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Pharmacokinetics of [^{18}F]Fleroxacin in Patients with Acute Exacerbations of Chronic Bronchitis and Complicated Urinary Tract Infection Studied by Positron Emission Tomography

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The pharmacokinetics of fleroxacin, a new broad-spectrum fluoroquinolone, were measured by positron emission tomography (PET) with [^{18}F]fleroxacin in five patients with acute bacterial exacerbations of chronic bronchitis and in five patients with symptomatic, complicated urinary tract infection. Two studies were performed with each patient, one within 24 h of the initiation and one within 24 h of the completion of a 7-day course of fleroxacin, 400 mg/day. For each study, the patient received an infusion of that day's therapeutic dose of fleroxacin (400 mg) supplemented with ~740 MBq of [^{18}F]fleroxacin, and serial PET images and blood samples were collected for 6 to 8 h starting at the initiation of the infusion. Between studies, the drug was administered orally. In all infected tissues, there was rapid accumulation of radiolabeled drug, with stable levels achieved within 1 h after completion of the infusion. In kidneys, accumulation was greater in the presence of active infection ($P < 0.01$), while in lungs, accumulation was lower ($P < 0.02$). Infection of the lung or urinary tract had no effect on drug delivery to uninvolved tissues. Also, there was no difference between the results obtained at the beginning and the end of therapy. Overall, peak concentrations of drug many times the MIC at which 90% of the infecting organisms are inhibited (MIC_{90}) were achieved in the kidneys (>30 μg/g), prostate glands (>11 μg/g), and lungs (>14 μg/g). Plateau concentrations (2 to 8 h; given as mean micrograms per gram ± standard error of the mean) of drug in kidneys (15.11 ± 0.55), prostate glands (5.08 ± 0.19), and lungs (5.75 ± 0.22) were also well above the MIC_{90} for most relevant pathogens. All patients had a good therapeutic response to fleroxacin.

Fleroxacin is a new fluoroquinolone that has been shown to possess a number of desirable characteristics: excellent bioavailability after oral administration, high concentrations in plasma relative to the susceptibilities of relevant pathogens, a long elimination half-life which is consistent with a once-a-day administration schedule, and good tissue penetration (2, 3, 5–9, 11, 19–23, 25–30, 32, 35–39, 43–50). In addition, the initial clinical experience with fleroxacin in the treatment of sexually transmitted diseases, urinary tract infection, skin and soft tissue infection, gastrointestinal infection, and acute bacterial exacerbations of chronic bronchitis has been encouraging (4, 10, 24, 33, 34, 37, 39, 40, 42).

To further evaluate the possible utility of this drug, we developed and validated an approach in which positron emission tomography (PET) was utilized to study the tissue delivery of fleroxacin in humans over time (16, 31). We have shown that in healthy volunteers, particularly high concentrations of the drug are achieved in the kidneys, livers, lungs, myocardium, and spleens (17). In the present study, this PET technique was applied to the study of two groups of patients with active infection who represent categories of patients that might benefit from this new therapy: patients with acute bacterial exacerbations of chronic bronchitis and those with complicated urinary tract infection. The goal was to determine the effects of infection and inflammation on the delivery of fleroxacin to affected tissues.

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MATERIALS AND METHODS

Preparation of [^{18}F]fleroxacin. [^{18}F]fleroxacin was prepared from its methylsulfonyl ester precursor with a radiochemical yield of 5 to 8% within 90 min. The product was identical to authentic fleroxacin by elemental analysis, mass spectroscopy, thin-layer chromatography, high-pressure liquid chromatography, nuclear magnetic resonance spectroscopy, and in vitro microbiological studies. The specific activity of the radiolabeled drug was >1,850 MBq/μmol. Further details of the synthesis of [^{18}F]fleroxacin have been described elsewhere (31). Acute toxicity studies with [^{18}F]fleroxacin were performed as previously described (17). On the basis of biodistribution data in healthy human subjects, medical internal radiation dosimetry dose calculations indicated that approximately 740 MBq of [^{18}F]fleroxacin can be administered without delivering a radiation burden in excess of 20 mGy to any organ (17).

Patient selection. Ten patients were entered in this study, five with acute bacterial exacerbations of chronic bronchitis and five with complicated urinary tract infections. Chronic bronchitis was defined by a history of significant cough and sputum production for at least 3 months per year during the preceding 2 years. The subjective criteria for the acute exacerbation were increased dyspnea,

cough, and sputum production as well as objective evidence of increased sputum neutrophils and Gram stain evidence of increased numbers of bacteria (13). The bacteriologic criteria for inclusion were a positive culture for respiratory pathogenic bacteria such as *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, or *Pseudomonas aeruginosa* susceptible to fleroxacin (1, 14). All of these patients had significant degrees of pulmonary fibrosis as determined by plain radiographs.

Complicated urinary tract infection was defined by the presence of pyuria and the isolation of $>10^5$ CFU of a fleroxacin-susceptible uropathogen from the urine of a patient who had symptoms referable to the urinary tract and who met one or more of the following criteria: neurogenic bladder requiring intermittent catheterization; >100 ml of residual urine retained after voiding; obstructive uropathy due to bladder outlet obstruction, a calculus, or other causes; vesicoureteral reflux or other urologic abnormalities, including surgically created ileal loops; or the presence of signs and/or symptoms of prostatitis (42). All patients entered in this study had serum creatinine levels of <1.5 mg/dl and were free of indwelling urinary tract catheters.

Each patient underwent an [^{18}F]fleroxacin PET study on two occasions: the first study was performed within 24 h after initiation of therapy with fleroxacin, and the second study was done within 24 h of completion of therapy. Prior to the first PET study, each patient had a complete medical history and physical examination, urinalysis, complete blood count and blood chemistries (blood urea nitrogen, creatinine, total protein, albumin, globulin, alkaline phosphatase, and serum glutamic oxalacetic transaminase). A therapeutic course of fleroxacin, 400 mg/day, was administered for a total of 7 days, orally on the days that a PET scan was not carried out and intravenously in conjunction with the performance of the PET scan (see above). One week after the second imaging study, the physical examination, urinalysis, bacteriologic studies, complete blood count, and blood chemistries were repeated.

The protocol was approved by the Massachusetts General Hospital's committees on human studies, pharmacy, and radioisotopes. All patients signed an informed-consent form prior to participation in the study.

Pharmacokinetics of fleroxacin. This study was designed to evaluate the detailed pharmacokinetics of fleroxacin in infected tissues of patients with acute bacterial exacerbations of chronic bronchitis and urinary tract infections. The protocols for PET imaging and data analysis were similar to the procedure that was used previously to measure the pharmacokinetics of fleroxacin in noninfected subjects (17).

Prior to injection of fleroxacin, venous catheters were placed in each arm, one for drug infusion and one for blood sampling. Unlabeled fleroxacin (400 mg) containing 370 to 740 MBq of ^{18}F-labeled drug was administered intravenously over 30 min. Serial PET imaging and blood sampling were initiated at the start of the infusion and continued for 6 to 8 h. Blood samples (2 ml) were collected at 1, 2, 5, 10, 20, 25, 30, and 45 min and 1, 1.5, 2, 4, and 6 to 8 h after the start of infusion. For studying patients with bronchitis, images were acquired at four bed positions, starting at the lung apices and extending to the upper abdomen. For studying patients with urinary tract infections, images were acquired at two bed positions, centered over the kidneys and the bladder and prostate.

The patients were positioned supine on the imaging bed of the PET camera with arms extended out of the field of view. The organs of interest were positioned on the basis of reconstructed transmission data. For delayed imaging, positioning marks were drawn on the patient's thorax, abdomen, and pelvis. During the first 2 h, serial 2-min images were acquired in all bed positions. The imaging bed was switched between positions under computer control. After the initial 2 h of imaging, the patients were allowed to resume normal activity. At 4 and 6 to 8 h after the start of the infusion, additional 10- and 15-min images in each position were acquired. A transmission scan was acquired after each repositioning.

Images were acquired with a PC-4096 PET camera (Scanditronix AB, Uppsala, Sweden), and concentrations of fleroxacin in blood were measured with a well counter. This PET camera is well described in the literature (41). The primary imaging parameters of the PC-4096 camera are in-plane and axial resolutions of 6.0 mm full width at half maximum, 15 contiguous slices of 6.5-mm separation, and a sensitivity of ~135 cps/kBq. All images were reconstructed by using a conventional filtered back-projection algorithm to an in-plane resolution of 7 mm full width at half maximum. Attenuations were measured with a rotating pin source containing ^{68}Ge. Postinjection transmission measurements were corrected for emissions from the patients by a previously reported procedure (12). All projection data were corrected for nonuniformity of detector response, dead time, random coincidences, and scattered radiation. Regions of interest were circular with a fixed diameter of 16 mm. The PET camera was cross-calibrated to a well scintillation counter by comparing the PET camera response from a uniform distribution of an ^{18}F solution in a 20-cm-diameter cylindrical phantom with the response of the well counter to an aliquot of the same solution.

Tissue concentrations of fleroxacin in each organ (in micrograms per milliliter) were calculated by dividing the concentration of [^{18}F]fleroxacin determined by PET (37 Bq/ml) by the specific activity of the total injected dose of drug (in megabecquerels per microgram). Since the density of most organs is ~1 g/ml, concentrations expressed in micrograms per milliliter are nearly equal to concentrations expressed in micrograms per gram. For lungs, concentrations were corrected for density, ~0.26 ± 0.03 g/ml (18). The following pharmacokinetic parameters were determined for each organ: peak concentration, plateau concentration (average concentration from 2 to 8 h after injection), and normalized area under the concentration-time curve (AUC) (AUC/interval of measurement [6 to 8 h]). AUCs were calculated by numerical integration by using the trapezoidal rule.

TABLE 1. Characteristics of patients studied

Patient age	Diagnosis	Pathogen isolated
69	Acute bronchitis[a]	*Heamophilus influenzae*
52	Acute bronchitis	*Moraxella catarrhalis*
63	Acute bronchitis	*Heamophilus influenzae*
73	Acute bronchitis	*Heamophilus influenzae*
43	Acute bronchitis	*Moraxella catarrhalis*
71	Prostatitis and bladder cancer	*Pseudomonas aeruginosa*
52	Nephrostomy[b]	*Enterobacter* sp.
39	Pyelonephritis[b]	*Proteus rettgeri*
55	Pyelonephritis[b]	*Proteus mirabilis*
64	Prostatitis and pyelonephritis	*Escherichia coli*

[a] The term "acute bronchitis" refers to patients with acute exacerbations of chronic bronchitis.

[b] All patients with complicated urinary tract infections were assumed to have prostate involvement.

Statistical methods. The results of the pharmacokinetic studies with infected patients were compared with the results of our previous studies with healthy subjects (17) by one- or two-way analysis of variance (ANOVA). Post-hoc comparisons of drug concentration were performed by Duncan's new multiple-range test (15). All results are expressed as means ± standard errors of the means.

Although the use of historical controls is not optimal for pharmacokinetic studies, the complexity and expense of PET imaging preclude the study of an unlimited number of subjects. Furthermore, since both studies were performed in the same laboratory under identical conditions, we feel that the comparisons are valid.

RESULTS

All 10 patients studied were men (Table 1). None of these patients demonstrated adverse effects attributable to fleroxacin during the course of the intravenous infusion or imaging studies, and all had a good therapeutic response to fleroxacin. Two of the patients had mild headaches or nausea while receiving the drug orally that resolved with cessation of the drug. In no case was a patient removed from the study because of side effects related to fleroxacin. There were no injection site abnormalities related to the administration of intravenous fleroxacin.

Pharmacokinetics of fleroxacin in patients with acute exacerbations of chronic bronchitis. The time dependence of the distribution of [^{18}F]fleroxacin in the lungs of patients with acute bacterial exacerbations of chronic bronchitis before and after effective treatment with fleroxacin is illustrated in Fig. 1. Figure 2 shows representative transverse, sagittal, and coronal PET images of the thorax of a patient with acute bacterial exacerbation of chronic bronchitis after infusion with [^{18}F]fleroxacin plus unlabeled fleroxacin (400 mg). In infected lung tissue, the overall time course of drug accumulation was very similar to our previous results with healthy volunteers. However, the peak concentration of drug in infected tissue was lower (13.10 ± 1.33 versus 18.73 ± 0.72 μg/g).

Table 2 summarizes the pharmacokinetic parameters of fleroxacin in the lungs of patients with chronic bronchitis; our previous results with healthy volunteers are reproduced for comparison. Since two-way ANOVA failed to demonstrate a significant effect of 1 week of drug treatment on any of the parameters, the values were pooled in Fig. 3. One-way ANOVA demonstrated that all three pharmacokinetic parameters were significantly lower in patients with chronic bronchitis: peak, 14.20 ± 1.52 versus 20.09 ± 0.61 μg/g ($P < 0.02$); plateau, 5.75 ± 0.22 versus 8.65 ± 0.40 μg/g ($P < 0.001$); and normalized AUC, 5.89 ± 0.65 versus 7.44 ± 0.61 μg/g ($P < 0.005$).

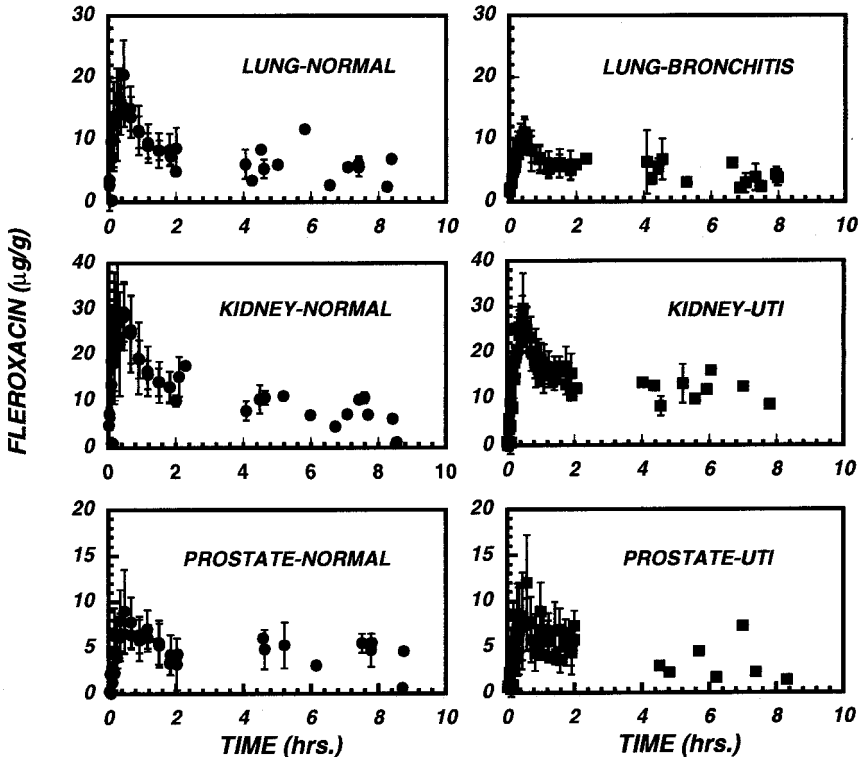

FIG. 1. Time dependence of the distribution of [18F]fleroxacin in infected tissues of patients with chronic bronchitis ($n = 5$) and complicated urinary tract infections (UTI) ($n = 5$). Since ANOVA failed to show a significant effect of fleroxacin treatment, pre- and posttreatment measurements were pooled. The corresponding data for healthy volunteers ($n = 9$) are included for comparison. Tissue concentrations of fleroxacin were measured by PET and are expressed as means ± SEM.

Pharmacokinetics of fleroxacin in the kidneys and prostates of patients with complicated urinary tract infections. The time dependence of the distribution of [18F]fleroxacin in kidneys and prostates of patients with complicated urinary tract infections before and after effective treatment with fleroxacin is illustrated in Fig. 1. Figure 4 shows representative transverse and coronal PET images of the kidneys of a patient with urinary tract infection after infusion with [18F]fleroxacin plus unlabeled fleroxacin (400 mg). The time course of drug accumulation in the kidneys and prostates of these patients was nearly identical to our previous results with healthy volunteers.

Table 2 summarizes the pharmacokinetic parameters of fleroxacin in kidneys and prostates of patients with complicated urinary tract infections: our previous results with healthy volunteers are reproduced for comparison. Since two-way ANOVA failed to demonstrate a significant effect of 1 week of drug treatment on any of the parameters, the values were pooled in Fig. 5. One-way ANOVA demonstrated that for kidneys, the normalized AUC was significantly greater in tissue of patients with complicated urinary tract infection, 14.47 ± 0.84 versus 12.01 ± 0.79 μg/g ($P < 0.01$). Significant differences were not detected for the other parameters.

DISCUSSION

The success of antimicrobial therapy in eradicating an infection is predicted on the presence of concentrations of drug at the site of infection that exceed the MIC for the infecting organism for an adequate period. Until recently, determination of the doses of drug necessary to achieve this goal has been largely an indirect process, based on pharmacokinetic studies in animals, detailed measurements of drug levels in blood and other accessible bodily fluids in humans, and the assay of occasional human biopsy specimens that become available for study. Because of the importance of tissue drug delivery in determining the success of antimicrobial therapy, we previously developed and validated a noninvasive technique for applying PET to the assessment of the pharmacokinetics of fleroxacin in human tissues (16, 17, 31). The fact that PET measurements yield only total concentrations of drug per gram of tissue and cannot differentiate between intra- and extracel-

FIG. 2. Representative transverse, sagittal, and coronal PET images of the thorax of a patient with chronic bronchitis after infusion with [18F]fleroxacin plus unlabeled fleroxacin (400 mg). The images represent summed data acquired between 2 and 8 h after injection. Concentrations of drug in pulmonary tissue can be calculated by correcting for density as indicated in the text.

TABLE 2. Pharmacokinetic parameters for fleroxacin in patients and healthy volunteers

Group	Status	Tissue	Concn (μg/g)[a]		AUC (μg/g)[a,b]
			Peak	Plateau	
Patients with bronchitis[c]	Pretreatment	Lung	13.10 ± 1.33	5.87 ± 0.34	5.79 ± 1.03
	Posttreatment	Lung	15.30 ± 3.13	5.62 ± 0.34	5.98 ± 1.02
Patients with UTI[d]	Pretreatment	Kidney	35.03 ± 4.05	14.30 ± 0.84	14.01 ± 1.66
	Posttreatment	Kidney	31.03 ± 3.35	15.91 ± 0.75	14.93 ± 0.86
	Pretreatment	Prostate	12.33 ± 3.89	5.67 ± 0.34	4.74 ± 0.69
	Posttreatment	Prostate	11.22 ± 1.23	4.48 ± 0.25	4.14 ± 0.16
Volunteers	Pretreatment	Lung	18.73 ± 0.72	8.55 ± 0.57	7.14 ± 0.72
	Posttreatment	Lung	21.45 ± 1.16	8.74 ± 0.69	7.74 ± 1.16
	Pretreatment	Kidney	34.77 ± 3.59	15.84 ± 1.18	11.92 ± 1.15
	Posttreatment	Kidney	33.28 ± 2.81	14.21 ± 1.03	12.10 ± 1.35
	Pretreatment	Prostate	9.35 ± 1.61	5.56 ± 0.30	4.29 ± 0.66
	Posttreatment	Prostate	8.09 ± 0.71	4.16 ± 0.31	4.46 ± 0.39

[a] Values are means ± SEM.
[b] Normalized to the interval of measurement (6 to 8 h).
[c] Patients with acute exacerbations of chronic bronchitis.
[d] UTI, complicated urinary tract infections.

lular drug somewhat limits the conclusions that can be drawn. However, rough relationships between total tissue concentrations and MICs are suggested.

Our previous PET studies with healthy volunteers have demonstrated that fleroxacin, at a therapeutic dose of 400 mg, has excellent penetration in almost all human tissues (with the notable exception of the brain). Although promising, these studies with healthy volunteers left unanswered the question of whether tissue infection or its treatment would alter the pharmacokinetics of the drug.

In the present study, patients with acute bacterial exacerbations of chronic bronchitis or complicated urinary tract infection were treated with 400 mg of fleroxacin per day, and PET scans were carried out at the beginning and end of therapy. The findings are clear-cut: (i) in the patients with urinary tract infections, drug accumulation was slightly greater in infected renal tissues; (ii) in the patients with chronic bronchitis, drug accumulation was lower in infected lung tissues; (iii) the presence of infection in the lung or urinary tract had no influence on the delivery of drug to uninvolved tissues; and (iv) effective treatment of infected patients did not have a significant effect on the pharmacokinetics of this drug. The decrease in fleroxacin accumulation in the lungs of patients with chronic bronchitis is most probably due to significant pulmonary fibrosis with resultant decreased perfusion and drug delivery in this patient group. This hypothesis is supported by the observation that the patient with the most severe fibrosis had the lowest accumulation of drug. The use of normal lung density data for calculating drug concentrations in diseased tissue limits the accuracy of the estimates, since the primary plain radiographic finding in the patients with bronchitis was fibrosis and density was probably higher. Clearly, use of a higher density in the calculations would have increased the measured difference between normal and diseased lung tissues.

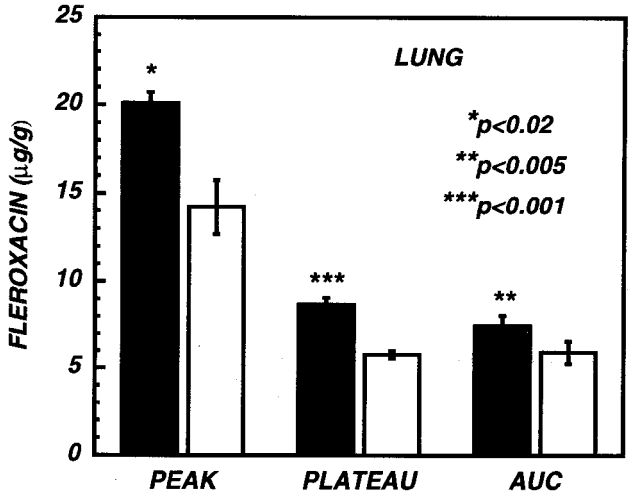

FIG. 3. Peak and plateau concentrations of and normalized AUCs for fleroxacin in the lungs of patients with chronic bronchitis (n = 5; open bars). Previous data for healthy volunteers are reproduced for comparison (n = 9; solid bars). All values are the means ± SEM for five or nine male subjects.

FIG. 4. Representative transverse and coronal PET images of the kidneys of a patient with urinary tract infection after infusion with [^{18}F]fleroxacin plus unlabeled fleroxacin (400 mg). The images represent summed data acquired between 2 and 8 h after injection.

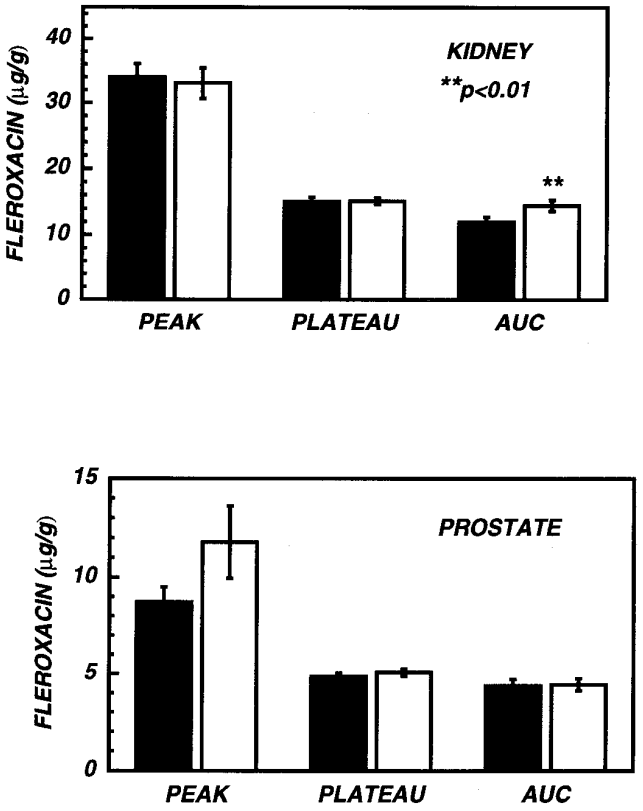

FIG. 5. Peak and plateau concentrations and normalized AUCs for fleroxacin in kidneys and prostates of patients with complicated urinary tract infections (n = 5; open bars). Previous data for healthy volunteers are reproduced for comparison (n = 9; solid bars). All values are the means ± SEM for five or nine male subjects.

Although there was a decrease in delivery of drug to the lungs of patients with acute bacterial exacerbations of chronic bronchitis, it should be emphasized that the concentrations achieved during the 6- to 8-h sampling period (peak, 14.2 ± 1.52 μg/g; plateau, 5.75 ± 0.34 μg/g; AUC, 5.89 ± 0.65 μg/g) are still well above the MICs at which 90% of isolates are inhibited for the relevant pathogens: *H. influenzae*, *Streptococcus pneumoniae*, and *M. catarrhalis* (3, 6). This is underscored in this study by the excellent clinical response of the chronic bronchitis patients to treatment.

In contrast to the findings with the patients with chronic bronchitis, comparison of fleroxacin delivery to the urinary tract between individuals with complicated urinary tract infection and healthy volunteers revealed increased concentrations in the kidneys. Presumably, anatomic derangement has a lesser effect on drug delivery in this circumstance and inflammation-induced increases in blood flow are responsible for these observations. Whether changes in pH have any effect on drug distribution cannot be determined.

In summary, in this study and others, fleroxacin has been shown to be an effective therapy for acute exacerbations of chronic bronchitis and complicated urinary tract infection. The PET studies described here demonstrated that there is rapid accumulation of radiolabeled drug in affected tissues of patients with urinary tract infections and acute bacterial exacerbations of chronic bronchitis. Although measurable changes in drug delivery to the lungs and urinary tract can be caused by scarring and changes in blood flow, clinically these appear not to be important since drug delivery still remains well above the MICs at which 90% of isolates are inhibited for the relevant pathogens in both groups of patients.

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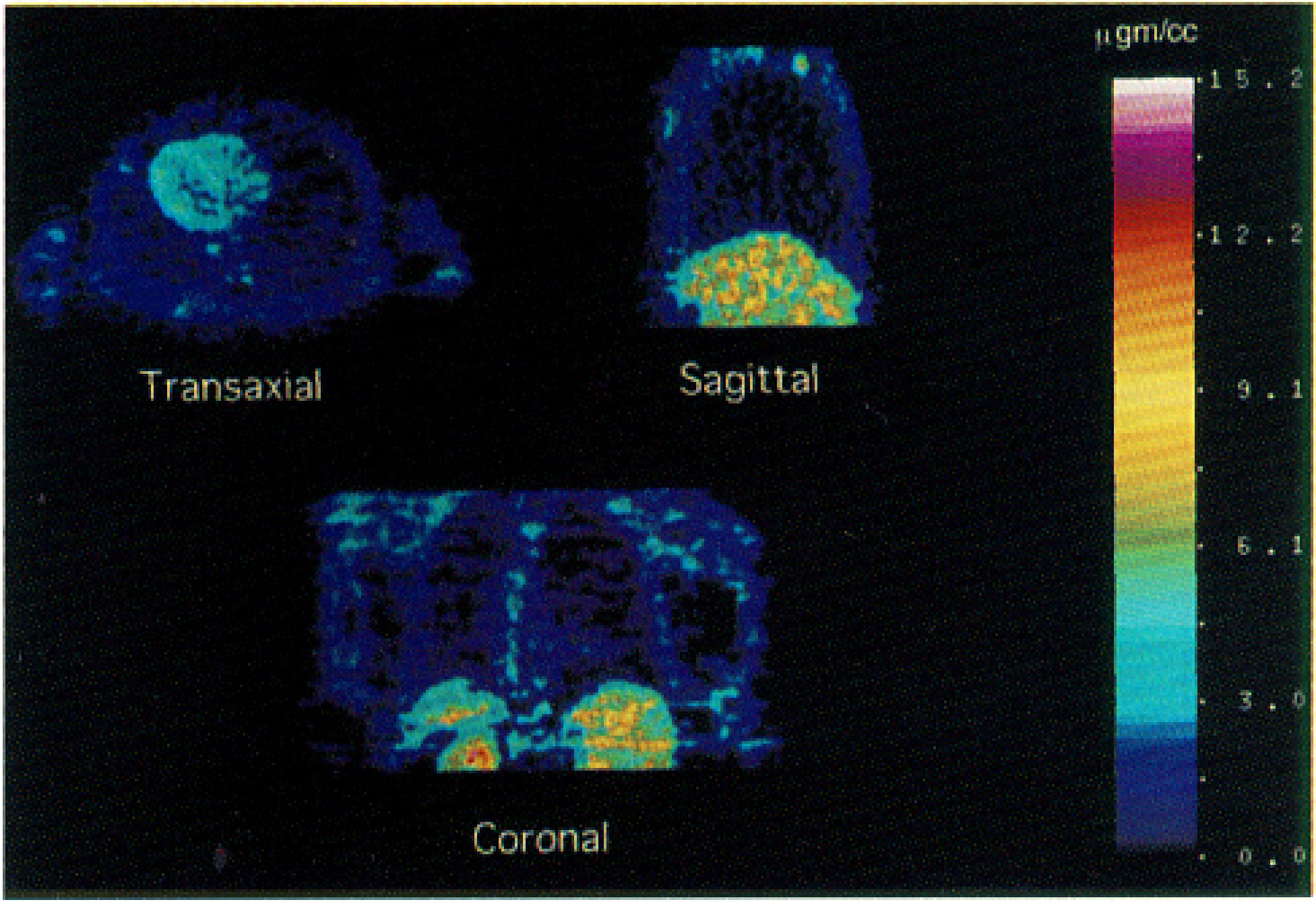
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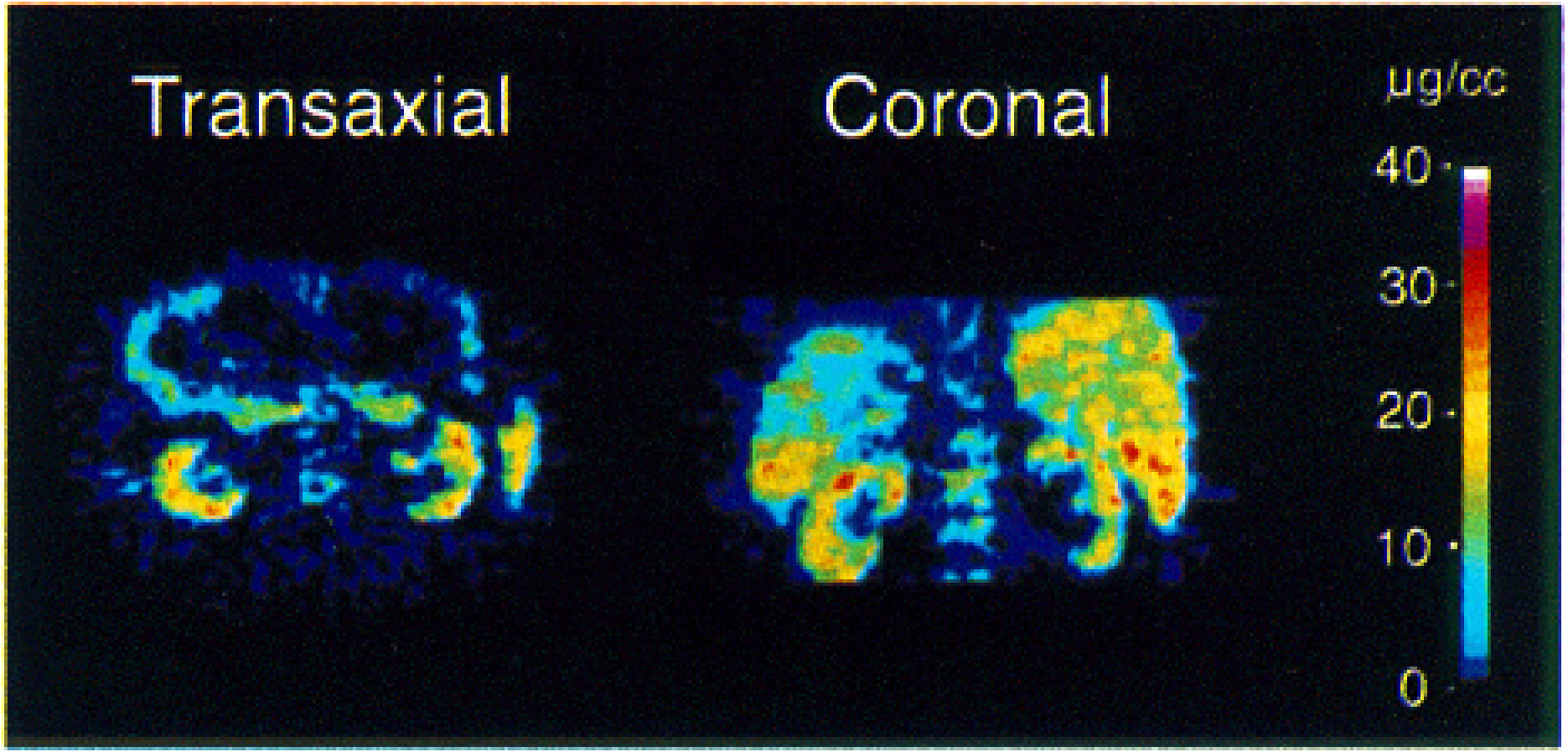
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