Effect of Chronic Treatment with None Steroidal Anti-Inflammatory Drug (Diclofenac) on Kidney Scinitgraphy

Seham Mustafa
Department of Biomedical Sciences, College of Nursing, Public Authority for Applied Education & Training, Kuwait, Kuwait
Email: mustafaseham@yahoo.com

Abdelhamid H. Elgazzar
Department of Nuclear Medicine, Faculty of Medicine, Kuwait University, Kuwait, Kuwait
Email: aelgazzar49@hotmail.com

***Abstract*—Our previous study investigated the effect of a single dose of NSAID diclofenac, which is the most commonly used to relieve kidney pain, on the renograms using radiopharmaceuticals. The objective of this study is to examine the effect of long-term use of diclofenac on renography. A baseline study (control) was done by injecting the rabbits ^{99m}Tc-DTPA and a renography was performed. Two days later an i.v. dose of diclofenac was given daily for 8 days. M *Results*: Diclofenac treatment shifted the renogram to the right compared to the control curves indicating that there was a delayed renal uptake of the tracer and clearance of radioactivity. The calculated average values of Tmax and T ½ for control and treated rabbits were (5.4±0.5 and 12.9±1.5 min) & (13.35±3 and 29.50±4 min) respectively, (n=12; *p<0.05). Diclofenac, prostaglandins synthesis inhibitor, delayed both the time to reach peak renal activity (Tmax) and the subsequent renal clearance time (T½), and tracer arrival in the bladder was delayed. These results prove that long-term use or a single dose of NSAID have similar effect on Renography. Therefore, we suggest not to use NSAIDs before doing renography to avoid misleading results.**

***Index Terms*—NSAIDs, diclofenac, Radiopharmaceuticals, technetium-99m-DTPA, renal scintigraphy, rabbit.**

I. Introduction

Renal function in many renal diseases is evaluated by dynamic radionuclide renography studies [1]-[5]. The results and calculations obtained from the time activity curves generated by computer processing. These include initial cortical uptake of the radiotracer, cortical retention, first visualization of collecting system and time to peak cortical activity and half clearance. These results are known to be affected by many factors. These factors mainly include the type of radiotracer, hydration status of the patient, position of individual kidney, camera set-up, bladder status and data processing. Renal scintigraphy using the rapidly excreted radiopharmaceuticals generally involves dynamic acquisition over a period of 30 min after radiotracer administration. Images are grouped in 2-min frames and a time-activity curve is obtained. Assessment of function is based on a number of items such as initial cortical uptake of the radiotracer, cortical retention and time to peak cortical activity.

The first minute after radiotracer administration represents the vascular delivery phase while the next 2 min compose the parenchymal phase. Uptake in the kidney between 1 and 3min after radiotracer injection, is proportional to its function. In practice, renal counts are obtained over a 1-min period, and expressed as a percentage of the combined renal counts.

The cortical retention of radiotracer which is calculated by expressing renal counts at 20–30min on the time-activity curve as a percentage of the peak uptake. It is a measure of the rapidity with which the radiotracer is excreted by the kidney. As renal function deteriorates, the percentage retained increases.

The interval between radiotracer administration and maximum cortical activity (Time to Peak) is another parameter of function. It is measured from the time-activity curve.

Chronic use of non-steroidal anti-inflammatory inflammatory and anti-pyretic are always taken by the patients for number of diseases. They are ranking the first drugs as over the counter drugs. It is well known drugs (NSAIDs) were found to affect renal function as side effects [6]-[8]. NSAIDs are the most widely used of all therapeutic agents worldwide. Diclofenac is the drug most commonly used to relieve kidney pain and uretic colic [9], [10].

Our previous study Mustafa & Elgazzar, 2013 [11] examined the effect of a single dose of NSAID diclofenac on the renograms The study showed that Diclofenac-induced kinetic changes for 99mTc DTPA and had an effect on the kidney function.

Therefore, in the present study we investigated the long-term use of diclofenac which is administered by the kidney patients before doing the renogram.

Manuscript received July 25, 2015; revised September 26, 2015.

doi: 10.18178/ijpmbs.4.4.232-235

II. Materials and Methods

A. Experimental Animals

Twelve (12) adult male New-Zealand White rabbits of the same age (10 weeks) weighing 3-3.5 kg were used in this study. All the animals were given adequate food and water in our animal house facility. Marginal veins in ears were connected to butterfly needles. Each rabbit was anaesthetized with ketamine (40 mg/kg i.v). Additionally, 60 ml of normal saline was administered intravenously. The saline was given 30 min prior to the administration of the radiopharmaceutical to ensure adequate and consistent hydration. Each rabbit served as its control and rabbits administered diclofenac were referred to as treated. Baseline (control) followed by experimental renographic studies were performed in all the rabbits. The treated rabbits were administered 2mg/kg diclofenac by iv injections for 8 days. Experiments were performed in accordance with guidelines approved by the Institutional Animal Care and Use Committee of Kuwait University.

B. Radionuclide Imaging

Baseline imaging studies were performed in each rabbit following injection of 96 MBq (2.6 mCi) 99mTc-DTPA. Two days later the same rabbit was given i.v doses of diclofenac (2 mg/kg) and the renogram was done. Dynamic images were acquired using Gamma camera (Meridian System, T55B-1473) equipped with a low energy, high resolution, parallel hole collimator interfaced with a dedicated computer. Rabbits were positioned after anesthesia in the supine position. The dynamic images were acquired in the posterior projection for 2 s frames for the first 1 min (flow phase) and every 30 s for the next 30 min (sequential functional phase) using a matrix of 64x64. Post-void static images were acquired for 60 s on a matrix of 256x256. Regions of interest (ROI) were drawn over the whole kidneys and the urinary bladder manually. Radioactivity-time curves (renograms) were automatically generated, and latter corrected for background radioactivity for both kidneys. Curves were drown using Xeloris workstation (GE Medical system, version 1.06). The time to peak activity (Tmax), time from peak to 50% activity (T½) and the uptake slope of each kidney were automatically calculated from the renograms.

C. Statistical Analysis

Data are presented as mean ± (S.E.M) of number of rabbits (n) used in the studies. Where necessary, differences between two mean values were compared using Students-t-test paired or unpaired as appropriate. Multiple comparisons one way analysis of variance (ANOVA) was used followed by Student-Newman-Keuls test. The difference was assumed to be significant at $p<0.05$.

III. Results

A. Radionuclide Imaging

For the control groups, renograms were normal. After diclofenac treatment the renograms were shifted the experimental curves to the right compared to the control curves. These results indicated that the function of the kidney was reduced and there were delayed renal uptake of the tracer and clearance of radioactivity. The calculated average values of Tmax for control and treated rabbits were (5.4±0.5 and 12.9±1.5 min). The T ½ for control and treated rabbits were (13.35±3 and 29.5±4 min) respectively, (n=12; *p<0.05), as shown in Table I and Fig. 1.

TABLE I. Calculated Mean Values of Time to T_{MAX}; and $T_{1/2}$ for the Control and Rabbits Treated with Diclofenac.

	^{99m}Tc-DTPA	
	T_{max}	$T_{1/2}$
Control	5.4±0.5	10.1±1.0
Diclofenac	12.9±1.5*	29.75±3.0*

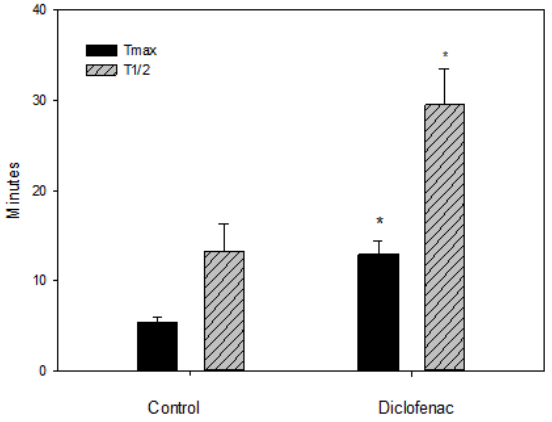

Figure 1. Average of time to peak activity (Tmax), and time from peak to 50% activity (T ½) for control rabbits and after treatment with diclofenac.

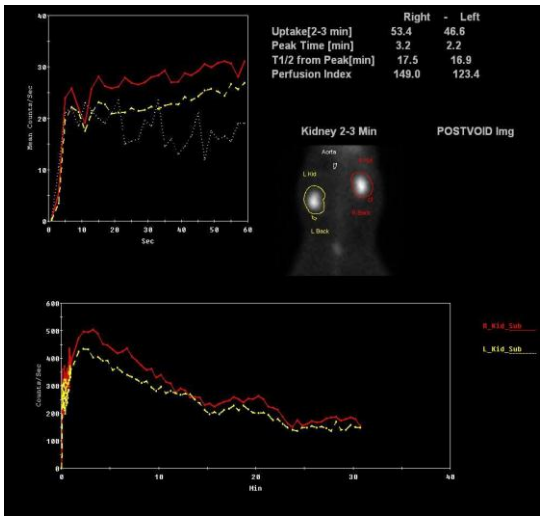

Figure 2. Time activities curves (renograms) for control rabbit using 99mTc-DTPA. Note the peak and the clearance of activity from kidneys. Also note that flow curves in the left upper corner of figures show any change after diclofenac treatment. Within 2-3 min the radiotracer appeared in the urine.

The typical renograms before and after diclofenac administration are shown in Fig. 2 and Fig. 3. Treatment with diclofenac significantly shifted the curves to the right of the control indicating that there was marked delayed renal uptake of 99mTc-DTPA and also marked

delayed in clearance of radioactivity. The sequential functional images of the same rabbit before and after diclofenac are shown in Fig. 4 and Fig. 5. There was a significant delay in the appearance of the bladder and significant delay in clearance of renal activity. Both left and right kidneys have the same results in all renograms. The mean split function is 48.8 ±0.2 and ranged between 49%-51%.

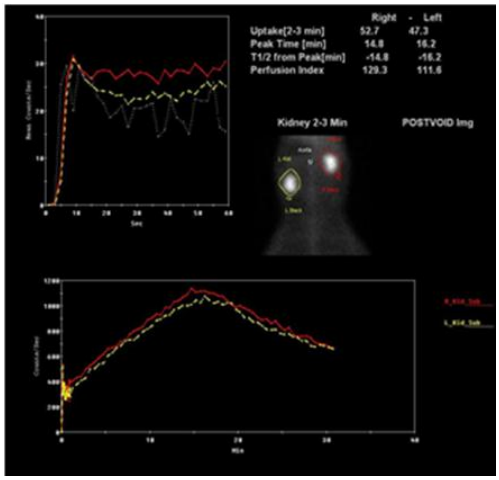

Figure 3. Time activities curves (renograms) after diclofenac treatment using 99mTc-DTPA. Note the significant delay in peak and apparent delayed clearance of activity from kidneys. Also note that flow curves in the left upper corner of figures did not show any change after diclofenac treatment. Within 2-3 min the radiotracer did not appeare in the urine.

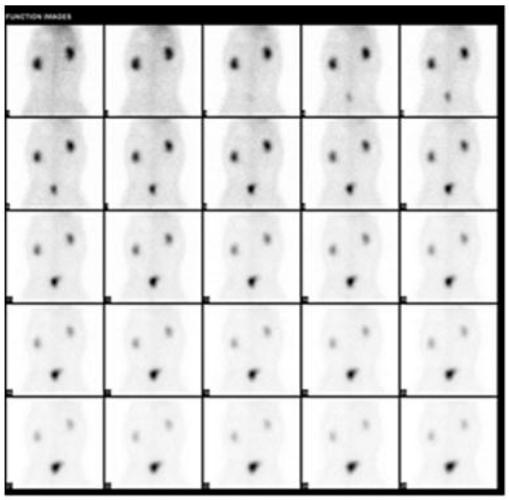

Figure 4. Sequential functional images of the same control rabbit using ^{99m}Tc-DTPA.

IV. Discussion

Renography is used for evaluation of many kidney diseases and help determine the suitable treatment. It can show the perfusion and function of kidney. Delayed appearance of the radiopharmaceuticals from collecting system is associated with renal insufficiency. The interval between radiotracer administration and maximum cortical activity is another parameter of function. It is more easily measured from the time-activity curve

Our work studied the effects of NSAID on renography using the glomerular agent 99mTc-DTPA and showed delay in Tmax and $T_{1/2}$.

99mTc-DTPA shows insignificant protein binding (about 5%). Therefore it is freely filtered by glomerular capillaries but is neither reabsorbed nor secreted. Its excretion rate is equal to the rate at which it was filtered.

The cortical retention of radiotracer, quantified by expressing renal counts on the time-activity curve for 20–30 min as a percentage of the peak uptake, is a measure of the rapidity with which the radiotracer is excreted by the kidney. The time-activity curves showed excretion around 75% as shown in Fig. 2. As renal function deteriorates, the percentage retained increases.

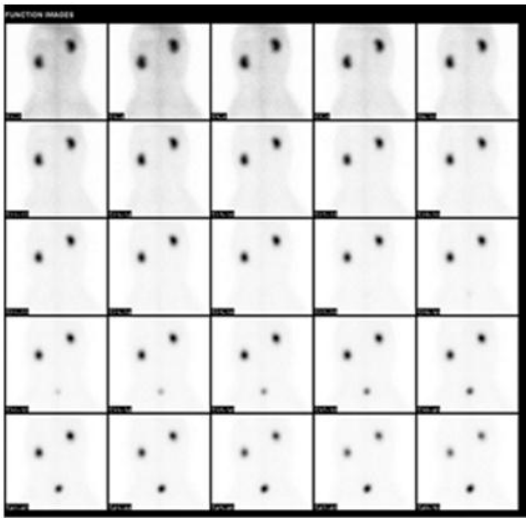

Figure 5. Sequential functional images of the same rabbit after diclofenac treatment, show more retention of radioactivity in the kidneys after diclofenac treatment using ^{99m}Tc-DTPA.

The mechanism of actions of NSAIDs is due to the inhibition of arachidonic acid cyclogenase (COXs), leading to decrease in prostaglandins synthesis [12]. Prostaglandins (PGs) PGE2 and PGI2 are vasodilators [13]. They have great effect the rate of glomerular filtration (GFR) [14]. The administration of NSAID inhibit PGs synthesis and reduce renal perfusion. Therefore, they reduce GFR, depress renin and aldosterone secretion and decrease antidiuretic hormone secretion [15]-[18].

Therefore, it is clear that PGs inhibition by NSAIDs will have a great effect on the glomerular filtration so they will have a great effect on glomerular agent 99mTc-DTPA. Therefore the delay in Tmax and $T_{1/2}$ are significantly affected after diclofenac administration.

V. Conclusions

Our study invistigated the influence of long-use of diclofenac (NSAID) on renal scintigraphy. The results showed that NSAIDs significantly changed the radionuclide renography studies using 99mTc-DTPA which is excreted exclusively by glomerular filtration. Therefore we suggest not to use NSAIDs before doing renography to avoid misleading results.

ACKNOLEDGMENT

This work supported and funded by The Public Authority for Education and Training. Research Project No (CN-13-01).

REFERENCES

[1] J. O. Heikkinen, J. T. Kuikka, A. K. Ahonen, and P. J. Rautio, "Quality of dynamic radionuclide renal imaging: Multicentre evaluation using a functional renal phantom," *Nucl Med Commun*, vol. 22, pp. 987-995, 2001.

[2] R. A. Jafri, K. E. Britton, C. C. Nimmon, *et al*., "Technetium-99m-MAG3: A comparison with iodine-123 and iodine-131 orthoiodihippurate in patients with renal disorders," *J. Nucl Med*, vol. 29, pp. 147-158, 1988.

[3] G. S. Turiev, A. S. Ametov, and N. L. Davitinidze, "Radionuclide methods in the diagnosis of diabetic nephroangiopathy," *Med Radiol*, vol. 34, pp. 59-65, 1989.

[4] A. Munoz, R. Puchal, A. M. Castelao, *et al*., "Renogram deconvolution in the management of diabetic nephropathy: Utility of the measurement of initial tracer uptake," *Nucl Med Commun*, vol. 18, pp. 1029-1035, 1997.

[5] H. Suzuki, T. Katoh, Y. Sakuma, *et al*., "Multiple endocrine neoplasia type 1 in end-stage renal failure," *Clin Exp Nephrol*, vol. 8, pp. 380-383, 2004.

[6] S. Harirforoosh and F. Jamali, "Renal adverse effects of nonsteroidal anti-inflammatory drugs," *Expert Opin Drug Saf*, vol. 8, pp. 669-681, 2009.

[7] P. E. Kulling, E. A. Backman, A. S. Skagius, and E. A. Beckman, "Renal impairment after acute diclofenac, naproxen, and sulindac overdoses, " *J. Toxicol Clin Toxicol* , vol. 33, pp.173-177, 1995.

[8] K. Gooch, B. F. Culleton, B. J. Manns, *et al*., "NSAID use and progression of chronic kidney disease," *Am J. Med*, vol. 120, pp. 280-287, 2007.

[9] S. Lundstam, O. Jonsson, B. Kihl, and S. Pettersson, "Prostaglandin synthetase inhibition of renal pelvic smooth muscle in the rabbit," *Br J. Urol*, vol. 57, pp. 390-393, 1985.

[10] M. Porena, P. Guiggi, A. Balestra, and C. Micheli, "Pain killers and antibacterial therapy for kidney colic and stones," *Urol Int*., vol. 72, pp. 34-39, 2004.

[11] S. Mustafa and A. H. Elgazzar, "Effect of the NSAID diclofenac on99mTc-MAG3 and 99mTc-DTPA Renography," *J. Nucl Med*, vol. 54, no. 5, pp. 801-806, 2013.

[12] F. P. Esteves, A. Taylor, A. Manatunga, R. D. Folks, M. Krishnan, and E. V. Garcia, "99mTc-MAG3 renography: Normal values for MAG3 clearance and curve parameters, excretory parameters, and residual urine volume," *AJR Am J. Roentgenol*, vol. 187, pp. 610-617, 2006.

[13] W. G. Lee, J. H. Kim, J. M. Kim, *et al*., "Renal uptakes of 99mTc-MAG3, 99mTc-DTPA, and 99mTc-DMSA in rabbits with unilateral ureteral obstruction," *Vivo*, vol. 24, no. 2, pp. 137-139, 2010.

[14] R. M. Botting, "Inhibitors of cyclooxygenases: Mechanisms, selectivity and uses," *J. Physiol Pharmacol*, vol. 57, pp. 113-124, 2006.

[15] K. Davenport and E. Waine, "The role of non-steroidal anti-inflammatory drugs in renal colic," *Pharmaceuticals*, vol. 3, pp. 1304-1310, 2010.

[16] A. Perlmutter, L. Miller, L. A. Trimble, D. N. Marion, E. D. Vaughan, and D. Felson, "Toradel, an NSAID used for renal colic, decreases renal perfusion and ureteral pressure in a canine model of unilateral ureteral obstruction," *J. Urol*, vol. 149, pp. 926–930, 1993.

[17] R. S. Cole, C. H. Fry, and K. E. D. Shuttleworth, "The action of the prostaglandins on isolated human ureteric smooth muscle," *Br J. Urol*, vol. 61, pp. 19–26, 1988.

[18] G. M. Lennon, J. Bourke, P. C. Ryan, and J. M. Fitzpatrick, "Pharmacological options for the treatment of acute ureteric colic," *Br J. Urol*, vol. 71, pp. 401–407, 1993.

Seham Mustafa was born in Egypt. She got her B.Pharm., Faculty of Pharmacy, Cairo University, Egypt, M.Sc., Faculty of Medicine, Kuwait University, and Ph.D., Faculty of Pharmacy and Pharmacology, Bath University, England. She attended many courses in Radiopharmacy and Nuclear Medicine.

She is a professor at College of Nursing, Department of Biomedical Sciences, Public Authority for Applied Education & Training, Kuwait.

Dr. Seham has more than 40 publications with more than 300 citations in the most prestigious international journals and attended many conferences. She is an active reviewer in many respectable journals.

Prof. Mustafa is a member of: British Pharmacological Society (BPS), UK, Professional Society of Pharmacists, Egypt, Professional Society of Pharmacists, Kuwait, Kuwait Association of British Aluminae (KABA), Kuwait. She got many international and local scientific Awards.

Abdelhamid H. Elgazzar was born in Egypt. He got his MD, Faculty of Medicine, Cairo University, Egypt, Diplomate, American Board of Pathology, Diplomate, American Board of Nuclear Medicine, USA.

He is a Professor and chairman of Nuclear Medicine Department, Faculty of Medicine, Kuwait University, Kuwait. Dr. Abdelhamid has more than 70 publications with 600 citations in the most prestigious international journals and attended hundreds of conferences. He is an active reviewer in many respectable journals.

Prof. Elgazzar is a member of many International and local associations.