Procedure Guideline for Brain Death Scintigraphy

TO THE EDITOR: We read the article by Donohoe et al. with great interest and appreciation that the Society would attempt some standardization for brain death in the *Journal of Nuclear Medicine* (*1*). There is, however, some valuable information that should accompany this procedure guideline. It is vital for interpreting physicians to understand that the results must completely meet the strict criteria for whole-brain death. This is important for the protection of both the patient and the physician.

To meet the criteria for whole-brain death, perfusion must be absent from the whole brain, both cerebrum and cerebellum (*2*). Without the use of persistent agents, accurate evaluation of brain perfusion is not possible (*2*). Spieth et al. state, "Unlike DTPA (technetium 99m-diethylene-triaminepentaacetic), HMPAO (technetium 99m-hexamethylpropylene amine oxime) normally visualizes the gray matter of the cerebellum, midbrain, and medulla. These areas must be evaluated to meet the strict criteria for brain death." (*3*). These findings suggest that persistent agents are a better choice for cerebral perfusion studies to determine brain death (*3*). Spieth et al. explain, "Although HMPAO is more expensive than DTPA, it is less expensive than the total cost of a repeat study using DTPA. A single HMPAO dosage can be reimaged should there be equipment or other technical failures during acquisition." (*3*). At that time, HMPAO was the only available technetium-labeled agent able to meet the strict criteria for the clinical confirmation of whole-brain death (*3*). Neurolite (Bristol-Myers Squibb Medical Imaging, Inc.) is another persistent agent available since the above articles were written.

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REPLY: The authors of the recently published "Procedure Guideline for Brain Death Scintigraphy" (*1*) would like to thank Drs. Spieth, Devadas, and Gauger for their comments. Indeed, the point they raise was one of the more difficult issues to address during the writing of the guideline. Several authors of the guideline believed, for similar reasons to those stated by the authors of the letter, that hexamethylpropyleneamine oxime and ethylcysteinate dimer were the preferred agents to use for the diagnosis of brain death. However, other guideline authors believed that limiting the diagnosis of brain death to brain-specific agents alone was too restrictive, particularly in light of the long track record of success with the nonspecific perfusion agents.

We looked to the literature for guidance and found no convincing evidence comparing the specific and nonspecific perfusion agents. The articles cited by Spieth et. al. in *Clinical Nuclear Medicine* are interesting, but they did not demonstrate the superiority of one agent over another and did not provide evidence that the ultimate patient outcome was affected differently by one agent compared with the other. We believed that before we dismiss the usefulness of the nonspecific perfusion agents, more evidence needs to be published.

Our final decision was to present the 2 alternatives and discuss the relative advantages and disadvantages of each, allowing the readers of the guideline to choose that with which they were most comfortable.

We encourage readers of all the procedure guidelines to forward any comments to the Guideline and Communications Committee. All procedure guidelines are available for download from the Society of Nuclear Medicine Web site at http://interactive.snm.org/index.cfm?PageID=772. Comments on any of the guidelines are encouraged and should be sent to Matt Cross at mcross@snm.org. The guidelines are frequently updated, and with each review cycle, all comments offered on each guideline are considered.

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Ability of ^{99m}Tc-Ciprofloxacin Scintigraphy to Discriminate Between Septic and Sterile Osteoarticular Diseases

TO THE EDITOR: Sarda et al. (*1*) have results that appear to confirm their previous acknowledgement that their preparation of ^{99m}Tc-ciprofloxacin contained ^{99m}Tc-colloid. However, they now state that their preparation of ^{99m}Tc-ciprofloxacin "excluded a significant amount of radiolabeled colloids," although details of the evidence for this statement are scant. We now know that some of the original 2-stage Infecton kits (^{99m}Tc-ciprofloxacin) (unlike the new, 1-stage Infecton kit [Draximage]) tended to produce increasing amounts of colloid, particularly if they were diluted or if the pH or ionic strength of the preparation varied. This tendency may have depended, in part, on the ^{99m}Tc generator used; the wet generators had a greater tendency than the dry type.

The clinical evidence for the presence of ^{99m}Tc-colloid in the studies of Sarda et al. (*1*) is particularly obvious in their Figure 4,

which appears to be a 4-h image. Changes typical of weight-bearing osteoarthritis are seen in the medial femoral and tibial condyles of the left knee. The active inflammation in the right knee would show persistent uptake of ^{99m}Tc-colloid even when the ^{99m}Tc-Infecton diffuses out. We conclude that their high sensitivity was due to the combination of ^{99m}Tc-Infecton and ^{99m}Tc-colloid and their poor specificity was due to diffusion of ^{99m}Tc-Infecton from the osteoarthritic joints but persistence of ^{99m}Tc-colloid.

Sarda et al. (*1*) stated that their results "were visually evaluated by 2 experienced nuclear medicine physicians unaware of the patient group. . . ." However, no data are presented that a learning curve was established for a new technique such as Infecton imaging. As is apparent from problematic results in some clinical publications (*2*), there is a learning curve for understanding the pharmacokinetics of Infecton and how they differ from the pharmacokinetics of radiolabeled white cells (*3*,*4*). Specific uptake of Infecton increases with time, until reaching a plateau at 24 h. Nonspecific uptake after the initial distribution decreases with time as the blood level falls. This is exemplified by the study of Larikka et al. (*5*), in which the specificity of Infecton for prosthetic hip infections was shown to increase greatly over time, having been 41% at 1 h, 68% at 4 h, and 95% at 24 h. Thus, obtaining 24-h images is essential for correct interpretation and should be standard practice for suspected bone and joint, cardiac valve, and vascular prosthesis infections. For all other suspected infections, 1- and 4-h images are usually sufficient.

It appears that Sarda et al. (*1*) have collected the region-of-interest data from anterior views only and from knees without knee supports. We know that a support for each knee is essential to achieve the same position in serial images of patients with pain or discomfort in their knees (*6*). The geometric mean of combined anterior and posterior regions expressed as a percentage of the injected activity when both knees are affected is the preferred method for reproducible quantitation, not a ratio between pairs of joints.

It is interesting that Sarda et al. (*1*) and Dumarey et al. (*2*)—the 2 groups of investigators who found reduced specificity in clinical studies—received Infecton kits from us for pilot studies but failed to communicate any problems with us. If they had done so, we could have checked the batch numbers of the kits they received to assess for any increased tendency to colloid formation. Other groups kept in touch with us about their problems and progress. We also know that, on occasion, quality control testing of the preparation may show negligible colloid soon after preparation but that under some circumstances colloid may form before injection if injection is delayed. The authors stated that only up to 1 h elapsed between preparation and injection, yet in a previous presentation of their data the injection was given up to 6 h after preparation. In contrast, the results of the groups who discussed their problems with us showed an overall mean sensitivity of 85% and mean specificity of 84% in a total of 1,405 patients, as summarized in our commentary on imaging bacterial infection (*3*). The multinational trial on 879 patients contained 194 patients with an orthopedic prosthesis, and a sensitivity of 96% and specificity of 91.6% were obtained (*4*).

The limitations of the 2-stage kit have been addressed by Draximage, the licensed manufacturer of Infecton kits. Its new 1-stage Infecton kit is beginning clinical trials. In conclusion, ^{99m}Tc-Infecton is a bacteria-specific imaging agent if prepared correctly and used correctly and if the results are interpreted correctly.

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REPLY: Contrary to what Britton and collaborators affirm in this letter, we did not acknowledge that our preparation of ^{99m}Tc-ciprofloxacin contained ^{99m}Tc-colloids. As indicated in our publication, we verified the absence of colloids in the preparation by paper chromatography and Sep-Pak (Waters Corp.) chromatography. Further contrary to what is stated, we did not inject the preparation more than 1 h after radiolabeling (to be able to inject the preparation as soon as possible after quality control, we always verify that the patient is present in our department before we perform the radiolabeling). We did not indicate in a previous presentation that the preparation was given up to 6 h after the preparation. We agree that delayed 24-h images may be essential for correct interpretation, to discriminate between specific and nonspecific uptake. This is why we obtained 24-h images for all our patients, considering findings as negative when the ^{99m}Tc-ciprofloxacin uptake decreased on 24-h images, as explained in our publication. But 24-h images did not help to discriminate between infected and uninfected disease.

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^{123}I-β-CIT SPECT for Imaging Serotonin Transporters in Parkinson's Disease

TO THE EDITOR: We read with interest the article by Kim et al. published in the June 2003 issue (*1*), in which the authors reported on results of ^{123}I-β-2β-carbomethoxy-3β-(4-iodophenyl)-tropane (β-CIT) SPECT studies performed on patients with Parkinson's disease (PD) and a matched control group. SPECT scanning was repeated up to 24 h after radiotracer injection to determine the time dependency of midbrain serotonin transporter (SERT) and striatal dopamine transporter (DAT) binding. Kim et al. correlated the obtained SPECT data with clinical scores on

severity of parkinsonian symptoms, including depression (the mentation, behavior, and mood subscale of the Unified Parkinson's Disease Rating Scale; Hamilton Depression Scale). They found the specific midbrain uptake of the radiotracer to reach a peak at about 6 h after injection. No differences in midbrain SERT availability were detected between patients and controls, despite a significantly lower striatal DAT availability for the PD patients. In 7 depressed PD patients, the midbrain SERT data did not correlate with severity of depression (*1*).

From their results, the authors concluded that DAT and SERT are differentially affected in PD. We want to stress, however, that the authors neglected to discuss their findings in light of the results of a previous study of very similar design. Using the same radiotracer and imaging technique, our group studied cerebral SERT and DAT in patients with PD in 2001 (*2*). We reported on differential patterns of midbrain SERT and striatal DAT availability in this disorder (*2*), results that have now been confirmed by Kim et al. (*1*). In contrast to the results of Kim et al., however, we found the midbrain SERT availability to correlate with the severity of depression, expressed as the mentation, behavior, and mood subscale of the Unified Parkinson's Disease Rating Scale (*2*). By comparing the methods used to detect SERT in both studies, we presume that the difference in results between the 2 studies was caused by different approaches to define the target brain regions or by different scanner characteristics. First, in our study, we defined the midbrain region after coregistering the SPECT data with the individual MRI data of the scanned subjects. In contrast, Kim et al. did not coregister the SPECT data with morphologic imaging data. Image coregistration, however, is an effective tool to overcome the lack of anatomic information in SPECT images. Previously, for instance, our group showed that diagnosis of PD improves by applying SPECT–MRI image coregistration rather than solely SPECT analysis (*3*). Second, optimized spatial resolution and scanner sensitivity seem indispensable for minimizing partial-volume effects while detecting SERT density in the relatively small midbrain region. In our study, we therefore used a brain-dedicated SPECT scanner (Ceraspect; DSI). In comparison with a triple-head scanner such as that used in the study by Kim et al. (the authors did not specify the scanner applied), the dedicated brain scanner provides not only higher spatial resolution but also count ratios that are closer to the true activity distribution, as reported recently by our group (*4*).

Apart from these methodologic drawbacks, the findings of the dynamic SPECT data analysis in the publication by Kim et al. (*1*) confirm the results of Brücke et al. that had already been published in 1993 (*5*). With respect to those results, we cannot distinguish the novelty in the results of Kim et al. Also, we regret that the authors again neglected to discuss their data in light of the cited literature.

Finally, from our point of view, the paper by Kim et al. (*1*) does not provide an up-to-date overview of current knowledge on SERT imaging using ^{123}I-β-CIT SPECT in neuropsychiatry. No studies on that issue were cited in their publication. Instead, the authors claimed that ". . .^{123}I-β-CIT. . .should be useful for studying serotonergic neuronal integrity in cerebral degenerative processes." (*1*). To formulate this statement in such a presumptive form does not seem appropriate. Clearly, there is a list of disorders in which cerebral SERT has already been clinically investigated using ^{123}I-β-CIT and SPECT. A review of current knowledge in that field was published in 2002 by the University of Vienna group, which was among the first to apply this technique clinically (*6*). Recently, our group investigated cerebral SERT availability in patients with Wilson's disease. In keeping with the results in PD patients, we found the degree of depression to correlate negatively with availability of brain SERT (*7*). Altogether, because of the extensive experience in ^{123}I-β-CIT SPECT imaging of SERT acquired by the brain-imaging community over the last few years, this method can undoubtedly be considered an established clinical research technique.

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Radioimmunotherapy of Non-Hodgkin's Lymphoma

TO THE EDITOR: The contrast between 2 papers on this topic published side by side in *The Journal of Nuclear Medicine* is quite striking. The first, by Koral et al. (*1*), concentrates on tumor dosimetry and response using ^{131}I-tositumomab therapy. The second, by Wiseman et al. (*2*) on radiation dosimetry results with ^{90}Y-ibritumomab tiuxetan, never mentions tumor dosimetry, and the authors appear to have measured tumor dosimetry in only 9 patients in previous studies (*3*,*4*). The basic principle of nuclear medicine therapy is to use the therapeutic agent on tumors that are shown by imaging to take up the agent. Whether lack of uptake be shown for ^{131}I or ^{123}I for ^{131}I therapy of differentiated thyroid cancer, ^{123}I-metaiodobenzylguanidine (MIBG) for ^{131}I-MIBG therapy of neuroendocrine tumors, or ^{111}In-octreotide imaging before therapy with ^{90}Y-octreotide derivatives for somatostatin receptor–bearing tumors, the principle is the same. Failure to demonstrate uptake of the potential agent helps to exclude from unnecessary radiation treatment those patients whose tumors are without avidity for the agent (*5*). This principle is already being eroded when ^{131}I therapy for thyroid cancer is given on the basis of the patient's thyroglobulin being raised and ^{131}I tracer findings being negative. This situation, which may arise because ^{131}I tracer is a poor imaging agent, is being solved through the use of 185 MBq (5

mCi) of ^{123}I (*6,7*). No outcome benefit from the treatment of non–iodine-avid differentiated thyroid cancer with ^{131}I therapy has been published. The arguments for dosimetry-guided radioactive iodine treatment in patients with metastatic differentiated thyroid cancer are given in a paper (*8*) in the same issue as the papers by Koral et al. (*1*) and Wiseman et al. (*2*).

Assessing the therapeutic dose to the tumor, whether visually (e.g., tumor uptake is greater than or equal to liver uptake for therapy or is less than liver uptake for no therapy, as in the Novartis trial for the use of ^{90}Y-OctreoTher) or by detailed dosimetry as in the paper by Koral et al. (*1*), is a basic principle of radionuclide therapy. In no example above was the therapeutic dose calculated using body weight, and in no way can body weight determine the dose to a tumor. The fact that on a whole-body–based calculation, it can be argued that the bone marrow dose can be minimized does not justify giving the therapy for a tumor that has not been shown to take up the agent. In our first case of non-Hodgkin's lymphoma treated with ^{90}Y-ibritumomab, in which we calculated the dose using the body weight as stipulated by the manufacturers, we in fact gave approximately one third the dose limit of the bone marrow. In other words, on the basis of our dose calculation, the amount of activity that could have been given to treat this patient's tumor was 3 times that determined on a body-weight basis. Whereas there may be an upper limit above which a further increase in therapeutic dose has no benefit to the patient with a tumor, there is clearly a lower limit at which insufficient therapy has no benefit to the patient with a tumor.

We face, therefore, a dilemma. Should we insist on the nuclear medicine approach to cancer therapy, in which potential nonresponders are excluded by imaging, or should we follow an apparently oncologic approach whereby as long as the marrow is safe, it does not matter whether the tumor receives an adequate or inadequate amount of therapy or whether the patient receives unnecessary radionuclide therapy? Should not we uphold the basic principles of nuclear medicine and radiation protection for radionuclide therapy?

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