JPPT

REVIEW ARTICLE

# Nuclear Medicine Imaging in the Pediatric Patient

*Vivian Loveless, PharmD*

*Department of Pharmaceutical Science, College of Pharmacy, The University of Tennessee Center for the Health Sciences, Memphis, Tennessee*

Pediatric nuclear medicine provides a wealth of information on a variety of disease states; however, precautions on dosing have to be taken into consideration. Also, expertise in conducting procedures and interpreting the results in pediatric patients is necessary. Emphasis is placed on diagnostic studies involving the central nervous system, musculoskeletal system, genitourinary system, gastrointestinal system, endocrine system, pulmonary system, and cardiovascular system along with a brief explanation of the mechanism of localization of the radiopharmaceuticals involved. Radiation safety issues are addressed when the expectant mother or nursing mother is administered radiopharmaceuticals.

**KEYWORDS** nuclear medicine, pediatric, radiopharmaceutical

J Pediatr Pharmacol Ther 2006;11:200–211

## INTRODUCTION

When comparing adult and pediatric nuclear medicine, specific considerations must be made for the pediatric population since these individuals cannot be considered just small adults.[1] Adult and pediatric nuclear medicine procedures are often the same; however, the indications can be different. Expertise is needed not only in choosing and preparing the optimal radiopharmaceutical and dosage, but also in conducting the procedure and interpreting the nuclear medicine imaging study (scintigram) of a pediatric patient. Pediatric patients differ from adults in the complex physiology and biochemistry of growth and development, organ and body sizes, diseases unique to pediatric practice, and radiation dosimetry.[2-5]

With the combination of short-lived radiopharmaceuticals, such as $^{99m}$Tc- and $^{123}$I-labeled agents, and the sensitivity of the instrumentation, an acceptable activity dosage can be administered which yields useful diagnostic information.[6] In choosing the radiopharmaceutical and dosage administered, the concept of benefit gained versus risk of radiation exposure must be embraced. Relative to an adult, the dosage of radioactivity has to be reduced, and it must be based on the patient's weight or body surface area.[3,6] However, there is a minimal acceptable dosage that has to be administered in order to provide a successful diagnostic examination.[2,3,6] If insufficient activity is administered resulting in a non-diagnostic study, the patient has been exposed to radiation without the benefit of

**ABBREVIATIONS** CT, Computed tomography; FDG, $^{18}$F-fluorodeoxyglucose; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; RNA, radionuclide angiography; SPECT, single photon emission computed tomography; $^{99m}$Tc-DISIDA, $^{99m}$Tc-disofenin; $^{99m}$Tc-MAA, $^{99m}$Tc-labeled human serum albumin macroaggregrates; $^{99m}$Tc-DTPA, $^{99m}$Tc-pentetate; $^{99m}$Tc-MDP, $^{99m}$Tc-medronate; $^{99m}$Tc-MAG$_3$, $^{99m}$Tc-mertiatide; VCUG, voiding cystourethrogram

Address correspondence to: Vivian Loveless, PharmD, 26 S Dunlap, Feurt Research Bldg, Suite 214, Memphis, TN 38163, email: vloveless@utmem.edu

receiving diagnostic information. In this situation a repeat study would have to be performed which includes a second administration of the radiopharmaceutical resulting in the patient receiving more radiation than he/she would have if an acceptable radioactivity dosage had been administered initially. Likewise, there is also possible exposure to a second course of procedural sedation.

It is necessary in some nuclear medicine procedures for the patient to remain still for 15 to 60 minutes thus posing a problem in patients unable or unwilling to cooperate. Conscious sedation of the patient is helpful in these types of situations. The nuclear medicine facility must be equipped to administer the required medications, handle emergency situations due to sedation, and have adequate nursing professionals monitor the patients. Policies and procedures have to be in place to address issues concerning sedation of pediatric patients, and these would already be in place in dedicated pediatric facilities as opposed to facilities whose primary patient population is adults.[2,6]

## DIAGNOSTIC IMAGING MODALITIES

The topic of diagnostic imaging encompasses radiography, magnetic resonance imaging (MRI), ultrasonography, and nuclear medicine. Radiography is an X-ray based modality that may or may not utilize radiopaque contrast media, and it involves the generation of X-rays which are passed through the patient's body to produce images of internal organs and vasculature. The basic principle of operation is that the radiation interacts with the body's tissues through excitation and ionization, and the degree of interaction is dependent on the radiation energy as well as the density and atomic number of body tissue. Less dense tissue permits more radiation to pass through whereas high density tissue, such as bone, blocks the passage of radiation. The detection of a bone fracture is possible because a greater amount of radiation passes through the break as compared to the intact bone. Computed tomography (CT) also involves the passage of X-rays through the body but this image is created when X-rays are transmitted through the tissue from multiple directions. The result is an image with far greater resolution, i.e., the ability to see small tissue differences better than other radiographic X-ray modalities. MRI does not involve ionizing radiation but exposes the patient to a strong magnetic field, and it provides high resolution anatomical information. Contrast agents, paramagnetic pharmaceuticals, may or may not be utilized with this study. Another modality not involving ionizing radiation is ultrasonography which presents no known hazard to the fetus during obstetrical exams. With this procedure a transducer is utilized to emit sound waves that are reflected back from organs and tissues and then captured. With the use of a computer, the sound wave's image is reconstructed and displayed on a monitor. Even though the resolution and clarity are not as great as CT or MRI, it provides information about the fetus or an abnormality in the fetus.[7]

Nuclear medicine imaging studies involve the administration of ionizing radiation in the form of radioactive drugs (radiopharmaceuticals) to the patient, and the biodistribution of these agents is most commonly detected by means of a gamma camera. This modality includes planar imaging, single photon emission computed tomography (SPECT), and positron emission tomography (PET). SPECT utilizes a specially designed gamma camera to produce tomographic images. The most common type of radiopharmaceutical utilized in nuclear medicine imaging (scintigraphy) is a technetium-99m, $^{99m}$Tc, radiolabeled pharmaceutical. $^{99m}$Tc has a six hour half-life which is a suitable half-life for imaging, and it also emits a 140 keV gamma photon which is easily detected by the gamma camera. $^{99m}$Tc can be radiolabeled to a variety of ligands which determine the biodistribution within the body. PET imaging is limited to positron emitting radiopharmaceuticals that yield annihilation photons which are detected utilizing even more sophisticated instrumentation than the type used in traditional nuclear medicine. Even though nuclear medicine provides anatomical information, it does not compare to the high resolution obtained with CT or MR imaging. Nuclear medicine scintigraphy's advantage is that it provides functional (metabolic) information prior to anatomic change.[7] The use of a PET/CT camera provides both functional

and anatomical information. Since both CT and PET imaging are utilized, this results in significantly more radiation exposure than using only one modality.

A radiopharmaceutical is a radioactive, legend drug that can only be prescribed by a physician who is an authorized user of radioactive materials for medical application. A radiopharmaceutical is a chemical substance containing radioactive atoms within its structure and is suitable for administration to humans for diagnosis or treatment of disease.[8] This article's scope is limited to diagnostic nuclear medicine. Because diagnostic radiopharmaceuticals are administered in extremely small quantities, toxicity is not as great a concern as with traditional drugs.[8] (An exception to this will be presented when $^{99m}$Tc-MAA is covered in pulmonary perfusion imaging.) A pharmacologic response is not elicited by a standard diagnostic radiopharmaceutical dosage. Thus, FDA does not generally require as extensive premarket testing to identify acute and chronic toxic effects of radiopharmaceuticals as it does for traditional pharmaceuticals.[8]

## BRAIN SCINTIGRAPHY

Radiopharmaceuticals for evaluating the central nervous system can be categorized as follows: diffusible agents, nondiffusible agents, metabolism agents, cerebrospinal fluid agents, and receptor imaging agents.[9] This topic is limited to the those radiopharmaceuticals that are either diffusible agents, nondiffusible agents, or metabolic agents.

$^{99m}$Tc-exametazime and $^{99m}$Tc-biscisate are two brain imaging agents useful for depicting and/or measuring regional cerebral blood flow with SPECT. These diffusible agents are lipophilic and thus cross an intact blood-brain barrier; however, pharmacokinetics of elimination differ for each. After crossing the blood-brain barrier, the agents' regional uptake and retention reflect the regional perfusion at the time of injection. After crossing the blood-brain barrier, these agents lose their lipophilicity and are retained in the brain in their original biodistribution for several hours.[9,10] Retaining the biodistribution at the time of injection allows the radiopharmaceutical to be administered during a seizure and then imaged after the acute event.[10] Focal epileptogenic sites have been identified by alterations in the regional cerebral blood flow. The demonstration of a hypoperfused focus after injection during the interictal state is not as sensitive in detecting an epileptogenic focus as compared to an injection made during the ictal phase, which identifies the focus usually as an increase in blood flow.[2,11]

Radiopharmaceuticals can provide functional assessment of epilepsy using 2 techniques, SPECT and PET. The method chosen is likely to be determined by local availability, and this indication is usually limited to those pediatric patients being considered as surgery candidates. However, functional neuroimaging utilizing SPECT or PET may not be required when clinical evaluation, electroencephalography, and high resolution MRI infer unilateral mesial temporal sclerosis. When using the SPECT technique, a diffusible agent, such as $^{99m}$Tc- exametazime, is used, and the biodistribution represents the regional cerebral blood flow. This pattern of distribution can identify epileptogenic foci both interictally and ictally. The SPECT findings have to be correlated with those of any other cross-sectional imaging technique, such as MR imaging. When PET is utilized, $^{18}$F-fluorodeoxyglucose (FDG), a metabolic agent, allows evaluation of the cerebral metabolic rate of glucose utilization as demonstrated by the uptake of the $^{18}$F-FDG. Primarily, interictal studies have been conducted since it is difficult to evaluate ictal states due to the uptake of $^{18}$F-FDG occurring over 45 minutes. With PET scans, areas of decreased uptake (hypometabolism) are indicative of pathology.[11]

Another accepted use for $^{18}$F-FDG is in the evaluation of a patient for a brain tumor or recurrence. An increase in activity relative to surrounding area, or hypermetabolic activity, is suspicious for a neoplasm. Figure 1 is a study of a 7-year-old patient being evaluated for recurrence of anaplastic astrocytoma after having the tumor surgically removed. In this case there is an absence of radioactivity involving a portion of the right occipital/parietal region due to the post surgical cystic encephalomalacia. This study is negative for recurrence. The PET scanner acquires images throughout multiple slices of the brain, and the images are displayed for the physician's interpretation.

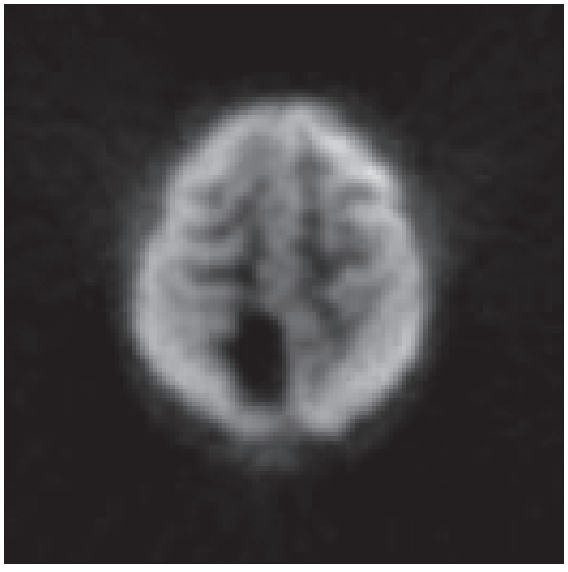

**Figure 1.** A 7-year-old patient being evaluated for recurrence of anaplastic astrocytoma following surgical resection of the tumor. The absence of radioactivity involving a portion of the right occipital/parietal region due to the post surgical cystic encephalomalacia suggests there is no recurrence of disease.

Figure 2 provides a sample of 3 of the slices through the brain in the same patient.

Radionuclide cerebral perfusion studies can be used to aid in the diagnosis of brain death as demonstrated by the lack of uptake in the cerebral cortex. Sodium $^{99m}$Tc-pertechnetetate and $^{99m}$Tc-pentetate ($^{99m}$Tc-DTPA) are non-diffusible agents that do not cross an intact blood-brain barrier, and are normally demonstrated only in vascular brain structures. Alternatively, $^{99m}$Tc-exametzime or $^{99m}$Tc-bicisate can be used. Delayed planar images are obtained at 10 minutes to 2 hours post-injection with either class of brain agent. The study report states whether cerebral perfusion is present or absent.[2,10]

## MUSCULOSKELETAL SCINTIGRAPHY

The mechanism of incorporating $^{99m}$Tc-labeled diphosphonates into bone is not completely understood, but it is thought that the main variables influencing uptake are regional blood flow, osteoblastic activity, and extraction efficiency.[12] Important factors in binding of the radiopharmaceutical to bone are the bone surface chemical composition and the structural properties of the $^{99m}$Tc complex. It is thought that the diphosphonate complexes interact with bone by binding to $Ca^{++}$ ions present in bone crystals.[13] There is a high sensitivity for identification of skeletal pathology with these radiopharmaceuticals, but without the necessary clinical history, the specificity is relatively low. Specificity can be improved if the clinical history is known along with the results of physical examination, laboratory tests, and other imaging studies.[2] Adequate hydration, if not contraindicated by the patient's condition, is desirable for bone imaging.[14] Diphosphonates are excreted via the kidneys so by increasing hydration and voiding frequently, the background activity is decreased.[13] Also, frequent voiding is encouraged to decrease the gonadal radiation dose.[15] The patient should void immediately prior to imaging, especially if pelvic imaging is necessary, in order to prevent activity in bladder from overshadowing the pelvic bones.[14]

Two major indications for the nuclear scintigraphy in benign bone diseases are pain and fever/infection. Covered in this section will be the use of bone imaging in the diagnosis of osteomyelitis, cellulitis, septic arthritis, Legg-Perthes' Disease, and trauma. Prior to a nuclear medicine study being conducted, a plain film X-ray study should be performed, and it is not uncommon for a CT study to be obtained for the detection and characterization of a lesion.[4] Also, scintigraphy is useful for detecting metastatic disease from a primary bone malignancy, and the radiopharmaceuticals used for this indication are diphosphonates and $^{18}$F-FDG.

Bone scintigraphy with $^{99m}$Tc-labeled diphosphonate, such as $^{99m}$Tc-medronate ($^{99m}$Tc-MDP), usually demonstrates osteomyelitis as a focal area of increased uptake on the delayed images, representing increased metabolic activity.[4] A corresponding area of increased activity is seen on blood pool imaging representing hyperemia of the affected site.[4] Rarely, edema may decrease blood flow resulting in a normal study or low uptake of the radiopharmaceutical in acute osteomyelitis. In this situation the bone study can be repeated after a delay of 48 hours, or other imaging studies such as imaging with $^{67}$Ga, radiolabeled leukocytes, or MR imaging should be performed.[2] Figure 3 is an example of a $^{99m}$Tc-MDP bone study of a 15-year-old male with osteomyelitis of the right knee.

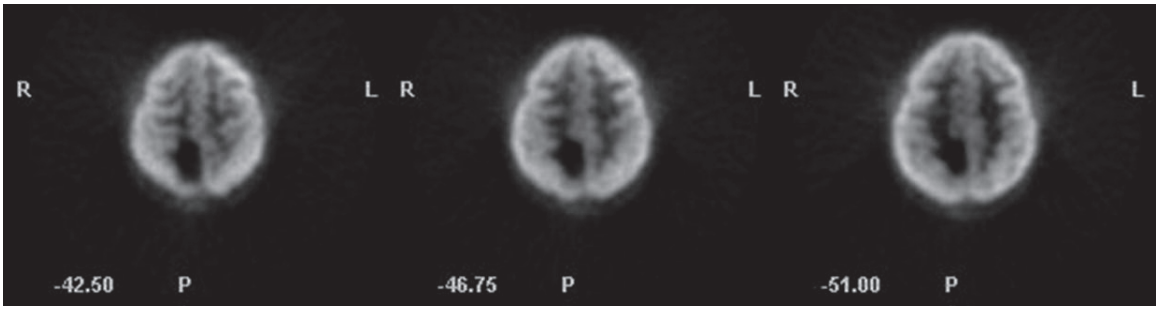


**Figure 2.** Three of the slices through the brain in the same patient described in Figure 1.

Diphosphonate bone imaging of cellulitis exhibits increased blood flow and blood pool but no significant bone uptake on the delayed imaging.[13] With septic arthritis there is an increase in radioactivity in the periarticular areas involving both sides of the joint, and the radionuclide angiogram's early images show inflammatory signs.[2,4]

Avascular necrosis of the proximal femoral capital epiphysis, Legg-Calvé-Perthes' disease, is thought to be a result of interruption of blood supply in the area of the proximal femoral epiphysis. Lack of $^{99m}$Tc-MDP uptake is used to demonstrate avascularity associated with this disease process. This is usually detected with radiographs; however, if the radiographic study is normal or demonstrates mild capsular distention, MR imaging has been shown to be the primary method to evaluate the hip. Nuclear medicine scintigraphy is useful as an adjunct in the determination of the degree of viability or the identification of avascular necrosis in the event the MRI study is inconclusive.[2,4]

Immediately after bone has been subjected to trauma, it undergoes a reparative process, and bone scintigraphy conducted 24 to 48 hours later can yield increased uptake of $^{99m}$Tc-MDP at the site of injury. Even though the scintigraphy results are nonspecific, lesions can be characteristic of a specific diagnosis given the correct clinical setting.[2,15,16]

Stress reaction occurs when osteoclastic activity is in excess of osteoblastic repair, and it can cause cortical disruption. This type of fracture can occur in active people such as athletes and dancers. When a patient presents with a suspected stress fracture, bone scintigraphy approaches 100% in sensitivity and specificity, and this modality is recommended for both whole body and regional screening. When the stress fracture is causing back pain, it has been documented that SPECT imaging is more useful than planar imaging.[2,15]

In the assessment of suspected physical child abuse, skeletal scintigraphy is complimentary to radiographic survey.[16] With a single injection of a $^{99m}$Tc-labeled diphosphonate, skeletal survey of the entire body is possible. Child abuse trauma can have a characteristic pattern on scintigraphy since the long bones, ribs, and skull are the most frequent sites associated with this type of injury.[2,4,16]

Osteosarcoma is a malignancy involving the osteoid and osseous tissue, and it is primarily found in individuals in the age range of 10 to 25 years. The initial diagnosis of this malignancy is made with radiographs; however, the appearance on plain film X-ray studies can be indistinguishable from other diseases such as chronic osteomyelitis. Scintigraphy aids in demonstrating the extent of the primary tumor, which is beneficial in planning the treatment as well as detection of local recurrence, metastatic lesions, or therapeutic complications.[2,4,15] Figure 4 depicts an $^{18}$F-FDG study of a 17-year-old female with a history of osteosarcoma of the left tibia. The current study demonstrates a partially calcified metastatic lesion in the right thigh.

Follow-up of a primary malignancy with $^{99m}$Tc-labeled diphosphonate radiopharmaceutical scintigraphy is limited because the image remains positive due to ongoing bone remodeling.[4] Also, skeletal scintigraphy is used in determination of metastatic disease in Ewing's sarcoma. Skeletal metastatic lesions are detected as an increase in localization of $^{99m}$Tc-MDP, and these lesions may be present at the time of diagnosis in 10% to 20% of this patient population.[2,15]

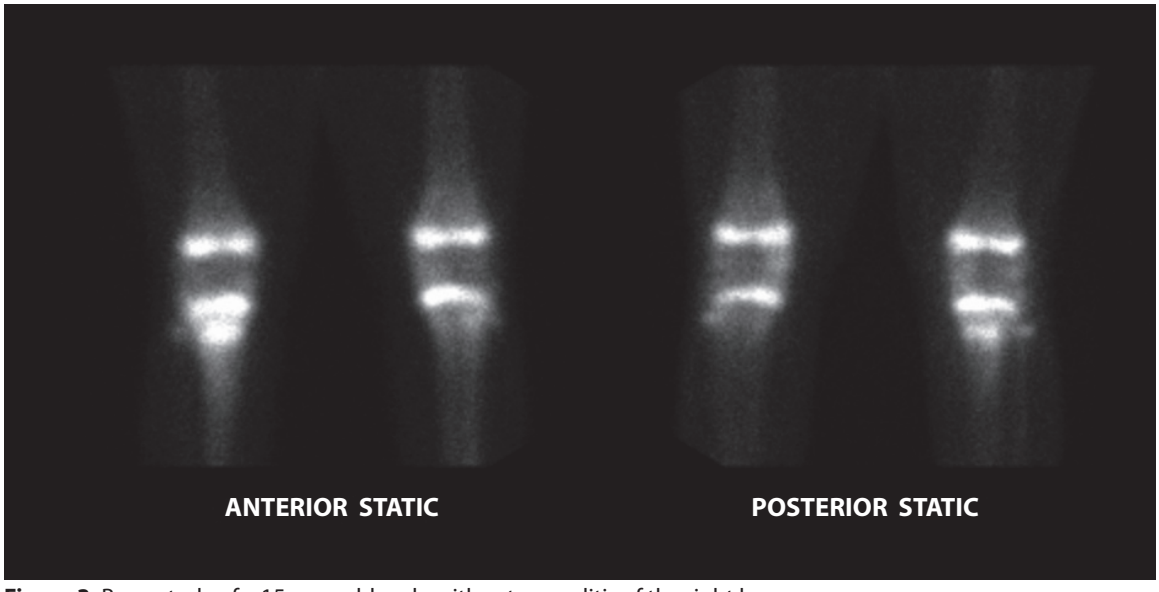


**Figure 3.** Bone study of a 15-year-old male with osteomyelitis of the right knee.

## GENITOURINARY SCINTIGRAPHY

Scintigraphy's role in genitourinary disorders encompasses the evaluation of renal cortical lesions, hydronephrosis, urinary reflux, and scrotal pain. The radiopharmaceuticals used in these studies are radiolabeled with technetium Tc99m. The choice of agent is based on the pharmacokinetics of the radiopharmaceutical.

Common indications for renal cortical imaging include acute pyelonephritis, renal scarring, relative functioning of a renal mass, solitary or ectopic renal tissue, horseshoe and pseudohorseshoe kidneys, and allergic reaction to iodinated radiographic contrast agents.[17,18] Two radiopharmaceuticals used for renal cortical imaging are $^{99m}$Tc-succimer ($^{99m}$Tc-DMSA) and $^{99m}$Tc-gluceptate.

After intravenous administration of $^{99m}$Tc-succimer, the majority of the dose is loosely bound to plasma protein, and there is little or no diffusion into erythrocytes.[18] At two hours post injection, 16% of the dose undergoes renal excretion and 40% to 65% is bound to the cells of the proximal convoluted tubules. The mechanism of localization has been demonstrated to be fixation within the cortical cells after extraction from the peritubular blood. There is improved resolution of cortical defects due to the significant amount of radiopharmaceutical localization within the cortex. $^{99m}$Tc-gluceptate is 50% to 75% loosely bound to plasma proteins at 1 to 6 hours post administration. By 2 hours, 50% of the injected dose is excreted in the urine, and 10% to 20% of the dose has localized within the cortical proximal convoluted tubules. Also, 40% to 65% of the administered radiopharmaceutical undergoes glomerular filtration.[17,18] $^{99m}$Tc-succimer is considered the radiopharmaceutical of choice for cortical scintigraphy.[19]

The nuclear medicine physician evaluates the images according to the size, position, and morphology of the functioning renal tissue. It should be noted that using cortical radiopharmaceuticals permits vesicoureteral reflux or retained radioactivity in the collecting systems to interfere with determination of the percent differential renal function. When the patient has a capacious collecting system or has an obstructed system, furosemide can be given before the delayed imaging to facilitate interpretation. An alternative to this would be to image the patient 24 hours after the radiopharmaceutical administration. Catheterization with continuous drainage is needed when there is retained activity in the collecting system as a result of a back pressure effect of a very distended neurogenic bladder.[17]

Diuretic renography is indicated in the evaluation of hydronephrosis to determine if the etiology is due to obstructive or nonobstructive causes.[20] The child should be well

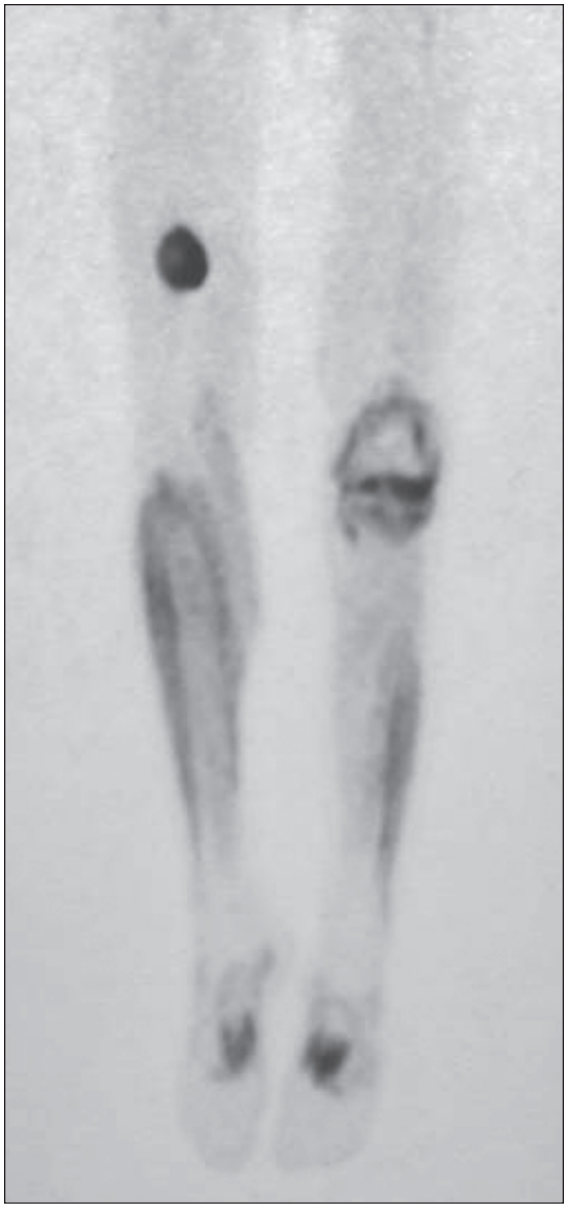

**Figure 4.** A 17-year-old female with metastatic lesion in right thigh abutting the femur.

hydrated so if the patient is not going to be administered intravenous fluids, oral hydration is recommended prior to arrival and while in the nuclear medicine department.[20] For the diuretic phase, the pediatric patient is administered furosemide 1 mg/kg, with 40 mg being the usual maximum dose.[20,21] In cases of severe renal failure, a greater diuretic dose may be necessary.[20] The two radiopharmaceuticals used in pediatric renography are $^{99m}$Tc-pentetate ($^{99m}$Tc-DTPA) and $^{99m}$Tc-mertiatide ($^{99m}$Tc-MAG$_3$). $^{99m}$Tc-DTPA undergoes glomerular filtration almost entirely while $^{99m}$Tc-MAG$_3$ is rapidly excreted via tubular secretion.[18,20] In comparison to $^{99m}$Tc-DTPA, $^{99m}$Tc-MAG$_3$ has a higher extraction fraction so that at the time of diuretic administration, less $^{99m}$Tc-MAG$_3$ will be entering the kidney from the blood resulting in less compromise of the washout curve due to radiopharmaceutical entering the kidney from the blood.[21] $^{99m}$Tc-MAG$_3$ provides a high initial renal uptake, thus yielding high target-to-nontarget ratios with good temporal resolution.[20] These considerations make $^{99m}$Tc-MAG$_3$ the radiopharmaceutical recommended for neonatal renography and patients whose renal function is impaired.[21]

Radionuclide cystography is useful in evaluating vesicoureteral reflux, and the radiation dose to the gonads is significantly less than a voiding cystourethrogram (VCUG or VCU), a conventional radiographic procedure. Radionuclide cystography can either be conducted via the direct method or indirect method.[4,22]

The direct method requires bladder catheterization and instillation of a non-absorbable radiopharmaceutical ($^{99m}$Tc-pertechnetate, $^{99m}$Tc-MDP, or $^{99m}$Tc-DTPA) mixed with saline or irrigating solution. Imaging is conducted during filling, voiding, and post voiding.[4,22] Direct radionuclide cystography is equal to or better than VCUG for the detection rate of reflux; however, VCUG provides superior anatomic detail.[4,22] Of the two methods of radionuclide cystography, the direct method is preferred.[4]

Bladder catheterization is not necessary with the indirect method of radionuclide cystography. With this method either $^{99m}$Tc-MAG$_3$ or $^{99m}$Tc-DTPA is administered intravenously, and imaging is performed for the evaluation of renal function as well as urine drainage. Imaging is continued during the voiding phase for the detection of vesicoureteral reflux. A high rate of failure has been observed with the indirect method since the child either cannot void at the designated time or may not be able to void at all. Even though this method is more physiological, it has a false negative rate of 41% in identifying reflux. Reflux may be masked if pelvic dilatation is present resulting in retention of radioactive urine.[4,22]

An ischemic condition of the scrotum, such as acute testicular torsion, requires surgery

whereas inflammatory processes, such as acute epididymitis, do not. Scrotal scintigraphy aids in differentiation between the two, but it does not replace the urologist's clinical assessment. It is indicated when there are equivocal findings with the urologist's examination and the Doppler ultrasonography study.[2,23] $^{99m}$Tc-pertechnetate is the radiopharmaceutical used, and the study consists of a flow phase (radionuclide angiogram) and a tissue phase (static imaging). Fifteen to thirty minutes before imaging, if time permits, the patient receives potassium perchlorate orally in a dose to prevent radiation exposure to the thyroid gland by blocking uptake.[2,23] Increased radiopharmaceutical uptake is evident in both the radionuclide angiogram and static imaging with acute epididymitis. The radionuclide angiogram is generally normal with acute testicular torsion; there is rarely an apparent decrease in the blood flow in acute torsion. However, the tissue phase has low or absent activity at the site of the affected testis. It must be kept in mind that the scintigraphic findings in acute testicular torsion are dependent on the elapsed time from the acute event.[2,24,25]

## GASTROINTESTINAL SCINTIGRAPHY

This section includes the use of the various radiopharmaceuticals in the evaluation of gastroesophageal reflux, gastric emptying disorders, pulmonary aspiration, Meckel's diverticulum, and hepatobiliary disease. A variety of radiopharmaceuticals are used but all share the common characteristic of being radiolabeled with technetium Tc99m.

A gastric emptying study is indicated in patients who have gastroesophageal reflux, abdominal pain, loss of appetite, weight loss, vomiting, failure to thrive, asthma and/or wheezing.[2,14] This study can be performed by adding $^{99m}$Tc-sulfur colloid to the child's milk or formula and acquiring images after the child has ingested the feeding. It is important that the volume administered, temperature, and feeding time correspond to the child's usual feeding. Serial images are obtained during the first hour every 30 seconds, and then images are acquired at 2, 4, 6, and 24 hours if needed for delayed emptying. With the aid of a computer, time-activity curves are generated for the evaluation of reflux and gastric emptying.[2]

Salivagraphy can be useful in detecting aspiration. This study is performed by administering sublingually a small drop of $^{99m}$Tc-sulfur colloid (100 μCi) that mixes with the child's saliva. After administration of the radiopharmaceutical, the patient is placed in the supine position to facilitate imaging of the oropharynx, the chest, and upper abdomen. The movement of the radioactive saliva is then observed as it moves through the esophagus into the stomach. With pulmonary aspiration, the radiopharmaceutical is observed in the major bronchi. In severe cases, the radiopharmaceutical can even be demonstrated in the periphery of the lungs. Delayed imaging may be necessary when aspiration is not seen immediately because of aspiration occurring after the initial swallow. If aspiration is not observed on delayed imaging, this does not rule out aspiration since coughing could clear the aspirate. When insufficient radioactive saliva is present in the stomach at the time of reflux and aspiration, a false negative study can also result.[2,26]

Meckel's diverticulum is a congenital anomaly that is a common cause of a gastrointestinal bleed. Meckel's diverticula contain ectopic gastric mucosa 10% to 30% of the time,[26] but usually ileal mucosa is present.[2] However, Meckel's diverticula can also contain pancreatic tissue, duodenal mucosa, jejunal mucosa, and colonic mucosa. When $^{99m}$Tc-pertechnetate is administered intravenously, approximately 20% of the dose accumulates in the gastric mucosa.[2] The time of activity appearing in ectopic gastric mucosa parallels the time of normal gastric mucosa accumulation. To increase the sensitivity and specificity of the study by promoting retention of the radiopharmaceutical within the gastric mucosa, ranitidine is administered intravenously 1 hour prior to the examination.[4]

The most common indication for pediatric hepatobiliary imaging is the evaluation of neonatal jaundice. In the majority of infants undergoing hepatobiliary scintigraphy, neonatal hepatitis or biliary atresia is the differential diagnosis. Biliary atresia requires surgical treatment while neonatal hepatitis does not. For 5 days prior to administration of either $^{99m}$Tc-disofenin ($^{99m}$Tc-DISIDA) or $^{99m}$Tc-mebrofenin, the infant can be pretreated with

phenobarbital for the purpose of enhancing liver excretion, which demonstrates a patent biliary tree by passage of radioactivity into the bowel.[4,27] Biliary atresia usually demonstrates normal liver uptake of the radiopharmaceutical in patients younger than 2 months of age unless severe hepatic dysfunction is present. Excretion of the radiopharmaceutical into the bowel rules out the possibility of biliary atresia. If radioactivity is not visualized in the bowel on imaging up to 24 hours, then a distinction cannot be established between biliary atresia and severe hepatocellular disease.[27] Neonatal hepatitis typically exhibits decreased hepatic uptake and delayed clearance of the radiopharmaceutical with bowel activity within 24 hours.[4]

## ENDOCRINE SCINTIGRAPHY

In this section, the topics are limited to congenital hypothyroidism and neuroblastoma as well as the radiopharmaceuticals used in the diagnosis of these disease states. A radionuclide that has previously not been covered in this article will be introduced in this section. It is sodium iodide $^{123}$I, and the body cannot distinguish it from stable iodide. This radionuclide has a half-life of 13.2 hours and favorable radioactive decay characteristics for detection.

Newborns with abnormal thyroid laboratory profiles can be referred for thyroid imaging.[14] The two radiopharmaceuticals that are used in evaluation of the thyroid gland in children are sodium iodide $^{123}$I and sodium pertechnetate $^{99m}$Tc. Schoen et al. conducted a study using thyroid scintigraphy in defining and managing congenital hypothyroidism, and these investigators found $^{123}$I to be superior to $^{99m}$T-pertechnetate. The study time period was in excess of 25 years and included 210 infants. No increase in risk of thyroid cancer was found in this group of patients. Treatment of congenital hypothyroidism does not have to be delayed while awaiting the nuclear medicine study. The validity of thyroid scintigraphy for the evaluation of congenital hypothyroidism is dependent on the patient's thyroid stimulating hormone (TSH) level being normal or elevated. The TSH level continues to be elevated for many days after initiation of the treatment so scintigraphy can be conducted during this time period.[28] Also, thyroid scintigraphy is used in children to determine the level of functioning of thyroid masses. The pattern of radioiodine accumulation aids in the diagnosis and treatment planning.[2]

In childhood, the most common type of extracranial malignant solid tumor is neuroblastoma. This tumor originates from neural crest derivatives in the adrenal medulla or from the sympathetic nervous system.[29,30] Sympathetic neuroeffector cells take up metaiodobenzylguanidine (MIBG) in a manner similar to the uptake of norepinephrine; however, unlike norepinephrine, there is no interaction between MIBG and postsynaptic α and β adrenergic receptors.[31]

Radioiodinated MIBG scintigraphy has proven useful in diagnosing and staging neuroblastoma and in the assessment of therapy response. For diagnostic imaging, the preferred radioisotope of iodine to use in radiolabeling MIBG is $^{123}$I as opposed to $^{131}$I since the whole-body radiation dosimetry for $^{123}$I-MIBG is about 5% of $^{131}$I-MIBG, and $^{123}$I has superior imaging characteristics.[29] Unlike $^{131}$I-MIBG, $^{123}$I-MIBG is not available commercially, and it has to be made extemporaneously. Staging sensitivity ranges from 90% to 95%, while specificity of this modality for detecting neuroblastoma approaches 100%.[29]

Because free radioiodide results from the *in vivo* deiodination of radiolabeled MIBG, the thyroid gland will take up the radioiodide, resulting in increased radiation exposure to the thyroid gland, unless it is blocked.[29] To decrease thyroid uptake of free radioiodide, potassium iodide is given orally starting preferably the day prior to the injection of $^{131}$I-MIBG and continuing for 1 week post-administration of $^{131}$I-MIBG.[29] For diagnostic doses of radiolabeled MIBG, the dose of potassium iodide is 32 mg every day for patients 1 month to 3 years of age, 65 mg for patients 3 to 13 years of age, and 130 mg for patients older than 13 years.[29] The recommended dose for newborns is 16 mg only on the day prior to radiopharmaceutical administration.[29] Bonnin et al. reported administering potassium iodide to 24 children ranging in age from newborn to 10 years of age for three days before and three days after the injection of $^{123}$I-MIBG.[32]

A large number of pharmaceuticals block the uptake of MIBG. Included are catecholamine agonists, antipsychotics (thiothixines and phenothiazines), tricyclic antidepressants, calcium channel blockers, a few long-acting beta-blockers, drugs of abuse (cocaine), and those that deplete stores of catecholamines in neurosecretory storage granules.[33]

## PULMONARY SCINTIGRAPHY

Pulmonary scintigraphy involves a perfusion phase performed with $^{99m}$Tc-labeled human serum albumin macroaggregrates ($^{99m}$Tc-MAA) and a ventilation phase using either $^{133}$Xe gas or $^{99m}$Tc-pentetate ($^{99m}$Tc-DTPA) as an aerosol. $^{99m}$Tc-MAA is administered intravenously while $^{133}$Xe and $^{99m}$Tc-pentetate are administered by inhalation. There are a variety of indications for pulmonary imaging including, but not limited to, evaluation of regional pulmonary perfusion and ventilation before and/or after lung surgery, pulmonary aspiration, and cystic fibrosis. Perfusion scintigraphy has proved useful in evaluating children with recurrent localized pneumonia for a potential structural abnormality. $^{67}$Ga citrate and radiolabeled leukocyte imaging are useful in identifying and quantifying pulmonary infections in pediatric patients. Even though white blood cells can be radiolabeled with either $^{99m}$Tc or $^{111}$In, the $^{99m}$Tc label is preferred due to its more favorable radiation dosimetry characteristics, i.e., lower radiation dose.[2]

$^{99m}$Tc-MAA is a particulate radiopharmaceutical localizing in the pulmonary vessels via capillary blockade. The USP requirements are that 90% of the observed MAA particles have a diameter ranging from 10 μm to 90 μm with none of the observed particles having a diameter in excess of 150 μm.[34] In addition to the radioactivity being adjusted from the adult dose, the number of particles administered has to be decreased for the pediatric patient in order to prevent particle toxicity. Heyman reported that during the first few years of life there is a significant increase in the number of alveoli and pulmonary arteries, obtaining adult levels at approximately 8 years of age. His recommendation was to limit newborns to 50,000 MAA particles and children up to 1 year of age to 165,000.[35]

## CARDIOVASCULAR SCINTIGRAPHY

Scintigraphy of the cardiovascular system of pediatric patients can be used for evaluating myocardial perfusion as well as monitoring cardiac function.[2,14,36,37] Indications for cardiac blood pool imaging performed with $^{99m}$Tc-labeled erythrocytes include evaluation of left ventricular ejection fraction, cardiomyopathies, and assessment of chemotherapy cardiotoxicity.[2,14] Indications for pediatric myocardial perfusion imaging include evaluation of anomalous left coronary artery, cardiomyopathies, impaired myocardial blood flow present in Kawasaki disease, and postoperative evaluation of cardiac surgery. Radiopharmaceuticals used in myocardial perfusion include $^{99m}$Tc labeled radiopharmaceuticals, such as $^{99m}$Tc-sestamibi and $^{99m}$Tc-tetrofosmin, and thallous chloride $^{201}$Tl.[2,36,37]

## CONCERNS FOR THE EMBRYO/FETUS AND NURSING CHILD

The embryo/fetus can be exposed to ionizing radiation from the mother undergoing a nuclear medicine procedure or an X-ray procedure. It is the physician's responsibility to determine if the benefit the mother receives from the procedure outweighs the risk incurred by the radiation exposure to both the mother and fetus. In making the decision, the physician uses the absorbed dose estimate to the embryo/fetus from a nuclear medicine examination and considers other factors concerning the patient.[38] Another source of radiation exposure to children is via nursing if the mother has been administered a radiopharmaceutical. The nursing child could consume the radioactivity from the milk if the radionuclide or radiopharmaceutical is secreted in the breast milk. Based on the radiation exposure to the child, a decision has to be made whether the child will cease breastfeeding temporarily or permanently.[39,40] Also, radiation exposure from the mother's body can result in exposure to the child by the mother just holding the child, so the mother should be advised to minimize holding the child during the radiation exposure period.[39]

## CONCLUSION

The nuclear medicine procedures described

above are to provide the reader with an introduction to the usefulness of nuclear medicine scintigraphy in the pediatric population; it is beyond the scope of this article to address all the pediatric nuclear medicine procedures.

Pediatric nuclear medicine procedures provide useful diagnostic information for all ages of children, and the information obtained outweighs the radiation risk as long as the appropriate radiopharmaceutical selection and dosing guidelines are followed.

**DISCLOSURE** The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

## REFERENCES

1. Nadel HR. Pediatric Nuclear Medicine: Why are children not small adults? Presentation at: American Pharmacists Association Annual Meeting and Exposition; April 1 – 5, 2005; Philadelphia, PA
2. Treves ST, Connolly LP, O'Tuama LA, et al. Pediatrics. In: Wagner HN, Szabo Z, Buchanan JW, eds. Principles of Nuclear Medicine. Philadelphia, PA: W.B. Saunders Company; 1995:1137-1170.
3. Taylor A, Schuster DM, Alazraki N. Pediatrics. In: A Clinician's Guide To Nuclear Medicine. Reston, VA: Society of Nuclear Medicine, Inc.; 2000:245-247.
4. Gilday D. Pediatric nuclear medicine. In: Leslie WD, Greenberg ID, eds. Nuclear Medicine. Georgetown, TX: Landes Bioscience; 2003:365-383.
5. Freeman LM, Blaufox MD. Letter from the editors. Semin Nucl Med 1993;23:265.
6. Weiss SC. Radiopharmaceuticals for pediatric imaging. In: Henkin RE, Boles MA, Dillehay GL, et al., eds. Nuclear Medicine. St. Louis, MO: Mosby-Year Book, Inc.; 1996:1685-1689.
7. Shaw S. Diagnostic imaging: an overview for the pharmacist. J Am Pharm Assoc (Wash) 1997;NS37:99-108.
8. Kowalsky RJ, Falen SW. Radiopharmaceuticals, nuclear medicine, and nuclear pharmacy: an overview. In: Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine, 2nd ed. Washington, D.C.: American Pharmaceutical Association; 2004:1-15.
9. Kowalsky RJ, Falen SW. Brain. In: Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine, 2nd ed. Washington, D.C.: American Pharmaceutical Association; 2004:451-494.
10. Taylor A, Schuster DM, Alazraki N. The central nervous system. In: A Clinician's Guide To Nuclear Medicine. Reston, VA: Society of Nuclear Medicine, Inc.; 2000:153-180.
11. Wright NB. Imaging in epilepsy; a paediatric perspective. Br J Radiol 2001;74:575-89.
12. Forstrom LA. Infection-bone. In: O'Connor MK, ed. The Mayo Clinic Manual of Nuclear Medicine. New York, NY: Churchill Livingstone; 1996:425-458.
13. Kowalsky RJ, Falen SW. Bone. In: Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine, 2nd ed. Washington, D.C.: American Pharmaceutical Association; 2004:671-693.
14. Veitch TA. Pediatric nuclear medicine, part II: common procedures and considerations. J Nucl Med Technol 2000;28:69-75.
15. Conolly LP, Treves ST, Convway JJ. Pediatric skeletal scintigraphy. In: Henkin RE, Boles MA, Dillehay GL, et al., eds. Nuclear Medicine. St. Louis, MO: Mosby-Year Book, Inc.; 1996:1690-1724.
16. Conway JJ, Collins M, Tanz RR, et al. The role of bone scintigraphy in detecting child abuse. Semin Nucl Med 1993;23:321-333.
17. Mandell GA, Eggli DF, Gilday DL, et al. Procedure guideline for renal cortical scintigraphy in children. J Nucl Med 1997;38:1644-1646.
18. Kowalsky RJ, Falen SW. Kidney. In: Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine, 2nd ed. Washington, D.C.: American Pharmaceutical Association; 2004:633-670.

19. Piepsz A, Blaufox MD, Gordon I, et al. Consensus on renal cortical scintigraphy in children with urinary tract infection. Semin Nucl Med 1999;29:160-174.
20. Mandell GA, Cooper JA, Leonard JC, et al. Procedure guideline for diuretic renography in children. J Nucl Med 1997;38:1647-1650.21.
21. Taylor A. Radionuclide renography: a personal approach. Semin Nucl Med 1999;29:102-127.
22. Mandell GA, Eggli DF, Gilday DL, et al. Procedure guideline for radionuclide cystography in children. J Nucl Med 1997;38:1650-1654.
23. Ziessman HA, Rehm P. In: Case Review Nuclear Medicine. St. Louis, MO: Mosby, Inc.; 2002:100.
24. Thrall JH, Ziessman HA. Genitourinary System. In: Nuclear Medicine: The Requisites, 1st ed. St. Louis: Mosby-Year Book, Inc.; 1995:283-320.
25. Hauser MF, Collins DA. Genitourinary system. In: O'Connor MK, ed. The Mayo Clinic Manual of Nuclear Medicine. New York, NY: Churchill Livingstone; 1996:367-423.
26. Taylor A, Schuster DM, Alazraki N. The gastrointestinal system. In: A Clinician's Guide To Nuclear Medicine. Reston, VA: Society of Nuclear Medicine, Inc.; 2000:95-115.
27. Nadel HR. Hepatobiliary scintigraphy in children. Semin Nucl Med 1996;26:25-42.
28. Schoen EJ, Clapp W, To TT, Fireman BH. The key role of newborn thyroid scintigraphy with isotopic iodide (123I) in defining and managing congenital hypothyroidism. Pediatrics 2004;114:683-688.
29. Pashankar FD, O'Dorisio MS, Menda Y. MIBG and somatostatin receptor analogs in children: current concepts on diagnostic and therapeutic use. J Nucl Med 2005:46:55S-61S.
30. Matthay KK, Edeline V, Lumbroso J, et al. Correlation of early metastatic response by $^{123}$I-metaiodobenzylguanidine scintigraphy with overall response and event-free survival in stage IV neuroblastoma. J Clin Oncol 2003;21:2485-2491.
31. Kowalsky RJ, Falen SW. Total-body and miscellaneous procedures. In: Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine, 2nd ed. Washington, D.C.: American Pharmaceutical Association; 2004:695-732.
32. Bonnin F, Lumbroso J, Tenenbaum F, et al. Parmentier C. Refining interpretation of MIBG scans in children. J Nucl Med 1994;35:803-810.
33. Gelfand MJ. Meta-iodobenzylguanidine in children. Semin Nucl Med 1993;23:231-242.
34. General official monographs. In: United States Pharmacopeia, 28th rev: national formulary, 23rd ed. Rockville, MD: United States Pharmacopeial Convention; 2005: 1850-1851.
35. Heyman S. Toxicity and safety factors associated with lung perfusion studies with radiolabeled particles [letter]. J Nucl Med. 1979;20:1098-1099.
36. Fukuda T, Ishibashi M, Yokoyam T, et al. Myocardial ischemia in Kawaski disease: evaluation with dipyridamole stress Technetium 99m tetrofosmin scintigraphy. J Nucl Cardiol 2002;9:632-637.
37. Fukuda T, Akagi T, Ishibashi M,et al. Noninvasive evaluation of myocardial ischemia in Kawasaki disease: comparison between dipyridamole stress thallium imaging and exercise stress testing. Am Heart J 1998;135:482-487.
38. Russell JR, Stabin MG, Sparks RB, Watson E. Radiation absorbed dose to the embryo/fetus from radiopharmaceuticals. Health Phys 1997;73:756-769.
39. NCRP Commentary No.9: Considerations regarding the unintended radiation exposure of the embryo, fetus or nursing child. Bethesda: National Council on Radiation Protection and Measurements; 1994.
40. Rubow S, Klopper J, Wasserman H,et al. The excretion of radiopharmaceuticals in human breast milk: additional data and dosimetry. Eur J Nucl Med 1994;21:144-153.