Indonesian Journal of Clinical Pharmacy, August 2024 Available online at:
Vol. 13 No. 2, pp. 107–119 http://ijcp.or.id
ISSN: 2252-6218, e-ISSN: 2337-5701 DOI: 10.15416/ijcp.2024.13.2.48713
Review Article

Pharmacokinetics and Pharmacodynamics of Glyburide: Insights for Optimizing Treatment in Type 2 Diabetes

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Abstract
Glyburide is a widely used oral antidiabetic agent for managing type 2 diabetes. Despite its long history, evolving insights into its pharmacokinetics (PK) and pharmacodynamics (PD) have highlighted knowledge gaps, especially in the context of genetic variability, drug-drug interactions, and use in special populations. This narrative scoping review synthesizes recent evidence to provide a comprehensive and updated understanding of glyburide's PK/PD profiles. A thorough literature search of studies published in English, including manual reference checks, was conducted. Glyburide exhibits complex pharmacokinetics, extensive absorption throughout the gastrointestinal tract, significant plasma protein binding, hepatic metabolism via CYP2C9 and CYP3A4 enzymes, and predominantly renal elimination. Its pharmacodynamic effects involve stimulating insulin secretion and enhancing peripheral insulin sensitivity. Common side effects include hypoglycemia and weight gain, while drug-drug interactions and monitoring are crucial for safe and effective use. Understanding glyburide's pharmacokinetics and pharmacodynamics is key to optimizing diabetes management. Tailoring dosages based on patient factors can improve efficacy, minimize adverse effects, and enable personalized care. Further research on genetic influences, drug interactions, and its use in special populations is needed to refine treatment strategies and enhance safety and effectiveness.

Keywords: Glyburide, glibenclamide, pharmacokinetics and pharmacodynamics

Farmakokinetik dan Farmakodinamik Glibenklamid: Wawasan untuk Mengoptimalkan Pengobatan Diabetes Tipe 2

Abstrak
Glibenklamid (juga dikenal sebagai glyburide) adalah agen antidiabetik oral yang banyak digunakan untuk mengelola diabetes tipe 2. Meskipun telah digunakan sejak lama, wawasan terbaru mengenai farmakokinetik (FK) dan farmakodinamik (FD)-nya mengungkapkan adanya celah pengetahuan, terutama dalam konteks variabilitas genetik, interaksi obat, dan penggunaannya pada populasi khusus. Kajian tinjauan naratif ini mensintesis bukti terbaru untuk memberikan pemahaman yang komprehensif dan terkini mengenai profil FK/FD glibenklamid. Penelusuran literatur menyeluruh terhadap studi yang dipublikasikan dalam bahasa Inggris, termasuk pengecekan referensi manual, telah dilakukan. Glibenklamid menunjukkan farmakokinetik yang kompleks, dengan penyerapan luas di saluran gastrointestinal, pengikatan protein plasma yang signifikan, metabolisme hati melalui enzim CYP2C9 dan CYP3A4, serta eliminasi utama melalui ginjal. Efek farmakodinamiknya melibatkan stimulasi sekresi insulin dan peningkatan sensitivitas insulin perifer. Efek samping umum meliputi hipoglikemia dan peningkatan berat badan, sementara interaksi obat dan pemantauan sangat penting untuk penggunaan yang aman dan efektif. Pemahaman mengenai farmakokinetik dan farmakodinamik glibenklamid sangat penting untuk mengoptimalkan pengelolaan diabetes. Penyesuaian dosis berdasarkan faktor pasien dapat meningkatkan efikasi, meminimalkan efek samping, dan memungkinkan perawatan yang dipersonalisasi. Penelitian lebih lanjut mengenai pengaruh genetik, interaksi obat, dan penggunaannya pada populasi khusus diperlukan untuk menyempurnakan strategi pengobatan serta meningkatkan keamanan dan efektivitasnya.

Kata kunci: Glibenklamid, glyburide, farmakokinetik dan farmakodinamik

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Introduction

Diabetes mellitus (DM) is one of the oldest known diseases, with evidence of its existence dating back approximately 3000 years in ancient Egyptian manuscript.[1] A key milestone in understanding DM occurred in 1936, when the distinction between type 1 and type 2 diabetes was made.[2] Type 1 DM is an autoimmune disorder characterized by a localized inflammatory response within and surrounding the islets of Langerhans, leading to the specific destruction of insulin-secreting cells.[3] On the other hand, Type 2 DM represents the prevailing form of diabetes and is distinguished by elevated blood glucose levels, insulin resistance, and a relative deficiency of insulin.[4] In 1988, type 2 DM was initially identified as a part of the metabolic syndrome,[5] caused by the interplay of behavioral, environmental, and genetic risk factors.[6] Effective management of type 2 DM is crucial to prevent complications and enhance patients' quality of life. Oral antidiabetic agents play a vital role in treating type 2 DM, with various classes of drugs available to help control blood glucose levels.

One prominent class of oral antidiabetic agents is the sulfonylureas, which are often well tolerated but provide a risk of hypoglycemia since they enhance endogenous insulin secretion.[7] Among them, glyburide (also known as glibenclamide) has garnered substantial recognition and remains one of the most commonly prescribed sulfonylureas worldwide. It stimulates insulin release from pancreatic beta cells and enhances peripheral tissue sensitivity to insulin, ultimately reducing blood glucose levels.[8] Despite its widespread use, there is limited knowledge regarding the pharmacokinetics and pharmacodynamics of glyburide. This review aims to provide healthcare professionals with a comprehensive understanding of glyburide's pharmacological properties, facilitating informed decisions regarding its clinical use. Additionally, by exploring the relationship between glyburide, individual genetics, and clinical outcomes, we hope to contribute to the advancement of precision medicine and support more personalized and effective diabetes management strategies.

Methods

Our review aimed to conduct a literature review exploring the pharmacokinetics and pharmacodynamics of the oral antidiabetic agent glyburide. To achieve this, we performed an extensive computerized search for relevant studies published in English. We searched multiple databases, including PubMed and Google Scholar, using a combination of search terms such as "glyburide", "glibenclamide", "sulfonylureas", "pharmacokinetics", "pharmacodynamics", "diabetes management", "insulin secretion", "insulin sensitivity", "hypoglycemia", "precision medicine", "pharmacological properties", "genetic factors", and "clinical outcomes". This search strategy aimed to identify articles that provide insight into the pharmacokinetic and pharmacodynamic properties of glyburide. In addition to the computerized searches, we manually reviewed the reference lists of the retrieved articles to identify any additional relevant studies. All articles selected for inclusion were assessed for their relevance and quality based on their focus on glyburide's pharmacological characteristics and the factors influencing its clinical effectiveness and safety. This comprehensive approach ensured a thorough synthesis of the available literature on glyburide.

Pharmacokinetic Profile of Glyburide

It is well known that second-generation sulfonylurea drugs like glyburide, gliclazide, and glipizide are about 100 times more potent than first-generation drugs like tolbutamide, chlorpropamide, and tolazamide.[9] However, glyburide exhibits a complex pharmacokinetic profile.[10] Therefore, understanding the pharmacokinetics of glyburide is crucial for tailoring dosages, ensuring efficacy, and minimizing the risk of adverse effects in patients with diabetes. Key pharmacokinetic aspects significantly influence the drug's behavior include absorption, distribution, metabolism, and elimination. Furthermore, the COVID-19 pandemic highlights the need for careful monitoring and potential dose adjustments of glyburide in type 2 diabetes, as infection-related inflammation may alter its pharmacokinetics and pharmacodynamics.[11]

Absorption involves the movement of the drug across biological barriers, such as cell membranes, and can be influenced by factors such as solubility, formulation, and gastrointestinal conditions. Absorption and bioavailability of glyburide, in vivo, are determined by dissolution behavior.[12] The solubility of glyburide in gastrointestinal fluids and the gastrointestinal tract's pH environment significantly influence its dissolution characteristics.[13] Glyburide demonstrates extensive absorption throughout the gastrointestinal tract, which is facilitated by its dissociation constant (pKa) of 5.1 and partition coefficient (logP) of 4.5.[14] These properties indicate that glyburide is less likely to ionize in the gastrointestinal tract, enhancing its absorption profile.[15] This pKa value suggests that glyburide is less likely to ionize in the gastrointestinal tract, potentially aiding absorption, while the high logP value indicates its favorable partitioning into lipid-rich environments, further supporting its absorption across biological barriers. Previous studies have also reported that glyburide exhibits a time to reach maximum concentration (Tmax) of 3.6 hours,[16] and 2.6 hours.[17]

Distribution describes the movement of a drug throughout the body after it has entered the bloodstream. It involves the drug's passage from the bloodstream into various tissues and organs, facilitated by blood flow and the drug's affinity for different tissues. Distribution can be affected by factors such as volume of distribution (Vd) and plasma protein binding (PPB). Vd, also called the "apparent volume of distribution," represents the fluid volume in which a drug appears evenly distributed. For glyburide, the reported values of volume of distribution (Vd) were determined to be 40.903.[18] It is important to note that glyburide demonstrates significant PPB (99%),[19] which may contribute to its relatively lower volume of distribution compared to oral hypoglycemic agents of the biguanide class, such as phenformin or metformin.

Metabolism refers to the enzymatic conversion of a drug into metabolites, which are often less active or more easily eliminated from the body. Most drug metabolism occurs in the liver, where enzymes modify the drug's chemical structure through various reactions. Metabolism can affect a drug's duration of action, potency, and potential for drug interactions. The maximum plasma concentrations (Cmax) of glyburide were 131.856 ng/ml.[18] As highlighted by (Niemi and Cascorbi, 2002), glyburide undergoes metabolism mediated by the enzyme Cytochrome P450 (CYP) 2C9, which exhibits genetic polymorphisms.[20] The polymorphic expression of CYP2C9 can lead to pharmacokinetic variations among individuals, as enzymatic activity differs across populations.[21] These genetic variations may influence glyburide metabolism,

potentially affecting treatment outcomes and the risk of side effects. Understanding these genetic differences is crucial for developing personalized medicine strategies, allowing for tailored dosing to improve efficacy and minimize adverse effects in diverse patient populations.[22] It is worth noting that observed variations in Cmax fell within the therapeutic safety range of the drug, suggesting that they do not adversely affect the therapeutic effects of glyburide. Glyburide also undergoes hepatic metabolism via CYP3A4, forming several metabolites, including the active metabolite 4-trans-hydroxy glyburide. These metabolites are predominantly eliminated through the kidneys, with a small fraction excreted in the bile.[23]As a consequence, impaired liver or renal function may alter glyburide's pharmacokinetic parameters, necessitating dose adjustments in patients with hepatic or renal impairment.

Elimination is how a drug and its metabolites are removed from the body. The elimination rate can be influenced by factors such as Vd, PPB. The total body clearance (ClT) is a parameter that determines the overall rate of drug elimination from the body, while the half-life (t1/2) represents the time taken for the concentration of unbound drug in the bloodstream to decrease by half. These parameters are crucial in understanding the elimination kinetics of a drug and play a significant role in guiding dosing regimens and determining the duration of drug effects. In the case of glyburide, a study reported a ClT value of 5.465 L/h.[18] Furthermore, it was reported that a plasma t1/2 of glyburide was 5.251 hours.[18] These pharmacokinetic characteristics are important for determining dosing schedules and ensuring optimal therapeutic effects. A summary of glyburide's pharmacokinetic profile is provided in Table 1.

Pharmacodynamic Profile of Glyburide

The pharmacodynamic profile of glyburide is essential for understanding its mechanism of action, therapeutic efficacy, and potential side effects, such as the increased risk of hypoglycemia due to its insulin-stimulating effect.[24] Glyburide can also interact with

Table 1 Summary of the Pharmacokinetic Profile of Glyburide

Pharmacokinetic Aspect	Parameter	Information
Absorption	pKa	5.1
	logP	4.5
	Tmax	2.6–3.6 hours
Distribution	Vd	40.9 L
	PPB	99%
Metabolism	Enzymes involved	CYP2C9 and CYP3A4
	Active metabolite	4-trans-hydroxyglyburide
Elimination	Elimination routes	predominantly through the kidneys, with a small fraction excreted in the bile
	ClT	5.465 L/h
	T1/2	5.251 hours

pKa: dissociation constant, logP: partition coefficient, Tmax: peak concentration time, Vd: volume of distribution, PPB: plasma protein binding, ClT: total clearance, T1/2: half-life, L/h: liters per hour, CYP: cytochrome P450

other medications, affecting blood glucose control, and may be contraindicated in patients with certain conditions, such as renal or hepatic impairment.[25,26] Monitoring glyburide's effects is crucial to manage the risk of hypoglycemia, ensure consistent blood glucose levels, and optimize treatment outcomes.[27] Understanding this profile helps healthcare professionals optimize dosing, enhance efficacy, and reduce adverse effects in diabetic patients.

Mechanism of Action

Glyburide exhibits its pharmacodynamic effects primarily by stimulating insulin secretion from pancreatic beta cells. As a member of the sulfonylurea class of drugs, glyburide acts by binding to the sulfonylurea receptor (SUR1) on the beta cell membrane, which is a subunit of the ATP-sensitive potassium channel. This binding leads to the closure of the potassium channels, depolarization of the cell membrane, and subsequent opening of voltage-gated calcium channels. The calcium influx triggers the exocytosis of insulin-containing vesicles, resulting in increased insulin release into the bloodstream.[28,29] Furthermore, glyburide enhances the binding of insulin to its receptors on target tissues, which activates downstream signaling pathways, including the insulin receptor substrate (IRS)-1 pathway.[30] This activation promotes glucose uptake by skeletal muscle cells through the translocation of glucose transporter 4 (GLUT4) to the cell membrane.[31] As a result, glyburide helps reduce blood glucose levels by increasing insulin sensitivity in peripheral tissues. This effect complements its insulin-secreting action and contributes to better overall glycemic control (Figure 1).

It is crucial to acknowledge the glucose-dependent pharmacodynamic effects exhibited by glyburide, which distinguish it from other insulin secretagogues. Glyburide's action on insulin secretion is enhanced when blood glucose levels are elevated, meaning that it stimulates the release of insulin primarily in response to high glucose concentration.[32] This glucose-dependent mechanism helps to prevent hypoglycemia, a common risk with other sulfonylureas that can stimulate insulin secretion regardless of blood glucose levels. By selectively promoting insulin release only when needed—i.e., when blood

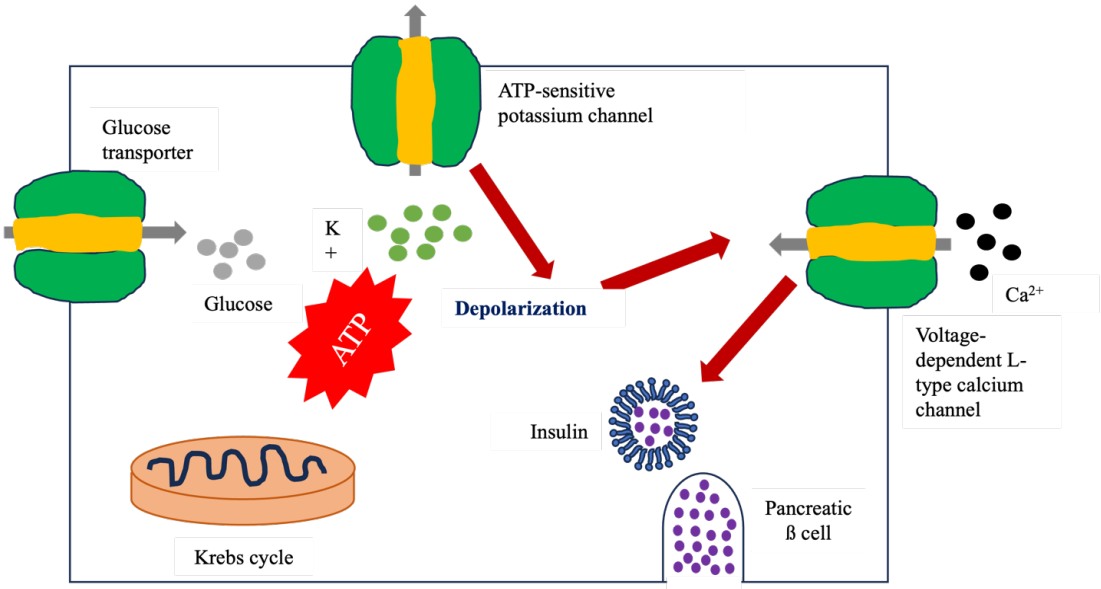

Figure 1 Mechanism of Action of Glyburide [65]

glucose is high—glyburide minimizes the risk of excessive insulin secretion during periods of normal or low blood glucose levels.[33] However, this characteristic does not eliminate the risk of hypoglycemia entirely, especially in patients with impaired glucose regulation. Individuals with conditions such as impaired fasting glucose or type 2 diabetes may have fluctuations in blood glucose levels that make them more susceptible to episodes of hypoglycemia when using glyburide.[33] Therefore, while glyburide's glucose-dependent effect reduces the risk of hypoglycemia compared to non-glucose-dependent agents, careful monitoring and dose adjustments are essential, particularly in patients with compromised insulin sensitivity or fluctuating blood glucose levels.

Dose and Administration

Glyburide is typically administered orally at initial dosages of 2.5 mg to 5 mg, with a maximum daily dosage of 40 mg, although higher doses are rarely needed as most patients with type 2 diabetes mellitus respond well to dosages not exceeding 10 mg per day. Clinical effects are not significantly enhanced beyond total daily doses of 10 to 15 mg. This is likely due to the saturation of the insulin secretory capacity of pancreatic beta cells at higher doses.[34] After reaching a certain threshold, additional doses do not result in increased insulin release or improved glucose control, as the receptors and mechanisms involved in insulin secretion become maximally engage.[35] Additionally, higher doses may increase the risk of adverse effects, such as hypoglycemia, without providing further therapeutic benefit.[36]

Food intake can slow the rate of glyburide absorption, which may reduce its early effect. To optimize absorption and ensure its antidiabetic effect, it is recommended to take glyburide approximately 30 minutes before meals. For lower doses (up to 10 mg), it is typically taken with breakfast or immediately after, while higher daily doses (above 10 mg) are usually divided between breakfast and evening meals.[37] This timing helps minimize the impact of food and hyperglycemia on glyburide's absorption.

Side Effects

The most commonly encountered side effects of glyburide are hypoglycemia and weight gain. While glyburide is a commonly prescribed sulfonylurea, a systematic review conducted by the American Diabetes Association (ADA) has found that it is associated with a significantly higher risk of hypoglycemic episodes compared to other insulin secretagogues and sulfonylureas, with an increased risk of 80% and 44%, respectively. Compared with other sulfonylureas, weight gain is a potential side effect of glyburide. This is due to their stimulation of insulin release, which can promote fat storage and increase appetite.38 However, according to the systematic review conducted by the ADA, weight gain was not a significant outcome when comparing glyburide with other insulin secretagogues. Nonetheless, if weight gain does occur, one approach to address this issue is to consider co-administration with metformin, a weight-neutral biguanide agent, which can help mitigate weight-related concerns.[39]

In a cohort study involving patients with DM type 2, the comparison of glyburide and metformin for blood glucose management revealed significant differences in all-cause and cardiovascular mortality rates, with the risk profile potentially varying based on patient-specific factors, such as renal function and cardiovascular history, which should be considered when choosing the appropriate therapy. The study observed that

patients receiving glyburide monotherapy had higher percentages of all-cause (6.3% vs. 1.6%) and cardiovascular (4.1% vs. 0.4%) deaths compared to those on metformin. Additionally, glyburide use was associated with increases in plasma creatinine levels. These findings have been further supported by other nationwide studies, retrospective cohort studies, and recent research, consistently highlighting metformin's lower all-cause mortality rates and higher survival rates compared to glyburide and other medications within the same class.[40]

Contraindication

Multiple studies have concerned glyburide use in pregnant patients with gestational diabetes mellitus (GDM). Although the FDA considers glyburide a Category C drug, physicians started using glyburide as a possible alternative to insulin for the therapy of GDM. Glyburide crosses the placenta in utero and has metabolized by placental microsomes, exposing the fetus to the drug.[41]

In treating gestational diabetes (GDM), Song et al. reported no significant differences in maternal short-term outcomes between glyburide and insulin groups.[42] Glyburide is a second-generation sulfonylurea considered safe and effective for treating GDM. However, association guidelines do not recommend glyburide as a first-line treatment for GDM because it is known to cross the placenta, and there is a lack of data on safety for offspring.[9,43] A meta-analysis reported that glyburide ranked the worst with the highest incidence of macrosomia, preeclampsia, hyperbilirubinemia, neonatal hypoglycemia, preterm birth, and low birth weight.[44] In contrast, other drugs like metformin or insulin have been associated with a lower risk of these adverse outcomes.[45]

Concerning lactation, glyburide, along with its second-generation counterpart glipizide, is compatible with breastfeeding and does not cross into breast milk to affect breastfed children.[46] Moreover, glyburide therapy should not be re-initiated if the patient has a history of allergic reactions to the medication. However, patients with previous allergic reactions to drugs of the same class may not necessarily react to glyburide.[47] Also, it is essential to use caution with glyburide in hospitalized patients, who are malnourished, misuse alcohol, have renal and cardiac dysfunctions, or with gastrointestinal disease.[9]

Drug-Drug Interactions

Drug-drug interactions with glyburide primarily involve its metabolism through the CYP2C9 enzyme. For instance, salicylates and sulfonamides may enhance glyburide's hypoglycemic effect by increasing its plasma concentration.[48] Conversely, rifampin, a known CYP2C9 inducer, can reduce glyburide levels, potentially diminishing its efficacy.[49] Monitoring is essential when glyburide is co-administered with these or other interacting agents, such as fibric acid derivatives and warfarin, to mitigate risks and optimize therapeutic outcomes.[50] Other medications that inhibit or induce CYP2C9, affecting glyburide metabolism, include azole antifungals, carbamazepine, phenobarbital, rifampin, St. John's wort, and dexamethasone. To mitigate the toxicity associated with sulfonylureas and glyburide, the primary approach is to restore the patient's blood glucose levels to the normal range, considering the specific clinical setting.[40,51]

Monitoring

Close monitoring for signs and symptoms of declining blood glucose levels is crucial

when using glyburide, as it has higher rates of hypoglycemia than other oral antidiabetic agents. Hypoglycemia can be life-threatening, making it important to take appropriate measures, especially in circumstances that may provoke its onset, such as exercise, inadequate food intake, or accidental overdosages. Knowledge of the signs and symptoms of hypoglycemia, along with regular self-monitoring of blood glucose and scheduled testing of blood glucose and HbA1C, is vital when initiating glyburide treatment.[52] The American Diabetes Association (ADA) recommends that HbA1C levels be tested every 3 months in patients starting a new medication or whose therapy has been adjusted to ensure effective glycemic control and timely identification of potential issues.[53] Fasting glucose levels should be checked more frequently, depending on individual patient needs and the risk of hypoglycemia, to guide day-to-day management and optimize treatment outcomes. The coexistence of diabetes and hypertension requires careful management, as both conditions can influence each other's pathophysiology and complicate treatment strategies.[54] While rare, glyburide and other sulfonylureas may also cause liver dysfunction, necessitating monitoring of liver function tests, particularly in patients with pre-existing liver issues, to ensure their safety.[51]

Clinical Implications and Further Directions

Several critical areas should be further explored to improve our understanding of the pharmacokinetics and pharmacodynamics of glyburide, ultimately enhancing its clinical utility. Firstly, pharmacogenomics and personalized medicine offer significant promise in optimizing glyburide therapy.[55] While glyburide has been used for many years, genetic variations, particularly in enzymes such as CYP2C9 and CYP3A4, can substantially affect its metabolism and efficacy. Future research should focus on identifying specific genetic markers that influence glyburide's pharmacokinetic profile.[56] This would enable the development of individualized dosing strategies tailored to a patient's genetic makeup, helping to optimize therapeutic outcomes and reduce the risk of adverse effects such as hypoglycemia.[57] In addition to pharmacogenomics, another crucial area for future research is drug-drug interactions. Glyburide is often prescribed alongside other medications, and interactions can significantly impact its effectiveness and safety.[58] A detailed investigation of glyburide's interactions with commonly prescribed drugs, particularly those that influence hepatic enzymes, is essential for helping clinicians avoid potentially harmful interactions and make more informed decisions when prescribing glyburide in combination with other therapies.[59] Incorporating such findings into clinical practice guidelines will help ensure safer, more effective treatment regimens for patients with type 2 diabetes.[60] Furthermore, there is a need for a deeper understanding of glyburide's pharmacokinetics and pharmacodynamics in special populations. Pregnant women, elderly individuals, and patients with hepatic or renal impairments may experience altered drug absorption, metabolism, and elimination.[61] Research focusing on these populations is essential to develop tailored dosing recommendations that account for these variations. Such studies would ensure that glyburide therapy remains effective and safe, even for patients with unique health conditions or physiological changes.[62] Finally, long-term safety and efficacy studies, as well as comparative trials with other antidiabetic agents, are necessary to better define glyburide's place in modern diabetes management.[63] These studies would provide valuable insights into the long-term risks and benefits of glyburide, especially in comparison with newer medications.

Comparative effectiveness studies will help clinicians make evidence-based decisions about which treatments are most appropriate for different patient populations, considering factors such as comorbidities and the risk of adverse events.[64]

Conclusion

This narrative literature review has provided a comprehensive understanding of the pharmacokinetics and pharmacodynamics of the oral antidiabetic agent glyburide. The review underscores the importance of its pharmacokinetic profile, spanning absorption, distribution, metabolism, and elimination, in guiding dosage adjustments to maximize efficacy while minimizing adverse effects. Its pharmacodynamic properties, notably its ability to stimulate insulin secretion and enhance peripheral insulin sensitivity, play a pivotal role in glycemic control. These insights can directly inform clinical decision-making, helping clinicians evaluate glyburide's suitability compared to other agents based on patient-specific factors. Furthermore, with the increasing emphasis on precision medicine, investigating genetic variations holds promise for developing individualized treatment plans that improve safety and efficacy across diverse populations. This approach could enhance personalized dosing strategies and optimize glyburide's role in managing type 2 diabetes, ultimately improving patient outcomes.

Acknowledgments

The authors would like to extend their sincere gratitude to the esteemed faculty of pharmacy at Padjadjaran University for providing the opportunity to publish this research in their journal.

Funding

There is no fund to report.

Conflict of Interest

The authors declare no conflicts of interest.

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