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CASE REPORT

A Rare Case of Mannitol-Induced Anaphylaxis During Treatment of Cerebral Edema

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Abstract

Introduction: Mannitol, an osmotic diuretic, is widely used to manage raised intracranial pressure (ICP), including cases of cerebral venous thrombosis (CVT). Although generally well-tolerated, hypersensitivity reactions, including anaphylaxis, have been rarely reported. **Case Presentation:** A 38-year-old male with hyperhomocysteinemia and a history of chronic alcohol use presented with a five-day history of progressive frontal headache. Imaging confirmed chronic cerebral venous thrombosis with gliosis and partial recanalization. On hospital day three, intravenous mannitol (20%) was initiated for cerebral edema. Within minutes of infusion, the patient developed a generalized erythematous rash, pruritus, dizziness, profound weakness, bradycardia, and unrecordable blood pressure. Mannitol was discontinued and anaphylaxis was managed with intramuscular adrenaline, intravenous corticosteroids, antihistamines, and fluids. He stabilized in the intensive care unit and was later anticoagulated. The patient was discharged in stable condition. **Discussion:** Mannitol hypersensitivity, though rare, can involve IgE-mediated or non-IgE pathways. Reported cases describe reactions ranging from mild urticaria to life-threatening cardiovascular collapse, with both intravenous and oral exposures documented. Atopic individuals may be particularly vulnerable, with occasional cross-reactivity to environmental allergens. **Conclusion:** Despite its indispensable role in neurocritical care, mannitol may rarely trigger severe hypersensitivity. Careful monitoring during infusion and preparedness for immediate intervention are essential to minimize risk.

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Keywords:

- Anaphylaxis
- Cerebral Edema
- Thrombosis
- Mannitol

Introduction:

Mannitol, a sugar alcohol, is commonly used in clinical practice as an osmotic diuretic and also as pharmaceutical excipient. It is a cornerstone in the management of raised intracranial pressure (ICP) and has been used to increase cerebral venous perfusion especially in cerebral venous thrombosis (CVT) [1-3]. Its efficacy lies in its ability to increase plasma osmolarity, thereby drawing fluid out of cerebral tissues to reduce cerebral edema and ICP [3]. Hyperosmolar agents such as corticosteroids and hypertonic saline are also occasionally used for similar indications [2]. While mannitol is generally well-tolerated, rare instances of hypersensitivity reactions, including anaphylaxis, have been reported in both intravenous and oral forms. These adverse events, although infrequent, necessitate increased clinical awareness due to their potential severity.

Review of Literature:

Anaphylaxis is an acute, life-threatening systemic hypersensitivity reaction, typically mediated by IgE antibodies and release of mediators from basophils and mast cells. Upon re-exposure to a sensitizing allergen, IgE molecules bound to high-affinity FcεRI receptors on mast cells and basophils cross-link, triggering degranulation and the release of mediators such as histamine, tryptase, and platelet-activating factor. This results in systemic vasodilation, increased vascular permeability, and bronchoconstriction. Alternative IgG-mediated pathways and non-IgE-mediated mechanisms, such as direct mast cell activation via the MRGPRX2 receptor, have also been proposed, particularly in drug-induced reactions [4-6].

Hypersensitivity to mannitol is believed to be predominantly IgE-mediated. In sensitized individuals, mannitol may act as a hapten, binding to carrier proteins to form immunogenic complexes. This mechanism has been supported by positive skin tests and the presence of mannitol-specific IgE in some cases.

Reactions have ranged from urticaria and angioedema to life-threatening anaphylaxis. Patients with underlying atopic conditions, including asthma, allergic rhinitis, or food allergies, appear to be at higher risk. Cross-reactivity with pollen allergens has also been observed in a few reports [7,8].

Prevention and management involve strict avoidance of mannitol-containing products in sensitized individuals and considering alternative agents. In select cases, premedication with corticosteroids and antihistamines has been attempted, though evidence remains limited. The use of epinephrine autoinjectors is recommended for patients with a history of severe reactions [8,9]. Despite the potential severity, literature on mannitol hypersensitivity remains scarce and warrants further investigation.

Several individual case reports provide insight into the clinical manifestations of mannitol-induced hypersensitivity:

These cases emphasize the need for vigilance, especially in high-risk individuals or when high concentrations of mannitol are administered.

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Citation	Patient	Context	Reaction	Mechanism/Notes	Management/Outcome
Schmid & Wüthrich (1992)(10)	40-year-old man	Surgery for retro medullary tumor; 20% mannitol	Hypotension, tachycardia, atrial fibrillation	Proposed IgE-mediated histamine release; possibly concentration-related	Supportive management reported
Biro et al. (1992)(11)	39-year-old non-atopic male	Under general anesthesia; 20% mannitol	~40 mmHg BP drop; ventricular fibrillation	Not specified	Immediate resuscitation required
Calogiuri et al. (2015)(8)	Middle-aged man with pollen allergy	Ingested medication containing mannitol (excipient)	Immediate-onset symptoms; testing confirmed mannitol allergen	Demonstrates potential for oral, non-parenteral reactions in atopic individuals	Not specified
Lamb & Keogh (1979)(12)	16-year-old male with childhood atopy	IV mannitol initiation	Acute hypotension, periorbital edema, bronchospasm	Considered anaphylactoid rather than classic IgE-mediated	Resolved after stopping infusion and supportive care
McNeill (1985)(9)	60-year-old woman	IV mannitol for intracranial pressure	First exposure: chest tightness; re-exposure: respiratory distress, cyanosis, urticaria, hypotension	Suggested non-IgE mechanism; worsening on re-challenge	Resolved with antihistamines and supportive treatment
Parker & Priyadarshi (2022)(13)	26-year-old Caucasian man; IV drug use; MSSA tricuspid endocarditis with septic emboli and ICH	IV mannitol for mass effect/herniation risk	Immediate anaphylaxis with hypotension, tachycardia, respiratory compromise	No other medications given; mannitol strongly implicated	Required intubation, corticosteroids, antihista

Case Presentation:

We present the case of Mr. Santosh, a 38-year-old male with a known history of hyperhomocysteinemia, chronic alcohol use, and smokeless tobacco consumption, who reported to the Medicine Outpatient Department of our tertiary care hospital with a 5-day history of headache. The headache was insidious in onset, progressive, and localized predominantly to the frontal region, more on the right side. He described 1–2 episodes of headache daily without associated symptoms such as fever, vomiting, visual disturbances, or seizures. He also reported a similar episode the previous year, during which he experienced transient loss of consciousness followed by involuntary movements of the limbs. At that time, he was diagnosed with Cerebral Venous Sinus Thrombosis (CVST) and hyperhomocysteinemia at a local center.

On arrival, his vital signs were: blood pressure 110/72 mmHg, pulse rate 52 bpm, and SpO_2 98% on room air. Physical examination revealed bilateral conjunctival congestion. Neurological examination was within normal limits. His gait, limb power, and sensory functions—including vibration sense, joint position sense, two-point discrimination, stereognosis, and graphesthesia—were all intact. Cranial nerve assessment and both superficial and deep tendon reflexes were normal. Plantar reflexes were bilaterally flexor. cardiovascular, respiratory, and abdominal evaluations, were unremarkable. Ophthalmology referral was sought to rule out papilledema, which was not present.

The patient was admitted to the Internal Medicine ward for further management. MRI brain with contrast and MR venography revealed chronic infarct with gliosis and hemorrhagic degradation products in the temporal lobe, along with partial canalization

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of the right transverse sinus—consistent with chronic cerebral venous thrombosis.

Routine blood investigations were performed on admission and subsequently monitored daily. Initial laboratory findings showed hemoglobin 14.6 g/dL, platelet count 320 × 10^3/μL, and normal red blood cell indices (MCV, MCH, MCHC). Red cell distribution width (RDW) was 13.1%. Coagulation profile revealed an APTT of 54.2 seconds, PT of 15 seconds, and INR of 1.09. Renal function tests were within normal limits (creatinine 0.8 mg/dL). Liver function tests showed elevated transaminases: AST 111 U/L and ALT 115 U/L, with total protein 8 g/dL, total bilirubin 0.5 mg/dL, and an albumin-to-globulin ratio of 1.5. Serum electrolytes and lipid profile were within normal ranges. Thyroid function tests were also normal. Urine analysis showed the presence of fungal elements and bacteria with slightly elevated pus cells.

Serial monitoring of coagulation parameters revealed gradual normalization. On day 3 of admission, APTT was 32.0 seconds, PT was 12.4 seconds, but INR was 0.88. On the day of discharge, APTT was 39.1 seconds, PT was 12.8 seconds, and INR was 0.91.

On June 30th, 2023, the patient was initiated on intravenous mannitol (20%) for as part of the initial therapeutic strategy to relieve cerebral edema secondary to the cerebral venous thrombosis.

However, shortly after the administration of approximately 20 ml, he developed a sudden onset of generalized erythematous rash, itching, giddiness, and profound weakness. His pulse rate remained bradycardic at 52 bpm, blood pressure was unrecordable, although oxygen saturation remained at 96% on room air. Auscultation of the chest revealed bilateral air entry without adventitious sounds, Mannitol was promptly discontinued, and a clinical diagnosis of anaphylaxis was made.

Emergency management included intramuscular adrenaline (0.5 ml), intravenous hydrocortisone (100 mg), and intravenous pheniramine (2 ml), along with rapid infusion of two pints of normal saline. The patient was stabilized and transferred to the intensive care unit for close monitoring and supportive care. Following resuscitation, he was maintained on intravenous normal saline at a rate of 100 ml per hour. His hemodynamic parameters gradually normalized, and no further hypersensitivity reactions were observed during the remainder of his hospital stay. Subsequently, he was started on low molecular weight heparin due to hypercoaguble state and was later bridged to warfarin. Follow-up imaging confirmed partial resolution of the thrombus. He was discharged in a stable condition with instructions for close INR monitoring and continuation of oral anticoagulation for secondary prophylaxis.

Discussion:

Although rare, mannitol-induced hypersensitivity reactions present a serious clinical challenge. The exact pathophysiological mechanisms remain unclear, but evidence suggests both IgE-mediated and non-IgE-mediated pathways may be involved. Our review of the literature highlights the variability in clinical presentation, ranging from mild cutaneous manifestations to life-threatening cardiovascular collapse.

This case, along with the reviewed literature, underscores the importance of comprehensive patient assessment and monitoring when administering mannitol, especially in high-

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concentration doses or in individuals with known atopic predispositions. Patient characteristics appear to play a significant role in risk. Individuals with an atopic background—such as asthma, allergic rhinitis, or food allergies—exhibit heightened susceptibility (7,8,12) In some cases, cross-reactivity with environmental allergens such as pollens has been reported, reinforcing the importance of a careful allergy history prior to use [7,8]. Reactions can also occur with oral exposure, where mannitol acts as an excipient, as illustrated by early documented cases of ingestion-related anaphylaxis in atopic individuals [8].

Given mannitol's clinical value, awareness of its rare but significant hypersensitivity potential allows for better risk assessment, especially in acute care settings where rapid infusion is common. Identifying at-risk populations, coupled with preparedness for immediate intervention, can help minimize the potential for adverse outcomes.

Conclusion:

Mannitol continues to be an indispensable agent in neurosurgical and critical care settings, particularly for the rapid reduction of intracranial pressure and management of cerebral edema. However, the documented incidence of hypersensitivity reactions, although rare, warrants caution—especially when administering rapid, high-concentration infusions or prescribing mannitol-containing oral preparations. Clinical evidence supports that both IgE-mediated mechanisms and non-IgE immunological pathways may underlie such reactions, and that individuals with atopic backgrounds are at comparatively higher risk. Reports of cross-reactivity with environmental allergens further highlight the need for a detailed allergy history prior to use. In acute care contexts, early recognition of signs such as hypotension, bronchospasm, or cutaneous manifestations, followed by immediate discontinuation of mannitol and supportive measures, remains the cornerstone of management. Focused research aimed at elucidating the precise immunopathogenesis, developing sensitive diagnostic tools, and evaluating cross-reactive allergens will be instrumental in ensuring that the therapeutic advantages of mannitol can be leveraged safely, with minimal risk to susceptible patients.

Conflict of Interest: Authors not declare any conflict of interest.

Ethical Consideration: The patient provided informed consent for their clinical information to be included in this report. All efforts were made to ensure confidentiality. As this is a single-patient case report, formal institutional review board approval was not required.

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