Effect of the NSAID Diclofenac on ^{99m}Tc-MAG3 and ^{99m}Tc-DTPA Renography

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Renal function and disease are commonly evaluated by radionuclide studies. The choice of radiopharmaceutical agent for various studies is crucial for proper interpretation. ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) is excreted almost exclusively by the renal tubules, whereas ^{99m}Tc-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) is predominantly excreted by glomerular filtration. The present study compared the effect of the nonsteroidal antiinflammatory drug (NSAID) diclofenac, which is the most commonly used drug to relieve kidney pain, on the kinetic behavior of administered ^{99m}Tc-MAG3 and ^{99m}Tc-DTPA in experimental animals. **Methods:** Two groups of 12 New Zealand White rabbits (^{99m}Tc-MAG3 and ^{99m}Tc-DTPA) were used for the renography. Each rabbit served as its own control. The animals were given 60 mL of saline intravenously 30 min before each renographic study. A baseline study (control) was done by injecting 48 MBq (1.3 mCi) of ^{99m}Tc-MAG3, and renography was performed. Two days later, a single intravenous dose of diclofenac (2 mg/kg) (treated animals) was given, and after 20 min, ^{99m}Tc-MAG3 renography was performed. This procedure was repeated for the ^{99m}Tc-DTPA group after administration of 96 MBq (2.6 mCi) of the tracer. Dynamic images (as 2-s frames for the first minute and 30-s frames for the next 30 min on a 64 × 64 matrix) were acquired using a γ-camera equipped with a low-energy high-resolution collimator interfaced with a computer. Regions of interest were drawn over the whole kidneys. Time–activity curves were generated from the region of interest. Time to peak activity (T_{max}), time from peak to 50% activity ($T_{1/2}$), and the uptake slope of each kidney were calculated from the renograms for control and treated rabbits. **Results:** Administration of diclofenac shifted the experimental renogram curves to the right, compared with the control curves, indicating that there was a delayed renal uptake of the 2 tracers and clearance of the radioactivity. The calculated average values of T_{max} for control and treated rabbits using ^{99m}Tc-MAG3 were 1.8 ± 0.5 and 6.35 ± 0.4 min, respectively, whereas those of ^{99m}Tc-DTPA were 3.4 ± 0.4 and 18.2 ± 2 min, respectively. The $T_{1/2}$ for control and treated rabbits for ^{99m}Tc-MAG3 were 3.2 ± 0.07 and 6.6 ± 0.07 min, respectively, whereas those for ^{99m}Tc-DTPA were 10.1 ± 1 and 35 ± 4 min, respectively. The differences were statistically significant ($P < 0.05$). **Conclusion:** This study showed that diclofenac delayed both T_{max} and $T_{1/2}$. The NSAID-induced kinetic changes were considerably greater for ^{99m}Tc-DTPA than for ^{99m}Tc-MAG3. On the basis of these findings, it is suggested that ^{99m}Tc-MAG3 be used to perform renography for studies involving the use of NSAID administration to decrease any change that may occur due to the type of tracer and not to the condition of the kidney.

Key Words: radionuclide; NSAIDs; diclofenac; ^{99m}Tc-MAG3; ^{99m}Tc-DTPA; renal scintigraphy; rabbit

Dynamic radionuclide renographic studies are commonly and effectively used to evaluate renal function and a variety of renal diseases (*1–5*), both by visual evaluation of the acquired dynamic images and by analysis of time–activity curves generated by computer processing and quantitative criteria. The images include initial cortical uptake of the radiotracer, cortical retention, first visualization of the collecting system, and time to peak cortical activity (T_{max}) and half clearance ($T_{1/2}$). The results of these studies and interpretation of such criteria are known to be influenced by numerous factors, such as the radiotracer used, hydration status of the patient, position of individual kidneys, camera set-up, bladder status, and data processing.

Chronic use or overdosing of nonsteroidal antiinflammatory drugs (NSAIDs) has been shown to affect renal function and hence may influence the criteria used for interpretation of such studies (*6–8*). NSAIDs are probably the most widely used therapeutic agent worldwide because they can be used without prescriptions as analgesic, antiinflammatory, and antipyretic drugs. Furthermore, the NSAID diclofenac is the drug most commonly used to relieve kidney pain and uretic colic (*9,10*). Only 2 studies using ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) have been performed (*11,12*). One reported that diclofenac treatment can lead to overestimation of ureteral stone disease by delaying renal excretion predominantly on the side of the calculus (*11*). The other showed that diclofenac caused a profound disruption to both uretic peristalsis and the ^{99m}Tc-MAG3 renogram curve (*12*). However, to our knowledge, no studies have been performed using ^{99m}Tc-diethylenetriamine

pentaacetic acid (^{99m}Tc-DTPA) in animals treated with diclofenac. The 2 most frequently used radiotracers for evaluation of renal function are ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 (13–21). Although many institutions use ^{99m}Tc-MAG3, many others are using ^{99m}Tc-DTPA because it is much less expensive.

Hence, in this study we investigated the effect of diclofenac on the kinetic behavior of ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 in experimental animals.

MATERIALS AND METHODS

Experimental Animals

Twenty-four adult male New Zealand White rabbits of the same age (10 wk) and weighing 3–3.5 kg were used for the study. They were divided into 2 groups of 12, one undergoing ^{99m}Tc-MAG3 imaging and the other ^{99m}Tc-DTPA imaging. All animals were given adequate food and water in our animal housing facility. Marginal veins in the ears were connected to butterfly needles. Each rabbit was anesthetized with ketamine (40 mg/kg intravenously). Additionally, 60 mL of normal saline were administered intravenously. The saline was given 30 min before the administration of the radiopharmaceutical to ensure adequate and consistent hydration. Each rabbit served as its own control, and rabbits that had been administered diclofenac were referred to as treated. Baseline (control) studies followed by experimental renographic studies were performed on all rabbits. The treated rabbits were administered a 2 mg/kg dose of diclofenac by intravenous injection 20 min before the radionuclide was injected. The experiments were performed in accordance with guidelines approved by the Institutional Animal Care and Use Committee of Kuwait University.

Radionuclide Imaging

Baseline imaging studies were performed on each rabbit after injection of 48 MBq (1.3 mCi) of ^{99m}Tc-MAG3. Two days later, the same rabbit was given a single intravenous dose of diclofenac (2 mg/kg), and the ^{99m}Tc-MAG3 renogram was performed 20 min later. These procedures were repeated using 96 MBq (2.6 mCi) of ^{99m}Tc-DTPA. Dynamic images were acquired using a γ-camera (T55B-1473; Meridian Systems) equipped with a low-energy, high-resolution, parallel-hole collimator interfaced with a dedicated computer. The rabbits were positioned supine after receiving anesthesia. The dynamic images were acquired in the posterior projection, with 2-s frames being obtained for the first minute (flow phase) and frames being obtained every 30 s for the next 30 min (sequential functional phase) using a 64×64 matrix. Postvoiding static images were acquired for 60 s on a 256×256 matrix. Regions of interest were drawn manually over the whole kidneys and the urinary bladder. Time–activity curves (renograms) were automatically generated and were corrected for background radioactivity for both kidneys. Curves were drawn using a Xeloris workstation (version 1.06; GE Healthcare). T_{max}, $T_{1/2}$, and the uptake slope of each kidney were automatically calculated from the renograms.

Statistical Analysis

Data are presented as mean $\pm$ SEM for the number of rabbits used in the studies. When necessary, differences between 2 mean values were compared using the Student t test, paired or unpaired as appropriate. Multiple-comparison 1-way ANOVA was used, followed by the Student–Newman–Keuls test. The difference was assumed to be significant at a P value of less than 0.05.

RESULTS

Renograms were normal, with a T_{max} of 1.8 ± 0.5 and 3.4 ± 0.5 min and a $T_{1/2}$ of 3.2 ± 0.07 and 10.1 ± 1 min for the control kidney using ^{99m}Tc-MAG3 and ^{99m}Tc-DTPA, respectively ($n = 12$; $P < 0.05$). After diclofenac administration, overall function decreased with the delay in cortical clearance, and the renograms for the 2 radiotracers shifted to the right. There was a delay of T_{max} and a prolongation of $T_{1/2}$ in all treated rabbits. These values were 6.35 ± 0.4 and 6.6 ± 0.07 min, respectively, with ^{99m}Tc-MAG3 and 18.2 ± 2 and 35 ± 4 min, respectively, with ^{99m}Tc-DTPA ($n = 12$; $P < 0.05$) (Table 1).

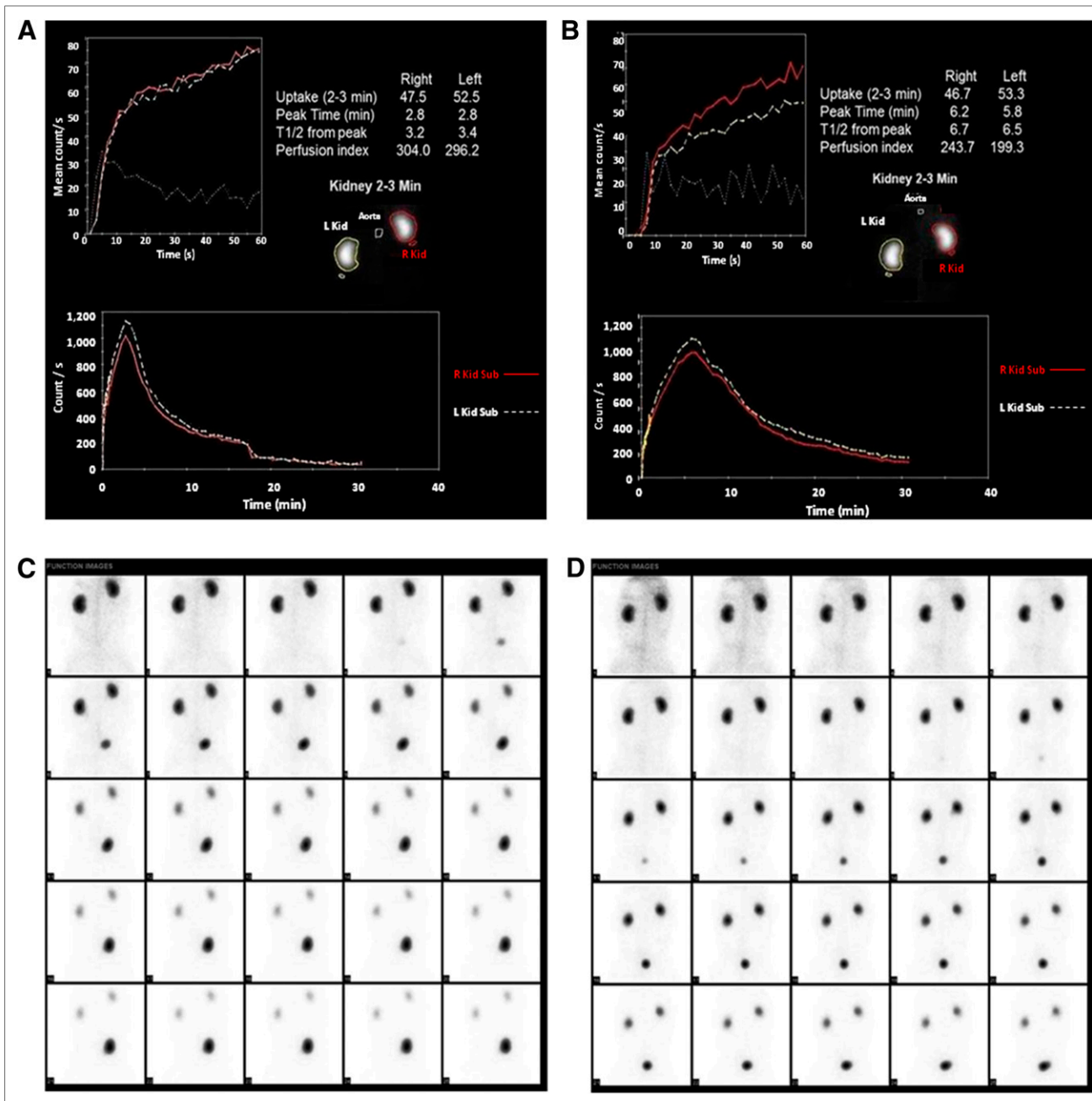Typical renograms obtained using ^{99m}Tc-MAG3 before and after diclofenac administration are shown in Figures 1A and 1B. After NSAID treatment, the curves shifted to the right of the control curves, indicating slightly delayed renal uptake of ^{99m}Tc-MAG3 and clearance of radioactivity. The sequential functional images of the same rabbit before and after diclofenac administration are shown in Figures 1C and 1D. Delays in the appearance of the bladder and in the clearance of renal activity are evident. Typical renograms obtained with ^{99m}Tc-DTPA before and after diclofenac administration are shown in Figures 2A and 2B. Again, after treatment with diclofenac the curves significantly shifted to the right of the control curves, indicating a pronounced delay in renal uptake of ^{99m}Tc-DTPA and in clearance of radioactivity. Sequential functional images of the

TABLE 1
Mean T_{max} and $T_{1/2}$ for Control and Diclofenac-Treated Rabbits

| Group | ^{99m}Tc-MAG3 | | ^{99m}Tc-DTPA | |
	T_{max} (min)	$T_{1/2}$ (min)	T_{max} (min)	$T_{1/2}$ (min)
Control	1.8 ± 0.5	3.2 ± 0.07	3.4 ± 0.4	10.1 ± 1.0*
Diclofenac	$6.35 \pm 0.4^{\dagger}$	$6.6 \pm 0.07^{\dagger}$	$18.2 \pm 2.0^{*\dagger}$	$35 \pm 4.0^{*\dagger}$

*$P < 0.05$ for comparison between ^{99m}Tc-MAG3 and ^{99m}Tc-DTPA.
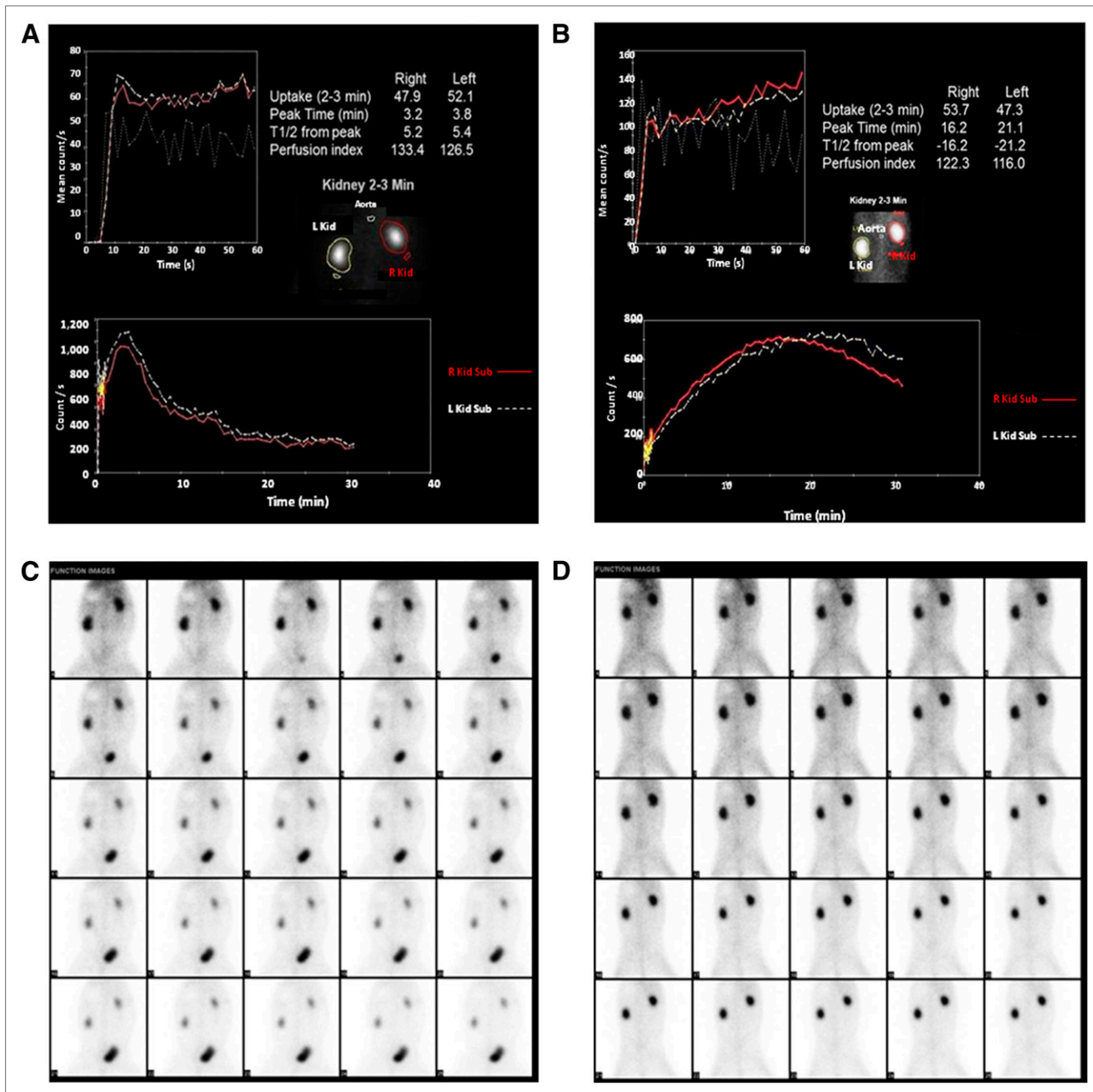$^{\dagger}P < 0.05$ for comparison between control and diclofenac-treated animals.

FIGURE 1. Time–activity curves (renograms) obtained using ^{99m}Tc-MAG3 for control rabbit (A) and rabbit treated with diclofenac (B). Peak activity and clearance of activity are delayed. Flow curves in left upper corners show no change after diclofenac treatment. Sequential functional images obtained using ^{99m}Tc-MAG3 show more retention of radioactivity in diclofenac-treated rabbit (D) than in control rabbit (C).

same rabbit before and after diclofenac are shown in Figures 2C and 2D. There was a significant delay in the appearance of the bladder and in clearance of renal activity, and retention of radioactivity in the kidney was greater after NSAID administration. In none of the flow studies did it appear to have changed, indicating that blood flow to the kidney was not affected by diclofenac administration. Both left and right kidneys had the same results in all renograms. The mean split function was 49.9% ± 0.1%, and the range was 49.6%–50.4%.

DISCUSSION

Radionuclide renography has a role in evaluating the perfusion and function of the kidney. The technique is used to evaluate many kidney diseases and transplanted kidneys and to help determine suitable treatment. Rapidly excreted radiopharmaceuticals are used to assess individual renal function. The interval between radiotracer administration and excretion of activity into the collecting system is a measure of cortical function. The delayed appearance of the collecting system is associated with renal insufficiency.

FIGURE 2. Time–activity curves (renograms) obtained using ^{99m}Tc-DTPA for control rabbit (A) and rabbit treated with diclofenac (B). Peak activity is significantly delayed, and clearance activity shows an apparent delay. Flow curves in left upper corners show no change after diclofenac treatment. Sequential functional images obtained using ^{99m}Tc-DTPA show more retention of radioactivity in diclofenac-treated rabbit (D) than in control rabbit (C).

The interval between radiotracer administration and maximum cortical activity is another parameter of function and is more easily measured from the time–activity curve.

This study investigated the effects of an NSAID on renographic studies obtained using the glomerular agent ^{99m}Tc-DTPA and the tubular agent ^{99m}Tc-MAG3 and showed a delay in T_{max} and $T_{1/2}$ for both tracers. The effect on the glomerular agent ^{99m}Tc-DTPA was a delay 3 times greater than that with the tubular agent. The mechanism that results in this difference between the 2 tracers has not, to our knowledge, been previously studied.

The renal artery enters the kidney and then branches progressively to afferent arterioles, which lead to the glomerular capillaries in the glomeruli, where urine begins to form. The distal ends of these capillaries form the efferent arteriole and lead to the peritubular capillaries, which surround the renal tubules. The high hydrostatic pressure in the glomerular capillaries causes a rapid fluid

filtration, whereas a much lower hydrostatic pressure in the peritubular capillaries permits rapid fluid reabsorption. The peritubular capillaries empty into the renal vein.

^{99m}Tc-DTPA shows insignificant protein binding (~5%) and is therefore freely filtered by glomerular capillaries but is neither reabsorbed nor secreted. Its excretion rate is equal to the rate at which it is filtered. ^{99m}Tc-MAG3 is 90% protein-bound and consequently is predominantly secreted from peritubular capillaries and is not filtered at the glomerular capillaries or reabsorbed. ^{99m}Tc-MAG3, the tubular tracer, is secreted by active transport ([13–21]).

^{99m}Tc-DTPA is less expensive than ^{99m}Tc-MAG3 and may be used as an alternative to ^{99m}Tc-MAG3, particularly if a quantitative estimate of glomerular filtration rate (GFR) is also needed. Functional assessment generally is concordant between ^{99m}Tc-MAG3 and ^{99m}Tc-DTPA.

Cortical retention of radiotracer, quantified by expressing renal counts on the time–activity curve for 20–30 min as a percentage of peak uptake, is a measure of the rapidity with which the radiotracer is excreted by the kidney. The time–activity curves showed almost complete excretion after 30 min for ^{99m}Tc-MAG3, whereas ^{99m}Tc-DTPA excretion was approximately 75% as shown in Figure 2. Generally, as renal function deteriorates, the percentage retained increases, as probably explains the higher retention of ^{99m}Tc-DTPA.

The pharmacologically desirable actions of NSAIDs result mainly from the inhibition of arachidonic acid cyclooxygenase (either of 2 forms, cyclooxygenase 1 or cyclooxygenase 2) and the resultant decrease in prostaglandin synthesis ([22]). Prostaglandin E_2 and prostaglandin I_2 are vasodilators ([23]). Prostaglandins generated in the kidney modulate its hemodynamic and excretory functions. Factors that stimulate synthesis of prostaglandins include bradykinin, antidiuretic hormone, and angiotensin II ([24]). Prostaglandins promote glomerular afferent arteriolar vasodilatation and increase vascular permeability, resulting in increased urine output and renal pelvic pressure ([25,26]). Inhibition of prostaglandin production also reduces ureteric edema and inflammation and enables better drainage, all of which act to reduce ureteric activity or peristalsis. Furthermore, NSAIDs may have a direct effect on ureteric smooth muscle resulting in relaxation ([27–29]).

Glomerular filtration rate depends critically on vasodilator prostaglandin biosynthesis ([30]). Prostaglandins have a major role in regulating renal blood flow and glomerular filtration rate to oppose vasoconstriction of afferent arterioles due to endogenous vasoconstrictor agents ([31,32]). Prostaglandins also help prevent excessive reductions in glomerular filtration rate. The administration of NSAIDs inhibits prostaglandin synthesis, reduces renal perfusion, and may cause a significant reduction in glomerular filtration rate. Additionally, NSAIDs indirectly depress renin and aldosterone secretion by inhibiting renal prostaglandin I_2 biosynthesis and decrease antidiuretic hormone secretion ([33–36]).

The balance of vascular resistance in afferent and efferent arterioles is a crucial factor in determining glomerular hemodynamics. It has been proven that NSAIDs potentiate angiotensin II vasoconstriction in afferent arterioles but have no effect on efferent arterioles ([24]). It has also been shown that the vasodilator effect on efferent arterioles is not mediated only by prostaglandins. Bradykinin plays a role in the regulation of renal hemodynamics. The vasodilator effect of bradykinin on efferent arterioles is not mediated by cyclooxygenase products ([22]). Prostaglandin E_2 is recognized to play a critical role in modulating renal vasoconstriction. In 1985, Edwards ([23]) reported that prostaglandin E_2 elicited afferent arteriolar vasodilatation but had no effect on the efferent arteriole and that prostaglandin E_2 blocked the afferent arteriolar response to norepinephrine but had no effect on the efferent arteriolar actions of either norepinephrine or angiotensin II. In 2000, Tang et al. ([32]) also indicated that prostaglandin E_2 exerts a selective effect only on the afferent arteriole.

Up to 80% of renal plasma flow passes on to the peritubular capillaries of the proximal tubule (the other 20% is filtered through the glomerulus). The carriers can transport the radiotracer molecules against an electrochemical gradient and can reduce the plasma concentration to zero. Tubular secretion is potentially the most effective mechanism of renal drug elimination. Unlike glomerular filtration, carrier-mediated transport can achieve maximal drug clearance even when most of the drug is bound to plasma protein.

Prostaglandin inhibition by NSAIDs will have a great effect on glomerular filtration and thus will also have a great effect on the glomerular agent ^{99m}Tc-DTPA. Therefore, the delay in T_{max} and $T_{1/2}$ is significantly affected by diclofenac administration. However, tubular secretion is affected by diclofenac to a much lesser extent because it occurs through carrier-mediated transport.

CONCLUSION

The results showed that NSAIDs significantly changed radionuclide renography findings using ^{99m}Tc-DTPA, which is excreted exclusively by glomerular filtration, but did not significantly change the findings using ^{99m}Tc-MAG3, which is excreted almost exclusively by the renal tubules. Therefore, we recommend that ^{99m}Tc-MAG3 be used rather than ^{99m}Tc-DTPA for performing renographic studies on patients who are receiving NSAIDs.

DISCLOSURE

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