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**Research Title**

**Effect of Calcium Channel Blockers (Verapamil) on Renal Scintigraphy**

**تأثير الأدوية المانعة لدخول الكالسيوم (فيراباميل) على صور رسم الكلى باستخدام المواد المشعة**

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**الملخص باللغة العربية :**

الادوية المانعة لدخول الكالسيوم هي من اكثر الادوية شيوعا لعلاج امراض القلب والاوعية الدموية. وهذه الدراسة تبحث في تأثير دواء فيراباميل وهو اكثر الادوية استخداما في مجموعة الادوية المانعة لدخول الكالسيوم على وظائف الكلى وعلى صور رسم الكلى باستخدام المواد المشعة.

استخدم في هذه الدراسة ارانب نيوزيلاند بيضاء وذلك لدراسة قياس الشد الاذومتري للشريان الكلوي المقطع حلقات بعد استئصاله من الارنب ووضعه بالأجهزة المخصصة لهذا الغرض وتصوير الكلى باستخدام المواد المشعة 99mTc-MAG3 و الجاما كاميرا والارنب حي.

ويقاس كل من الوقت الذي تستغرقه المادة المشعة للوصول الى اعلى نقطة في شكل منحنى رسم الكلى ويسمى(Tmax) و الوقت الذي تستغرقه المادة المشعة لتصل الى نصف المسافة ويسمى (T½) للأرانب قبل وبعد الحقن بدواء فيراباميل.

أوضحت النتائج ان منحنى تركيزات الفينيل افينيفرين على الشريان الكلوي انحرف لليمين وان اعلى انقباض له يقل بعد الدواء 30±3 % عن قبل إعطاء الدواء. كما بينت ان متوسط القيم Tmax للارانب قبل وبعد أخذ الفيراباميل هي 2.8±0.1و 2.2±0.2 دقيقة. و T½  للارانب قبل وبعد أخذ الفيراباميل هي 4.7±0.05 و 4.2±0.08 دقيقة. وأيضا الانخفاض في القيمتين يساوي 30±4 % وهذا يثبت سرعة وصول المادة المشعة الى الكلى والتخلص منها عند استعمال دواء فيراباميل.

نستنتج من هذه الدراسة تأثير دواء فيراباميل وانه يوسع شريان الكلى ويسرع من عملها ويزيد سرعة Tmax و T½علىصور رسم الكلى باستخدام المواد المشعة. فهو يزيد من وصول الدم الى الكلى ويحافظ على وظيفتها مما يحسن من عملها.

ولكن ننصح بعدم استخدام دواء فيراباميل اثناء عمل صور رسم الكلى باستخدام المواد المشعة. فقد أثبتت هذه الدراسة تأثير هذه الادويه على تغييرصور رسم الكلى مما يؤثر على دقة تشخيص أمراض الكلى ويؤدي إلي نتائج غير سليمة في صور الفحص المشع و التشخيص و العلاج.

**Abstract:**

Calcium channel blockers are among the most widely used prescribed drugs for the treatment of cardiovascular diseases. The present study investigates the effect of verapamil, which is the most commonly used as a calcium channel blocker, on radionuclide imaging. Ten New Zealand White rabbits were used in vitro and vivo studies. Isometric tensions were recorded for isolated renal artery ring segments. Renographic studies were performed using Technetium-99m mercaptoacetyltriglycine (99mTc-MAG3) and Gamma camera. Time to peak activity (T max), time from peak to 50% activity (T ½), were calculated from the renograms for control and treated rabbit with verapamil. In vitro, verapamil shifted the curve of phenylephrine concentration-dependent contraction on renal artery to the right, and decrease the highest contraction by 30±3 %. In vivo, the calculated average values of Tmax for control and treated rabbits were 2.8±0.1 and 2.2±0.2 min, respectively. The T½ for control and treated rabbits were 4.7±0.05 and 4.2±0.08 min, respectively. The differences were statistically significant: p<0.05. There is 30±4 % decrease in the two values. This indicated that there was a rapid renal uptake of the tracer and clearance of the radioactivity after verapamil. This study proved that verapamil dilated the renal artery and had effect on renogram by accelerating both the Tmax and T½.

We conclude that verapamil dilated the renal artery and had effect on renogram by accelerating both the Tmax and T½. It increases renal blood perfusion and glomerular filtration rate, protects kidney function and improves its work. Based on these findings it is suggested not to use calcium channel blockers when the patient have to perform renography to avoid any misleading results for the kidney condition.

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# Introduction

Calcium channel blockers drugs have been prescribed with increasing frequency because of their valuable therapeutic effects. They are used for the treatment of cardiovascular diseases such as hypertension, angina pectoris, cardiac arrhythmias, and other disorders. They also have benefit effects on the kidney.

Renal function in many renal diseases is evaluated by dynamic radionuclide renography studies. Technetium-99m mercaptoacetyltriglycine (99mTc-MAG3) is excreted almost exclusively by the renal tubules. Therefore, in the present study we investigated the effect of calcium channel blockers, verapamil, on the renal artery and on the function of the kidney using renographic imaging technique.

The kidneys filter the blood to remove waste substances. The body discharges these wastes mixed in water as urine. The fluid is collected in the kidneys and discharged through the ureters, which join the kidneys to the bladder. There are diagnostic tools to investigate the kidney problems to help in the clinical management and treatment. The main one is radionuclide studies which allow kidney function to be evaluated and have the advantage of low associated radiation exposure compared with intravenous urography. In a nuclear medicine renal scan, images are made of the delivery of fluid into the kidneys via the bloodstream, concentration of wastes in the kidney and excretion or flow from the kidneys through the ureters and filling of the bladder. This test provides information on the blood supply, function and excretion of urine from the kidneys.

The use of calcium blockers were found to affect renal function and hence may influence the criteria utilized for interpretation of such studies.

# Background & Literature Review

Calcium channel blockers (CCBs) are widely used in clinical practice. These drugs have been prescribed with increasing frequency because of their valuable therapeutic effects. They are used for the treatment of cardiovascular diseases such as hypertension, angina pectoris, cardiac arrhythmias, and other disorders [1-3]. All CCBs inhibit the L-type calcium channels, preventing the entry of calcium, which has a vital role in the cell. Verapamil is one of the most commonly used drug in this group [4-7]. CCBs exert also important vascular and tubular effects on the kidney [8-10]. Experimental studies in animals and humans showed the potential therapeutic uses of CCBs in attenuating the course of acute renal failure and slowing the progression of chronic renal failure. They also assist in preserving renal function in renal transplantation.

A Nuclear Medicine Renogram is performed using a special radioactive material, Technetium-99m (99mTc), that when injected into the blood stream shows the kidney blood supply and filtering action of the kidneys. The radioactive material is usually bound to other non-radioactive elements. These combined elements are called "radionuclides", Technetium-99m mercaptoacetyltriglycine (99mTc-MAG3). The radionuclides emit energy called "photons". Once a radionuclide is distributed in kidney, the photon energy is collected by a "Gamma Camera". The Gamma Camera detects the pattern of distribution of the radionuclide in the urinary system and sends this information to a computer. The computer processes the information and displays them in a picture called renogram.

Different suitable radionuclide investigations have been used as tools to investigate physiological, pathological and pharmacological studies for different body organs such as brain, lung and kidney [11-13]. Renogram evaluates renal function by measuring radiotracer uptake and excretion by the kidney. The images include initial cortical uptake of the radiotracer, cortical retention, first visualization of collecting system and time to peak cortical activity and half clearance [14].

The present study investigate the effect of Calcium channel blockers, verapamil, on the renal artery and on the function of the kidney using renographic imaging technique.

# Methods and Materials

**Experimental Animals**

Ten adult, male New Zealand White rabbits of the same age (10 weeks) weighing 3.5–4 kg were used, four rabbits for in vitro experiments and sex rabbits for in vivo imaging. Experiments were performed in accordance with guidelines approved by the Institutional Animal Care and Use Committee of Kuwait University.

**In-vitro experiments**

Four rabbits were anaesthetized with sodium pentobarbital (50 mg/kg, iv) given via the marginal ear vein and were exsanguinated by cutting the carotid artery. The abdominal cavity was opened and renal artery was immediately removed and placed in Krebs’ solution with the following composition (in mM): NaCl 118, KCl 5.9, MgSO4 1.2, CaCl2 2.2, KH2PO4 1.2, NaHCO3 26 and glucose 11.1, at pH 7.4. The arteries were cut into rings segments 4 mm in length which were mounted on triangular wire supports and suspended in 10-ml organ baths containing Krebs’solution, maintained at 37°C and gassed with 95% O2 and 5% CO2. Care was taken not to injure the endothelium during the preparation. Isometric tension of the renal artery was continuously recorded using UF1 dynamometer transducers connected to 2-channel Lectromid recorder. The segments were initially loaded to a tension of 1 g, which had been previously determined as an optimal load, and allowed equilibrating for 60 min, during which time they were washed twice. A cumulative concentration curves for phenylephrine were established and then repeated after incubation the segments with verapamil for 30 minutes. The responses were calculated as % to the maximum response.

**In-vivo experiments**

Sex adult male New-Zealand White rabbits were used for 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) given via the marginal ear vein. 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 verapamil were referred to as treated animals.

**Radionuclide Imaging**

Baseline imaging studies were performed in each rabbit following injection of 48 MBq (1.3 mCi) of 99mTc-MAG3. Two days later the same rabbit was given a single i.v dose of verapamil 2 mg and the 99mTc-MAG3 renogram repeated 20 minutes later. 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. Regions of interest (ROI) were drawn over the whole kidneys 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.

**Statistical Analysis**

Values are presented as mean ± (S.E.M) of number of rabbits (n) used in the studies. Differences between mean values were compared using Students-t-test paired. The difference was considered significant where P<0.05.

# Results & Discussions

**In-vitro experiments**

To study the vasodilator effect of verapamil, the tone of renal artery should be elevated by a vasoconstrictor substance as phenylephrine, an α-adrenoceptor agent. A cumulative concentration curves for phenylephrine were established. Phenylephrine (0.05 – 50 µL) produced concentration-dependent contractions of renal artery segments. After obtaining control responses, the tissues were incubated for 30 min in the presence of calcium channel blocker, verapamil 10 µL. Then the concentration-dependent contractions of phenylephrine were repeated. The responses were calculated as % to the maximum contraction response. Verapamil shifted the curve to the right and the maximal response decreased by 30±3 % as shown in Fig. 1.

**Radionuclide Imaging**

In the present study, the data collected by the gamma camera were analyzed by a computer and plotted on time graphs, renograms. Counts (how much 99mTc-MAG3 is in the kidneys) is shown on the Y axis, and time from injection is shown on the X axis. The response of each kidney is plotted separately.

Both kidneys take up the isotope rapidly so the curves are steeply rising between 1 and 3 minutes. The concentration of 99mTc-MAG3 peaks at 3-5 minutes and then starts to fall. Normally at least half of the tracer is excreted and drained from the kidneys within 20 minutes. Renograms were normal, with time to peak of Tmax for control and treated rabbits were 2.8±0.1 and 2.2±0.2 min, respectively. The T½ for control and treated rabbits were 4.7±0.05 and 4.2±0.08 min, respectively. The differences were statistically significant: P<0.05. After verapamil administration, the overall function increased with acceleration in cortical clearance, and the renograms were shifted to the left. There were decrease in Tmax and T1/2 in all treated rabbits than control and there is 30 ± 4% decrease in the two values, as shown in Table 1.

The typical renograms using 99mTc-MAG3 before and after verapamil administration are shown in figures 2A & B. After verapamil treatment the curves shifted to the left of the control curves indicating that there

was slightly increase in renal uptake of 99mTc-MAG3 and acceleration in the clearance of radioactivity. The retention of radiotracer 99mTc-MAG3 in left kidney and right kidney after 2-3 min was more after verapamil treatment as represented in figure 3 A& B. The sequential functional images of the same rabbit before and after verapamil administration are shown in figures 4A & B. Evidently, acceleration in the appearance of the bladder and in the clearance of renal activity can be seen. This indicates that the blood flow to the kidney is increased by verapamil administration. Both left and right kidneys have the same results in all renograms.

**Table 1**

Calculated mean values of time to Tmax ; and T1/2 for the control and rabbits treated with verapamil.

|  |  |
| --- | --- |
|  | **99mTc-MAG3** |
| **Tmax** | **T1/2** |
| **Control** | **2.8±0.1** | **4.7±0.05** |
| **Verapamil** | **2.2±0.2**\* | **4.2±0.08**\* |

Tmax : Time to peak activity (min).

 T1/2 : Time from peak to 50% activity (min).

\*P<0.05 for the comparison between control and after verapamil.

\*

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\*

Figure 1

Effect of verapamil 10 µL on phenylephrine-induced contractions of renal artery ring segments. Each point on the graph represents mean ± SE of four rabbits, \*P<0.05.



 A) Control



 B) After verapamil treatment

Figure 2

Time activities curves (renograms) for (A) control rabbit; and (B) after verapamil treatment using 99mTc-MAG3. Note the acceleration for the peak and the clearance of activity from kidneys after verapamil.

  

 A) Control B) After verapamil treatment

Figure 3

The retention of radiotracer 99mTc-MAG3 in left kidney (L Kid) and right kidney (R Kid) after 2-3 min (A) control rabbit; and (B) after verapamil treatment. The urinary bladder did not showed radioactivity in control while there is retention of radioactivity in the bladder after verapamil treatment indicating the start of clearance.

 

 A) Control B) After verapamil treatment

Figure 4

Sequential functional images obtained (the dynamic images acquired for every 30 s frames for the first 30 min after administration of 99mTc-MAG3 show more retention of radioactivity in verapamil-treated rabbit (B) than in control rabbit (A), reflecting the more clearance by the kidney.

The results of this study showed that verapamil promoted renal artery vasodilatation. Therefore, induced afferent arteriolar vasodilatation, oppose vasoconstriction due to endogenous vasoconstrictor agents, and increase vascular permeability. This will lead to increase in glomerular filtration rate (GFR) resulting in increased urine output. It is known that the main effects of calcium channel blockers, as used therapeutically are on cardiac and vascular smooth muscle. They cause generalized arterial dilatation, thereby reducing blood pressure.

It has been proved their effectiveness for the treatment of essential hypertension with normal maintenance of renal function [15,16]. In this respect, there are reports indicating that calcium blockers are particularly effective in a subgroup of patients with essential hypertension who exhibit subtle but detectable alterations in calcium metabolism [17]. CBBs have other effect in normal animals and humans such as diuretic and natriuretic properties and inhibition of aldosterone secretion [18].

The renal artery enters the kidney and branches, one of the branch is afferent arterioles. Each afferent arteriole branches into the glomerular capillaries, the distal glomerular capillaries merge to form the efferent arteriole. Efferent arterioles subdivide to form peritubular capillaries in the cortex., while decreased tone in the efferent arteriole or increase tone in the afferent arteriole lowers GFR.

Glomerular capillary hydrostatic pressure is modulated by the tone of the afferent and efferent glomerular arterioles. Increased tone in the afferent arteriole or decreased tone in the efferent arteriole rises capillary hydrostatic pressure and GFR. The high hydrostatic pressure in the glomerular capillaries causes a rapid fluid filtration in the glomeruli.

Angiotensin II increases the afferent arteriolar and glomerular capillary hydrostatic pressure [19]. Angiotensin II type 1 receptors are localized in both afferent and efferent arterioles [20]. The increase in tone of efferent arteriole decreases hydrostatic pressure in peritubular capillaries and increase of sodium and water reabsorption [21]. Renin-angiotensin system antagonists play an important role in blood pressure and renal function. From our results verapamil dilates the afferent and efferent arterioles since they needs calcium to contract, therefore it increase hydrostatic pressure in peritubular capillaries. The high hydrostatic pressure is mainly due to the difference between the afferent and efferent arterioles diameters.

Radionuclide renography has a role in evaluating perfusion and kidney function. It is used for evaluation many kidney diseases and transplanted kidneys [22-26]. The interval between radiotracer administration and excretion of activity into the collecting system, is a measure ofcortical function. Delayed appearance of the collecting system is associated with renal insufficiency. The interval between radiotracer administration and maximum cortical activity is another parameter of function. It can be easily measured from the time-activity curve, renogram. The computer-generated renogram curve using a radiopharmaceutical consists of three phases. Perfusion phase, renal peak activity during the perfusion phase. The second phase is the cortical or tubular concentration phase of initial parenchymal transit. This phase occurs during minutes 1 through 5 and contains the peak of the curve. The initial uptake slope closely correlates with effective renal plasma flow (ERPF) values. The third phase is the clearance or excretion phase, which represents the down slope of the curve and is produced by excretion of the radiopharmaceutical from the kidney and clearance from the collecting system. A renal scan is performed to look at the blood supply, function and excretion of urine from the kidneys.

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 almost complete excretion after 30 min for 99mTc-MAG3 as shown in figures 2. Generally, as renal function improved, the percentage retained decreases. Verapamil then can be renoprotective in the presence of a preserved GFR. From the previous discussion, CCBs will have a great effect on the glomerular filtration. Since verapamil significantly accelerated of Tmax and T1/2.

**CONCLUSIONS**

Radionuclides imaging can be used as a new tool to prove the effect of CCBs on kidney function. CCBs as verapamil significantly dilate the renal artery and the afferent and efferent arterioles leading to increase renal blood flow and GFR. These results conclude that verapamil is a renoprotective agent.

# Future research

We want to examine different radiopharmaceuticals to suggest the best one for different kind of clinical investigations with their main drug of choice.

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