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*An Update of Radiopharmaceuticals
for
Renal Imaging and Function Studies*

by: Dennis Eshima, Ph.D.

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Renal Imaging and Function Studies**

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UPDATE OF RADIOPHARMACEUTICALS FOR RENAL IMAGING AND FUNCTION STUDIES

STATEMENT OF OBJECTIVES

Upon successful completion of this course you should be able to:

1. Describe general renal anatomy and physiological processes.
2. Identify radiopharmaceutical agents which are useful in the commonly performed renal imaging procedures:
 - a. perfusion imaging
 - b. determination of functioning renal mass
 - c. measurement of glomerular filtration rate (GFR)
 - d. measurement of effective renal plasma flow (ERPF)
3. Compare common clinical methods to perform quantitative measurements of GFR and ERPF.
4. Discuss the usefulness of the Tc-99m tubular function agent, Tc-99m mertiatide.

COURSE OUTLINE

- I. INTRODUCTION
- II. RENAL ANATOMY.
- III. RENAL PHYSIOLOGY.
- IV. RADIOPHARMACEUTICAL AGENTS.
- V. RADIONUCLIDE RENOGRAPHY.
- VI. RENAL BLOOD FLOW AND PERFUSION AGENTS.
- VII. STATIC IMAGING AGENTS.
- VIII. QUANTITATIVE RENAL STUDIES.
 - A. Constant Infusion Clearance Measurements.
 - B. Single Injection Clearance Determinations.
 - C. Simplified Clearance Calculations Based on 1 or 2 Plasma Samples or Camera Images.
- IX. AGENTS FOR THE MEASUREMENT OF GLOMERULAR FILTRATION RATE.
- X. AGENTS FOR THE MEASUREMENT OF EFFECTIVE RENAL PLASMA FLOW.
 - A. Ortho-Iodohippuric Acid: An Iodinated Tubular Function Agent.
 - B. Tc-99m Tubular Function Agent: Tc-99m Mertiatide.
 - C. Tc-99m Mertiatide: Comparison to OIH.
 - D. Tc-99m Mertiatide Clearance Measurements.
 - E. Clinical Comparison of Tc-99m Mertiatide to Tc-99m Pentetate.
 - F. Kit Formulation of Tc-99m Mertiatide.
 - G. Development of Improved Tc-99m Renal Tubular Agents.
- XI. CONCLUSION

UPDATE ON RADIOPHARMACEUTICALS FOR RENAL IMAGING AND FUNCTION STUDIES

By

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INTRODUCTION

Nuclear medicine renal studies are extremely valuable in the noninvasive evaluation of renal anatomy and physiology and provide alternatives to other imaging modalities. Radiopharmaceuticals are available which provide methods of evaluating renal morphology and can be used to measure functional parameters such as the renal blood flow, effective renal plasma flow and glomerular filtration rate. Because of the close association between anatomy and physiology it is important to review these processes to better understand what diagnostic information can be provided by the various radiopharmaceutical agents and to understand the differences which exist between them. This continuing education article will review the anatomy and physiology of the kidney, renal kinetics, and discuss radiopharmaceutical agents which are used in the evaluation of kidney function.

RENAL ANATOMY

The kidneys are located in the posterior portion of the abdominal cavity, one on either side of the vertebral column, behind the peritoneal cavity. The kidney is encapsulated by a thin membrane, the renal capsule, which has convex lateral borders and concave medial borders. In the central portion of the concave border there is a deep longitudinal fissure called the hilus where the nerves and renal artery enter and the renal vein and ureter exit.

A longitudinal cut through the kidney demonstrates three separate areas: the cortex, the medulla and the pelvis (which are illustrated in figure 1). The cortex is the outer portion of the kidney and lies immediately beneath the renal capsule. The renal medulla is the region below the cortex and lacks the granular appearance associated with the cortex. Deeper into the kidney lies the renal pelvis which is the expanded upper end of the ureter into which the collecting system of the kidney empties.

The functioning subunit within the kidney is the nephron with each kidney containing approximately 1.2 million nephrons. The nephron is subdivided into four major segments: Bowman's capsule, the proximal tubule, the loop of Henle and the distal tubule. These segments of the nephron are shown in figure 2. The cortex contains all the glomeruli, the proximal and distal convoluted tubules as well as the

beginning of the collecting tubules. The medulla consists essentially of the loops of Henle and the collecting tubules.

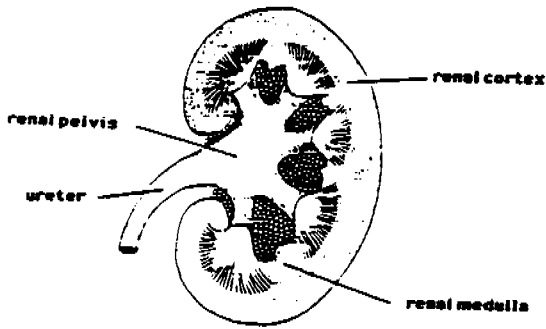


Figure 1. Longitudinal cross section through the kidney demonstrating the renal cortical area, renal medullary area, renal pelvis area and ureter.

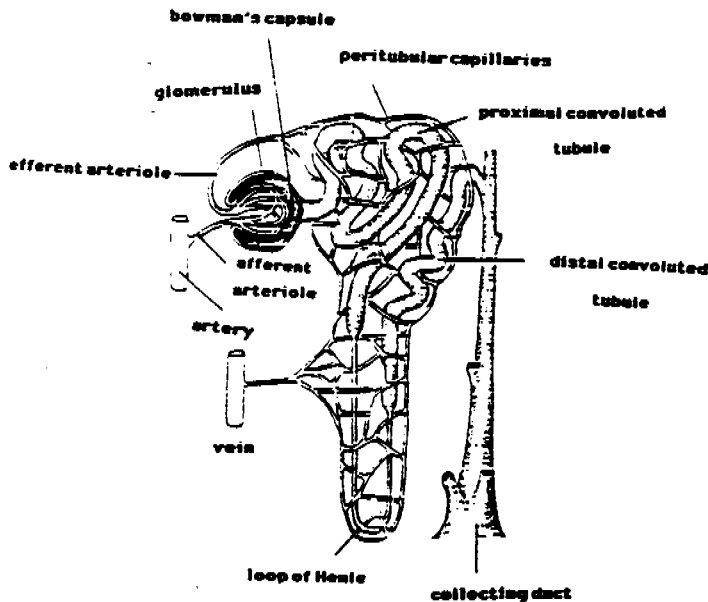


Figure 2. Diagram of the nephron showing the different anatomical sections and the location of the various blood vessels.

The kidneys are highly perfused organs receiving approximately 25% of the cardiac output, which is equivalent to a blood flow of 1200 ml/min or a plasma flow of 600 ml/min. The renal artery is the major vessel which supplies blood to the kidney. After entering the kidney the renal artery subdivides into the smaller interlobar and arcuate arteries. The arcuate arteries further branch into interlobular arteries which give off numerous short branches called afferent arterioles each of which supplies one glomerulus (figure 2). The glomerulus is a compact tuft of interconnected capillary loops that protrudes into Bowman's capsule, which is the beginning of the nephron. The glomerulus is connected on the other end to the efferent arteriole which is generally smaller in diameter than the afferent arteriole. The efferent arteriole is connected to a second capillary bed, the peritubular capillaries, which is an extensive network that surrounds the renal tubules. The peritubular capillaries subsequently

recombine eventually forming the renal vein which allows blood to exit from the kidney.

Bowman's capsule is the expanded closed end of the nephron into which the glomerular capillaries protrude with the capsule having a space into which fluid can be filtered. Connected with Bowman's capsule is the proximal tubule which is that portion of the nephron that drains the capsule. The proximal tubule is subdivided into a coiled section, the proximal convoluted tubule, followed by a relatively straight segment, the pars recta. The loop of Henle is the next portion of the tubule which forms a sharp hairpin loop. The loop of Henle includes the descending thick limb, descending and ascending thin limbs and the ascending thick limb, which may be the pars recta of the distal tubule. The last portion of the nephron is the distal tubule, which begins as the ascending thick limb of the loop of Henle rising upward toward the glomerulus and continuing in a nearly straight course toward the region of its glomerulus, at which point it begins to convolute. The tubule then passes between its afferent and efferent arteriole; this short segment is known as the macula densa. Once past the macula densa, the tubule once more becomes coiled and forms the rest of the distal convoluted tubule. At the terminal end of the distal tubule the nephron joins with the collecting system.

The collecting duct is the beginning of the urinary tract which begins in the outer cortex by the junction of two or more transition segments of the distal tubules, which join together to form cortical collecting tubules. These collecting tubules then turn downward where they enter the medulla. Once in the medulla, several collecting ducts fuse to form one of the many papillary ducts that drain into the renal calyx. The calyces subsequently empty into the pelvis which is drained by the ureter and allows fluid to eventually empty into the urinary bladder.

RENAL PHYSIOLOGY

The kidneys are important organs as they receive a large fraction of the cardiac output and are used to regulate homeostasis by performing a variety of complex physiological processes. The kidneys regulate fluid volume, adjust the body concentration of inorganic ions and organic metabolites and eliminate toxic or potentially toxic metabolites using active and passive transport mechanisms.

The physiological processes start as arterial blood passes into the glomerulus. The arrangement of the glomerular capillaries and the presence of the efferent arteriole, which acts as a second resistant vessel, maintain the hydrostatic pressure in the glomerular capillary network. Blood in this network is subject to a filtration process which causes movement of solvents and solutes through the glomerular capillary walls into Bowman's capsule. The forces which favor filtration are the glomerular-capillary hydrostatic pressure and the oncotic pressure of the fluid in Bowman's capsule. The forces opposing filtration are the hydrostatic pressure in Bowman's capsule and the oncotic pressure in the glomerular-capillary plasma. These factors, as they relate to filtration, are shown in equation [1],

$$[1] \quad \text{Filtration} = (HP_{GC} + OP_{BC}) - (HP_{BC} + OP_{GC})$$

where HP_{GC} is the hydrostatic pressure in the glomerular capillaries, OP_{BC} is the oncotic pressure in Bowman's capsule, HP_{BC} is the hydrostatic pressure in Bowman's capsule and OP_{GC} is the oncotic pressure in the glomerular capillaries. Filtration does not occur throughout the entire length of the glomerular capillaries but rather continues until the two opposing forces become equal.

The filtration process results in the bulk flow of water through the glomerular capillary wall which carries with it solutes which are small enough to pass through this filter. This process separates the plasma water and its nonprotein constituents from the blood cells and protein macromolecules. Molecular size and charge are two major factors which determine whether a substance will be filtered or remain in the capillary. The molecular-weight cut-off for filtration through the glomerulus is about 70,000 with negatively charged macromolecules being restricted more than neutral molecules. Plasma albumin, with a molecular weight of 69,000 and hindered by its charge, passes through the filter only in minute quantities. Smaller molecules pass through the filter easily but the filter is freely permeable only to those molecules with a molecular weight less than about 5,000 to 7,000. Since the glomerular filter permits the free passage of small molecular weight compounds the initial filtrate contains small molecules and ions (e.g., glucose, amino acids, urea, sodium, and potassium) in the same concentration as the afferent arteriolar concentration. Compounds which are plasma protein bound effectively take on the size of the plasma protein and only a fraction of the total amount of the substance which is free in the plasma is able to undergo filtration. The ultrafiltrate which is formed in Bowman's capsule then flows into the proximal tubule and immediately begins to undergo changes being altered by the various transport processes.

The proximal tubule cells are able to both reabsorb and secrete small molecules and ions. Reabsorption involves the movement of compounds from the tubular lumen into the peritubular capillaries. A significant amount of filtrate (sodium, potassium, and other compounds) is reabsorbed from the tubular lumen. The reabsorption of filtered sodium is an important transport process as it leads to electrical, concentration and osmotic gradients which facilitate the passive reabsorption of various solutes like chloride, potassium, urea, water, glucose, amino acids, phosphate, calcium and bicarbonate as well as the secretion of hydronium ions, in an effort to maintain a homeostatic environment.

The proximal tubular cells also secrete a wide range of compounds in order to eliminate waste and foreign products, and toxic or potentially toxic compounds from the body. The secretory process provides a major alternate pathway by which material may be eliminated from the body as it allows material to enter into the tubular lumen directly from the peritubular capillary network. Secretion may be a passive diffusion, non energy-requiring process, or an active transport, energy-requiring process. Figures 3 and 4 pictorially represent these processes. Secretion begins with the diffusion of a compound out of the peritubular capillary into the interstitial fluid. Once inside the interstitial space compounds may enter into the

lumen passively by diffusion through the tight junctions or through the cellular membranes. Active secretion is thought to occur by an active transport process on the peritubular capillary side which results in the transport of a compound across the basolateral membrane. The resulting high intracellular concentration allows movement across the cellular membrane into the lumen of the nephron by either a simple or facilitated mechanism (figure 3). Several active transport secretory systems for organic molecules exist in the proximal tubule. These systems display characteristics which are common to other active transport systems; they have a maximum transport capacity, may be competitively inhibited and the transport may be blocked by pharmacologic agents. There are two major proximal tubular secretory systems, one which actively transports anions, and the other which actively transports cations.

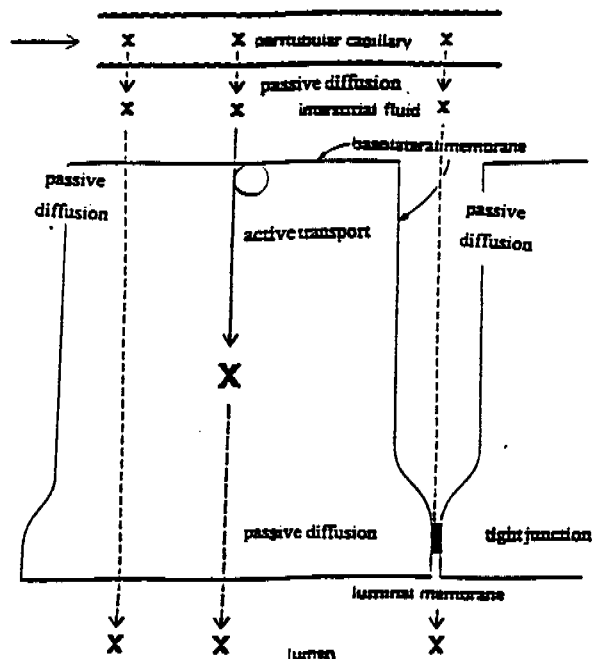


Figure 3. Cellular representation of the passive diffusion and active transport process. Passive diffusion may occur by a compound passing through the tight junctions or through the cellular membranes. Active transport of organic compounds occurs by being actively transported from the interstitial fluid into the tubular cell and then diffusing into the tubular lumen.

The renal secretion of a plasma protein-bound compound follows a similar pattern, however the compound must initially dissociate from the plasma protein before it can enter into the interstitial fluid. If the compound is avidly transported by the tubule cells, a low concentration in the interstitial fluid results; this favors additional dissociation from the plasma proteins allowing more of the compound to be extracted in a single pass (figure 4). For compounds which are tightly protein bound the transit time through the glomerulus and peritubular capillaries has been thought to be too short for complete dissociation of a compound to occur thereby reducing its total renal clearance.

The fluid which leaves the proximal convoluted tubule and enters the loop of Henle is isotonic to plasma. The loop of Henle and the highly organized arrangement of medullary and cortical components facilitate the concentrating capacity of the

kidney, increasing fluid osmolality. The fluid then enters the distal tubule where sodium, chloride and water, to varying extents, are reabsorbed. The water permeability of the early distal tubule is extremely low, however, the permeability of the late distal tubule and the collecting duct is subject to physiological control and may vary from extremely low to fairly high depending upon the concentration of antidiuretic hormone (ADH). Thus, functionally, the loop of Henle, the distal tubule, and the collecting duct act to concentrate the tubular fluid and conserve water. The concentrated fluid which finally exits the collecting duct passes into the renal pelvis where it flows through the ureters and empties into the bladder without undergoing any further change.

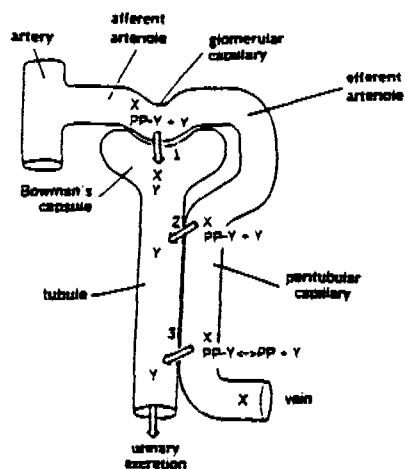


Figure 4. Diagrammatic representation of the glomerular filtration and tubular secretion process. Compound X is cleared by glomerular filtration only, while Compound Y is plasma protein bound and can also be actively transported by the tubular cells. [1] A fraction of Compound X and a fraction of Compound Y that is not protein bound is filtered at the glomerulus. [2] The remainder of Compound X travels through the peritubular capillary network into the venous system without undergoing any further change. The remaining portion of Compound Y—both the plasma protein bound and free fraction—passes into the peritubular capillary network where Compound Y is actively transported into the tubular lumen. [3] The removal of the unbound Compound Y allows more to dissociate from the plasma proteins thus making more available for extraction.

In summary, the kidneys are important homeostatic organs which conserve water, electrolytes and nutrients while eliminating waste products. The filtration, reabsorption and secretion of compounds by the kidney is dependent upon the various physiological processes: renal blood flow, glomerular filtration, tubular secretion and tubular reabsorption. Radiopharmaceuticals have been developed whose localization depends upon these same processes; therefore, by monitoring the uptake and elimination of specific radiopharmaceutical agents, clinical information on the functional status of a patient's renal system can be obtained.

RADIOPHARMACEUTICAL AGENTS

Nuclear medicine studies, with the aid of different classes of radiopharmaceutical agents, have made significant contributions in the diagnosis of numerous renal diseases. Radiopharmaceutical agents have been useful for the evaluation of renal blood flow and morphology, for

measurement of the glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF), and for performing perfusion imaging and renography. The most commonly used agents are listed in Table 1. Studies utilizing an appropriate gamma emitting photon will provide information not only on total renal function but on individual kidney function as well. Utilizing computer-interfaced image acquisitions, kidney time-activity curves (renogram curves) can be constructed, thus providing additional diagnostic information.

RADIONUCLIDE RENOGRAPHY

The renogram curve is a time-activity curve which describes the transit of a radiopharmaceutical agent through the kidney. The curve is obtained by drawing a region of interest over the whole kidney (whole kidney curve) or the renal cortex (cortical curve) and obtaining counts for a predetermined time interval (e.g., 30 sec/frame for 60 frames). The renogram curve is often divided into three periods: tracer appearance, tracer extraction and tracer elimination. Tracer appearance describes the period of blood flow to the kidneys. Tracer extraction provides information on renal function; the renogram curve peaks when the rate of tracer accumulation is equal to the rate of tracer elimination. The elimination phase provides information on the function of the excretory processes of the kidney. Renal disease may result in a decreased accumulation of the tracer (shorter peak height), accumulation of the tracer at a slower rate (longer time to maximum peak height) and/or elimination at a slower rate (shallow downslope of the curve). The renogram curve is an important diagnostic tool which provides functional information that can assist in elucidating various disease processes.

RENAL BLOOD FLOW AND PERFUSION AGENTS

Radiopharmaceuticals are able to measure total renal blood flow as well as flow to the outer and inner cortical regions. The agents which have been historically used to assess renal blood flow include 1] non-diffusible intravascular agents such as iodinated or Tc-99m-labeled albumin or erythrocytes, 2] agents which are highly extracted from the blood stream such as labeled microspheres and 3] noble gasses such as Kr-85 and Xe-133. These agents do not undergo any significant extraction by the nephrons and provide direct measurements of renal blood flow without the need to correct for activity which has accumulated within the nephrons. These studies, however, are not routinely performed.

In contrast to quantitative renal blood flow studies, renal perfusion imaging has played an important clinical role as an alternative to the more invasive angiographic studies. Due to their noninvasive nature, renal perfusion studies are especially valuable for the routine evaluation of renal perfusion following transplantation to monitor the integrity of the vascular supply. A normal graft has a radionuclide histogram with a well defined peak. Obstruction of the renal artery or vein results in non-visualization of the kidneys. The loss of the histogram

Table 1
CLASSES OF RENAL RADIOPHARMACEUTICAL AGENTS

Renal Blood Flow

- a. Non-Diffusible Intravascular Agents
Labeled Albumin
Labeled Erythrocytes
- b. Highly Extractable Agents
Labeled Microspheres
- c. Inert Gasses
Kr-85
Xe-133

Perfusion Agents

- a. Tc-99m Pentetate (Tc-99m Diethylenetriaminepentaacetic acid [Tc-99m DTPA])
- b. Tc-99m Gluceptate (Tc-99m Glucoheptonate)
- c. Tc-99m Mertiatide (Tc-99m Mercaptoacetyltriglycine [Tc-99m mertiatide])
- d. Other Tc-99m Based Radiopharmaceutical Agents
- e. I-123 o-iodohippuric acid (I-123 OIH)

Static Imaging Agents

- a. Tc-99m Gluceptate (Tc-99m Glucoheptonate)
- b. Tc-99m Succimer (Tc-99m Dimercaptosuccinic Acid [Tc-99m DMSA])

Glomerular Filtration Agents

- a. Inulin
- b. I-125 Iothalamate
- c. Cr-51 Edetate (Cr-51 Ethylenediaminetetraacetic Acid [Cr-51 EDTA])
- d. Tc-99m or In-111 Pentetate (Tc-99m or In-111 Diethylenetriaminepentaacetic acid [Tc-99m or In-111 DTPA])

Tubular Function Agents

- a. Para-aminohippuric acid (PAH)
 - b. I-131 or I-123 Ortho-iodohippuric acid (I-131 or I-123 OIH)
 - c. Tc-99m Mertiatide (Tc-99m Mercaptoacetyltriglycine [Tc-99m MAG₃])
-

peak may indicate a decrease in perfusion suggestive of a rejection episode. Perfusion imaging is performed following an intravenous (IV) bolus injection of a gamma-emitting radiopharmaceutical agent. The most popular agents are Tc-99m pentetate (Tc-99m diethylenetriaminepentaacetic acid [Tc-99m DTPA]), Tc-99m gluceptate (Tc-99m glucoheptonate) and Tc-99m mertiatide (Tc-99m mercaptoacetyltriglycine [Tc-99m MAG₃]). However, it is possible to use any Tc-99m based radiopharmaceutical agent.

STATIC IMAGING AGENTS

The two prominent radiopharmaceuticals which are used for renal parenchyma imaging are Tc-99m gluceptate (Tc-99m glucoheptonate) and Tc-99m succimer (Tc-99m dimercaptosuccinic acid [Tc-99m DMSA]). The uptake of these agents are related to the relative functioning renal tubular mass and do not measure a specific functional parameter. The structures of these ligands are shown in Figure 5.

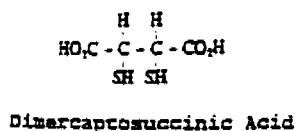
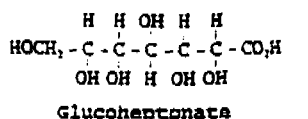


Figure 5. Structure of the ligands used for static renal imaging.

Tc-99m gluceptate is predominately cleared by glomerular filtration, however, it also undergoes tubular secretion to a minor extent. Tc-99m gluceptate is actively transported by the anionic transport system of the proximal tubular cells. Following an IV bolus injection, approximately 5%-15% of the dose remains bound to the renal tubular cells with 30%-45% of the injected dose being excreted into the urine within the first hour. Since a large fraction of Tc-99m gluceptate accumulates in the collecting system, this activity may present problems in interpreting parenchymal images, potentially producing erroneous estimates of differential renal function especially in patients with urinary tract obstruction.

The renal handling of Tc-99m succimer is reported to be different than Tc-99m gluceptate. The exact mechanism by which Tc-99m succimer localizes in the kidney is unclear, however, glomerular filtration is known to play a role and it has been suggested that tubular secretion and potentially reabsorption from the lumen into the proximal tubular cells may facilitate its renal uptake. The renal extraction of Tc-99m succimer is estimated to be 4%-5% per pass with approximately 40%-50% accumulating in the cortical tubules within one hour which remains for 24 hours. The urine excretion of Tc-99m succimer is 4-8% within one hour, 16%

within 2 hours and increases to 30% by 14 hours. Tc-99m succimer, in contrast to Tc-99m gluceptate, produces renal parenchyma imaging with minimal interference from renal pelvis activity; however, a problem with its use is that it delivers a higher radiation dose to the patient.

Tc-99m gluceptate is available by reconstituting a lyophilized stannous chloride/gluceptate kit with Tc-99m sodium pertechnetate. The commercial multi-dose vial allows reconstitution with 200-300 mCi of Tc-99m sodium pertechnetate producing a radiochemical purity of greater than 90%. The reconstituted kit has a shelf life of 6 hours post reconstitution. Tc-99m succimer is commercially available in a kit formulation, which can be reconstituted by the addition of approximately 40-50 mCi of Tc-99m sodium pertechnetate producing a radiochemical purity of greater than 85%. The reconstituted Tc-99m succimer has a shelf-life of only 30 minutes post reconstitution.

QUANTITATIVE RENAL STUDIES

Quantitative nuclear medicine studies have been developed to determine differential renal function, the glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF). Differential function can be determined by comparing the relative renal uptake of a radiopharmaceutical agent by acquiring gamma camera images and drawing regions of interest over the kidneys and determining the counts within each region. This procedure provides an easy method to quantitate individual kidney function. The quantitative measurements of GFR and ERPF can be determined utilizing a variety of techniques including constant infusion, single injection, simplified single injection and camera-based techniques.

Constant Infusion Clearance Measurements

Renal clearance is generally most accurately measured from a constant infusion study. This technique requires the infusion of a compound at a rate which maintains it at constant plasma levels. Ideally the compound should be taken up and excreted by the kidneys with no significant renal retention. The constant infusion clearance is calculated according to equation [2],

$$[2] \quad \text{Cl} = (\text{U} \times \text{V}) / \text{P}$$

where Cl is clearance in ml/min, U is urine radiopharmaceutical concentration in counts/ml, V is urine flow rate in ml/min and P is plasma radiopharmaceutical concentration in counts/ml. The constant infusion clearance technique provides an accurate renal clearance value, however, it is not amenable to routine clinical situations.

Single Injection Clearance Determinations

The plasma clearance can be used to quantitate renal clearance provided agents are used which are cleared exclusively by the kidney. The plasma clearance can be calculated following an IV bolus injection of a compound utilizing

the generalized pharmacokinetic equation (equation [3]),

$$[3] \quad Cl = \text{Dose}/\text{AUC}$$

where D is the administered dose and AUC is the area under the plasma concentration-time curve. The AUC is determined by plotting the plasma concentration as a function of time following the IV injection of a radiopharmaceutical agent. The AUC may be calculated utilizing both model-dependent and model-independent approaches with the two-compartment model being the most widely accepted model. The two-compartment model describes the plasma concentration-time curve utilizing a biexponential equation (equation [4]), where C_p is the plasma concentration, $K[1]$ and $K[2]$ are the time-zero plasma concentration intercepts and a and b are related to the slopes of the disposition curves.

$$[4] \quad C_p = K[1]e^{-at} + K[2]e^{-bt}$$

The $K[1]$, a , $K[2]$ and b values may be determined graphically or mathematically utilizing various curve stripping techniques. After these values have been determined, the AUC may then be calculated from equation [5]:

$$[5] \quad \text{AUC} = K[1]/a + K[2]/b$$

Alternatively, a model-independent approach can be used where the AUC can be calculated by applying the trapezoidal rule.

The two-compartment clearance calculation has compared favorably to values obtained utilizing the constant infusion clearance technique. There are, however, a significant number of practical problems which can be encountered when applying this procedure clinically. The accurate determination of the plasma disappearance curve is time-consuming and inconvenient to the patient since it requires multiple blood samples. In addition, meticulous attention must be given to details, i.e., the determination of the dose injected, the preparation of standards and samples, and the assurance that a bolus injection was administered is mandatory in order to obtain accurate results.

Simplified Clearance Calculations Based on 1 or 2 Plasma Samples or Camera Images

To circumvent some of the problems associated with constant infusion clearance determinations and multiple plasma sampling, simplified clearance methods have been developed to facilitate the routine clinical measurements. These techniques require either a) drawing fewer blood samples or b) determining the early kidney uptake using gamma camera image data.

Renal clearances have been estimated from one or two plasma samples as the plasma activity has been found to be inversely related to renal function. These approaches attempt to extrapolate the plasma disappearance curve from one or two points on the curve. The plasma activity can be extrapolated to a clearance value by 1) incorporating values for the slope of the exponential plasma disappearance curve and the volume

of distribution into a standard equation or 2) fitting the sample to a known parabolic or exponential function. The one and two sample clearance methods have compared favorably to the multiple plasma-sample clearance technique provided the time the blood sample was obtained is exact and the standard and plasma samples were prepared accurately.

Camera-based techniques have also been developed to estimate renal clearances as these techniques relate the early renal uptake to renal function. The renal uptake depends on the injected activity, uptake by the kidneys, distance from the kidney to the camera and tissue attenuation. The injected activity is determined by imaging the syringe prior to injection and then imaging the syringe after injection and subtracting the counts which remain in the syringe. Renal uptake is determined from gamma camera images by drawing regions of interest over the kidneys and obtaining integral counts in the region after subtracting the background counts. The kidney depth can be estimated from the patient's height and weight, however a more accurate measurement can be made using ultrasound. The camera-based technique provides reasonably good estimates of renal function and is not dependent on in-vitro techniques. However, there are several potential problems associated with this technique. Among other things, there is lack of standardization regarding the size, shape, and location of the region of interest used to determine background activity. As alluded to previously, the use of patient height and weight as determinants of renal depth can sometimes result in inaccurate estimations. Moreover, the injection site should also be imaged to ensure that no extravasation occurred, as an extravasated dose will reduce the renal uptake.

These simplified methods provide techniques which can be easily applied in a routine clinical setting and which can provide quantitative renal function information.

AGENTS FOR THE MEASUREMENT OF GLOMERULAR FILTRATION RATES

The extraction efficiency of glomerular filtration markers in normal volunteers is 20% which results in a glomerular filtration rate of 120 ml/min. An ideal GFR marker is a substance that is freely filterable at the glomerulus and is neither secreted nor reabsorbed. Ideally, a GFR marker should not 1) have pharmacological activity 2) be bound to plasma proteins, and 3) undergo metabolism, synthesis or storage in the kidney.

The clearance of a large number of compounds, both nonradioactive and radioactive, have been used as indexes of GFR (figure 6). The gold standard for the measurement of GFR is based on the clearance of inulin. Inulin is a starch-like polymer of fructose with a molecular weight of about 5,000. Inulin is not bound to plasma proteins, has a diameter of about 30 angstroms, is not charged and readily passes through the glomerular capillary membrane. In addition, it is not reabsorbed, secreted, synthesized nor metabolized by the renal tubules. The main limitation to the use of inulin is the lack of routine (simple and quick) analytical methods to determine its concentration in plasma and urine.

Substances besides inulin which have been used to measure GFR include creatinine, iothalamate and various radioactive metal complexes. Creatinine is routinely used for the measurement of GFR, however creatinine undergoes tubular secretion and therefore may overestimate the GFR. Iothalamate labeled with I-125 meets many of the requirements for a good GFR marker and it has been reported to be only minimally bound to plasma proteins. Iothalamate clearance has been found to correspond fairly closely to inulin clearances, however, it also slightly overestimates the inulin clearance values. I-125 iothalamate has been useful in determining GFR by counting plasma samples, but can not be used for imaging due to the low-energy gamma photons emitted by I-125. In addition to these agents, metal complexes of ethylenediaminetetraacetic acid (EDTA, edetate) or diethylenetriaminepentaacetic acid (DTPA, pentetate) (figure 6) have been shown to have clearances similar to inulin. The metal complexes which have been reported for the measurement of GFR include Cr-51 edetate, Yb-169 pentetate, In-113m pentetate, La-140 pentetate and Tc-99m pentetate. These agents allow the total GFR to be determined, and by using imageable quantities of gamma-emitting radionuclides they can provide diagnostic information on individual kidney function.

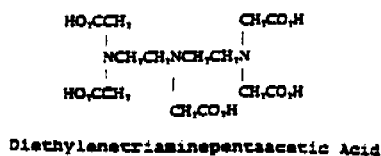
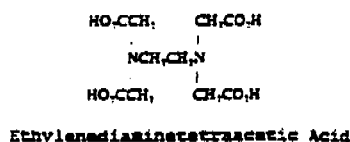
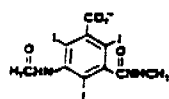
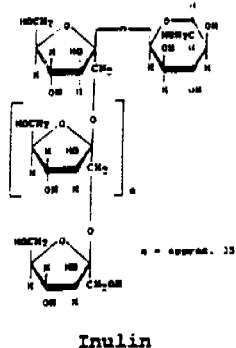


Figure 6. Structure of agents used for the measurement of the glomerular filtration rate.

The optimal combination of ideal imaging properties and convenience of a lyophilized kit formulation has facilitated the widespread acceptance of Tc-99m pentetate for imaging and GFR studies. Technetium-99m is readily available, emits a monoenergetic gamma photon of 140 keV and has a 6 hour

half-life, thus giving the patient a low radiation dose per imageable photon. Tc-99m pentetate meets a majority of the criteria for an ideal GFR marker. The clearance of Tc-99m pentetate has correlated well with inulin and iothalamate and does not undergo tubular secretion or reabsorption. However, approximately 5-10% of the injected dose is plasma protein bound with differences in the percent protein bound occurring between kit formulations from various manufacturers. In addition to providing GFR information, Tc-99m pentetate can be used to image renal perfusion by obtaining rapid serial images during the first pass circulation. Tc-99m pentetate studies also provide diagnostic information on total and individual renal function and can be used to generate renogram curves.

Clinical methods which have been developed to estimate GFR using Tc-99m pentetate employ either a blood sampling technique or a camera-based technique. A single plasma sample obtained at 3 hours post injection or two plasma samples, obtained at 30 minutes and 3 hours post injection, are combined with a two-compartment model to estimate GFR. A camera-based technique has been developed where counts in the kidney are obtained from 2 to 3 minutes post injection and, after correcting for background activity, the 1 minute integral kidney counts are used to determine GFR. Providing good technique is used, these methods result in reasonably good estimates of GFR.

Tc-99m pentetate is easily prepared by the addition of Tc-99m sodium pertechnetate to a lyophilized vial containing stannous chloride and pentetate and is commercially available from several manufacturers. Up to approximately 150-200 mCi of Tc-99m sodium pertechnetate may be added to multidose vials producing a radiochemical purity of greater than 90%. The reconstituted kit has a 6 hour shelf life post reconstitution, however, the shelf life is limited to one hour post reconstitution if the agent is to be used to quantitate GFR.

AGENTS FOR THE MEASUREMENT OF EFFECTIVE RENAL PLASMA FLOW

The use of agents which are highly or completely extracted and have the ability to measure renal plasma flow can provide important clinical information on renal function. Para-aminohippuric acid (PAH) is the gold standard in this category as it is avidly secreted by the anionic transport system, is not extensively bound to serum proteins, not metabolized to a major extent, nor retained by the kidneys. PAH approaches the ideal of complete extraction, however its extraction is only 85-95%, therefore its clearance is an approximation of renal plasma flow. The extent to which PAH escapes extraction is thought to be determined principally by the fraction of the blood that passes from the postglomerular vessels directly into the medulla and papilla. Therefore, PAH measures the flow of blood that traverses tissue that can effectively remove it from the plasma. This is called the effective renal plasma flow (ERPF) and provides clinical information about proximal tubular cell function.

PAH has been found to be cleared by glomerular filtration and tubular secretion with the filtration component being

related to its plasma protein binding. PAH is only 18% to 26% plasma protein bound; therefore a significant portion (approximately 15%) of its clearance occurs by glomerular filtration. The largest percentage of its clearance, however, occurs by tubular secretion. PAH clearances, like inulin clearances, are rarely measured in a routine clinical setting because of the time involved with the measurement of PAH in plasma and urine which requires chemical or chromatographic analysis.

Ortho-Iodohippuric Acid: An Iodinated Tubular Function Agent

In 1960, in an effort to develop a radiolabeled PAH analog, I-131 was incorporated into the ortho position of hippuric acid (I-131 ortho-iodohippuric acid, OIH, hippuran). OIH is structurally similar to PAH (figure 7) and is actively secreted by the kidneys utilizing the same active transport system as PAH. The plasma clearance of OIH is approximately 10% lower than for PAH, however its clearance is clinically used to measure the ERPF. OIH also has a lower extraction efficiency, approximately 10% to 30% lower than PAH. I-131 OIH has gained widespread acceptance as a tubular function agent as it has the advantage of having a higher extraction efficiency than GFR markers and gives higher kidney-to-background ratios and may allow the detection of mild renal disease that would not be detectable with agents cleared by glomerular filtration alone. The glomerular filtration rate of OIH is believed to be low with estimates ranging from 6% to 20% of its total clearance. The filtration of OIH is reduced by its ability to enter into red blood cells and its binding to plasma proteins. OIH has also been used to generate renogram curves to aid in the diagnosis of renal disease.

Alternatively, ERPF measurements can be obtained from gamma camera images utilizing the integral kidney counts from one to two minutes post injection. The OIH clearance values are lower than the actual ERPF value due to the lower extraction of OIH in comparison to PAH, but does provide reasonably good clinical values.

I-131 OIH is commercially available, however the disadvantages to its use are attributed to (a) potential radiochemical impurities present in the preparation, e.g., free iodide and iodobenzoic acid, and (b) the I-131 radionuclide. These radiochemical impurities have different distribution and/or kinetic properties than OIH and, therefore, may adversely affect image quality and measurements of renal function. Iodine-131 has suboptimal imaging properties as it emits a 364 keV gamma photon which results in poor spatial resolution; it also has particulate emission and an 8.08 day half-life. Thus the patient receives a high radiation dose per imageable photon. Due to the poor radionuclidic properties of I-131 and the propensity of free iodide to localize in the thyroid, the maximum administered dose is limited to approximately 300 uCi. As a result, I-131 OIH cannot be used clinically to evaluate renal perfusion. To circumvent these problems, OIH has been labeled with iodine-123. Iodine-123 OIH has better imaging characteristics due to its 159 keV gamma photon; the lack of beta emission lowers the radiation dose and allows the administration of higher doses resulting in a higher photon flux (higher count rate) and better spatial resolution. I-123 OIH also makes it possible to study renal perfusion, morphology and tubular function with a single study. Overall, I-123 OIH was found to be a superior imaging agent compared to I-131 OIH. However, I-123 OIH did not gain widespread acceptance in the United States and its production has been discontinued partially due to its 13 hour half life, limited availability and relatively high cost.

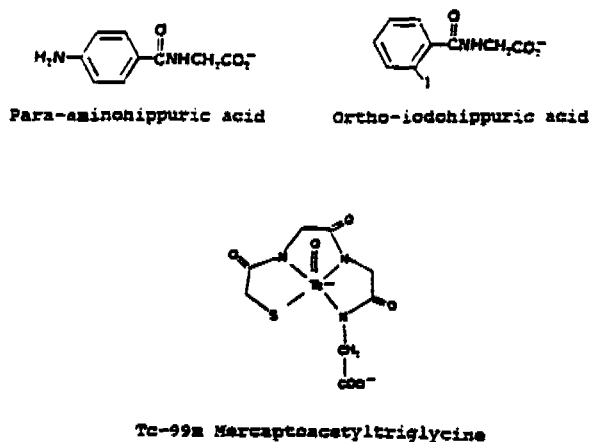


Figure 7. Structure of the agents used for evaluation of tubular cell function.

Simplified methods, i.e., single plasma sample and camera-based techniques, have been developed to determine the clearance of OIH. The single plasma sample technique requires obtaining a blood sample at 44 minutes post injection. Plasma counts are then obtained and related to the dose injected; this value is then utilized in a mathematical equation to derive a reasonably good estimate of the ERPF.

Tc-99m Tubular Function Agent: Tc-99m Mertiatide

The development of a Tc-99m based tubular function agent to replace I-131 OIH has provided a superior alternative as it combines the imaging properties and availability of Tc-99m with the convenience of a kit formulation. A complex of this type enhances the ability to study renal morphology, function and perfusion in a single noninvasive study, thus potentially replacing I-131 OIH for function studies and Tc-99m pentetate for perfusion studies. Technetium-99m has optimal imaging properties compared to I-131 and is relatively inexpensive and readily available, in contrast to I-123.

Numerous Tc-99m complexes have been identified which are accumulated by the kidneys to varying degrees. In addition to the static imaging agents, Tc-99m gluceptate and Tc-99m succimer, Tc-99m complexes of thiodiglycolic acid, diamide dithiol ligands (N₂S₂), and derivatives of paraaminohippuriciminodiacetic acid have been evaluated as tubular function agents. The low extraction fraction, lack of renal specificity and stereochemistry problems associated with these complexes precluded their commercial development as a replacement for OIH.

The agent which has recently obtained approval as a Tc-99m renal tubular function agent belongs to the triamide

mercaptide (N₃S) class of ligands and is Tc-99m MercaptoAcetylGlycylGlycyl-Glycine (Tc-99m MAG₃, Tc-99m mertiatide). The structure is shown in figure 7.

Tc-99m Mertiatide: Comparison to OIH

Since its introduction in 1986, Tc-99m mertiatide's chemical, biologic and kinetic properties have been extensively evaluated. The plasma clearance of Tc-99m mertiatide has been compared to I-131 OIH utilizing bolus injections and constant infusion studies. The clearance of Tc-99m mertiatide ranges from 30% to 50% lower than the clearance of OIH in normal volunteers; it produces a clearance value of approximately 340 ml/min versus a clearance of 600 ml/min for OIH. A further reduction in the plasma clearance occurs when the radiochemical purity of the kit formulation decreases. Although the plasma clearance of HPLC-purified Tc-99m mertiatide is consistently less than I-131 OIH, the urine excretion remains essentially the same. These observations have been attributed to Tc-99m mertiatide's higher protein binding and smaller volume of distribution compared to I-131 OIH. The plasma protein binding for Tc-99m mertiatide has been reported to range from 79-90% compared to a value of 53-71% for OIH. The higher protein binding and a smaller volume of distribution implies that more Tc-99m mertiatide remains in the intravascular space and available for renal extraction. Therefore, even though the calculated plasma clearance of Tc-99m mertiatide is less than I-131 OIH, the urine excretion is almost identical.

The extraction ratio for Tc-99m mertiatide and OIH in patient studies have demonstrated a lower extraction for Tc-99m mertiatide when compared to OIH. The initial extraction ratio for Tc-99m mertiatide is approximately 60% to 70% that of OIH, however falls to 41% within 30 minutes. The lower extraction of Tc-99m mertiatide may be due to its higher protein binding; the transit time through the glomerulus and peritubular capillaries may be too short for Tc-99m mertiatide to completely dissociate from plasma proteins thereby reducing its extraction. Tc-99m mertiatide may also have a lower affinity for the tubular transport protein. Experimental evidence suggests that the affinity for the tubular transport of Tc-99m mertiatide is less than for OIH, as competitive inhibition of the tubular transport system following the administration of PAH reduces the Tc-99m mertiatide clearance by 79% while reducing the OIH clearance by only 31%.

In summary, the overall renal clearance of Tc-99m mertiatide occurs by both glomerular filtration and tubular secretion processes. In comparison to OIH, a smaller percentage of Tc-99m mertiatide's clearance occurs by glomerular filtration mechanisms due to its higher plasma protein binding. The fraction of the unbound Tc-99m mertiatide which is not filtered, as well as the plasma protein-bound Tc-99m mertiatide, passes through the glomerulus and efferent arteriole into the peritubular capillaries. Within the peritubular capillaries the non-protein-bound Tc-99m mertiatide is available for active transport by the proximal tubular cells. After being transported out of the capillaries the complex diffuses into the lumen of the nephron to be excreted.

This active transport changes the equilibrium condition between free and plasma protein-bound Tc-99m mertiatide. As equilibrium is reestablished, a portion of the bound complex dissociates making more of it available for tubular transport, thus increasing its renal extraction (figure 4).

A number of volunteer and patient studies have compared the image quality and renogram curves for Tc-99m mertiatide and OIH. In normal volunteers the Tc-99m mertiatide images were uniformly superior to I-131 OIH which may be attributed to the 140 keV gamma photon emitted by Tc-99m and the ability to administer larger doses. However, when equal activities of Tc-99m mertiatide and I-123 OIH were administered, images of equal quality were obtained. Whole kidney and cortical renogram curves in the vast majority of cases show similar curve shapes with no significant differences in the time to peak height between the two agents, which has been reported to be approximately 240 sec. However, the time from peak to 50% of peak activity has been reported to be longer for Tc-99m mertiatide than for OIH, implying a slower rate of renal elimination. Because there are differences in the kinetic properties between Tc-99m mertiatide and OIH, the two agents may not perform the same in every clinical situation; in a limited number of patient studies, differences in the renogram curve between the two agents have been observed.

In a recent study utilizing a purified Tc-99m mertiatide preparation, computer-assisted anterior images of the liver and gallbladder were obtained in a group of patients with serum creatinine levels ranging from 1.6 to 10.1 mg/dl. Biliary activity was observed on the images of one patient in this series. Biodistribution studies utilizing the commercially-available Tc-99m mertiatide kit formulation were conducted in normal volunteers and hemodialysis patients. In general, some radioactivity from the kit formulation was eliminated through the hepatobiliary system with approximately 3% of the injected activity found in the gallbladder, gastrointestinal tract and liver in normal volunteers with this value correlating well to the radiochemical impurities found in the kit. Utilizing kits with similar radiochemical purities, the hepatobiliary uptake in three hemodialysis patients averaged 7% at 30 minutes which increased to 10% by 210 minutes. Recent patient studies have also reported sporadic liver activity, with the liver occasionally being visualized on the Tc-99m mertiatide images but not on the OIH images. In other reports the Tc-99m mertiatide images showed slight hepatic uptake which was unrelated to the level of renal function. Biliary activity has also been reported in patients with poor renal function. Some of the liver activity may be due to Tc-99m in the blood pool, however, this would not account for the hepatobiliary activity occasionally observed. Other than liver, gallbladder and intestinal activity there has been no documentation of uptake by other organ systems.

Tc-99m Mertiatide Clearance Measurements

The clearance of Tc-99m mertiatide is clearly slower than the clearance of OIH. Attempts to correlate the Tc-99m mertiatide clearance to OIH clearance and ultimately to ERPF measurements has resulted in the production of a variety of

regression equations. Various simplified methods have been developed to estimate Tc-99m mertiatide clearances. The Tc-99m mertiatide clearance can be estimated by obtaining one or two blood samples and relating the activity in the plasma to the dose injected. The results in over 200 patients have validated this approach. A camera-based technique to determine Tc-99m mertiatide clearance is currently under development where the early (2 to 3 minute) renal uptake, following a bolus injection of Tc-99m mertiatide, is used to determine the Tc-99m mertiatide clearance.

However, because of the differences which exist between OIH and Tc-99m mertiatide, some investigators oppose the conversion of a Tc-99m mertiatide clearance to an ERPF value and suggest reporting Tc-99m mertiatide clearances directly and comparing them to normal Tc-99m mertiatide clearance values.

Clinical Comparison of Tc-99m Mertiatide to Tc-99m Pentetate.

In addition to replacing OIH, Tc-99m mertiatide has been proposed as a replacement for Tc-99m pentetate, and several studies have been performed comparing these two agents in routine clinical situations. The disadvantage of Tc-99m pentetate is that it is cleared by glomerular filtration only and has a maximum renal extraction of 20 percent. This low extraction may result in a low target-to-background ratio producing poor quality images, especially in patients with impaired renal function. The higher extraction of Tc-99m mertiatide increases renal uptake, producing higher kidney-to-background ratios. Comparative studies demonstrated that Tc-99m mertiatide images are generally superior to those obtained with Tc-99m pentetate and may offer significant advantages in patients with severe renal disease. Tc-99m mertiatide, however, cannot be used to measure GFR and if an accurate GFR measurement is needed then a GFR agent such as Tc-99m pentetate must be used.

Kit Formulation of Tc-99m Mertiatide

The kit formulation available in the United States utilizes a transchelation reaction to form the Tc-99m mertiatide complex. In this reaction Tc-99m pertechnetate is reduced by stannous ions in the presence of tartaric acid forming a Tc-99m tartrate complex. Subsequent heating in the presence of the betiatide ligand (the benzoate-protected mertiatide ligand) provides Tc-99m mertiatide in high radiochemical yields. The Tc-99m mertiatide complex has been characterized by X-ray crystallographic studies and corresponds to a complex where one Tc-99 atom is complexed by one mertiatide ligand (figure 7). The Tc-99m complex is dianionic at physiologic pH due to a negatively charged Tc-oxo metal center and ionization of the carboxylate group. The current kit requires the addition of Tc-99m sodium pertechnetate, 20 to 100 mCi in 4 to 10 ml, to the lyophilized contents of a betiatide vial, followed by the addition of 2 ml of filtered air and heating for 10 min in a boiling water bath. The addition of air consumes residual stannous ion and increases the stability of the kit. The radiochemical purity should be greater than 90% and the

reconstituted kit has a 6 hour shelf life post reconstitution.

Development of Improved Tc-99m Renal Tubular Agents

Tc-99m mertiatide is an excellent renal tubular function agent that can be supplied in high purity from an easily-prepared kit formulation; however its clearance ranges from 50%-70% that of OIH. An agent which would provide a direct measure of ERPF would be an improvement and therefore a number of complexes have been synthesized and evaluated as an alternative to Tc-99m mertiatide.

Preliminary reports have been published on a new Tc-99m complex which has biological characteristics very similar to Tc-99m mertiatide, the Tc-99m 1,1-ethylene dicysteine complex (Tc-99m EC). Volunteer studies have been performed comparing Tc-99m mertiatide with Tc-99m EC and preliminary results are encouraging as it has been reported to have a 25% higher plasma clearance. Tc-99m EC can be prepared from a kit formulation at room temperature and yields the desired complex in greater than 98% purity. The resulting complex has been found to be stable for greater than 8 hours. However, additional patient studies need to be performed to validate its biological properties in various renal disease conditions.

Another group of Tc-99m complexes currently under investigation utilizes the cationic renal tubular transport mechanism. A series of substituted ethylene diamine compounds which form cationic complexes after complexation with Tc-99m have been synthesized and tested. In a limited study, gamma camera images in volunteers demonstrated rapid renal uptake and clearance of the Tc-99m bis-1,2-aminocyclohexane complex with no accumulation in other organs.

CONCLUSION

There are a number of complexes which have been developed and which are available for the routine clinical evaluation of kidney function. Renal blood flow studies are not commonly/ performed, however, there are a variety of tracers which can be utilized to perform this procedure. Static imaging is optimally performed utilizing Tc-99m gluceptate or Tc-99m succimer. GFR studies routinely use Tc-99m pentetate while ERPF and tubular cell function studies have utilized I-131 OIH. There are numerous simplified methods which have been developed which allow quantitation of these functional processes. Tc-99m mertiatide is a new tubular function agent which may replace OIH for the evaluation of tubular function and Tc-99m pentetate for perfusion imaging. Tc-99m mertiatide, however, has different pharmacokinetic properties than either OIH or Tc-99m pentetate and its clearance does not directly measure either the ERPF or the GFR.

In conclusion, the use of renal radiopharmaceutical agents and the ability to make quantitative measurements have made nuclear medicine renal studies an important diagnostic tool.

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QUESTIONS

1. Which portion of the nephron is responsible for the secretion of the majority of the organic compounds which are eliminated from the body?
 - A. Bowman's Capsule
 - B. Proximal Tubule
 - C. Loop of Henle
 - D. Distal Tubule
2. The upper-limit molecular size cut-off for a compound to be filtered at the glomerulus is approximately:
 - A. 150,000
 - B. 70,000
 - C. 7,000
 - D. 1,000
3. Which is not considered to be a major subcomponent of the nephron?
 - A. Bowman's Capsule
 - B. Proximal Convoluted Tubule
 - C. Distal Convoluted Tubule
 - D. Collecting Duct
4. The glomerulus is situated between the afferent arteriole and the _____ which acts as a second resistant vessel.
 - A. Efferent Arteriole
 - B. Peritubular Capillaries
 - C. Arcuate artery
 - D. Renal Vein
5. The plasma flow to the kidneys is approximately:
 - A. 1200 ml/min.
 - B. 600 ml/min
 - C. 340 ml/min
 - D. 120 ml/min
6. To accurately measure glomerular filtration a compound should:
 - A. not be plasma protein bound
 - B. be synthesized by the kidneys
 - C. be retained by the kidneys
 - D. be metabolised by the kidneys
7. The radiopharmaceutical of choice for imaging functioning tubular mass in a patient with urinary tract obstruction is:
 - A. Tc-99m Glucoptate
 - B. Tc-99m Succimer
 - C. Tc-99m Pentetate
 - D. I-131 OIH

8. Which agent provides the best quantitative information on the glomerular filtration rate?
- Tc-99m Gluceptate
 - Tc-99m Succimer
 - Tc-99m Pentetate
 - Tc-99m Mertiatide
9. Which of the following Tc-99m agents has the fastest rate of renal elimination?
- Tc-99m Gluceptate
 - Tc-99m Succimer
 - Tc-99m Pentetate
 - Tc-99m Mertiatide
10. The plasma clearance of Tc-99m pentetate is:
- 1200 ml/min.
 - 600 ml/min
 - 340 ml/min
 - 120 ml/min
11. The plasma clearance of Tc-99m mertiatide is:
- 1200 ml/min.
 - 600 ml/min
 - 340 ml/min
 - 120 ml/min
12. Which agent provides the most diagnostic information on proximal tubular function?
- Tc-99m Gluceptate
 - Tc-99m Succimer
 - Tc-99m Pentetate
 - I-131 OIH
13. Which of the following agents does not undergo any significant amount of secretion?
- Tc-99m Gluceptate
 - I-131 OIH
 - Tc-99m Pentetate
 - Tc-99m Mertiatide
14. Which procedure provides the best quantitative information on renal function?
- Constant Infusion
 - Single Injection Multiple Plasma Clearance Determination
 - Clearances Based on 1 or 2 Blood Samples
 - Camera Based Techniques
15. The shelf life (post reconstitution) of Tc-99m pentetate which is going to be used to quantitate GFR is:
- 12 hours
 - 6 hours
 - 1 hour
 - 30 minutes
16. Reconstitution of which of the following radiopharmaceutical kits requires the addition of air to the vial?
- Pentetate
 - Succimer
 - Mertiatide
 - None of the above
17. Which one of the following kits has a 30 minute shelf life post reconstitution?
- Tc-99m Gluceptate
 - Tc-99m Succimer
 - Tc-99m Pentetate
 - Tc-99m Mertiatide
18. Which of the following agents cannot be used to image renal perfusion?
- I-131 OIH
 - Tc-99m Mertiatide
 - Tc-99m Pentetate
 - Tc-99m Gluceptate
19. Which of the following agents provides a direct measurement of ERPF utilizing a count-based or camera-based technique?
- PAH
 - I-131 OIH
 - Tc-99m Mertiatide
 - Tc-99m Pentetate
20. The plasma protein binding for Tc-99m mertiatide ranges from:
- 10-15%
 - 30-40%
 - 50-70%
 - 80-90%
21. Which imaging agent has the highest renal retention?
- Tc-99m Succimer
 - Tc-99m Gluceptate
 - Tc-99m Mertiatide
 - Tc-99m Pentetate
22. Tc-99m mertiatide is cleared by the kidneys by:
- Glomerular filtration
 - Tubular secretion
 - Tubular reabsorption
 - A and B
 - B and C
 - A and C

23. Tc-99m mertiatide has a plasma clearance which is _____.
- A. Equivalent to OIH
 - B. 10% less than OIH
 - C. 30-50% less than OIH
 - D. 50-80% less than OIH
24. Tc-99m mertiatide has kinetic and imaging properties which are similar to:
- A. I-131 OIH
 - B. Tc-99m Pentetate
 - C. Tc-99m Gluceptate
 - D. None of the above
25. Tc-99m mertiatide may also localize in the:
- A. Liver
 - B. Spleen
 - C. Heart
 - D. Lung