

Original article

Sensitivity and specificity of the Tc-99m ciprofloxacin scan in pediatric osteomyelitis

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ABSTRACT. *Introduction:* the Tc-99m-ciprofloxacin complex, introduced in 1993, has been extensively evaluated all over the world with good results for the diagnosis of active bacterial osteoarticular infections. There are only a few publications on the use of this procedure in pediatric ages. In our study we evaluated the efficacy of the Tc-99m ciprofloxacin scan for the diagnosis of osteoarticular infections in the pediatric population assessing its sensitivity, specificity, and positive and negative predictive value. *Material and methods:* a retrospective, descriptive, observational study was done in 94 patients with clinical suspicion of osteoarticular infection in whom a Tc-99m ciprofloxacin bone scan was performed; the diagnosis was confirmed with intraoperative cultures and blood cultures. The results obtained with the Tc-99m ciprofloxacin scan and the culture reports were analyzed, as well as the sensitivity, specificity and the positive and negative predictive values of the Tc-99m ciprofloxacin scan. *Results:* Among the patients with intraoperative and blood cultures, 80 cases (85.1%) were positive and 14 cases (14.9%) were negative for bone infection. In the Tc-99m ciprofloxacin scan 78 cases (83%) were found to be positive for infection and 16 cases (17%) were

RESUMEN. *Introducción:* El complejo ciprofloxacin-Tc^{99m} introducido en 1993, ha sido evaluado extensamente alrededor del mundo, con buenos resultados en el diagnóstico de infecciones bacterianas activas osteoarticulares. Son pocas las publicaciones de la aplicación de este procedimiento en edades pediátricas. En nuestro estudio evaluamos la eficacia del gammagrama con ciprofloxacin-Tc^{99m} en el diagnóstico de infecciones osteoarticulares en la población infantil, valorando su sensibilidad, especificidad, el valor predictivo positivo y negativo. *Material y métodos:* Se realizó un estudio retrospectivo, descriptivo, observacional en 94 pacientes con sospecha clínica de infección osteoarticular a quienes se realizó gammagrama óseo con ciprofloxacin-Tc^{99m} y se corroboró el diagnóstico por medio de cultivos transquirúrgicos y hemocultivos. Se analizaron los resultados obtenidos con el gammagrama con ciprofloxacin-Tc^{99m} y con los reportes de los cultivos, determinando la sensibilidad, especificidad, así como los valores predictivos positivos y negativos del gammagrama con ciprofloxacin-Tc^{99m}. *Resultados:* De los pacientes con cultivos transquirúrgicos y hemocultivos, 80 casos (85.1%) resultaron positivos para infección ósea y 14 casos (14.9%) negativos para infección ósea. En

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negative. There were two false negatives. We found a 97.6% sensitivity and 100% specificity, with a 100% positive predictive value and an 87.5% negative predictive value. Conclusion: the Tc-99m-ciprofloxacin complex is useful to make the differential diagnosis between inflammation and infection in pediatric patients in whom an osteoarticular infectious process is suspected.

Key words: scan, ciprofloxacin, osteomyelitis, diagnosis.

el gammagrama con ciprofloxacino-Tc^{99m} se encontraron 78 casos (83%) positivos para infección y 16 casos (17%) negativos. Obteniendo 2 falsos negativos. Encontramos una sensibilidad de 97.6% y una especificidad de 100%, con un valor predictivo positivo de 100% y un valor predictivo negativo de 87.5%. Conclusión: El complejo ciprofloxacino-Tc^{99m} es útil para diagnóstico diferencial entre inflamación e infección en pacientes pediátricos con sospecha de proceso infeccioso osteoarticular.

Palabras clave: gammagrama, ciprofloxacino, osteomielitis, diagnóstico.

Introduction

Infections, particularly those affecting the osteoarticular system, are one of the major causes of morbidity and mortality in all countries, regardless of their economic development.¹⁻³ They have social and economic impacts, result in significant morbidity and mortality if detected late or if the initial treatment is incorrect, and they cause a high incidence of the chronic forms, and esthetic and functional sequelae. An early diagnosis, determining the extension, and following-up these conditions with non-invasive methods is therefore important.⁴ X-ray and high anatomical resolution images, such as MRI and CT scan, are morphologic and need an abscess to form to allow visualizing it. Nuclear medicine images are functional and can therefore identify the infection early on. There are nuclear medicine methods for the detection of infections which have proven to be sensitive but unspecific; this is the case of bone scans. Radiolabeled antibiotics and Tc-99m-labelled antimicrobial peptides have been recently used.^{2,4-7}

This study focuses on the use of the Tc-99m - ciprofloxacin complex for the early detection of such infections, given its proven high sensitivity and specificity for the detection of active bone bacterial foci; it is the only one with 2 studies including pediatric patients in whom it has been used without adverse effects.^{2,7}

The Tc-99m - ciprofloxacin complex was introduced in 1993 and has been extensively evaluated by different groups all over the world in a wide variety of scenarios, with very good results in the diagnosis of active bacterial infections.^{3,8-10}

There are few publications in the world literature about the use of this procedure in pediatric patients.^{2,10} The National Pediatrics Institute is the only facility using this procedure in children in Mexico, and thus this study was conducted to assess the usefulness of the Tc-99m ciprofloxacin bone scan for the diagnosis of osteoarticular infection in the pediatric population.

Material and methods

We conducted a retrospective, descriptive, observational study that included a total of 106 patients admitted to the National Pediatrics Institute with clinical suspicion of osteoarticular infection during the period from June 2005 to December 2006. Twelve patients were excluded for not having complete records. We ended up analyzing 94 patients, 60 male (63.8%) and 34 female (36.2%), with a mean age of 10.9 years (17 days-17 years). Seventy-one of the 94 patients included underwent a blood culture and 23 underwent surgery with an intraoperative culture. Inclusion criteria: patients under 17 years of age, with an informed consent signed by the person legally responsible of them, with clinical suspicion of osteoarticular infection and with two or more of the following signs: fever, local pain, swelling, erythema, local heat, leukocytosis, increased ESR; patients who underwent a Tc-99m ciprofloxacin scan in whom the presence or absence of osteoarticular infection was later confirmed by surgery, with an intraoperative culture and a blood culture. Exclusion criteria: patients over 17 years of age, without clinical suspicion of osteoarticular infection, without a Tc-99m ciprofloxacin scan. Exclusion criteria: patients with incomplete records.

The diagnosis resulting from the scan was compared with the definitive diagnosis based on the results of the surgery and the intraoperative and blood cultures.

A statistical analysis was performed to determine the specificity, sensitivity, and the positive and negative predictive value.

Results

Among patients who underwent intraoperative and blood cultures, 80 cases (85.1%) were positive for bone infection with various etiologic agents and 14 cases (14.9%) were negative for bone infection and positive for an inflammatory process (*Figure 1*). In the Tc-99m ciprofloxacin scan 78 cases (83%) were found to be positive for infection (*Figure 2*) and

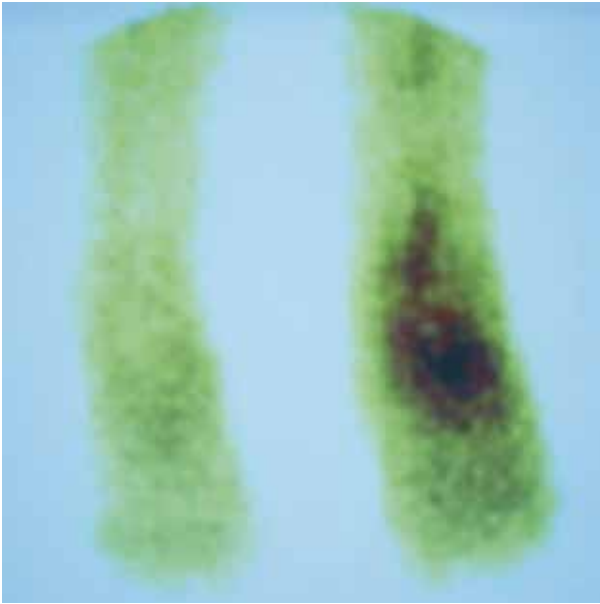


Figure 1. Patient with clinical suspicion of right ankle osteoarticular infection, with a hyper uptake Tc-99m ciprofloxacin scan.

16 cases (17%) were negative. The former data show 2 false negatives; *Candida albicans* was isolated in one of them.

The results of the Tc-99m ciprofloxacin scan were 78 true positive cases, 14 true negatives, 2 false negatives, and no false positives; this represents a sensitivity of 97.6% and a 100% specificity, with a positive predictive value of 100% and a negative predictive value of 87.5%. Youden's J statistic was 0.976.

Discussion

In the search for the perfect compound for the early diagnosis of bone infection, the pathophysiology of the infectious and inflammatory processes has been investigated and different intermediaries and receptors which are activated and externalized during the acute and chronic infectious and inflammatory processes have been used. The latter have been designed to obtain specific images of the processes that are suspicious of inflammation/infection.^{2,4-7}

Radioisotopic techniques, considered as the «gold standard» for infections, have been mentioned, such as Tc99-labelled leukocytes, but their use is limited because they cannot help make the differential diagnosis between a bacterial and a non-bacterial process; moreover, this technique involves blood manipulation with its resulting risks. The purpose of labeling antibiotics was to obtain a radiolabeled drug with a high diagnostic specificity, selective for the infectious process, providing a positive image in cases of infection, and without scintigraphic uptake in the cases of inflammation. The most widely used ones have been ciprofloxacin and ceftizoxime, and Tc-99m-labelled ubiquicidine, among antimicrobial peptides, which has the drawback of its high cost when compared to antibiotics.^{3-5,7,10,11}

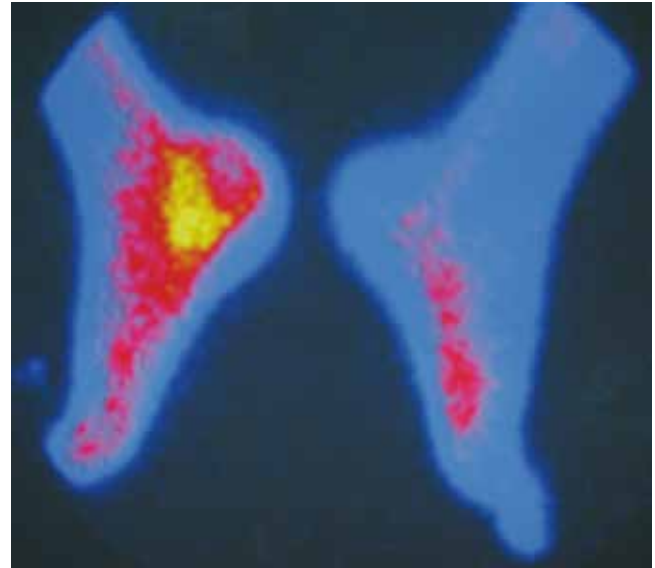


Figure 2. Hyper uptake Tc-99m ciprofloxacin scan of a bone infectious process in the left ankle.

Ciprofloxacin is a broad spectrum antibiotic effective against gram positive and gram negative bacteria as it inhibits bacterial DNA synthesis by binding to the DNA gyrase enzyme. It is obtained by reducing 2mg of ciprofloxacin with 500ng of stannous chloride in a buffer with a pH of 4.0 and it is labeled with 10 mCi (370 MBq) of Tc-99m. Administration is through the IV route, and *in vitro* and *in vivo* studies have shown that there is drug accumulation in bacterial abscesses with causative agents that include *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus*, and it is not absorbed in the absence of infection; it is metabolized in the liver and cleared through renal excretion within the first 24 hours and through the bile in the following 5 days.^{3-5,10,15} Tagging with Tc-99m ciprofloxacin does not require discontinuation of antibiotic therapy even if the patient is on ciprofloxacin.^{5,13-16}

The choice of the method to diagnose infection depends on several factors such as: patient age, location of the infectious process, route of infection and immunologic status.

The Tc-99m - ciprofloxacin complex is stable, does not cause any side effects, and is economic and affordable for Mexican hospitals. The scan using this agent is useful to make the differential diagnosis between bone inflammation and infection given its specificity and sensitivity. It would be useful to design a protocol to assess the effectiveness of this test in bone infectious activity, under the assumption that it will be sensitive and specific, and will thus contribute to avoid prolonged and unnecessary antimicrobial therapies. None of our patients had drug hypersensitivity, signs of toxicity or unwanted side effects, all of which has been previously reported.

Conclusions

The Tc-99m ciprofloxacin scan is highly sensitive and specific to make the differential diagnosis between inflam-

mation and infection; it is reliable and can be used in pediatric patients with an osteoarticular infectious process. No adverse effects were detected after performing this study. This procedure may be performed at tertiary care hospitals in our country and, as it may increase the accuracy of the early diagnosis of bone infection, it may be useful to avoid the functional, cosmetic and socioeconomic sequelae of the severe bone infections that are diagnosed and treated at a late stage.

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