p-Aminosalicylic acid

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summary

p-Aminosalicylic acid (PAS) is a pharmaceutical compound primarily used as a second-line treatment for multidrug-resistant tuberculosis (MDR-TB). Recognized for its ability to inhibit bacterial growth by interfering with folic acid synthesis, PAS is particularly crucial when first-line therapies fail due to resistance or patient intolerance.[1][2] The drug's significance in the fight against TB is underscored by its role in preventing the development of resistance to other antituberculosis medications, making it a vital component of combination therapy regimens aimed at enhancing treatment efficacy.[3][4]

Chemically, PAS is a bi-dentate ligand that can complex with various transition metal ions, exhibiting significant antioxidant activity through its metal complexes. Studies have shown that PAS and its complexes demonstrate superior antioxidant properties compared to standard antioxidants like ascorbic acid, with implications for applications in biomedical fields where oxidative stress is a concern.[5][6] Furthermore, the compound's synthesis has evolved to improve efficiency and yield, with methods like the Sandmeyer reaction being commonly utilized to produce PAS in laboratory settings.[7][8][9]

Despite its therapeutic benefits, the use of PAS is not without challenges. It can lead to side effects ranging from gastrointestinal disturbances to severe liver toxicity, necessitating careful monitoring and patient evaluation.[10][11] Additionally, the socio-economic factors influencing TB treatment adherence complicate the landscape of PAS usage, particularly in low-resource settings where access to healthcare is limited.[12][13] Addressing these challenges is crucial for optimizing PAS's effectiveness and improving patient outcomes in the ongoing battle against tuberculosis.

Research continues to explore innovative drug delivery systems and formulations to enhance PAS's bioavailability and targeting capabilities, highlighting its ongoing relevance in TB therapy.[14][15] The integration of supplemental support interventions has also shown promise in improving adherence and treatment outcomes, further emphasizing the importance of PAS in public health initiatives aimed at controlling MDR-TB.[16][17]

Properties

Complexation Behavior

Para-aminosalicylic acid (PAS) exhibits complexation behavior with various transition metal ions, including manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), copper (Cu), and zinc (Zn). The complexation process has been investigated through conductance and magnetic measurements, as well as spectroscopic techniques such as UV-visible, infrared (IR), and ^1H nuclear magnetic resonance (NMR) spectroscopy. The results indicate that PAS acts as a monobasic bi-dentate ligand, coordinating to metal ions through the oxygen atoms of carboxylate and phenolic groups[5][6].

Antioxidant Activity

The antioxidant properties of PAS and its metal complexes have been evaluated using the DPPH radical scavenging assay. It was found that both PAS and its metal complexes exhibit low IC50 values compared to the standard antioxidant ascorbic acid, indicating superior antioxidant activity. Among the complexes, the nickel complex demonstrated the lowest IC50 value, suggesting it possesses the highest antioxidant capacity[5]. The mechanism behind the enhanced antioxidant activity in metal complexes may involve modifications in the chemical structure and stabilization of the phenoxyl radical through metal ion coordination[5][6].

Thermal Properties

The thermal stability and decomposition characteristics of PAS and its metal complexes were assessed using thermogravimetric analysis (TGA). This analysis provided insights into the thermal behavior and potential applications of these complexes in various fields, particularly in biomedical contexts where oxidative stress reduction is crucial[5][6].

Spectroscopic Properties

IR spectroscopy plays a significant role in elucidating the structure of PAS and its metal complexes. Key IR bands, such as the O-H stretching vibration at 3495 cm{^{1} (which disappears upon complexation) and the N-H stretching vibration at 3387 cm{^{1} (which broadens), indicate the coordination of PAS with metal ions. This information helps in understanding the structural dynamics of the complexes formed[5][6].

Synthesis

Overview of Synthesis Methods

The synthesis of p-aminosalicylic acid (PAS) has evolved significantly since 2015, with various methods reported to improve yields and efficiency. A common approach involves the Sandmeyer reaction, where potassium cyanide is used to synthesize p-nitrosalicylic acid, which is subsequently reduced to form p-aminosalicylic acid[7-

][8][9]. This method leverages the unique reactivity of the nitro group to facilitate the conversion, showcasing an effective strategy for producing PAS in the laboratory.

Metal Complexes Synthesis

Recent advancements in the synthesis of metal complexes containing p-aminosalicylic acid have been reported, utilizing a method adapted from Soliman and Mohamed (2013)[5]. In this procedure, metal acetates are added to a methanolic solution of salicylic acid in a 1:2 ratio. The reaction mixture is stirred for three hours at room temperature while monitoring progress. After the reaction, the complexes are collected through slow solvent evaporation, followed by washing with methanol and air-drying, which yields high-purity metal complexes suitable for further applications.

Polyfluorinated Analogs

Additionally, polyfluorinated analogs of salicylamide and p-aminosalicylic acid have been synthesized from methyl polyfluorosalicylates, indicating a diversification in synthetic strategies aimed at enhancing the properties of PAS derivatives[18]. These analogs may offer improved pharmacological profiles and are of interest in ongoing research.

Challenges in Synthesis

Despite these advancements, challenges remain in the synthesis of ±,±-disubstituted ±-aminosalicylic acids, which require careful optimization of reaction conditions to maximize yield and purity[19]. The complex nature of these syntheses necessitates ongoing research to address the limitations of current methodologies and explore new synthetic routes.

Medical Uses

p-Aminosalicylic acid (PAS) is primarily utilized as a second-line treatment for multidrug-resistant tuberculosis (MDR-TB) and is administered in conjunction with other active agents to enhance efficacy and reduce the risk of resistance development[1][2]. It is particularly valuable when first-line treatments, such as isoniazid and rifampin, are ineffective due to drug resistance or patient intolerance[1].

Treatment of Tuberculosis

The standard dosing for adults with active tuberculosis typically involves administering 4 grams of PAS orally three times a day, though this can vary based on individual patient circumstances[2][10]. It is critical that PAS is not used alone in patients with confirmed or suspected drug resistance; rather, it should be combined with at least one other agent to which the Mycobacterium tuberculosis strain is susceptible[2].

Mechanism of Action

p-Aminosalicylic acid (PAS) exhibits a complex mechanism of action primarily targeting Mycobacterium tuberculosis, the causative agent of tuberculosis (TB). It acts as a bacteriostatic agent, meaning it inhibits the growth and reproduction of bacteria rather than killing them outright[20][21]. One of the primary mechanisms is the inhibition of folic acid synthesis, where PAS competitively blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid, a crucial step in the bacterial folate pathway[22][23].

Additionally, PAS disrupts iron metabolism by inhibiting the synthesis of mycobactin, a cell wall component essential for M. tuberculosis, thereby reducing iron uptake necessary for bacterial growth[24][4]. This multifaceted action not only enhances its efficacy against sensitive strains of TB but also helps to prevent the development of bacterial resistance to other antituberculosis agents, such as streptomycin and isoniazid[4][25].

The pharmacological profile of PAS reveals that about 50-60% of the drug is protein-bound, which can be influenced by nutritional status, such as in cases of kwashiorkor[4]. The drug is primarily excreted in the urine, with significant portions appearing in an acetylated form, and its absorption is affected by the form in which it is administered; for example, enteric-coated granules delay absorption until they leave the stomach[4][26]. These properties underline the importance of proper formulation and dosing practices to maximize the therapeutic benefits of PAS in treating tuberculosis[27][28].

Challenges and Considerations

The management of tuberculosis with PAS should be approached carefully. The presence of other medical conditions, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, may complicate its use, necessitating a thorough patient evaluation before treatment initiation[11]. Furthermore, treatment adherence is crucial, as irregular intake of PAS can lead to inadequate drug concentrations and contribute to the development of further drug resistance[29][3].

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Side Effects and Toxicity

p-Aminosalicylic acid (PAS) can lead to a variety of side effects, some of which may require medical attention. Common side effects include gastrointestinal disturbances such as nausea, abdominal pain, and diarrhea[30][11]. While these symptoms are often mild and can improve as the body adjusts to the medication, they may persist in some patients[31].

Common Side Effects

Patients may experience more prevalent side effects, including:

Diarrhea

Loss of appetite

Nausea and vomiting

Mild stomach pain[11].

These symptoms can often be managed with guidance from healthcare professionals, who can offer strategies to mitigate discomfort[11].

Serious Adverse Effects

One of the more severe potential side effects associated with PAS is drug-induced hepatitis, which manifests as significantly elevated serum AST levels. Hepatotoxicity is a serious concern and requires immediate discontinuation of the drug if symptoms arise[10]. Serologic testing for hepatitis viruses and an evaluation for other hepatotoxins are recommended if liver inflammation occurs[10].

Additionally, while less common, other severe reactions may include:

Allergic reactions that may require urgent medical care

Cutaneous reactions, including pruritus and rashes, which, although typically self-limited, may indicate hypersensitivity in rare cases[10].

Management of Side Effects

For those experiencing gastrointestinal symptoms, it is advised to take PAS with food to minimize adverse effects such as nausea and vomiting[10]. In cases where side effects are persistent or bothersome, patients should consult with their healthcare provider for further evaluation and management options.

Socio-Economic Factors

Socio-economic factors play a critical role in the susceptibility to tuberculosis (TB) and the outcomes of treatment. Numerous studies have highlighted that individuals with low socio-economic status are at a higher risk for transitioning from latent TB infection (LTBI) to active TB disease due to a variety of interconnected variables, including living conditions, healthcare access, and health-related lifestyle factors[12][13].

Measurement of Socio-Economic Status

The measurement of socio-economic status (SES) can be complex, often utilizing surveys that assess household characteristics such as income, expenditure, and ownership of essential items like computers and automobiles. For instance, a survey developed by the Mexican Association of Marketing Research and Public Opinion Agencies (AMAI) employed a 10-item measure to evaluate various household assets and conditions, assigning points to each item to create an overall SES score. This scoring system allows researchers to categorize households into low, medium, and high socio-economic strata[12][32].

Impact of Socio-Economic Disparities

Research indicates that socio-economic disparities significantly influence TB treatment outcomes. Factors such as overcrowding, poverty, and malnutrition are known to increase vulnerability to TB infection and decrease the effectiveness of treatment. Malnutrition, in particular, can lead to weakened immune responses, exacerbating the risk of developing active TB[33][13]. Additionally, the lack of access to healthcare often results in delayed diagnosis and treatment, further complicating outcomes for individuals with low SES[13][34].

Treatment Challenges

The challenges faced by low socio-economic groups extend to treatment adherence as well. Individuals from these backgrounds may struggle with logistical barriers, such as transportation costs to medical facilities and the financial burden associated with ongoing treatment. Studies have shown that multi-sectoral approaches are essential to address these barriers effectively and improve treatment outcomes[34][29]. Moreover, enhancing patient-centered care, which includes education and shared decision-making, has been highlighted as crucial in promoting better adherence to treatment regimens[29][10].

Regulatory Status

p-Aminosalicylic acid (5-ASA) is a drug that has undergone rigorous evaluation and regulatory processes in various countries to ensure its safety and efficacy for treating conditions such as ulcerative colitis. The regulatory approval process typically follows ethical guidelines, such as those outlined in the Declaration of Helsinki, which emphasize the importance of ethical research practices and participant consent[13][35].

Approval and Guidelines

In the United States, 5-ASA has been approved for clinical use based on substantial clinical trial evidence that demonstrates its effectiveness in inducing and maintaining remission in patients with ulcerative colitis[6]. The recommended treatment regimens are derived from data collected through these trials and are rated by the United States Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA). This rating system assesses the strength of the recommendations and the quality of supporting evidence[10].

Monitoring and Compliance

The treatment and management of patients using 5-ASA are subject to public health oversight to ensure adherence to therapy. In cases where patients exhibit non-compliance, particularly in the presence of complications such as drug-resistant tuberculosis, legal measures may be employed to ensure that patients complete their therapy[10]. Such measures underscore the public health authorities' responsibility in maintaining treatment regimens to protect community health.

Limitations and Considerations

While 5-ASA is a well-regarded treatment, its regulatory status is also informed by the limitations observed in studies. For example, the determination of what constitutes a treatment interruption can vary, which impacts adherence rates reported in clinical evaluations[6]. Additionally, challenges in accessing comprehensive medical data can affect the understanding of 5-ASA's utilization in specific populations, particularly those outside statutory health insurance systems[6].

Research and Development

Overview of p-Aminosalicylic Acid (PAS) Research

Research surrounding p-Aminosalicylic acid (PAS) has focused on its application in the treatment of tuberculosis (TB), particularly multidrug-resistant tuberculosis (MDR-TB). Recent studies have reviewed the dosing recommendations for PAS, assessing its efficacy and tolerance as part of treatment regimens[36]. The exploration of PAS highlights its relevance in the context of long-standing challenges associated with TB therapy.

Advances in Drug Delivery Systems

A significant area of development in the context of PAS has been the advancement of novel drug delivery systems (NDDSs). These systems aim to enhance the bioavailability and targeting ability of drugs, thus optimizing treatment outcomes for TB[14]. Innovative formulations, including nanoparticles and liposomes, have been identified as promising methods to improve drug administration while minimizing adverse effects[15]. By refining the delivery mechanisms of PAS, researchers hope to increase patient compliance and therapeutic effectiveness[15][10].

Systematic Reviews and Clinical Trials

A systematic review was conducted to evaluate the effects of supplemental support interventions (SSI) on treatment adherence and outcomes in TB and MDR-TB patients, including those receiving PAS[16]. This review utilized established methodologies defined by the Cochrane Handbook and the PRISMA guidelines, ensuring rigorous assessment of the available literature. Key findings indicated that the successful implementation of SSIs could significantly reduce the financial burden of TB treatment, thereby improving adherence and overall patient outcomes[16][17].

Future Perspectives

The future of PAS research is promising, particularly with ongoing innovations in drug delivery technologies. Efforts are being directed toward ensuring that these advancements are scalable and cost-effective, especially in low-resource settings where TB is prevalent[15]. Continuous investigation into optimizing PAS formulations and exploring combination therapies could provide new avenues for enhancing treatment regimens for patients suffering from TB and MDR-TB[1].

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