Neurosurgical implications of mannitol accumulation within a meningioma and its peritumoral region demonstrated by magnetic resonance spectroscopy

Case report

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Mannitol is widely considered the hyperosmolar therapy of choice in routine neurosurgical practice for the reduction of intracranial pressure (ICP). The authors present a unique case of a patient with a large meningioma treated with mannitol, in which mannitol accumulation within the tumor and its surrounding parenchyma was shown using in vivo magnetic resonance spectroscopy (MRS). This rare appearance of mannitol on MRS was characterized by a wide-based peak at 3.8 ppm, which remained detectable several hours after the last dose. These findings provide the first in vivo evidence in support of the prevailing theory that mannitol leakage into the peritumoral edematous region may contribute to rebound increases in ICP and suggest that this phenomenon has the potential to occur in extraaxial tumors. Judicious use of mannitol in the setting of elevated ICP due to tumor may be indicated to avoid potentially deleterious side effects caused by its accumulation. (DOI: 10.3171/JNS/2008/108/5/1010)

KEY WORDS • chemical shift imaging • magnetic resonance spectroscopy • mannitol • meningioma

Mannitol is widely considered the hyperosmolar therapy of choice in routine neurosurgical practice for the reduction of ICP and is used mainly in the setting of cerebral swelling secondary to head injury. It is also frequently used as a means of preventing neurological deterioration in cases of severe mass effect and vasogenic edema accompanying brain tumors, although such use is not supported by strong evidence and may be accompanied by potentially deleterious side effects. In particular, it is believed that brain tumors may disrupt the BBB, producing leakage of mannitol from the vasculature into the peritumoral parenchyma with a resultant reversal of the osmotic gradient and a rebound increase in ICP. To date, mannitol accumulation in the peritumoral region has never been demonstrated in vivo. In this report, we present a unique case of a patient with a large meningioma, who was treated with mannitol as a temporizing measure, and in whom mannitol accumulation within the tumor and its surrounding parenchyma was demonstrated using in vivo MRS.

Case report

History and Examination. This 73-year-old man with a medical history of Type II diabetes mellitus, hyperlipidemia, and medically controlled hypertension presented to a different hospital with a 6-month history of headache, intermittent confusion, and subtle right-sided weakness. A CT scan demonstrated a large, slightly hyperdense left frontal mass in contact with the falx causing significant mass effect, midline shift, and compression of the left lateral ventricle. A presumptive diagnosis of brain tumor was made and the patient was transferred to our institution for further evaluation and treatment.

On admission, the patient was drowsy and disoriented to time and place with upper extremity pronator drift on the right. Initial blood test results, including serum creatinine, were within normal limits. A routine MR image with contrast administration was obtained revealing a large, extraaxial, uniformly enhancing, left frontal mass consistent with a meningioma causing significant mass effect, midline shift, and compression of the ipsilateral lateral ventricle (Fig. 1A). Due to imaging features suggestive of intracranial hypertension and concern about his reduced level of consciousness, the patient was transferred to the neurosurgical intensive care unit. He began receiving intravenous dexamethasone and was given intravenous mannitol (20%) at a dose of 25 g (approximately 0.5 g/kg body weight) every 6 hours, with resection of the tumor scheduled for the following day.

Preoperative Imaging. In accordance with the usual protocol at our institution, the patient underwent repeated MR
Mannitol accumulation demonstrated using in vivo MRS

imaging on the morning of the operation to assist surgical navigation, to which additional spectroscopic sequences were added. Using the automated Proton Brain Examination (PROBE) sequence (GE Medical Systems) at 1.5 T, intratumoral single-voxel spectroscopy was obtained at short (TE = 35 msec) and intermediate (TE = 144 msec) echo times. Multivoxel 2D chemical-shift imaging at TE 144 msec was also obtained over the tumor and peritumoral (edematous) area.

Intratumoral single-voxel spectroscopy at short TE demonstrated a prominent choline peak at 3.2 ppm, the absence of a creatine peak at 3.0 ppm, a broad-based peak at 2.0–2.5 ppm consistent with glutamate/glutamine, and the presence of lactate/lipid at 1.3 ppm (Fig. 1B). Single-voxel spectroscopy at intermediate TE demonstrated an inverted alanine doublet at 1.4 ppm (Fig. 1C). These spectroscopic findings are characteristic of meningioma. In addition, single-voxel spectroscopy at both echo times revealed a large, broad-based peak at 3.8 ppm, slightly decreased in height at intermediate TE. This peak was also noted on chemical-shift imaging, more prominently in intratumoral voxels, but was also present at reduced concentration within the peritumoral region (Fig. 2). Although this large peak fit none of the standard metabolites, it had the same chemical shift as mannitol allowing us to conclude that the peak represented accumulated mannitol within the tumor and in the surrounding edematous brain parenchyma. By this point the patient had received a total of 7 mannitol doses, with the last dose administered 8 hours prior to spectroscopic imaging.

Operation and Postoperative Course. The patient subsequently underwent a left frontotemporoparietal craniotomy with microsurgical intradural exploration and resection of the left frontal falcine tumor without complications. Postoperative MR imaging showed excellent resection of the tumor. The patient had a persistent right pronator drift. Pathological analysis of the resected mass confirmed a World Health Organization Grade I meningothelial/transitional meningioma. Following an uncomplicated recovery, the patient was eventually discharged to an inpatient rehabilitation facility 7 days after surgery.

Discussion

To the best of our knowledge, the case reported here represents the first conclusive in vivo demonstration of mannitol accumulation within a meningioma, and, interestingly, within the surrounding peritumoral edematous parenchyma.

A review of the literature reveals that MRS has been used in a few selected cases to show mannitol accumulation, although under different circumstances than in the case presented in this study. Peeling and Sutherland used ex vivo MRS to analyze perchloric acid extracts of resected brain tumor specimens in patients who had received mannitol during craniotomy. Considering mannitol concentration to be the integrated signal intensity of peaks in the range of 3.65–3.91 ppm—where all 6-CH protons of mannitol are known to resonate—these investigators found high levels of accumulated mannitol in meningiomas, malignant astrocytomas, schwannomas, and metastases. Mannitol accumulation appeared to be limited to tumors that

![Preoperative MR image (A) and intratumoral single-voxel spectroscopy results of the MRS procedure (B and C). A: Axial T1-weighted image after intravenous contrast administration shows a large, extraxial, uniformly enhancing left frontal tumor causing significant mass effect, midline shift, and significant compression of both lateral ventricles. Pathological assessment confirmed the tumor to be a World Health Organization Grade I meningothelial/transitional meningioma. The area delimited by the square marked “1” represents the intratumoral voxel selected for analysis using single-voxel MRS. B: Graph showing spectroscopy results obtained at TE = 35 ms. Note the prominent mannitol peak at 3.8 ppm and the large choline (Cho) peak at 3.2 ppm. The absence of a creatine peak at 3.0 ppm and the broad-based glutamate/glutamine (Glx) peak at 2.0–2.5 ppm is characteristic of a meningioma. C: Graph showing spectroscopy results obtained at TE = 144 msec. The mannitol peak is still clearly noted at 3.8 ppm. The inverted alanine doublet at 1.4 ppm is nearly pathognomonic of a meningioma. Ala = alanine.](image-url)
enhanced with contrast administration on CT although the peritumoral area was never examined. Maioriello and colleagues, in an in vivo MRS study of a patient who had sustained a large stroke, reported a wide singlet mannitol peak at 3.8 ppm—identical to the peak we report in our patient—in voxels located within the area of ischemia, suggesting that degradation of the BBB leads to the accumulation of mannitol within an infarct. The patient they presented did not, however, have a brain tumor, and had a clinical course complicated by renal failure requiring dialysis, with obviously impaired mannitol clearance. Finally, Danielsen and Ross illustrated the same mannitol peak at 3.8 ppm using in vivo single-voxel spectroscopy in a patient with an intraxial malignant astrocytoma, but did not use chemical-shift imaging to assess the peritumoral region.

Mannitol uptake into an extraaxial tumor such as the meningioma in this report is probably explained by the same anatomical mechanism that produces homogeneous contrast enhancement in such tumors: vessels within the tumor bed are abnormal and lack endothelial tight junctions. These leaky vessels then permit intravascular mannitol to escape into the extracellular space of the tumor, where it remains long after it is cleared from the circulation. Presumably, the concentration of accumulated mannitol is related to the cumulative dose and duration of mannitol therapy; our patient received several large doses of mannitol that may account for the high concentration of intratumoral mannitol we observed, as evidenced by the large area under the mannitol peaks shown in Figs. 1 and 2.

Our finding of mannitol accumulation in the peritumoral edematous region surrounding a meningioma is novel and somewhat unexpected. Vasogenic edema formation in malignant gliomas has long been considered etiologically related to a defective BBB in the peritumoral region. In such tumors mannitol might readily leak from the vasculature to accumulate within the peritumoral region, although such accumulation has never been demonstrated in vivo. On the other hand, edema surrounding meningiomas has traditionally been believed to evolve through fundamentally different mechanisms. The accumulation of peritumoral mannitol in our case, however, points to the existence of a disrupted BBB surrounding meningiomas as well. The recent report of a high permeability factor measured in the peritumoral area using perfusion CT in two extraaxial tumors lends support to this possibility. Alternately, the observed peritumoral mannitol accumulation may have resulted from direct contiguous extravasation from the meningioma, especially because our patient received a large cumulative dose of mannitol. It has been reported that some meningiomas can breach a portion of their apposing leptomeningeal surface. In our case, this would have provided a suitable corridor for mannitol that had collected within the meningioma to spill into the surrounding brain parenchyma.

Irrespective of how mannitol entered the peritumoral edematous region in our patient, its persistence long after clearance from the circulation was indisputably confirmed using in vivo MRS. This finding may be clinically relevant. First, recent in vitro work has shown that osmotic stress caused by mannitol is harmful to glia. Although the effect of prolonged contact between mannitol and normal cells in the brain remains unknown, it is possible that avoidable cerebral injury due to peritumoral mannitol accumulation may result from aggressive mannitol use in treating presumed ICP elevation due to the tumor. This consideration may compel the clinician to reconsider initiating mannitol therapy when the indications for doing so are equivocal. Second, this case may help to clarify the mechanism underlying a well-described hazard of mannitol use in treating tumor vasogenic edema, the so-called rebound phenomenon, in which ICP becomes elevated above pretreatment levels following several mannitol doses. Rebound is believed to be caused by the penetration of mannitol into the
brain parenchyma surrounding a tumor, which reverses the osmotic gradient between the blood and the extracellular space leading to a subsequent increase in edema. 10,16,17 To date there has been a paucity of evidence supporting this putative mechanism. Kaufmann and Cardoso 17 used an animal model of cerebral edema induced by cortical contusion to demonstrate worsening edema following mannitol therapy, but none of the animals in the study had brain tumors, precluding generalization to tumor-related rebound. In a more recent study in humans, Palma and associates 19 used an ex vivo assay to quantify the mannitol content of the peritumoral white matter sampled during craniotomy in patients with brain tumors who each received a single perioperative dose of mannitol at a dose of 1 g/kg body weight. They found a significantly higher peritumoral white matter mannitol concentration relative to plasma in patients with malignant gliomas and concluded that this could lead to rebound ICP increase. Our case serves as the first in vivo confirmation of these results. Admittedly, our patient did not worsen clinically during the period of mannitol administration, nor did we measure ICP, so extrapolation to the true clinical rebound phenomenon cannot be made with certainty. Yet none of the patients in the report by Palma and colleagues experienced clinical deterioration. Furthermore, patients in that study received only a single dose of mannitol, unlike our patient who was treated with several doses in a typical mannitol regimen. This difference may account for the Palma study’s failure to detect peritumoral mannitol in meningiomas, because the single-administered dose may have been insufficient to cause accumulation in the setting of a less compromised BBB. In contrast, our findings in a patient with a large meningioma suggest that the rebound phenomenon may not only occur with gliomas, but may also occur in the setting of an extraxial tumor.

Conclusions

We have presented the first in vivo evidence, obtained using MRS, of mannitol accumulation within a meningioma, and of particular neurosurgical relevance, in its surrounding peritumoral edematous parenchyma. The mannitol peak is a wide-based singlet at 3.8 ppm in the in vivo spectrum and can be detected several hours after the last administered dose. Our findings lend support to the prevailing theory that mannitol leakage into the peritumoral edematous region may be implicated in rebound increases in ICP and suggest that the rebound phenomenon may also manifest in patients with extraxial tumors. Judicious use of mannitol in the setting of elevated ICP due to tumor may be indicated to avoid potentially deleterious side effects caused by its accumulation.

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References


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