

Streptozamine

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summary

Streptozamine is a nitrosourea-derived cytotoxic glucose analog primarily known for its significant role in oncology, particularly in the treatment of pancreatic neuroendocrine tumors and certain leukemias. This compound is notable for its unique

mechanism of action, which involves preferential accumulation in pancreatic beta cells via the GLUT2 glucose transporter, leading to the generation of reactive oxygen species and subsequent cell apoptosis. As such, streptozamine serves as a vital tool for studying beta cell dysfunction and type 1 diabetes pathology, marking its relevance in both therapeutic and research contexts.[\[1\]\[2\]\[3\]](#).

Originally derived from streptomycin, streptozamine operates by interfering with cellular metabolic pathways and promoting oxidative stress, making it a crucial agent in chemotherapy regimens. Its effectiveness is often enhanced when combined with other drugs, allowing for lower doses and reduced toxicity, thereby optimizing patient outcomes in cancer treatment.[\[4\]\[5\]](#). However, the drug is associated with a range of adverse effects, including nephrotoxicity and ototoxicity, particularly when used alongside other nephrotoxic agents. Monitoring and management of these side effects are essential to ensure safe administration and effectiveness in clinical settings.[\[6\]\[7\]\[8\]](#).

The discovery and development of streptozamine highlight its critical contributions to modern medicine, emphasizing the ongoing need for research into its mechanisms and potential applications. Its role in oncology, coupled with the exploration of supportive therapies to mitigate toxicity, underscores the importance of understanding the complexities associated with this potent chemotherapeutic agent.[\[9\]\[5\]](#).

Discovery and Development

Streptomycin, a significant aminoglycoside antibiotic, was discovered in 1943 by graduate student Albert Schatz and his advisor, Professor Selman Waksman, in the Waksman Microbiology Museum at Rutgers University. This breakthrough was remarkable because streptomycin exhibited activity against a broader spectrum of pathogens compared to penicillin, and it was notably the first effective treatment for tuberculosis caused by *Mycobacterium tuberculosis*[\[10\]\[11\]\[12\]](#).

The discovery of streptomycin marked a pivotal moment in microbiology and medicine, receiving international acclaim when Selman Waksman was awarded the Nobel Prize in Physiology or Medicine in 1952 for his contributions to the field, making it Rutgers University's only Nobel Prize to date[\[10\]\[13\]](#). Despite Waksman's recognition, the contribution of Schatz has often been overlooked, leading to a controversy regarding credit and royalties from the antibiotic. Schatz later expressed concerns that Waksman received undue credit for the discovery and downplayed Schatz's role, resulting in a legal dispute over royalties which ultimately awarded Schatz a small percentage and acknowledgment of his contributions[\[12\]\[14\]](#).

The Waksman Laboratory's research not only solidified the foundation for antibiotics but also emphasized the importance of soil microbiology, an area in which Rutgers has a long-standing tradition[\[11\]](#). The discovery of streptomycin catalyzed further research into antibiotics and laid the groundwork for the development of new therapeutic agents, ultimately shaping modern medicine's approach to bacterial infections and public health[\[10\]\[13\]\[12\]](#).

Mechanism of Action

Streptozamine, a nitrosourea-derived cytotoxic glucose analog, exhibits a unique mechanism of action primarily through its interaction with pancreatic beta cells. Structurally, it features a glucose molecule that facilitates its preferential accumulation in these cells via the GLUT2 glucose transporter, a process that is critical for its cytotoxic effects on insulin-producing cells[\[1\]\[15\]](#).

Once inside the beta cells, streptozamine induces toxicity through the generation of reactive oxygen species and subsequent cellular damage, ultimately leading to the apoptosis of these insulin-producing cells[\[1\]\[2\]](#). The cytotoxic action is closely related to its ability to disrupt normal cellular metabolism and induce stress responses that the cells are unable to withstand, particularly in the context of elevated blood glucose levels[\[9\]](#).

Furthermore, streptozamine has been observed to inhibit various metabolic pathways within the beta cells, affecting amino acid (AA) metabolism as well as the synthesis of important metabolites like glutathione (GSH). This inhibition is believed to contribute to the diminished antioxidant defenses in the cells, thereby exacerbating the toxic effects of oxidative stress[\[16\]\[17\]](#).

The interplay between streptozamine and the metabolic state of pancreatic beta cells highlights its role as a potent chemical agent in the context of inducing diabetes in experimental models, serving as a tool to study the underlying mechanisms of beta cell dysfunction and type 1 diabetes pathology[\[3\]](#).

Pharmacology

Streptozamine, a derivative of streptomycin, exhibits pharmacological properties that are closely related to its mechanism of action as an antibiotic. It operates primarily by interfering with bacterial protein synthesis, which renders it effective against a broad spectrum of microbial organisms[\[18\]](#). The pharmacokinetics of streptozamine indicate that it follows a three-compartment model of elimination, with a significant portion of the drug (approximately 90%) being excreted unchanged through the kidneys[\[19\]](#). This renal excretion pattern is crucial for maintaining therapeutic concentrations in the body while minimizing potential toxicity.

Dosage and Administration

Streptozamine is administered via various routes, with intramuscular (IM) injections being common. The absorption of the drug is rapid, achieving peak blood concentrations within 30 to 90 minutes post-administration[\[19\]](#). For safety and efficacy, it is typically dosed once daily, as shorter intervals may increase the risk of toxicity and bacterial resistance. In cases of renal impairment, the dosing regimen may need to be adjusted to avoid excessive accumulation and toxicity[\[19\]](#).

Adverse Effects and Drug Interactions

The use of streptozamine is not without risks. Notable adverse effects include nephrotoxicity and ototoxicity, particularly when combined with other nephrotoxic agents such as diuretics or certain antibiotics[6][20]. Patients with pre-existing renal dysfunction or those receiving concurrent therapies that can exacerbate these side effects should be closely monitored. Neuromuscular blockade is another concern, especially when administered alongside skeletal muscle relaxants[6].

To mitigate the risks associated with nephrotoxicity, clinicians often recommend pre-treatment with folic acid supplementation, particularly in patients undergoing high-dose methotrexate therapy, to support renal function during treatment[9]. Furthermore, the combination of streptozamine with aminoglycosides or other potentially nephrotoxic medications should be approached with caution due to the heightened risk of renal damage[6][19].

Clinical Applications

Streptozamine is primarily utilized in the treatment of various bacterial infections and has shown efficacy in managing tuberculosis (TB) as well[6]. Its application extends to specific oncological treatments where it can play a role in combination regimens designed to enhance therapeutic outcomes against resistant strains of bacteria or in the context of cancer therapy[9].

Therapeutic Uses

Streptozamine is primarily utilized in the treatment of specific types of cancer, particularly pancreatic neuroendocrine tumors and some forms of leukemia. Its efficacy is largely attributed to its mechanism of action, which involves targeting rapidly dividing cells, a characteristic feature of many cancer types[4]. This chemotherapeutic agent has been shown to be effective when combined with other treatments, allowing for synergistic effects that enable lower doses and subsequently reduce toxicity[5].

Chemotherapy Regimens

Streptozamine is often incorporated into various chemotherapy regimens. Notable combinations include CHOP (Cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisone) for non-Hodgkin lymphomas, and ABVD (Adriamycin, Bleomycin, Vinblastine, and Dacarbazine) for Hodgkin lymphomas[5]. The drug's ability to enhance the effects of other cytotoxic agents underscores its role in comprehensive cancer treatment protocols.

Routes of Administration

The most common route of administration for streptozamine is intravenous (IV), although it may also be delivered orally in certain contexts, depending on the clinical scenario and specific patient needs[5][4]. In some cases, intrathecal administration may be utilized to manage cancers that have spread to the central nervous system, highlighting the flexibility in delivery methods based on patient-specific factors[5].

Supportive Therapies

In conjunction with its use as a chemotherapeutic agent, there are ongoing investigations into supportive therapies that could mitigate potential side effects, including nephrotoxicity associated with its administration[9]. Strategies such as intravenous hydration and targeted pharmacological interventions are being explored to improve patient outcomes and enhance the therapeutic index of streptozamine-based treatments[9][5].

Side Effects and Toxicity

Streptozamine is associated with a variety of side effects, which can range from mild to severe. Understanding these potential adverse effects is crucial for patients receiving this treatment.

Common Side Effects

The most frequently reported side effects of streptozamine include gastrointestinal issues such as nausea and vomiting, myelosuppression, and alopecia.[7] Additionally, patients may experience skin reactions, such as hives, redness, and mild itching.[21][22] Other common symptoms may involve dizziness, headache, and a sensation of lightheadedness.[23]

Serious Side Effects

Patients receiving streptozamine should be aware of serious side effects that require immediate medical attention.

Ototoxicity: Hearing loss, which may be permanent, is a significant risk associated with streptozamine use. This risk increases with higher doses and prolonged treatment duration, especially in patients with pre-existing kidney conditions.[8]

Nephrotoxicity: Impairment of kidney function can occur, necessitating monitoring during treatment.[8]

Neurological Issues: Symptoms such as dizziness, feelings of constant movement, and potential nerve damage may arise, indicating possible vestibular dysfunction.[24]

Allergic Reactions: Although rare, allergic responses can be severe and include symptoms such as rash, swelling, and difficulty breathing, which may progress to anaphylaxis.[8]

Less Common Effects

Some patients may experience less common side effects, including:

Gastrointestinal discomfort: Symptoms like diarrhea may be reported and can often be managed through dietary adjustments.[8]

Skin reactions: More severe skin issues such as exfoliative dermatitis and angioedema can occur in rare cases.[\[25\]](#)

Hemolytic Anemia: Blood-related issues, such as a drop in red blood cells, can also manifest.[\[25\]](#)

Monitoring and Management

Due to the potential for severe side effects, particularly in vulnerable populations like the elderly or those with impaired renal function, regular monitoring through audiometric tests and other evaluations is recommended during intensive therapy with streptozamine.[\[25\]](#) Patients are encouraged to report any side effects to their healthcare providers promptly to assess the need for treatment adjustments.[\[26\]](#)

Research and Future Directions

Antioxidant Defense Mechanisms

Recent studies have highlighted the role of amino acids (AAs) in enhancing antioxidant defenses, particularly in the context of diabetes. Glycine (Gly), a simple amino acid that serves as a substrate for glutathione (GSH) biosynthesis, has been observed to diminish in the serum and various tissues, including the heart and brain, in type 1 diabetic models. This reduction indicates a potential compromise in antioxidant defenses when blood glucose levels are elevated[\[17\]](#). Similarly, aspartic acid (Asp) has been shown to support myocardial function by delivering essential potassium (K⁺) and magnesium (Mg²⁺) ions, thereby enhancing cardiac performance, especially under hypoxic conditions[\[17\]](#). However, the cardiac levels of Asp are also reduced in the presence of high blood glucose, suggesting further impairment of protective myocardial mechanisms[\[17\]](#).

Implications for Future Research

The correlation between amino acid levels and oxidative stress in diabetic conditions opens avenues for research into dietary and supplemental strategies to mitigate these effects. Future studies could explore the therapeutic potential of Gly and Asp in preserving myocardial and neural health during hyperglycemic episodes. Additionally, the broader implications of amino acids in regulating energy metabolism in brain tissue could lead to innovative approaches for managing cognitive decline associated with diabetes[\[17\]](#).

Natural Products and Antioxidants

Emerging evidence supports the effectiveness of various natural products and antioxidants in combating oxidative stress. Compounds such as resveratrol, quercetin, and vitamins C and E have demonstrated anti-inflammatory properties that may counteract chemotherapy-induced nephrotoxicity and other oxidative stress-related conditions[\[12\]](#). These findings prompt further investigation into the application of

these substances as adjunctive therapies in the management of conditions associated with oxidative damage, including acute kidney injury and other forms of nephrotoxicity[12].

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