Tc-99m Ciprofloxacin SPECT of Pulmonary Tuberculosis

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Abstract

Purpose Tc-99m ciprofloxacin is available for imaging infection. However, there has been no study on employing single photon emission computed tomography (SPECT) with using Tc-99m ciprofloxacin to image active pulmonary tuberculosis. Therefore, we conducted this study to assess the efficacy of Tc-99m ciprofloxacin SPECT for imaging active pulmonary tuberculosis.

Methods Twenty-one participants were enrolled in this prospective study. They were divided into two groups according to the clinical and radiological assessment. Group one (Gr. 1) consisted of five normal volunteers and six patients with inactive pulmonary tuberculosis. Group two (Gr. 2) consisted of ten patients with active pulmonary tuberculosis. SPECT was performed 3 h after injecting 555 MBq (15 mCi) of Tc-99m ciprofloxacin. The findings of Tc-99m ciprofloxacin SPECT were interpreted by a nuclear medicine specialist and then the results were analyzed according to the patients' clinical and radiological classifications.

Results The results of Tc-99m ciprofloxacin SPECT were as follows: eight true-positive cases, ten true-negative

cases, one false-positive case and two false-negative cases. The sensitivity and specificity was 80.0% and 90.9%, respectively. The positive predictive value was 88.9% and the negative predictive value was 83.3%.

Conclusions Tc-99m ciprofloxacin SPECT is feasible for imaging active pulmonary tuberculosis. It is a useful nuclear-imaging method for discriminating between the active and inactive tuberculosis states in patients with a past medical history of pulmonary tuberculosis.

Keywords Tc-99m ciprofloxacin · Single photon emission computed tomography · Active pulmonary tuberculosis

Introduction

A new radiopharmaceutical, Tc-99m ciprofloxacin, has been developed and it has been studied for imaging many different types of infections. [1–3] It is composed of a radioisotope (Tc-99m) and an antibiotic (ciprofloxacin). Tc-99m has been widely used for nuclear imaging and its physical half-life ($T_{1/2}$) is 6.02 h [4]. Ciprofloxacin is a fluorinated quinolone, and this antibiotic inhibits the gyrase-mediated DNA supercoiling of bacteria [5]. Tc-99m ciprofloxacin can be used for imaging such infections as osteomyelitis, septic arthritis, prosthetic device infections, endocarditis, deep-seated abscesses and extrapulmonary tuberculosis [3, 6].

There are several radiopharmaceuticals available for detecting inflammation/infection, such as Ga-67 citrate, [7] In-111-labeled leukocytes, Tc-99m hexamethylpropyleneamine oxime (HMPAO)-labeled leukocytes [8] and In-111-labeled IgG [9]. However, these radiopharmaceuticals are basically not specific to detect bacterial infection, whereas Tc-99m ciprofloxacin can be more specific for

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bacterial infections because it is taken up by living bacteria and it inactivates DNA gyrase. [2] Britton et al. [3] demonstrated the results of a large-scale study on imaging bacterial infection with Tc-99m ciprofloxacin (Infecton). Eight hundred and seventy-nine patients with suspected bacterial infection underwent imaging of their infections in the anterior and posterior planar views; these patients had infections such as tuberculosis, osteomyelitis, septic arthritis, endocarditis and infections in orthopedic prostheses, the abdomen and surgical wounds. The overall sensitivity and specificity for detecting infective foci were 85.4% and 81.7%, respectively. For the cases of tuberculosis, the sensitivity and specificity were 79.5% and 76.9%, respectively. Although Britton et al. [3] researched various infectious diseases on a large scale with using Tc-99m ciprofloxacin, there has been no report on using Tc-99m ciprofloxacin single photon emission computed tomography (SPECT) for detecting active pulmonary tuberculosis. SPECT [10, 11] is superior and different from imaging in only the anterior and posterior planar images [3] in that SPECT can reconstruct images into the transaxial, coronal and sagittal views. Making the diagnosis of sputum smear-negative pulmonary tuberculosis is not easy and the diagnosis of this illness is generally based on the clinical signs and symptoms, the sputum culture and chest radiographic findings [3]. The sensitivity of a sputum smear has been reported to be variable (43–76%) and using chest radiography as the only diagnostic test for tuberculosis can result in over-diagnosis or missed diagnoses [3]. In addition, a sputum culture of *Mycobacterium tuberculosis* takes a long time to provide the results. Additionally, there is no well-established nuclear imaging method for detecting active pulmonary tuberculosis under these circumstances. The aim of this feasibility study is to assess the efficacy of performing Tc-99m ciprofloxacin SPECT for imaging active pulmonary tuberculosis, which remains a global health problem [3].

Materials and Methods

Demographics

Twenty-one participants (13 males and eight females) were enrolled in this prospective study (Table 1). The patients' mean age was 44 ± 18 years (range: 22–85 years). The participants were divided into two groups by the clinical and radiological assessment. Group one (Gr. 1) consisted of five normal volunteers and six patients with inactive pulmonary tuberculosis. Group two (Gr. 2) consisted of ten patients with active pulmonary tuberculosis. Sputum cultures were performed in Gr. 2 before starting chemotherapy for the active tuberculosis. The patients in this group were followed up for at least 6 months. This study

Table 1 Imaging results (*M* male, *F* female, + positive, - negative, *Before* before treatment, *After* after treatment, *No* no study)

Age/sex	Group	Tc-99m ciprofloxacin	
		Before	After
25/M	Normal	-	No
31/M	Normal	-	No
26/M	Normal	-	No
24/M	Normal	-	No
24/M	Normal	-	No
44/M	Inactive	-	+
34/M	Inactive	-	-
40/F	Inactive	-	-
41/M	Inactive	-	+
22/F	Inactive	-	-
52/M	Inactive	+	+
27/M	Active	+	No
60/M	Active	+	+
76/F	Active	+	+
55/F	Active	-	+
42/F	Active	-	-
77/F	Active	+	+
41/F	Active	+	-
85/F	Active	+	No
50/M	Active	+	-
45/M	Active	+	-

was approved by the IRB (Institutional Review Board) at our hospital and written informed consent was obtained from the participants.

Preparation of Tc-99m Ciprofloxacin

The Tc-99m ciprofloxacin kit was custom-formulated. In a vial, 10 mg of stannous tartrate was dissolved with 1 ml of 1 N hydrogen chloride for 3 min. Two milligrams of ciprofloxacin was mixed with 0.1 ml of the stannous tartrate solution, and then 555 MBq (15 mCi) Tc-99m pertechnetate was added to the ciprofloxacin vial. The vial was incubated for 30 min at room temperature. The Tc-99m ciprofloxacin was filtered through a sterilized filter (pore size: 0.22 μ m). Instant thin-layer chromatography (ITLC) was performed for quality control by using acetone as a solvent. Labeling of Tc-99m ciprofloxacin has become convenient because of the packaging as a kit, and the labeling efficiency is more than 98% [10–13].

SPECT Imaging and Interpretation

SPECT was performed 3 h after injecting the Tc-99m ciprofloxacin. Every subject was imaged in the supine

position with the hands raised over the head. A Siemens gamma camera MultiSPECT 3 (Hoffman Estates, Ill., USA) was used with a low-energy, high-resolution collimator. The parameters for acquisition were 30 frames (40 s/frame), a 128×128 matrix size and 140 KeV with a 15% energy window. [13] The filtered back projection with using a Butterworth filter was used for reconstructing the images. A nuclear medicine specialist visually assessed the Tc-99m ciprofloxacin SPECT images, which demonstrated the thorax in the transaxial, coronal, and sagittal views. A more increased uptake than the surrounding pulmonary parenchyma was considered a positive finding and the SPECT findings were interpreted without the nuclear medicine specialist having any information on the patients' clinical classification.

Results

In this study, the radiolabeling efficiency of Tc-99m ciprofloxacin was more than 98%, and imaging for detecting active pulmonary tuberculosis and the results were as follows (Table 1): there were eight true-positive cases (Fig. 1), ten true-negative cases, one false-positive case (Fig. 2) and two false-negative cases (Fig. 3). The

sensitivity and specificity of Tc-99m ciprofloxacin SPECT for detecting active pulmonary tuberculosis before treatment were 80.0% and 90.9%, respectively (Table 2). The positive predictive value was 88.9% and the negative predictive value was 83.3%. The results of the sputum culture for all the active cases were positive. All the Gr. 2 patients were converted to an inactive state after anti-tuberculosis medication, as judged by the chest radiography. All the inactive cases in Gr. 1 group continued to be stable without medication.

Discussion

This is the first trial of using Tc-99m ciprofloxacin SPECT for imaging active pulmonary tuberculosis. In this study, one inactive patient (Fig. 2) was imaged positive, which was defined as false-positive, and two active patients (one of them was shown in Fig. 3) were imaged negative, which was defined as false-negative. Obviously, the inactivity was judged by the negative chest X-ray. However, which diagnostic modality has more detectability or efficacy is not yet known. Moreover, since there is no definite “gold standard” test, intelligent interpretation regarding the cases with discrepant results such as positive or negative conversion

Fig. 1 [True-positive case] A 45-year-old man was examined by Tc-99m ciprofloxacin SPECT. An increased uptake was noted in the apical region in the right lung on the transaxial (a) and coronal (b) views. Chest radiography showed reticulonodular infiltrates that were suggestive of active pulmonary tuberculosis in the right upper lung (c). The result of the sputum culture was positive for *Mycobacterium tuberculosis*. Chest radiography shows an inactive state 6 months after the treatment of the disease (d)

Fig. 2 [False-positive case] A 52-year-old man with a past medical history of pulmonary tuberculosis was examined by Tc-99m ciprofloxacin SPECT. Two foci of increased uptake were observed in the right lower lung on the transaxial (a) and sagittal (b) views. However, chest radiography shows no lesion suggestive of active pulmonary tuberculosis in the right lower lung and the sequelae of tuberculosis were observed in the right upper and left lung (c). He has been followed-up clinically and radiologically and he has remained in an inactive state without medication

is not absolutely possible. This study should be considered as a feasibility test at this time. After the chemotherapy, two inactive patients with negative SPECT images and one inactive patient with a positive SPECT image (before chemotherapy) showed positive SPECT results, although all of them were continuously clinically stable without medication. Unfortunately, bacteriologic studies or follow-up chest X-rays on these three patients were not available.

Tc-99m ciprofloxacin packaged as a kit is technically quicker, easier and less labor-intensive to use than that of In-111 leukocytes, which requires ex vivo preparation [2]. Additionally, Tc-99m ciprofloxacin can be used for early imaging and it has a lower radiation burden than the conventional nuclear methods [3]. In spite of the good preparation and the excellent results, there is a theoretical limitation. Ciprofloxacin is a broad-spectrum antibiotic that is used to treat infectious diseases and it is not only effective for tuberculosis but it is also effective for a large number of infections, including other bacterial pneumonias. Therefore, uptake of Tc-99m ciprofloxacin is possible in any infectious disease besides tuberculosis. However, the results in this study showed that Tc-99m ciprofloxacin SPECT could be helpful for discriminating between the active and inactive tuberculosis states in patients with a past

medical history of pulmonary tuberculosis. There were limitations in this study. There were no results of sputum culture or staining in the follow-up studies, so analysis after treatment was impossible. Therefore, we simply made a summarized table of pre-treatment (Table 2) without any post-treatment analysis.

Some research groups have demonstrated good results in favor of imaging infections with using Tc-99m ciprofloxacin [2, 3, 13–23]. Further, case reports have been published on the use of Tc-99m ciprofloxacin for many different illnesses: osteomyelitis of the axial skeleton and hip joint [24, 25], tuboovarian abscess [12], acute bacterial prostatitis [10], seminal vesiculitis caused by chlamydia [11], renal abscess [26], infectious spondylodiscitis [27, 28], evaluating the response of postsurgical bony infection to antibiotic therapy [29], and the absence of uptake by infection in a renal abscess [30].

However, other researchers [31–35] have asserted that Tc-99m ciprofloxacin was not specific for detecting bacterial osteoarticular infection. Sarda et al. [34] prospectively investigated a group of patients with suspected osteoarticular infections (group 1; $n=16$) and a group of the patients with osteoarticular disease and who showed no suggestive infectious signs (group 2; $n=11$). As a result, the

Fig. 3 [False-negative case] A 42-year-old woman showed linear opacities in the right upper lung on chest radiography (a). She was examined by Tc-99m ciprofloxacin SPECT. There is no abnormality in the region (b, c, d) where the linear opacities were previously

observed on chest radiography. The result of sputum culture was positive for *Mycobacterium tuberculosis*. After treatment of active pulmonary tuberculosis, the linear opacities disappeared on chest radiography (e)

sensitivity, specificity and accuracy for imaging osteo-articular infection were 100%, 37.5% and 63%, respectively. They also suggested the possibility of the accumulation of Tc-99m ciprofloxacin in the exudates of the interstitial space and this was facilitated by increased capillary permeability [36] and the uptake of Tc-99m ciprofloxacin by inflammatory cells and activated chondrocytes, osteoblasts and fibroblasts. [37] After the article [34] was published, Britton and Sarda, commented on this topic. Britton et al. [3] demonstrated in the results of a large-scale study on imaging bacterial infection that Tc-99m ciprofloxacin might be a bacteria-specific imaging agent only if

it maintains good radiolabeling efficiency without the Tc-99m colloid and if it is durable for up to 1 h from the time of preparation to the time of injection.

We need to take note of the possibilities of the other mechanisms of Tc-99m ciprofloxacin in the human body, as proposed by Sarda et al. [36] and this is despite the great efforts that have been made to improve the quality of Tc-99m ciprofloxacin at a time when the structure of the Tc-99m complexes of ciprofloxacin has not been completely determined. [38, 39] In this article, the term “Tc-99m ciprofloxacin” has been used in the field of nuclear medicine because of the convenience, although Tewson [38] recommended “Tc-99m complexes of ciprofloxacin” until the structure of the compounds is determined. It is important to follow the guideline for the preparation and usage of Tc-99m ciprofloxacin, as suggested by Britton et al. [3], when using this agent for imaging.

There are currently efforts to develop radiopharmaceuticals that are composed of other antibiotic agents for detecting tuberculosis. Isonicotinic acid hydrazide (isoniazid) is a primary drug that is used in tuberculosis chemotherapy [40–42]. Singh et al. [41] developed a Tc-99m-isoniazid

Table 2 Statistical analysis of imaging results (pre-treatment) (+ positive, - negative)

Tc-99m ciprofloxacin SPECT	Active pulmonary tuberculosis	
	+	-
+	8	1
-	2	10

complex for which the labeling efficiency is more than 95% and this Tc-99m-isoniazid complex demonstrated persistent uptake in rabbit tubercular (*Mycobacterium tuberculosis*) lesions, but transient uptake was noted by non-tubercular (*Staphylococcus aureus*) lesions. Samuel et al. [42] synthesized Tc-99m isoniazid derivatives with different Tc-99m cores, although these did not demonstrate any appreciable uptake by *Mycobacterium tuberculosis* in the in vitro cell-binding studies. Another trial was done for detecting tuberculosis with Tc-99m ethambutol and using a SPECT/CT camera [43]. They reported a sensitivity of 92.8% and a specificity of 87.5% for detecting tuberculosis in patients with suspected pulmonary tuberculosis (six cases), spondylitis (14 cases) and meningitis (two cases).

Tc-99m ciprofloxacin SPECT is currently a good imaging method for detecting active pulmonary tuberculosis. The development of better radiopharmaceuticals and imaging methods in the field of nuclear medicine can be expected to improve the detection of active pulmonary tuberculosis.

Conclusion

Performing Tc-99m ciprofloxacin SPECT is feasible for imaging active pulmonary tuberculosis. It is a useful imaging method for discriminating between the active and inactive states in patients with a past medical history of pulmonary tuberculosis.

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