ADVERSE REACTIONS FOLLOWING $^{111}$In-DTPA CISTERNOGRAPHY

Philip O. Alderson and Barry A. Siegel

Edward Mallinckrodt Institute of Radiology,
Washington University School of Medicine, St. Louis, Missouri

**Two cases of aseptic meningitis following cisternography with $^{111}$In-DTPA are presented. Such reactions appear to be quite infrequent and are characterised by similar clinical and laboratory findings as the reactions that follow $^{111}$I-albumin cisternography.**

The use of chelated radiopharmaceuticals for cisternography has been suggested by several authors (1–3). The DTPA chelate of $^{111}$In has nearly ideal properties that include a 2.8-day half-life permitting delayed imaging beyond 24-hr, decay by electron capture, and a high yield of gamma photons (0.173 and 0.247 MeV) of suitable energy for imaging with both rectilinear scanner and the Anger camera. Hosain and Som (3) have reported satisfactory use of $^{111}$In-DTPA in over 50 patients without any adverse reactions. We have recently encountered two patients who developed aseptic meningitis following intrathecal administration of this agent. A description of these reactions forms the basis of this report.

**CASE REPORTS**

**Case 1.** GS, a 10-year-old boy, was first admitted to St. Louis Children’s Hospital on March 27, 1971 with pneumococcal meningitis. He recovered without sequelae on ampicillin therapy and was discharged.

He was well until March 17, 1972 when he was re-admitted with pneumococcal meningitis, which again responded well to antibiotics. Because of recurrent meningitis, a CSF fistula was considered. An isotope cisternogram was requested, but specific instructions regarding the purpose of the study were not transmitted. The examination began March 27, following lumbar subarachnoid injection of 300 µCi $^{111}$In-DTPA. The baseline CSF obtained at this time exhibited normal cell count, protein, and glucose. The study was uneventful, and the CSF flow pattern was normal except for slow ascent of tracer to the parasagittal region. No CSF leak was shown, but since the diagnosis had not been specifically sought, a repeat study was advised.

On April 3, a repeat cisternogram began with injection of 300 µCi $^{111}$In-DTPA. Baseline CSF showed no cells, protein 19 mg%, glucose 50 mg% (blood glucose 94 mg%). Eight hour after radiopharmaceutical injection, he complained of headache. He was afebrile, had slight nuchal rigidity, a positive Kernig’s sign, and marked bilateral quadriceps hyperreflexia. The plantar responses were flexor. A fever of 38.8°C was first noted on April 4, 30 hr after injection. A repeat lumbar puncture revealed 1,000 white cells/mm³ (73% polymorphonuclear cells), protein 68 mg%, and glucose 42 mg% (blood glucose 84 mg%). CSF gram stain showed no organisms, and cultures were subsequently reported as sterile. He was begun on intravenous penicillin G, 12 million units daily. By the night of April 4, approximately 36 hr after injection, he defervesced. Nuchal rigidity resolved, but both Kernig’s and Brudzinski’s signs were still detected on April 5. The next day physical examination was unremarkable, and a repeat lumbar puncture on April 10 showed 20 mononuclear cells/mm³, protein 19 mg%, and glucose 34 mg% (blood glucose 68 mg%). The second cisternogram showed a normal pattern and no evidence for a CSF leak on either the images or serial counting of nasal packs. Antibiotics were discontinued after 6 days. He was discharged and has subsequently done well.

**Case 2.** TS, a 10-month-old boy, was admitted to St. Louis Children’s Hospital on March 21, 1972 with somnolence, difficulty in walking, fever, and vomiting. Two days before admission he had fallen

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For reprints contact: Barry Siegel, 510 S. Kingshighway Blvd., St. Louis, Mo. 63110.
once, striking his head. Initial physical, laboratory, and CSF examination established a diagnosis of pneumococcal meningitis, and penicillin therapy began. However, he remained febrile, anorectic, and lethargic, and developed lower extremity hyporeflexia. A repeat lumbar puncture on April 1 showed persistent pleocytosis and protein elevation, and a nitroblue tetrazolium test suggested partially treated bacterial infection. A 99mTc-pertechnetate brain scan was normal. Antibiotic therapy was changed to ampicillin.

Because of the poor clinical response, the possibility of a CSF fistula was suggested. A cisternogram with 125 μCi 111In-DTPA was begun on April 4 showing transient ventricular activity and delayed, incomplete ascent of tracer over the right convexity. No fistula was visualized, but significantly increased activity was detected in the right nasal pack. Subsequently, a left subdural collection was suggested by transillumination and a repeat brain scan. On April 8, a left subdural tap yielded 40 ml of fluid, and thereafter he steadily improved. A repeat lumbar puncture on April 15 showed 32 white cells/mm³, protein 16 mg%, glucose 50 mg%, and negative stain and culture.

To evaluate for change, a second cisternogram with 150 μCi 111In-DTPA was begun on April 18. Nasal pack counts again showed increased right-sided activity. There was still transient ventricular penetration, but convexity flow was symmetrical. The morning after radiopharmaceutical injection, he vomited once but otherwise exhibited no adverse effects. Antibiotics were discontinued and he was discharged April 25.

He remained well and was seen in clinic on May 9 when a third cisternogram was requested to determine if CSF rhinorrhea persisted. Intrathecal 111In-DTPA (125 μCi) was administered without difficulty. Baseline CSF studies were not performed. The images again showed transient ventricular reflux but were otherwise unremarkable; nasal pack counts were not increased. He returned home, but 6–8 hr after injection became irritable and vomited once. When he returned for 24-hr images, he was noted to be irritable, had minimal neck stiffness but no focal neurologic signs, and was afebrile. Several hours later he returned to the emergency room with fever of 38.4°C. Lumbar puncture showed 3,000 white cells/mm³ (60% polymorphonuclear cells), protein 32 mg%, and glucose 64 mg% (blood glucose 124 mg%). Gram stain showed no organisms, and a culture was performed that was subsequently sterile. Intravenous ampicillin therapy began, and he was admitted to the hospital. All subsequent temperatures were normal, and he rapidly improved clinically. A repeat lumbar puncture 4 days after tracer injection showed 81 white cells/mm³ (80% mononuclears), protein 24 mg%, and glucose 51 mg% (blood glucose 87 mg%). Ampicillin was discontinued, he remained well, and was discharged 4 days later.

**DISCUSSION**

The clinical and laboratory findings in these two patients suggest aseptic meningitis secondary to intrathecal 111In-DTPA. Both patients had clinically recovered from bacterial meningitis before cisternography, but developed signs of meningeal irritation within 8 hr after radiopharmaceutical injection. This was followed, within 30 hr, by transient fever, CSF pleocytosis, and elevation of CSF protein concentration. Spinal fluid cultures were sterile, and the offending lots of the radiopharmaceutical were cultured and tested for pyrogen by the manufacturer before shipment with negative results. The clinical course of these episodes was quite brief. Both patients were afebrile by 36 hr and had fully recovered by 72 hr. Followup CSF studies showed a return toward normal of cells counts and protein concentrations within several days. Neither patient exhibited permanent sequelae.

These findings are similar to those which have been reported in chemical meningitis complicating cisternography with 131I-albumin (4–8). In the patients reported by Barnes and Fish (7), fever was generally noted earlier than in our patients and occurred by 12 hr postinjection. The fever duration in their patients was also somewhat longer and four of their five patients had temperature spikes to 38.3°C or more for at least 3 days. However, the fifth patient had fever and meningismus only on the day after injection and a maximum temperature of 37.8°C. It is of interest that this patient was much younger (37 years old) and in better general health than the other four patients.

Both of our patients were children and in good general health at the time of cisternography and these factors may have contributed to the relatively mild courses of their reactions.

In both of our patients, significant CSF pleocytosis (1,000 and 3,000 cells/mm³, respectively) occurred. This is comparable to the cellular responses reported by Barnes and Fish (7) but greater than those encountered by Messert and Rieder (8). In this latter series only 1 of 12 patients with a definite reaction to IHSA exhibited an increase in CSF cell count of over 350/mm³, and the majority showed increases of about 100 cells/mm³ at 24 hr. Our patients initially showed a predominant polymorphonuclear cellular response, as seen in patients with reactions
to IHSA. The elevations in CSF protein we encountered are also comparable to those reported in meningitis following $^{131}$I-albumin, with increments of several mg to several hundred mg/100 ml. Similarly, there were no significant changes in CSF glucose concentrations, and all CSF cultures were sterile.

The pathogenesis of the meningeal reaction in these patients is uncertain. The clinical course and CSF culture results exclude a bacterial etiology. Although the batch tests for pyrogens performed by the manufacturer were negative before shipment, we were unable to perform repeat pyrogen tests on the offending vials as they had been discarded before the patients showed clinical illness. However, as noted by others (7), the human subarachnoid space may be much more sensitive to pyrogens than the standard rabbit pyrogen test, and the use of more sensitive methods may be necessary to detect low levels of pyrogen contamination in radiopharmaceuticals (9). Contamination by trace quantities of irritant chemicals such as detergent solution used to clean pharmaceutical vials might have resulted in chemical irritation. The fact that both of our patients had multiple cisternographic studies is intriguing and suggests that previous sensitization might be of some pathogenetic significance. Finally, the relationship to the preceding pneumococcal meningitis is unexplained but might somehow be related to the increased meningeal permeability to chelated radiopharmaceuticals shown in experimental meningitis (10).

To our knowledge, these are the first cases of adverse reactions to $^{111}$In-DTPA or other chelated radiopharmaceuticals reported in the literature. In the past 14 months, we have performed over 130 cisternograms with $^{111}$In-DTPA. In a third patient, a 55-year-old woman being evaluated for dementia, a similar reaction occurred 12 hr after intrathecal administration of 500 μCi $^{111}$In-DTPA. Cultures of CSF were negative and the remaining radiopharmaceutical was cultured and tested for pyrogen with negative results. She recovered over several days. However, she had also undergone an intrathecal saline infusion study just before injection of $^{111}$In-DTPA, and we cannot be certain which agent was responsible for the adverse response. Our experience suggests that adverse reactions to $^{111}$In-DTPA are quite infrequent; only three other cases of aseptic meningitis have been reported to the manufacturer during a period when over 3,000 patients have been studied (11). This experience compared quite favorably to that with $^{131}$I-albumin cisternography, in which symptomatic meningitis has been encountered in as many as 14% of patients (8).

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REFERENCES


11. Lieberman E: Personal communication