Chapter

Clinical Pharmacokinetics of Metformin

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Abstract

Metformin, the only biguanide oral antidiabetic agent available, was first used clinically in the late 1950s. Metformin remains the first-line pharmacologic treatment for type 2 diabetes patients. It can be used as a single agent or in combination therapy with other antidiabetes agents, including insulin. Metformin is absorbed predominately from the small intestine. It is rapidly distributed following absorption and does not bind to plasma proteins. It is excreted unchanged in urine. The elimination half-life of Metformin during multiple dosages in patients with good renal function is approximately 5 hours.

Keywords: metformin, clinical pharmacokinetics, type 2 diabetes

1. Introduction

Metformin is a biguanide developed from galegine, aguanidine derivative found in *Galega officinalis*. Chemically, it is a hydrophilic base which exists at physiological pH as the cationic species [1, 2]. Metformin is the first-line drug for type 2 diabetes and the most commonly prescribed drug for this condition worldwide, either alone or in combination with insulin or other oral antidiabetes patients [3]. Metformin works by inhibiting the production of hepatic glucose, reducing intestinal glucose absorption and improving glucose uptake and utilization. Besides lowering the blood glucose level, metformin may have additional health benefits, including weight reduction, lowering plasma lipid levels, and prevention of some vascular complications [4]. Metformin is also used for other indications such as polycystic ovary syndrome (PCOS) [5]. Metformin is increasingly recognized as a potential anticancer agent due to a reduced cancer incidence in diabetic patients treated with the drug, and recently, patients taking metformin were associated with a reduced risk of COVID-19-related mortality [6].

Metformin can be determined in biological fluids by various methods, mainly using high performance liquid chromatography (HPLC), which allows pharmacokinetic studies in healthy volunteers and diabetic patients. Metformin disposition is apparently unaffected by the presence of diabetes and only slightly affected by the use of different oral formulations [2]. The oral absorption, hepatic uptake and renal excretion of metformin are mediated very largely by organic cation transporters [7].

2. Absorption

Metformin is orally administered in the dose range of 500 mg/b.i.d. or t.i.d. and up to a total of 2,550 mg/day or approximately 35 mg/kg/day. The immediate-release formulation of metformin is rapidly absorbed from the small intestine following an oral dose. It has an onset of action of about 1.5 hours, half-life in the circulation of about 1.5–4.9 hours, and duration of action of 16–20 hours [8]. About 20% of a total dose can be absorbed from the duodenum, up to 60% from the jejunum and ileum but only very small amounts from the colon. The rest is excreted in the feces [9]. Higher doses slow the rate of absorption and reduce the bioavailability [10]. Oral absorption of metformin from the immediate-release dosage forms is incomplete in man, with an estimated population mean of 55% for bioavailability [6]. Metformin has an absolute oral bioavailability of 40 to 60%, and gastrointestinal absorption is apparently complete within 6 hours of ingestion [11]. Its hydrophilicity is associated with the low intestinal and cell membrane permeability, which is recognized as a primary limiting step for metformin oral absorption [6].

The extended-release formulation has a similar onset of effect; however, its half-life is 6.5 hours, and its duration of action is 24 hours. Therefore, it can be administered once daily. It is associated with fewer gastrointestinal side effects compared with the immediate-release formulation. The half-life of metformin may be prolonged in patients with renal impairment, resulting in a theoretical risk of the rare but fatal lactic acidosis. It has been suggested that this risk may be a consequence of the action of metformin to suppress gluconeogenesis resulting in the inhibition of lactic acid metabolism in the liver, and thus accumulation of lactate [8].

The intestinal absorption of metformin may be primarily mediated by plasma membrane monoamine transporter (PMAT). However, there is no in-vivo data which indicates the role of PMAT in the disposition and pharmacological effect of metformin [5].

3. Distribution

Metformin is rapidly distributed following absorption and does not bind to plasma proteins [11]. The volume of distribution has been reported to range from 63 to 276 L after intravenous administration [1]. The concentration of metformin in the liver is three to five fold higher than that in the portal vein (40–70 μmol/L) after single therapeutic dose (20 mg/kg/day in humans or 250 mg/kg/day in mice) [3, 8], and metformin in general circulation is 10–40 μmol/L [8]. As the antihyperglycemic effect of metformin is mainly due to the inhibition of hepatic glucose output and the concentration of metformin in the hepatocytes is much higher than in the blood, the liver is therefore presumed to be the primary site of metformin function [12]. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL [4].

4. Metabolism and elimination

Metformin is not metabolized and is excreted unchanged in the urine, with a half-life of ~5 hrs. The population mean for renal clearance (CLr) is 510±120 ml/min. Active tubular secretion in the kidney is the principal route of metformin elimination [5]. The total amount of metformin excreted under steady-state conditions with 1 g BID is around 6 mmol. The average feces volume is 150 ml per 24 hours; the

calculated drug concentration in the distal colon is 40 mM. Not all of this may be free drug, as *E. coli* (with membrane potentials of −120 to −240 mV) may concentrate Metformin with subsequent block of its dihydrofolate reductase. The other 6 mmol reach the general circulation via the portal vein and, passing the liver, are rapidly cleared by the kidneys. The plasma elimination rate, about 500 ml per min, is similar to the kidney plasma flow, indicating active secretion [9].

The factors probably contribute to high clearance of metformin include: the low molecular weight associated with a negligible plasma protein binding; the presence of transporters in the kidney; and the low lipid solubility which makes negligible the passive reabsorption. The clearance is reduced in proportion to the reduction of renal function [13]. Metformin is contraindicated if serum creatinine levels ≥1.5 mg/dL in males, and ≥1.4 mg/dL in females or abnormal creatinine clearance. It should not be initiated in patients 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced [14].

5. Therapeutics range

The therapeutic range of plasma concentrations of metformin is unclear; however, concentrations above 5 mg/L are considered elevated [15]. Metformin immediate release (IR) taken BID and metformin extended release (XR), taken once daily (QD) in the evening with a meal, have almost equal areas under the curve (AUCs) for the same total dose. Both formulations have similar efficacy and safety profiles [9].

Metformin accumulation is a risk factor for fatal lactic acidosis. Therefore, therapeutic drug monitoring of metformin is required as an effort to ascertain that metformin concentration is within the recommended therapeutic range [16]. It is suggested that the mean plasma concentrations of metformin over a dosage interval be maintained below 2.5 mg/L in order to minimize the development of this adverse effect [7].

6. Therapeutics monitoring

Administration of ≥ 900 mg/kg/day of metformin resulted in morbidity/mortality and clinical signs of toxicity in rats. Increased incidence of minimal necrosis with minimal to slight inflammation of the parotid salivary gland for male rats given 1200 mg/kg/day, body weight loss and clinical signs in rats given ≥ 600 mg/kg/day were observed. Metformin was also associated with evidence of minimal metabolic acidosis at doses ≥ 600 mg/kg/day in rats [17]. In a preclinical study, intravenous and intragastric administration of metformin produced a significant increases in lactate AUC at the higher metformin doses (500 and 750 mg/kg), but intra-ileum administration did not produce an increase in lactate AUC relative to vehicle at either dose [18].

Large overdoses of metformin can lead to lactic acidosis. Suicide with metformin is rare. Intake of 35 g of metformin has been shown to be lethal [19]. The clinical study observed that patients on treatment with metformin developed lactic acidosis with metformin levels ranging from 256 to 682 μmol/L. This indicates that high levels of serum metformin are needed to cause lactic acidosis [20]. Metformin plasma levels >5 μg/mL are generally found when metformin is implicated as the cause of lactic acidosis [21]. Metformin plasma concentration levels do not exceed 5 μg/mL during controlled clinical trials, even at maximum doses [4]. Renal dysfunction,

sepsis, alcohol abuse, liver failure, radiologic contrast media administration, acute coronary syndrome, acute congestive heart failure, and shock increase the risk of metformin-related lactic acidosis [22].

Metformin plasma concentrations are approximately 2–4 fold higher in patients with moderate to severe renal impairment [21]. According to the Food and Drug Administration (FDA) recommendation, metformin is contraindicated in patients with an estimated glomerular filtration (eGFR) <30 mL/min/1.73 m^2. Those with an eGFR between 30 and 45 mL/min/1.73 m^2 should not be initiated on metformin. If a person's eGFR falls between 30 and 45 mL/min/1.73 m^2 and they are already treated with metformin, their provider should assess their risk and benefit associated with continued use [22].

Elderly patients, who often have reduced muscle mass, should have their creatinine clearance rate estimated before use. If the creatinine clearance rate is < 70–80 ml/min, metformin should not be given [23]. Because hepatic function impairment may significantly limit the ability to clear lactate, generally avoid using metformin in patients with clinical or laboratory evidence of hepatic disease. Caution patients against excessive alcohol intake, either acute or chronic, when taking metformin because alcohol potentiates the effects of metformin on lactate metabolism [24].

Gastrointestinal intolerance occurs quite frequently in the form of abdominal pain, flatulence, and diarrhea. Most of these effects are transient and subside once the dose is reduced or when administered with meals. Metformin may reduce vitamin B12 absorption due to calcium-dependent ileal membrane antagonism, an effect that can be reversed with supplemental calcium. This vitamin B12 deficiency is rarely associated with megaloblastic anemia [25].

7. Drug interaction

Metformin is a cation at physiological pH, as it is a strong base. Hence, the absorption, distribution and excretion of Metformin depend on the transporters such as organic cation transporters, multidrug and toxin extruders and plasma membrane monoamine transporter [26]. The oral absorption and hepatic uptake of Metformin are mediated possibly by organic cation transporters-1 and -3 and renal excretion of Metformin is largely mediated by Metformin transporters such as multidrug and toxin extruders-1 and 2-k and organic cation transporter 2 [5]. The drugs inhibiting the Metformin transporters could decrease the elimination of Metformin and increase its plasma concentrations leading to elevated risk of Metformin associated lactic acidosis [27].

Since Metformin is not metabolized, it is not expected to be involved in many drug–drug interactions. Thus, clinically significant drug interactions involving metformin are rare [25]. Some cationic agents such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin that are eliminated by renal tubular secretion may compete with metformin for elimination. Concomitant administration of cimetidine, furosemide, or nifedipine may also increase the concentration of metformin [23, 25].

The studies found many drugs which interact with metformin, but only a small number of clinically relevant drugs were identified which include cimetidine, contrast agents, dolutegravir, phenprocoumon, pyrimethamine, ranolazine, rifampicin, St John's wort, trimethoprim, vandetanib and verapamil (**Table 1**) [26]. Verapamil remarkably decreases the glucose-lowering effect of metformin, without altering its pharmacokinetics. This is likely mediated by competitive

Medication	Mechanism of interaction	Consequences/effects	Recommendation
Cimetidine	Elimination It competes with metformin for renal elimination and decreases the excretion of metformin.	It increases exposure of Metformin and risk of Metformin associated lactic acidosis.	It is recommended to reduce the dose of Metformin when Cimetidine is co-prescribed.
Trimethoprim	It inhibits Metformin elimination moderately through the inhibition of OCTs and MATEs.	It decreases Metformin clearance and increases plasma concentration.	Monitor carefully in patients with renal dysfunction or patients taking higher doses of Metformin
Rifampin	Absorption The mechanism may involve rifampin-mediated induction of the OCT1 in the gastrointestinal tract.	Rifampin may increase the gastrointestinal absorption and therapeutic efficacy of metformin.	Close clinical monitoring of glycemic control is recommended, and the dosage of metformin may be adjusted as necessary.
Dolutegravir	It is an inhibitor of both OCT2 and MATE1 transporters within the renal tubules.	It may increase the risk of hypoglycemia and GI intolerance due to increased plasma concentrations of Metformin.	Prescribers may adjust the Metformin dose to prevent intolerable adverse effects while prescribing both drugs.
Pyrimethamine	Elimination It decreases renal clearance of Metformin by the inhibition of OCT2 and MATE transporters.	Co-administration of Pyrimethamine with Metformin results in elevated plasma concentrations Metformin.	Metformin dose adjustment should be considered.
Ranolazine	Elimination It may decrease the Metformin elimination through the inhibition of OCT2 transporter.	The plasma concentration of Metformin is elevated by the co-administration of Ranolazine.	This interaction is dose dependent and it is recommended that the daily dose of Metformin should not exceed 1700 mg in patients taking Ranolazine 1000 mg two times daily.
Vandetanib	Elimination Vandetanib is a potent inhibitor of MATE1 and MATE2K transporters.	Its co-administration with Metformin may result in increased plasma concentration of Metformin due to decreased elimination.	The patients receiving both drugs should be monitored carefully for Metformin toxicity.

OCT- Organic cation transporter; MATEs-Multidrug and toxin extruders; GI-Gastrointestinal

Table 1.
Clinically a significant pharmacokinetic drug interactions of metformin.

inhibition of organic cation transporter 1 [28]. Metformin should be discontinued at least 48 hours prior to the administration of iodinated contrast media which can produce acute renal failure and should only be restarted if renal function is normal [25]. Study observed that Metformin decreases the anticoagulant effect of phenprocoumon [29].

8. Conclusion

Metformin is widely used for the treatment of type 2 diabetes mellitus. Metformin is a highly ionized, water-soluble drug that is absorbed, distributed and eliminated by transporters [15]. It undergoes active tubular secretion in the kidney and is excreted unchanged in the urine. A change in pharmacokinetics can alter drug exposure and predispose the patient to either over- or under dosing, potentially resulting in adverse drug reactions or therapeutic failure [30]. Most of the possible drug interactions of Metformin occur through the inhibition of organic cation transporter and multidrug and toxin extruders and increase the risk of Metformin associated lactic acidosis. Metformin administration should be stopped and urgent medical attention given to the patients developing first signs of lactic acidosis such as severe vomiting and diarrhea [27].

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References

[1] Graham GG, Punt J, Arora M, Day RO, Doogue MP, Duong JK, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 2011;50(2):81-98.

[2] Scheen AJ. Clinical pharmacokinetics of metformin. Clinical pharmacokinetics. 1996;30(5):359-371.

[3] Flory J, Lipska K. Metformin in 2019. Jama. 2019;321(19):1926-1927.

[4] Dumitrescu R, Mehedintu C, Briceag I, Purcărea V, Hudita D. Metformin-clinical pharmacology in PCOs. Journal of medicine and life. 2015;8(2):187.

[5] Gong L, Goswami S, Giacomini KM, Altman RB, Klein TE. Metformin pathways: Pharmacokinetics and pharmacodynamics. Pharmacogenetics and genomics. 2012;22(11):820.

[6] Jeong Y-S, Jusko WJ. Meta-assessment of metformin absorption and disposition pharmacokinetics in nine species. Pharmaceuticals. 2021;14(6):545.

[7] Graham GG, Punt J, Arora M, Day RO, Doogue MP, Duong J, et al. Clinical pharmacokinetics of metformin. Clinical pharmacokinetics. 2011;50(2):81-98.

[8] Apampa B. Pharmacology and safe prescribing of metformin. Nurse Prescribing. 2012;10(12):597-602.

[9] Glossmann HH, Lutz OM. Pharmacology of metformin—An update. European journal of pharmacology. 2019;865:172782.

[10] Kinaan M, Ding H, Triggle CR. Metformin: An old drug for the treatment of diabetes but a new drug for the protection of the endothelium. Medical principles and practice. 2015;24(5):401-415.

[11] Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 1996;30(5):359-371.

[12] Song R. Mechanism of metformin: A tale of two sites. Diabetes care. 2016;39(2):187-189.

[13] Vecchio S, Giampreti A, Petrolini V, Lonati D, Protti A, Papa P, et al. Metformin accumulation: Lactic acidosis and high plasmatic metformin levels in a retrospective case series of 66 patients on chronic therapy. Clinical Toxicology. 2014;52(2):129-135.

[14] Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: A systematic review. Jama. 2014;312(24):2668-2675.

[15] Duong JK, Kumar SS, Kirkpatrick CM, Greenup LC, Arora M, Lee TC, et al. Population pharmacokinetics of metformin in healthy subjects and patients with type 2 diabetes mellitus: Simulation of doses according to renal function. Clinical pharmacokinetics. 2013;52(5):373-384.

[16] Wibowo A, Ningrum VD, Izzah N, editors. Stability Test of Metformin Hydrochloride in Human Plasma Using HPLC-UV for the Protocol of Therapeutic Drug Monitoring of Metformin. AIP Conference Proceedings; 2018: AIP Publishing LLC.

[17] Quaile MP, Melich DH, Jordan HL, Nold JB, Chism JP, Polli JW, et al. Toxicity and toxicokinetics of metformin in rats. Toxicology and applied pharmacology. 2010;243(3):340-347.

[18] Bailey C, Wilcock C, Scarpello J. Metformin and the intestine. Diabetologia. 2008;51(8):1552-1553.

[19] Gjedde S, Christiansen A, Pedersen SB, Rungby J. Survival

following a metformin overdose of 63 g: A case report. Pharmacology and toxicology. 2003;93(2):98-99.

[20] Anders Frid M, Sterner GN, Löndahl M, Wiklander C, Cato A, Ellen Vinge M, et al. Novel assay of metformin levels in patients with type 2 diabetes and varying levels of renal function. Diabetes Care. 2010;33(6):1291.

[21] DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism. 2016;65(2):20-29.

[22] Wooley AC, Kerr JL. Monitoring patients on metformin: Recent changes and rationales. Journal of Pharmacy Technology. 2018;34(1):28-36.

[23] Triplitt C. Drug interactions of medications commonly used in diabetes. Diabetes Spectrum. 2006;19(4):202-211.

[24] Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron B, Stanifer J, Mock CK, et al. Metformin use in patients with historical contraindications or precautions. 2017.

[25] Rojas LBA, Gomes MB. Metformin: An old but still the best treatment for type 2 diabetes. Diabetology and metabolic syndrome. 2013;5(1):1-15.

[26] Stage TB, Brøsen K, Christensen MMH. A comprehensive review of drug–drug interactions with metformin. Clinical pharmacokinetics. 2015;54(8):811-824.

[27] Maideen NMP, Jumale A, Balasubramaniam R. Drug interactions of metformin involving drug transporter proteins. Advanced pharmaceutical bulletin. 2017;7(4):501.

[28] Cho SK, Kim CO, Park ES, Chung JY. Verapamil decreases the glucose-lowering effect of metformin in healthy volunteers. British journal of clinical pharmacology. 2014;78(6):1426-1432.

[29] Wijnen J, Van de Riet I, Lijfering W, Van der Meer F. Metformin use decreases the anticoagulant effect of phenprocoumon. Journal of Thrombosis and Haemostasis. 2014;12(6):887-890.

[30] Roberts DM, Sevastos J, Carland JE, Stocker SL, Lea-Henry TN. Clinical pharmacokinetics in kidney disease: Application to rational design of dosing regimens. Clinical Journal of the American Society of Nephrology. 2018;13(8):1254-1263.