

Acute hypersensitivity to mannitol: a case report

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Abstract. Mannitol is an osmotic diuretic agent that has been considered a main therapeutic option in cerebral edema for the past several decades. The most common adverse effect reported is acute kidney injury and electrolyte imbalance. Hypersensitivity associated with mannitol is not a usual finding. Here we describe a case of a traumatic brain injury patient who had a hypersensitivity reaction to mannitol. It is the first reported case report about hypersensitivity to Mannitol in Indonesia.

1. Introduction

Mannitol is a D-mannose hexitol crystalline sugar that is before sugar cane. It was not metabolized and excreted unchanged in the urine.[1] Due to its hyperosmotic feature, mannitol has been used to reduce cerebrospinal fluid pressure extensively. The main effect of mannitol is increasing the osmolality of blood, causing the osmotic equilibrium to make fluid flowing into the vessels.[2]

Mannitol is used to decrease intracranial pressure in head injury patients. Mannitol is administered intravenously or orally in varying concentration. The preferred route was intravenous as the hypothesis that administering mannitol at faster route caused the rapid development of concentration gradient between plasma and interstitium.[3] The most common complication of mannitol are fluid and electrolyte imbalance. Other complications that may occur are cardiopulmonary edema and rebound cerebral edema.[4]

Although not so frequently reported in the literature, mannitol is known to cause immediate-type hypersensitivity reactions when given intravenously.[5] This case report is a rare case of intravenous mannitol hypersensitivity reaction.

2. Case Report

An 18-year-old girl presented with decreased of consciousness after amotor vehicle accident, a head to head motorcycle collision. On physical examination, we found a bruise on frontal region and multiple excoriations on the lower extremity. Neurological examination revealed GCS 13/15 with anequal pupil. Brain CT Scan revealed contusion on frontal region, without any significant mass effect. We treated her conservatively with analgesic and mannitol. Bolus mannitol infusion is a loading dose of 1 gr/kgBW. Fifteen minutes after the infusion, she developed tachycardia, shortness of breath, and maculopapular rash. She was in the treatment with dexamethasone, 10 mg IV, and the symptoms were clear. On later history taking, there was no history of prior allergic reactions to either drug or food. The patient's atopic status was unknown. A positive skin test with 6 mm size appeared after mannitol testing. We then discontinued the mannitol and medicated her with hypertonic saline. After three days, she regained her consciousness back and went back home without any neurological deficit.



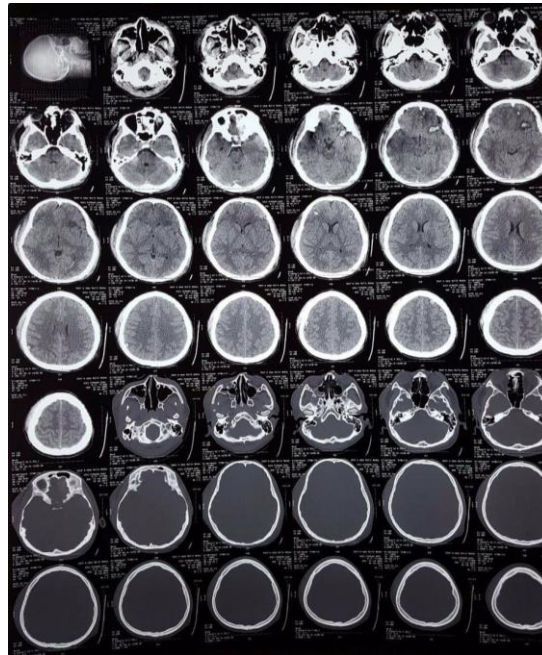


Figure 1. CT-Scan show contusion in the left frontal region.



Figure 2. Maculopapular rash on patient's body after mannitol infusion.

3. Discussion

Mannitol is a sugar alcohol solution used to treat elevated intracranial pressure (ICP). A 1995 survey of the critical care management of head-injured patients in the United States showed that 83% of centers used osmotic diuretics in more than half of severely head-injured patients.[5] The Brain Trauma Foundation Guidelines Task Force of the American Association of Neurological Surgeons and Joint Section on Neurotrauma and Critical Care recommend that mannitol is needed if patients have either

severe traumatic brain injury or intracranial emergency (a GCS score of 8 or less). A clear neurological deterioration (defined as a documented decline in GCS score of 2 or more points), or pupillary abnormalities indicative of transtentorial herniation or brainstem dysfunction (unilateral or bilateral fixed and/or dilated pupils).[6,7]

Mannitol as an inert structure does not have immunogenic covalent properties.[8] It was the intermediate D-mannitoyl from Schiff base reaction that forms hypersensitivity reaction with IgE. Although it could bind non-covalently to lectin or transporter, such a binding interaction was unavailable to elicit an immune response.[9] The D-mannitoyl intermediate was established by nucleophilic reduction of D-mannose forming a Schiff base by its reaction to a free N-terminal amino group. Some unstable Schiff base will undergo Amadori rearrangement to form more stable ketoamine. The Schiff base intermediate will then evoke IgE response causing immediate hypersensitivity.[10]

The D-mannitoyl as an antigen was sensitive with dendritic cells, B cells, or antigen-presenting cells evoked by the presence immunogen.[11] If the sensitization was the first time, the complex was then recognized by MHC class II on Th0 surface. In the presence of cytokines IL-4, Th0 developed to Th2, a memory cell. In the second sensitization, allergen will bind to IgE membrane on B cells, B cells then bind to Th2, as well as CD40 to CD40 ligand.[12] The IL-4 and IL-13 released can act on the B cell to promote class switching from immunoglobulin M production to antigen-specific IgE production. The antigen-specific IgE antibodies can then bind to mast cells and basophils, causing the release of cytokines. Once mannitol-specific IgE antibodies sensitize an individual, D-mannitol can act as a univalent elicitor, resulting in an anaphylactic reaction.[13]

In other drug preparation, the compositions of preservatives, excipients or dyes could be the culprit for a hypersensitivity reaction.[14] In pomegranate (*Punicagranatum*) and cultivated mushroom (*Agaricusbisporus*), mannitol was identified as the confirmed allergen. As no detection of mannitol-specific IgE in the allergic subject's serum, it was proposed that the difficulty of binding hydrophilic mannitol (or any other sugar alcohol) to the hydrophobic polystyrene surface of microtiter wells. By conjugate mannitol to a carrier protein, conjugation of D-mannose to protein was positively in ELISA. In the latest study by Hedge et al., they proved that D-mannitol single epitope that serves as an immunogen. By using D-mannitol specific polyclonal antibodies from rabbit, ELISA test showed the high specificity affinity to D-mannitol only, yielding only less than 5% with other sugar. The inhibition studies provided evidence for the haptenic nature of mannitol and confirmed that the mannitol group is a single epitope.[15,16]

The hypersensitivity of mannitol was on the route of administration. Some authors stated that hypersensitivity would occur by administering mannitol intravenously and by inhalation. Administering mannitol by oral will be the most preferred route. However, challenge test of intravenous mannitol can be done and stopped if any anaphylactic reaction occurred.[5]

Even the latest guideline for the management of severe traumatic brain injury still do not enlist hypertonic saline as a main therapeutic option as hyperosmotic agent [17], there is increasing of reviews stating hypertonic saline at least has the same effectivity as mannitol. In this case, we chose hypertonic saline as an alternative and found a good outcome. Even so, it is difficult to make a head to head comparison between mannitol and hypertonic saline since there is a lack of good quality data.[18]

To the best of our knowledge, there are less than five reports regarding hypersensitivity reaction after mannitol administration.[19-22] In Indonesia, this is the first reported case report about hypersensitivity to mannitol. In conclusion, despite mannitol's widespread use, there was the possibility of hypersensitivity to intravenous mannitol administration. The physician should be aware that hypersensitivity reactions may occur.

References

- [1] Nissenson A R, Weston R E and Kleeman M R 1979 Mannitol *West. J. Med.* **131** 277-84

- [2] Shawkat H, Westwood M and Mortimer M 2012 Mannitol: a review of its clinical use *Cont. Edu. Anaesth. Crit. Care Pain* **12**(2) 82-5
- [3] Rockwell K 2015 Therapeutic review *Ther. Rev.* **24**(1) 120-2
- [4] Dziedzic T, Szczudlik A, Klimkowicz A, Rog T M and Slowik A 2003 Is mannitol safe for patients with intracerebral hemorrhages? Renal considerations *Clin. Neurol. Neurosurg.* **105** 87-9
- [5] Calogiuri G F, Muratore L, Netti E, Casto A M, Di Leo E and Vacca A 2015 Immediate-type hypersensitivity reaction to Mannitol as drug excipient (E421): a case report *Eur. Ann. Allergy Clin. Immunol.* **47**(3) 99-102
- [6] Ghajar J, Hariri R J and Narayan R K 1995 Survey of critical care management of comatose, head-injured patients in the United States *Crit. Care Med.* **23**(3) 560-7
- [7] Task force of the American Association of Neurological Surgeons and Joint Section in Neurotrauma and Critical Care 1995 *Guidelines for the management of severe head injury* (Brain Trauma Foundation)
- [8] Bratton S L, Chestnut R M, Ghajar J, McConnell, Hammond F F, Harris O A, Hartl R, *et al.* 2007 Guidelines for the management of severe traumatic brain injury: II Hyperosmolar therapy *J. Neurotrauma* **24** 14–20
- [9] Wantke F, Focke M, Hemmer W, *et al.* 2000 Exposure to formaldehyde and phenol during an anatomy dissecting course: Sensitizing potency of formaldehyde in medical students *Allergy* **55** 84-7
- [10] Ventakesh Y P and Hedge V L 2003 A hypothesis for the mechanism of immediate hypersensitivity to mannitol *Allergol. Int.* **52** 165-70
- [11] Labuza T P, Reineccius G A, Monnier V M, O'Brien J, Baynes J W 1994 *Maillard reactions in chemistry, food, and health* (Cambridge: Royal Society of Chemistry)
- [12] Hegde V L and Venkatesh Y P 2004 Anaphylaxis to excipient mannitol: evidence for an immunoglobulin E-mediated mechanism *Clin. Exp. Allergy* **34** 1602-9
- [13] Wu L C and Zarrin A A 2014 The production and regulation of IgE by the immune system *Nat. Rev. Immunol.* **14**(3) 1-5
- [14] Larche M, Akdis C A and Valenta R 2006 Immunological mechanisms of allergen-specific immunotherapy *Nat. Rev. Immunol.* **6** 761-71
- [15] Grims H R, Kranke B and Aberer W 2006 Pitfalls in drug allergy skin testing: false positive reaction due to (hidden) additives *Contact Dermatitis* **54** 290-4
- [16] Hegde V L and Venkatesh Y P 2007 Generation of antibodies specific to D-mannitol, a unique haptenic allergen, using reductively aminated D-mannose-bovine serum albumin conjugate as the immunogen *Immunobiol.* **212**(2) 119-28
- [17] Carney N, Totten A M, O'Reilly C, Ullman J S, Hawryluk G W J, Bell M J, *et al.* 2017 Guidelines for the management of severe traumatic brain injury, fourth edition *Neurosurg.* **80**(1) 6–15
- [18] Torre-Healy A, Marko N F and Weil R J 2011 Hyperosmolar therapy for intracranial hypertension *Neurocrit. Care* **17**(1) 117–30
- [19] Lamb J D and Keogh J A M 1979 Anaphylactoid reaction to mannitol *Can. Anaesth. Soc. J.* **26** 435-6
- [20] McNeill I Y 1985 Hypersensitivity reaction to mannitol *Drug Intell. Clin. Pharm.* **19** 552-3
- [21] Schmid P and Wuthrich B 1992 Perianesthetic anaphylactoid shock due to mannitol *Allergy* **47** 61-2
- [22] Findlay S R, Kagey -Sobota A and Lichtenstein L M 1984 In vitro basophil histamine release induced by mannitol in a patient with mannitol-induced anaphylactoid reaction *J. Allergy Clin. Immunol.* **73** 578-3