



THE UNIVERSITY OF NEW MEXICO
COLLEGE OF PHARMACY
ALBUQUERQUE, NEW MEXICO

The University of New Mexico

Correspondence Continuing Education Courses
for
Nuclear Pharmacists and Nuclear Medicine Professionals

VOLUME IV, NUMBER 5

*Therapeutic Drug Monitoring
Using Nuclear Medicine Techniques*

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THERAPEUTIC DRUG MONITORING USING NUCLEAR MEDICINE TECHNIQUES

STATEMENT OF OBJECTIVES

The purpose of this correspondence lesson is to increase the awareness of healthcare practitioners to the fact that nuclear medicine techniques can be used to monitor the safety and efficacy of drug therapy. Basic concepts are discussed and examples are presented.

Upon successful completion of this material, the reader should be able to:

1. Explain the concept of therapeutic drug monitoring (TDM).
2. Describe how TDM can improve patient care.
3. List and discuss various general parameters of drug therapy that should be monitored.
4. Describe the various techniques available to monitor drug therapy.
5. Discuss the usefulness and limitations of monitoring serum concentrations of drugs.
6. Explain how imaging modalities can be used to monitor drug therapy.
7. Give specific examples where nuclear medicine techniques have been successfully utilized to monitor drug therapy.
8. Logically consider whether nuclear medicine may be of value for monitoring drug therapy in a specific patient.

COURSE OUTLINE

Therapeutic Drug Monitoring Using Nuclear Medicine Techniques

- I. INTRODUCTION
- II. OVERVIEW OF THERAPEUTIC DRUG MONITORING (TDM)
- III. IMAGING AND TDM: BASIC CONCEPTS
- IV. EXAMPLES FROM THE LITERATURE
- V. CONCLUSIONS

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INTRODUCTION

As pharmacists continue to redirect their efforts to optimize patient outcomes, each is challenged to implement pharmaceutical care in his/her practice. At the heart of pharmaceutical care is therapeutic drug monitoring (TDM). The value of pharmacist participation in TDM to improve patient outcomes has been demonstrated in many practice settings. Monitoring drug therapy provides information upon which to base critical interventions that prevent or resolve drug-related problems which would otherwise result in untoward effects (toxicities) and/or a lack of efficacy.

Thus far, nuclear pharmacists have not been intimately involved in TDM activities. As pharmacists continue to accept responsibilities for individual patient outcomes and are accepted as a member of the healthcare team, generalist pharmacists are recognizing the value of consulting specialist pharmacists, including nuclear pharmacists. In this regard, nuclear pharmacists may be called upon more in the future to apply their specialized knowledge in the management of patients receiving drug therapy. As pharmacotherapy specialists practicing in the field of nuclear medicine, nuclear pharmacists will be consulted to determine when imaging modalities may be appropriately utilized in TDM. This continuing education lesson describes the general concept of TDM and illustrates how imaging can be used effectively for this purpose.

OVERVIEW OF THERAPEUTIC DRUG MONITORING (TDM)

In order to understand how nuclear medicine imaging can be used to monitor drug therapy, one must place it in context with the full concept of TDM. Many techniques and resources are available for monitoring drug therapy, by both direct and indirect means. Regardless of the method employed, the goal of TDM is to individualize and optimize drug therapy for each patient. This is necessary because of the wide interpatient and inpatient pharmacokinetic and/or pharmacodynamic variability. Because the pharmacokinetic behavior of a drug in a patient often changes during the course of disease, it is desirable to monitor each patient's response to drug therapy. Likewise, the pharmacodynamic response to a specific dosage of an administered drug is dependent upon many variables such as receptor affinity, occupancy, and activity; therefore, a patient's response to a given dosage cannot be predicted. Using data obtained from drug monitoring, adjustments in drug therapy attempt to compensate for patient variation and/or response in order to optimize therapy. Some of the commonly-employed techniques include physical assessment, evaluation of clinical laboratory values, direct measurement of physiologic/biologic parameters such as blood pressure, weight, body temperature, etcetera, interpretation of serum drug concentrations, and assessment of results from various imaging modalities including nuclear medicine (see Table 1).

Table 1. What techniques and resources are available for monitoring drug therapy?

-
- Assessment of serum drug levels
 - Physical assessment
 - Assessment of clinical laboratory values (e.g., SMAC, CBC, etc.)
 - Assessment of physiologic/biologic parameters with specific tests (e.g., blood pressure, temperature, electrophysiology of the heart, etc.)
 - Assessment of results obtained from various imaging modalities
-

As mentioned previously, the motivation for therapeutic drug monitoring is to prevent or resolve medication-related problems thereby eliminating or minimizing resultant untoward consequences. Strand et al. (1) have suggested that these problems may be classified into seven categories:

- Unnecessary Drug Therapy
- Wrong Drug
- Dosage Too Low
- Dosage Too High
- Adverse Drug Reaction
- Inappropriate Compliance
- Need Additional Drug Therapy

Several causes of each type of problem have been described. For example, the drug therapy problem of "Dosage Too High" may be due to any of several causes such as wrong dose, inappropriate frequency or duration, or the existence of a drug interaction.

When monitoring drug therapy, several parameters must be considered (Table 2). *Drug selection* is of paramount importance when initiating drug therapy. One must take into account the patient's history and clinical presentation in conjunction with other relevant laboratory data such as the results of blood culture and sensitivity testing (if bacteremia is suspected). In certain disease states, it may be necessary or helpful to employ a modality (such as diagnostic imaging) that will assist in predicting therapeutic success by identifying patients who will likely respond favorably to a specific drug therapy. In the event of a problem with patient compliance, safety, or efficacy of the initial therapy, drug selection again becomes an issue when selecting subsequent alternatives. Another important consideration is *drug bioavailability* which can be profoundly influenced by the route of administration and dosage form of the drug. *Drug safety* and *efficacy* are the two most obvious parameters typically monitored in efforts to optimize patient response. Finally, in order to determine if an unanticipated clinical response is due to an inappropriate dosage (e.g., due to *patient non-compliance*), one must also monitor drug intake patterns.

Table 2. What parameters of drug therapy are typically monitored?

-
- Drug selection
 - Drug administration (dosage/regimen)
 - Drug safety
 - Drug efficacy
 - Patient compliance
-

The standard approach to therapeutic drug monitoring involves monitoring serum drug concentrations. Serum drug concentrations are evaluated to ensure that they are within a therapeutic range, i.e., a range below which the drug would likely be ineffective and above which toxicities often occur. In practice, this TDM technique is often applied to a small group of drugs in which there exists a correlation between serum drug concentration and patient response, as well as a narrow therapeutic range of serum concentrations within which the drug is typically both safe and effective. Serum drug concentrations have historically been used as the most practical indirect measurement of the appropriateness of drug treatment when more directly-observable endpoints, such as blood pressure and temperature, are not available to indicate the patient's response to drug therapy. Because the premise of a therapeutic range is based on Bayesian phenomena (or probability) we must recognize that individual patients must be treated according to their individual response to drug therapy. The therapeutic range is recognized as the levels of serum drug concentration within which there is a high probability of obtaining some desired clinical response and a relatively low probability of experiencing untoward effects. Because therapeutic ranges are developed as indicators of a population's response to serum drug levels, in some instances an individual patient may not respond as anticipated to serum drug concentrations that were predicted to be appropriate for a given drug and disease state. Some patients will respond favorably to serum drug concentrations below the therapeutic range while others may not respond except at levels exceeding the therapeutic range. Other patients may develop toxicities at levels below the ceiling of the drug's therapeutic range, while others may

not develop toxicities even when the upper limit of the therapeutic range is surpassed.(2)

IMAGING AND TDM: BASIC CONCEPTS

Diagnostic imaging can be used in many aspects of patient care and disease management (Table 3).

Table 3. How are imaging modalities used for patient care?

-
- Diagnosis and monitoring of disease
 - Screening test
 - Definitive test
 - Confirmatory test
 - Monitoring of interventional modalities
 - Drug therapy
 - Surgery
 - Radiation therapy
 - Other (catheter placement, etc.)
-

There are several diagnostic imaging modalities available for such purposes (Table 4).

Table 4. What imaging modalities are available to healthcare practitioners?

-
- Nuclear medicine
 - Magnetic resonance imaging
 - Ultrasound
 - X-ray
 - Positron emission tomography
 - Computed tomography
-

All of these modalities are useful for monitoring therapy. However, nuclear medicine, because of its functional imaging capabilities (not limited to anatomical imaging), has found wide application as a therapeutic drug monitoring tool. Broadly speaking, nuclear medicine techniques can be used in two ways to monitor drug therapy.

1. Nuclear medicine can be used as a tool to monitor drug effects in a *population of patients*: As a means of discovery, nuclear medicine techniques have been used to

elucidate the *pharmacokinetics* of drugs. The kinetics of many therapeutic drugs are often initially determined using radiometric techniques. These drugs are labelled with PET radioisotopes and imaging studies are employed to visualize the biodistribution and clearance of the drug. **Example:** 5-Fluorouracil (5-FU) has been labelled with ^{18}F and administered to cancer patients to determine the degree of uptake in different types of malignant lesions. Certain tumor types, such as colorectal cancer, were found to accumulate 5-FU to a greater extent than others, thereby suggesting the potential efficacy of this drug in these tumor types. (3)

Likewise, the *pharmacodynamics* of therapeutic drugs can be characterized in this manner. **Example:** Following chemotherapy, patients often receive cytokines, such as GM-CSF or G-CSF, in an effort to stimulate the recovery of their bone marrow and rescue hematopoietic stem cells vital to the formation of peripheral blood elements such as white blood cells. These patients often experience bone pain that is indistinguishable from metastatic bone pain. In order to rule out metastasis as the cause of bone pain in patients receiving GM-CSF, a study of several patients experiencing this phenomena was conducted. The results of ^{18}FDG PET imaging showed increased accumulation of the radiotracer along the shaft of the bone corresponding to areas of increased metabolic activity within the bone marrow. This scintigraphic pattern suggested that the bone pain was not due to newly forming (or worsening of existing) bone metastasis, but rather an expected result or endpoint of this therapy, i.e., the stimulation of certain pluripotent stem cell lineages. Further, when the cytokine therapy was withdrawn in these patients, the pain subsided (4). This example illustrates that nuclear medicine techniques can be used to distinguish pharmacodynamic from untoward effects. Once this pharmacodynamic response is

understood, scintigraphy may or may not be useful as a routine monitoring tool in individual patients.

2. Once a nuclear medicine procedure has been proven, through extensive clinical testing, to be a valid and reliable method for monitoring a specific parameter of patient response to therapy, it can be applied in the patient care setting when appropriate. In this fashion, nuclear medicine techniques can be used to influence *the care of individual patients*. **Example:** In a patient receiving prophylactic aerosolized pentamidine, ^{67}Ga scintigraphy revealed bilateral localization of the radiotracer in the base of the lungs. This was later confirmed to be *Pneumocystis carinii* pneumonia (PCP). The patient was subsequently placed on intravenous (i.v.) pentamidine and a repeat gallium scan showed resolution of the infection. Ventilation imaging using aerosolized $^{99\text{m}}\text{Tc}$ pentetate (DTPA) following completion of the course of i.v. pentamidine demonstrated ventilatory defects in the lung bases corresponding to the regions of previous ^{67}Ga uptake. This latter study provided strong evidence that the underlying ventilatory abnormality contributed to poor drug delivery to the lung bases. In this example, nuclear medicine not only identified a drug-related problem, but also was useful in monitoring the resolution of the problem, and identifying the cause of the problem. (5)

EXAMPLES FROM THE LITERATURE

There are now numerous citations in the literature to document the impact of imaging modalities, including nuclear medicine, used to monitor drug therapy. The following examples were selected to illustrate just a few of these techniques that can be used by healthcare providers to help ensure optimum patient outcomes.

Lung scan evaluation of thrombolytic therapy for pulmonary embolism

One of the most important applications of

ventilation/perfusion imaging has been the diagnosis of acute pulmonary embolism and the evaluation of restoration of pulmonary blood flow following therapy.

Data from three trials of thrombolytic therapy for pulmonary embolism were combined to assess the utility of perfusion lung imaging in predicting the response to thrombolytic therapy. Pre- and post-therapy lung scans were scored for defects and correlated with duration of symptoms in a total of 221 patients. Of these, 167 patients were treated with various thrombolytic regimens and 54 were treated with heparin alone. Improvement in the lung scan defect score was correlated with larger initial defect score ($r = 0.53$), segmental appearance ($r = 0.31$), and shorter duration of symptoms ($r = 0.20$). This study suggests that baseline perfusion imaging defect severity helps to predict the response to thrombolytic therapy. (6)

Although these and several other authors have described the use of serial pulmonary perfusion studies to evaluate recovery from acute pulmonary embolism following thrombolytic and anticoagulation therapy (7,8), a case reported by Langer and Velchik (9) offers probably the most dramatic example of rapid normalization of pulmonary blood flow. A patient with massive acute pulmonary emboli (as documented by an initial ventilation/perfusion study) was begun on aggressive streptokinase and heparin therapy. Repeat scintigrams performed 36 hours following the initiation of therapy had significantly improved and had reverted almost completely to normal. This case is in contrast to many other reported instances where embolic episodes may more typically take from weeks to months to achieve full recovery of blood flow.

Use of ^{99m}Tc exametazime to monitor changes in regional cerebral blood flow in chronic cocaine polydrug users treated with buprenorphine

Chronic cocaine and polydrug abuse have been associated with regional abnormalities in cerebral perfusion that are partially reversible after drug abuse treatment with buprenorphine. This study compared the effects of abstinence from drug use to therapy with buprenorphine. Fifteen cocaine- and heroin-dependent men were studied with ^{99m}Tc -exametazime brain SPECT. Following detoxification, the patients were randomly assigned to receive placebo or treatment with 6 or

12 mg daily buprenorphine treatment. SPECT imaging was performed at baseline, at maximum dosage, and after tapering off drug therapy. Subjects receiving buprenorphine had a significant reduction in the number of cerebral perfusion defects between baseline and maximum buprenorphine dose compared with those receiving placebo. These differences were dose-related, temporary, and returned to baseline after tapering off drug therapy. This study leads one to 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 (10). It is notable that nuclear medicine was useful in documenting these results.

Monitoring of cerebral perfusion using ^{99m}Tc -exametazime in an obsessive-compulsive patient treated with clomipramine

Cerebral perfusion in a previously untreated patient with obsessive-compulsive disorder (OCD) was studied qualitatively and semi-quantitatively with SPECT imaging prior to, during, and six weeks after treatment with clomipramine. The patient's symptoms disappeared while on medication and relapsed after drug withdrawal. At baseline, there was increased perfusion in the bilateral orbitofrontal, anterior cingulate, frontotemporal and right caudate regions. These alterations disappeared during drug therapy. After treatment discontinuation and symptomatic relapse, the same pattern of hyperactivity was observed. Semiquantitative measurements after treatment withdrawal showed a return to perfusion values similar to those observed before treatment in subcortical structures. In cortical areas this level was not completely achieved. Subtraction SPECT images showed perfusion changes at the orbitofrontal, caudate, and thalamic levels (11). As evidenced by this case, cerebral perfusion imaging may have applications in diagnosis and in selection of appropriate drug therapy in OCD.

^{99m}Tc -exametazime brain SPECT and psychopathology in schizophrenic patients: comparison of unmedicated acute and neuroleptic treated patients

Twenty-one drug-naive patients with a first manifestation of schizophrenia were examined with SPECT to assess regional cerebral perfusion

(rCBF) and psychopathologically by PANSS (positive and negative syndrome scale of schizophrenia). Of these, 18 were controlled after neuroleptic treatment. Of the 21 patients, six revealed areas of hyperperfusion, three showed hypoperfusion, and 12 demonstrated normal perfusion. Under neuroleptic treatment, five of the hyperperfused and two of the hypoperfused patients completely normalized; the remaining two patients normalized only in some areas. rCBF in all patients was significantly reduced in frontal, left parietal, left temporal, left basal ganglia, and anterior cingulate gyri when negative symptoms (PANNS) were predominant. In contrast, rCBF was significantly higher in superior frontal, right parietal, right inferior temporal areas, and in basal ganglia when positive symptoms (PANNS) were prevailing. After neuroleptic treatment, rCBF was reduced significantly in frontal areas and increased significantly in the left basal ganglia. Therefore, negative symptoms correlate with changes in rCBF mainly in the left hemisphere. Positive symptoms are associated with increased rCBF in superior frontal, right parietal, and right inferior temporal areas. After neuroleptic therapy of acute schizophrenics, rCBF (superior frontal) and positive symptoms decreased significantly in parallel (12). SPECT imaging of rCBF appears to be useful in diagnosing and monitoring schizophrenia and in evaluating potential drug therapy.

Clinical usefulness of serial ^{99m}Tc-sestamibi scintigraphy in evaluating tumor response to preoperative chemotherapy in patients with various sarcomas

The histological response of sarcomas to preoperative chemotherapy is important as it influences the selection of a surgical procedure and further treatment planning in cases of poor response. CT and MRI imaging demonstrate poor correlation with tumor response to chemotherapy. ^{99m}Tc sestamibi imaging has been used for detection of tumors and staging of the disease. It may also be useful for evaluating response to therapy.

Graham et al. (13) have described the results of a pilot study involving three patients with various sarcomas. These patients were given chemotherapy for 8-12 weeks followed by resection of the tumor. SPECT imaging was

performed just before or immediately after initiation of drug therapy and again just before resection. The ratio of radiotracer uptake in tumor-to-normal tissue was obtained in each case. Results in this limited population indicate that localization of ^{99m}Tc sestamibi in tumors is excellent and that a marked drop in uptake over time appears to be consistent with a good response to treatment.

In a study conducted by Nagaraj et al. (14), twenty-eight patients (10 osteogenic sarcomas and 18 soft tissue tumors of the extremities) underwent pre- and post-chemotherapy ^{99m}Tc sestamibi planar scintigraphy. ^{99m}Tc sestamibi response was compared to baseline imaging results, and change was graded as Category I (worse or no response), Category II (definite response but lesion still present), Category III (marked response with no lesion detectable). All patients underwent limb salvage procedures and the percent tumor necrosis at surgery was correlated with the sestamibi scans performed within 10 days of surgery.

| Category | No. of Patients | Necrosis Range | Mean Necrosis |
|----------|-----------------|----------------|---------------|
| I | 6 | 5-25% | 25% |
| II | 14 | 30-80% | 54% |
| III | 8 | 90-100% | 98% |

This investigation indicates that ^{99m}Tc sestamibi scintigraphy is an excellent indicator of tumor viability through its ability to localize in metabolically active tissues. Serial scans provide accurate correlation between ^{99m}Tc sestamibi uptake and histological response to treatment, thus allowing optimization of chemotherapy prior to limb salvage. On occasion, optimization may include discontinuation of chemotherapy in order to achieve the highest quality of life despite the lack of cure.

Measurement of the effects of chemotherapy on bony metastases using quantitative skeletal scintigraphy

Uptake of ^{99m}Tc diphosphonate compounds into skeletal lesions can be quantified using computer-assisted techniques. Pre- and post-therapy values can be compared to trace the effectiveness of therapy in metastatic and metabolic bone disease.

Although blood chemistry assay methods (e.g., carcinoembryonic antigen and alkaline phosphatase) provide an average value of lesion response to therapy, the quantitative bone scan represents a means to analyze individual lesions and provide a better understanding of bone disease therapy. DeLuca et al. (15) have illustrated the benefits of quantitative bone imaging in a patient before and after initiation of spirogermanium therapy. The quantitative results show that specific bony metastases accumulate ^{99m}Tc diphosphonate to different degrees, and that bone lesions are not uniformly affected by therapy. It is suggested that this differential uptake can be evaluated by quantitative bone scanning at various times during therapy. [Note: *Although this technique may have merits, caution must be taken in interpreting bone scans following chemotherapy. Certain chemotherapeutic agents can cause a 'flare' effect on the scan which makes the lesion appear to worsen when, in fact, the flare sign may indicate a healing lesion (16,17).*]

The value of skeletal scintigraphy in the detection of drug induced diseases of bone

To determine the usefulness of noninvasive bone imaging for the detection of ischemic necrosis of bone (INB), a prospective study was performed in 36 patients at high risk for this disease, i.e., patients with systemic lupus erythematosus receiving corticosteroid therapy. Comparison was made with radiographs and intraosseous pressure determinations. All patients had scintigraphic and radiographic images taken of the hip, knee, and shoulder joints, and 10 of the 36 patients had intraosseous pressure determinations in the marrow space of affected joints. Bone scans showed abnormally increased joint activity in 28 of 36 patients and 97 of 216 joints imaged. Of the 27 joints with elevated bone marrow pressure, 24 were abnormal on bone scans (sensitivity = 89%) and 11 were abnormal on radiographs (sensitivity = 41%). Bone scans and radiographs were considered to be normal in only two of the four joints that had normal bone marrow pressures (specificity = 50%). The results of this study support the conclusions that bone scans are sensitive in the diagnosis of INB, and that bone scintigraphy identifies an earlier stage of INB than radiography (18).

A recent case report also discusses the

usefulness of bone scanning in conjunction with other imaging modalities for the confirmation of INB (19).

Sodium fluoride is used for the treatment of post-menopausal osteoporosis, stimulating bone formation in the axial and appendicular skeleton. Extremity pain due to periostitis, or a stress fracture-like condition, is a common side effect observed in women receiving this therapy. In such cases, bone scintigraphy demonstrates increased uptake in the extremities, consistent with increased osteoblastic activity. According to the reports of two case studies, if the pain is actually caused by the sodium fluoride therapy, discontinuation of this medication should lead to a decrease in symptomatology, and repeat bone scans should also normalize over time (20,21).

Cyclic oral phosphate and etidronate increase femoral and lumbar spine bone mineral density and reduce lumbar spine fracture rate as assessed by dual-photon absorptometry (DPA)

A study of the safety and efficacy of cyclic sequential oral phosphate, diphosphonate, and calcium carbonate was performed on 42 postmenopausal women with osteoporosis diagnosed by dual-photon absorptometry. These patients received a sequential cyclic regimen of oral phosphate for three days, etidronate for two weeks, and then a calcium salt for 12 weeks. This was repeated cyclically for three years. They were reassessed using dual-photon absorptometry after every second 101-day cycle of therapy. A control group of 20 patients receiving only the calcium salt was matched for age, time since menopause, race, and sex. The group treated with cyclic phosphate, etidronate, and calcium regimen had 80% fewer fractures than the control group over the three year follow-up period. Significant response in halting bone mineral loss and increasing bone mineral density was seen in none of the controls but in 90% of treated patients' lumbar spine and 70-80% of the three regions of the femoral neck examined (22). DPA can play an important role in assessing the outcome of therapy in osteoporotic women.

Bone scintigraphy following intravenous pamidronate for Paget's disease of bone

Pamidronate is one of several powerful diphosphonates capable of producing remissions of

Paget's disease. Ryan et al. (23) examined to what extent bone scan changes parallel the clinical response and whether there is variability in the behavior of individual lesions. Twenty-five patients with pagetic bone pain for more than two years were examined with bone scintigraphy before, and an average of eight months after, six 30 mg infusions of pamidronate given weekly. Serum alkaline phosphatase levels and urinary hydroxyproline-to-creatinine ratios were measured before and six months after treatment. A second course of pamidronate was given to 13 patients who had clinical or biochemical relapse. Of 136 pagetic lesions, 13 (10%) completely resolved, 90 (65%) improved, and 33 (24%) remained unchanged. There was no significant difference in response between bony sites, although less active lesions were more likely to resolve completely. In conclusion, pamidronate has a powerful effect on bone scan appearances in Paget's disease. Most lesions improve but complete resolution is uncommon. Less active lesions are more likely to resolve and are less likely to require further therapy. [Note: *If bone scintigraphy is performed during diphosphonate therapy, potentially false negative findings may appear due to the drug interaction between the diagnostic drug (^{99m}Tc -diphosphonate) and the diphosphonate therapeutic drug (24,25).]*

Evaluation of somatostatin receptor density in glomus tumors as possible a predictor of successful pentatetreotide therapy

^{111}In pentatetreotide (Octreoscan®) binds specifically to somatostatin receptors in neuroendocrine tumors. This study evaluated the biodistribution of ^{111}In pentatetreotide in glomus tumors as a possible predictor of successful pentatetreotide therapy in non-resectable tumors. Three patients (three females, age 40 +/- 15 years) with surgically not resectable but histologically verified glomus tumors were studied. Planar and SPECT imaging of the head and neck region was performed four and 24 hours after i.v. administration of ^{111}In pentatetreotide. Regions of interest (ROI) were drawn over the tumor and the ratio to a mirrored background-ROI was calculated. Before therapy all glomus tumors demonstrated high regional ^{111}In pentatetreotide accumulation. Six months after therapy with pentatetreotide a 40% reduction of tumor volume

was paralleled by about a 50% reduction of ^{111}In pentatetreotide accumulation. These data suggest that ^{111}In pentatetreotide uptake was present in all tumors which responded to non-radioactive pentatetreotide therapy and was, therefore, an excellent predictor of tumor response to somatostatin therapy (26). Further marginal uptake of ^{111}In pentatetreotide is likely a predictor of poor response to this therapy.

Use of radionuclide gastric emptying studies to assess the effects of erythromycin on gastric emptying and esophageal motility in patients with non-insulin-dependent diabetes mellitus

Abnormal gastrointestinal motility is a well recognized complication of diabetes mellitus, and disordered gastric emptying may hamper glycemic control. The effects of oral erythromycin on gastric emptying and, subsequently, on glycemic control was investigated in 20 patients with type II (non-insulin-dependent) diabetes mellitus [NIDDM] and delayed solid gastric emptying diabetic gastroparesis.

Eighteen males and two females, aged 49 to 72 years (mean age 65 years) were given erythromycin (erythromycin estolate) orally at a dose of 250 mg three times daily, 30 minutes before each meal. Radionuclide-labelled solid phase gastric emptying and fasting blood sugar (FBS) determinations were made prior to therapy, after one day of erythromycin therapy, and again after two weeks of erythromycin therapy. The gastric emptying half-time (GET1/2) identified the time needed for 50% of the initial radioactivity to leave the stomach, and was used to monitor the gastric emptying status.

The GET1/2 decreased from 198.0 ± 58.9 minutes at baseline to 139.1 ± 67.6 minutes following one day of erythromycin therapy ($p < 0.01$), and to 137.1 ± 71.2 minutes after two weeks of treatment ($p < 0.01$ vs. baseline). The FBS decreased from 159.0 ± 40.2 mg/dl at baseline to 149.0 ± 38.5 mg/dl following one day of therapy ($p = 0.12$, non-significant), and to 139.2 ± 39.8 mg/dl after two weeks of treatment ($p < 0.02$ vs. baseline).

The authors concluded that erythromycin is an effective prokinetic agent for diabetic gastroparesis, and this therapy to correct gastric emptying improved diabetic control, as demonstrated using nuclear medicine imaging (27).

In another investigation, fifteen NIDDM patients (age 58-72 years), with a duration of diabetes for 12 to 28 years, were studied. Criteria for patient selection included: 1) no history of peptic ulcer disease, neuromuscular disease, connective tissue disease, or endocrine disease, except DM, that might affect esophageal motility, 2) no history of gastrointestinal surgery, and 3) negative findings from panendoscopy or X-ray series of the upper gastrointestinal tract. Esophageal motility, including esophageal mean transit time (MTT), residual fraction (RF), and retrograde index (RI), was evaluated and calculated by radionuclide esophageal transit test (REET). The baseline study was performed before oral erythromycin therapy. After a two week course of treatment, the patients underwent a second study.

In comparison with 11 normal males (age > 60 years), 93% (14/15) of the NIDDM patients had a longer MTT (> 6.97 seconds), 67% (10/15) had a higher RF (> 0.24) and 80% (12/15) had a higher RI (> 0.15) in the baseline study. After a two week course of oral erythromycin therapy, the esophageal dysmotility improved (decreased MTT) in 73% (11/15) of NIDDM patients, the esophageal clearing function improved (decreased RF) in 73% (11/15) of the patients, and the severity of gastroesophageal reflux was reduced (decreased RI) in 60% (9/15) of the patients.

The authors concluded that 1) most of the NIDDM patients had esophageal disorders and 2) a two week course of erythromycin therapy can improve diabetic esophagaparesis, as evaluated by non-invasive REET (28). Although these examples examine groups of patients, therapy of gastric emptying and/or esophageal motility disorders can also be evaluated on a patient by patient basis.

Thrombolytic therapy in myocardial infarction as assessed with ^{99m}Tc-sestamibi

Following myocardial infarction, thrombolytic therapy with streptokinase, urokinase, or tissue plasminogen activator (rTPA) has demonstrated utility in efforts to reperfuse ischemic but still viable myocardium. Baseline ^{99m}Tc-sestamibi studies have been performed in which the radiotracer was administered to patients presenting to the emergency room with a high suspicion of myocardial infarction within the previous 3-6

hours. These patients then received thrombolytic therapy in efforts to reperfuse obstructed coronary arteries. Several days following thrombolytic therapy sestamibi imaging was repeated and compared to the baseline information. The degree of reperfusion following thrombolytic therapy has been used as a prognostic tool when evaluating these patients for subsequent interventions such as transluminal percutaneous angioplasty (PTCA), coronary artery bypass graft (CABG), or endarterectomy. In conclusion, serial ^{99m}Tc sestamibi imaging is a valuable tool for assessing the extent of ischemia during and following myocardial infarction, including patients receiving thrombolytic therapy (29,30).

Detection of drug-induced pulmonary disease and subsequent monitoring of therapy

⁶⁷Ga has, on several occasions, been reported to be useful in identifying drug-induced pneumonitis. Khan et al. (31) presented a case in which hypersensitivity to phenytoin was detected by ⁶⁷Ga imaging, with scintiphotos showing intense bilateral uptake of the radiotracer in the lungs. Successful steroid treatment of the condition was demonstrated 25 days later by decreased pulmonary localization of ⁶⁷Ga concurrent with an improved clinical condition.

Accurate detection of amiodarone pulmonary toxicity is essential due to the life-threatening nature of this disease. By the same token, unnecessary withdrawal of amiodarone may likewise lead to serious consequences. Commonly-encountered scintigraphic patterns associated with amiodarone pulmonary toxicity include focal, patchy, and/or diffusely increased lung uptake. Rarely, gallium abnormalities may be the only manifestation of amiodarone pulmonary toxicity. More typically, abnormalities in gallium imaging parallel the development of amiodarone pulmonary toxicity and aid in the diagnosis of this disease when chest x-rays are ambiguous. Serial increments in scintigraphic abnormalities appear especially helpful for diagnosis in the population at risk, and suggest a place for baseline gallium scans in patients initiated on amiodarone therapy. Following a decrease in dosage or discontinuance of the drug, gallium scintigraphy is also useful for monitoring improvement in patient condition (32).

In a patient who developed eosinophilia, fever,

fatigue, muscular weakness, dyspnea, and skin rash (eosinophilia myalgia syndrome [EMS]) after taking high doses of tryptophan, gallium-67 scanning revealed diffuse increased bilateral uptake in the lung, thus indicating pneumonitis as one component of the patient's disease. Although not specifically demonstrated in this case study, the authors propose that follow-up monitoring post therapy for EMS may also be useful since steroids apparently diminish ^{67}Ga uptake at previously inflamed sites (33).

Ventilation-perfusion imaging has also been shown to be capable of identifying drug-induced lung disease. Confirmation of nitrofurantoin-induced lung disease (hypersensitivity reaction) was reported in one patient by the findings of xenon trapping in lower and mid lung fields with diffuse but non-specific alterations in blood flow distribution on the $^{99\text{m}}\text{Tc}$ microsphere perfusion study. The drug was subsequently withdrawn and the patient was placed on an H_2 antagonist and intravenous corticosteroids. Within 24 hours the patient had improved significantly clinically. A repeat ventilation study showed wide distribution of the radioactive gas and the second perfusion study was much improved with only minor abnormalities persisting (34).

The predictive value of ^{67}Ga in patients treated for lymphoma

Reliable evaluation of the effectiveness of lymphoma therapy is critical since subsequent patient management is based upon these results. After completion of a course of therapy, there may be radiologic evidence of the presence of a mass even in patients in clinical remission. In addition, the absence of disease radiologically may not be a good indicator of clinical response. Front et al. (35) studied the predictive diagnostic values of gallium-67 imaging and computed tomography (CT) after therapy in 43 patients with Hodgkin disease and 56 patients with non-Hodgkin lymphoma. The usefulness of these diagnostic studies in predicting survival was also assessed. The predictive value of a negative gallium study was 0.84 in both Hodgkin and non-Hodgkin patients, and the predictive value of a negative CT study in these same patient populations was 0.88 and 0.80, respectively. However, the positive predictive value of gallium in patients with Hodgkin disease was 0.80 but only 0.29 for CT.

Similarly, the positive predictive value for ^{67}Ga was 0.73 in patients with non-Hodgkin disease, but only 0.35 for CT. In both groups of patients, the difference in disease-free survival between patients with positive and negative studies was significant for ^{67}Ga but not for CT. Therefore, ^{67}Ga scintigraphy is apparently a good predictor of clinical response in patients who have received chemotherapy for the treatment of lymphoma.

Diagnosis of anthracycline-induced cardiomyopathy using various scintigraphic techniques

The major limiting factor associated with anthracycline (e.g. doxorubicin) chemotherapy is the development of an often-irreversible cardiomyopathy. Because of this problem, the maximum recommended cumulative dose of doxorubicin is 400-600 mg/m² body surface area. Attention to dosage reduction is particularly important in patients with pre-existing heart disease. These dosage limitations can result in the premature discontinuation of doxorubicin therapy in patients who might benefit from higher dosages without experiencing myocardial toxicity. In an effort to optimize individual patient response to doxorubicin therapy, radionuclide ventriculography has been effectively used to monitor for signs of cardiac decompensation. The objective of this technique is to continue therapy as long as possible while avoiding the development of congestive heart failure. Although several decision algorithms are available for determining whether to continue doxorubicin in a particular patient, one commonly-employed suggests that therapy be discontinued if the left ventricular ejection fraction (LVEF) decreases by greater than or equal to 15% and to a final value of 45% or less (36). Other studies (37,38) have been used in conjunction with radionuclide ventriculography in order to elucidate more sensitive prognostic information, as illustrated in the following example.

Detection of myocyte cell damage with ^{111}In -antimyosin and impairment of adrenergic neuron function with ^{123}I -MIBG during doxorubicin therapy can identify patients at risk of significant functional impairment of the myocardium. Thirty-six patients who underwent chemotherapy including doxorubicin were assessed. ^{123}I -MIBG scans, ^{111}In -antimyosin scans, and radionuclide

ejection fraction measurements were performed prior to receiving doxorubicin, and at intermediate and maximal cumulative doses of doxorubicin. ^{123}I -MIBG uptake was quantified by heart-to-mediastinum ratio and ^{111}In -antimyosin uptake was quantified by heart-to-lung ratio. All patients had absent antimyosin uptake (mean ratio 1.40 ± 0.06) and normal MIBG uptake (ratio 1.85 ± 0.29) before chemotherapy with a mean ejection fraction of $61 \pm 8\%$. At cumulative doses of 240-300mg/m² doxorubicin, an increase in ^{111}In -antimyosin uptake (ratio 1.85 ± 0.2) was observed with no increase in ^{123}I -MIBG uptake (mean ratio 1.80 ± 0.2) and a mean ejection fraction of $59 \pm 5\%$. At 420-600 mg/m² doxorubicin, increased ^{111}In -antimyosin uptake (ratio 2.02 ± 0.3), and decreased ^{123}I -MIBG uptake (mean ratio 1.76 ± 0.2) was observed with a mean ejection fraction of $52 \pm 8\%$. Patients with more intense antimyosin uptake at intermediate doses tended to be those with more severe functional impairment at maximal cumulative doses. At cumulative doses of 420-600 mg/m², doxorubicin, ^{111}In -antimyosin and ^{123}I -MIBG studies detect cell damage and impaired adrenergic neuron activity in patients with maintained or slightly decreased ejection fraction (39). Therefore, these imaging studies may be more sensitive in detecting doxorubicin-induced cardiomyopathies than measurements of ejection fractions in patients receiving this therapy.

CONCLUSIONS

It is probably fair to say that nuclear medicine has been underutilized as a drug therapy monitoring tool and that its full potential has not been adequately explored. On the other hand, those of us who are aficionados of medical imaging must be careful to place its value for monitoring therapy into the proper perspective with other modalities used for this purpose. One must carefully examine the clinical relevance of these techniques in each patient. Certainly the safety of some drug therapies can be monitored using nuclear medicine techniques, particularly in the assessment of patients suspected of experiencing drug-induced disease (Table 5).

Table 5. Monitoring of SAFETY using nuclear medicine techniques

-
- Detection of drug induced disease
 - Cardiomyopathies
 - Nephritis
 - Thyroiditis
 - Pneumonitis
 - Pseudomembranous colitis
 - Lymphadenopathy
 - Hyperprolactinemia
 - Hypercalcemia (extraosseous calcification)
-

These techniques are also appropriate for monitoring the efficacy of drug therapy in a wide variety of disease states as illustrated by the previous citations (Table 6).

Table 6. Monitoring of EFFICACY using nuclear medicine techniques

-
- Therapy of a wide variety of disorders
 - Pulmonary embolus
 - Coronary artery disease
 - Gastroparesis
 - Gastrointestinal bleeding
 - Osteomyelitis
 - Various cancers
 - Asthma
 - Baseline studies are important
-

From the examples and discussion above, it is clear that nuclear medicine techniques have been used for a wide variety of therapeutic drug monitoring applications. Although one typically thinks of these studies as benefiting the recipient by ruling in or out a given disease that may have been suggested by other clinical findings, or by staging a previously diagnosed disease, these techniques clearly have applications in the realm of drug monitoring. Perhaps the true and full extent of the application of nuclear medicine as a tool for TDM is only now beginning to be realized. The challenge before those of us with special training and interest in radiopharmaceuticals and diagnostic imaging is to

improve our understanding of the capabilities of these techniques and to demonstrate the applicability of these studies as drug monitoring tools. Clinicians often instinctively refer patients (with certain disease states) for nuclear medicine studies and incorporate the results of these studies into the patient's therapeutic plan. However, they may also be using these studies for monitoring drug therapy without recognizing this as the purpose of the study itself. The opportunities before us are multidimensional. We should strive to identify nuclear medicine procedures useful for monitoring drug therapy and publicize these techniques to healthcare providers. We must also strive to standardize and validate newer studies on larger populations of patients. In the end, our best role in this arena may be to simply highlight the drug monitoring aspect of existing procedures. In doing so, we must also be prepared to realize our role as pharmacotherapists by assisting referring physicians in the selection of appropriate drug therapy and in the identification and/or resolution of drug related problems identified using these nuclear medicine techniques.

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2. Therapeutic drug monitoring is useful for preventing or resolving _____.
- diagnostic errors
 - poor nursing care
 - medication-related problems
 - Varicella Zoster*
3. Monitoring of serum drug concentrations is most useful in drugs which have a _____.
- high cost
 - correlation between serum concentration and patient response
 - narrow therapeutic range
 - answers (b) and (c)
4. When a patient has a drug serum concentration "in the therapeutic range", this implies that:
- there is a high probability of obtaining the desired clinical response
 - there is a low probability of experiencing untoward effects
 - the patient's therapy should be discontinued
 - answers (a) and (b)
5. Which of the following techniques can be used to monitor drug therapy?
- physical assessment
 - evaluation of clinical laboratory values
 - imaging modalities
 - all of the above
6. Drugs are commonly labelled with PET radioisotopes in order to visualize and monitor the _____ of these drugs.
- kinetics
 - side effects
 - bioavailability
 - therapeutic range
7. As a monitoring tool, nuclear medicine has been used to _____.
- study the safety and efficacy of drugs in large populations of patients
 - assess the safety and efficacy of drugs in individual patients
 - measure blood pressure
 - answers (a) and (b)

QUESTIONS

1. Which of the following drug therapy parameters is (are) commonly monitored?
- drug safety
 - drug efficacy
 - drug selection
 - all of the above

8. Pulmonary perfusion imaging has been successfully employed to monitor the effectiveness of:
- therapy of manic depression
 - thrombolytic therapy
 - antihypertensive therapy
 - antiarrhythmic therapy
9. As evidenced by ^{99m}Tc -exametazime SPECT imaging, buprenorphine is capable of reducing _____ in drug abusers.
- the frequency of seizures
 - the number of cerebral perfusion defects
 - the incidence of hypercortisolism
 - the craving for narcotics
10. The effect of clomipramine in obsessive-compulsive patients has been evaluated using which of the following nuclear medicine imaging procedures?
- brain SPECT imaging
 - myocardial SPECT imaging
 - hepatobiliary planar imaging
 - adrenocortical planar imaging
11. Drug-naive schizophrenic patients evaluated using ^{99m}Tc -exametazime SPECT imaging showed _____ regional cerebral perfusion prior to drug therapy.
- decreased
 - increased
 - normal
 - any of the above
12. ^{99m}Tc -sestamibi imaging has been used to monitor tumor _____ following chemotherapy.
- drug resistance
 - necrosis
 - viability
 - metastasis
13. Which of the following findings is consistent with ischemic necrosis of bone?
- decreased bone marrow pressure
 - abnormally increased radiotracer uptake in joints
 - elevated serum calcium
 - elevated serum parathormone
14. The kinetics of 5-Fluorouracil (5-FU) have been studied using which of the following radioisotopes?
- ^{18}F
 - ^{99m}Tc
 - ^{123}I
 - ^{111}In
15. The effectiveness of drug treatment for glomus tumors can be predicted by which of the following?
- ^{131}I -MIBG SPECT imaging
 - ^{131}I -NP59 imaging
 - ^{111}In -Pentatreotide imaging
 - serum somatostatin levels
16. Localization of ^{18}F -Fluorodeoxyglucose in the intramedullary space of long bones following therapy with GM-CSF is most likely indicative of?
- metastatic extension of the primary tumor
 - normal uptake into cortical bone
 - increased metabolic activity in the bone marrow
 - destruction of pluripotent stem cells
17. It is possible to monitor the pattern of aerosolized drug delivery using which of the following radiopharmaceuticals?
- ^{99m}Tc -MAA
 - ^{111}In -leukocytes
 - ^{201}Tl Chloride
 - ^{99m}Tc -DTPA
18. Quantitative bone imaging must be interpreted with caution following therapy with certain chemotherapeutic agents because of:
- the pain induced by the therapy
 - a possible scintigraphic flare pattern
 - potential chemotherapy interference with the uptake of ^{99m}Tc -diphosphonates
 - altered elimination due to renal tubular damage

19. Women sometimes experience pain following therapy with sodium fluoride for osteoporosis. Normalization of bone scans following discontinuation of drug therapy confirms that the:
- pain was psychosomatic
 - pain was due to worsening of osteoporosis
 - affected bone should be surgically debrided
 - pain was due to drug-induced bone remineralization
20. Diphosphonate therapy for osteoporosis is most commonly monitored using which of the following diagnostic modalities?
- skeletal scintigraphy
 - dual-photon absorptometry
 - magnetic resonance imaging
 - computed tomography
21. In patients with non-insulin dependent diabetes mellitus, nuclear medicine techniques have been used to monitor erythromycin therapy for which of the following disorders?
- neuropathy
 - gastroparesis
 - peripheral vascular disease
 - nephropathy
22. Radionuclide studies which evaluate therapeutic effects on gastric emptying and esophageal motility are administered:
- intravenously
 - intrathecally
 - orally
 - by inhalation
23. Drug-induced pneumonitis detected by ^{67}Ga scintigraphy is usually manifested as which of the following?
- hyperactivity in the nasal mucosa
 - absence of radiotracer in the liver
 - patchy localization of ^{67}Ga in one lung
 - diffuse bilateral lung uptake of the radiotracer
24. Which of the following statements is true regarding the use of nuclear medicine to monitor therapy of lymphoma?
- ^{111}In -leukocytes is the most common radiotracer used
 - The predictive value of a negative study is much lower for ^{67}Ga scintigraphy than for computed tomography
 - The predictive value of a positive study is higher for computed tomography than for ^{67}Ga scintigraphy
 - ^{67}Ga scintigraphy is a better predictor of survival and of response to chemotherapy than is computed tomography
25. Cardiomyopathies resulting from anthracycline therapy can be monitored by which of the following serial techniques?
- ejection fraction measurements using radionuclide ventriculography
 - ^{111}In -antimyosin imaging
 - ^{123}I -MIBG adrenergic neuron mapping
 - all of the above

