Intraoperative Administration of Radiologic Contrast Agents: Potential Neurotoxicity

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Anesthetists are frequently asked to administer dyes or other nonanesthetic substances to facilitate performance of a surgical procedure. Sometimes these agents are injected by a member of the surgical team. Inappropriate administration can lead to clinically significant local or systemic toxicity. Subarachnoid instillation of ionic radiologic contrast media has been associated with severe central nervous system side effects, including seizures, coma, and permanent neurologic impairment or death. 1–3

This case report illustrates the importance of knowing the appropriate route of administration of ionic contrast agents and of never injecting them into the intraventricular or subarachnoid spaces. Also discussed are the consequences of and management of ionic contrast neurotoxicity.

Case Report

An 11-yr-old, 33-kg girl with mild developmental delay but who was otherwise healthy was brought to the operating room for revision of a C6–T1 syringoperitoneal shunt to alleviate progressive neural dysfunction of her lower extremities. Previous procedures included closure of a meningomyelocele at birth, several ventriculoperitoneal shunts with revisions, a syringoperitoneal shunt, Harrington rod instrumentation, and spinal cord detethering. Preoperative evaluation of her weakness included a magnetic resonance imaging scan, which revealed a nondecompressed lower cervical syrinx; in addition, a computerized tomographic scan with injection of 3 ml dilute iohexol (Omnipaque, Winthrop Pharmaceuticals, New York, NY) into the shunt showed extravasation of the dye into the subarachnoid space, suggesting that the proximal end of the syringoperitoneal catheter was dislodged.

After premedication with 20 mg oral midazolam, anesthesia was induced with intravenous thiamylal. The patient was placed in the right lateral position, and anesthesia was maintained for more than 5 h with intravenous morphine (total dose 6 mg) and isoflurane in nitrous oxide and oxygen as well as intermittent doses of vecuronium. The surgery was difficult because of extensive scarring from the previous procedures, and an intraoperative contrast study to determine shunt position was performed. At the end of the procedure the neuromuscular blockade was antagonized (full train-of-four recovery); however, despite an end-tidal carbon dioxide tension of 60 mmHg, the patient did not breathe. After administration of naloxone (0.12 mg in divided doses) followed by flumazenil (0.2 mg in divided doses), she opened her eyes and responded to commands but remained apneic. Shortly thereafter, her right periobital muscles began to twitch; the twitching progressed to involve the entire facial musculature and was associated with left arm posturing. By nodding her head, she denied pain but admitted to being frightened.

During discussion of the episode and twitching, it became apparent that 1.5–2 ml (0.05–0.06 ml/kg) of the contrast agent diatrizoate meglumine 60% (Hypaque 60% [Winthrop Pharmaceuticals], 0.6 g salt/ml, 0.03–0.04 g salt/kg) diluted in 2 ml sterile saline had been injected into the shunt. The shunt was then immediately irrigated with sterile saline in an attempt to remove the dye.

The patient was then given 0.3 mg/kg dexamethasone and taken to the intensive care unit, where treatment included head elevation and administration of phenytoin in divided doses (total dose 500 mg). The focal seizures returned 45 min after administration of phenytoin and progressed to generalized tonic–clonic seizures requiring phenobarbital and lorazepam for control. Postictally, she was afebrile with no response to pain; her pupils were equal and weakly reactive. Computerized tomographic scanning of the cranial showed subarachnoid contrast material over the right cerebral hemisphere and within the basal cisterns. There was loss of gray–white differentiation in her temperom, parietal, and inferior frontal lobes, consistent with edema. Hyperventilation therapy was added to treat the potential development of increased intracranial pressure associated with the cerebral edema.

Subsequently, hypotension developed and necessitated administration of dopamine 10 µg/kg·min−1 intravenously for 12 h; lactic acidosis (lactate = 11.8 mmol/l; normal = 0.5–1.6 mmol/l) was treated with 1 meq/kg intravenous sodium bicarbonate. The next day the patient had nonlocalizing but symmetric reaction to deep pain and no spontaneous respiration. Her seizures were well controlled and blood lactate concentration returned to normal. A second computerized tomographic scan showed persistent subarachnoid contrast and increased density of gray matter consistent with absorption of contrast in the right cerebral hemisphere. Ventricular configuration was stable. Over the next 2 days the patient resumed spon-

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Table 1. Positive Contrast Agents in Common Clinical Use

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Anion</th>
<th>Cation</th>
<th>Iodine (mg/ml)</th>
<th>Osmolality (mOsm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypaque 60</td>
<td>Diatrizoate</td>
<td>Meglumine</td>
<td>282</td>
<td>1,415</td>
</tr>
<tr>
<td>Hypaque 30–76</td>
<td>Diatrizoate</td>
<td>Meglumine and/or sodium</td>
<td>141–370</td>
<td>633–2,016</td>
</tr>
<tr>
<td>Conray 30–400</td>
<td>Iothalamate</td>
<td>Meglumine or sodium</td>
<td>141–400</td>
<td>681–2,348</td>
</tr>
<tr>
<td>Hexabrix</td>
<td>Ioxaglate</td>
<td>Meglumine and sodium</td>
<td>320</td>
<td>600</td>
</tr>
<tr>
<td>MD-50–MD-76</td>
<td>Diatrizoate</td>
<td>Meglumine and/or sodium</td>
<td>300–370</td>
<td>1,546–2,179</td>
</tr>
<tr>
<td>Renografin 60–76</td>
<td>Diatrizoate</td>
<td>Meglumine and sodium</td>
<td>292–370</td>
<td>1,549–2,188</td>
</tr>
<tr>
<td>Vascoray</td>
<td>Iothalamate</td>
<td>Meglumine and sodium</td>
<td>400</td>
<td>2,513</td>
</tr>
<tr>
<td>Nonionic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iovue 128–370</td>
<td>Iopamidol</td>
<td></td>
<td>128–370</td>
<td>290–796</td>
</tr>
<tr>
<td>Omnipaque 140–350</td>
<td>Iohexol</td>
<td></td>
<td>140–350</td>
<td>322–844</td>
</tr>
<tr>
<td>Optiray 160–320</td>
<td>Ioversol</td>
<td></td>
<td>160–320</td>
<td>355–702</td>
</tr>
</tbody>
</table>

Some physical properties of ionic and nonionic radiologic contrast agents. In most cases concentrations of ionic agents refer to the percent salt concentration (±0.8 g/100 ml), whereas concentrations of nonionic agents denote the iodine concentration (±128 mg/ml).

Toneous respiration, and her level of consciousness improved. Her tracheal was extubated on the 4th postoperative day. She had moderate dysarthria and lower-extremity weakness. A third computerized tomographic scan, on the 5th postoperative day, showed normalization of gray and white matter appearances with no visible intra- or extraparenchymal contrast. The patient was discharged on the 8th postoperative day with normal speech and with improvement in lower-extremity strength compared with that before surgery.

Discussion

This report demonstrates the substantial neurotoxicity of intrathecal administration of an ionic, high-osmolality radiologic contrast agent intended for oral or intravascular administration. Apnea and focal seizures occurred on emergence from anesthesia; subsequently, the seizures became generalized, and lactic acidosis and hypotension developed. Comprehensive supportive care and perhaps early saline irrigation to remove the agent allowed full recovery from this serious event.

Iodinated compounds are commonly used as positive contrast agents for intravascular, intrathecal, and other radiographic studies. Iodine content is an important factor in the quality of radiographic visualization. Conventional agents for intravascular administration are salt solutions of benzoic acid derivatives: radiopaque iodine-containing anions like diatrizoate are formulated with sodium or methylglucamine (meglumine) cations, with two osmotically active particles to each three iodine atoms. To obtain iodine concentrations high enough to provide useful contrast, these agents are hypertonic compared with blood (plasma 285 mOsm/kg water) and cerebrospinal fluid (301 mOsm/kg water) (table 1). For example, Hypaque 60% has an osmolality of 1,415 mOsm/kg; a 13% solution is isotonic. More recently, nonionic iodine-containing monomers have been introduced. These compounds provide equivalent iodine content at a far lower osmolality than that possible with ionic agents (table 1), but they cost 10–20 times as much.

The significant difference in tonicity between ionic and nonionic contrast agents plays a role in toxicity; however, some neurotoxicity is specific to the chemical, independent of osmolality. For example, metrizamide (Amipaque), the original nonionic contrast agent, is no longer used because its neurotoxicity is significantly higher than that of iohexol (Omnipaque) or iopamidol (Iovue, Bracco Diagnostics, Plainsboro, NJ). Also, dilution of an ionic contrast agent to a concentration less than or equal to that of nonionic agents produces neurotoxicity significantly greater than that observed with the latter.

Toxicity of Ionic Contrast Agents in the Subarachnoid Space

Previous reports of patients and of animals have described serious sequelae from subarachnoid injection

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of ionic, high-osmolality contrast agents. After intrathecal administration of ionic contrast media for myelography, painful spasms of the lower extremities initially develop; these often spread cephalad into generalized seizures, with associated fever, hypotension or hypertension, metabolic acidosis, disseminated intravascular coagulopathy, anxiety, or renal failure.\textsuperscript{1,2} Fifty percent of these patients died, some less than 12 h after dye administration.\textsuperscript{2} Issues central to these patients' clinical courses were the dose and type of dye injected, the site of administration, and the timely institution of definitive therapy. Our patient received approximately one-third to one-half the dose per kilogram of the same agent given to one patient who died;\textsuperscript{2} however, the site of injection in the cervical syringoperitoneal shunt of our patient was much closer to the brain than that of the adult patient injected for lumbar myelogram. This difference may explain the prominence of respiratory failure among her symptoms.

**Dye Distribution and Clearance**

Patient position and movement and the use of positive pressure ventilation are among the factors that can influence the preferential distribution of hyperosmolar dye within the cerebrospinal fluid. Intraoperatively, our patient was placed in the right lateral position; dye was initially demonstrated over the right cortex, as expected. Both ionic and nonionic contrast agents appear to penetrate the brain to similar depths; irrespective of the type (ionic or nonionic) of contrast material injected, absorption into the cerebral parenchyma is expected. The amount of dye at any given site depends also on the dye clearance rate. Normally, most intrathecally administered contrast agent is excreted in urine within 2 or 3 days;\textsuperscript{6} delayed clearance from the subarachnoid space would contribute to ongoing injury.

**Effects on Neuronal Function**

When ionic and even nonionic contrast media contact neural tissue, they have profound effects on neuronal function. The brain is particularly sensitive to contrast; the lethal dose of intravenous sodium diatrizoate is 1,400 times that of the same agent given intracisternally.\textsuperscript{10} Even isotonic ionic or nonionic contrast agents applied to the brain\textsuperscript{9} or spinal cord\textsuperscript{6} can cause abnormal electrical or reflex activity, thought to be attributable to a direct chemical effect. Ionic agents induce particularly abnormal spontaneous ventral root\textsuperscript{6} and electroencephalographic\textsuperscript{6} activity, perhaps by selective decreases in inhibitory synaptic events.\textsuperscript{8} This effect may account for the spasticity and seizure activity reported in other cases.\textsuperscript{1-3} The respiratory failure in rabbits after intraarterial diatrizoate sodium meglumine and absence of changes in ventilation in nonionic agent- or saline-treated controls,\textsuperscript{11} is one example of the greater toxicity of ionic contrast agents.

In addition to their epileptogenic effects, contrast agents also may induce neuronal edema.\textsuperscript{5} Reports of intrathecal\textsuperscript{12,13} or intraarterial\textsuperscript{12,13} contrast administration to animals\textsuperscript{13} and humans\textsuperscript{1,2,12} show development of edema in some\textsuperscript{2,12,13} but not in others.\textsuperscript{1}

**Clinical Management**

Treatment of a patient after inadvertent administration of an ionic contrast agent into the subarachnoid space requires removal of the contrast agent, including measures to prevent its flow toward more central structures, and supportive management of its neurotoxicity. Most authors emphasize the importance of minimizing the amount of agent reaching the brain by maintenance of a head-up position\textsuperscript{1-3} and, particularly when therapy is instituted soon after intrathecal injection, lavage of the intrathecal space with warm sterile isotonic saline\textsuperscript{1,3} may be useful. Lavage was used in our patient; in addition, the presence of a ventriculoperitoneal shunt may have allowed some cranial decompression and perhaps enhanced the clearance of contrast from the cranial vault.

Supportive intensive care includes effective seizure control\textsuperscript{1} and management of potential respiratory and circulatory collapse. Although no study has demonstrated unequivocal benefit from steroid administration, several authors recommend steroids for amelioration of brain or spinal cord contrast toxicity.\textsuperscript{1,12} Flumazenil has been reported to cause seizures\textsuperscript{14} and would not be appropriate in the setting of intrathecal administration of ionic contrast. In our patient, flumazenil was given before the onset of the seizures and before it was known that an ionic contrast agent had been given.

The package insert for Hypaque 60%\$ includes a warning that it is not intended for intrathecal use, but no warning appears on the bottle. This incident emphasizes the need for awareness of the type of contrast provided and perhaps establishment of a protocol for the use of radiographic contrast agents in the operating room.

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Acute Myocardial Ischemia during Thoracotomy in a Patient with Previous Coronary Artery Bypass Grafting

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PREVIOUS coronary artery bypass grafting (CABG) may be protective for patients undergoing subsequent noncardiac surgery.1-3 Patients with previous CABG may, however, be susceptible to acute intraoperative ischemic events when surgical manipulation occurs in the vicinity of functioning bypass grafts.

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