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Metformin—Pharmacokinetic and Pharmacodynamics Journey Through the Body

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Abstract

Metformin is a commonly prescribed drug used to treat type 2 diabetes. The drug works by decreasing the amount of glucose the liver produces, increasing the sensitivity of muscle cells to insulin, and delaying the absorption of glucose in the intestines. Approximately 50% - 55% of metformin is absorbed in the small intestines. Most of the drug is excreted in the urine, so a patient with renal impairment may need a lower dose of the drug. Common side effects include nausea, vomiting, and diarrhea. Metformin may increase the risk of vitamin B12 deficiency. A rare but serious complication of metformin treatment is lactic acidosis, which is characterized by a blood pH of less than 7.35 and a plasma lactate concentration of greater than 5.0 mmol/L. The risk of lactic acidosis increases with the dose of metformin. The current recommended maximum dose of metformin is 2.0 g per day.

Keywords

Diabetes, Metformin, Pharmacokinetic, Pharmacodynamic, Personalized Medicine

1. Introduction

Metformin, a derivative of French lilac, has become a cornerstone in the management of type 2 diabetes mellitus [1]-[4]. Its clinical benefits are well-documented and include potential reductions in weight gain, diabetic nephropathy, and cardiovascular complications [5] [6]. Moreover, metformin may improve diabetic neuropathy by mitigating inflammation by up-regulation of miR-146a and suppressing oxidative stress [3].

Despite these advantages, metformin presents certain limitations. The optimal therapeutic dose remains uncertain, with approximately 35% of patients experiencing inadequate glycemic control. Tolerance often develops with chronic use

[4]. To fully understand this complex interplay of benefits and limitations, a thorough understanding of metformin's pharmacokinetic and pharmacodynamic properties is essential. This review explores these properties in detail, examining the diverse clinical implications of metformin and the latest research developments surrounding this widely used drug. Figure 1 illustrates the journey of metformin through the body, highlighting key stages from absorption and distribution to its effects on various tissues and eventual excretion.

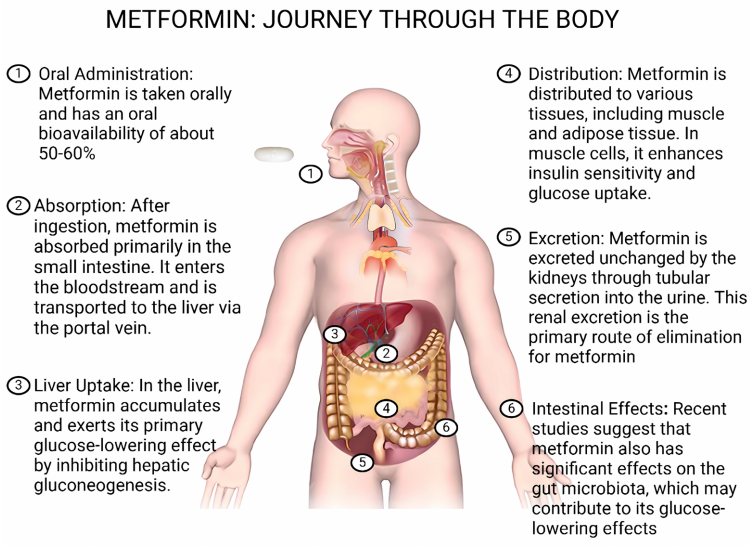

Figure 1. Journey of metformin through the body. The figure illustrates the six key stages of metformin's pharmacokinetic profile, from oral administration and absorption to distribution, hepatic uptake, excretion, and intestinal effects. Visual elements depict the passage of metformin through the digestive system, bloodstream, liver, and kidneys, highlighting its impact on glucose regulation in various tissues.

2. Physicochemical Properties and Absorption

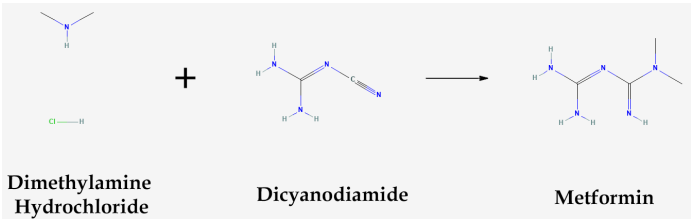

Figure 2. Simplified representation of metformin synthesis. Dimethylamine and dicyanodiamide react at elevated temperatures to form an intermediate (not shown), subsequently treated with hydrochloric acid to yield metformin hydrochloride. Note: This figure omits the hydrochloride salt of dimethylamine used in the first step and does not depict the intermediate compound (N,N-dimethylimidodicarbonimidic diamide) for clarity.

Metformin is primarily synthesized via a two-step process. Initially, dimethylamine and dicyanodiamide are reacted in an organic solvent at elevated temperatures

(100˚C - 180˚C), yielding N,N-dimethylimidodicarbonimidic diamide. This step proceeds through a nucleophilic addition-elimination mechanism involving an attack of the dimethylamine on dicyanodiamide, followed by cyclization and rearrangement. Subsequently, the resulting intermediate is treated with hydrochloric acid in an aqueous solution to form the final product, metformin hydrochloride. Figure 2 provides a simplified visual representation of this chemical process. Note that the figure omits the hydrochloride salt of dimethylamine used in the first step and does not depict the intermediate compound (N,N-dimethylimidodicarbonimidic diamide) for clarity.

2.1. Metformin: How It Reduces Blood Glucose

2.1.1. To Improve Insulin Sensitivity

- Normal Function: Insulin, produced by the pancreas, acts like a key to unlock cells, allowing glucose from the bloodstream to enter and be used as fuel.
- Insulin Resistance: Cells do not respond well to insulin, so glucose stays in the bloodstream. The pancreas produces more insulin, but glucose levels remain high.
- Metformin's Role: Helps insulin work better, allowing glucose to enter cells more effectively.

2.1.2. To Reduce Liver Glucose Production

- Fasting State: The liver becomes the main source of glucose.
- Normal Function: The liver or food provides glucose, and the pancreas produces insulin to help glucose enter cells for energy.
- Insulin Resistance: Glucose stays in the bloodstream, prompting the liver to produce more glucose.
- Metformin's Role: Stops the liver from producing excess glucose.

2.1.3. To Delay Glucose Absorption

- Digestive System: Glucose from food enters the bloodstream.
- Metformin's Role: Slows down the absorption of glucose from the digestive system, preventing rapid spikes in blood glucose levels.

2.2. Physicochemical Properties and Absorption

Metformin is typically administered orally as immediate-release or extended-release tablets [4] [7]. Its physicochemical properties significantly impact absorption and behavior within the body. At physiological pH, metformin exists as a hydrophilic, cationic base (pKa 11.5) with low membrane permeability (logP -1.43), hindering passive diffusion across cell membranes [5]. Consequently, gastrointestinal (GI) tract absorption is limited and slow. Most of the 50% - 55% of metformin ultimately absorbed occurs in the small intestine [6].

Specific transporter proteins, primarily organic cation transporters (OCTs) and plasma membrane monoamine transporters (PMAT), facilitate metformin's uptake in the small intestine [8]. These transporters act as carriers, shuttling

metformin across the intestinal epithelium into the bloodstream. Transporter activity can influence metformin's bioavailability and may contribute to the variability observed in patient responses [9].

3. Mechanisms of Action

3.1. Metformin's Pharmacokinetics

Metformin's pharmacokinetic behavior is characterized by its physicochemical properties and reliance on transporters. Limited passive diffusion restricts GI absorption. OCTs and PMATs facilitate their uptake in the small intestine [8]. Metformin exhibits low protein binding [10] and limited distribution into most tissues. Minimal metabolism leads to a predictable duration of action [11] [12]. Renal excretion is the primary elimination pathway, making kidney function critical in metformin therapy. Variations in pharmacokinetic parameters can occur due to age, renal impairment, and transporter gene polymorphisms [13] [14].

3.2. Key Pharmacodynamic Insights

Tucker *et al.* [14] investigated metformin pharmacokinetics in healthy volunteers and diabetic patients. Their findings highlighted similarities in absorption, clearance, and half-life across groups. After intravenous administration, key metrics were determined within 2 hours. Plasma half-life was 4 - 8 hours, with a 50% - 60% bioavailability. Absorption became negligible after 6 hours, and renal clearance was similar for intravenous and oral routes. The findings aligned with other studies; however, some reports indicate a longer half-life (9 - 20 hours) after multiple doses [14] [15] raising concerns about potential slow elimination and accumulation, which increases the risk of lactic acidosis [14] [16]. Importantly, the majority of metformin (~80%) is eliminated within the initial hours, with approximately 95% excreted unchanged in the urine due to its lack of metabolism.

3.3. Metformin's Primary Effects on Glucose Control

Metformin primarily works to improve glucose control in diabetes through its effects on the liver [17]. It suppresses hepatic gluconeogenesis, the process by which the liver produces new glucose. Although the exact molecular pathways remain an active research area, a leading hypothesis involves inhibiting mitochondrial complex 1. This inhibition alters cellular energy balance, potentially activating AMPK (AMP-activated protein kinase), a key regulator of metabolism [14]. However, the precise role of AMPK activation in metformin's therapeutic effects remains a subject of ongoing debate and investigation, with other AMPK-independent pathways also likely contributing to its glucose-lowering and other beneficial effects.

3.4. Metformin's Impact Beyond the Liver

Metformin's effects extend beyond its primary liver actions. Evidence suggests it may reduce inflammation within blood vessel walls, potentially contributing to decreased risk of cardiovascular complications in diabetic patients [18], though

the extent of this effect remains under investigation. Additionally, metformin may enhance glucose absorption in the gut, potentially mitigating some gastrointestinal side effects and glucose intolerance associated with diabetes.

3.5. Metformin and the Gut

3.5.1. Influence on Gut Function

While much of the orally administered metformin remains unabsorbed in the GI tract, it significantly affects gut function. Metformin increases intestinal glucose uptake and lactate production, elevates GLP-1 levels, alters the bile acid pool, and modifies the gut microbiome [19]. These actions contribute to metformin's glucose-regulating effects.

3.5.2. Impact on Gut Microbiome

A large-scale study by Forslund *et al.* [20] examined the gut microbiota of T2DM and non-diabetic individuals treated and untreated with metformin. They found that metformin use was associated with reduced abundance of Firmicutes bacteria, increased Escherichia spp., and decreased Intestinibacter spp. These changes may be linked to bacterial resistance mechanisms. Understanding these gut microbiome alterations could further clarify metformin's mechanisms of action and potential side-effect profile.

3.5.3. Distribution, Elimination, and Clearance

Metformin relies on transporters for movement into cells and tissues. After intravenous administration, it exhibits a variable volume of distribution (Vd) between 63 and 276 L. Oral administration results in a Vd of approximately 600 L, which, considering its bioavailability of ~50%, translates to an effective Vd of 300 L [6]. This significant Vd reflects metformin's low plasma protein binding and preferential accumulation within tissues.

Transporters play a dual role, facilitating metformin's distribution and subsequent return into circulation for renal excretion. Within the GI tract, significant amounts of metformin remain unabsorbed [21]. These high intestinal concentrations may contribute to common gastrointestinal side effects and dose-related intolerance [22]. This could result from the continuous transporter-mediated shuttling of metformin into the intestinal tract.

Metformin's primary elimination pathway is renal excretion in its unchanged form. Reduced kidney function leads to decreased metformin clearance, highlighting the importance of dose adjustments or alternatives in patients with renal impairment [23].

4. Metformin's Actions in Specific Organs

4.1. Liver

Metformin primarily enters liver cells (hepatocytes) via the transporters OCT1 and OCT3 [11]. In contrast, PMAT and other OCTs play a major role in facilitating metformin uptake within the small intestine [24]. OCTs on the basolateral side

of hepatocytes actively transport metformin into the liver.

In healthy individuals, insulin signals the liver to store glucose as glycogen [25] [26]. In diabetes, insulin production or its action is impaired, leading to the breakdown of stored glycogen into glucose (released into the bloodstream) and continued glucose production by the liver [27]. Metformin improves insulin sensitivity, enabling the liver to respond to insulin more effectively, aiding with glucose storage, and reducing excessive glucose production [6] [28].

4.2. Pancreas

Research indicates that metformin enhances circulating levels of glucagon-like peptide-1 (GLP-1), a key hormone involved in glucose regulation [29]. This increase in GLP-1, particularly following meals (postprandial), also occurs on the surface of GLP-1 receptors. Heightened GLP-1 signaling stimulates pancreatic β-cells, leading to increased insulin secretion. Consequently, the metformin-induced boost in insulin plays a crucial role in managing blood glucose levels [30].

4.3. Kidneys

Metformin relies on transporters to enter kidney cells, and its primary elimination pathway is excretion into the urine in an unchanged form [3]. This renal route applies to both oral and intravenous administration. While some orally administered metformin might pass unabsorbed into the feces, intravenous administration ensures complete absorption and subsequent renal clearance [5].

5. Modeling Metformin Behavior

5.1. PBPK Modeling: Insights and Limitations

Physiologically-based pharmacokinetic (PBPK) models offer valuable tools for studying metformin pharmacokinetics, but results can vary depending on modeling choices. For example, Duong *et al.* [31] developed a two-compartment PBPK model accommodating patients with diverse renal functions. Their results indicated a mean clearance rate (CLR) of 17 L/h and 49% metformin recovery in urine, significantly lower than the ~80% recovery reported elsewhere. This highlights the importance of considering model assumptions: by including patients with both healthy and impaired kidney function, this study likely lowered average urine recovery values compared to models focused solely on individuals with normal renal function.

5.2. Caco-2 Modeling: Focusing on Absorption

Caco-2 cell cultures, which form monolayers mimicking mature intestinal cells (enterocytes), provide a valuable model for studying metformin absorption mechanisms, particularly those involving OCT transporters [6]. Caco-2 studies reveal that a significant portion of metformin remains in the small intestine compared to amounts found in plasma or other tissues. Importantly, this modeling suggests that metformin absorption occurs primarily via a paracellular route (between

cells) with a smaller contribution from transcellular transport (through cells) facilitated by OCTs [6]. Caco-2 models represent one tool used to investigate metformin's complex kinetics and dynamics [32].

6. Clinical Considerations

6.1. Optimal Therapeutic Dose

Determining the optimal therapeutic dose of metformin remains challenging due to individual variability. Factors such as age, kidney function, and other health conditions significantly influence the appropriate dose. To minimize potential side effects, healthcare providers often adopt a "start low, go slow" approach, initiating therapy with a low dose and gradually increasing it as tolerated [4] [6].

Currently, no single dosage recommendation is universally accepted. Patients may be prescribed anywhere between 0.5 and 2.0 g daily. Higher doses (2.0 g) have the potential to show greater efficacy. This variability highlights the need for further studies on metformin pharmacokinetics and pharmacodynamics in diverse diabetic populations. A personalized medicine approach, tailoring dosage based on individual patient factors, could lead to significantly improved outcomes and a reduced risk of side effects [33].

6.2. Side Effects and Complications

Metformin's most common side effects involve gastrointestinal upset, such as nausea or diarrhea. Severe intolerance, preventing metformin use at any dose, occurs in approximately 5% of patients [4] [34]. While generally considered safe, metformin carries a rare but serious risk of lactic acidosis. This risk increases with certain pre-existing conditions, particularly those affecting kidney function [35].

6.3. Gastrointestinal Symptoms

Metformin, while generally well-tolerated, can cause gastrointestinal (GI) side effects in up to 30% of patients. These commonly include nausea, vomiting, diarrhea, and abdominal discomfort [36]. Taking metformin with meals can help mitigate the severity of these GI symptoms. However, approximately 5% of patients may experience severe GI intolerance, leading to treatment discontinuation [4].

6.4. Vitamin B12 Deficiency

Prolonged metformin use has been associated with an increased risk of vitamin B12 deficiency. Metformin's potential effects on vitamin B12 absorption mechanisms within the intestinal tract may be the cause. Regular monitoring of vitamin B12 levels is advisable in individuals taking metformin. Supplementation may be necessary to prevent deficiency-related complications [4] [37].

6.5. Lactic Acidosis: A Rare but Serious Risk

Metformin's actions include inhibiting pyruvate dehydrogenase and mitochondrial transport, potentially leading to elevated lactate levels [4]. Lactic acidosis is a

critical condition defined by blood pH below 7.5 and plasma lactate exceeding 5.0 mmol/L [6]. Although rare, the risk of lactic acidosis with metformin use increases significantly in individuals with impaired kidney function, advanced age, or those exceeding the recommended daily dose of 2.0 g [6]. Most cases of metformin-associated lactic acidosis involve patients with pre-existing risk factors. However, even patients with normal kidney function might be susceptible, as illustrated by a case study of a 77-year-old woman [38]. While the exact cause in this case remains unknown, it suggests potential disruptions in the expected pharmacokinetic behavior of metformin might play a role.

6.6. Metformin Accumulation and Half-Life

Metformin is absorbed primarily from the small intestine, with an oral bioavailability of approximately 50% [39]. Once absorbed, it is rapidly distributed to various tissues, including the liver, kidneys, and gastrointestinal tract. Metformin does not bind to plasma proteins, which influences its distribution and elimination profile [40].

The drug has a mean accumulation ratio of 1.0, indicating that it does not significantly accumulate in the body with repeated dosing [41]. This characteristic is crucial for maintaining its efficacy and safety over long-term use. The elimination half-life of metformin is approximately 6.2 hours, although, for immediate-release formulations, the half-life in circulation ranges from 1.5 to 4.9 hours [42].

Metformin is excreted unchanged in the urine, primarily through renal tubular secretion [43]. This excretion pathway underscores the importance of renal function in patients taking metformin, as impaired renal function can lead to drug accumulation and increased risk of adverse effects. Understanding these pharmacokinetic properties is essential for optimizing metformin therapy in managing type 2 diabetes.

7. Research Gaps and Future Directions

Personalized Metformin Therapy

The Promise of Personalized Metformin Therapy Personalized metformin therapy offers significant potential for improving diabetes management. This approach acknowledges the complex interplay of factors influencing a patient's response to metformin, including genetics, health conditions, other medications, lifestyle, and environment. By understanding these individual variations, dosages can be tailored for optimal effectiveness and minimized side effects.

To unlock the full potential of personalized metformin therapy, ongoing research efforts must prioritize several key areas.

- Firstly, a deeper understanding of individualized responses to metformin is crucial. Identifying how specific patient characteristics, including genetic, metabolic, and environmental factors, influence metformin's efficacy and safety will pave the way for precise, tailored dosing strategies.
- Secondly, expanding studies to encompass diverse diabetic populations is vital.

This will reveal potential variations in metformin's pharmacokinetic and pharmacodynamic profiles across different ethnicities, age groups, and those with varying disease severity.

- Finally, research must translate these findings into practical tools and guidelines that empower healthcare professionals to implement personalized metformin treatment plans in routine clinical practice easily.

Personalized metformin therapy promises to transform diabetes care. By optimizing dosing and minimizing side effects, patients are more likely to experience improved glucose control, potentially reducing long-term complications and enhancing their quality of life.

8. Conclusion

Metformin's pharmacokinetics and pharmacodynamics are complex and influenced by numerous factors, including genetics, co-existing health conditions, potential drug-drug interactions, lifestyle, and environmental variables. This complexity makes it challenging to isolate the effects of metformin alone, especially in diabetic patients who often experience multiple health issues. Consequently, this contributes to variability in the reported data regarding metformin's optimal dosing, mechanisms, and side-effect profile. Despite these challenges, metformin's impact on metabolic pathways and its positive effect on glucose management are well-established. Future research focusing on personalized approaches promises to optimize further metformin therapy for individuals with diabetes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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