇
Molar mass	267.28 g/mol
3D model (JSmol)	Interactive image
SMILES [show]	

[InChI](#)[\[show\]](#)

[\(verify\)](#)

Voglibose ([INN](#) and [USAN](#), trade name **Voglib**, marketed by Mascot Health Series) is an [alpha-glucosidase inhibitor](#) used for lowering post-prandial blood glucose levels in people with [diabetes mellitus](#). Voglibose delays the absorption of glucose thereby reducing the risk of macrovascular complications. Voglibose is a research product of [Takeda Pharmaceutical Company](#), Japan's largest pharmaceutical company. Voglibose was first launched in 1994, under the trade name BASEN, to improve postprandial hyperglycemia in [diabetes mellitus](#).

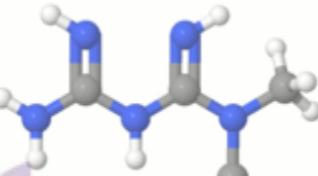
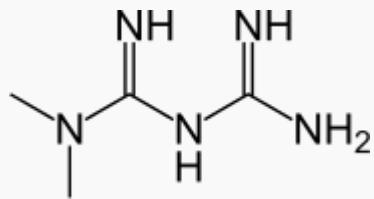
Postprandial hyperglycemia (PPHG) is primarily due to first phase insulin secretion. Alpha glucosidase inhibitors delay glucose absorption at the intestine level and thereby prevent sudden surge of glucose after a meal.

There are three drugs which belong to this class, [acarbose](#), [miglitol](#) and voglibose, of which voglibose is the newest.

References[▲]

https://www.takeda.com/news/2008/20080526_3621.html

Metformin



Vobryyl®
Systematic (IUPAC) name

Voglibose 0.2mg / 0.3mg +
N,N-Dimethylimidodicarbonimidic diamide

Clinical data

Trade names Glucophage, Etform

AHFS/Drugs.com [FDA Professional Drug Information](#)

MedlinePlus [a696005](#)

Licence data [US FDA](#):link

Pregnancy cat. C ([AU](#)) B ([US](#))

Legal status [Prescription Only \(S4\)](#) ([AU](#)) R-only ([CA](#)) POM ([UK](#)) R-only ([US](#))

Routes Oral

Pharmacokinetic data

Bioavailability 50–60%^{[1][2]}

<u>Protein binding</u>	Minimal ^[1]
<u>Metabolism</u>	Not by liver ^[1]
<u>Half-life</u>	4-8.7 hours ^[1]
<u>Excretion</u>	Urine (90%) ^[1]
Identifiers	
<u>CAS number</u>	657-24-9
<u>ATC code</u>	A10BA02
<u>PubChem</u>	Voglibose 0.2mg / 0.3mg + CID 4091 Metformin 500mg (SR) Tablets
<u>DrugBank</u>	DB00331
<u>ChemSpider</u>	3949
<u>UNII</u>	9100L32L2N
<u>KEGG</u>	D04966
<u>ChEBI</u>	CHEBI:6801
<u>ChEMBL</u>	CHEMBL1431
Chemical data	
<u>Formula</u>	C₄H₁₁N₅
<u>Mol. mass</u>	129.16364
<u>SMILES</u>	<ul style="list-style-type: none"> • C[n](C):c(:[nH]):[nH]:c(:[nH]):[nH2]

InChI

- InChI=1S/C4H11N5/c1-9(2)4(7)8-3(5)6/h1-2H3,(H5,5,6,7,8)

Key:XZWYZXLIPXDOLR-UHFFFAOYSA-N

Metformin (BAN, USAN and INN, pronounced /met'formin/, met-FAWR-min; sold as **Glucophage**) is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function.^{[3][4][5]} Its use in gestational diabetes has been limited by safety concerns although at least one study has been conducted which showed no concerns for children prenatally exposed to Metformin up to 2 years of age.^[6] It is also used in the treatment of polycystic ovary syndrome, and has been investigated for other diseases where insulin resistance may be an important factor.^[7] Metformin works by suppressing glucose production from three-carbon molecules (like propionic acid, a by product of dietary fibre fermentation in the large intestine and pyruvate, a by product of glucose breakdown in the muscles) by the liver.^[7]

Limited evidence suggests that metformin may prevent the cardiovascular and possibly the cancer complications of diabetes.^{[7][8][9]} It helps reduce LDL cholesterol and triglyceride levels and is not associated with weight gain; in some people it promotes weight loss.^{[7][8]} It is the only antidiabetic possibly associated with reduced risk of cardiovascular complications in those with type II diabetes mellitus. Metformin is one of only two oral antidiabetics in the World Health Organization Model List of Essential Medicines (the other being glibenclamide).^[10]

Metformin causes few adverse effects when prescribed appropriately (the most common is gastrointestinal upset) and has been associated with a low risk of hypoglycemia.^[7] Lactic acidosis (a buildup of lactate in the blood) can be a serious concern in overdose and when it is prescribed to people with contraindications, but otherwise, there is no significant risk.^[11]

First synthesized and found to reduce blood sugar in the 1920s, metformin was forgotten for the next two decades as research shifted to insulin and other antidiabetic drugs. Interest in metformin was rekindled in the late 1940s after several reports that it could reduce blood sugar levels in people, and in 1957, French physician Jean Sterne published the first clinical trial of metformin as a treatment for diabetes. It was introduced to the United Kingdom in 1958, Canada in 1972, and the United States in 1995. Metformin is now believed to be the most widely prescribed antidiabetic drug in the world; in the United States alone, more than 48 million prescriptions were filled in 2010 for its generic formulations.^{[12][13]}

Medical uses

Metformin is primarily used for type 2 diabetes, but is increasingly being used in polycystic ovary syndrome (PCOS),^[14] and in prediabetes.^[15]

Type 2 diabetes

The American Diabetes Association recommends metformin as a first-line agent to treat type 2 diabetes mellitus.^{[16][17]}

Efficacy

A large cardiovascular outcome trial performed in the late 1980's and early 1990's provided data suggesting that metformin reduces the rate of adverse cardiovascular outcomes in diabetes relative to other anti-hyperglycemic agents. The accumulation of data from other trials has reduced confidence in this conclusion. Treatment guidelines for major professional associations including the

European Association for the Study of Diabetes, the European Society for Cardiology, and the American Diabetes Association now describe evidence for the cardiovascular benefits of metformin as equivocal.^{[18][19]} According to the American College of Physicians there is low quality evidence that metformin monotherapy is associated with lower cardiovascular mortality than sulfonylurea monotherapy and there is low quality evidence that metformin monotherapy is associated with fewer cardiovascular events than metformin-sulfonylurea combination therapy. Evidence for other comparisons is described as unclear.^[20]

In the UK Prospective Diabetes Study (UKPDS), over 10 years metformin monotherapy reduced diabetes related endpoints and overall mortality in overweight diabetics by about 30% when compared with insulin and sulfonylureas (glibenclamide and chlorpropamide). When compared with the group only given dietary advice, metformin had risk reductions of 32% for any diabetes-related endpoint, 42% for diabetes-related death, and 36% for all-cause mortality. (UKPDS study)^[21] This difference held in people who were followed up for five to 10 years after the study.^[22] In the UKPDS study metformin was the only drug associated with decreased mortality.^[23] Since intensive glucose control with metformin appears to decrease the risk of diabetes-related endpoints in overweight people with diabetes, and is associated with less weight gain and fewer hypoglycaemic attacks than are insulin and sulphonylureas, it may be the first-line pharmacological therapy of choice in this group. In addition, metformin had no effect on body weight: Over the 10-year treatment period, the metformin group gained about 1 kg, the same as the dietary advice group, while the sulfonylureas group gained 3 kg, and the insulin group, 6 kg.^{[21][24]}

In contrast, a 2011 meta analyses found no benefit but also no harm on cardiovascular events in 35 trials. There was an effect on cardiovascular events against placebo, but not against comparator treatments. It found a possibly (nearly significant) survival benefit in mono therapy with metformin against comparators. Survival was reduced when metformin was combined with sulfonylurea. Additional analyses found the drug appeared to be more beneficial in longer trials enrolling younger patients.^[25] Another 2012 meta analysis confirmed that if all trials against placebo or no treatment or other anti-diabetics (13 trials) were combined there was no effect on all cause and cardiovascular survival. This meta analysis included treatment arms in which metformin plus a sulfonylurea was compared to treatment with a sulfonylurea alone.^[26]

Advantages

Metformin may be associated with a decreased risk of cardiovascular mortality compared with other oral diabetes agents or placebo.^[24] All-cause mortality was slightly lower with metformin than with a sulfonylurea in observational studies, but results differed between trials and observational studies. Risk for bias in the studies was moderate. Cardiovascular mortality was slightly lower with metformin than with a sulfonylurea, but results were imprecise and had moderate risk for bias.(Low strength of evidence). Observational studies were associated with a lower risk for all-cause mortality and cardiovascular disease mortality and morbidity than were sulfonylureas.^[16]

Metformin has a lower risk of hypoglycemia than the sulfonylureas,^{[27][28]} although it has uncommonly occurred during intense exercise, calorie deficit, or when used with other agents to lower blood glucose.^{[29][30]}

Metformin is not associated with weight gain, rather weight loss.^{[27][28]} In comparison with thiazolidinediones or sulfonylureas, the mean differences in body weight were about -2.5 kg.^[31]

Metformin modestly reduces LDL and triglyceride levels.^[27] Metformin decreased low-density lipoprotein cholesterol levels compared with pioglitazone, sulfonylureas, and DPP-4 inhibitors.^[16]

Metformin is similarly efficacious as most diabetes medications when used as mono therapy and decreased HbA1c levels by 1 absolute percentage point on average over the course of a study. Metformin reduced HbA1c levels more than the DPP-4 inhibitors as mono therapy. Combination

therapy (including the combination of metformin and a DPP-4 inhibitor) decreased HbA1c levels more than monotherapy did, by about 1 absolute percentage point.^[16]

Metformin is not expensive.^[32]

Prediabetes

Metformin treatment of people at risk for type 2 diabetes may decrease their chances of developing the disease, although intensive physical exercise and dieting work significantly better for this purpose. In a large U.S. study known as the Diabetes Prevention Program, participants were divided into groups and given either placebo, metformin, or lifestyle intervention, and followed for an average of three years. The intensive program of lifestyle modifications included a 16-lesson training on dieting and exercise followed by monthly individualized sessions with the goals to decrease the body weight by 7% and engage in a physical activity for at least 150 minutes per week. The incidence of diabetes was 58% lower in the lifestyle group and 31% lower in those given metformin. Among younger people with a higher body mass index, lifestyle modification was no more effective than metformin, and for older individuals with a lower body mass index, metformin was no better than placebo in preventing diabetes.^[33] After ten years, the incidence of diabetes was 34% lower in the group of participants given diet and exercise and 18% lower in those given metformin.^[34] It is unclear whether metformin slowed down the progression of prediabetes to diabetes (true preventive effect), or the decrease of diabetes in the treated population was simply due to its glucose-lowering action (treatment effect).^[35]

A systematic review analysed children and adolescents with clinical insulin resistance or pre-diabetes. Four randomized controlled trials were identified. All compared the effect of 6 months of metformin plus or minus lifestyle intervention with placebo plus or minus lifestyle intervention. It was found that metformin improves markers of insulin sensitivity and reduces BMI.^[15]

Polycystic ovary syndrome

Antidiabetic therapy has been proposed as a treatment for polycystic ovary syndrome (PCOS), a condition frequently associated with insulin resistance, since the late 1980s.^[36] The use of metformin in PCOS was first reported in 1994, in a small study conducted at the University of the Andes, Venezuela.^{[37][38]} The United Kingdom's National Institute for Health and Clinical Excellence recommended in 2004 that women with PCOS and a body mass index above 25 be given metformin for anovulation and infertility when other therapies have failed to produce results.^[39] However, two clinical studies completed in 2006–2007 returned mostly negative results, with metformin being no better than placebo, and a metformin-clomifene combination no better than clomifene alone.^{[40][41]} Reflecting this, subsequent reviews noted large randomized controlled trials have, in general, not shown the promise suggested by the early small studies. UK and international clinical practice guidelines do not recommend metformin as a first-line treatment^[42] or do not recommend it at all, except for women with glucose intolerance.^[43] The guidelines suggest clomiphene as the first medication option and emphasize lifestyle modification independently from the drug treatment.

In a dissenting opinion, a systematic review of four head-to-head comparative trials of metformin and clomifene found them equally effective for infertility.^[44] A BMJ editorial noted four positive studies of metformin were in people not responding to clomifene, while the population in the negative studies was drug-naïve or uncontrolled for the previous treatment. The editorial suggested metformin should be used as a second-line drug if clomifene treatment fails.^[45] Another review recommended metformin unreservedly as a first-line treatment option because it has positive effects not only on anovulation, but also on insulin resistance, hirsutism, and obesity often associated with PCOS.^[46] An updated Cochrane Collaboration review found metformin was associated with improved clinical pregnancy but there was no evidence that metformin improves live birth rates whether it is used alone or in combination with clomiphene, or when compared with clomiphene. Therefore, the role of metformin in improving reproductive outcomes in women with PCOS appears to be

limited.^[47] However, in a recent multicenter, randomized, double-blind, placebo-controlled study, metformin increased live-birth rates compared to placebo with the most beneficial effect seen in obese women. These results are consistent with another study that evaluated pretreatment with metformin for 3 months before in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI). Although the role of metformin for ovulation induction in PCOS has been limited, these results suggest that metformin may play an important role in improving live birth rates when administered 3 months prior to and concurrent with standard infertility treatments.^[48]

The use of metformin throughout pregnancy in women with polycystic ovary syndrome reduces the rates of early pregnancy loss and preterm labor and protects against fetal growth restriction.^[49]

Contraindications

Metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders (creatinine levels over 150 µmol/l (1.7 mg/dL),^[50] although this is an arbitrary limit), lung disease and liver disease. According to the prescribing information, heart failure (in particular, unstable or acute congestive heart failure) increases the risk of lactic acidosis with metformin.^[51] A 2007 systematic review of controlled trials, however, suggested metformin is the only antidiabetic drug not associated with any measurable harm in people with heart failure, and that it may reduce mortality in comparison with other antidiabetic agents.^[52]

Metformin is recommended to be temporarily discontinued before any radiographic study involving iodinated contrast agents, (such as a contrast-enhanced CT scan or angiogram), as the contrast dye may temporarily impair kidney function, indirectly leading to lactic acidosis by causing retention of metformin in the body.^{[53][54]} Metformin can be resumed after two days, assuming kidney function is normal.^{[53][54]}

Adverse effects

The most common adverse effect of metformin is gastrointestinal irritation, including diarrhea, cramps, nausea, vomiting and increased flatulence; metformin is more commonly associated with gastrointestinal side effects than most other antidiabetic drugs.^[28] The most serious potential side effect of metformin use is lactic acidosis; this complication is very rare, and the vast majority of these cases seem to be related to comorbid conditions, such as impaired liver or kidney function, rather than to the metformin itself.^[55]

Metformin has also been reported to decrease the blood levels of thyroid-stimulating hormone in people with hypothyroidism.^[56] The clinical significance of this is still unknown.

Gastrointestinal

In a clinical trial of 286 subjects, 53.2% of the 141 given immediate-release metformin reported diarrhea, versus 11.7% for placebo, and 25.5% reported nausea/vomiting, versus 8.3% for those on placebo.^[57]

Metformin was associated with a 4.27 significantly higher incidence of gastrointestinal disturbances than placebo in 5 trials in women with poly cystic ovary syndrome.^[47]

Gastrointestinal upset can cause severe discomfort; it is most common when metformin is first administered, or when the dose is increased. The discomfort can often be avoided by beginning at a low dose (1 to 1.7 grams per day) and increasing the dose gradually. Gastrointestinal upset after prolonged, steady use is less common.

Vitamin B12 deficiency

Long-term use of metformin has been associated with increased homocysteine levels^[58] and malabsorption of vitamin B₁₂.^{[59][60]} Higher doses and

prolonged use are associated with increased incidence of vitamin B₁₂ deficiency,^[61] and some researchers recommend screening or prevention strategies.^[62]

Lactic acidosis

The most serious potential adverse effect of biguanide use is lactic acidosis ("metformin-associated lactic acidosis" or MALA), the incidence for which is 9 per 100,000 person-years.^[63] Phenformin, another biguanide, was withdrawn from the market because of an increased risk of lactic acidosis (rate of 40–64 per 100,000 patient-years).^[63] However, metformin is safer than phenformin, and the risk of developing lactic acidosis is not increased by the medication as long as it is not prescribed to known high-risk groups, as in advanced renal insufficiency and alcoholism.^[64]

Lactate uptake by the liver is diminished with metformin administration because lactate is a substrate for hepatic gluconeogenesis, a process that metformin inhibits. In healthy individuals, this slight excess is simply cleared by other mechanisms (including uptake by the kidneys, when their function is unimpaired), and no significant elevation in blood levels of lactate occurs.^[27] When there is impaired renal function, however, clearance of metformin and lactate is reduced, leading to increased levels of both, and possibly causing lactic acidosis due to a buildup of lactic acid. Because metformin decreases liver uptake of lactate, any condition that may precipitate lactic acidosis is a contraindication to its use. Common causes of increased lactic acid production include alcoholism (due to depletion of NAD+ stores), heart failure, and respiratory disease (due to inadequate oxygenation of tissues); the most common cause of impaired lactic acid excretion is kidney disease.^[65]

Metformin has also been suggested to increase production of lactate in the small intestine; this could potentially contribute to lactic acidosis in those with risk factors.^[66] However, the clinical significance of this is unknown, and the risk of metformin-associated lactic acidosis is most commonly attributed to decreased hepatic uptake rather than increased intestinal production.^{[27][65][67]}

Overdose

A review of intentional and accidental metformin overdoses reported to poison control centers over a five-year period found serious adverse events were rare, though the elderly appeared to be at greater risk.^[68] A similar study where cases were reported to Texas poison control centers between the years 2000 and 2006 found ingested doses of more than 5,000 mg were more likely to involve serious medical outcomes in adults.^[69] Survival following intentional overdoses with up to 63,000 mg (63 g) of metformin have been reported in the medical literature.^[70] Fatalities following overdose are rare, but do occur.^{[71][72][73]} In healthy children, unintentional doses of less than 1,700 mg are unlikely to cause any significant toxic effects.^[74]

The most common symptoms following overdose appear to include vomiting, diarrhea, abdominal pain, tachycardia, drowsiness, and, rarely, hypoglycemia or hyperglycemia.^{[69][72]} The major potentially life-threatening complication of metformin overdose is lactic acidosis, which is due to lactate accumulation.^{[75][76]} Treatment of metformin overdose is generally supportive, as there is no specific antidote. Lactic acidosis is initially treated with sodium bicarbonate, although high doses are not recommended, as this may increase intracellular acidosis.^[73] Acidosis that does not respond to administration of sodium bicarbonate may require further management with standard hemodialysis or continuous veno-venous hemofiltration. In addition, due to metformin's low molecular weight and lack of plasma protein binding, these techniques also have the benefit of efficiently removing metformin from blood plasma, preventing further lactate overproduction.^{[77][78][79]}

Metformin may be quantitated in blood, plasma, or serum to monitor therapy, confirm a diagnosis of poisoning, or assist in a medicolegal death investigation. Blood or plasma metformin concentrations are usually in a range of 1–4 mg/L in persons receiving the drug therapeutically, 40–120 mg/L in victims of acute overdosage, and 80–200 mg/L in fatalities. Chromatographic techniques are commonly employed.^{[80][81]}

Interactions

The H₂-receptor antagonist cimetidine causes an increase in the plasma concentration of metformin, by reducing clearance of metformin by the kidneys;^[82] both metformin and cimetidine are cleared from the body by tubular secretion, and both, particularly the cationic (positively charged) form of cimetidine, may compete for the same transport mechanism.^[83] A small double-blind, randomized study found the antibiotic cephalixin to also increase metformin concentrations by a similar mechanism;^[84] theoretically, other cationic medications may produce the same effect.^[83]

Mechanism of action

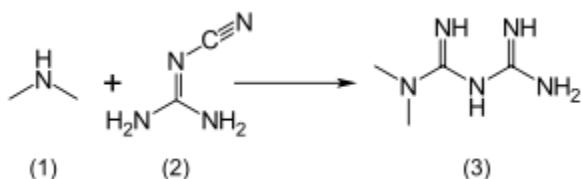
Metformin decreases glucose production in the liver, increases insulin sensitivity and enhances peripheral glucose uptake. It does not stimulate secretion of endogenous insulin.

Metformin decreases hyperglycemia primarily by suppressing glucose production by the liver (hepatic gluconeogenesis).^[66] The "average" person with type 2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one third.^[85] The molecular mechanism of metformin is incompletely understood: inhibition of the mitochondrial respiratory chain (complex I), activation of AMP-activated protein kinase (AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP) and consequent activation of protein kinase A (PKA), and an effect on gut microbiota have been proposed as potential mechanisms.^{[86][87]} A study in 2001 suggested that activation of AMPK, an enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats,^[88] was required for metformin's inhibitory effect on the production of glucose by liver cells.^[89] Research published in 2008 further showed that activation of AMPK was required for an increase in the expression of SHP, which in turn inhibited the expression of the hepatic gluconeogenic genes PEPCK and Glc-6-Pase.^[90] Metformin is frequently used in research along with AICAR as an AMPK agonist. More recent studies using mouse models in which the genes for AMPKα1 and α2 catalytic subunits (Prkaa1/2) or LKB1, an upstream kinase of AMPK, had been knocked out in hepatocytes have raised doubts over the obligatory role of AMPK, since the effect of metformin was not abolished by loss of AMPK function.^[86] The mechanism by which biguanides increase the activity of AMPK remains uncertain; however, research suggests that metformin increases the concentration of cytosolic AMP (as opposed to a change in total AMP or total AMP/ATP).^[91] Increased cellular AMP has also been proposed to explain the inhibition of glucagon-induced increase in cAMP and activation of PKA.^[86] Metformin and other biguanides may antagonize the action of glucagon, thus reducing fasting glucose levels.^[92] Metformin also induces a profound shift in the faecal microbial community profile in diabetic mice and it has also been proposed that this may contribute to its mode of action possibly through an effect on Glucagon-like peptide-1 (GLP-1) secretion.^[87]

In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (by inducing the phosphorylation of GLUT4 enhancer factor), decreases insulin-induced suppression of fatty acid oxidation,^[93] and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors.^[94] The increase in insulin binding after metformin treatment has also been demonstrated in patients with NIDDM [95]. AMPK probably also plays a role, as metformin administration increases AMPK activity in skeletal muscle.^[96] AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake. Some metabolic actions of metformin do appear to occur by AMPK-independent mechanisms; a 2008 study found "the metabolic actions of metformin in the heart muscle can occur independent of changes in AMPK activity and may be mediated by p38 MAPK- and PKC-dependent mechanisms."^[97]

Chemistry

The usual synthesis of metformin, originally described in 1922 and reproduced in multiple later patents and publications, involves the reaction of dimethylamine hydrochloride and 2-cyanoguanidine (dicyandiamide) with heating.^{[98][99]}



According to the procedure described in the 1975 Aron patent,^[100] and the *Pharmaceutical Manufacturing Encyclopedia*,^[101] equimolar amounts of dimethylamine and 2-cyanoguanidine are dissolved in toluene with cooling to make a concentrated solution, and an equimolar amount of hydrogen chloride is slowly added. The mixture begins to boil on its own, and after cooling, metformin hydrochloride precipitates with a 96% yield.

Structure

The structure of metformin was generally represented in a wrong tautomeric form for a number of years. This was corrected in 2005.^[102] The energy difference between the correct tautomer and the generally represented tautomer is about 37 kJ/mol (9 kcal/mol). The drug is administered as metformin hydrochloride. The structure of the metformin hydrochloride was also corrected recently.^[103] According to these studies, the metformin has different electronic structure compared to its protonated form. The neutral species is a simple conjugated system. Upon protonation, (i) the conjugation breaks down, (ii) the intramolecular hydrogen bond breaks down, (iii) the molecule becomes non-planar (iv) two lone pairs get accumulated at the central nitrogen (v) dynamism increases in the system via C=N rotational process and via N-inversion process. Thus, electronically, metformin hydrochloride should be treated as a simple extension of metformin. The nucleophilicity of metformin hydrochloride is moderate and that is a desired property. Metformin is shown to belong to a new class of compounds called nitreones.

Pharmacokinetics

Metformin has an oral bioavailability of 50–60% under fasting conditions, and is absorbed slowly.^{[83][104]} Peak plasma concentrations (C_{max}) are reached within one to three hours of taking immediate-release metformin and four to eight hours with extended-release formulations.^{[83][104]} The plasma protein binding of metformin is negligible, as reflected by its very high apparent volume of distribution (300–1000 L after a single dose). Steady state is usually reached in one or two days.^[83]

Metformin has acid dissociation constant values (pK_a) of 2.8 and 11.5 and, therefore, exists very largely as the hydrophilic cationic species at physiological pH values. The metformin acid dissociation constant values (pK_a) make metformin a stronger base than most other basic drugs with less than 0.01% unionized in blood. Furthermore, the lipid solubility of the unionized species is slight as shown by its low logP value [log(10) of the distribution coefficient of the unionized form between octanol and water] of -1.43. These chemical parameters indicate low lipophilicity and, consequently, rapid passive diffusion of metformin through cell membranes is unlikely. The logP of metformin is less than that of phenformin (-0.84) because two methyl substituents on metformin impart lesser lipophilicity than the larger phenylethyl side chain in phenformin. More lipophilic derivatives of metformin are presently being investigated with the aim of producing prodrugs with better oral absorption than metformin itself.^[105]

Metformin is not metabolized. It is cleared from the body by tubular secretion and excreted unchanged in the urine; metformin is undetectable in blood plasma within 24 hours of a single oral

dose.^{[83][106]} The average elimination half-life in plasma is 6.2 hours.^[83] Metformin is distributed to (and appears to accumulate in) red blood cells, with a much longer elimination half-life: 17.6 hours^[83] (reported as ranging from 18.5 to 31.5 hours in a single-dose study of non-diabetic people).^[106]

History

The biguanide class of antidiabetic drugs, which also includes the withdrawn agents phenformin and buformin, originates from the French lilac or goat's rue (*Galega officinalis*), a plant used in folk medicine for several centuries.^[107]

Metformin was first described in the scientific literature in 1922, by Emil Werner and James Bell, as a product in the synthesis of *N,N*-dimethylguanidine.^[98] In 1929, Slotta and Tschesche discovered its sugar-lowering action in rabbits, noting it was the most potent of the biguanide analogs they studied.^[108] This result was completely forgotten, as other guanidine analogs, such as the synthalins, took over, and were themselves soon overshadowed by insulin.^[109]

Interest in metformin, however, picked up at the end of the 1940s. In 1950, metformin, unlike some other similar compounds, was found not to decrease blood pressure and heart rate in animals.^[110] That same year, a prominent Philippine physician, Eusebio Y. Garcia,^[111] used metformin (he named it *Fluamine*) to treat influenza; he noted the drug "lowered the blood sugar to minimum physiological limit" and was nontoxic. Garcia also believed metformin to have bacteriostatic, antiviral, antimalarial, antipyretic and analgesic actions.^[112] In a series of articles in 1954, Polish pharmacologist Janusz Supniewski^[113] was unable to confirm most of these effects, including lowered blood sugar; he did, however, observe some antiviral effects in humans.^{[114][115]}

While training at the Hôpital de la Pitié, French diabetologist Jean Sterne studied the antihyperglycemic properties of galegine, an alkaloid isolated from *Galega officinalis*, which is related in structure to metformin and had seen brief use as an antidiabetic before the synthalins were developed.^[12] Later, working at Laboratoires Aron in Paris, he was prompted by Garcia's report to reinvestigate the blood sugar lowering activity of metformin and several biguanide analogs. Sterne was the first to try metformin on humans for the treatment of diabetes; he coined the name "Glucophage" (glucose eater) for the drug and published his results in 1957.^{[12][109]}

Metformin became available in the British National Formulary in 1958. It was sold in the UK by a small Aron subsidiary called Rona.^[116]

Broad interest in metformin was not rekindled until the withdrawal of the other biguanides in the 1970s. Metformin was approved in Canada in 1972,^[117] but did not receive approval by the U.S. Food and Drug Administration (FDA) for type 2 diabetes until 1994.^[118] Produced under license by Bristol-Myers Squibb, Glucophage was the first branded formulation of metformin to be marketed in the United States, beginning on March 3, 1995.^[119] Generic formulations are now available in several countries, and metformin is believed to have become the most widely prescribed antidiabetic drug in the world.^[12]

Research

There is tentative evidence that metformin may decrease the risk of cancer.^[127] A direct action of metformin on cancer cells is suspected. Metformin exhibits a strong and consistent antiproliferative action on several cancer cell lines, including breast, colon, ovarian, pancreatic, lung and prostate cancer cells. These cellular studies were generally completed by preclinical studies showing a reliable antitumoral effect in various mouse models. In addition, the first clinical trials demonstrated a beneficial effect in breast and colon cancer.^[128]

Metformin appears to be effective and safe for the treatment of *gestational diabetes mellitus* (GDM), particularly for overweight or obese women, to immediate pregnancy outcomes. However, patients with multiple risk factors for insulin resistance may not meet their treatment goals with metformin alone and may require supplementary insulin. Evidence suggests that there are potential advantages for the use of metformin over insulin in gestational diabetes mellitus with respect to maternal weight gain and neonatal outcomes.^[49] Nonetheless, several concerns have been raised regarding studies published thus far, and evidence on the long-term safety of metformin for both mother and child is still lacking.^[129]

Metformin in conditions as *non-alcoholic fatty liver disease* (NAFLD)^[130] and *premature puberty*,^[131] two diseases that feature *insulin resistance* are still considered experimental. The benefit of metformin in NAFLD has not been extensively studied and may be only temporary;^[132] although some *randomized controlled trials* have found significant improvement with its use, the evidence is still insufficient.^{[133][134]}

Metformin is seen to possess antiaging properties though the mechanism remains unclear. Using a quantitative proteomics approach metformin was found to extend the lifespan in the model organism (*C. elegans*) through mitohormesis. The mitohormetic pathway is propagated by the peroxiredoxin PRDX-2.^[135]

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