

LETTERS TO THE EDITOR

A DIFFICULT THERAPEUTIC PROBLEM WITH A NUCLEAR MEDICINE SOLUTION: A CASE REPORT

To the Editor: I am writing to express concern regarding the intrathecal administration of radiopharmaceuticals not approved for intrathecal use (approved for intravenous administration only) in response to the article entitled "A Difficult Therapeutic Problem with a Nuclear Medicine Solution: A Case Report" which appeared in the September 1995 issue of the *Journal of Nuclear Medicine Technology* (1). In this article Corley et al. describe the preparation of ^{32}P chromic phosphate for an intracranial administration. While the attention to good aseptic technique described is thorough and certainly appropriate, the authors failed to include a far more important consideration, that of testing for the presence of pyrogens (bacterial endotoxins). Perhaps the authors actually did perform this crucial test and chose to omit it from their discussion. Intrathecally administered radiopharmaceuticals have been reported to cause aseptic meningitis when excessive levels of pyrogens have been present (2). Because of this, their presence in pharmaceuticals for parenteral administration is the cause of great concern. It is imperative that end-product testing for the presence of bacterial endotoxins be performed *prior to patient administration* of intrathecally or intracranially administered medications not manufactured for the express purpose of intrathecal administration.

Endotoxins are lipid A fragments from the cell walls of gram-negative lipidopolysaccharide bacteria that are thought to cause many of the clinical features of bacterial sepsis (3). These include fever, muscle proteolysis, uncontrolled intravascular coagulation and shock. These effects appear to be mediated by production of IL-1, TNF α and IL-6 from mononuclear cells. These molecules exhibit potent hypothermic activity, increase vascular permeability, alter the activity of endothelial cells and induce these cells to procoagulant activity.

Currently, the USP endotoxin limit formula for radiopharmaceuticals, *except for intrathecally administered*

products, is 175 EU/V where V equals the largest recommended dose, in ml, at the expiration date or time (4). The USP endotoxin limit for radiopharmaceuticals administered intrathecally is 14 EU/V (4). Any product manufactured expressly for or FDA-approved for intrathecal use must meet this 14 EU/V criteria. It is, therefore, the standard of practice that any medication extemporaneously compounded for intrathecal (or intracranial) administration should satisfy this requirement. All other parenteral medications are manufactured to meet the nonintrathecal endotoxin limit of 175 EU/V which is 12.5-fold greater than the intrathecal limit.

Whenever a medication is used for an off-label indication (e.g., an intrathecal dose is prepared from any source other than a drug with FDA approval for intrathecal administration as evidenced by specific package insert indication(s) for this route of administration) the responsibility and burden of proof that it is acceptable for this use rests entirely with the end user. The current, USP XXIII test for bacterial endotoxins is the Limulus Amebocyte Lysate (LAL) test (5). The term *apyrogenic* is often applied to parenteral medications. However, nothing is truly without pyrogens, but they may exist at levels below the limits of detection. In the case of intravenous radiopharmaceuticals and reagent kits, manufacturers are required to use the limit of 175 EU/V for those approved for other than intrathecal administrations (i.e., most drugs). When they state that an injectable drug is apyrogenic or pyrogen free this should always be interpreted to mean that the level of bacterial endotoxins is below the FDA mandated limit of 175 EU/V for parenterals rather than truly without pyrogens.

Diluents for intrathecal dosage forms must also be chosen quite carefully and tested for the presence of bacterial endotoxins (6,7). Most diluents are intended for routes of administration other than intrathecal. They, like the medication for which they act as a vehicle, must also be tested for pyrogens. Often it is advan-

tageous to prepare the final dosage form, add the diluent, make whatever dilutions are necessary and then perform end-product LAL testing for the level of bacterial endotoxins. In this manner, one validates the technique used in the dose preparation as well as the actual dose administered.

Therefore, the accepted standards of practice mandate that all injectables administered intrathecally must be subjected to end-product testing for bacterial endotoxins (LAL) *prior to administration*. If this preparation is performed in-house then you, as a licensed professional, and the institution are responsible. If, on the other hand, the dose is prepared by a commercial nuclear pharmacy, they have the capacity to perform the LAL test and provide documentation regarding the level of pyrogens. In any case, the testing is required and must be performed prior to patient administration.

A second consideration in the preparation of the intracranial dose was the use of 5% excess with the rinsing technique described in the article. If, during the administration, a mixture of the dose and the cystic fluid was "withdrawn into the syringe and reinjected two times" then the calculated void volume is no longer valid as described. If one rinses the syringe during administration as they describe, one is administering more than the "to deliver volume" which the authors approximated in their mock-up. Therefore, the patient would have received more than the intended or prescribed dose using the methods described. Whether this has a clinically significant impact on the patient outcome is a further question. However, this method of dose calculation and adjustment is fundamentally flawed and should be re-evaluated with added caution.

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LETTERS TO THE EDITOR

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Reply: We would like to thank the writer for his interest and comments on our recent paper, "A Difficult Therapeutic Problem with a Nuclear Medicine Solution: A Case Report", published in the September 1995 issue of the *Journal of Nuclear Medicine Technology*. The writer has given an excellent review of the requirements and the need to test radiopharmaceuticals for pyrogens prior to administration.

We did administer the proper dose. Several trials were made to measure the residual ^{32}P in the syringe and needle. The amount of residual radioactive material was determined to be 5% retention after withdrawing into the syringe and reinjected two

times in a mock up tumor volume. If the 5% retention was not accounted for, the patient would have received a dose lower than the intended therapeutic dose. The goal was to deliver sufficient radiation to stop the growth of the tumor. An effort was also made to assure that none of the dose leaked out of the cyst by creating a slightly negative pressure in the cyst to retain the intracavity dose of ^{32}P chromic phosphate suspension.

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