European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2024 vol. 13, ISSUE N. 2, May-August

CARDIAC AND CIRCULATORY PARAMETERS IN THE TREATMENT OF CEREBRAL EDEMA WITH OSMOTIC DIURETICS

A. Pellati*

Department of Translational Medicine, University of Ferrara, Ferrara, Italy.

Correspondence to:
Dr. Agnese Pellati,
Department of Translational Medicine,
University of Ferrara,
44121 Ferrara, Italy.
e-mail: agnese.pellati@unife.it

ABSTRACT

Cerebral edema can occur following harmful insults to the brain such as hemorrhage, stroke, and mechanical trauma, and can lead to a state of coma. The infusion of osmotic diuretics is considered a valid method of therapeutic treatment. These treatments are intended to reduce intracranial pressure. Mannitol is one of the osmotic substances which is often used in the treatment of edema, although the side effects must be taken into account. This article reports the effect of mannitol in patients in coma due to acute cerebrovascular insufficiency and any cardiovascular and renal alterations.

KEYWORDS: *stroke, hemorrhage, edema, mannitol, trauma, cardiovascular*

INTRODUCTION

Cerebral edema can occur in conditions of traumatic brain injury, cerebral hemorrhage, subarachnoid hemorrhage, brain tumor, and ischemic stroke, and can be relieved with an infusion of various hypotonic solutions (1). For many years, the use of osmotic diuretics has been considered one of the most valid methods for the treatment of cerebral edema (2). The objective of the administration of these drugs is to quickly, and for a short period, create an effective osmotic gradient between the vascular compartment and the edematous brain tissue. This allows for the movement of interstitial and glial fluids towards the vascular district, with a consequent reduction in intracranial pressure.

Among osmotic diuretics, mannitol is the most frequently used (3). In cerebral edema, mannitol may be helpful as a diuretic in the treatment of patients with untreatable edema and to increase urine flow by clearing debris from the renal tubules (4). The administration method currently considered most suitable consists of a venous perfusion of 20% mannitol solution at a dosage of 1g/kg of body weight to be carried out over a time span of 10-20 minutes.

While recognizing the validity and usefulness of this drug, we must remember a series of side effects resulting from its administration that have been described in the literature (5). Although allergic reactions have been reported to occur with mannitol treatment, they do not seem to occur more frequently than with the infusion of other macromolecular solutions (6). However, the most prominent side effects seem to be those affecting the cardiovascular system and among these, the most severe is undoubtedly circulatory overload, which can result in pulmonary edema (7). However, this danger was considered negligible given that the administration of mannitol in serious cardiac patients was not seen to lead to a single case of pulmonary edema in a large study (8). Experimental research demonstrated an increase in cardiac output that was presumably linked to a direct positive inotropic action on the myocardial fiber and/or to an indirect action

Received: 10 April, 2024
Accepted: 04 June, 2024

2974-6345 (2024)

mediated by the sympathetic nervous system, or to increased left ventricular end-diastolic volume (8). Furthermore, continuous, or sub-continuous infusion of mannitol appears to be able to cause metabolic acidosis and renal failure (9). These complications certainly occur when plasma osmolarity is very high. However, the circulatory and the renal side effects would require more careful investigation, given the important clinical implications that may be linked to them (10). Both one and the other can be promptly treated and/or partially prevented, provided that their onset is known with certainty. With this study, we attempted to clarify whether the administration of 20% mannitol in comatose patients due to acute cerebrovascular insufficiency could cause dangerous cardiovascular changes or could give rise to hyperosmolarity, which is harmful to the renal system.

METHODS

Osmotic diuresis with mannitol was used to treat cerebral edema in 45 patients in coma due to acute cardiovascular failure. 27 patients were female and 18 were male, with an average age of 62 years. The anamnesis showed 26 patients were affected by arterial hypertension, 7 were affected by diabetes mellitus, and 6 patients had experienced an episode of transient ischemic attack (TIA) in the previous years. 2 patients had electrocardiographic signs of previous myocardial infarction. The study was approved by the institutions' local committee and patients gave their informed consent.

All patients came experienced problems of ventilatory failure. After providing immediate ventilatory assistance, we proceeded with cannulation of the subclavian vein via the subclavicular route, with monitorization of the central venous pressure (CVP), the electrocardiogram (ECG), and blood pressure (BP).

In 9 patients, upon admission it was necessary to rapidly administer diazoxide venously, in order to reduce dangerous levels of blood pressure. The degree of coma was assessed according to the Plum and Posner method. The cerebrospinal fluid (CSF) pressure was monitored in only 6 patients by positioning an intrathecal catheter. In these 6 patients, mannitol administrations were carried out coinciding with increases in CSF pressure. In the other cases, the criterion followed was purely clinical based mainly on repeated neurological examinations and observations of the ocular fundus.

Before initiating the mannitol infusion, a blood sample was taken to determine the parameters reported in the table below (Table I). These samples were repeated 5/10/15/20/30/60 and 90 minutes after the start of the infusion. Urine was also collected to control both the water balance and to study the parameters expressed in Table I. The 20% mannitol solution was administered by venous infusion at a dose of 1 g/kg of body weight. The duration of administration was 10 minutes in 16 patients (group 1) and 20 minutes in the other 29 patients (group 2). It should be noted that the mannitol infusion was started after at least 15 minutes of stable blood pressure values.

Table I. *Blood and urinary parameters studied.*

Blood parameters:	Plasma osmolarity, Na, K, Ca^{2+}, Blood sugar, Cytometric blood count, Hematocrit, Arterial gas analysis
Urinary parameters:	Electrolyte balance (24 hours), Na, K, Ca^{2+}, Osmolarity

RESULTS

Blood pressure significantly decreased in all patients during the rapid infusion of mannitol. The mean arterial pressure (MAP) in the first group of patients decreased on average by 19 +/- 2 mmHg and by 16 +/- 5 mmHg in the second group (+/- SE). Diastolic blood pressure had a greater percentage reduction than systolic blood pressure. The greatest reduction in almost all patients occurred on average after 6 +/- 2 minutes from the start of the infusion of the osmotic diuretic in the first group and after 9 +/- 3 minutes in the second group.

Gradually and progressively, the MAP values reached the baseline values after 25 +/- 5 min from the moment coinciding with the lowest value of the MAP in the first group, and after 20 +/- 7 min in the second group. In patients treated with diazoxide (a molecule structurally related to thiazide diuretics and characterized by the ability to activate potassium channels) before the start of mannitol infusion, the variations in MAP were completely comparable to those of the other patients.

No statistically significant changes in heart rate were observed. During the second half of the mannitol infusion, CVP increased, although not significantly. Electrocardiographic alterations were recorded in 23 patients (electrocardiogram: long QT; flattened diphasic T; above sub-level St; supraventricular extrasystoles). These alterations were already present before the start of treatment in 60% of patients. The highest peak of plasma osmolarity behavior was always recorded after the first half of the infusion (5 min in the 1st group and 10 min in the 2nd group). The blood gas variations were not significant in the two groups of patients.

It is interesting to underline a slight reduction in PO_2 values in over half of the patients during and immediately after the infusion. The variations in Na, K, and Ca^{2+} in the blood (although not important for our study) had a statistically significant duration in relation to the infusion period of the osmotic diuretic. The hematocrit value underwent a progressive reduction during the infusion which was slightly delayed compared to the increase in osmolarity.

DISCUSSION

Although the initial values of BP and CVP were at the upper limits of normal, neither an increase in blood pressure nor signs of cardiovascular overload were observed, except in two anesthetized hypertensive patients. The rapid infusion of mannitol through a rapid increase in blood volume could have caused the feared circulatory overload, the most striking manifestation of which is pulmonary edema.

Instead, a reduction in arterial BP was documented in almost all patients and a non-significant increase in CVP after the second half of the infusion. The lowest MAP values preceded, albeit slightly in almost all patients, the moment in which the plasma osmolarity values progressively increased until reaching the highest levels, always after half the infusion time, in both the first and second groups. Subsequently, the osmolarity curve progressively returned towards lower values as water was drawn into the vascular district.

The decrease in systolic blood pressure could be explained by the vasodilatory action of mannitol (11). In fact, it has been experimentally demonstrated that mannitol directly, and/or through the effects of increasing plasma osmolarity, would cause significant vasodilation, especially in the vascular district of skeletal muscles (12). The decrease in peripheral vascular resistance of venous return and blood viscosity would be the main factors contributing to the reduction in BP (13). It is interesting to note that the lowest values of MAP and diastolic pressure precede the moment of the highest degree of plasma osmolarity (12). The high plasma osmolarity would probably lead to a release of chemical mediators capable of inducing district vasodilation responsible for the decrease in peripheral vascular resistance (14). The documented increase in cardiac output, secondary to the positive inotropic action of mannitol, would therefore not be sufficient to cancel the opposite effect of the reduction in peripheral vascular resistance, at least initially. Subsequently, the pressure gradually returns to baseline values thanks to a reflex vasoconstriction with the participation of some receptors located in the skeletal muscles and central nervous system (CNS) (15).

The feared circulatory overload was not observed in any case. However, in 50% of patients, although mechanical ventilation was kept constant, the PO_2 curve underwent a momentary and slight reduction. This could be justified by an alteration of gas exchange at the alveolar-capillary level caused by an increase in interstitial fluid (16).

The electrocardiographic alterations that were observed did not appear to be caused by mannitol as these appeared in more than half of the cases before the infusion of the osmotic diuretic (17). Furthermore, they appear to be due to the brain lesion responsible for the coma state (18).

CONCLUSIONS

In conclusion, we report that blood pressure significantly decreased in all patients of this study during the rapid infusion of mannitol. In fact, more specifically, the diastolic blood pressure had a greater percentage reduction than systolic blood pressure. Mannitol infusion caused cardiovascular side effects with electrocardiographic alterations in almost half of the patients treated.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Desai A, Damani R. Hyperosmolar therapy: A century of treating cerebral edema. *Clinical Neurology and Neurosurgery*. 2021;206:106704. doi:https://doi.org/10.1016/j.clineuro.2021.106704
2. Okoromah CA, Afolabi BB, Wall EC. Mannitol and other osmotic diuretics as adjuncts for treating cerebral malaria. *Cochrane Database of Systematic Reviews*. 2011;2011(4). doi:https://doi.org/10.1002/14651858.cd004615.pub3
3. Harley HR. The use of hypothermia and dehydration in the treatment of severe cerebral hypoxia. *British journal of anaesthesia*. 1964;36(9):581-590. doi:https://doi.org/10.1093/bja/36.9.581

4. Koenig MA. Cerebral Edema and Elevated Intracranial Pressure. *CONTINUUM: Lifelong Learning in Neurology*. 2018;24(6):1588. doi:https://doi.org/10.1212/CON.0000000000000665
5. Bereczki D, Liu M, Fernandes do Prado G, Fekete I. Mannitol for Acute Stroke. *Stroke*. 2008;39(2):512-513. doi:https://doi.org/10.1161/strokeaha.107.496778
6. Witz CA, Silverberg KM, Burns WN, Schenken RS, Olive DL. Complications associated with the absorption of hysteroscopic fluid media. *Fertility and Sterility*. 1993;60(5):745-756. doi:https://doi.org/10.1016/s0015-0282(16)56268-2
7. Baigelman W, O'Brien JC. Pulmonary effects of head trauma. *Neurosurgery*. 1981;9(6):729-740. doi:https://doi.org/10.1227/00006123-198112000-00021
8. Zornow MH, Prough DS. Fluid management in patients with traumatic brain injury. *New horizons: an official publication of the Society of Critical Care Medicine*. 1995;3(3):488-498.
9. Tasker RC, Acerini CL. Cerebral edema in children with diabetic ketoacidosis: vasogenic rather than cellular? *Pediatric Diabetes*. 2014;15(4):261-270. doi:https://doi.org/10.1111/pedi.12153
10. Ott P, Larsen FS. Blood–brain barrier permeability to ammonia in liver failure: a critical reappraisal. *Neurochemistry International*. 2004;44(4):185-198. doi:https://doi.org/10.1016/s0197-0186(03)00153-0
11. Hartwell RC, Sutton LN. Mannitol, Intracranial Pressure, and Vasogenic Edema. *Neurosurgery*. 1993;32(3):444-450. doi:https://doi.org/10.1227/00006123-199303000-00017
12. Boulard G, Marguinaud E, Sesay M. [Osmotic cerebral oedema: the role of plasma osmolarity and blood brain barrier]. *Annales Francaises D'anesthesie Et De Reanimation*. 2003;22(3):215-219. doi:https://doi.org/10.1016/s0750-7658(03)00009-1
13. Diringer MN, Scalfani MT, Zazulia AR, Videen TO, Dhar R, Powers WJ. Effect of Mannitol on Cerebral Blood Volume in Patients with Head Injury. *Neurosurgery*. 2012;70(5):1215-1219. doi:https://doi.org/10.1227/NEU.0b013e3182417bc2
14. Poon KS, Pan YL, Liao KH, et al. Isoflurane attenuates carbogen-induced blood–brain barrier disruption independent of body temperature in mice and rats. *NeuroReport/Neuroreport*. 2020;31(2):118-124. doi:https://doi.org/10.1097/wnr.0000000000001390
15. Abassi Z, Khoury EE, Karram T, Aronson D. Edema formation in congestive heart failure and the underlying mechanisms. *Frontiers in Cardiovascular Medicine*. 2022;9(933215). doi:https://doi.org/10.3389/fcvm.2022.933215
16. Qureshi AI, Suarez JI. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. *Critical Care Medicine*. 2000;28(9):3301-3313. doi:https://doi.org/10.1097/00003246-200009000-00032
17. Dabrowski W, Siwicka-Gieroba D, Robba C, et al. Plasma Hyperosmolality Prolongs QTc Interval and Increases Risk for Atrial Fibrillation in Traumatic Brain Injury Patients. *Journal of clinical medicine*. 2020;9(5):1293-1293. doi:https://doi.org/10.3390/jcm9051293
18. Qureshi AI, Suarez JI, Castro A, Bhardwaj A. Use of Hypertonic Saline/Acetate Infusion in Treatment of Cerebral Edema in Patients with Head Trauma: Experience at a Single Center. *The Journal of Trauma: Injury, Infection, and Critical Care*. 1999;47(4):659. doi:https://doi.org/10.1097/00005373-199910000-00009