Special safety considerations in preparation of technetium Tc-99m DTPA for cerebrospinal fluid–related imaging procedures

James A. Ponto

Abstract

**Objective:** To review special safety considerations in the preparation of technetium 99m (Tc-99m) diethylenetriaminepentaacetic acid (DTPA; generic name, pentetate) for cerebrospinal fluid (CSF)–related imaging procedures.

**Data sources:** Review of practices and results at one institution supplemented with findings and recommendations from the literature. Literature searches were conducted via Medline/PubMed using the following terms: Tc-99m DTPA/pentetate, CSF, cisternography, intrathecal, and adverse reactions. The author’s own files were also searched for articles (e.g., in newsletters) not indexed by Medline/PubMed.

**Study selection:** Articles considered appropriate for review included all human research studies, reviews, case reports, abstracts, and letters published in English on Tc-99m DTPA use in CSF-related imaging procedures, especially with regard to safety or adverse reactions.

**Data extraction:** All information related to safety precautions and adverse reactions associated with Tc-99m DTPA injected intrathecally or otherwise used for CSF-related imaging procedures were considered.

**Data synthesis:** 18 years’ experience in one institution was reviewed with the added perspective of literature findings and recommendations.

**Conclusion:** With proper attention to safety considerations, Tc-99m DTPA can be safely used in CSF-related imaging procedures.

**Keywords:** Adverse drug effects, bacterial endotoxins test, sterile product preparation, medication safety, off-label medication use, radiopharmaceuticals.


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evaluation of cerebrospinal fluid (CSF) flow by radioisotope imaging methods was first introduced in the mid-1960s. At that time, a radiopharmaceutical, generally iodine 131–labeled human serum albumin (I-131 HSA), was administered by intrathecal or intracisternal injection. Disturbances in CSF flow, such as those occurring with hydrocephalus, were evaluated by nuclear medicine imaging over 24 to 48 hours. Although less frequent in current practice, radionuclide cisternography continues to be performed using indium-111 (In-111) DTPA (diethylenetriaminepentaacetic acid; pentetate).

CSF-related imaging procedures have evolved to address other diagnostic situations. These include detection of CSF leaks, evaluation of ventriculoperitoneal shunt patency, and evaluation of intrathecal drug delivery with implantable pumps. Although technetium-99m (Tc-99m), because of its short half-life of 6 hours, is not practical for traditional cisternography imaging procedures that extend over 1 to 2 days, Tc-99m DTPA can be used for these other CSF-related procedures that require shorter imaging times. Advantages of Tc-99m DTPA compared with In-111 DTPA for use in these procedures include availability, cost, radiation dose, and image quality. However, unlike In-111 DTPA, Tc-99m DTPA is not FDA-approved for intrathecal injection.

This institution began using Tc-99m DTPA for CSF-related procedures in 1988. Based on the literature available at the time, anecdotal information, and professional judgment, policies and procedures were developed for the preparation and off-label use of Tc-99m DTPA that were reasonable and practical and considered safe and effective. The following practices were developed and then consistently observed for use of Tc-99m DTPA in these CSF-related procedures:

1. Use a preservative-free, calcium trisodium DTPA kit.
2. If possible, obtain Tc-99m sodium pertechnetate from an elution vial that has been punctured the fewest number of times.
3. Reconstitute the DTPA kit with sufficient Tc-99m radioactivity so that the patient dose will contain no more than 1 mg of DTPA.
4. For dilution, use preservative-free 0.9% sodium chloride injection from a previously unused vial.
5. Perform aseptic handling in a vertical-flow ISO class 5 laminar air hood.
6. Perform Limulus Amebocyte Lysate (LAL) testing at a sensitivity appropriate to ensure that the bacterial endotoxin content is no more than 14 endotoxin units (EU)/dose.
7. Administer no more than 1 mg of DTPA associated with the prescribed radioactivity dose.
8. Withdraw and administer only one patient dose per vial of Tc-99m DTPA.

The use of Tc-99m DTPA for CSF-related procedures in our institution was recently reviewed along with the added perspective of literature findings and recommendations. Literature searches were conducted via Medline/PubMed using the following terms: Tc-99m DTPA/pentetate, CSF, cisternography, intrathecal, and adverse reactions. The author’s own files were also searched for articles (e.g., in newsletters) not indexed by Medline/PubMed. Articles considered appropriate for review included all human research studies, reviews, case reports, abstracts, and letters published in the English language regarding the use of Tc-99m DTPA in CSF-related imaging procedures, especially with regard to safety or adverse reactions. All information related to safety precautions and adverse reactions associated with Tc-99m DTPA injected intrathecally or otherwise used for CSF-relating imaging procedures was considered.

Review of available findings and recommendations for the off-label use of Tc-99m DTPA for CSF-related studies prompts continued consideration of three important safety issues: bacterial endotoxin, DTPA salt/mass, and preservatives.

**Bacterial endotoxin**

Numerous reports of aseptic meningitis following intrathecal injection of radiopharmaceuticals, especially I-131 HSA, were later linked to the presence of bacterial endotoxin. Although such products passed the United States Pharmacopeia (USP) Pyrogen (Rabbit) Test, they were found to contain low levels of bacterial endotoxin using the LAL test. Thus, apparent...
“safe levels” of endotoxin administered intravenously to rabbits are capable of producing severe neurologic reactions when administered into the CSF of humans.

In response to the problem of aseptic meningitis associated with I 131 HSA, nonbiologic metal chelates such as ytterbium-169 (Yb-169) DTPA and In-111 DTPA became common replacements.1 Although these metal chelates are not as prone to bacterial endotoxin contamination as albumin products, aseptic meningitis was not completely eliminated.10,11 Thus, absence of endotoxin reactions from Tc-99m DTPA cannot be assumed.

By USP standards, radiopharmaceuticals intended for intravenous administration must contain “not more than 175 EU/V USP Endotoxin Unit per mL of the Injection, when compared with the USP Endotoxin RS [Reference Standard], in which V is the maximum total dose, in mL, at the expiration date or time.”12 Given that the entire contents of the vial could be administered as one dose, this limit for intravenous administration is equivalent to not more than 175 EU/dose. For radiopharmaceuticals intended for intrathecal injection, however, the USP specifies a limit of “not more than 14 EU/V.”12 Hence, a radiopharmaceutical that complies with the USP Bacterial Endotoxins standard for intravenous injection may or may not also comply with the USP Bacterial Endotoxin standard for intrathecal injection. Therefore, the commercial Tc-99m DTPA product, which is intended for intravenous injection, should be LAL tested at a sensitivity appropriate to verify compliance with the USP Bacterial Endotoxins standard for intrathecal injection.8

If LAL testing is not available, it appears reasonable to limit potential endotoxin administration by limiting the volume of the injection based on the ratio of the endotoxin limits for intrathecal and intravenous administrations (i.e., 14 EU/V: 175 EU/V),13 which equates to not more than 8% of the vial contents.

**DTPA salt/mass**

Various chelating agents can readily sequester cations present in CSF. Depletion of Ca²⁺ and/or Mg²⁺ ions in CSF may produce muscular tetany, convulsions, and other neurologic dysfunction.1 The free acid form and sodium salts of pentetic acid readily chelate Ca²⁺ and Mg²⁺ ions, whereas CaNa₂DTPA does not.5,10 For example, relatively low concentrations (5 mEq/L) of H₂Na₃DTPA were found to cause irreversible blockade of nerve conduction in isolated ischiatic rat nerves, whereas CaNa₂DTPA, even in much higher concentrations (20 mEq/L), caused no effect.5

A number of serious neurologic adverse reactions, presumably related to sequestration of ions in CSF, have been reported with intrathecal injection of Tc-99m DTPA products,5,10,14 including several cases of permanent saddle anesthesia and loss of sphincter control and possibly one death.6 Whether four reported fatalities (one in Australia, one in Canada, and two in the Netherlands) resulted from high endotoxin levels or from the ionic composition of the Tc-99m DTPA remains unknown.15

Although CaNa₂DTPA does not readily chelate Ca²⁺ and Mg²⁺ ions, a conservative approach is to limit the mass administered to no more than 1 mg.5 (Note: Although In 111 DTPA is formulated with pentetic acid instead of the calcium trisdodium salt, the entire vial contains only 30 to 75 µg DTPA.16)

**Preservatives**

Chemical and antimicrobial preservatives frequently used in injections administered by common routes (e.g., intravenous, intramuscular) may present safety issues if administered into CSF. Several such preservatives, including alcohol, phenol, and sodium metabisulfite, have been identified as neurotoxic.17 Therefore, only preservative-free formulations of Tc-99m DTPA should be used for CSF-related procedures.5,8

**An 18-year experience using Tc-99m DTPA**

The use of Tc-99m DTPA for CSF-related imaging procedures at this institution during an 18-year period (1988–2006) was reviewed. Practices consistently observed for the preparation and administration of Tc-99m DTPA for these procedures were as described above. The preservative-free calcium trisodium DTPA kits used were Technetlex (no longer marketed; E.R. Squibb, Princeton, N.J.) and AN-DTPA (CIS-US, Bedford, Mass.). A maximum administration mass of DTPA 1 mg was selected based on the practicality of minimizing DTPA mass per administered dose while still ensuring radiochemical purity. For example, preparation of a Technetlex vial containing 10 mg of calcium trisodium DTPA with 100 mCi Tc-99m would allow a patient dose of 5 mCi to contain less than 1 mg of DTPA up to its 6-hour expiration time. Aseptic handling procedures focused on avoiding touch contamination, washing hands, wearing gloves, and working in a vertical-flow ISO class 5 laminar air hood. Because this experience predated implementation of USP <797>, the practices did not involve secondary engineering controls (i.e., the laminar flow hood was not located inside an ISO class 8 cleanroom), cleanroom garbing, or cleanroom personnel training. Adoption of USP <797> standards for all compounded sterile products, including Tc-99m DTPA for CSF-related imaging procedures, may incrementally enhance safety vis-à-vis sterility. The traditional LAL gel clot method was used to test for bacterial endotoxin. Use of newer LAL kinetic methods may potentially provide equivalent endotoxin test results in a shorter period of time.

During this 18-year period, 514 preservative-free calcium trisodium Tc-99m DTPA kits were aseptically prepared and tested for bacterial endotoxin appropriate for CSF-related imaging procedures, and 503 doses, each containing 1 mg of DTPA or less, were administered to patients for CSF-related imaging procedures. Eleven vials, though meeting all quality control criteria, were not used because of patient cancellations. None of the 514 Tc-99m DTPA vials exceeded a bacterial endotoxin concentration of 14 EU/dose. None of the 503 patients receiving Tc-99m DTPA for CSF-related imaging procedures were reported to have experienced any type of adverse reaction.
Special safety considerations and recommendations for the preparation and administration of Tc-99m DTPA for CSF-related imaging procedures, reaffirmed by this review, are summarized in Table 1.

**Table 1. Special safety considerations and recommendations for the preparation and administration of Tc-99m DTPA for CSF-related imaging procedures**

<table>
<thead>
<tr>
<th>Safety consideration</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Bacterial endotoxin</td>
<td>Verify acceptable bacterial endotoxin concentration of the Tc-99m DTPA product for CSF use (i.e., ≤14 EU/dose) and/or administer no more than 8% of the vial contents.</td>
</tr>
<tr>
<td>DTPA salt/mass</td>
<td>Use only the calcium trisodium salt formulation of DTPA and administer no more than 1 mg DTPA.</td>
</tr>
<tr>
<td>Preservatives</td>
<td>Use only preservative-free formulations of DTPA.</td>
</tr>
</tbody>
</table>

Abbreviations used: CSF, cerebrospinal fluid; DTPA, diethylenetriaminepentaacetic acid; EU, endotoxin units; technetium-99m.

**References**


**Conclusion**

With proper attention to special safety considerations (i.e., bacterial endotoxin, DTPA salt/mass, preservatives), Tc-99m DTPA can be safely used in CSF-related imaging procedures.