Abnormal Biologic Distribution Related to Normal Saline Among ^{99m}Tc-Dimercaptosuccinic Acid Scans

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The primary aim was to describe the incidence and causes of abnormal distribution of ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) among patients who underwent renal scans in Royal Hospital (Oman) in 2020. The secondary aim was to assess the effect of a specific batch of normal saline A (batch 132129) compared with another normal saline, B (batches 132589 and 133325), used in the preparation of ^{99m}Tc-DMSA on the abnormal biodistribution of ^{99m}Tc-DMSA. **Methods:** This was an ambidirectional cohort study that included all patients who underwent ^{99m}Tc-DMSA renal scanning between January and December 2020. Both prospective and retrospective data collection was used. The collected data included possible causes of abnormal biodistribution, quality of ^{99m}Tc-DMSA and normal saline, and time of ^{99m}Tc-DMSA injection. **Results:** The total incidence of abnormal biodistribution was 26.5%, with the most common cause being a high creatinine level (29%). Normal saline batch A was significantly associated with abnormal biodistribution (49.7%), compared with batch B (6.6%) ($P < 0.001$). This association was more prominent among patients injected with the ^{99m}Tc-DMSA preparation after 2 h (83.0%) compared with before 2 h (13.3%). **Conclusion:** A high incidence of abnormal biodistribution of ^{99m}Tc-DMSA was detected and—for what is the first time, to our knowledge, in the literature—a specific preservative-free, normal saline that is up to standard has been identified as a significant cause of abnormal biodistribution. Nuclear medicine professionals and pharmaceutical companies should take note of this possible cause of abnormal ^{99m}Tc-DMSA biodistribution.

Key Words: renal scintigraphy; ^{99m}Tc-DMSA; normal saline; biodistribution; liver uptake

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The kidneys, one of the most vital organs in the human body, can develop a wide range of diseases that can affect bodily functions and homeostasis. Therefore, a well-timed renal disease diagnosis and an efficient treatment plan play an important role in promoting patient health and reducing side effects from prolonged treatment (*1*). To visualize any abnormalities in the kidneys, various noninvasive techniques are used, such as radiologic examinations through ultrasound and CT and nuclear medicine examinations through γ-camera scanning (*2*).

Nuclear medicine imaging is worthwhile in clinical practice, 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*). ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) is the most routinely used radiopharmaceutical for renal cortex imaging because of its nuclear properties, ready availability, low cost (*4*), accumulation in the renal cortex, and guidance in detecting any morphologic 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, on the binding of proteins in the plasma (*6*).

Knowledge about the causes of, and factors involved in, interference with normal biodistribution of radiopharmaceuticals is worthwhile to achieve accurate diagnoses (*7*). It is well known that human physiology, as well as physicochemical alterations of radiopharmaceuticals, can cause disturbances in ^{99m}Tc-DMSA biologic distribution (*8,9*). The literature describes many reasons for altered ^{99m}Tc-DMSA biodistribution; these can be categorized mainly as related to ^{99m}Tc-DMSA preparation and formulation, such as product concentration, labeling efficiency, and pH; patients' medical conditions, such as renal tubular acidosis and renal failure; or patients' medications, such as urinary alkalinizer drugs, which contain sodium bicarbonate.

Studying the factors affecting biodistribution is important to discover unexpected trends that may significantly affect the accuracy of nuclear medicine procedures and reporting. Hence, when uptake occurs in an uncommon location, such as the liver or gallbladder, it is important to avoid attributing it to pathologic reasons, potentially reducing the procedure's diagnostic yield (*10*).

Between January and December 2020, we observed a difference in physiologic uptake in our renal ^{99m}Tc-DMSA patients that did not appear to stem from any of these known reasons. Furthermore, in the same period we observed abnormal biodistribution in our patients that could not be explained by any of the

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causes mentioned in the literature. Most of these patients had been injected 2 h after the ^{99m}Tc-DMSA had been prepared. It was assumed that a specific new batch of normal saline A used in the ^{99m}Tc-DMSA preparation was responsible for the abnormal biodistribution in general and at the 2-h interval specifically.

This study had 2 main objectives. The first was to estimate the incidence of abnormal ^{99m}Tc-DMSA distribution and the prevalence of its well-known causes among patients who underwent renal scans at the Royal Hospital, Oman, from January to December 2020. The second objective was to assess the effect of using a new batch of normal saline A (batch 132129) on the abnormal biodistribution of ^{99m}Tc-DMSA, compared with using saline B (batches 132589 and 133325). All of these are routinely used in the preparation of ^{99m}Tc-DMSA; however, B batches had been routinely used before A batches were recently introduced into the service.

MATERIALS AND METHODS

All patients (n = 339) who underwent a renal scan during the study period were included. Those who presented in January or February were retrospectively assessed using their medical records in the hospital information system (Al-Shifa +3), picture archiving and communication system (PACS). Those who presented from March to December were prospectively assessed. The assessors of biodistribution outcome were unaware of the ^{99m}Tc-DMSA preparation procedures and the patients' medical histories.

Evaluation of Health Condition and Medications

Patient data such as age, sex, scan indication, renal function test results, underlying health conditions, and medications were gathered. For assessing the incidence and possible causes of abnormal biodistribution, all ^{99m}Tc-DMSA scans during the study period were independently reviewed by an experienced nuclear medicine physician who was asked to report any abnormal biodistribution. In addition, a senior expert was consulted to resolve any issues, and an interobserver agreement assessment was done. Possible causes for any abnormality were assessed by a senior technologist and radiopharmacist by reviewing the clinical notes from the medical records.

^{99m}Tc-DMSA Injection and Scanning

The administered radioactivity for adults ranged from 150 to 200 MBq, and for children, radioactivity was calculated using the European Association of Nuclear Medicine dosage card (2016) with a minimum dose of 40 MBq. The volume of each dose was maintained at around 0.5–1 mL. Children were injected through an intravenous cannula, whereas adults were injected directly into a vein in the antecubital or dorsal metacarpal region. The patients were asked to stay well hydrated after injection. In addition, they were instructed to empty their bladders just before undergoing scanning. The patients were positioned supine for scanning, and static anterior, posterior, and bilateral oblique images of the abdomen were acquired 2 h after radiotracer injection using a low-energy high-resolution parallel-hole collimator. Each image was developed for 300 kilocounts and a 256 × 256 matrix. Images were processed to acquire split function for both kidneys and analyzed for the presence of any scars. Three different calibrated γ-cameras were used on a random basis for imaging: a Siemens Intevo (SPECT/CT), a Siemens Evo (SPECT), and a GE Healthcare Discovery (SPECT). A Symbia.net (Siemens) processing station (Symbiote) was used for the Intevo and the Evo, and a Xeleris (GE Healthcare) processing station was used for the Discovery. All acquired data were stored on a computer, including counts and measurement times. For all images of kidneys, count rates were determined by choosing suitable regions of interest, and a region surrounding each region of interest 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; Mallinckrodt) 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 day of the procedure. Storage temperature, air bubbles, and syringe type were controlled. The Technescan DMSA was stored according to its commercial leaflet instructions at a controlled temperature (2°C–8°C). The radiopharmaceuticals were prepared strictly following manufacturer criteria and stored at room temperature (21°C–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 expiration date, which was documented along with batch number.

Quality Control. The quality of the eluted solution was routinely tested for ^{99}Mo breakthrough, aluminum breakthrough, and pH. The DMSA reagent was prepared with 5 mL of ^{99m}Tc-sodium pertechnetate solution using varied tracer activities of 1,200–3,700 MBq. It was then incubated at room temperature for 15 min. 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. Patients for whom different batches of normal saline were routinely used in the preparation of ^{99m}Tc-DMSA during the study period were compared for abnormal biodistribution.

The normal saline brand used, along with the different batch numbers and their expiration dates, were checked. Three different routinely used normal saline batches were assessed in this study: a newly introduced batch A (batch 132129, used for 17 wk during the study) and 2 batches of B (batches 133325 and 132589, used for 15 wk during the study). The pH meter SI Analytics Lab 850 was used to check the pH of normal saline and to compare with validated pH strips. The limulus amebocyte lysate test was performed to check for bacterial endotoxins in normal saline using a calibrated Charles River Endosafe PTS. Blood platelets, chocolate agar plate, and brain heart infusion broth were used to test normal saline sterility in an institutional microbiology lab.

Data Analysis

Data were analyzed by SPSS, version 24 (IBM). Categorized variables and incidence were presented as frequencies and percentages. The difference in the incidence of abnormal biodistribution in the 2 compared groups (batches A and B) was assessed using the χ^2 test with relative risk and its 95% CI. A P value of less than 0.05 was considered significant.

RESULTS

In total, 339 patients who underwent a ^{99m}Tc-DMSA renal scan were included in this study, 54% of whom were male.

TABLE 1
Medical Conditions and Medication Affect ^{99m}Tc-DMSA Biodistribution

Cause	Patients (*n*)
High creatinine	26
Medication/urinary alkalinizer	3
Fatty liver	1
Liver and spleen enlargement	1
Poor quality control measures for ^{99m}Tc-DMSA	0

TABLE 2
Quality Control Test Results for Eluted Solutions and Final Products

Test	Accepted limit	Average result
^{99}Mo breakthrough	<0.1%	0.02%
Al^{+3} breakthrough	Eluted spot less intensely colored than standard solution	All passed
^{99m}Tc pH	4.0–8.0	5.0
^{99m}Tc-DMSA pH	2.5–3.5	3.1
Labeling efficiency	≥95%	98.2%

The sample included 48% children, 35% infants, and 17% adults. Indications for the ^{99m}Tc-DMSA renal scan included vesicoureteral reflux (19%), urinary tract infection (12%), renal scars (11%), posterior urethral valves (9%), and neuropathic bladder (7%), as well as evaluation for potential kidney donation (3%).

The incidence of abnormal biodistribution among the studied sample was 26.5% (90 patients); 31 of these patients were found to have obvious causes for abnormal biodistribution. Table 1 summarizes the data on 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 alkalinizer treatment was responsible for 3 cases. Fatty liver and enlargement of the liver and spleen were responsible for 2 cases, respectively.

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. The labeling efficiency and pH were within the acceptance level at 15 min and 2 h after preparation. Quality control results are shown in Table 2.

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

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. Among the batch A group, 78 scans (49.7%) showed abnormal biodistribution, compared with 12 (6.6%) among the 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 injection of ^{99m}Tc-DMSA after 2 h from preparation were all independent factors for abnormal biodistribution ($P < 0.001$).

Subanalysis showed that the association of normal saline A and abnormal biodistribution existed mainly among those who were injected after 2 h. In this regard, among this group (injected after 2 h), 83.0% of the normal saline A group developed abnormal biodistribution, compared with 8.1% in the normal saline B group ($P < 0.001$). However, in those who were injected before 2 h, 13.3% of the normal saline A group developed abnormal biodistribution, compared with 4.8% of the normal saline B group ($P = 0.6$).

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

DISCUSSION

Initiation of this study was based on clinical observation of an increased number of abnormal ^{99m}Tc-DMSA biodistribution

TABLE 3
Institutional Investigation Results Compared with Manufacturer Specifications for Normal Saline Quality Control

		Normal saline		
Test	Accepted limit	Batch A (132129)	Batch B (132589)	Batch B (133325)
Visual inspection	Clear, 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 or turbidity	Sterile	Sterile	Sterile

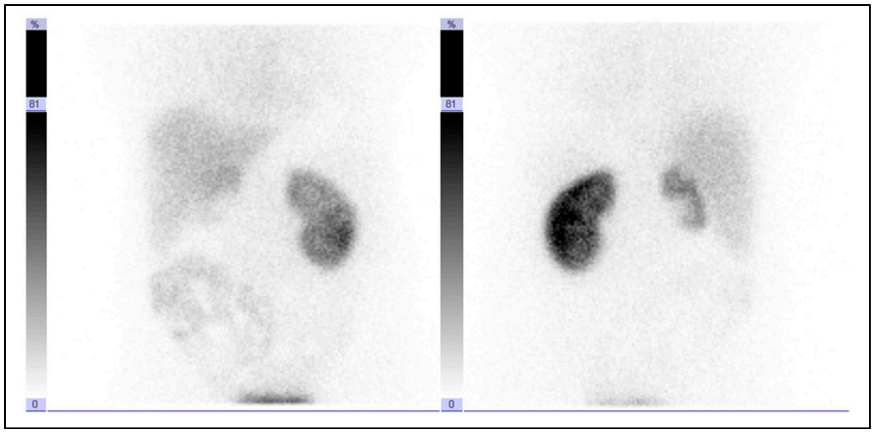

FIGURE 1. Anterior and posterior images of adult with abnormal ^{99m}Tc-DMSA distribution pattern in liver, colon, and background.

cases among patients who underwent ^{99m}Tc-DMSA scanning over a specific period. Unexpectedly, this study found a high incidence of abnormal ^{99m}Tc-DMSA biodistribution among the scanned patients. The radiotracer uptake was seen as a high background level with accumulation in the liver and, to a lesser extent, in the gallbladder and bowel loops. These are commonly reported sites for abnormal ^{99m}Tc-DMSA biodistribution, as shown in Figure 1 for adults and Figure 2 for children. The common reported causes for abnormal biodistribution in this study were high creatinine level, 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.

Although we found no study 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 batch B (6.6%), which had been routinely used before normal saline A batch was introduced into the service for preparation of ^{99m}Tc-DMSA.

According to Rajić et al. (*11*), impairment of tubular function is considered the most important cause of altered ^{99m}Tc-DMSA biologic behavior. 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 may also influence the biodistribution of ^{99m}Tc-DMSA (*5*). Two 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 for possible interference and impact on the bioavailability of the radiopharmaceutical at abnormal sites and, therefore, on image quality. Gomes et al. (*12*) and Bernardo et al. (*7*) found evidence that the biodistribution of radiopharmaceuticals may be altered

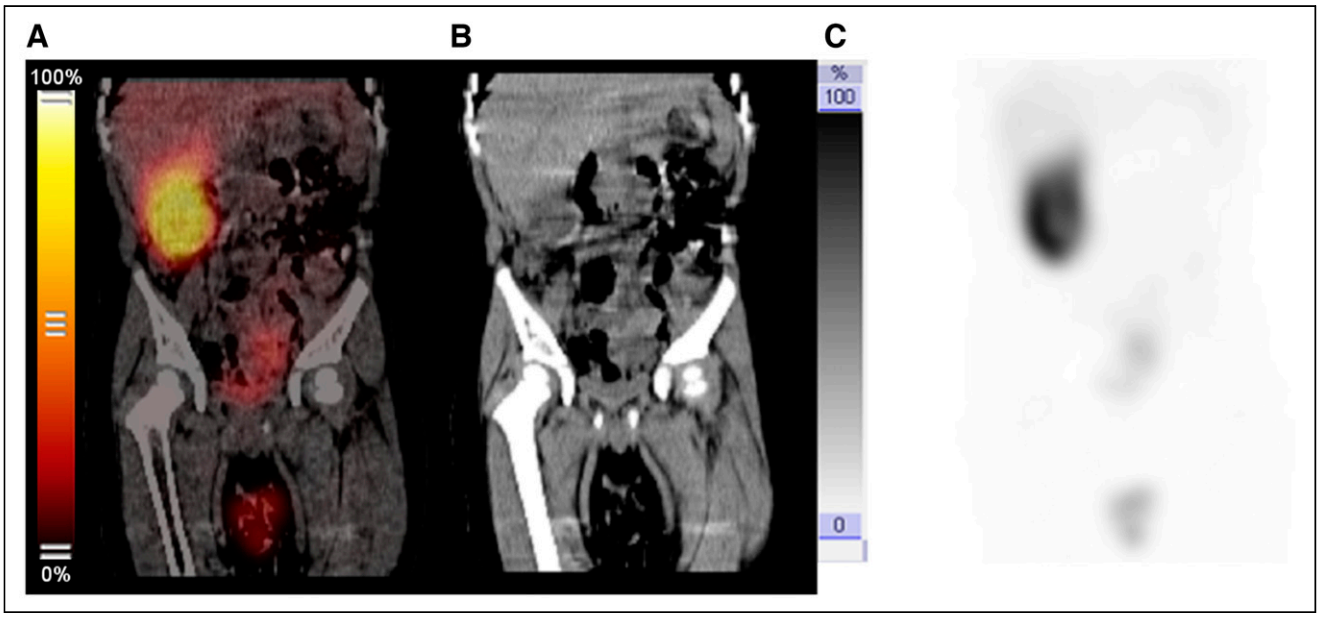

FIGURE 2. (A) Fused sagittal image of ^{99m}Tc-DMSA study of child with history of cross-fused ectopic kidney, showing high background, liver, and colon uptake. (B) Corresponding CT image. (C) Corresponding SPECT image.

by patient medications. 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 receiving urinary alkalinizer drugs, which contain sodium bicarbonate. Furthermore, contamination during dispensing or administering of antiseptics can lead to abnormal biologic distribution of ^{99m}Tc-DMSA. One example is chlorhexidine antiseptic, which can interfere with ^{99m}Tc-DMSA and lead to the formation of a colloidal complex and, subsequently, to unfavorable liver and spleen uptake (*13*). In this study, the antiseptic used contained isopropyl alcohol.

On the other hand, Fakhari et al. (*5*) reported that dehydrated patients have less kidney uptake of ^{99m}Tc-DMSA 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 standardized in this study, with the kits prepared in the same manner and following the manufacturer's instructions. Temperature can also affect biodistribution, as 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°C–8°C), and labeled vials are stored at a temperature below 25°C. Furthermore, it is known that liver uptake can increase when 1 mL of air is bubbled into the ^{99m}Tc-DMSA solution 20 min before injection (*15*). During preparation in this study, the solutions were not exposed to oxygen and the product was used within 4 h after preparation. In addition, it has been documented by Vallabhajosula et al. (*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 1,200–3,700 (MBq/5mL) to achieve an acceptable labeling efficiency according to the manufacturer's instructions. The radiochemical purity test, used just before administration of the radiotracer, revealed acceptable results with less than 2% radiochemical impurity.

It has been proven that ^{99m}Tc-DMSA stability is sensitive to pH and reactants (*16*). In our study, the eluted solution of ^{99m}Tc had an average pH of 5.0, and 3.1 was the average pH of the ^{99m}Tc-DMSA. The quality, safety, and efficacy of all products were confirmed by quality control tests performed for all products before clinical use. In particular, the labeling efficiency and pH were tested at 15 min and 2 h after ^{99m}Tc-DMSA preparation. However, there was still a profoundly abnormal biodistribution.

The effect of normal saline used in the preparation of ^{99m}Tc-DMSA on the abnormal biodistribution of ^{99m}Tc-DMSA 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 with the manufacturer specifications and showed laboratory results similar to other tested batches.

Our study showed that normal saline batch A was responsible for the unexpected increase in abnormal ^{99m}Tc-DMSA biodistribution and that the abnormality was present mainly in patients injected 2 h after preparation of the ^{99m}Tc-DMSA. To our knowledge, this was the first study to discover that a specific preservative-free normal saline that is up to standard is a significant cause of abnormal biodistribution. Other studies have attributed a similar finding to the preservatives that may be added to the saline. 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 ^{99m}Tc-radiopharmaceuticals, can adversely affect radiochemical purity, stability, and biodistribution compared with preparation with preservative-free normal saline (*19*). Furthermore, it has been reported that dilution of ^{99m}Tc-pertechnetate with bacteriostatic normal saline increases 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 standard, was 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, to our knowledge, include studies evaluating such a factor. This should alert nuclear medicine professionals to question the validity of 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 marketing the batches.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

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

PERTINENT FINDINGS: The incidence of abnormal biodistribution among patients who underwent a ^{99m}Tc-DMSA renal scan was high when a specific batch of normal saline was used to prepare the ^{99m}Tc-DMSA, especially in patients injected 2 h after preparation.

IMPLICATIONS FOR PATIENT CARE: Awareness by nuclear medicine professionals that a specific preservative-free normal saline can cause abnormal ^{99m}Tc-DMSA biodistribution will benefit patient care.

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