Pharmacy Practice

Evaluation of Renal Function Using Nuclear Medicine Techniques

Gilbert Matte and Douglas N. Abrams

INTRODUCTION

Nuclear medicine techniques are one of the diagnostic tools used to assess renal function. Injection of tracer amounts of radiolabelled pharmaceuticals with subsequent imaging with a gamma camera can provide information on physiologic function. As well, pharmacologie manipulation via the concomitant administration of certain drugs can be used to obtain clinically relevant information. While many variations of a specific test may be performed this paper will provide an overview of how the information is determined and applied in current practice.

Assessment of Kidney Function

The majority of nuclear medicine techniques used in kidney studies assess abnormal renal function or pathophysiology rather than kidney anatomy, which is generally evaluated by x-ray techniques. The effects of kidney pathophysiology are related to the area of the kidney affected. Therefore, the assessment of kidney function usually involves either determining the glomerular filtration rate (GFR) (relative renal blood flow), assessing tubular activity (function), or measuring global kidney function (urinary excretion).

The GFR estimates the volume of blood passively filtered by the glomerulus. It can be estimated by determining the clearance of a substance excreted by glomerulofiltration without any reabsorption or secretion. Historically, inulin and creatinine have been used to measure GFR.[1] However, calculation of inulin clearance is too cumbersome since it requires the collection and analysis of biological samples and hence creatinine clearance is now used clinically to assess GFR. When GFR is normal, tubular secretion of creatinine contributes little, but with diminished GFR the contribution of tubular secretion may become substantial. Hence, if GFR is severely impaired, the GFR estimated under these circumstances may not be precise.[2] Serum creatinine levels also reflect kidney filtration but are less precise than nuclear medicine techniques and can not be used to differentiate the degree of function between kidneys.

A single bolus injection of the radiopharmaceutical (usually diethylenetriaminopentaacetic acid (DTPA) labelled with techaectium (^{99m}Tc DTPA) is administered to the patient. Two to 3 blood samples are taken 1 to 3 hours after injection and their radioactive concentration is estimated.[3] The results are expressed as a percentage of the injected dose as a function of time. Both the excretion and distribution volumes are extrapolated from the curve and are used to calculate clearance of the radiopharmaceutical.

In addition to the information obtained from the blood samples (*in vitro*) after the injection of ^{99m}Tc DTPA, the gamma emission from ^{99m}Tc allowed visualization of the tracer through the kidneys *in vivo*. The sequential images (dynamic imaging) can be displayed on a computer monitor (Figure 1).

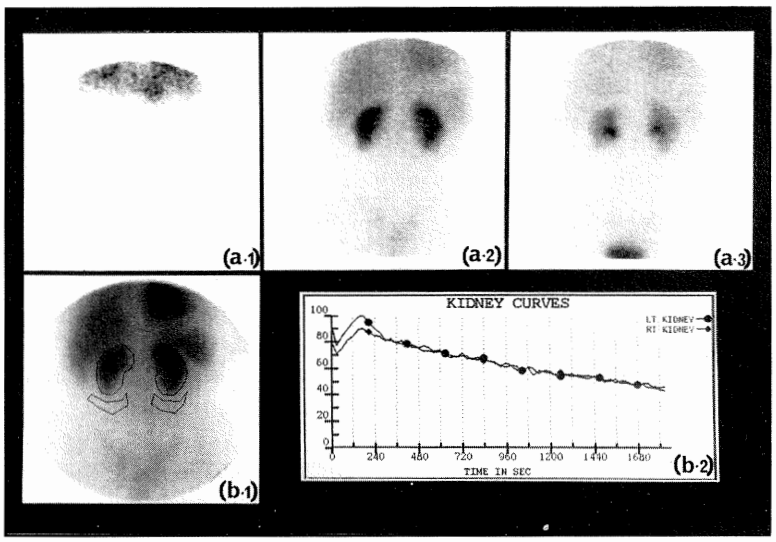

Figure 1. Abdominal Images Obtained at Different Intervals after IV Injection of ^{99m}Tc-DTPA

(a-1) 10 seconds after injection the radiopharmaceutical has not reached the kidneys.
(a-2) 4 minutes post injection, the kidneys are visualized and excretion has started.
(a-3) 20 minutes post injection the radiopharmaceutical is collected in the bladder.
(b-1) a region of interest is drawn on a computer around each kidney and a background area is defined.
(b-2) matching renogram.

Gilbert Matte, BPharm, PhD, is an Assistant Professor, Department of Medical Imaging, College of Medicine, University of Saskatchewan, Allied Scientists, Saskatoon Health Board, Saskatoon, Saskatchewan.
Douglas N. Abrams, PhD, is Assistant Director, Radiopharmacy, Health Sciences Centre, Winnipeg Manitoba, and Assistant Professor, University of Manitoba.
Address correspondence to: Gilbert Matte, PhD, Department of Nuclear Medicine, Royal University Hospital, 103 Hospital Drive, Saskatoon SK S7N 0W3.

In Figure 1, ^{99m}Tc DTPA injected into a normal individual can be observed to distribute in the blood pool (Figure 1 a.1), followed shortly thereafter by visualization of the 2 kidneys (Figure 1 a.2). Finally the radioactivity flows into the bladder (Figure 1 a.3). Regions of interest can be drawn around each kidney. Analysis of the radioactivity detected within each area allows assessment of each kidney separately (Figure 1 b.1). The amount of radioactivity in each kidney can be determined directly as a function of time immediately following injection. The resultant renogram (Figure 1 b.2) is a graphical analysis of the accumulation and elimination of radioactivity by each kidney individually.

The GFR can be determined from the renogram either by estimating the fraction of the injected dose present in the kidney within the first 2 or 3 minutes after injection or by studying the slope of the uptake or accumulation phase of the renogram. This method does not require any blood work, however, it is not as precise as the method using blood samples.[4]

The renal plasma flow (RPF) is the amount of plasma flowing through the kidneys per unit time (approximately 650 mL per minute). The effective renal plasma flow (ERPF) is the amount of plasma that perfuses the renal tubules (approximately 10% less than the RPF), the functional portion of the kidney.[1] The ERPF differs from the GFR in that it measures tubular function (major clearance mechanism) in addition to glomerular filtration.

The ERPF can be estimated from plasma clearance if the appropriate substance meets all the requirements of an effective GFR agent and is also efficiently secreted so that little remains in the blood leaving the kidney.

Historically, para-aminohippuric acid was used to assess ERPF. As in the case of GFR determinations, nuclear medicine techniques were seen as a means to simplify the procedure and increase the accuracy of the data by the use of a radio-iodinated analog ortho-iodo-hippuric acid (OIH) radiolabelled with ^{131}I.[5]

Initially, ERPF was calculated by obtaining serial blood samples (every 5 to 10 minutes) for 1 hour post-injection. This method was very labour intensive and required a significant amount of blood, especially in children. In addition, the assumptions used to simplify the GFR calculation could not be used to calculate ERPF. To circumvent these problems a mathematical model was developed and applied which reduced the number of blood samples required.[5]

Unfortunately the emission characteristics of ^{131}I limits its usefulness as an imaging agent due to its higher radiation dose and poor imaging properties. It does not afford as high quality images as with ^{99m}Tc labelled agents and hippuric acid derivatives can not be readily labelled with ^{99m}Tc. However, because of its low cost, ^{131}I-OIH is still used in many centres to assess ERPF.

Recently, a ^{99m}Tc labelled radiopharmaceutical, mercaptoacetyltriglycine (MAG3), has been introduced to replace ^{131}I-OIH.[6]

Clinical Application of Nuclear Medicine Renal Studies

Information from a patient study can be derived from both the graphical display of the radiopharmaceutical kinetics (renogram) and from an analysis of the image itself. A renogram can be obtained with either ^{99m}Tc DTPA (Figure 1) or ^{99m}Tc MAG3. It is inspected to evaluate the symmetry and intensity of kidney uptake (Figure 1 b.1) and will selectively identify which kidney might be deficient. In a normal individual the activity detected in the kidneys should parallel each other throughout all phases of the renogram and emptying usually occurs rapidly. The presence of an obstruction or hydronephrosis is indicated if the radioactivity does not leave the kidney (Figure 2).

Various renal function pathologies can be identified by analysis of the renogram combined with an inspection of the images. For example, in acute tubular necrosis, the kidneys show fair perfusion and uptake with delayed excretion and poor ERPF. In kidneys with cortical necrosis, the cortex will not visualize. In pyelonephritis the cortex will present with a defect. The unilateral absence of perfusion will be apparent due to the lack of radiopharmaceutical uptake in the presence of a renal artery embolus. Obstruction of the urinary system will present with diminished cortical uptake and a prolonged transit, followed by delayed or absent drainage (Figure 2). This is in contrast to renal artery stenosis where early uptake and excretion will be decreased and the kidney will appear smaller.

Nuclear medicine is particularly effective in the assessment of renal function in transplanted kidneys. It is very effective in the first few days to weeks after surgery, when the patient may be oliguric or anuric due to

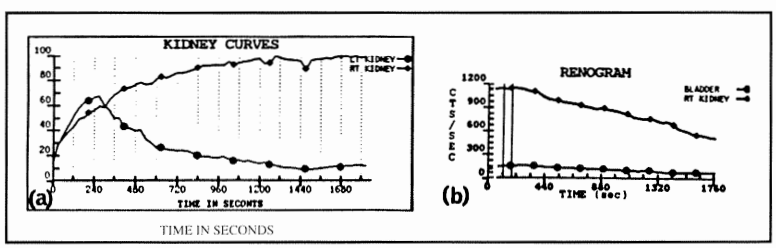

Figure 2. Renogram of a Patient with Suspected Right Kidney Obstruction.
(a) The activity in the kidneys expressed as a percentage of normalized content as function of time shows that accumulation is delayed in the right kidney with little excretion.
(b) The effect of furosemide is shown. New urine formation induced by the furosemide pushes the tracer out of the kidney and rules out the possibility of mechanical obstruction.

cortical or acute tubular necrosis, uretal obstruction, extravasation of urine, arterial or venous thrombosis or rejection. The GFR and ERPF can be determined within 24 hours of surgery and followed at 2 -3 day intervals until the patient is stable. In a successful transplant, activity should appear in the graft soon after injection, achieve a peak level then decrease.

Renal arterial or venous thrombosis, acute cortical necrosis and hyperacute rejection are indistinguishable, resulting in a total absence of flow and function. All of these conditions require removal of the graft. Cadaveric allografts demonstrate an element of acute tubular necrosis which manifests as a slight decrease in perfusion and uptake of the radiopharmaceutical. Rejection presents with similar but more pronounced characteristics and a progressive deterioration of function. Postoperative tubular necrosis may be demonstrated but will usually resolve without therapy within a few days.[8,9]

Pharmaceutical Intervention

The physiologic effects of therapeutic drugs can help in the evaluation of renal function. Nuclear medicine utilizes the effects of diuretics (such as furosemide) and angiotensin converting enzyme inhibitors (such as captopril) to monitor changes in kidney uptake and excretion of the radiopharmaceutical in establishing a differential diagnosis of renal dysfunction.

Furosemide is used to differentiate between obstruction and hydronephrosis.[10] Hydronephrosis is a distension of the pelvis and calyces of the kidney with urine. It can be produced by a number of causes such as uropathy due to obstruction of outflow independent of kidney function, or nephropathy with renal dysfunction due to a past or present uropathy. It can also be caused by a simple dilatation of the renal collecting system.

After injection of the radiopharmaceutical, the activity in the hydronephrotic kidney will plateau, exhibiting delayed washout. If at this phase IV furosemide is administered, urine production should increase and wash the radioactivity out of a hydronephrotic kidney and the plateau observed on the renogram will washout. If an obstruction is present, the kidney activity will not change and the plateau will remain unchanged.[10]

The renograms shown in Figure 2 were obtained after the administration of ^{99m}Tc MAG3 in a 62 year-old female presenting with flank pain after a previous right pyeloplasty. Sequential imaging revealed accumulation in both kidneys with delayed excretion by the right kidney (Figure 2.a). Figure 2.b shows the renogram following administration of furosemide. The decrease of activity in the right kidney excludes the possibility of significant mechanical obstruction.

Another area, where pharmaceutical intervention is beneficial, is in the differentiation between kidney dysfunction associated with essential hypertension or renal artery stenosis.[11,12] The test takes advantage of the fact that the production of angiotensin II is high in patients with renal artery stenosis (RAS), resulting in vasoconstriction of the efferent artery to maintain glomerular pressure. In patients with RAS, administration of captopril, inhibits the angiotensin converting enzyme (ACE) and offsets the overproduction of angiotensin II. This results in dilatation of the efferent arteriole and in a drop of the transglomerular pressure. The overall result is a decrease in GFR and ERPF with delayed renal uptake of the radiotracer by the kidney and the renogram will show a slow increase in radioactivity that does not clear from the kidney. In hypertensive patients without RAS dilatation of the afferent arteriole occurs following injection of an ACE inhibitor to maintain glomerular pressure and no changes in the GFR, ERPF or in the renogram are observed.

To prevent hypotensive episodes following administration of the ACE inhibitor, it is recommended that antihypertensive medications be discontinued 48 hours prior to the test.[9] ACE inhibitors should be discontinued even earlier.

Figure 3 shows the renal studies from a 57 year-old female with a history of refractory hypertension and blood pressure greater than 160/110mmHg. Ultrasound showed a bruit on the right side and nuclear medicine was requested to confirm the presence of a

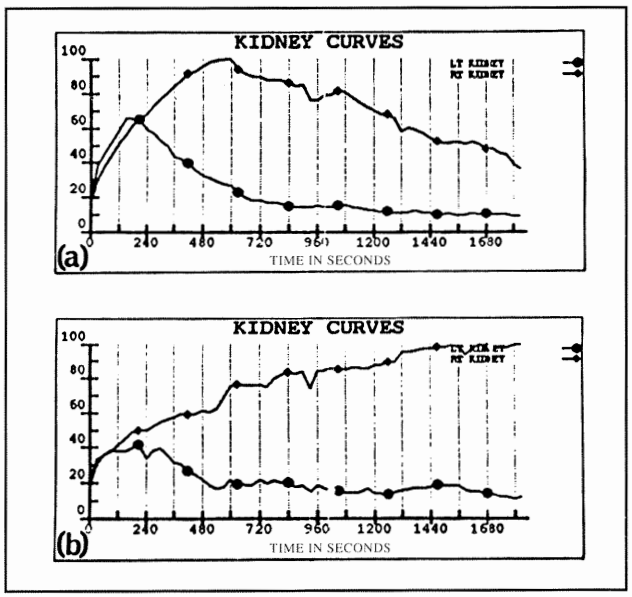

Figure 3. Renogram of a Patient with Suspected Right Renal Artery Stenosis.
(a) Accumulation prior to captopril administration shows delayed uptake and excretion in the right kidney.
(b) Repeat study after captopril administration shows delayed uptake and no excretion. The deterioration of function is consistent with renal artery stenosis.

right RAS. A ^{99m}Tc MAG renogram of the kidney prior to captopril administration showed slow uptake and excretion of the radiopharmaceutical by the right kidney (Figure 3-a). Repeat study following administration of captopril one day later showed slow accumulation of the activity within the right kidney (Figure 3-b). The deterioration of function in the right kidney following captopril administration was consistent with the presence of RAS and was later confirmed by angiography.

In summary, radiopharmaceuticals and pharmaceutical manipulation play an important role in the evaluation of renal function and as a diagnostic tool for determining the etiology of renal dysfunction.

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