Editorial: Noncardiac Applications of Hexakis-(alkylisonitrile) Technetium-99m Complexes

Hexakis(alkylisonitrile) complexes of technetium-99m, in particular hexakis(2-methoxyisobutyl isonitrile)technetium(I) (^{99m}Tc-MIBI), have shown significant clinical promise as myocardial perfusion imaging agents (*1,2*). Laboratory and clinical studies to date have emphasized various myocardial applications, although experience acquired early in the development of these complexes indicated that myocardium was not the target tissue. Significant uptake in a broad range of organs, including liver, skeletal muscle, lung, thyroid, and kidney was demonstrated with biodistribution data in animals and humans that varied in magnitude depending on the charge of the complex, lipophilicity, and functionalization of the isonitrile ligands (*3–5*). Lack of tissue specificity might therefore predict multiple uses for these organometallic complexes.

Use of hexakis(t-butyl isonitrile) technetium(I) (^{99m}Tc-TBI) for visualization of suppressed thyroid tissue as reported by Ramanathan et al. (*6*) in this issue of *The Journal of Nuclear Medicine* is another interesting example of the expanding noncardiac applications of ^{99m}Tc-isonitrile complexes currently being explored in many clinics and laboratories. For example, mediastinal and pulmonary metastases from thyroid cancer have been successfully identified in 13 of 14 patients with ^{99m}Tc-MIBI single-photon emission computed tomography (SPECT) imaging (*7*). These investigators also reported that ^{99m}Tc-MIBI uptake in thyroid carcinoma was not dependent on thyrotropin (TSH) stimulation. Preliminary results have indicated that ^{99m}Tc-MIBI can also successfully localize parathyroid adenomas (*8*). In that study, one false-positive image was produced by ^{99m}Tc-MIBI uptake into a thyroid adenoma that was also identified with thallium-201.

Localized uptake of ^{99m}Tc-MIBI in 10 of 11patients with untreated malignant lung lesions has been reported by Hassan et al. (*9*). These investigators reported no evidence of localized uptake in one patient with untreated poorly differentiated squamous-cell carcinoma, two patients with treated lung cancers, and four patients with non-malignant lesions. Two patients with fibrosing alveolitis showed diffuse lung uptake. In another study, 20 of 22 tumors were detected by ^{99m}Tc-MIBI SPECT imaging in patients with known bronchial carcinomas, similar to the detection rate for ^{201}Tl SPECT imaging (*10*).

Received Apr. 11, 1990; revision accepted Apr. 11, 1990.
Cellular studies reported from this department were supported in part by a grant from the NIH (HL 42966).
For reprints contact: David Piwnica-Worms, MD, PhD, Department of Radiology, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

As a variant on imaging regional blood flow, application of ^{99m}Tc-TBI as a lung perfusion agent in dogs with experimental pulmonary embolic disease has also been attempted with some success (*11,12*).

Accumulation of ^{99m}Tc-isonitrile complexes in several noncardiac tissues in vitro has also been demonstrated. For example, human erythrocytes accumulated ^{99m}Tc-TBI and hexakis(isopropylisonitrile) technetium(I) (^{99m}Tc-IPI) to plateau levels within 5 min (*13*). The majority of these particular agents, both highly lipophilic, were strongly associated with the cell membrane upon cell lysis. Hexakis (2 carbomethoxy isopropylisonitrile) technetium(I) (^{99m}Tc-CPI), an agent of moderate lipophilicity, showed net uptake in noncontractile fibroblast preparations derived from embryonic chick hearts that approached a plateau more slowly (20 min) (*14*). Technetium-99m-TBI net uptake has been shown in Chinese hamster V79 lung fibroblasts (*3*) while ^{99m}Tc-MIBI accumulation has been demonstrated in several human carcinoma cell lines in vitro (*15*) as well as in nontransformed and v-src transformed NIH 3T3 fibroblasts (*16*).

What is the cellular mechanism of localization of this class of agents and how might this provide insight into clinical imaging? Previous experiments indicated that neither the lipophilic properties nor cationic charge alone were sufficient to characterize tissue uptake of a large series of ^{99m}Tc-isonitrile complexes (*5*). The wide variety of clinical circumstances and preparations in vitro demonstrating uptake of these complexes, in addition to constraints of general transcapillary exchange and interstitial transport (e.g., *17*), indicate at least four biologic properties for any proposed mechanism of tissue localization:

1. The uptake mechanism must account for a relative lack of tissue specificity.
2. The uptake mechanism must allow the agent to initially distribute and be relatively retained in proportion to regional blood flow.
3. The retention mechanism must allow the agent to respond to the metabolic status of tissues under selected circumstances.
4. The localization mechanism should provide for increased uptake and retention in tumors.

Recent data have shown that ^{99m}Tc-MIBI, a less lipophilic cationic complex compared to earlier agents such as ^{99m}Tc-TBI, can be sequestered within the cytoplasm and mitochondria of cells in response to the electrical potentials generated across the membrane

bilayers (*15,16,18*). Strongly negative mitochondrial and plasma membrane potentials can promote concentration of the agent within the mitochondrial inner matrix at equilibrium (*18*). This mechanism would be constrained as described above and could provide a model to better understand the initial biodistribution of ^{99m}Tc-isonitrile complexes within heart, liver, kidney, and skeletal muscle. All these tissues maintain negative plasma membrane potentials or are rich in mitochondrial content. Therefore, alterations in cell metabolism which affect membrane potential could influence accumulation of this agent. Furthermore, it has been proposed that malignant tumors maintain higher (more negative) mitochondrial and plasma transmembrane potentials secondary to their increased metabolic requirements (*19*) which could promote increased accumulation of ^{99m}Tc-MIBI within these tissues. This model of cellular accumulation of ^{99m}Tc-MIBI requires further verification, but may provide insight for a wide variety of new non-cardiovascular applications of ^{99m}Tc-isonitrile complexes.

David Piwnica-Worms
B. Leonard Holman
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

REFERENCES

1. Holman BL, Jones AG, Lister-James J, et al. A new Tc-99m-labeled myocardial imaging agent, hexakis (t-butylisonitrile) technetium (I) [Tc-99m TBI]: initial experience in the human. *J Nucl Med* 1984; 25:1350–1355.
2. Wackers FJTh, Berman DS, Maddahi J, et al. Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. *J Nucl Med* 1989; 30:301–311.
3. Jones AG, Abrams MJ, Davison A, et al. Biological studies of a new class of technetium complexes: the hexakis(alkylisonitrile) technetium(I) cations. *Int J Nucl Med Biol* 1984; 11:225–234.
4. Kronauge JF. Functionalized isonitrile complexes of technetium. PhD Thesis, Massachusetts Institute of Technology. Cambridge, Massachusetts. 1987; pp. 259.
5. Piwnica-Worms D, Kronauge JF, Holman BL, Davison A, Jones AG. Comparative myocardial uptake characteristics of hexakis(alkylisonitrile) technetium(I) complexes: effect of lipophilicity. *Invest Rad* 1989; 24:25–29.
6. Ramanathan P, Patel RB, Subrahmaniyam N, Nayak UN, Sachdev SS, Ramamoorthy N. Visualization of suppressed thyroid tissue by ^{99m}Tc-tertiarybutyl isonitrile (^{99m}Tc-TBI): an alternative to post-TSH stimulation scanning. *J Nucl Med* 1990; 31:1163–1165.
7. Muller ST, Guth-Tougelides B, Creutzig H. Imaging of malignant tumors with Tc-99m-MIBI SPECT. [Abstract] *J Nucl Med* 1987; 28:562.
8. Coakley AJ, Kettle AG, Wells CP, O'Doherty MJ, Collins REC. ^{99m}Tc-sestamibi: a new agent for parathyroid imaging. *Nucl Med Comm* 1989; 10:791–794.
9. Hassan IM, Sahweil A, Constantinides C, et al. Uptake and kinetics of Tc-99m hexakis 2-methoxy isobutyl isonitrile in benign and malignant lesions in the lungs. *Clin Nucl Med* 1989; 14:333–340.
10. Muller SP, Reiners C, Paas M, et al. Tc-99m-MIBI and Tl-201 uptake in bronchial carcinoma [Abstract]. *J Nucl Med* 1989; 30:845.
11. Jones AG, Davison A, Abrams MJ, et al. Investigations on a new class of technetium cations [Abstract]. *J Nucl Med* 1982; 23:P16.
12. Jones AG, Davison A, Abrams MJ, et al. A new class of water soluble low valent technetium unipositive cations: hexakisisonitrile technetium(I) salts. *J Labelled Compounds Radiopharm* 1982; 19:1594–1595.
13. Sands H, Delano ML, Gallagher BM. Uptake of hexakis(t-butylisonitrile) technetium(I) and hexakis (isopropylisonitrile) technetium(I) by neonatal rat myocytes and human erythrocytes. *J Nucl Med* 1986; 27:404–408.
14. Piwnica-Worms D, Kronauge JF, Holman BL, Lister-James J, Davison A, Jones AG. Hexakis(carbomethoxyisopropylisonitrile) technetium(I), a new myocardial perfusion imaging agent: binding characteristics in cultured chick heart cells. *J Nucl Med* 1988; 29:55–61.
15. Delmon-Moingeon LI, Piwnica-Worms D, Van den Abbeele AD, et al. Uptake of the cation hexakis (2-methoxyisobutyl isonitrile) technetium-99m by human carcinoma cell lines in vitro. *Cancer Res* 1990:in press.
16. Chiu ML, Kronauge JF, Piwnica-Worms D. Effect of mitochondrial and plasma membrane potentials on accumulation of hexakis(2-methoxyisobutylisonitrile) technetium(I) in cultured mouse fibroblasts. *J Nucl Med* 1990:in press.
17. Meerdink DJ, Leppo JA. Comparison of hypoxia and ouabain effects on the myocardial uptake kinetics of technetium-99m hexakis 2-methoxyisobutyl isonitrile and thallium-201. *J Nucl Med* 1989; 30:1500–1506.
18. Piwnica-Worms D, Chiu ML, Kronauge JF. Membrane potential-sensitive retention of Tc-99m MIBI in cultured chick heart cells [Abstract]. *Radiology* 1989; 173(P):281.
19. Chen LB. Mitochondrial membrane potential in living cells. *Ann Rev Cell Biol* 1988; 4:155–181.