J of Nuclear Medicine Technology, first published online October 4, 2022 as doi:10.2967/jnmt.122.264241

Abnormal Biological Distribution Related to Normal Saline Among Technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) Scans

Running title: Abnormal Distribution in 99mTc-DMSA Scan

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Reprints are not available.

This work did not receive any financial support from any agency.

Abstract

Aim: The primary aim is to describe the incidence and causes of abnormal distribution of ^{99m}Tc-DMSA among patients who underwent renal scans in Royal Hospital (Oman), in 2020. The secondary aim is to assess the effect of a specific batch of normal saline A (batch NO 132129) compared to another normal saline B (batches NO 132589 and NO 133325) used in the preparation of ^{99m}Tc-DMSA on the abnormal biodistribution of ^{99m}Tc-DMSA.

Methods: An ambidirectional cohort study that included all patients who underwent ^{99m}Tc-DMSA renal scan between January and December 2020. Both prospective and retrospective data collection were utilized. Collected data included possible causes of abnormal biodistribution, quality of ^{99m}Tc-DMSA and normal saline, and time of ^{99m}Tc-DMSA injection. Data analysis was conducted by SPSS-25.

Results: The total incidence of abnormal biodistribution was 26.5% with the most common cause being high creatinine (29%). Normal saline batch A, used in the preparation, was found to be significantly associated with abnormal biodistribution (49.7%) compared to batch B (6.6%) ($p-< 0.001$). This association was more prominent among patients injected after two hours with ^{99m}Tc-DMSA preparation (83.0%) compared to within two hours (13.3%).

Conclusion: High incidence of abnormal biodistribution of ^{99m}Tc-DMSA was detected and for the first time in the literature, a specific preservative-free, normal saline that is up to standard, has been identified as a significant cause of abnormal biodistribution. Therefore, it should be listed by nuclear medicine professionals and pharmaceutical companies as a possible cause for abnormal ^{99m}Tc-DMSA biodistribution.

Key Words: Renal Scintigraphy, ^{99m}Tc-DMSA, Normal Saline, Biodistribution, Liver Uptake.

Introduction

Kidneys are one of the most vital organs in the human body which can develop a wide range of diseases that can affect body activity and homeostasis. Therefore, a well-timed renal disease diagnosis and an efficient treatment plan play an important role in patient promotion and reduction of prolonged side effects (*1*). To visualise any abnormalities in the kidneys, different non-invasive techniques are used such as radiological examinations using ultrasound and Computed Tomography (CT scan) and nuclear medicine imaging through gamma camera scanning (*2*).

Nuclear medicine imaging is worthwhile in clinical practices, and its analysis and correct interpretation aid professionals in making correct decisions and taking subsequent therapeutic measures. Renal scintigraphy is a nuclear medicine technique that uses medical radioisotopes to evaluate renal function (*3*). Tchnetium-99m meso-2,3-dimercaptosuccinic acid (^{99m}Tc-DMSA) is the most routinely used radiopharmaceutical for renal cortex imaging due to its nuclear properties, availability, low-cost (*4*), accumulation in the kidney's cortex and guidance detection of any morphological parenchymal abnormality (*5*). Uptake of ^{99m}Tc-DMSA in the kidneys, as normal biodistribution, provides an index to evaluate functional tubular mass, which depends on the proximal tubular cell membrane transport function and renal blood flow (*3*). Biodistribution of ^{99m}Tc-DMSA depends on its physical and chemical characteristics and, to a high degree, to the binding of proteins in the plasma (*6*).

Knowledge about the causes/factors capable of interfering with normal biodistribution of radiopharmaceuticals is worthwhile for accurate diagnoses (*7*). It is well known that human physiology, as well as physicochemical alterations of radiopharmaceuticals, can cause disturbances in ^{99m}Tc-DMSA biological distribution (*8,9*). There are many causes published in the literature that describe the effect on the biodistribution of ^{99m}Tc-DMSA and which can be categorised mainly into (a) ^{99m}Tc-DMSA preparation and formulation such as product concentration, labelling efficiency and pH. (b) Patients' medical conditions such as renal tubular acidosis and renal failure. (c) Patients' medications, for example, urinary alkalinizer, which contains sodium bicarbonate.

Apart from the previous discussion regarding the reasons for abnormal physiologic uptake, we observed a different physiologic uptake in our renal ^{99m}Tc-DMSA patients in the period between January to December 2020. Furthermore, in addition to the causes of abnormal biodistribution discussed in previous studies, we have observed some abnormal biodistribution in our patients, in the same time period, that cannot be explained alone by the causes mentioned in the literature. Moreover, it was clearly observed that most of these patients were injected after 2 hours of the ^{99m}Tc-DMSA preparation. It was assumed that a

specific new batch of normal saline A used in the ^{99m}Tc-DMSA preparation was responsible for the unexplained abnormal biodistribution in general, and the 2-hour interval post injection specifically. Studying the factors affecting the biodistribution is important for nuclear medicine physicians and technologists to further the investigation of abnormal and unexpected trends and causes which may significantly affect the accuracy of nuclear medicine procedures and reporting. Hence, when an uncommon uptake occurs in such organs like the liver and gallbladder, it is important to avoid attributing it to pathologic reasons which may reduce the procedure's diagnostic yield (*10*).

This study included two main objectives. The first aim is to estimate the incidence of the abnormal distribution of ^{99m}Tc-DMSA and prevalence of its well-known causes among patients who underwent renal scans at the Royal hospital, Oman, in 2020. The secondary aim is to assess the effect of using a new batch of normal saline A (batch NO 132129) on the abnormal biodistribution of ^{99m}Tc-DMSA compared to using saline B batches (NO 132589 and NO 133325), all of which are routinely used in the preparation of ^{99m}Tc-DMSA, however, normal saline B batches have been routinely used before normal saline A batches, which were recently introduced in the service.

Materials and Methods

This is a cohort study that was conducted at the Royal hospital, Oman, during the period between January and December 2020, during which all patients (339) who underwent a renal scan were included. Prospective and retrospective data collection were both utilized and eligible patients who presented from March to December 2020 were prospectively assessed. However, those who presented before March were retrospectively tracked using their medical records in the hospital information system (Alshifaa +3), picture archiving and communication system (PACS). Biodistribution outcome assessors were blinded to the ^{99m}Tc-DMSA preparation procedures and to the patients' medical backgrounds.

Evaluation of Patient's health condition and medications

Patients' data such as age, gender, scan indication, Renal Function Test (RFT) results, underlying health conditions and medications were gathered. For assessing the incidence and possible causes of abnormal biodistribution, all ^{99m}Tc-DMSA scans conducted during the study period were independently reviewed by an experienced nuclear medicine physician who was requested to report any abnormal biodistribution in the studied images. In addition, a senior expert was consulted for resolving any issues and inter-observer agreement assessment was done. Possible causes for any abnormality were assessed by a senior technologist and radiopharmacist through reviewing the clinical notes from patients' medical records.

^{99m}Tc-DMSA injection and scanning

The administered radioactivity for adults ranged from 150 MBq to 200 MBq, and for paediatric patients, radioactivity was calculated using EANM dosage card (2016) with a minimum dose of 40 MBq. The volume of each dose was maintained around 0.5 –1 ml. Paediatric patients were injected through an IV cannula, whereas adult patients were injected directly into a vein in the antecubital or dorsal metacarpal region. Patients were asked to stay well hydrated after injection. In addition, patients were instructed to empty their bladders just before scanning. Patients were positioned supine for scanning and static anterior, posterior and bilateral oblique images of the abdomen were acquired two hours post-radiotracer injection using a low-energy high-resolution parallel hole collimator. Each image was developed for 300 kilo counts and a 256 x 256 matrix. Images were processed to acquire split function for both kidneys and analysed for the presence of any scars. Three different calibrated gamma cameras were used on a random bases for imaging: SIEMENS INTEVO (SPECT-CT), SIEMENS EVO (SPECT) and GE-DISCOVERY (SPECT). Symbiote processing station for siemens and Xelris processing station were used for GE. All acquired data was stored on a computer, including counts and measurement times. For all images of kidneys, count-rates were determined by choosing suitable regions of interest (ROIs), and a region surrounding each ROI was used for background correction.

The central research and ethics committee at the Royal Hospital approved this study and the requirement to obtain informed consent was waived.

^{99m}Tc-DMSA preparation and formulation evaluation

The DMSA lyophilized reagent (Technescan DMSA®) and the sodium pertechnetate (^{99m}Tc) solutions eluted from the Mallinckrodt Ultra-Technekow ® generator were used in this study. All kits were prepared on the same day of the procedure. Storage temperature, air bubbles and syringe type were controlled. The Technescan DMSA® was stored following its commercial leaflet instructions in a controlled temperature (2-8 °C). The radiopharmaceuticals were strictly prepared following manufacturer criteria and stored at room temperature (21-24 °C). Air bubbles were physically removed during preparation. In addition, the time between preparation and injection was recorded. Other parameters that may have influenced the ^{99m}Tc-DMSA preparation and formulation, such as product concentration and product quality control measures, were gathered and evaluated. The DMSA vials were checked for expiry date, which was documented along with batch number.

Quality control

The quality of the eluted solution was routinely tested for Mo-99 breakthrough, aluminium breakthrough and pH. The DMSA reagent was prepared with 5 mL of sodium pertechnetate (^{99m}Tc) solution using varied tracer activities 1200 - 3700 MBq. It was then incubated at room temperature for 15 minutes. The radiochemical purity was determined using biodex chromatography strips and acetone as a mobile phase. The pH of the final product was checked using validated Merck pH indicator strips.

Normal saline batches

For assessing the effect of the studied batches of normal saline on abnormal biodistribution, patients who were routinely exposed to different batches of normal saline (which were used in the preparation of ^{99m}Tc-DMSA) during the period of the study were compared for abnormal biodistribution.

The normal saline brand used, along with different batch numbers, as well as their expiry date were checked. Three different routinely used normal saline batches were assessed in this study: a newly introduced batch A (NO 132129 used for 17 weeks during the study) and two batches of B (batch NO 133325 and NO 132589 used for 15 weeks during the study). The pH meter SI Analytics Lab 850 was used to check the pH of normal salines and to compare with validated pH strips. The LAL test was performed to check for bacterial endotoxins in normal salines using a calibrated CHARLES RIVER ENDOSAFE PTS. Blood platelets, chocolate plate and Brain Heart Infusion Broth were used to test normal saline sterility in an institutional microbiology lab.

Data analysis

Data was analysed by SPSS-24. Categorised variables and incidence were presented as frequencies and percentages. The difference in the incidence of abnormal biodistribution in the two compared groups (batch A and batch B) was assessed using the Chi-square test with relative risk and its 95% confidence interval (95% CI). P value of < 0.05 was considered significant.

Results

A total of 339 patients who underwent a ^{99m}Tc-DMSA renal scan were included in this study, 54% of which were males. The sample included 48% children, 35% infants and 17% adults. Indications of the ^{99m}Tc-DMSA renal scan included Vesicoureteral reflux (19%), urinary tract infection (12%), renal scars (11%), posterior urethral valves (9%), neuropathic bladder (7%) and for potential donors (3%).

The incidence of abnormal biodistribution among the studied sample was 26.5% (90 patients) of which 31 patients were found to have obvious causes for abnormal biodistribution. Table 1 summarises the data regarding patients with known causes of abnormal biodistribution. High creatinine in patients with chronic kidney disease was responsible for 26 (29%) of the abnormal cases. Urinary alkaliniser treatment was responsible for 3 abnormal cases. Fatty liver and liver and spleen enlargement conditions were responsible for 2 abnormal cases, respectively.

TABLE 1 Medical conditions and medication affect 99mTc-DMSA biodistribution

Causes	Number of patients
High creatinine	26
Medication/urinary alkaliniser	3
Fatty liver	1
Liver and spleen enlargement	1
Poor quality control measures of ^{99m}Tc-DMSA	0

Regarding the quality control measures, none of the abnormal biodistribution cases were attributed to poor quality control measurement for ^{99m}Tc-DMSA. The quality control tests of prepared ^{99m}Tc-DMSA were performed for all eluted solutions and final products before clinical use. In this study the labelling efficiency and pH were within the acceptance level after 15 minutes and two hours of preparation. Quality control results are shown in Table 2.

TABLE 2 Quality control test results for eluted solutions and final products

Test	Accepted limit	Average result
MOL-99 Breakthrough	< 0.1%.	0.02 %
Al^{+3} Breakthrough	**Eluted spot less intensely coloured than the standard solution**	**All passed**
Tc-m99 pH	4-8	5.0
^{99m}Tc-DMSA pH	2.5-3.5	3.1
Labelling efficiency	≥ 95 %	98.2 %

In relation to normal saline quality control, all three normal saline batches used were preservative free. All institutional investigation results for the three normal saline batches complied to manufacturer specifications in the certificate of analysis. Table 3 shows the quality control results of normal saline batches compared to manufacturer standards.

TABLE 3 Institutional investigation results compared to manufacturer specifications for normal saline quality control

Test	Accepted Limit	Result		
		Normal saline A	*Normal saline B*	*Normal saline B*
Visual inspection	Clear and Colorless	Clear Colorless	Clear Colorless	Clear Colorless
pH	4.5-7.0	5.5	5.6	5.8
Osmolarity mmol/L	308	287	282	280
Endotoxin/Pyrogen IU/mL	< 2.5	< 2.5	< 2.5	< 2.5
Sterility	No growth and turbidity	Sterile	Sterile	Sterile

Out of the total number of patients, 157 (46%) were injected with ^{99m}Tc-DMSA, prepared using batch A normal saline, and 182 (54%) were injected using batch B normal saline. Among batch A group, 78 scans (49.7%) showed abnormal

biodistribution compared to 12 (6.6%) among batch B group. The relative risk was 7.5 (95% CI: 4.3 – 13.3). This difference was statistically significant ($p < 0.001$).

Regression analysis revealed that the use of normal saline A, the presence of a cause and injecting ^{99m}Tc-DMSA after 2 hours from preparation are all independent factors for abnormal biodistribution (p-value < 0.001).

In sub-analysis, it was observed that the association of normal saline A and abnormal biodistribution mainly exists among those who were injected after 2 hours. In this regard, among this group (injected after 2 hours) 83.0% of the normal saline A group developed abnormal biodistribution compared to 8.1% in the normal saline B group (p-value < 0.001). However, those who were injected within 2 hours, 13.3% of normal saline A group developed abnormal biodistribution compared to 4.8% among the normal saline B group (p-value 0.6).

With regard to the association between different factors and abnormal biodistribution, 88.2% of those who reported obvious causes for abnormal biodistribution and developed abnormal biodistribution, compared to 19.7% among those who did not report any obvious cause (p-value <0.001), with regards to time of injection, 42.0% of those who were injected after 2 hours from ^{99m}Tc-DMSA preparation developed abnormal biodistribution compared to 8.9% among those who were injected within 2 hours (p-value <0.001).

Discussion

This study was initiated based on a clinical observation of an increased number of abnormal ^{99m}Tc-DMSA biodistribution cases among patients who underwent ^{99m}Tc-DMSA scanning over a specific point of time. In the present study, the incidence of abnormal biodistribution among the studied sample was observed to be high. The abnormal biodistribution was high visual uptake in the liver, presence of gallbladder and clear bowel loops in DMSA scan. The common reported causes for abnormal biodistribution in this study were high creatinine, medications and liver diseases. In addition, we found that a certain batch of normal saline used in the preparation of ^{99m}Tc-DMSA was associated with abnormal biodistribution of ^{99m}Tc-DMSA.

Unexpectedly, this study observed a high incidence of ^{99m}Tc-DMSA abnormal biodistribution among the scanned patients. The radiotracer uptake was seen as high background with accumulation in the liver and, to a lesser extent, in the gallbladder and

bowel loops. These are commonly reported sites for ^{99m}Tc-DMSA abnormal biodistribution as shown in Figure 1 for adult patient and Figure 2 for paediatric. Although no study was found in the literature addressing the incidence of abnormal biodistribution of ^{99m}Tc-DMSA, in a normal situation and according to clinical observation, the incidence of abnormal biodistribution is expected to be lower than the reported 26%. This can be extrapolated from the incidence of abnormal biodistribution among patients who received normal saline B batch (6.6%), which was routinely used before normal saline A batch was introduced in the service for the preparation of ^{99m}Tc-DMSA, hence this study was initiated.

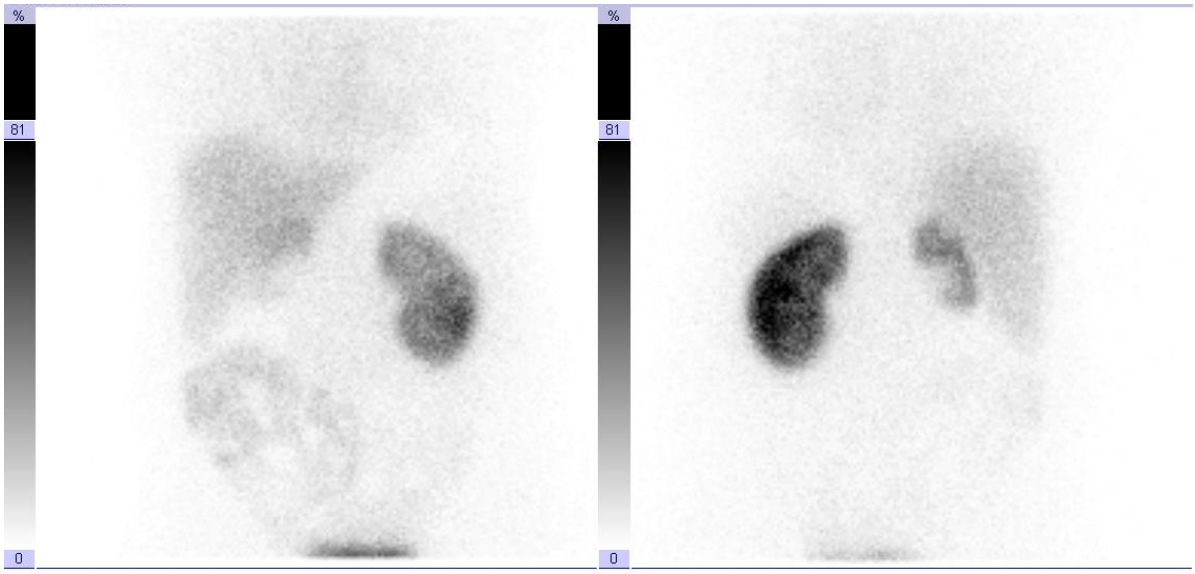

Figure 1. Anterior and Posterior images of adult patient with abnormal ^{99m}Tc-DMSA distribution pattern in liver, colon and background.

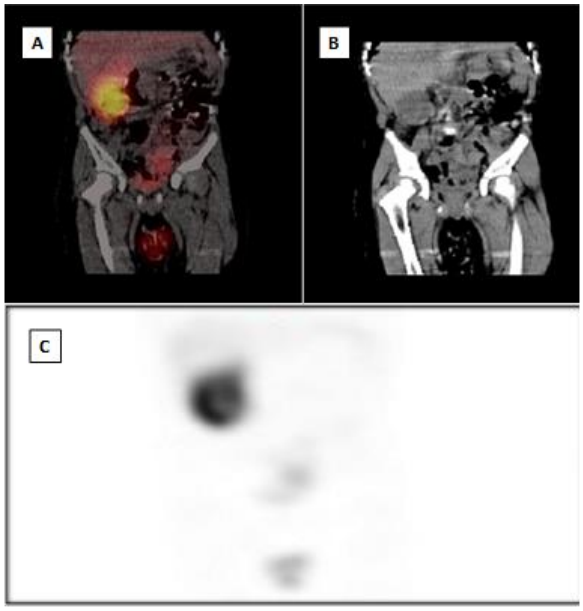

Figure 2. (A) Fused Sagittal images of Technetium-99m-DMSA studies for pediatric patients with history of cross-fused ectopic kidney, showing high background, liver and colon uptake. (B) Corresponding CT image. (C) Corresponding SPECT only Images.

According to Rajic (*11*), the impairment of tubular function is considered the most important cause of altered ^{99m}Tc-DMSA biological behaviour. In this study, 26 patients with abnormal biodistribution had renal problems with high creatinine levels; therefore, this was the explanation for high background and liver uptake among these patients. In addition, liver and spleen diseases could also influence the biodistribution of ^{99m}Tc-DMSA (*5*). Based on this, 2 of the evaluated patients in our study, who demonstrated abnormal biodistribution, had liver and spleen diseases.

Besides disease status, recent medication history was assessed for all patients to evaluate possible interference and impact on the bioavailability of the radiopharmaceuticals on abnormal sites and therefore the image quality. Gomes (*12*) and Bernardo (*7*) found evidence that biodistribution of radiopharmaceuticals may be altered by patient medications. Patients' own medications such as ammonium chloride and sodium bicarbonate can reduce renal uptake and increase liver uptake (*10*). Three of the patients in this study were on urinary alkaliniser drugs which contains sodium bicarbonate. Furthermore, contamination during dispensing or administering of antiseptics can lead to abnormal biological distribution of ^{99m}Tc-DMSA. One example is chlorhexidine antiseptic which can interfere with ^{99m}Tc-DMSA leading to the formation of colloidal complex and subsequently to unfavourable liver and spleen uptake (*13*). In this study, the antiseptic used contained isopropyl alcohol.

On the other hand, it was reported by Fakhari (*5*) that dehydrated patients have less kidney uptake of ^{99m}Tc-DMSA (III) because of decreasing kidney capacity, leading to abnormal biodistribution of ^{99m}Tc-DMSA. Hydration significantly alters the biologic distribution of ^{99m}Tc-DMSA, thus maintaining adequate hydration is an important factor to decrease background levels of ^{99m}Tc-DMSA (*9*). As part of our local departmental procedural protocol, all patients in this study were instructed to stay well hydrated after injection.

Moreover**,** small changes in preparation procedures can cause differences in the formation of different types of products and lead to differences in their biodistribution (*14*). Therefore, procedures for kit preparation and injection were studied, and made a standard in this study to prepare kits in the same manner and to follow the manufacturer's instructions. Temperature can also affect biodistribution as the product stability decreases when temperature is raised (*2*). The ^{99m}Tc-DMSA cold kits used in our department are stored in a calibrated-controlled temperature refrigerator (2-8^{o}C) and labelled vials are stored at a temperature below 25^{o}C. Furthermore, it is known that liver uptake can increase when 1 mL of air is bubbled into the ^{99m}Tc-DMSA solution twenty minutes prior to the injection (*15*). During preparation in this study, the solutions were not exposed to oxygen and the product prepared was used within four hours after preparation. In addition, it has been documented by Vallabhajosula (*10*) that in the preparation of ^{99m}Tc-DMSA, radiochemical impurities increase with decreased product concentration. In our study, ^{99m}Tc-DMSA products were prepared with an appropriate concentration of 1200 – 3700 to achieve an acceptable labelling efficiency according to the manufacturer's instructions. The radiochemical purity test, utilized just before the administration of the radiotracer, revealed acceptable results with less than 2% radiochemical impurity.

It has been proven that ^{99m}Tc-DMSA stability is very sensitive to pH and reactants (*16*). In our study, the eluted solution (pH of ^{m99}TC) was 5.0 on average and 3.1 was the average pH value of the ^{99m}Tc-DMSA. Quality, safety and efficacy of all products were confirmed from quality control tests performed for all products before clinical use. In particular, the labelling efficiency and pH were tested after 15 minutes and two hours of ^{99m}Tc-DMSA preparation. However, there was still profound abnormal biodistribution.

The effect of normal saline used for preparation on the ^{99m}Tc-DMSA biodistribution was checked by comparing different batches. These batches were tested and compared with the manufacturer's certificate of analysis to investigate any problem.

All institutional investigation results complied to manufacturer specification and showed similar laboratory results to other tested batches.

The evaluation of a different normal saline used for all patients, which resulted in abnormal biodistribution, showed that the specific normal saline batch A was responsible for the unexpected increase in the ^{99m}Tc-DMSA abnormal biodistribution. In addition, it was noticed that the association of normal saline A and the incidence of abnormal biodistribution mainly exists among patients who were injected after two hours of preparation. This is the first study to discover a preservative-free normal saline that fulfills quality standards. Other studies have attributed a similar finding to the preservatives that may be added to the normal saline used. Most of these effects were linked to reactions with benzyl alcohol, the most common preservative used in sterile normal saline (*17*,*18*). Another finding is that bacteriostatic normal saline, used in the preparation and dilution of many Tc-99m radiopharmaceuticals, can adversely affect the radiochemical purity, stability and biodistribution compared to preparation with preservative-free normal saline (*19*). Furthermore, it has been reported that the dilution of Tc-99m pertechnetate with bacteriostatic normal saline increased the percentage of insoluble and colloidal impurities (*19*).

Conclusion

In this study, the abnormal biodistribution of ^{99m}Tc-DMSA among scanned patients was high. We clearly observed that a certain preservative-free batch of normal saline, which was up to standards, can be a parameter in abnormal biodistribution for ^{99m}Tc-DMSA procedures. Although the effect of normal saline on ^{99m}Tc-DMSA kit preparation is yet to be revealed, the literature does not include studies evaluating such a factor. This should alert nuclear medicine professionals to any unexpected abnormal biodistribution among scanned patients. It seems that quality control measures are not enough to judge the use of any new batch of normal saline in ^{99m}Tc-DMSA preparation. Pharmaceutical companies should consider testing new manufactured normal saline batches on a sample of patients before being marketed.

Disclosure

No potential conflicts of interest relevant to this article exist.

Key points

QUESTION: Can a preservative-free normal saline be a significant cause of abnormal biodistribution of ^{99m}Tc-DMSA among patients underwent a renal scan?

PERTINENT FINDINGS: In an ambidirectional cohort study the incidence of abnormal biodistribution among the 339 patients who underwent a ^{99m}Tc-DMSA renal scan was observed to be high with specific batch of normal saline used in preparation of ^{99m}Tc-DMSA. The abnormal biodistribution was more reported in patients injected with ^{99m}Tc-DMSA after two hours of preparation.

IMPLICATIONS FOR PATIENT CARE: Alert nuclear medicine professionals to a specific preservative-free normal saline can cause abnormal ^{99m}Tc-DMSA biodistribution.

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