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

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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. 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 T½ 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, 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 was 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 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 3 min 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 20–30 min 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 ureteric 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 $^{99m}$Tc 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.
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.

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<th>Tmax</th>
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<tr>
<td>Control</td>
<td>5.4±0.5</td>
<td>10.1±1.0</td>
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<tr>
<td>Diclofenac</td>
<td>12.9±1.5*</td>
<td>29.75±3.0*</td>
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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.

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 appear in the urine.

Figure 4. Sequential functional images of the same control rabbit using 99mTc-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 T1/2. 

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 99mTc-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 T1/2 are significantly affected after diclofenac administration.

V. CONCLUSIONS

Our study investigated 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.
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REFERENCES


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