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Pharmacokinetics of [^{18}F]Fleroxacin in Healthy Human Subjects Studied by Using Positron Emission Tomography

ALAN J. FISCHMAN,[1,2]* E. LIVNI,[1] JOHN BABICH,[1] NATHANIEL M. ALPERT,[1] YU-YING LIU,[3] EDNA THOM,[3] ROY CLEELAND,[3] BARBARA L. PROSSER,[3] JOHN A. CORREIA,[1] H. WILLIAM STRAUSS,[1,2] AND ROBERT H. RUBIN[1,2]

Division of Nuclear Medicine of the Department of Radiology[1] and The Clinical Investigation Program of the Medical Service,[2] Massachusetts General Hospital and the Departments of Radiology and Medicine, Harvard Medical School, Boston, Massachusetts 02114, and Hoffmann-La Roche Inc., Nutley, New Jersey 07110[3]

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Positron emission tomography (PET) with [^{18}F]fleroxacin was used to study the pharmacokinetics of fleroxacin, a new broad-spectrum fluoroquinolone, in 12 healthy volunteers (9 men and 3 women). The subjects were infused with a standard therapeutic dose of fleroxacin (400 mg) supplemented with ~20 mCi of [^{18}F]fleroxacin. Serial PET images were made and blood samples were collected for 8 h, starting at the initiation of the infusion. The subjects were then treated with unlabeled drug for 3 days (400 mg/day). On the fifth day, infusion of radiolabeled drug, PET imaging, and blood collection were repeated. In most organs, there was rapid accumulation of radiolabeled drug, with stable levels achieved within 1 h after completion of the infusion. Especially high peak concentrations (in micrograms per gram) were achieved in the kidney (>34), liver (>25), lung (>20), myocardium (>19), and spleen (>18). Peak concentrations of drug more than two times the MIC for 90% of *Enterobacteriaceae* strains tested (>10-fold for most organisms) were achieved in all tissues except the brain and remained above this level for more than 6 to 8 h. The plateau concentrations in tissues (2 to 8 h, in micrograms per gram ± standard error of the mean) of drug were as follows: brain, 0.83 ± 0.032; myocardium, 4.53 ± 0.24; lung, 5.80 ± 0.48; liver, 7.31 ± 0.33; spleen, 6.00 ± 0.47; bowel, 3.53 ± 0.74; kidney, 8.85 ± 0.64; bone, 2.87 ± 0.29; muscle, 4.60 ± 0.33; prostate, 4.65 ± 0.48; uterus, 3.87 ± 0.39; breast, 2.68 ± 0.11; and blood, 2.35 ± 0.09. Concentrations of fleroxacin in tissue were similar in males and females, before and after pretreatment with unlabeled drug.

Fleroxacin, 6,8-difluoro-1,4-dihydro-1-(2-fluoroethyl)-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinolinecarboxylic acid, is a new fluoroquinolone with broad antimicrobial activity against both gram-negative and gram-positive bacteria. Both in vitro and in animal models, fleroxacin's anti-gram-negative-bacterium activity has been shown to be comparable to that of the earlier fluoroquinolones (norfloxacin, pefloxacin, ciprofloxacin, and ofloxacin) (1, 2, 7, 11, 13, 19, 29, 36, 37, 40). In addition, however, studies in endocarditis models, as well as in vitro, have shown that fleroxacin has significant activity against both methicillin-susceptible and -resistant *Staphylococcus aureus* (1, 6, 25, 28).

Pharmacokinetic studies in humans have demonstrated that fleroxacin is rapidly and completely absorbed from the gastrointestinal tract, achieving a high concentration in the plasma after either oral or intravenous therapy, is metabolized to a minor extent, and has a long elimination half-life, making once-a-day therapy possible (8, 21, 39, 49, 51, 52, 54). Animal studies have suggested that there is excellent penetration of drug into most tissues (5, 18, 30–34, 41, 49, 53), but only limited information on tissue penetration of fleroxacin in humans is available (22, 26, 41, 44, 53). Initial clinical experience in the treatment of sexually transmitted diseases, urinary tract infection, skin and soft tissue infections, gastrointestinal infection, and even acute exacerbations of chronic bronchitis has been quite promising, with 74 to 100% bacteriological cure rates and a tolerability comparable to those for other drugs of this class (3, 12, 27, 35, 38, 42, 43, 45, 47). However, to optimize the clinical use of fleroxacin, detailed pharmacokinetic data on the distribution of drug to healthy and infected tissues are required. Such information will be useful in the design of dosing schedules that will maximize therapeutic efficacy and minimize drug toxicity for different types of infection.

To accomplish this goal, we have developed a noninvasive technique, using positron emission tomography (PET) and [^{18}F]fleroxacin to determine the tissue pharmacokinetics of this drug. Previous studies in animals have validated this technique and demonstrated that PET imaging will permit the precise, noninvasive measurement of the concentrations of fleroxacin in various tissues over time (15, 34). We report here the results of tissue pharmacokinetic studies utilizing this technique in healthy human subjects.

MATERIALS AND METHODS

Preparation of [^{18}F]fleroxacin. 6,8-Difluoro-1,4-dihydro-1-(2-[^{18}F]fluoroethyl)-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinolinecarboxylic acid ([^{18}F]fleroxacin) was synthesized 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-performance liquid chromatography, nuclear magnetic resonance spectroscopy (NMRS) (^{1}H, ^{13}C, and ^{19}F), and in vitro microbiological studies. The specific activity of the radiolabeled drug was >50 mCi/μmol. Further details of the synthesis of [^{18}F]fleroxacin have been described elsewhere (34).

Safety considerations. An acute toxicity study with the radiopharmaceutical was performed prior to human use. Briefly, groups of six rats were injected with [^{18}F]fleroxacin

* Corresponding author.

(at a dose 100-fold higher than the human dose) or vehicle. Food and water intake and body weight were measured for 7 days, and the animals were observed for signs of gross toxicity. At the end of the observation period, the rats were sacrificed and histological sections of brain, heart, lung, liver, spleen, kidney, skeletal muscle, bowel, testicle, bone, and prostate tissues were examined by a board-certified pathologist.

On the basis of data for biodistribution in rats, MIRDOSE calculations indicated that approximately 20 mCi of [18F]fleroxacin can be administered without delivering a radiation burden in excess of 20 mGy to any organ (unpublished results). With this dose of radioactivity, it would be possible to study fleroxacin pharmacokinetics in humans over an 8- to 10-h period by PET.

Human subjects. Nine healthy male (mean age, 31.78 ± 8.58 years; range, 19 to 47) and three healthy female (mean age, 30.00 ± 5.29 years; range, 26 to 36) volunteers were studied. The female subjects were required to have regular menstrual cycles. Each subject was studied twice; the first study was performed with subjects in the drug-naive state, and the second study was performed after a 3-day course of oral unlabeled fleroxacin (400 mg/day) that was begun on the day following the first PET study. The second study was designed to determine whether treatment with unlabeled drug induces saturation or feedback effects that alter distribution or clearance. Prior to the first PET study, each subject had a complete medical history and physical examination, urinalysis, complete blood count (with differential), and blood chemistries (blood urea nitrogen, creatinine, total protein, albumin, globulin, alkaline phosphatase, and serum glutamic oxalacetic transaminase). In female volunteers, a pregnancy test was performed within 24 h before injection of radiolabeled drug. After the first imaging, the subjects were treated with oral unlabeled fleroxacin, 400 mg/day for 3 days. Twenty-four hours after the last dose of unlabeled drug, the PET study was repeated. In order to measure uterine concentrations of fleroxacin in two physiologic states, the female subjects were studied within 3 days before their predicted day of menstruating and at 3 days postmenstruation. One week after the second imaging study, the physical examination, urinalysis, complete blood count, and blood chemistries were repeated.

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

Pharmacokinetics of fleroxacin. Experiments were designed to evaluate the detailed pharmacokinetics of fleroxacin in healthy human volunteers. Prior to imaging, venous catheters were placed in each arm, one for infusion of drug and one for blood sampling. Four hundred milligrams of unlabeled fleroxacin containing 10 to 20 mCi of ^{18}F-labeled drug was administered intravenously over 30 min. At the start of the infusion, serial PET imaging and blood sampling were initiated and continued for approximately 6 to 8 h. Blood samples (2 ml) were collected at 1, 2, 5, 10, 20, 25, 30, and 45 min, and at 1, 1.5, 2, 4, and 6 to 8 h after the start of infusion. Due to the limited field of view of the PET camera and the short physical half-life of ^{18}F, detailed pharmacokinetic studies were performed on specific groups of organs in different sets of subjects: extracranial organs in males (n = 6) and females (n = 3) and the brain in males (n = 3). Two imaging protocols were employed. For studying extracranial organs, three body regions were imaged: the first position included heart, lung, liver, spleen, and breast; the second position included bowel, bone, and kidney; and the third position included prostate, uterus, gluteal muscle, and bone. In female subjects, only the first and third regions were imaged.

The subjects were positioned supine on the imaging bed of the PET cameras, with arms extended out of the field of view. For imaging the extracranial organs, the subjects were positioned on the basis of reconstructed transmission data so that the organs of interest were included in the field of view. For later imaging, positioning marks were drawn on the subject's thorax, abdomen, and pelvis. During the first 2 h, serial 2-min images of all three organ groups were acquired. The bed was switched between positions under computer control. After the last image was acquired, the subjects were allowed to resume normal activity. At 4 and 6 to 8 h after the start of the infusion, the subjects were repositioned under the PET camera and 10- and 15-min images were acquired in each position. A transmission scan was acquired after each repositioning.

For brain studies, the subject's head was fixed with an individually fabricated head holder (Tru Scan Image Inc., Annapolis, Md.) and serial images were acquired in a two-bed position. The timing of imaging was identical to that described above.

Images were acquired with either a PC-384 (brain imaging) or a PC-4096 (peripheral organ imaging) PET camera (Scanditronix AB, Uppsala, Sweden), and concentrations of fleroxacin in blood were measured with a well counter. Both instruments are well-described in the literature (33, 46). The primary imaging parameters of the PC-384 camera are an in-plane resolution of 7.0 mm full width at half-maximum (FWHM), an axial resolution of 12 mm FWHM, five contiguous slices of 14-mm separation, and a sensitivity of ~22,000 cps/μCi. The corresponding imaging parameters for the PC-4096 camera are in-plane and axial resolutions of 6.0 mm FWHM, 15 contiguous slices of 6.5-mm separation, and a sensitivity of ~5,000 cps/μCi. All images were reconstructed by using a conventional filtered back-projection algorithm to an in-plane resolution of 7 mm FWHM. An analytic attenuation correction assuming a uniform distribution of absorber within the slice contour (10) was applied to data acquired with the PC-384, and measured attenuations were obtained for data from the PC-4096 by using a rotating pin source containing ^{68}Ge. 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 (8 mm for myocardium tissue). The PET cameras were cross-calibrated against 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. The measured tissue concentrations of radiolabeled drug were independent of the instrument used.

The concentration of fleroxacin in each organ (in micrograms per cubic centimeter) was calculated by dividing the concentration of [18F]fleroxacin determined by PET (in nanocuries per cubic centimeter) by the specific activity of the total injected dose of drug (in nanocuries per microgram). Since the density of most organs is ~1 g/cm^3, concentrations expressed as micrograms per cubic centimeter are approximately equal to concentrations expressed as micrograms per gram. For lung tissue, concentrations were corrected for density (~0.26 ± 0.03 g/cm^3 [16]). Since concentrations of fleroxacin in brain tissue were extremely low, radioactivity in blood made a significant contribution to

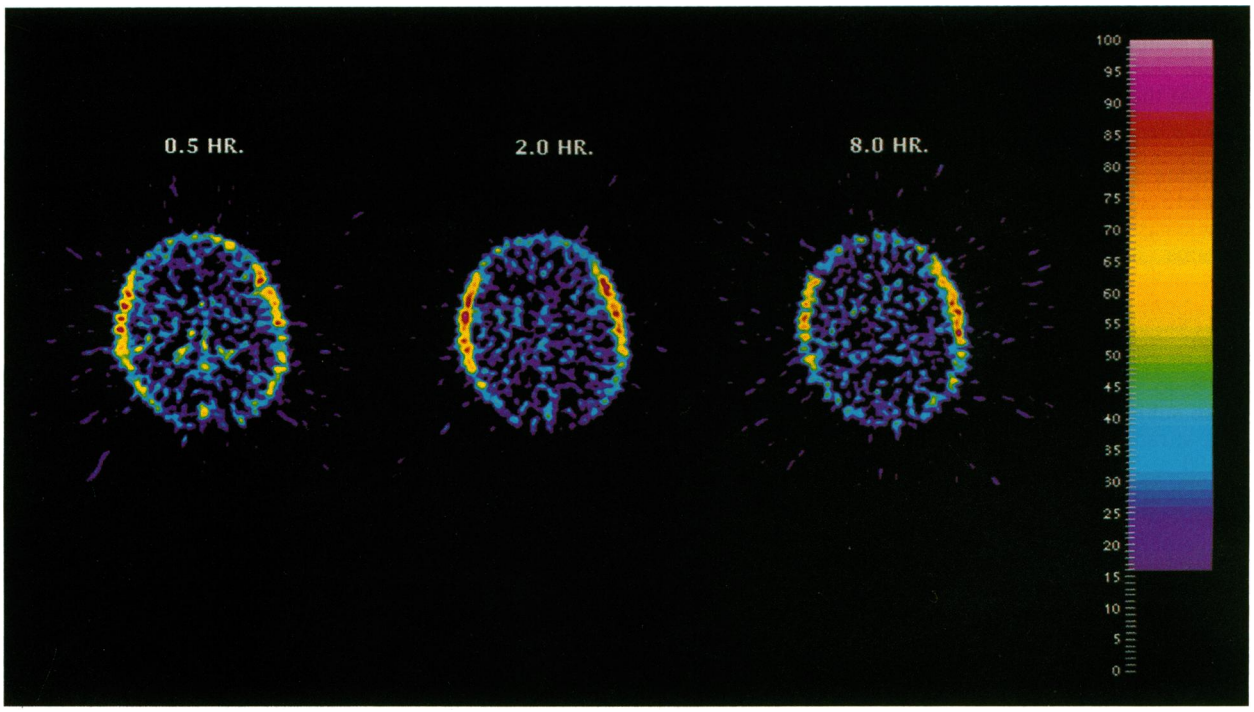

FIG. 1. Representative PET images of the brain of a healthy subject at the indicated times after intravenous injection of [^{18}F]fleroxacin plus unlabeled fleroxacin (400 mg). All images were recorded at 52 mm above the orbital-meatal line.

the concentrations measured by PET. To correct for this effect, concentrations in brain parenchyma were corrected by subtracting 4% of the concentration of drug in blood from the total tissue concentration. This correction did not have a significant effect on fleroxacin concentrations in the other tissues. 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 per interval of measurement). AUCs were calculated by numerical integration using the trapezoidal rule.

The lowest concentration of radioactivity that was measured in the present study was approximately 100 nCi/cm^3, with a precision of ±5%. This corresponds to a quantitation limit of ~2.0 μg/cm^3 of tissue. Injecting a larger dose of radioactivity and/or acquiring images for a longer period would result in a lower quantitation limit.

Statistical methods. The results of the pharmacokinetic studies were evaluated by analysis of variance with a linear model in which the organ and pretreatment with unlabeled drug were the classification variables: pharmacokinetic parameter = organ + pretreatment + organ * pretreatment. For the imaged organs that were common to males and females (blood, liver, lung, muscle, and myocardium), sex was included as an additional classification variable. Post hoc comparison of drug concentrations was performed by Duncan's new multiple range test (14). All results are expressed as means ± standard errors of the mean (SEM). To describe the time dependence of blood concentrations of fleroxacin in terms of a limited number of parameters, the concentrations of drug in blood from the end of the infusion to the conclusion of the study were fit to a biexponential function by unweighted nonlinear least squares using the program PROC NLIN (SAS Institute).

RESULTS

The results of the acute toxicological study did not demonstrate any ill effects of the drug. Similarly, in the human volunteers, the results of physical examination and laboratory tests were not affected by administration of radiolabeled fleroxacin.

Pharmacokinetics of fleroxacin in the brain. Figure 1 shows PET images of the brain (52 mm above the orbital-meatal line) of a subject at 30 min, 2 h, and 8 h after intravenous injection of [^{18}F]fleroxacin plus unlabeled fleroxacin (400 mg). These images indicate that fleroxacin accumulation in the brain largely parallels blood volume. The time dependence of fleroxacin accumulation in the brain is shown in Fig. 2. The peak, plateau, and normalized AUCs were 1.23 ± 0.044, 0.83 ± 0.032, and 0.93 ± 0.059 μg/g, respectively. From these data, it is apparent that fleroxacin enters the brain rapidly (peak concentration within 45 min after the start of infusion) and distributes uniformly, albeit at low concentrations, to all neural structures.

Pharmacokinetics of fleroxacin in peripheral tissues. The time dependence of the distribution of fleroxacin to the major organs of the body is illustrated in Fig. 2 and 3. Figure 4 shows representative PET images of the heart, lungs, and breast, the liver and spleen, and the bowel and kidneys of human subjects at 90 min after infusion of [^{18}F]fleroxacin plus unlabeled fleroxacin (400 mg). From these data, it is clear that when injected along with a pharmacological dose of unlabeled drug, [^{18}F]fleroxacin accumulates to a significant extent in all of the peripheral organs of humans. For most organs studied, stable levels of fleroxacin accumulation were reached by 60 min and the concentrations decreased only slightly over the remainder of the study. In the kidney, liver, lung, and myocardium, drug clearance was more rapid. Particularly high concentrations of fleroxacin were achieved

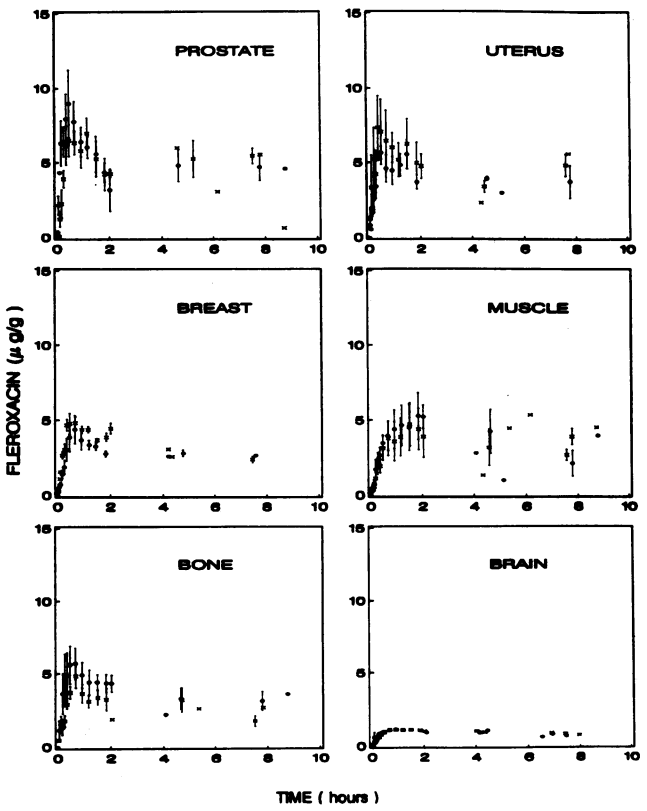

FIG. 2. Organ distribution curves of fleroxacin in prostate, uterus, breast, muscle (males), bone (males), and brain (males) tissues of healthy human subjects, before (circles) and after (crosses) pretreatment with daily oral doses of 400 mg of unlabeled drug for 3 days. Concentrations of fleroxacin in tissue (in micrograms per gram) were measured by PET and are expressed as means ± SEM for 12 subjects (9 males and 3 females).

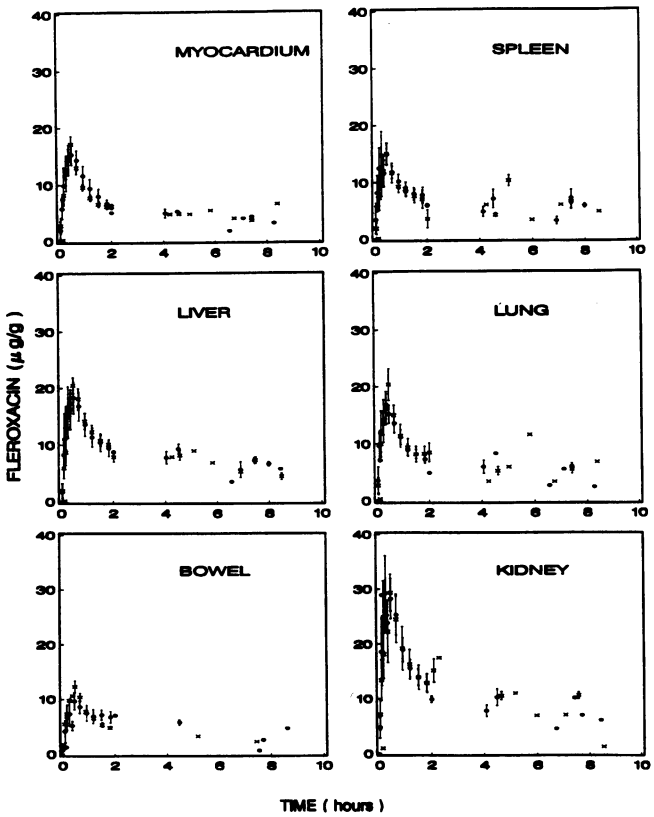

FIG. 3. Organ distribution curves of fleroxacin in the indicated tissues of healthy male subjects, before (circles) and after (crosses) pretreatment with daily oral doses of 400 mg of unlabeled drug for 3 days. Concentrations of fleroxacin in tissue (in micrograms per gram) were measured by PET and are expressed as means ± SEM for six subjects.

in the kidney (>34 μg/g), liver (>25 μg/g), lung (>20 μg/g), myocardium (>19 μg/g), and spleen (>18 μg/g). From the time after the end of infusion to the conclusion of PET imaging, removal of fleroxacin from the circulation was well described by biexponential functions (Fig. 5) as follows: for exam 1, [fleroxacin] = 11.19 ± 1.18 × exp((−2.67 ± 0.56)t) + 4.44 ± 0.27 × exp((−0.086 ± 0.014)t), and for exam 2, [fleroxacin] = 14.65 ± 3.60 × exp((−3.53 ± 1.39)t) + 4.46 ± 0.36 × exp((−0.055 ± 0.020)t). The fast component decreased from 15.56 ± 3.24 min in the first study to 11.76 ± 4.63 min after pretreatment with unlabeled drug (P not significant) while the slow component increased from 8.05 ± 1.27 to 12.70 ± 4.47 h (P not significant). The coefficients of the equations have been corrected for the infusion time of 30 min.

Figures 6 through 8 summarize the pharmacokinetic parameters of fleroxacin in all of the tissues that were evaluated. The data obtained after administration of drug to naive subjects as well as subjects who were pretreated with one dose of radiolabeled drug followed by unlabeled drug for 3 days prior to imaging are presented. Since analysis of variance failed to reveal a significant main effect of sex on any of the pharmacokinetic parameters, the data for males and females were pooled.

Analysis of variance of the peak concentration data (Fig. 6) demonstrated a significant main effect of the type of organ on fleroxacin accumulation (F = 68.75; P < 0.0001). The main effects of pretreatment with unlabeled drug and the pretreatment by organ interaction were not statistically significant. In order of decreasing peak fleroxacin concentration, human tissues can be divided into the following four groups (P < 0.01): group I, kidney; group II, liver, lung, spleen, and myocardium; group III, bowel, uterus, prostate, muscle, blood, bone, and breast; and group IV, brain.

Analysis of variance of the plateau concentration data (Fig. 7) demonstrated a significant main effect of the organ on fleroxacin accumulation (F = 27.87; P < 0.0001). The main effects of pretreatment with unlabeled drug and the pretreatment by organ interaction were not statistically significant. In order of decreasing plateau fleroxacin concentration, human tissues can be divided into the following five groups (P < 0.01): group I, kidney; group II, liver, lung, and spleen; group III, bowel, uterus, prostate, muscle, blood, bone, breast, and myocardium; and group IV, brain.

Analysis of variance of the normalized AUCs (Fig. 8) demonstrated a significant main effect of organ on fleroxacin accumulation (F = 45.39; P < 0.0001). As with the other pharmacokinetic parameters, the main effects of pretreatment with unlabeled drug and the pretreatment-organ interaction were not statistically significant. In order of decreasing normalized AUCs, fleroxacin concentrations in human tissues can be divided into the following four groups (P < 0.01): group I, kidney; group II, liver, lung, spleen, and

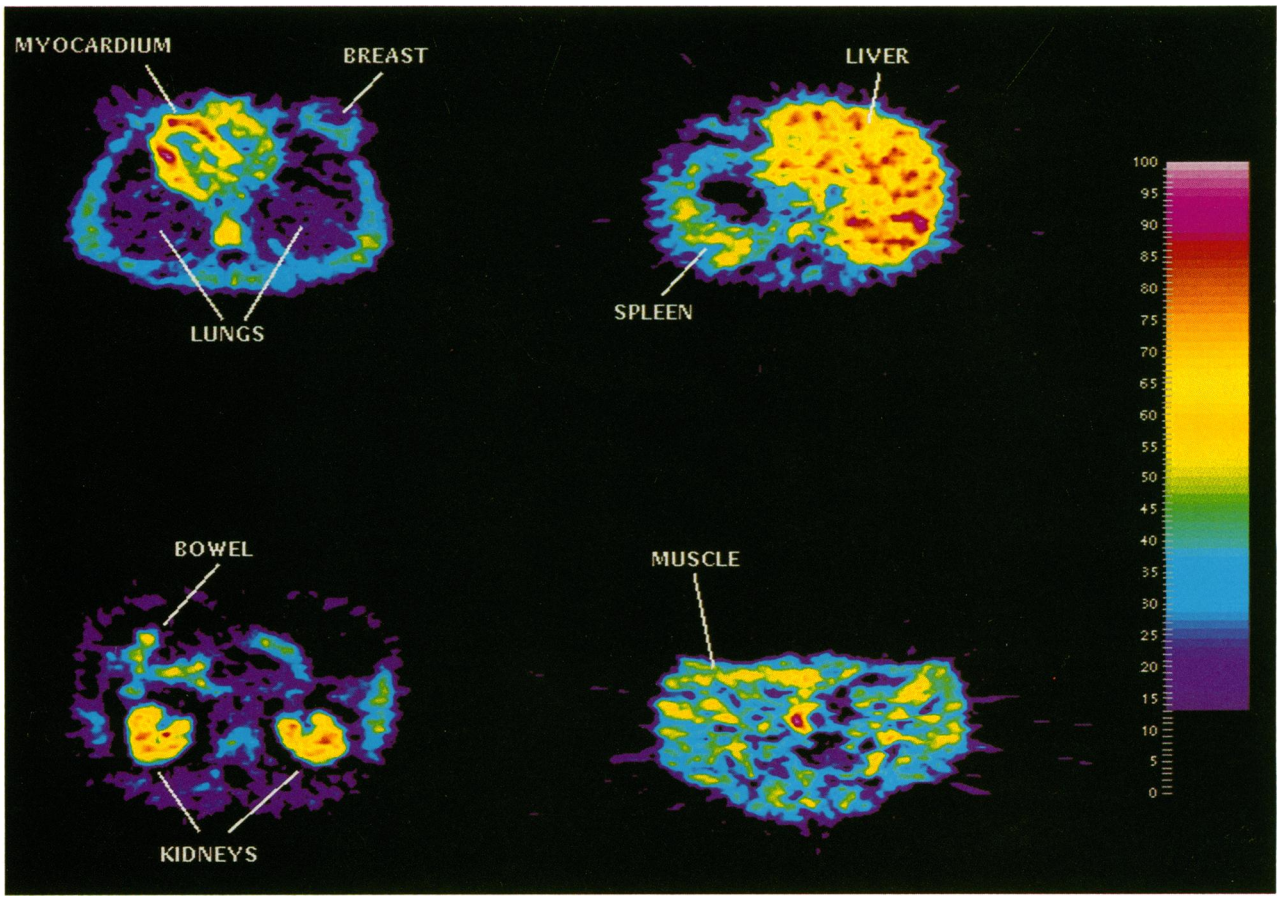

FIG. 4. Representative PET images of human subjects injected with [^{18}F]fleroxacin plus unlabeled fleroxacin (400 mg). The area of maximum concentration in each image represents 100% on the color scale.

myocardium; group III, bowel, uterus, prostate, muscle, blood, bone, and breast; and group IV, brain.

Although the concentration of fleroxacin in pulmonary tissue measured directly by PET is low, this is due to the fact that PET measurements yield drug concentrations in units of micrograms per cubic centrimeter of tissue. Since most tissues are of approximately unit density, concentrations measured by PET are similar to the results that would be expected from direct radioactivity measurements for excised tissues. In contrast, the density of lung tissue is approximately 0.26 ± 0.03 g/cm^3 [16]. When this correction is taken into account, the peak and plateau concentrations and normalized AUC of fleroxacin in lung are 20.01 ± 1.38, 5.94 ± 0.34, and 7.55 ± 0.47 μg/g, respectively, similar to the values for group II organs.

Since fleroxacin concentrations in the blood, liver, lung, muscle, and myocardium of both males and females were measured, the effect of sex on the pharmacokinetic parameters for these organs could be compared (Fig. 9). Analysis of variance of plateau concentrations demonstrated significant main effects of organ ($F = 30.42$; $P < 0.0001$), sex ($F = 13.01$; $P < 0.01$), and organ-by-sex interaction ($F = 12.09$; $P < 0.0001$). In males, drug accumulation was greater in muscle ($P < 0.05$) while in females accumulation was greater in liver ($P < 0.05$). Analysis of variance of the normalized AUCs demonstrated significant main effects of organ ($F = 44.93$; $P < 0.0001$), sex ($F = 8.00$; $P < 0.01$), and organ-by-

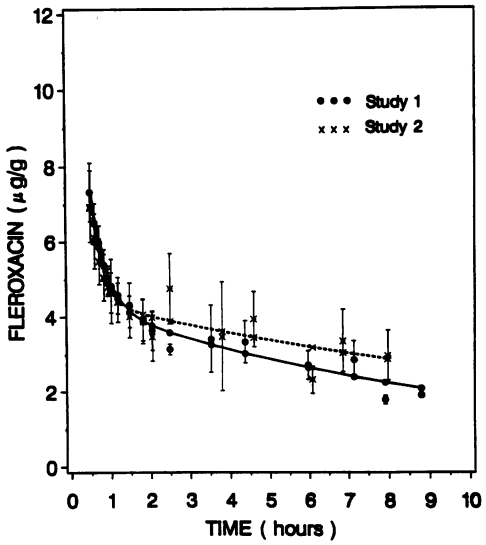

FIG. 5. Blood clearance of fleroxacin in nine healthy male subjects, before (circles) and after (crosses) pretreatment with daily oral doses of 400 mg of unlabeled drug for 3 days, as determined by direct radioactivity measurements. Results from individual subjects are not indicated. The data from the end of the infusion to the conclusion of the study were well described by biexponential functions.

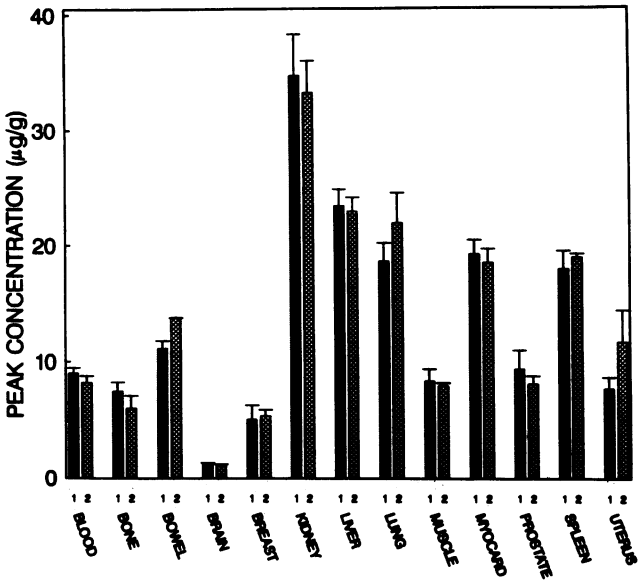

FIG. 6. Peak concentrations of fleroxacin (in micrograms per gram) in the indicated tissues of healthy human subjects, before (solid bars) and after (cross-hatched bars) pretreatment with daily oral doses of 400 mg of unlabeled drug for 3 days. All values are the means ± SEM for nine male subjects except for the data for breast and uterus tissues, for which only three female subjects were studied.

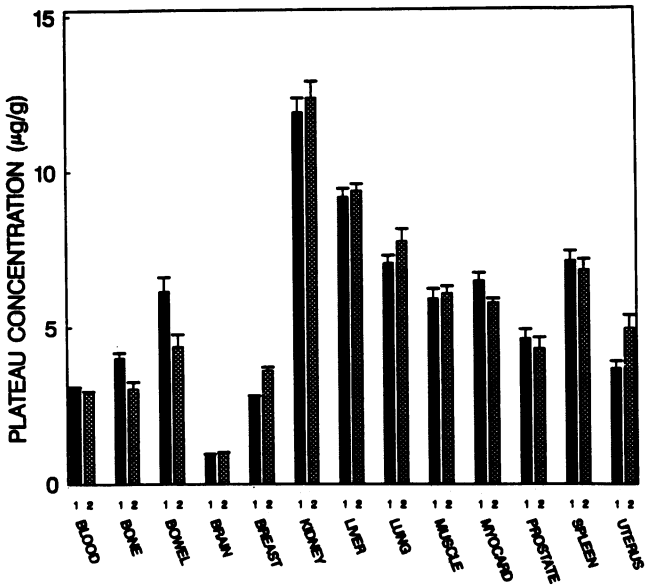

FIG. 7. Plateau concentrations of fleroxacin (in micrograms per gram) in the indicated tissues of healthy human subjects, before (solid bars) and after (cross-hatched bars) pretreatment with daily oral doses of 400 mg of unlabeled drug for 3 days. All values are the means ± SEM for nine male subjects except for the data for breast and uterus tissues, for which only three female subjects were studied.

sex interaction ($F = 10.71$; $P < 0.0001$). In males, drug accumulation was greater in muscle ($P < 0.01$) while in females accumulation was greater in the liver ($P < 0.01$), blood ($P < 0.05$), and myocardium ($P < 0.05$). Analysis of variance of the peak concentration data demonstrated a significant main effect of the organ ($F = 28.68$; $P < 0.0001$). However, the main effects of sex ($F = 0.24$; $P > 0.85$) and organ-by-sex interaction ($F = 1.19$; $P > 0.30$) were not significant. For all three pharmacokinetic parameters, the effect of pretreatment with unlabeled drug was not significant.

DISCUSSION

Fleroxacin is in most respects an ideal drug for PET studies. The presence of three fluorine atoms in the native structure of fleroxacin makes it possible to devise a radiolabeling procedure in which the positron-emitting ^{18}F radionuclide is substituted for a native F atom, creating a radiolabeled form of the drug of interest and not just a labeled analog. Since fleroxacin undergoes minimal in vivo metabolism in humans, measurements of radioactivity in tissue and blood accurately reflect concentrations of intact drug (4, 23, 50). Thus, PET imaging permits the precise noninvasive measurement of the concentration of drug over time in various tissues, including sites of infection. The limitations of this approach have to do with the spatial resolution of PET (tissue volumes of >1.0 cm^3) and the short physical half-life of ^{18}F, which limits the time frame of pharmacokinetic measurements to 8 to 10 h. In the case of fleroxacin, these constraints have not prevented the acquisition of detailed tissue pharmacokinetic data, previously for animals (15, 34) and now for humans. However, the fact that the sampling time was relatively short compared with the terminal half-life of fleroxacin limits the robustness of the method. Furthermore, the fact that PET measurements yield only total concentrations of drug per gram of tissue and cannot differentiate between intra- and extracellular drug concentrations somewhat limits the conclusions that can be drawn.

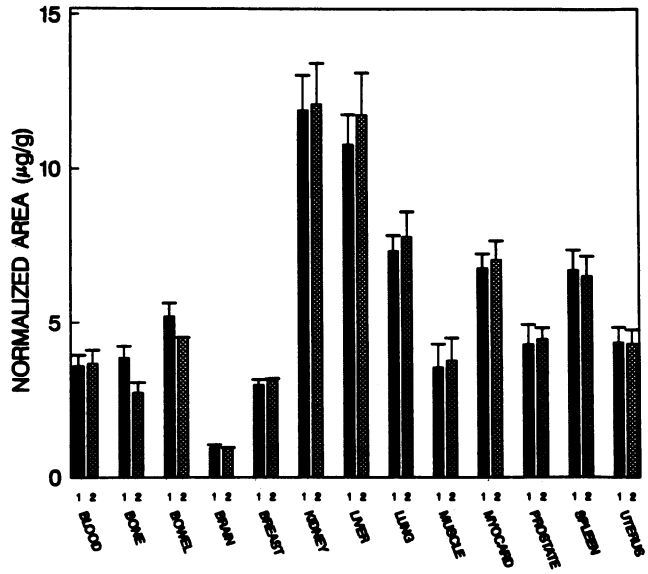

FIG. 8. Normalized AUCs for fleroxacin (in micrograms per gram) in the indicated tissues of healthy human subjects, before (solid bars) and after (cross-hatched bars) pretreatment with daily oral doses of 400 mg of unlabeled drug for 3 days. All values are the means ± SEM for nine male subjects except for the data for breast and uterus tissues, for which only three female subjects were studied.

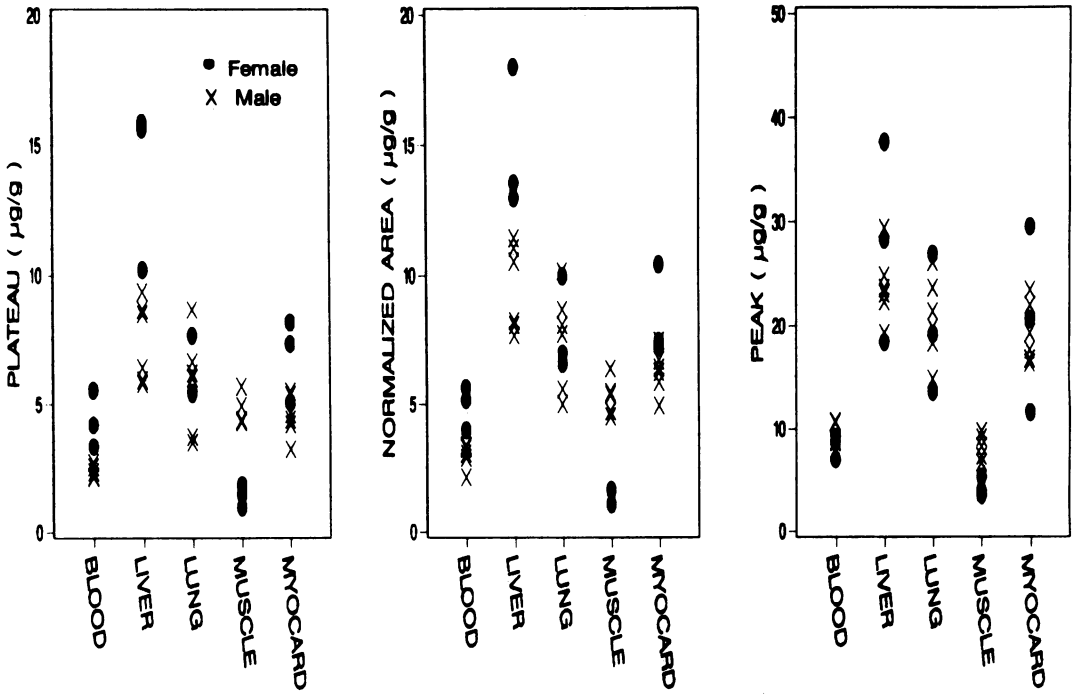

FIG. 9. Peak and plateau concentrations and normalized AUCs for tissues evaluated in both males (n = 6) and females (n = 3).

However, rough relationships between total concentrations in tissue and MICs are suggested.

In general, all of the organs studied could be classified into four groups on the basis of the three pharmacokinetic parameters. The only exception was the myocardium, which was classified into group II on the basis of peak concentration and AUC and into group III on the basis of plateau concentration. This transition is probably related to the high blood flow to this organ. Overall, the concentrations of fleroxacin achieved in human tissue appear quite promising compared with the sensitivity of a wide range of microorganisms to fleroxacin. Thus, while the MICs for 90% of strains tested (MIC_{90}s) for virtually all members of the family *Enterobacteriaceae* are <0.5 μg/ml (with the MIC_{90} for *Serratia marcescens* of <1 μg/ml and that for *Providencia* species of <2 μg/ml), peak concentration of fleroxacin are well over 5 μg/g in all extracranial tissues after a standard 400-mg dose, with a sustained concentration above the MIC_{90} in virtually all tissues for at least 6 to 8 h. In addition, the MIC_{90}s for such organisms as *Acinetobacter anitratus* (4 μg/ml) and methicillin-sensitive and methicillin-resistant *S. aureus* (1 μg/ml) are also within reach of the levels of fleroxacin achieved in tissues (2, 6). Thus, this study suggests that fleroxacin should be particularly useful against urinary tract, gastrointestinal, hepatobiliary, skeletal, and pulmonary infections and that it has promise for the treatment of infections due to these organisms at other sites such as the prostate, uterus, and muscle. Conversely, the low concentration of drug delivered to the brain suggests that fleroxacin may not be useful in infections of the central nervous system, although these studies were performed with volunteers who presumably had noninflammed meninges. These pharmacokinetic findings are consistent with human studies in which fleroxacin had no effect on cerebral blood flow, metabolism, or oxygen consumption and indicate that fleroxacin may be superior to other fluoroquinolones in this regard (9, 17, 20). The high concentrations of fleroxacin measured in the bowel and visualization of the gall bladder in several of the subjects (data not shown) are consistent with a recent report of ~40% elimination via the gastrointestinal tract (48).

The lack of a significant effect of multiple dosing with unlabeled fleroxacin on the tissue and blood pharmacokinetics of [^{18}F]fleroxacin indicates that this treatment does not induce saturation or feedback effects on distribution or clearance. Unfortunately, the short physical half-life of ^{18}F limits the analysis of accumulation in deep tissue.

Recently, the results of ^{19}F NMRS of the in vivo pharmacokinetics of fleroxacin in liver and muscle tissue of humans were published (24). The results of that study demonstrated a pattern of fleroxacin pharmacokinetics in these two tissues similar to that observed in the present investigation. It should be pointed out, however, that the low spatial resolution of NMRS restricts measurements to large volumes of tissue, and absolute quantitation is difficult. However, what this study does suggest is the possibility of combining the measurements obtainable with the two techniques. Whereas PET can provide precise measurements of total drug concentrations present, NMRS could be used to determine the contributions of different molecular species present (intact drug plus metabolites) and possibly to differentiate between intra- and extracellular drug. In the case of fleroxacin, in which >90% of the drug is in the intact form, such a combination approach is probably not necessary. However, for other antimicrobial agents that undergo a greater degree of metabolism, such complex analysis could be extremely useful.

In summary, the promise of PET scanning for delineating the tissue distribution of fleroxacin, an important new fluoroquinolone, which was suggested in earlier animal studies (15, 34), has been confirmed in the present studies of human volunteers. At doses of drug utilized to treat clinical infec-

tion, effective concentrations of fleroxacin are delivered to essentially all tissues, with the notable exception of the central nervous system. The reproducibility of the results obtained, as well as the noninvasive nature of the studies, should permit application of the technique to the study of drug distribution to the actual tissue sites of infection in humans, permitting for the first time a correlation between therapeutic efficacy and drug distribution.

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