REVIEW
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Biguanides and lactic acidosis: unraveling the complex relationship

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MALA, Metformin-associated lactic acidosis.
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Abstract
Biguanides, such as metformin, have long been established as frontline medications for the management of type 2 diabetes due to their glucose-lowering effects and favorable safety profiles. However, concerns regarding the risk of lactic acidosis associated with biguanide use have sparked considerable debate and scrutiny. This research article aims to provide a comprehensive analysis of the relationship between biguanides, particularly metformin, and lactic acidosis. We delve into the underlying mechanisms, epidemiological evidence, risk factors, clinical manifestations, diagnostic considerations, and management strategies related to biguanide-induced lactic acidosis. Additionally, we explore recent research developments, controversies, and future directions in this critical area of pharmacovigilance and clinical practice.

Keywords: Biguanides; metformin; lactic acidosis; type 2 diabetes; pharmacovigilance

Introduction

Biguanides, a class of oral antidiabetic agents, have garnered widespread use and acclaim for their efficacy, safety, and affordability in managing hyperglycemia in patients with type 2 diabetes mellitus (T2DM) [1, 2]. Metformin, the most commonly prescribed biguanide, exerts its glucose-lowering effects primarily by inhibiting hepatic gluconeogenesis and enhancing peripheral glucose uptake [2, 3]. Despite its established benefits and long-standing clinical use, concerns about the potential risk of lactic acidosis associated with metformin therapy have been a subject of ongoing research and clinical vigilance [3].

Mechanisms of biguanide-induced lactic acidosis

The pathophysiology of biguanide-induced lactic acidosis involves complex interactions between drug-related factors, patient characteristics, and metabolic pathways [3, 4]. Metformin is less likely to cause lactic acidosis compared to older biguanides like phenformin because it has a safer profile and is absorbed less by tissues [5, 6]. Nevertheless, under certain conditions, such as impaired renal function or concurrent use of nephrotoxic agents, metformin accumulation can lead to lactic acidosis.

Metformin-associated lactic acidosis (MALA) is thought to arise from several mechanisms, including mitochondrial dysfunction, altered lactate metabolism, impaired hepatic clearance of lactate, and tissue hypoxia [7, 8]. Metformin inhibits mitochondrial respiratory chain complex I, leading to reduced adenosine triphosphate (ATP) production and increased lactate generation [9]. Other factors like poor tissue blood flow, low oxygen levels, infections, or liver problems can worsen lactate buildup, leading to MALA in some people [10–12].

Epidemiological evidence and risk factors

The incidence of MALA with metformin monotherapy is exceedingly rare, estimated at less than 10 cases per 100,000 patient-years [13]. Epidemiological studies have consistently demonstrated a low risk of lactic acidosis associated with metformin use, particularly in patients without contraindications or significant comorbidities [14, 15]. The incidence of MALA is substantially higher in patients with renal impairment, where metformin clearance is reduced, leading to drug accumulation and potential metabolic disturbances [16].

Key risk factors for MALA include advanced age, renal dysfunction (e.g., chronic kidney disease), congestive heart failure, hepatic impairment, sepsis, hypoxia, and excessive alcohol intake [17, 18]. Close monitoring of renal function, adherence to prescribing guidelines, and cautious use of metformin in high-risk populations are essential strategies to mitigate the risk of lactic acidosis [19–22].

Clinical manifestations and diagnostic considerations

MALA typically presents with nonspecific symptoms, such as abdominal pain, nausea, vomiting, malaise, and altered mental status [23, 24]. Severe cases may manifest as metabolic acidosis, hypotension, respiratory distress, and organ failure [25, 26]. Differential diagnosis involves distinguishing MALA from other causes of metabolic acidosis, including diabetic ketoacidosis, sepsis, and drug-induced toxicities [27–29].

Diagnostic evaluation of suspected MALA includes serum lactate levels, arterial blood gas analysis, renal function tests, liver function tests, and assessment of metformin levels if available. Imaging studies, such as abdominal computed tomography (CT) scans, may be indicated to assess for potential causes of lactic acidosis, such as bowel ischemia or organ dysfunction [30–32].

Management strategies

MALA management includes stopping metformin, correcting metabolic abnormalities (fluid resuscitation, electrolyte balance), addressing precipitating factors (sepsis, hypoperfusion), and considering hemodialysis in severe cases to enhance metformin clearance and correct acid-base disturbances [33–35].

Preventive strategies for MALA include dose adjustments based on renal function, regular monitoring of serum creatinine and estimated glomerular filtration rate (eGFR), and avoidance of metformin in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or acute conditions predisposing to lactic acidosis [36–38].

Specific clinical practices

In certain clinical scenarios, such as patients with diabetic nephropathy undergoing enhanced CT, the risk of hyperlactacemia or lactic acidosis can increase due to large accumulation of metformin [39]. The administration of contrast agents in CT imaging can exacerbate renal impairment, leading to decreased clearance of metformin and increased risk of lactic acidosis. Enhanced CT can also induce contrast-induced nephropathy, further impairing renal function [40–42].

Molecular and immune mechanisms

In patients with diabetic nephropathy, impaired renal function leads to reduced excretion of metformin. The resulting accumulation of metformin inhibits mitochondrial respiratory chain complex I, reducing ATP production and increasing lactate production. Concurrent hypoxia and tissue ischemia exacerbate lactate buildup. Immune responses to infections or inflammatory states can also contribute to altered lactate metabolism and mitochondrial dysfunction [43, 44].

Recent studies have highlighted the roles of hypoxia-inducible factors (HIFs) and inflammatory cytokines in exacerbating mitochondrial dysfunction and increasing lactate production. For instance, elevated levels of HIF-1α under hypoxic conditions can enhance glycolysis and subsequently raise lactate production, thereby contributing to metabolic acidosis.

Limitations of the epidemiological studies and potential biases

Selection bias

Study Populations: The populations in these studies may not be representative of the broader population of metformin users [44]. For example, studies may have included predominantly patients with fewer comorbidities or those receiving regular medical care, potentially underestimating the risk of MALA in more diverse or high-risk populations [44, 45].

Hospital-Based Studies: Many studies are based on hospital records, which might exclude patients with milder forms of lactic acidosis who did not seek hospital care, thereby skewing the results toward more severe cases.

Confounding factors

Comorbid Conditions: Patients taking metformin often have multiple comorbid conditions (e.g., cardiovascular disease, renal impairment) that independently increase the risk of lactic acidosis. It can be challenging to isolate the specific contribution of metformin from these confounding factors.

Concurrent Medications: The use of other medications that affect renal function or lactic acid metabolism (e.g., diuretics, ACE inhibitors) might confound the association between metformin and lactic acidosis [46].

Data quality and reporting

Retrospective Design: Many studies are retrospective, relying on medical records and databases. The accuracy and completeness of the data can vary, potentially leading to misclassification of cases or incomplete capture of relevant clinical information.

Variability in Diagnostic Criteria: The criteria for diagnosing MALA can vary between studies, affecting the consistency and comparability of the results. Differences in the threshold for diagnosing lactic acidosis and in the availability of metformin level measurements can influence reported incidences [47, 48].

Epidemiological study design

Incidence Rates: The reported incidence rates of MALA are often derived from large cohort studies or pharmacovigilance databases. These sources may have inherent limitations, such as underreporting of adverse events or lack of denominator data to accurately calculate incidence rates.

Duration of Follow-Up: The duration of follow-up in epidemiological studies can impact the observed incidence of MALA. Shorter follow-up periods may miss late-onset cases, while longer studies might better capture the cumulative risk [49].

Geographical and healthcare system variations

Regional Differences: The incidence of MALA and the use of metformin can vary by region due to differences in healthcare practices, genetic factors, and environmental exposures. Studies conducted in specific regions may not be generalizable to other settings.

Healthcare Access and Quality: Differences in healthcare access and quality can influence the detection and management of MALA. Populations with limited access to healthcare may have a higher risk of severe outcomes due to delayed diagnosis and treatment.

Publication bias

Positive Findings: Studies reporting significant associations between metformin use and lactic acidosis are more likely to be published, while those with null or negative findings might be underrepresented in the literature. This can lead to an overestimation of the risk.

Recent developments and future directions

Recent studies have highlighted the safety and efficacy of metformin in diverse patient populations, including those with mild to moderate renal impairment and elderly individuals [50, 51]. New developments in pharmacogenomics and personalized medicine could help doctors assess risks individually and customize how they prescribe metformin. Ongoing research aims to elucidate the molecular mechanisms of metformin action, optimize dosing regimens, and identify biomarkers predictive of treatment response and adverse events, including lactic acidosis [52].

Conclusion

In conclusion, biguanides, particularly metformin, represent a cornerstone in the management of type 2 diabetes mellitus, offering substantial benefits in glycemic control and cardiovascular risk reduction. While the risk of metformin-associated lactic acidosis is rare and largely manageable with appropriate monitoring and clinical vigilance, healthcare providers must remain cognizant of potential risk factors, contraindications, and early recognition of lactic acidosis symptoms. Continued pharmacovigilance, research efforts, and evidence-based guidelines are essential for optimizing the safe and effective use of biguanides in clinical practice.

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