Pathophysiology of Drug Dependence

TO THE EDITOR: We have been following with great interest and appreciation the work of using radiotracers to attempt to elucidate the pathophysiology of drug dependence. A recent article in *JNM* by Dr. Levin et al. (*1*) probes the anti-addictive mechanism of buprenorphine. Fifteen cocaine- and heroin-dependent men were randomly assigned after detoxification to receive placebo or daily buprenorphine treatment. Technetium-99m-HMPAO SPECT studies performed at baseline and after dosing were compared with regard to the number and location of perfusion defects. Subjects receiving buprenorphine had a significant reduction in the number of defects per study between baseline and maximum buprenorphine dose as compared with those receiving placebo. The authors conclude that buprenorphine treatment, and not abstinence from drug use alone, leads to improvement in regional cerebral perfusion abnormalities in chronic cocaine- and heroin-dependent men.

The authors also point out that improvement of abnormal cerebral blood flow may help to explain the usefulness of buprenorphines in treating drug addiction. While the authors successfully demonstrated that buprenorphine reduces the number of defects in recently abstinent opiate users, this might not be necessarily related to the anti-addictive mechanism unique to buprenorphine. Opiate antagonists such as naloxone are vasoactive and augment cerebral perfusion in normal (*2*) as well as ischemic (*3*) brain. Additional studies using control groups receiving a mu-agonist, such as morphine or methadone, are needed to distinguish the effects of rCBF or buprenophine from that of other opiates.

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REPLY: We thank Dr. Galynker and colleagues for their thoughtful letter in response to our study, and we fully agree with their comments. Our blinded, placebo-controlled, dose-escalating study was designed to address the issue of whether buprenorphine treatment for polydrug dependence, or simply abstinence from polydrug use alone, is responsible for improvement in cerebral perfusion defects seen in those individuals. We did not attempt to address the more difficult issue of whether buprenorphine's anti-addictive mechanisms are related to the improvement in cerebral perfusion, and hope that we did not appear to suggest that we had done so.

Understanding the hemodynamic, along with other physiological and functional, effects of pharmaceutical agents is essential for fully understanding their biological mechanisms. Functional imaging has proven a valuable tool in this regard. We have used the perfusion abnormalities seen in polydrug-dependent individuals as a model for studying such hemodynamic effects. We agree that further studies comparing the effects of buprenorphine and other opiate agonists, as well as other pharmacological agents, are necessary before mechanistic conclusions can be drawn.

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What Is the Best Technique for Patient Positioning during Breast Scintigraphy?

TO THE EDITOR: I read with great interest the article by Taillefer et al. (*1*) on ^{99m}Tc-MIBI breast scintigraphy. Axillary lymph-node imaging is a promising area for ^{99m}Tc-MIBI and has significant value in the management of breast cancer. If the presence or absence of metastatic spread to the axillary lymph nodes can be reliably established by noninvasive methods such as ^{99m}Tc-MIBI imaging, then the number of surgical lymph node dissections would be eliminated. This would significantly decrease the morbidity in a patient with breast cancer because surgical dissection of axillary lymph nodes is associated with high morbidity. Taillefer et al. (*1*) used prone technique to image the primary breast lesion and supine technique to image axilla and to locate the primary tumor in the breast because the prone technique is insufficient to image axilla and to locate primary tumor, especially in the inner breast quadrants. While their results, particularly those of axillary lymph node imaging are encouraging, there are some points requiring comment.

They used an excessively high dose of ^{99m}Tc-MIBI for breast imaging (25–30 mCi: 900–110 MBq). Furthermore, they defended using such a high dose in their Discussion section (page 1763, paragraph 3). Use of such a high dose for breast scintigraphy is unnecessary. Our original article describing the use of ^{99m}Tc-MIBI for tumor imaging, including breast cancer imaging, shows that a dose of 10–20 mCi (370–555 MBq) is sufficient for both planar and SPECT techniques (*2*). After studying several patients with various malignant and benign diseases (*2–6*) for 6 yr, I can now confidently state that even a dose of 20 mCi is unnecessarily high; a dose of 10 mCi is perfectly sufficient for all tumors we studied, including breast cancer, with both planar and SPECT techniques.

Taillefer et al. (*1*) also showed that the upright position is not suitable for breast scintigraphy because patient movement can hardly be avoided during such a long imaging period (i.e. 10 min) and would detoriate the image quality. However, I do not agree with their comment on the supine position: "... diagnostic quality of images [obtained from supine and upright lateral positions] was so questionable that...." Other studies in the supine position revealed similar sensitivity and specificity with prone imaging (*2,7*). In addition, the supine position has more advantages than the prone technique. Nor does it require a positioning device as detailed in the Taillefer et al. (*1*) article, a device not commonly available and requires extra spending. A single supine image of 8–10 min obtained with a large field of view gamma camera can show both breasts and axillary regions, thereby significantly reducing imaging time (10 versus 40 min). Moreover, the supine view is more useful to visualize axillae and to locate primary tumors, especially those in the inner quadrant. In difficult cases, SPECT can be added to the imaging session.

Although Taillefer et al. (*7*) gave a balanced view about SPECT and reported that they presently prefer the planar technique, I believe that, a

prospective study with a large group of patients is required to compare supine planar, prone planar and SPECT techniques in the detection of both primary disease in the breast and secondary involvement in the axilla. Without such a study, all approaches implying that the prone technique is superior to the supine planar and SPECT are speculative. I think the best approach should be the combination of these three techniques in accordance with the patient's clinical condition, availability of the prone positioning device and the need for axillary imaging. It seems that none of the techniques would be applicable for every patient in all situations. Thus, none of these techniques should be excluded, and more data are needed, particularly for the supine and SPECT techniques.

In their Materials and Methods section, Taillefer et al. mentioned three patients with a mammary prosthesis, but they gave no data about ^{99m}Tc-MIBI uptake (i.e. result of the test) in the Results section, except in the legend of Figure 5, in which they only included the picture of one patient with a prosthesis. They ignored and did not discuss the results of other two patients. What kind of prostheses were they? Did the presence of a prosthesis interfere with tumoral uptake and interpretation of the uptake? Was the prone technique sufficient to image the patient with a prosthesis? Would it be better to use SPECT imaging on such patients to disclose uptake in a tumor hidden behind the prosthesis?

It was not surprising that, of the two patients with false-positive results, sarcoidosic lymphadenitis was discovered in one and a nonspecific chronic inflammatory reaction was diagnosed in the other, because it was previously shown that ^{99m}Tc-MIBI is also taken up by several benign conditions, including sarcoidosis (*5,8,9*). For these reasons, we should make use of the high sensitivity and negative predictive value rather than the specificity of ^{99m}Tc-MIBI imaging in oncology studies, including breast imaging.

I agree with Taillefer et al. that ^{99m}Tc-MIBI can be used as a marker of tumor viability (page 1762, paragraph 5) (*1*). We previously used ^{99m}Tc-MIBI to assess tumor viability in patients with lung cancer (*4*). Our results in humans clearly showed that ^{99m}Tc-MIBI is taken up by viable tumors only.

I object to their comment at the end of their article on a complementary role for ^{99m}Tc-MIBI breast scintigraphy (*1*). If both mammography and breast scintigraphy give the same information about the breast (i.e. presence or abscence of a breast tumor, location of tumor in the breast, number of tumors, etc.), why is breast scintigraphy a complementary tool to mammography, which reportedly has a lower sensitivity and specificity in establishing necessary diagnostic data (i.e., breast abnormalities)? In addition, breast scintigraphy has more advantages:

1. It can detect axillary lymph node metastasis.
2. It can be helpful in imaging breast with prosthesis.
3. It is far superior to mammography in evaluating dense breast.

I think it is the time to re-evaluate the exact role of breast scintigraphy (complementary versus primary). Specifically, in which clinical conditions is it complementary and when does it have a primary diagnostic role?

About the name of this test: is it scintimammography? Breast scintigraphy? Breast scan? Breast imaging? Once upon a time, words with a prefix scinti- were very popular. Is there anybody around who recently witnessed the use of the word scinti-tomography, a once extremely fashionable word (early 1980s) for SPECT or the word scintiscan?

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REPLY: We thank Aktolun et al. for their interest in our article on ^{99m}Tc-sestamibi scintimammography. Although their letter to the editor is entitled "What Is the Best Technique for Patient Positioning during Breast Scintigraphy?", other different issues were raised and many of them would require an in-depth reply, but we will focus our comments on the most important ones.

We certainly do not agree with the term "excessive high dose" used by Dr. Aktolun for describing a dose of 25–30 mCi ^{99m}Tc-sestamibi. Adequate counting statistics is one of the most basic and most important parameters for obtaining a satisfactory or optimal image in nuclear medicine. This can be achieved by injecting a sufficient amount of activity or increasing the imaging time (or both). This is especially obvious when the target (breast cancer in this case) shows a relatively low absolute uptake (less than 1% of injected dose) or the target-to-background ratio is low. In our study, we used a dose of 25–30 mCi and a data acquisition time of 10 min because the quality of the 5-min images was suboptimal. Furthermore, we would like to point out to Aktolun et al. that the standard dose used in SPECT myocardial perfusion imaging is 20–30 mCi and that the total dose of ^{99m}Tc-sestamibi may even exceed 40 mCi when a same-day injection protocol is used. Dr. Aktolun's comment that a dose of 25–30 mCi is excessive also seems quite contradictory to his suggestion of using SPECT in difficult cases (breast prosthesis for example). In our practice, SPECT imaging for breast cancer detection, even with 30 mCi is not always optimal. A 10-mCi dose could be certainly inadequate and may negatively affect the diagnostic accuracy of the scan. Stating that "a dose of 10 mCi is perfectly enough for the detection of all tumors and that a dose of 20 mCi is unnecessarily high" seems quite "excessive" to us and unless Dr. Aktolun or other groups present data in a comparative study showing that a dose of 10 mCi is sufficient, we will continue to recommend to use a higher dose to obtain optimal imaging parameters.

We did explain in our article why we (and other recent investigators on radionuclide imaging of the breast) chose to use prone imaging. We refer the readers to our original article. It is important to realize that ^{99m}Tc-sestamibi is significantly concentrated in the heart and liver (and sometimes in the bowel or in the stomach). If upright lateral images are obtained, especially in patients with pendulous breasts, many tumors will be masked by the uptake in these underlying organs. One of the major advantages of prone imaging is that the breast is vertically pending and there is no "contamination" from thoracic or abdominal uptake. This is particularly useful in the detection of small lesions situated close to the chest wall. Such lesions could be missed on supine imaging if they are superimposed on the heart or liver. Nevertheless, supine imaging, as stated in our article, is also very useful and this is why we have used it in our study and still continue to use it, especially for localizing inner lesions and for evaluating axillae (although lateral prone imaging is often more optimal to detect axillary lymph node involvement). Both supine anterior and lateral prone images thus give complementary information, thereby providing a better diagnostic evaluation of the patient.

As for the role of breast scintigraphy, it may be a little too early to define its exact clinical role at the present time. As long as there still remains a debate on basic parameters, such as injected dose of ^{99m}Tc-sestamibi,