

Title: ANESTHESIA FOR DISRUPTION OF THE BLOOD-BRAIN BARRIER

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Introduction. Malignant neoplasms of the central nervous system (CNS) respond poorly to chemotherapy. This appears to be at least partly due to poor penetration of agents through the blood-brain barrier (BBB). A technique has now been developed for safe and reversible osmotic disruption of the BBB in humans followed by intraarterial administration of methotrexate, and therapeutic trials of the method are underway.¹ We wish to report on the anesthetic management portion of a clinical study of this treatment modality.

Methods. Eighteen patients between the ages of 12 and 65 with tissue confirmed diagnoses of CNS glioma, medulloblastoma, lymphoma or metastasis from breast or lung cancer underwent a total of 71 BBB disruptions at three hospitals. Preoperatively, all patients were maintained on phenytoin and phenobarbital with therapeutic serum levels. Oral diazepam was used when premedication was necessary. Each patient was given oral antacids. Phenobarbital 1.5 mg/Kg and diazepam 0.15 mg/Kg were given i.v. on arrival in the angiography suite. Standard monitoring was used (electrocardiograph, blood pressure cuff and stethoscope). Thirty-three of the procedures have been performed under general endotracheal anesthesia with thiopental, N₂O/O₂ and small amounts of potent inhalation agent (< 0.5 MAC), the remainder have been performed with i.v. sedation. Ventilation has been controlled in the anesthetized patients. In all patients diuresis was established with mannitol 0.1 grams/Kg and furosemide 0.5 mg/Kg prior to the BBB disruption. Immediately prior to disruption, 1-4 mg/Kg of thiopental was administered and patients were hyperventilated with O₂ for 1 minute. For intracarotid injection 0.4 mg atropine was also administered. Disruption was performed with 250 to 320 ml of 25% mannitol solution injected over 25 to 30 seconds through the appropriate branch of the cerebral arterial system. One minute after injection 2.5 ml/Kg of a 60% solution of meglumine iohalamate was administered i.v. as contrast medium for a subsequent computed tomography (CT) scan. Arterial blood gases were then obtained. Beginning five minutes after disruption 500 to 1000 mg of methotrexate in saline was infused through the intraarterial catheter over 15 minutes. Repeat arterial blood gases were obtained during spontaneous ventilation. A CT scan under anesthesia was performed immediately after methotrexate injection. Patients were then transferred to the Intensive Care Unit for a minimum of 24 hours observation. Eighteen procedures have been followed by the systematic administration of procarbazine and cyclophosphamide 24 hours after disruption.

Results. Significant complications were observed in two patients under general anesthesia and three patients who were sedated. A total of 3 focal seizures were observed after injection of contrast media, one in an awake patient. In another the seizure occurred two hours after the procedure.

There have been two grand mal seizures following the injection of contrast media, one in an awake patient who had a transient bradycardia, to a rate of 23 bpm following intracarotid mannitol. This patient did not receive atropine before the injection. Shivering has been observed in 25/33 of anesthetized patients and 18/28 of sedated patients during the recovery phase. We have the clinical impression that the degree of BBB disruption is directly related to the degree of postoperative obtundation, although we do not have sufficient data to confirm this. There have been significant cerebral edema with neurologic deficit after one procedure. This resolved over 48 hours. Clinical results have been encouraging. There has been significant tumor regression in three of the six patients treated with systemic procarbazine and cyclophosphamide in addition to the intracerebral methotrexate. Detailed analysis of the therapeutic effectiveness of the protocol is continuing.

Discussion. Anesthetic management has been complicated by difficult access to the airway, the presence of large amounts of sedative drug in patients with abnormal intracranial compliance, and the need for hyperventilation and the frequency of seizures and obtundation during transport and CT-scanning. Based upon our results, we recommend a protocol which includes general endotracheal anesthesia and controlled ventilation for all patients until CT scan is completed. The recovery period can be complicated by seizures and obtundation with the possibility of intracranial hypertension and we recommend close observation in a recovery room or intensive care unit for at least 24 hours after the procedure. The poor response of CNS tumors to conventional systemic chemotherapy suggests that there will be more and more examples of multifactorial therapeutic approaches like this one. If these promising early results are born out by further investigation, then there will be an important new modality of CNS cancer therapy with new challenges for the anesthesiologist.

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References.

1. Neuwelt EA, et al: Ann Intern Med 94:449-454, 1981.