Biodistribution and dosimetry of ^{99m}Tc-ciprofloxacin, a promising agent for the diagnosis of bacterial infection

Frederic De Winter[1], Christophe Van de Wiele[1], Filip Dumont[2], Joost Van Durme[2], Kishor Solanki[3], Keith Britton[3], Guido Slegers[2], Rudi Andre Dierckx[1], Hubert Thierens[4]

[1] Division of Nuclear Medicine, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
[2] Department of Radiopharmacy, Ghent University, Belgium
[3] Department of Nuclear Medicine, St. Bartholomew's Hospital, London, UK
[4] Department of Biomedical Physics and Radiation Protection, Ghent University, Belgium

Received 18 November 2000 and in revised form 8 January 2001 / Published online: 21 March 2001

Abstract. This study reports on the biodistribution and dosimetry of technetium-99m ciprofloxacin, a radioligand developed for the visualisation of bacterial infection. Whole body scans were performed up to 24 h after intravenous injection of 370 MBq ^{99m}Tc-ciprofloxacin in three male and three female volunteers. Blood samples were taken at various times up to 24 h after injection. Urine was also collected up to 24 h after injection, allowing calculation of renal clearance and interpretation of whole body clearance. Time-activity curves were generated for the thyroid, heart, liver and whole body by fitting the organ-specific geometric mean counts, obtained from regions of interest. The MIRD formulation was applied to calculate the absorbed radiation doses for various organs. The images showed rapid, predominantly urinary excretion of ^{99m}Tc ciprofloxacin, with low to absent brain, lung and bone marrow uptake and low liver uptake and excretion. Accordingly, imaging conditions are excellent for both the thoracic and the abdominal region, even at early time points (60 min) post injection. In none of the volunteers was the gallbladder visualised. Approximately 60% of the injected activity was recovered in urine by 24 h post injection. The highest absorbed doses were received by the urinary bladder wall, the thyroid, the upper large intestine, the lower large intestine and the uterus. The estimated mean effective dose for the adult subject, taking into account the weight factors of the ICRP60 publication, was 0.0083 mSv/MBq. The amount of ^{99m}Tc ciprofloxacin required for adequate planar and tomographic imaging results in an acceptable effective dose to the patient.

Frederic De Winter (✉)
Division of Nuclear Medicine, Ghent University Hospital,
De Pintelaan 185, 9000 Ghent, Belgium
e-mail: Frederic.dewinter@rug.ac.be
Tel.: +32-9-2403028, Fax: +32-9-2403807

Keywords: ^{99m}Tc-ciprofloxacin – Biodistribution – Dosimetry

Eur J Nucl Med (2001) 28:570–574
DOI 10.1007/s002590100488

Introduction

Bacterial infection can pose a substantial diagnostic dilemma. Although radiolabelled leucocyte scintigraphy (RLS) can pinpoint the site of inflammation, it fails to distinguish between bacterial infection and non-bacterial inflammation. Compared with RLS, technetium-99m ciprofloxacin (infecton) scintigraphy is clinically more effective and specific for bacterial infection [1]. Its higher specificity for bacterial infection found in clinical trials is believed to be due to the ligand's specific binding to DNA gyrase in living bacteria [2].

Given the promising clinical results obtained with ^{99m}Tc-ciprofloxacin and its increasing use in clinical practice, we determined its human biodistribution and dosimetry.

Materials and methods

Radiopharmaceutical synthesis

^{99m}Tc-ciprofloxacin labelling was performed using a kit formulation provided by the Nuclear Medicine Department of Saint Bartholomew's Hospital (London, UK). The kit was reconstituted with 400 MBq sodium pertechnetate according to the radiolabelling protocol [3]. Radiochemical purity was >95%.

Subjects

This study was approved by the Medical Ethics Committee of Ghent University Hospital and performed according to Good Clin-

ical Practice. Six healthy volunteers (median age 22 years, range 19–24 years; median weight 70.5 kg, range 60–84 kg) were included in the study. Three were men, and three women. In all of these patients the injected dose of ^{99m}Tc-ciprofloxacin was 370 MBq. All subjects gave their written informed consent prior to participation in the study. Based upon anamnesis and physical investigation, none of them had any recent or chronic infectious or non-infectious disease. None of the subjects had known allergy to antibiotics.

Imaging

Subjects were positioned supine with their arms alongside their body. Whole body imaging was performed using a triple-headed gamma camera (Irix, Marconi, Cleveland, Ohio, USA) equipped with low-energy high-resolution parallel-hole collimators. The energy peak was centred at 140 keV with a 15% window. Whole body planar images were acquired 1, 2, 4, 6 and 24 h post injection (p.i.). Acquisition was performed simultaneously in the anterior and posterior projections with a scan speed of 11.44 cm/min. Matrix size was 128×512 pixels.

Urine sampling

For all subjects, all voided urine from the time of injection until 24 h post administration was collected. The subjects were requested to collect urine prior to each emission scan and at home ad libitum. For each voidance, the urine was collected in a separate container and the volume and time of voidance were recorded. For each voidance time, two 1-ml urine aliquots were sampled and the activity was determined in an NaI (Tl) counter (Cobra Packards Instruments Company) after the counting efficiency of the system had been determined. The amount of radioactivity in the urine at each voidance time was expressed as a percentage of the injected activity (%IA) of ^{99m}Tc-ciprofloxacin.

Blood sampling

Blood samples were taken at 15 s, 30 s, 45 s, 1 min, 1 min 15 s, 1 min 30 s, 2 min, 5 min, 7.5 min, 10 min, 12 min, 15 min, 20 min, 30 min, 55 min, 2 h, 4 h, 6 h and 24 h following injection of the tracer. From each blood sample, duplicate 1-ml aliquots were assayed for ^{99m}Tc radioactivity as described above. Total blood volume, and consequently activity, was calculated using a total blood volume based on body weight and height [4] and expressed as a percentage of the injected activity (%IA).

Dosimetry

Image analysis. For quantification of radioactivity uptake after injection of ^{99m}Tc-ciprofloxacin, regions of interest (ROIs) over the total body and organs of interest were drawn on the earliest images, and the shapes and sizes, i.e. the number of pixels, were kept constant over all subsequent images. Correction for activity in tissue in front of and behind the organ of interest was performed by using a region over the shoulder. For each ROI, i.e. each organ, the geometric mean, corrected for physical decay, of anterior and posterior counts was calculated. The total body geometric mean activity, calculated on the first image (1 h p.i.), was taken as total injected activity, considering that no urine was excreted prior to the first whole body scan. The activity in the total body and different organs was expressed as the percentage of the injected activity (% IA) calculated by the following equation: (geometric mean counts in organ or total body)/(geometric mean counts in first total body, decay corrected)×100.

Dosimetric calculations. For each individual, time-activity curves were generated for the thyroid, heart, liver and whole body. Using in-house-written curve-fitting software, time-activity curves were generated for these organs by bi-exponential fits. Urinary bladder residence times were derived from the individual excretion curves using a dynamic bladder model and assuming a voiding interval of 4.8 h. In keeping with the known tissue penetration of unlabelled ciprofloxacin, 15% of the dose injected was assumed to enter the small intestine through mucosal penetration [5]. Intestinal residence times were estimated using the gastrointestinal kinetics model as adopted in the ICRP30 report [6]. Activity in the intestines was assumed to pass through the various segments at standard rates, the mean transit time being 4 h for the small intestine, 13 h for the upper large intestine and 24 h for the lower large intestine. As the specific uptake in organs and tissues was low, the accuracy of five data points in time was not sufficient to enable a real compartmental model analysis with reliable determination of the transfer coefficients. Instead, source organ residence times were determined from integration of the time-activity curves. Residence times were then used to determine target organ radiation doses using the MIRD methodology [7] for the normal adult [8], applying the MIRDOSE software package [9].

Results

After injection of approximately 370 MBq ^{99m}Tc ciprofloxacin, no adverse or subjective effects were observed in any of the subjects. Whole body images of a female subject showing the biodistribution of radioactivity at different time points after the injection of ^{99m}Tc-ciprofloxacin are presented in Fig. 1. The whole body images obtained between 1 h and 24 h p.i. show most of the activity to be distributed in the heart cavity, great vessels, kidneys, bladder and liver. Uptake in the brain, bone marrow and lungs was low. Of interest, in none of the patients was gallbladder activity visualised on any of the images acquired. Although of low quality due to low counting statistics, images at 24 h p.i. showed most of the remaining activity distributed in the kidneys and bladder, though colon and thyroid uptake seemed to increase on the late images. Averaged ROI data over all subjects, expressed as %IA of ^{99m}Tc-ciprofloxacin in the total body and in various organs at the different points in time, were used to calculate residence times (Table 1; see also Fig. 2). Clearance of radioactivity from blood fitted a bi-exponential curve. After a rapid distribution phase, serum ^{99m}Tc-ciprofloxacin levels declined more slowly, with an average terminal half-life of 4.0 h. Approximately 60% of the injected activity was recovered in urine by 24 h p.i.

The residence time was highest for the remainder of the body in all subjects, followed by the urinary bladder and the upper and the small intestine (Table 1).

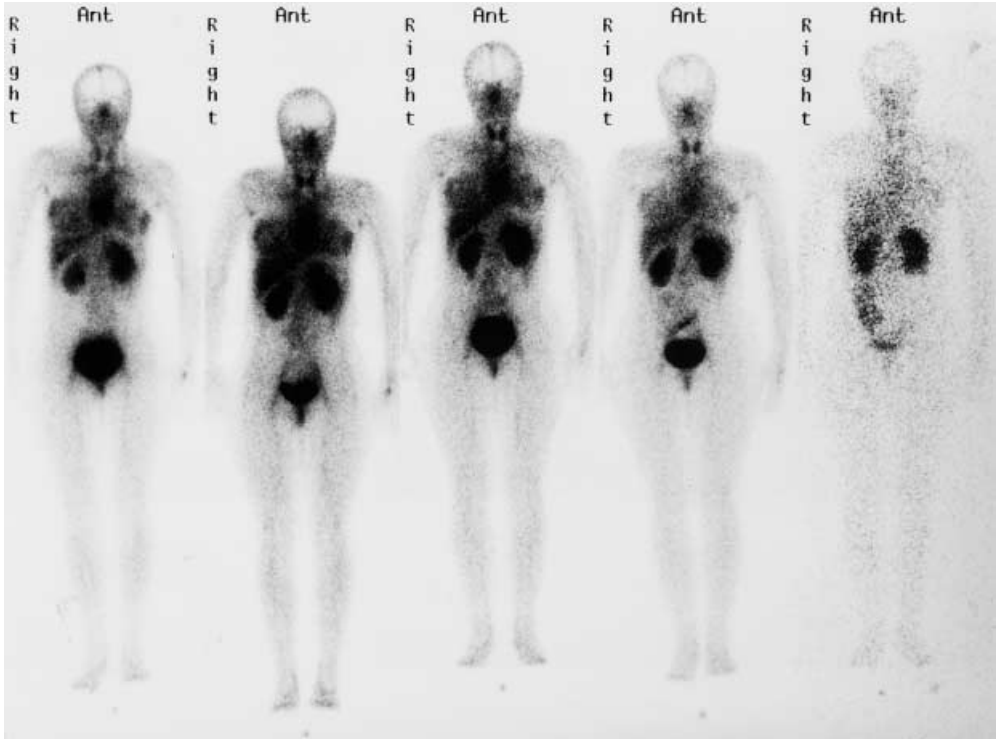

Fig. 1. The anterior whole body images obtained from a woman at (*from left to right*) 1, 2, 4, 6 and 24 h post injection

Table 1. The residence times (in hours) for ^{99m}Tc ciprofloxacin for each source organ

Organ	Subject							
	1	2	3	4	5	6	Mean	SD
Lower large intestine	0.134	0.067	0.080	0.138	0.127	0.168	0.119	0.040
Small intestine	0.210	0.106	0.126	0.216	0.199	0.263	0.186	0.060
Upper large intestine	0.274	0.138	0.164	0.282	0.259	0.342	0.243	0.077
Heart wall	0.072	0.118	0.092	0.120	0.133	0.112	0.108	0.022
Liver	0.140	0.171	0.165	0.187	0.109	0.251	0.171	0.048
Thyroid	0.016	0.024	0.021	0.023	0.028	0.027	0.023	0.004
Urinary bladder contents	0.210	1.010	0.922	0.818	1.390	1.310	1.110	0.230
Remainder	2.700	3.670	3.270	3.810	2.800	2.670	3.150	0.510

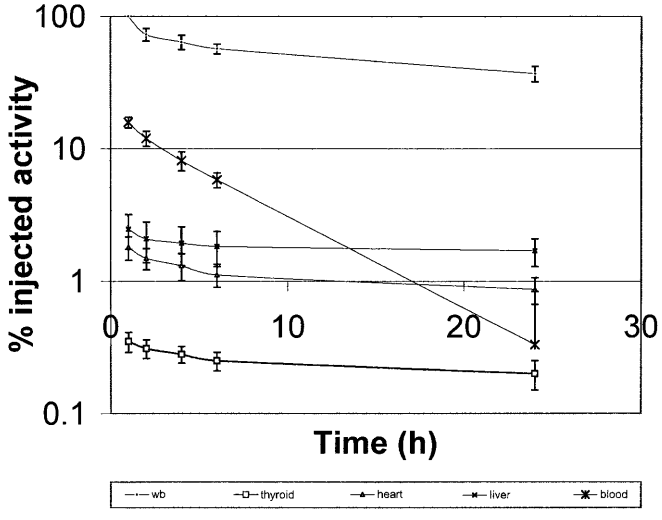

Fig. 2. Time-activity curves for the total body (*wb*), various organs and blood, calculated from direct measurements of counts in organ-specific ROIs or in blood. The physical decay-corrected data, expressed as %IA, are averaged over the six subjects. The *error bars* represent 1 SD

The mean absorbed dose estimates (±standard deviation) were calculated for each subject independently, and then averaged (Table 2). The organs receiving the highest absorbed doses were predominantly involved in the excretion of ^{99m}Tc-ciprofloxacin from the body. Owing to the high urinary excretion, the uterus also received a high radiation dose. Finally, the dose to the thyroid was also fairly high, probably due to uptake of free pertechnetate. On average, the highest dose was received by the

Table 2. Absorbed dose estimates (mGy/MBq) for ^{99m}Tc-ciprofloxacin

Target organ	Mean	SD
Adrenals	2.71E-03	0.49E-03
Brain	1.65E-03	0.32E-03
Breasts (w)	1.72E-03	0.29E-03
Gallbladder wall	3.97E-03	0.86E-03
Lower large intestine	1.11E-02	0.28E-02
Small intestine	7.86E-03	2.14E-03
Stomach	2.89E-03	0.56E-03
Upper large intestine	1.22E-02	0.38E-02
Heart	7.17E-03	1.91E-03
Kidneys	2.68E-03	0.48E-03
Liver	3.69E-03	1.01E-03
Lungs	2.26E-03	0.48E-03
Muscle	2.63E-03	0.39E-03
Ovaries (w)	8.10E-03	0.47E-03
Pancreas	3.05E-03	0.57E-03
Red marrow	2.67E-03	0.42E-03
Bone surface	4.21E-03	0.63E-03
Skin	1.49E-03	0.23E-03
Spleen	2.42E-03	0.45E-03
Thymus	2.26E-03	0.44E-03
Thyroid	1.59E-02	0.38E-02
Urinary bladder wall	5.87E-02	1.93E-02
Uterus (w)	1.04E-02	0.12E-02
Testes (m)	3.00E-03	0.26E-03
Remainder of the body	2.84E-03	0.45E-03
Effective dose equivalent[a]	9.00E-03	0.23E-03
Effective dose[a]	8.30E-03	1.98E-03

Radiation absorbed dose estimates for breasts (w), uterus (w) and testes (m) were obtained based on the individual data from the three women (w) and three men (m), respectively

[a] Units of the effective dose equivalent are mSv/MBq

urinary bladder wall (mean: 5.87E-02 mGy/MBq; SD 1.93E-02 mGy/MBq) followed by the thyroid (mean: 1.59E-02 mGy/MBq; SD: 0.38E-02 mGy/MBq), the upper large intestine (mean: 1.22E-02 mGy/MBq; SD: 0.38E-02 mGy/MBq), the lower large intestine (mean: 1.11E-02 mGy/MBq; SD: 0.28E-02 mGy/MBq) and the uterus (mean: 1.04E-02 mGy/MBq; SD: 0.12E-02 mGy/MBq). The estimated mean effective dose for the adult subject, taking into account the weight factors of the ICRP60 publication, was 8.30E-03 mSv/MBq (SD: 1.98E-03 mSv/MBq).

Discussion

The results of this study demonstrate the favourable biodistribution of ^{99m}Tc-ciprofloxacin in humans.

Consistent with data on the pharmacokinetics of unlabelled ciprofloxacin showing extensive and rapid extravascular distribution of ciprofloxacin due to the low extent of binding to serum proteins, ^{99m}Tc-ciprofloxacin was initially cleared rapidly from the circulation. The mean clearance half-life of 4 h derived from the second part of the bi-exponential fit is comparable to the 4.2 h value reported for unlabelled ciprofloxacin [10].

This study shows rapid, predominantly urinary excretion of ^{99m}Tc-ciprofloxacin, with low to absent brain, lung and bone marrow uptake and low liver uptake and excretion. Accordingly, imaging conditions are excellent for both the thoracic and the abdominal region, even at early time points (60 min) p.i. It is of interest that the gallbladder was not visualised in any of the patients, whereas the kidneys were visible throughout the study. The lack of uptake in the normal bone marrow makes evaluation of the spine and proximal limbs easier than when using other radiolabelled agents that have bone marrow uptake as part of their normal physiological distribution, e.g. radiolabelled leucocytes and gallium-67. The higher absolute % renal elimination of ^{99m}Tc-ciprofloxacin when compared to unlabelled ciprofloxacin (slightly less than 50% vs 60%) may be partly due to additional excretion of free pertechnetate. Unfortunately we were not able to confirm this supposition, as urine chromatography was not performed. The absence of gallbladder visualisation and the low liver uptake are in keeping with the documented negligible biliary elimination and low hepatic clearance (1.8 ml/min) of unlabelled ciprofloxacin [6, 10]. Finally, the visualisation of the thyroid from as early as 1 h p.i. is probably the result of uptake of free pertechnetate.

The MIRDOSE software provides a calculation of the effective dose as defined in the ICRP 60 [11]. Based on the mean effective dose of 8.30E-03 mSv/MBq obtained in this study, both patients and volunteers can be easily investigated with 370 MBq ^{99m}Tc-ciprofloxacin using either planar or single-photon emission tomography (SPET) imaging. The corresponding effective dose of 3.07 mSv is lower than the reported average effective dose per patient from nuclear medicine procedures in Europe [12]; furthermore, it is only one-third of the 10-mSv upper limit average effective dose of category IIa of the World Health Organisation and category IIb of the ICRP report [13]. The aforementioned mean effective dose for ^{99m}Tc-ciprofloxacin (8.30E-03 mSv/MBq) is lower than that for other tracers used in inflammation scintigraphy, such as radiolabelled leucocytes (59.0E-02 mSv/MBq for indium-111 and 17.0E-03 mSv/MBq for ^{99m}Tc-hexamethylpropylene amine oxime) and ^{67}Ga (12.0E-02 mSv/MBq) [14, 15, 16]. Since the bladder wall receives the highest dose, frequent voiding will reduce the absorbed dose not only to the urinary bladder but also to the uterus. After administration of 370 MBq ^{99m}Tc-ciprofloxacin, the dose to the uterus amounts to 3.8 mGy. In the event of accidental administration to a pregnant woman, the risk for teratogenic effects in the sensitive period (3–15 weeks post conception) will exceed 1 in 700.

In conclusion, the biodistribution of ^{99m}Tc-ciprofloxacin demonstrated low brain, lung, bone marrow and liver up-

take, allowing straightforward imaging of the whole body and specifically of the spine and limbs. Dosimetry was favourable for clinical SPET imaging.

References

1. Britton KE, Vinjamuri S, Hall AV, Solanki K, Siraj QH, Bomanji J, Das S. Clinical evaluation of technetium-99m infecton for the localisation of bacterial infection. *Eur J Nucl Med* 1997; 24:553–556.
2. Hooper DC, Wolfson JS, Ng EY, Schwartz MN. Mechanisms of action of and resistance to ciprofloxacin. *Am J Med* 1987; 82 Suppl 4A:12–20.
3. Nuclear medicine for infection and inflammation: a coordinated research project (E1.30.14 technical document). Vienna, Austria: International Atomic Energy Agency, 2000.
4. Hidalgo JU, Nadler SB, Bloch T. The use of electronic digital computer to determine best fit of blood volume formulas. *J Nucl Med* 1962; 3:94.
5. Wise R, Donovan IA. Tissue penetration and metabolism of ciprofloxacin. *Am J Med* 1987; 82 Suppl 4A:103–107.
6. International Commission on Radiobiological Protection. Limits for intakes of radionuclides by workers. ICRP Publication 30. New York: Pergamon Press, 1979.
7. Loevinger R, Budinger T, Watson E. MIRD primer for absorbed dose calculations. New York: Society of Nuclear Medicine, 1988.
8. Cristy M, Eckerman K. Specific absorbed fractions of energy at various ages from internal photon sources. ORNL/TM 8381/VII. Oak Ridge, Tenn.: Oak Ridge National Laboratory; 1987:7–29.
9. Stabin MG. MIRDOSE: personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med* 1996; 37:538–546.
10. Dudley MN, Mandler HD, Gilbert D, Ericson J, Mayer KH, Zinner SH. Pharmacokinetics and pharmacodynamics of intravenous ciprofloxacin. *Am J Med* 1987; 82 (Suppl 4A): 363–368.
11. Beekhuis H. Population radiation absorbed dose from nuclear medicine procedures in The Netherlands. *Health Phys* 1988; 54:287–291.
12. World Health Organisation Technical Report Series 611. Use of ionizing radiation and radionuclides on human beings for medical research, training, and non-medical purposes. Report of a WHO Expert Committee. Geneva: WHO, 1977.
13. Annals of the ICRP. Radiological protection in biomedical research. New York: Pergamon Press; 1991:12–13.
14. Seabold JE, Forstrom LA, Schauwecker DS, Brown ML, Datz FL, McAfee JG, Palestro CJ, Royal HD. Procedure guideline for indium-111-leucocyte for suspected infection/inflammation. Society of Nuclear Medicine. *J Nucl Med* 1997; 38: 997–1001.
15. Seabold JE, Palestro CJ, Brown ML, Datz FL, Forstrom LA, Greenspan BS, Mc Afee JG, Schauwecker DS, Royal HD. Procedure guidelines for gallium scintigraphy for gallium scintigraphy in inflammation. Society of Nuclear Medicine. *J Nucl Med* 1997; 38:994–997.
16. Datz FL, Seabold JE, Brown ML, Forstrom LA, Greenspan BS, McAfee JG, Palestro CJ, Schauwecker DS, Royal HD. Procedure guideline for technetium-99m-HMPAO-labeled leukocyte scintigraphy for suspected infection/inflammation. Society of Nuclear Medicine. *J Nucl Med* 1997; 38:987–990.