The Metabolism of Ofloxacin in Humans
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Ofloxacin (fig. 1), (\pm) -9-fluoro-2,3-dihydro-3-methyl-10- $(4-$ **The I**
Condition (organization), (the 1-piperazinyl)-7-oxo-7H-pyrido [1,2,
21 and 21 and 22 and 22 and 25 and Ofloxacin (fig. 1), (±)-9-fluoro-2,3-dihydro-3-methyl-10-(comethyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid, is a new broad spectrum antibacterial drug active against most Gram-negative ba Diloxacin (iig. 1), (± 1) -9-nuoro-2,3-umydio-3-neury-10-(4-
cmethyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxa-
zine-6-carboxylic acid, is a new broad spectrum antibacterial
drug active against most Gram-negat cmethyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxa-
zine-6-carboxylic acid, is a new broad spectrum antibacterial
drug active against most Gram-negative bacteria, many Gram-
positive bacteria, and some anaerobes. zine-6-carboxylic acid, is a new broad spectrum antibacterial
drug active against most Gram-negative bacteria, many Gram-
positive bacteria, and some anaerobes. It is currently under
investigation for urinary tract infecti drug active against most Gram-negative bacteria, many Gram-
positive bacteria, and some anaerobes. It is currently under
investigation for urinary tract infections and other indications
(1). Ofloxacin is a fluorinated quin positive bacteria, and some anaerobes. It is currently under investigation for urinary tract infections and other indications (1). Ofloxacin is a fluorinated quinolone and is structurally related to nalidixic acid, which e investigation for urinary tract infections and other indications (1). Ofloxacin is a fluorinated quinolone and is structurally related to nalidixic acid, which exerts its bactericidal activity through selective inhibition related to nalidixic acid, which exerts its bactericidal activity
through selective inhibition of bacterial DNA synthesis in the
presence of competent RNA and protein synthesis (2). The ex-
tent to which the quinolones are related to nalidixic acid, which exerts its bactericidal activity
through selective inhibition of bacterial DNA synthesis in the
presence of competent RNA and protein synthesis (2). The ex-
tent to which the quinolones are mough selective inhibition of bacterial DIVA synthesis in the
presence of competent RNA and protein synthesis (2). The ex-
tent to which the quinolones are metabolized appears to be
quite variable (3). This report describe besence of completent KIMA and protein synthesis (2). The extent to which the quinolones are metabolized appears to be quite variable (3). This report describes the metabolic fate of $[{}^{14}C]ofloxacin$ following administratio

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quite variable (3). This report describes the metabolic fate of $[{}^{14}C]$ ofloxacin following administration of single oral 400 mg
doses to human volunteers.
For this study, $[{}^{14}C]$ ofloxacin was synthesized with a spec doses to human volunteers.

For this study, $[^{14}C]$ ofloxacin was synthesized with a specific

activity of 5.2 μ Ci/mg. Chemical and radiochemical purity

(>95%) was established by HPLC. Unlabeled ofloxacin, des-

meth methylendian volumeters.

For this study, [¹⁴C]ofloxacin was synthesis

activity of 5.2 μCi/mg. Chemical and raas

(>95%) was established by HPLC. Unlabe

methyl ofloxacin [(±)-9-fluoro-2,3-dihydro-2

erazinyl)-7-oxo-7H activity of 5.2 μ Ci/mg. Chemical and radiochemical p
(>95%) was established by HPLC. Unlabeled ofloxacin,
methyl ofloxacin [(±)-9-fluoro-2,3-dihydro-3-methyl-10-(1-
erazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6 (>93%) was established by HPLC. Onlabeled onloxacin, des-
methyl ofloxacin [(±)-9-fluoro-2,3-dihydro-3-methyl-10-(1-pip-
erazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carbox-
ylic acid], and ofloxacin N-oxide [(±)methyl ofloxacin [(±)-9-fluoro-2,3-dihydro-3-methyl-10-(1-p
erazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carbo
ylic acid], and ofloxacin N-oxide [(±)-9-fluoro-2,3-dihydro
methyl-10-(4-methyl-1-piperazinyl)- 7-oxoerazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carbox-
ylic acid], and ofloxacin N-oxide [(±)-9-fluoro-2,3-dihydro-3-
methyl-10-(4-methyl-1-piperazinyl)- 7-oxo-7H - pyrido -[1,2,
3-de][1,4]benzoxazine-6-carboxylic ylic acid], and ofloxacin *N*-oxide [(±)-9-fluoro-2,3-dihydro-3-
methyl-10-(4-methyl-1-piperazinyl)- 7-oxo-7H - pyrido -[1,2,
3-de][1,4]benzoxazine-6-carboxylic acid piperazine-4-oxide]
were supplied by Daiichi Seiyaku Co. methyl-10-(4-methyl-1-piperazinyl)- 7-oxo-7H - pyrido -[1,2, 3-de][1,4]benzoxazine-6-carboxylic acid piperazine-4-oxide] were supplied by Daiichi Seiyaku Co., Tokyo, Japan. Six normal male volunteers were administered sin S -defi 1,4 joenzoxazine-o-carooxyinc acid piperazine-4-oxide)
were supplied by Daiichi Seiyaku Co., Tokyo, Japan. Six normal
male volunteers were administered single oral doses (100 μ Ci,
400 mg) of [¹⁴C]ofloxacin a male volunteers were administered single oral doses $(100 \mu\text{Ci})$, 400 mg) of [¹⁴C]ofloxacin as a peppermint-flavored solution in water (Peninsula Testing Corporation, Miami, FL). Smoking and the intake of caffeinated b 400 mg) of $[14C]$ ofloxacin as a peppermint-flavored solution in water (Peninsula Testing Corporation, Miami, FL). Smoking and the intake of caffeinated beverages were not allowed for 12 hr before and 12 hr after drug adm water (Peninsula Testing Corporation, Miami, FL). Smoking and
the intake of caffeinated beverages were not allowed for 12 hr
before and 12 hr after drug administration. Alcohol intake was
denied for 24 hr before and 72 hr the make of cantenated beverages were not anowed for 12 in
before and 12 hr after drug administration. Alcohol intake was
denied for 24 hr before and 72 hr after administration. Serial
plasma samples were collected for 48 before and 12 at after drug administration. Alcohor make was
denied for 24 hr before and 72 hr after administration. Serial
plasma samples were collected for 48 hr after the dose. Plasma
concentrations of ofloxacin were me by noncompartmental linear pharmacokinetic methods. Urine and feces were collected for 48 hr after the dose. Plasma concentrations of ofloxacin were measured by HPLC using a previously described method (4), and these data Concentrations of onoxacin were measured by HFLC using a
previously described method (4), and these data were analyzed
by noncompartmental linear pharmacokinetic methods. Urine
and feces were collected in 12- or 24-hr inte by noncompartmental linear pharmacokinetic methods. Urine
by noncompartmental linear pharmacokinetic methods. Urine
and feces were collected in 12- or 24-hr intervals after dosing.
Radioactivity in the urine samples was de and feces were collected in 12- or 24-hr intervals after dosing.

Radioactivity in the urine samples was determined by liquid

scintillation counting. Feces were homogenized after dilution

with methanol/water (50:50, v/v Radioactivity in the unne samples was determined by fiquid
scintillation counting. Feces were homogenized after dilution
with methanol/water (50:50, v/v). Aliquots of fecal homogenates
were combusted in a sample oxidizer a scintification counting. Peces were nonfogenized after diffusion
with methanol/water (50:50, v/v). Aliquots of fecal homogenate
were combusted in a sample oxidizer and analyzed by liquid
scintillation counting. Radioactivi with methanoly water (50:50, v/v). And does or lecal homogenates
were combusted in a sample oxidizer and analyzed by liquid
scintillation counting. Radioactivity in all samples was measured
in Scinti-Verse Bio HP scintill were comousted in a sample oxidizer and analyzed by induct

scintillation counting. Radioactivity in all samples was measured

in Scinti-Verse Bio HP scintillation fluid (Fisher Scientific, Fair-

flawn, NJ). To obtain met in Scinti-Verse Bio HP scintillation fluid (Fisher Scientific, Fair-
lawn, NJ). To obtain metabolite profiles, samples of urine and
fecal homogenate collected up to 48 hr after administration of
fecal homogenate collected acetate/methanol/phosphoric The analyzed by direct injection onto a Lichro-

[¹⁴C]ofloxacin were analyzed by direct injection onto a Lichro-

sorb SI-100 column (4.6 mm \times 25 cm) and isocratic elution with

tetrahydrofuran/ethyl acetate/methanol sorb SI-100 column (4.6 mm \times 25 cm) and isocratic elution with
tetrahydrofuran/ethyl acetate/methanol/phosphoric acid
(44:30:18:8, $v/v/v/v$) at a flow rate of 1.0 ml/min. The eluent
was monitored at 254 nm and passed dir Instrument Corp., Tampa, FL). Radioactivity in the eluent Corp., Tampa, FL). Radioactivity flow detector (Radiomatics). To massured in Flo-Scint II scintillation fluid (Radiomatics). To measured in Flo-Scint II scintillat detector to a model HS radioactivity flow detector (Radiomatics Instrument Corp., Tampa, FL). Radioactivity in the eluent was

Pharmaceutical Research Institute, Ortho Pharmaceutical Corporation, Route 202

OFLOXACIN N-OXIDE (III)

FIG. 1. The structure of ofloxacin and its metabolites.

*, Indicates position of the ¹⁴C-label.

measured in Flo-Scint II scintillation fluid (Radiomatics). To

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Send reprint requests to: F. A. Wong, Drug Metabolism Division, R. W. Johnson

Pharmaceutical Research In FIG. 1. *The structure of ofloxacin and its metabolites.*

*, Indicates position of the ¹⁴C-label.

confirm the structures of the principal metabolites, pooled urine

samples (0–48 hr) were percolated through a Chemtube FRG. 1. The structure of official and its metabolites.

*, Indicates position of the ¹⁴C-label.

confirm the structures of the principal metabolites, pooled urine

samples (0-48 hr) were percolated through a Chemtube CT-^{*}, Indicates position of the ¹⁴C-label.
confirm the structures of the principal metabolites, pooled us
samples (0–48 hr) were percolated through a Chemtube CT-2
column (Analytichem International, Harbor City, CA). Qua
 confirm the structures of the principal metabolites, pooled urine
samples (0–48 hr) were percolated through a Chemtube CT-2030
column (Analytichem International, Harbor City, CA). Quanti-
tative recovery of the radioactivi samples (0–48 hr) were percolated through a Chemtube CT-2030
column (Analytichem International, Harbor City, CA). Quanti-
tative recovery of the radioactivity was achieved by washing the
column successively with methylene column (Analytichem International, Harbor City, CA). Quanticolumn (Analytichem international, riarbor City, CA). Quanti-
tative recovery of the radioactivity was achieved by washing the
column successively with methylene chloride, methylene chlo-
ride/methanol (80:20, v/v), and me column successively with methylene chloride, methylene chloride/methanol (80:20, v/v), and methanol. Fractionation of the radioactivity was carried out by preparative TLC on 1-mm silica plates (Whatman, Clifton, NJ) using rial profile comparisons of the radioactivity was carried out by preparative TLC on 1-mm silica
plates (Whatman, Clifton, NJ) using methylene chloride/meth-
anol/ammonia (66:33:5, $v/v/v$) as the developing solvent. Co-
chro plates (Whatman, Clifton, NJ) using methylene chloride/meth-
anol/ammonia (66:33:5, v/v/v) as the developing solvent. Co-
chromatographic comparisons of synthetic standards with oflox-
acin and its metabolites confirmed th chromatographic comparisons of synthetic standards with oflox-
acin and its metabolites confirmed the absence or presence of
these compounds. The more polar urinary metabolites were
further purified by normal phase HPLC o acin and its metabolites confirmed the absence or presence of acin and its metaoonies committed the absence or presence or
these compounds. The more polar urinary metabolites were
further purified by normal phase HPLC on an Alltech SI-100
column (4.6 mm × 25 cm) and eluted isocratica these compounds. The more polar urinary metabolites were
further purified by normal phase HPLC on an Alltech SI-100
column (4.6 mm \times 25 cm) and eluted isocratically with ethy
acetate/methanol/trifluoroacetic acid (50:5 ly in the purined by normal phase $HPLC$ on an Altiech S1-100
column (4.6 mm \times 25 cm) and eluted isocratically with ethyl
acetate/methanol/trifluoroacetic acid (50:50:1, v/v/v) at a flow
rate of 1.5 ml/min. Metabolites column (4.6 mm × 2.5 cm) and ethed isocratically with ethyl
acetate/methanol/trifluoroacetic acid (50:50:1, $v/v/v$) at a flow
rate of 1.5 ml/min. Metabolites isolated from urine were ana-
lyzed on a Finnigan model 8230 mass acetate/methanol/trinuoroacetic acid (50:50:1, v/v/v) at a now
rate of 1.5 ml/min. Metabolites isolated from urine were ana-
lyzed on a Finnigan model 8230 mass spectrometer. Negative
ion direct chemical ionization experim lyzed on a Finnigan model 8230 mass spectrometer. Negative
ion direct chemical ionization experiments were run at 1.1 torr
using 1% ammonia in methane. After molecular ion spectra were
generated for the standards, the pur In direct chemical ionization experiments were run at 1.1 torr
ing 1% ammonia in methane. After molecular ion spectra were
nerated for the standards, the purified metabolites were sub-
ted to the same ionization technique

*frace 6 and 6 and 6 and 72 different 6 and 72 different minum CFC billions***
frecal samples collected 4-8 and 24-48 hr. respectively, after oral
daministration of [¹⁴C]ofloxacin to male volunteers.** *administration of* $\int^{14}C$ *Jofloxacin to male volunteers.*
Solid lines represent UV response; *broken lines represent radioactivity Solid lines representative HPLC profiles of the radioactivity in urine and*
fecal samples collected 4–8 and 24–48 hr, respectively, after oral
administration of [¹⁴C]ofloxacin to male volunteers.
Solid lines repres

response.

Solid lines represent UV response; *broken lines* represent radioactivity
response.
3.4 μ g/ml, and the time of maximum plasma concentration
(t_{max}) occurred from 0.5 to 1.5 hr after drug administration.
The harmonic The harmonic mean *t_w* value for the disappearance of ofloxacin

The harmonic mean *t_w* value for the disappearance of ofloxacin

The harmonic mean *t_w* value for the disappearance of ofloxacin

from plasma was 6.4 3.4 μ g/ml, and the time of maximum plasma concentration syn
 (t_{max}) occurred from 0.5 to 1.5 hr after drug administration.

The harmonic mean t_v value for the disappearance of ofloxacin

from plasma was 6.4 hr, w 3.4 μ g/ml, and the time of maximum plasma concentration (t_{max}) occurred from 0.5 to 1.5 hr after drug administration.
The harmonic mean t_{w} value for the disappearance of ofloxacin from plasma was 6.4 hr, wh (t_{max}) occurred from 0.5 to 1.5 in after drug administration.
The harmonic mean t_n value for the disappearance of ofloxacin
from plasma was 6.4 hr, while the mean AUC value was 28.3
 μ g.hr/ml, consistent with the The harmonic mean t_w value for the disappearance of ofloxacin
from plasma was 6.4 hr, while the mean AUC value was 28.3
 μ g·hr/ml, consistent with the results of a previous investigation
(5). Approximately 79% of the from plasma was 6.4 hr, while the mean AUC value was 28.3 μ g.hr/ml, consistent with the results of a previous investigation Dr (5). Approximately 79% of the dose was recovered in the urine R. and 8% in the feces during μ g. hr/ml, consistent with the results of a previous investigation *Drug M*(5). Approximately 79% of the dose was recovered in the urine *R. W.* and 8% in the feces during the 7 days following drug administra- *Ortho* (5). Approximately 79% of the dose was recovered in the urine R.
and 8% in the feces during the 7 days following drug administra-
tion. Nearly 71% of the dose was eliminated in urine within the
first day. HPLC analysis of and 8% in the feces during the 7 days following drug administra-
tion. Nearly 71% of the dose was eliminated in urine within the
first day. HPLC analysis of urine samples indicated that 90–95%
of the radioactivity was asso ion. Nearly 71% of the dose was eliminated in urine within the
first day. HPLC analysis of urine samples indicated that 90–95%
of the radioactivity was associated with intact of loxacin, while
the desmethyl and *N*-oxide m first day. HPLC analysis of urine samples indicated that 90–95%
of the radioactivity was associated with intact ofloxacin, while
the desmethyl and *N*-oxide metabolites each accounted for about
1%. In the fecal samples, of of the radioactivity was associated with intact of covacin, while
the desmethyl and *N*-oxide metabolites each accounted for about
1%. In the fecal samples, of loxacin generally accounted for about
80% of the radioactivity 1%. In the fecal samples, of loxacin generally accounted for about

80% of the radioactivity while desmethyl of loxacin and of loxacin

80% of the radioactivity while desmethyl of loxacin and of loxacin

80% of the radioa profiles from the urinary and fecal samples are shown in fig. 2. N-oxide each accounted for nearly 7%. The remainder of tradioactivity in both the urine and feces was associated with more polar, unknown metabolite. Representative HPLC elution profiles from the urinary and fecal samples radioactivity in both the urine and feces was associated with
more polar, unknown metabolite. Representative HPLC eluti
profiles from the urinary and fecal samples are shown in fig.
Upon percolation of the 0–48 hr urine po more polar, unknown metabolite. Representative HPLC elution
profiles from the urinary and fecal samples are shown in fig. 2.
Upon percolation of the 0–48 hr urine pool through the Chem-
tube column, 94% of radioactivity w profiles from the urinary and fecal samples are shown in fig. 2.
Upon percolation of the 0–48 hr urine pool through the Chem-
tube column, 94% of radioactivity was recovered in the methyl-
ene chloride eluate. Radiochromat Chemical ionization of the 0-46 in unite poor unlogging the Chemical
tube column, 94% of radioactivity was recovered in the methyl-
ene chloride eluate. Radiochromatography indicated that nearly
all of this radioactivity tube column, 94% of radioactivity was recovered in the methyl-
ene chloride eluate. Radiochromatography indicated that nearly
all of this radioactivity (R_F, 0.5) was associated with ofloxacin.
Chemical ionization mass s ene chloride eluate. Radiochromatography indicated that nearly
all of this radioactivity $(R_F, 0.5)$ was associated with ofloxacin.
Chemical ionization mass spectral analysis of this material
yielded an intense molecular i all of this radioactivity (R_F , 0.5) was associated with ofloxacin.
Chemical ionization mass spectral analysis of this material
yielded an intense molecular ion at m/z 361 and diagnostic
fragment ions at m/z 319, 294, Chemical ionization mass spectral analysis of this material
yielded an intense molecular ion at m/z 361 and diagnostic
fragment ions at m/z 319, 294, and 127. This spectrum was
identical to that of standard compound. Ra yielded an intense molecular ion at m/z 361 and diagnostic fragment ions at m/z 319, 294, and 127. This spectrum was identical to that of standard compound. Radiochromatography of the methylene chloride/methanol eluate fragment ions at m/z 319, 294, and 127. This spectrum was
identical to that of standard compound. Radiochromatography
of the methylene chloride/methanol eluate from the Chemtube
column showed the presence of two peaks, e

propene), consistent with the structure of desmethyl ofloxacin, WONG AND FLOR
and 0.2, respectively, and were associated with the desmethyl
and N-oxide metabolites. Mass spectral analysis of the material at R_F 0.4 vielded an intense molecular ion at m/z 347 as well as D FLOR
and 0.2, respectively, and were associated with the desmethyl
and *N*-oxide metabolites. Mass spectral analysis of the material
at R_F 0.4 yielded an intense molecular ion at m/z 347 as well as
a prominent fragme and 0.2, respectively, and were associated with the desmethyl
and *N*-oxide metabolites. Mass spectral analysis of the material
at R_F 0.4 yielded an intense molecular ion at m/z 347 as well as
a prominent fragment ion and 0.2, respectively, and were associated with the desmethyl
and *N*-oxide metabolites. Mass spectral analysis of the material
at R_F 0.4 yielded an intense molecular ion at m/z 347 as well as
a prominent fragment ion and *N*-oxide metabolites. Mass spectral analysis of the material
at R_F 0.4 yielded an intense molecular ion at m/z 347 as well as
a prominent fragment ion at m/z 305 (resulting from loss of
propene), consistent with a prominent fragment ion at m/z 305 (resulting from loss of propene), consistent with the structure of desmethyl of loxacin, while analysis of material at R_F 0.2 yielded a molecular ion at m/z 377 as well as prominent while analysis of material at R_F 0.2 yielded a molecular ion at m/z 377 as well as prominent fragment ions at m/z 361 (resulting from the loss of oxygen) and 319 (resulting from loss of propene), which were consistent while analysis of material at R_F 0.2 yielded a molecular ion at m/z 377 as well as prominent fragment ions at m/z 361 (resulting from the loss of oxygen) and 319 (resulting from loss of propene), which were consistent m/z 377 as well as prominent fragment ions at m/z 361 (resulting
from the loss of oxygen) and 319 (resulting from loss of propene),
which were consistent with the structure of ofloxacin N-oxide.
The remainder of the uri which were consistent with the structure of ofloxacin N-oxide.
The remainder of the urinary radioactivity (3%) , obtained in the
methanolic eluate from the Chemtube column, was associated
with a polar metabolite, which, which were consistent with the structure of ofloxacin *N*-oxide.
The remainder of the urinary radioactivity (3%), obtained in the
methanolic eluate from the Chemtube column, was associated
with a polar metabolite, which, The remainder of the urinary radioactivity (3%), obtained in the methanolic eluate from the Chemtube column, was associate with a polar metabolite, which, upon mass spectral analysiveled a strong fragment at m/z 361, the methanonc enate from the chemicle column, was associated
with a polar metabolite, which, upon mass spectral analysis,
yielded a strong fragment at m/z 361, the molecular ion of
ofloxacin. Furthermore, treatment of this ma yielded a strong fragment at m/z 361, the molecular ion of ofloxacin. Furthermore, treatment of this material with β -glu-
curonidase (type H-5; *Helix pomatia*; 400,000–600,000 units/g, Sigma Chemical Co., St. Louis, ofloxacin. Furthermore, treatment of this material with β -glu-
curonidase (type H-5; *Helix pomatia*; 400,000–600,000 units/g,
Sigma Chemical Co., St. Louis, MO) resulted in the quantitative
recovery of radioactivity a drug. gma Chemical Co., St. Louis, MO) resulted in the quantitative covery of radioactivity as intact of loxacin. Thus, it would pear that this metabolite is a glucuronide conjugate of parent ug.
In conclusion, this study has sh

FIG. 2. *Representative HPLC profiles of the radioactivity in urine and*
FIG. 2. *Representative HPLC profiles of the radioactivity in urine and*
FIG. 2. *Representative HPLC profiles of the radioactivity in urine an* recovery of radioactivity as intact ofloxacin. Thus, it would
appear that this metabolite is a glucuronide conjugate of parent
drug.
In conclusion, this study has shown that following a single oral
dose to humans, ofloxaci appear that this includent is a glucureline conjugate of parent
drug.
In conclusion, this study has shown that following a single oral
dose to humans, ofloxacin is rapidly absorbed and eliminated,
primarily in the urine. I In conclusion, this study has shown that following a single of dose to humans, of loxacin is rapidly absorbed and eliminated primarily in the urine. In both urine and feces, the drug eliminated mostly unchanged. Oxidative In conclusion, this study has shown that following a single oral
dose to humans, ofloxacin is rapidly absorbed and eliminated,
primarily in the urine. In both urine and feces, the drug is
eliminated mostly unchanged. Oxida dose to humans, ofloxacin is rapidly absorbed and elimina
primarily in the urine. In both urine and feces, the dru
eliminated mostly unchanged. Oxidative N-dealkylation, N-
dation, and glucuronidation, the only observable strate the matrix of the time. In hoth unit following a single or particular

drug.

In conclusion, this study has shown that following a single oral

of the umic. In both urine and feces, the drug is

eliminated mostly u dation, and glucuronidation, the only observable pathways, extensively investigated (6, 7).
Acknowledgments. We wish to thank Dr. P. L. Chien for the

synthesis of the [¹⁴C]ofloxacin, Dr. David Burinsky for helpful mation of the drug in humans appears to be nearly identical to
that in animals (rats, dogs, and monkeys), where it has been
extensively investigated (6, 7).
Acknowledgments. We wish to thank Dr. P. L. Chien for the
synthes **Example Branch Community Division, Dr. David Burinsky for helpful discussions, and Dr. S. M. Huang, Mr. S. Juzwin, and Ms. H. T.

Phan for their technical assistance.

Drug Metabolism Division, F. A. Wong R. W. Johnson Ph Phan** for their technical assistance.

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