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Original Article

Effect of sulfa drugs on kidney function and renal scintigraphy

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SUMMARY AT A GLANCE

This experimental study in rabbits showed that sulfa drugs cause deteriorations in renal function, by affecting both reabsorption and excretion of renal tubule. The drugs also induce pharmacokinetic changes by delaying T_{max} as well as $T_{1/2}$.

ABSTRACT:

Aim: **The sulfonamide group is widely used for bacterial diseases including kidney and urinary tract infections. The present study investigates the effect of a sulfa drug on kidney function and renography studies by using a radionuclide.**

Methods: **Renography studies were performed on New Zealand white rabbits. Each rabbit was injected with 48.1 MBq technetium-99*m* mercaptoacetyltriglycine (^{99m}Tc-MAG-3). Dynamic images were acquired using a gamma camera. Radioactivity time curves were generated from the regions of interest, time to peak activity (T_{max}) and time from peak to 50% activity ($T_{1/2}$). Each rabbit served as its own control. The sulfa drug was given to these rabbits for 7 days (i.v injection 130 mg/kg daily in two divided doses; i.e. the single dose is 65 mg/kg), then dynamic images were acquired.**

Results: **Treatment with sulfa shifted the experimental curves to the right of the control curves. This result showed that there was a delayed renal uptake of ^{99m}Tc-MAG-3 and its clearance. Calculated averages of T_{max} were 2.2 ± 0.3 and 5.9 ± 0.5 min; while for $T_{1/2}$ were 3.1 ± 0.3 and 8.4 ± 0.6 min for control and sulfa-treated rabbits, respectively ($n = 20$; $P < 0.05$).**

Conclusion: **Our results indicate that sulfa drug induced pharmacokinetic changes because of delaying both the T_{max} and $T_{1/2}$. Sulfa drug has an effect on the reabsorption from the renal tubules and the excretion process of ^{99m}Tc-MAG-3 which is excreted almost exclusively by the renal tubules. Therefore, sulfa drug causes a deterioration in kidney function and an alteration on radionuclide renography.**

Sulfa drugs are the first class of antibacterial preparations approved for widespread use. They possess bacteriostatic effects.[1,2] The chemical structure of sulfa is very close to p-aminobenzoic acid. Therefore, they compete with it for the enzyme dihydropteroate synthetase, which is important in the formation of folic acid. Folic acid is required for the synthesis of precursors of DNA and RNA both in bacteria and in mammals. While mammals obtain their folic acid in their diet, bacteria need to synthesize it.[3] Sulfa drugs are rapidly excreted and soluble in urine so they are used to treat infections of the urinary tract.[4] The sulfa drugs have a low solubility in the body fluids. After filtering out of the blood into the urinary fluid of the kidney, they are normally concentrated five times or more through the reabsorption of water from the filtrate by the kidneys.[4] The sulfa drugs may exceed their solubility and precipitate in the urinary system. Moreover, kidney dysfunction and decrease in renal excretion lead to accumulation of sulfa drugs and their metabolites and this significantly increases the risk of their nephrotoxic action up to severe interstitial nephritis and necrosis of renal tubules.[5] Sulfa drugs can be used to treat the infection of many body organs. Infection of the kidney (pyelonephritis) and the ureters also can be treated by sulfa. Chronic toxicity from sulfa drugs is more important than acute toxicity, because it can lead to renal failure.[6] The most significant form is kidney toxicity, which occurs after several days of therapy because the kidneys fail to excrete the sulfa properly.

In the last few years, high-dose sulfa therapy has been widely used for treatment of several important diseases such as toxoplasmic encephalitis in AIDS patients.[7] As a consequence, sulfa nephropathy has become increasingly common.[8] Sulfanilamides are used also to treat meningococcal

meningitis.[9] Halogenated sulfonamide derivatives have the potential for developing antimycobacterial agents against many strains exhibiting multidrug resistance.[10]

Nuclear radiology is valuable in assessing the pathophysiology of a variety of organ systems. Pharmacological interventions are often employed in radionuclide imaging to monitor the physiological changes, which in turn facilitate the diagnosis and clarify the effect of drugs on any organs such as the kidney.[11]

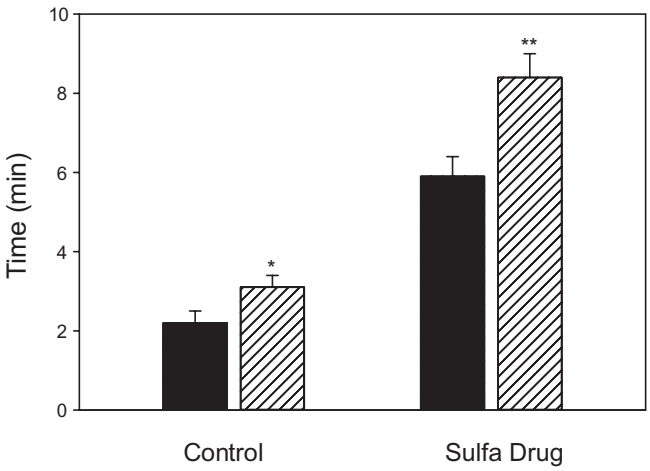

Fig. 1 Calculated mean values of time to T_{max} and $T_{1/2}$ for the control rabbits and after sulfanilamide treatment using technetium-99*m* mercaptoacetyltriglycine, $*P < 0.05$, $**P < 0.01$. Black bar, T_{max}; lined bar, $T_{1/2}$.

The aim of this study is to evaluate the effect of chronic use of the sulfa drug on kidney function by using radionuclides. The results will provide new evidence on their side-effects in kidney.

METHODS

Experimental animals

Twenty adult male New Zealand white rabbits of the same age (10 weeks) weighing 3–3.5 kg were studied. All animals were kept on adequate food and water in our animal house facility. Experiments were performed in accordance with guidelines approved by the Institutional Animal Care and Use Committee of Kuwait University.

Radionuclide imaging

Marginal veins in rabbits ears were connected to butterfly needles. Each rabbit was anaesthetized with ketamine (40 mg/kg i.v). Additionally, 60 mL of normal saline were administrated i.v. The saline was administrated 30 min prior to the administration of the radiopharmaceutical to further ensure adequate hydration. Renographic studies were performed for all the rabbits (control) then after their treatment with sulfanilamide. The treated rabbits were administrated 130 mg/kg sulfanilamide daily (in two divided doses, each 65 mg/kg) by i.v. injection for 1 week.

Each renographic study was performed using 48.1 MBq (1.3 mCi) technetium-99*m* mercaptoacetyltriglycine (^{99m}Tc-MAG-3). Studies were acquired using a gamma camera (T55B-1473; Meridian System, Denmark) equipped with a low-energy, high-resolution,

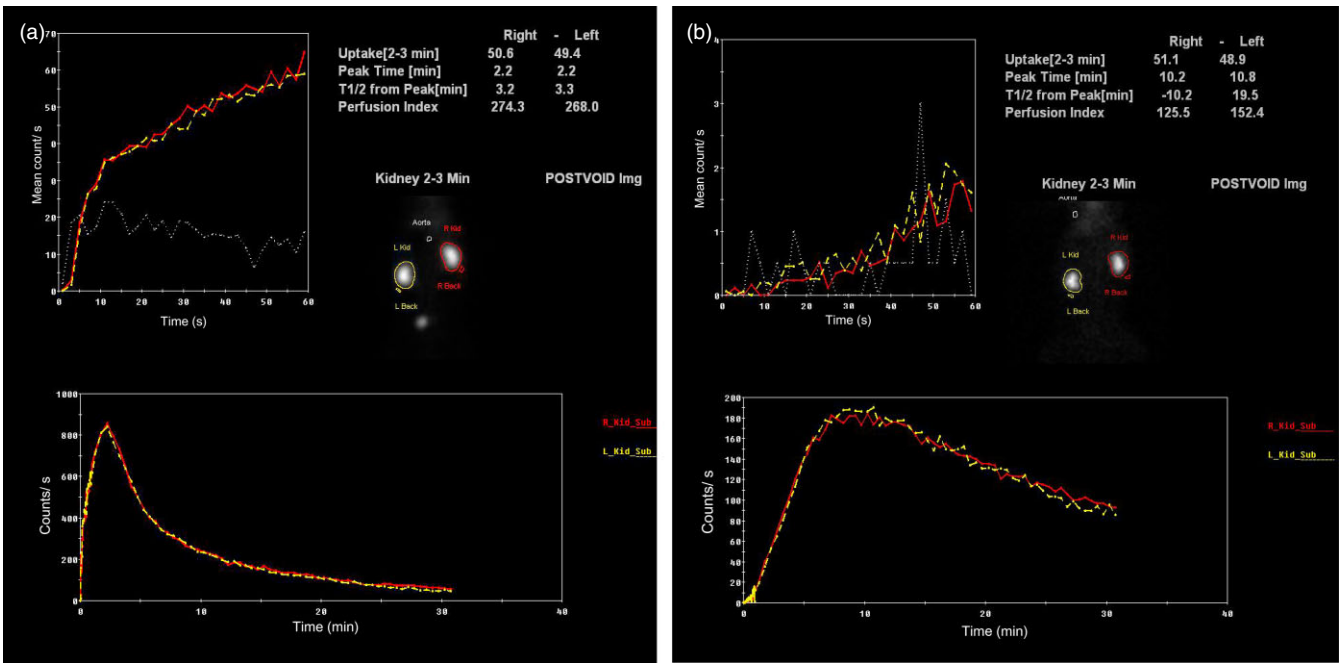

Fig. 2 Time–activity curves (renograms) for (a) control rabbit and (b) after sulfanilamide treatment using technetium-99*m* mercaptoacetyltriglycine. Note the delay in peak and the delayed clearance of activity from kidneys.

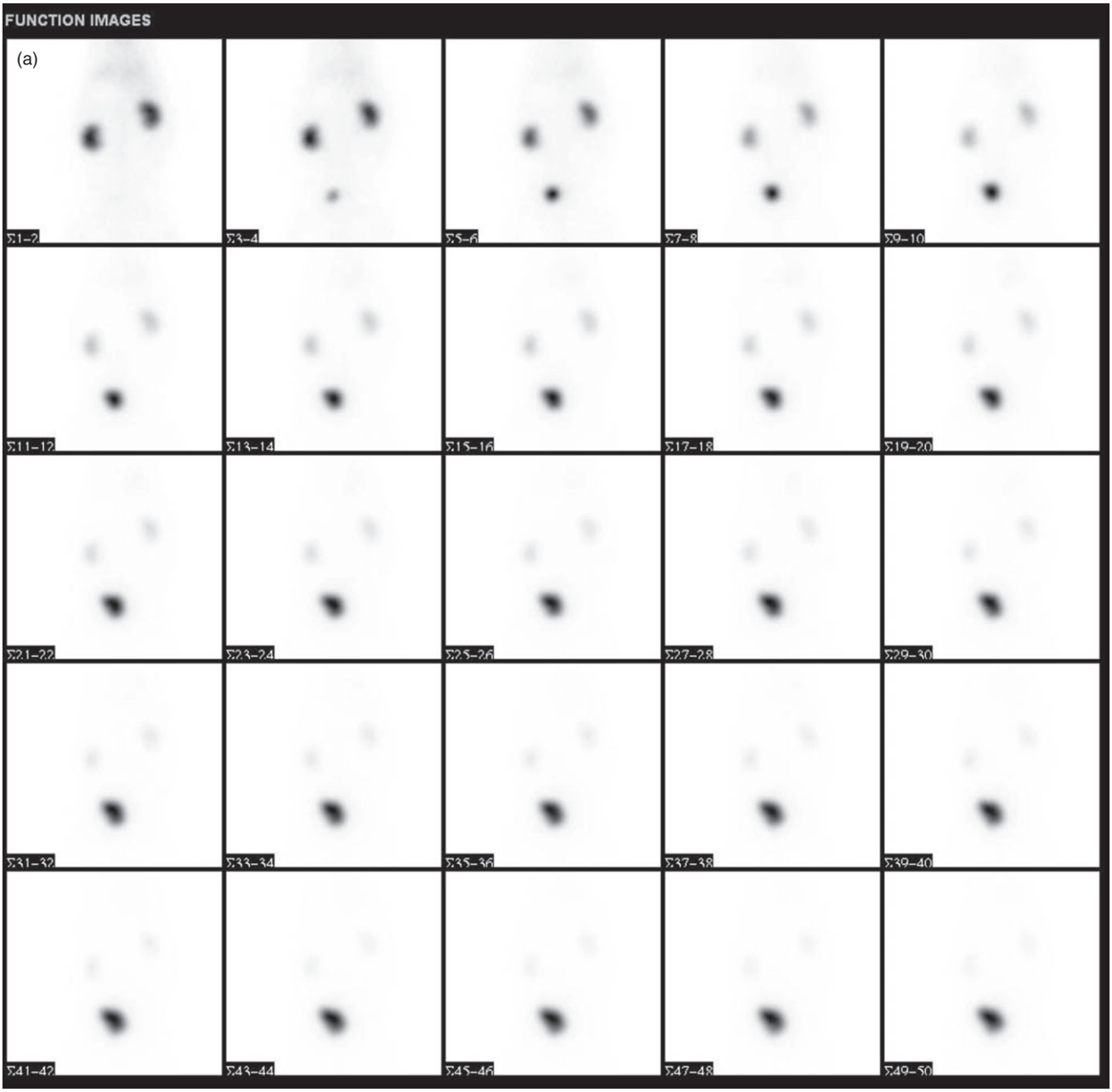

Fig. 3 Sequential functional images for (a) control rabbit and (b) after sulfanilamide treatment illustrate more retention of radioactivity in the kidneys after sulfanilamide treatment using technetium-99*m* mercaptoacetyltriglycine.

parallel-hole collimator interfaced with a dedicated computer. Rabbits were positioned after anesthesia in the supine position. 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) on a 64 × 64 matrix. Post-void static images were acquired for 60 s on a 256 × 256 matrix. Regions of interest were drawn over the whole kidneys and the urinary bladder manually. Radioactivity time curves (renograms) were automatically generated, and corrected for background of both kidneys. Curves were drawn by using a Xeloris workstation (version 1.06; GE Medical Systems, Cleveland, OH, USA). The time to peak activity (T_{max}), time from peak to 50% activity ($T_{1/2}$) and the uptake slope of each kidney were automatically calculated from the renograms. The same protocol was repeated for the same rabbits after sulfanilamide administration for 1 week using the same parameters and the same operator.

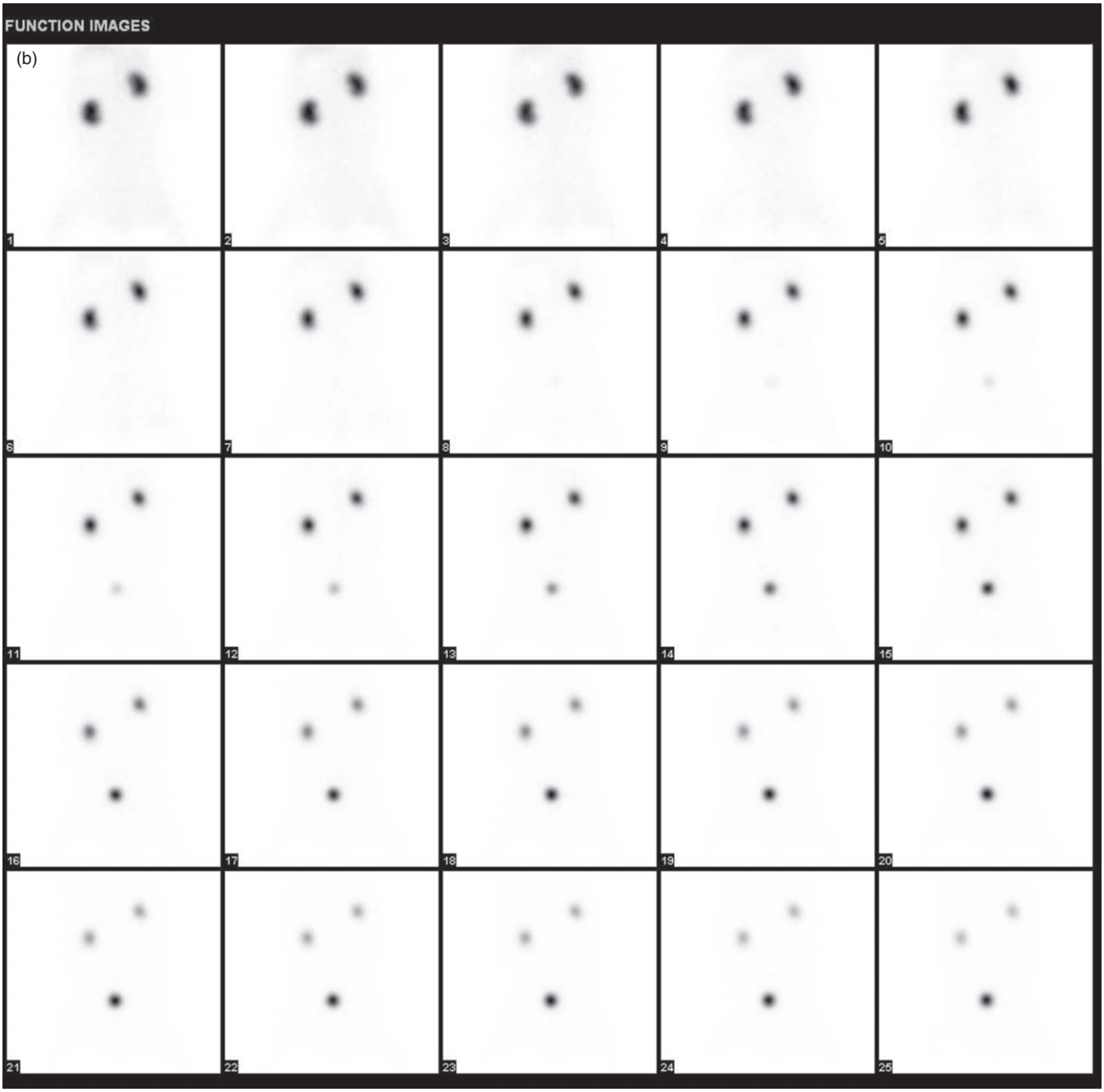

Fig. 3 *Continued*

RESULTS

Radionuclide imaging

Renograms were normal, sharp and exponential, with time to peak of 2.1 ± 0.3 min and $T_{1/2}$ = 3.1 ± 0.3 min for control kidney using ^{99m}Tc-MAG-3. After sulfanilamide administration, the overall function reduced with delayed cortical clearance, and the renograms were shifted to the right. There was a delay of T_{max} and prolongation of $T_{1/2}$ in all treated rabbits. The values were 5.9 ± 0.5 and 8.4 ± 0.6 min. (n = 20; *P < 0.05), (Fig. 1).

Figure 2 illustrates an example of renographic studies of one rabbit using ^{99m}Tc-MAG-3 before and after sulfanilamide administration. After the treatment, the curves shifted to the right compared to the control curves indicating that there was delayed renal uptake of ^{99m}Tc-MAG-3 and clearance of radioactivity. Conversely, Figure 3 illustrates sequential

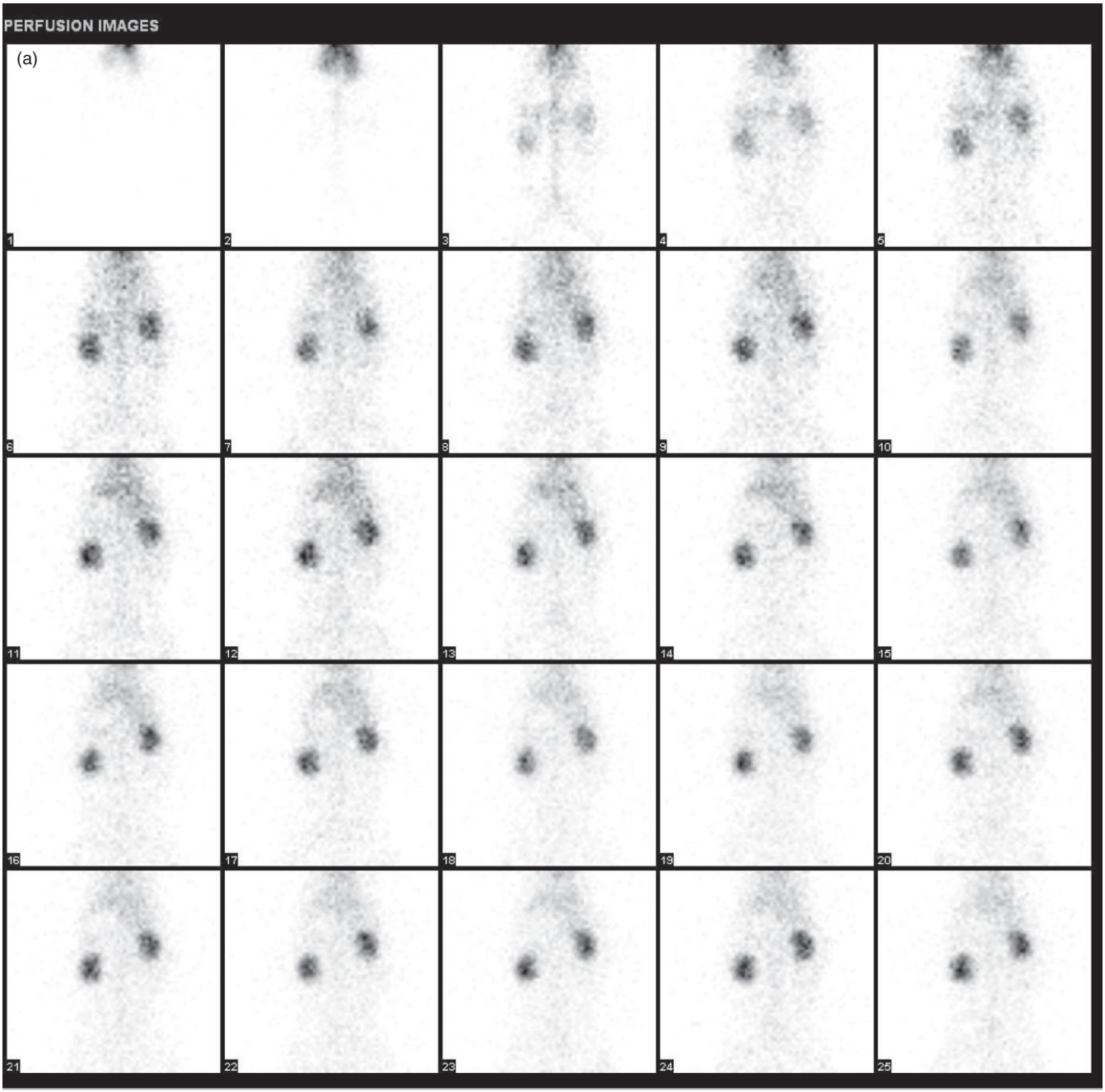

Fig. 4 Sequential perfusion images of (a) control rabbit and (b) after sulfanilamide treatment.

functional images of the same rabbit before and after sulfanilamide. Clear delays in the appearance of the bladder and in the clearance of renal activity are evident.

In all the flow studies, the kidney appeared at the same time as the appearance of the aorta as shown in Figure 4. This indicates that the blood flow to the kidney is not affected by sulfanilamide administration. Both left and right kidneys have the same results in all renograms. The mean split function is 49.9 ± 0.1 and ranged 49.6–50.4%.

DISCUSSION

Treatment with sulfanilamide is sometimes indicated in patients suffering from nephritis or in those with infections which may lead to renal disease. It is known that the kidney has an increased susceptibility to being damaged by this drug.[2,12] The sulfa drugs are widely used as antibacterial agents for many other conditions. These drugs, however, can cause hypersensitivity and severe skin rash,

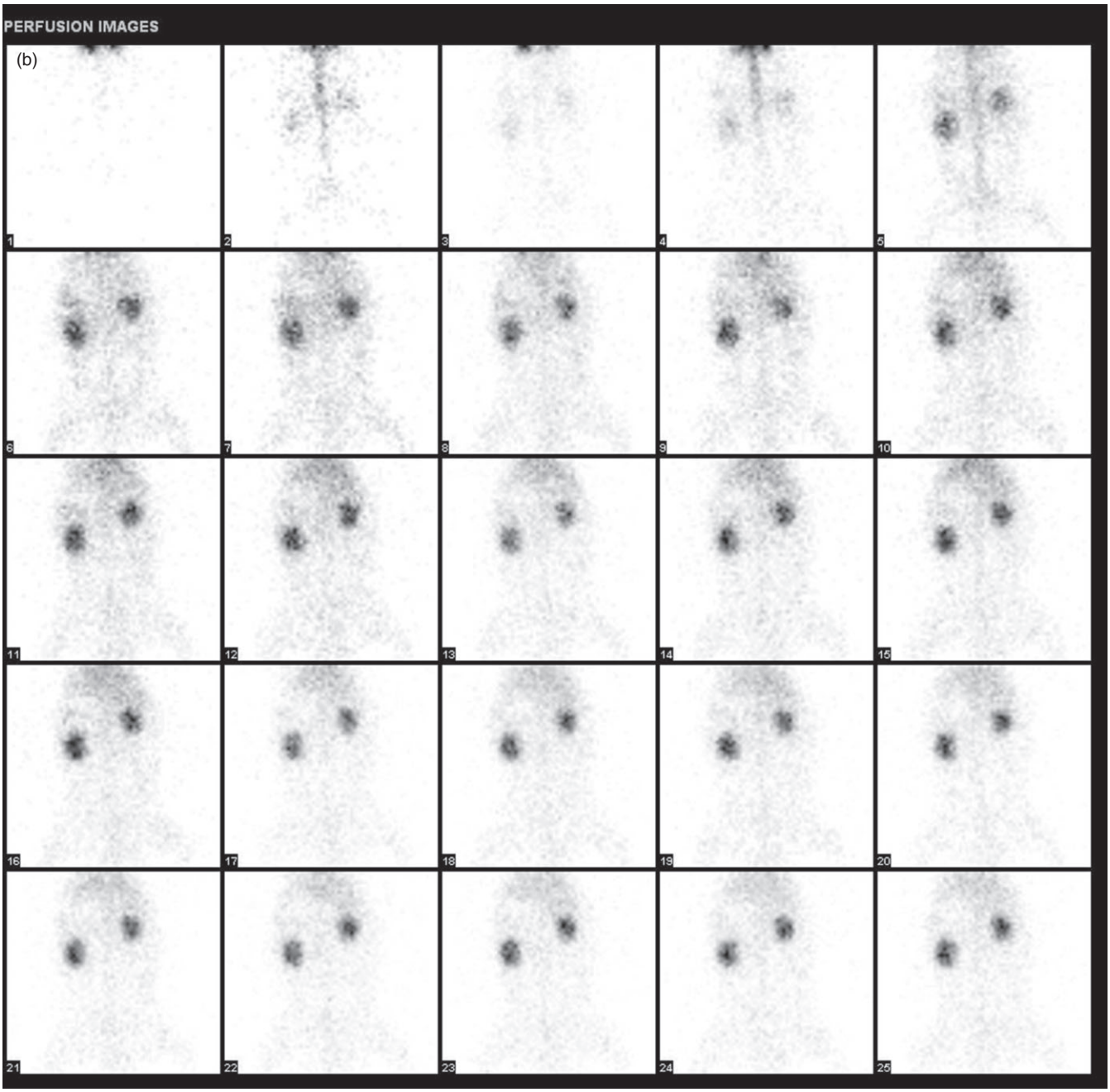

Fig. 4 *Continued*

toxicities which are now associated with the presence of the aniline structure (4-amino). Sulfanilamide metabolite 4-hydroxylaminobenzenesulfonamide (4-HABSA) was formed in the kidney. It was suggested that 4-HABSA plays an important role in the rat renal damage *in vitro*.[13,14] Sulfa drugs are known to possess low water solubility, and may precipitate in renal tubules in the face of dehydration. A major side-effect of sulfa therapy is the occurrence of crystallization in the urinary collecting system.[8,15,16] A previous report studied two cases of sulfadiazine-induced obstructive nephropathy that were diagnosed with ultrasound (US). Renal US demonstrated layered clusters of echogenic shadowing material presumed to be sulfa crystals which cleared when the crystalluria resolved. These sulfa calculi can lead to subsequent obstructive nephropathy.[16] Sulfa medications, although used in a variety of antibacterial, anticonvulsant and diuretic applications, can further complicate urinary calculi-associated problems, among others, by the crystalline aggregates in these drugs. Generally, however, the solubility of sulfa drugs and their ability to induce

calculi is significantly increased by higher urinary pH levels. This potentially serious complication can be managed easily with conservative treatment.[17] Clinicians should be aware of this complication as it is expected to occur more frequently as more patients are treated with sulfa drugs.

Radionuclide renography can be used to evaluate the perfusion and function of kidney. The 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. Delayed appearance of the collecting system is associated with renal insufficiency.[18–21] The interval between radiotracer administration and maximum cortical activity is another parameter of function. It is measured from the time–activity curve. This study investigated the effects of sulfanilamide on kidney function using the tubular agent ^{99m}Tc-MAG-3 and showed delay in T_{max} and $T_{1/2}$. The effect was threefold delay after sulfanilamide treatment compared with controls. The mechanism that results in this difference was not noticed or studied before. This study showed that sulfa drug has an effect on the reabsorption from the renal tubules and the excretion process of ^{99m}Tc-MAG-3 which is excreted almost exclusively by the renal tubules. Therefore, the adverse effects of sulfa drug are not only via the formation of calculi as known, but due also to induction of pharmacokinetic changes. Therefore, it is concluded that sulfa drug causes a deterioration in kidney function and also an alteration on radionuclide renography.

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