PRODUCT MONOGRAPH

NOROXIN®

(norfloxacin tablets, USP)

400 mg

THERAPEUTIC CLASSIFICATION

ANTIBACTERIAL AGENT

MERCK FROSST CANADA LTD.
KIRKLAND, QUEBEC, CANADA

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ACTION AND CLINICAL PHARMACOLOGY

NOROXIN® (norfloxacin) is a quinolone carboxylic acid antibacterial agent for oral administration. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal.

At the molecular level three specific actions have been attributed to norfloxacin in the inhibition of *E. coli* cells:

1) inhibition of the ATP-dependent DNA supercoiling reaction catalyzed by DNA gyrase,
2) inhibition of the relaxation of supercoiled DNA,
3) promotion of double-stranded DNA breakage.

INDICATIONS AND CLINICAL USE

The treatment of upper and lower urinary tract infections, specifically complicated and uncomplicated cystitis, pyelitis and pyelonephritis caused by susceptible strains of the following microorganisms:

Escherichia coli,
Klebsiella pneumoniae,
unspecified *Klebsiella* spp.,
unspecified *Enterobacter* spp.,
unspecified *Citrobacter* spp.,
Proteus mirabilis,
Staphylococcus aureus,
Streptococcus faecalis,
Pseudomonas aeruginosa,

The treatment of adults with gonococcal urethritis, or cervicitis due to penicillinase-producing and non-penicillinase-producing *Neisseria gonorrhoeae.*

Appropriate culture and susceptibility studies should be carried out prior to initiation of therapy with NOROXIN® (norfloxacin) and if clinically indicated during treatment. Therapy may be initiated before obtaining results of these tests (see MICROBIOLOGY), however, modification of such treatment may be required once the results become available.

CONTRAINDICATIONS

NOROXIN® (norfloxacin) is contraindicated in patients with known hypersensitivity to norfloxacin, to any component of this product or to other quinolone antibacterial agents.

WARNINGS

The safety of NOROXIN® (norfloxacin) in children is unknown. NOROXIN® should not be given to patients in whom epiphyseal closure has not occurred. In two animal species (dogs and rabbits) in which norfloxacin was administered to young animals, lameness and lesions (i.e., blister formation and eventual erosion) of the articular cartilage of the weight bearing joints were observed. In young dogs this occurred following a single dose several times the

recommended human dose. These changes were not observed in dogs 6 months of age or older. Similar changes in animals have been observed with other structurally related drugs.

NOROXIN® should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures. Convulsions have been reported rarely in patients receiving NOROXIN®; however, a causal relationship to NOROXIN® has not been established.

The safety of use of NOROXIN® in the treatment of infections in pregnant women is not established.

PRECAUTIONS

General

NOROXIN® (norfloxacin) should be used with caution in patients with a history of convulsions.

During therapy with NOROXIN®, patients should be reminded to drink sufficient amount of fluids to maintain adequate hydration in order to avoid possible development of crystalluria.

As with other quinolones, tendinitis and/or tendon rupture have been observed rarely in patients taking NOROXIN®, especially when corticosteroids are taken concomitantly. If a patient develops symptoms of tendinitis and/or tendon rupture, NOROXIN® should be discontinued immediately and the patient advised to seek appropriate medical management.

Rarely, hemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including NOROXIN® (see ADVERSE REACTIONS).

Photosensitivity reactions have been observed in patients exposed to sunlight while receiving quinolone antibiotics. While taking NOROXIN®, excessive exposure to sunlight should be avoided and therapy discontinued if photosensitivity should occur.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including NOROXIN®, in patients with myasthenia gravis (see ADVERSE REACTIONS).

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking norfloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to norfloxacin has not been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents.

Use in Obstetrics

The safety of use of NOROXIN® in the treatment of infections in pregnant women is not established; consider its use only if the anticipated benefits to the mother justifies the potential risks to the fetus. Following a single dose of 200 mg norfloxacin concentrations in umbilical cord serum ranged from non detectable levels to 0.5 mg/L and in amniotic fluid from non detectable levels to 0.92 mg/L. The pharmacokinetics of norfloxacin in pregnant patients have not been investigated.

Reproduction studies have been carried out in the mouse, rat, rabbit and monkey. Norfloxacin did not show any teratogenic effects in these studies. In the monkey, however, an increased incidence of embryonic loss has been observed at a dosage of 10 times the human dose which result in peak plasma levels approximately 2 to 3 times that in humans. In the rabbit, embryonic loss was observed when norfloxacin was given by the oral route but not by the subcutaneous route. The clinical significance of the study results observed in rabbits and monkeys is not known (see TOXICOLOGY).

Nursing Mothers

Norfloxacin was not detected in human milk following a single 200 mg dose. However, because this dose was low (half the recommended single dose) and as many drugs are secreted in human milk, caution should be exercised if NOROXIN® is to be administered to a nursing woman.

Elderly

Alterations in dosage are not recommended (see DOSAGE AND ADMINISTRATION and HUMAN PHARMACOLOGY). When NOROXIN® was administered to 4 females and 2 males, 67 to 74 years old, with normal renal function for their age, [i.e., creatinine clearance of 1.52 mL ± 0.2 mL/s/1.73 m^2 (91±14 mL/min/1.73 m^2)], the plasma half-life of the drug was only slightly prolonged.

Drug Interactions

Since urinary excretion of norfloxacin is diminished by concomitant administration of probenecid, NOROXIN® should not be administered concomitantly with probenecid.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline-related adverse reactions in patients on concomitant therapy with NOROXIN® and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporine have been reported with concomitant use with NOROXIN®. Therefore, cyclosporine serum levels should be monitored and appropriate cyclosporine dosage adjustments made when these drugs are used concomitantly.

NOROXIN® may enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glyburide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, products containing iron or zinc, antacids, sucralfate or didanosine (Videx) should not be administered concomitantly with, or within two hours of, the administration of NOROXIN® because they may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

NOROXIN® has been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

Antagonism has been demonstrated *in vitro* between NOROXIN® and nitrofurantoin.

Renal Impairment

Since norfloxacin is eliminated primarily by the kidney, NOROXIN® should be used with caution and at a reduced dosage in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). NOROXIN® is not recommended for anuric patients.

There is insufficient data on which to have a dosage recommendation for the treatment of gonorrhea in patients with a creatinine clearance of 0.5 mL/s/1.73 m^2 (30 mL/min/1.73 m^2) or less.

ADVERSE REACTIONS

NOROXIN® (norfloxacin) is generally well tolerated. In controlled clinical trials involving 1,528 patients, the overall incidence of drug-related adverse reactions was approximately 3%. The following adverse reactions were reported:

Gastrointestinal System	**Incidence (%)**
Nausea	2.0
Dyspepsia	0.3
Flatulence	0.3
Heartburn	0.3
Abdominal pain	0.3
Vomiting	0.2
Diarrhea	0.2
Anorexia	0.1
Nervous System	
Headache	1.6
Dizziness/Lightheadedness	1.2
Drowsiness	<1.0
Mood alterations	<1.0
Anxiety disorders	2 cases
Depression	4 cases
Disorientation	1 case
Dream abnormalities	1 case
Euphoria	2 cases
Explosive personality disorder	1 case
Hallucinations	1 case
Irritability	1 case
Nervousness	2 cases
Paresthesia	<1.0
Visual disturbances	<0.1
Epiphora	1 case
Insomnia	<0.4
Musculoskeletal System	

Tendinitis	0.1
Arthralgia	0.1

Hypersensitivity Reactions

Rash	0.4
Erythema	0.2
Urticaria	0.1
Pruritus	0.1

The following additional adverse reactions have been reported since the drug was marketed:

Musculoskeletal System

Tendon rupture
Exacerbation of myasthenia gravis
Elevated creatine kinase (CK)

Body as a Whole/Site Unspecific

Asthenia/fatigue

Hypersensitivity Reactions

Anaphylaxis
Angioedema
Dyspnea
Vasculitis
Urticaria
Arthritis
Myalgia
Interstitial nephritis

Ocular

Conjunctivitis
Eye pain/irritation

Skin

Photosensitivity
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Exfoliative dermatitis
Erythema multiforme
Pruritus

Gastrointestinal

Constipation
Flatulence
Pseudomembranous colitis
Pancreatitis (rare)
Hepatitis, jaundice, including cholestatic jaundice

Nervous System/Psychiatric

Convulsions
Confusion
Paresthesia
Polyneuropathy including Guillain-Barré syndrome
Psychic disturbances including psychotic reactions
Somnolence
Tremors
Myoclonus

Hematologic

Hemolytic anemia
Thrombocytopenia

Renal Function

Renal Failure

Special Senses

Tinnitus
Dysgeusia
Visual Disturbances

Genitourinary

Vaginal candidiasis

Laboratory

Abnormal adverse reactions observed rarely in clinical trials include leukopenia, eosinophilia, neutropenia, proteinuria and elevation of ALAT (SGPT), ASAT (SGOT), alkaline phosphatase, bilirubin, increased BUN, serum creatinine, and LDH, and decreased hematocrit.

On very rare occasions,the following have been reported:

Hypertonia
Dyspnea
Ataxia
Dysarthria
Dysphasia
Hemophthalmia
Nystagmus
Periorbital erythema
Fever
Dry mouth
Transient hearing loss

Others

Although the following adverse reactions were not observed in these clinical trials with NOROXIN®, they have been reported following treatment with other quinolone antibacterial agents:

- hemolytic anemia in patients with latent or actual defects in glucose-6-phosphate dehydrogenase (G6PD) activity
- restlessness
- bullae
- palpitation
- soreness of the gums
- joint stiffness
- swelling of the extremities
- metallic taste
- toxic psychosis (rare)
- perineal burning
- vertigo
- edema
- cholestasis

- metabolic acidosis
- (signs and symptoms of increased intracranial pressure in infants and children which usually disappeared rapidly with no sequelae when treatment was discontinued)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There has not been any case of overdose with NOROXIN® (norfloxacin) reported to date; consequently, neither the signs nor the symptoms of overdosage have been identified.

In the event of recent acute overdose, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration should be maintained to avoid the possible development of crystalluria. Norfloxacin is not dialyzable.

DOSAGE AND ADMINISTRATION

Adults:

The recommended dosage of NOROXIN® (norfloxacin) for urinary tract infections is one 400 mg tablet twice a day taken with a glass of water at least one hour before, or two hours after a meal or milk ingestion for 7-10 days.

For women with uncomplicated acute cystitis, the duration of therapy can be reduced to three (3) days.

For adults with gonococcal urethritis or cervicitis, the recommended dosage of NOROXIN® is two 400 mg tablets (800 mg) given as a single dose.

Elderly:

The recommended dosage of NOROXIN® in elderly patients with normal renal function for their age is the same as given for adults above.

Impaired Renal Function:

NOROXIN® may be used in the treatment of patients with renal insufficiency who do not require hemodialysis.

In patients with a glomerular filtration rate of less than 0.50 mL/s/1.73 m^2 (30 mL/min/1.73 m^2) but greater than 0.11 mL/s/1.73 m^2 (6.6 mL/min/1.73 $m^{2)}$ the recommended dose is one 400 mg tablet once daily (see PRECAUTIONS).

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males: $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$

Females: 0.85 x above value

To convert to international units multiply result by 0.01667

The administration of NOROXIN® to anuric patients is not recommended.

Children:

The safety and efficacy of NOROXIN® in prepubertal children have not been established. NOROXIN® should not be used in patients in whom epiphyseal closure has not occurred (see WARNINGS).

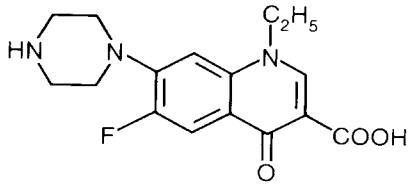
PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

Proper name: norfloxacin

Chemical name: 1-ethyl-6-fluoro-1,4 dihydro-4-oxo-7-(1- piperazinyl)-3-quinoline carboxylic acid.

Structural formula:



Molecular formula: $C_{16}H_{18}FN_30_3$

Molecular weight: 319.34

Description: Norfloxacin is an odourless, white to pale yellow crystalline powder with a bitter taste and a melting point of 220-224°C. It is freely soluble in glacial acetic acid; sparingly soluble in dichloromethane; slightly soluble in acetone and chloroform; very slightly soluble in ethanol, methanol, ethyl acetate and benzene; and practically insoluble in water. Solubility in water is minimal between pH 6.0 to 10. Dissociation constants are: pKa_1 = 6.3 and pKa_2 = 8.8.

II. COMPOSITION

Each tablet contains the following non-medicinal ingredients: carnauba wax, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, titanium dioxide, and red ferric oxide.

III. STABILITY AND STORAGE RECOMMENDATIONS

Store tablets at 15° - 30°C in tightly closed containers, protected from heat, moisture and direct light.

AVAILABILITY OF DOSAGE FORMS

NOROXIN® (norfloxacin tablets, USP) 400 mg are oval shaped, dark pink, film coated compressed tablets engraved “NOROXIN” on one side and “MSD 705" on the other. Available in bottles of 30 tablets.

INFORMATION FOR THE PATIENT

NOROXIN® Tablets

NOROXIN® is the brandname of Merck Frosst Canada Ltd. for the substance norfloxacin, available **only on prescription** from your physician. Norfloxacin is one of a group of medicines known as antibacterials. Antibacterials are used to treat infections caused by bacteria or germs; norfloxacin works against a large variety of species of bacteria, killing them or preventing them from developing.

Norfloxacin has been prescribed by your physician to treat an infection of the urogenital tract.

Remember: - This medicine is prescribed for the particular infection you have at this time. **Do not give to other people, nor use this for other infections.**

Keep all medicines out of the reach of children.

Read the following information carefully. **If you need any explanations, or further information, ask your physician or pharmacist.**

BEFORE TAKING THIS MEDICINE

This medicine may not be suitable for certain people. So, tell your physician if you think any of the following applies to you:

- You have previously taken norfloxacin or any related medicines, example, ciprofloxacin (Cipro) or nalidixic acid (NegGram), and were allergic, or had reacted badly to it.

- You suffer from kidney disease.

- You have any heart rhythm problems.

- You have ever suffered from convulsions.

- You are pregnant or intend to become pregnant or are breast-feeding or intend to breast-feed.

- Inform your physician if you are taking any of the following medications: probenecid, nitrofurantoin, theophylline, cyclosporine, blood thinning medicines, glyburide (a sulfonylurea agent), didanosine, multivitamins or products containing iron, zinc, caffeine.

- Also inform your physician if you are taking any other medications (prescription or non-prescription drugs).

This medicine is not recommended for children before puberty.

PROPER USE OF THIS MEDICINE

- Take this medicine exactly as your physician ordered for the specified number of days. **Do not stop even if you feel better. Stopping too soon might bring on your symptoms again.**

- It is best to take the tablet one hour **before**, or two hours **after** a meal or milk ingestion, with **a full glass of water**. It is good to drink plenty of liquids - water or juice - every day, unless your physician has told you otherwise. NOROXIN® should not be taken within two hours of taking iron, zinc supplements or multivitamins containing them.

- Sucralfate (Sulcrate), antacids (such as Diovol, Maalox or Amphojel), and didanosine (Videx) may interact with this medicine. If you have to take these medications, take them at least two to three hours before or after you take norfloxacin.

- If you forget to take a dose, take the recommended dose next time, as scheduled. **Do not double the dose to make up.** If you happen to take too

many tablets by accident, contact your physician or pharmacist as **soon** as possible.

- If you develop any new medical problem while using this medicine, or you wish to begin using any other medicine, on prescription or not, check with your physician or pharmacist.

- Store your tablets at 15°-30°C in a tightly-closed container, away from heat and direct light, and out of damp places such as the bathroom or kitchen.

SIDE EFFECTS OF THIS MEDICINE - AND WHAT YOU SHOULD DO

Along with its intended action, any medication, including norfloxacin, may cause side effects. Most people do not have any problem when taking this medicine; but if you notice any of the following effects, check with your physician or pharmacist as soon as possible:

- Dizziness, headache

- If you experience any of the above effects, or visual problems, avoid driving and any other activity or job that requires alertness, coordination or good vision.

Other possible effects which occur less commonly are: confusion, convulsions (seizures), swollen or inflamed joints, abdominal or stomach pain with: indigestion, gas, nausea, vomiting, diarrhea or loss of appetite; heartburn, rash, drowsiness and trouble sleeping.

STOP TAKING NOROXIN® AND CONTACT YOUR DOCTOR IMMEDIATELY IN ANY OF THE FOLLOWING CASES:

If you develop allergic reactions such as swelling of the face, lips and/or throat (with difficulty in breathing or swallowing), or hives;

If you develop skin reactions, including severe reaction to sunlight, such as rash, redness or increased sensitivity of skin or eyes to sunlight, swelling or blistering. **Stay out of direct sunlight**, wear protective clothing and use a sunblock preparation.

If you develop pain in your tendons (tendinitis, tendon rupture);

If you experience any worsening of your myasthenia gravis symptoms;

If you develop any signs of mental disturbances, including mood changes such as anxiety or depression.

Some people may have other reactions. If you notice any unusual effect, check with your physician or pharmacist.

INGREDIENTS

Active ingredient: Each tablet of NOROXIN® contains 400 mg of norfloxacin.

Non-medicinal ingredients: carnauba wax, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, titanium dioxide, and red ferric oxide.

MICROBIOLOGY

The *in vitro* activity of norfloxacin against clinical isolates of gram-positive and gram-negative aerobic bacteria is shown in Table 1. Susceptibility was determined by both agar and broth dilution tests, pH 7.1-7.4, using inoculum sizes ranging from 10^4 to 10^5 colony-forming units (cfu) per mL. Norfloxacin lacks useful activity against *Actinomyces* spp., *Fusobacterium* spp., *Bacteroides* spp., and *Clostridium* spp., other than *C. perfringens.*

The minimal inhibitory concentrations (MICs) of norfloxacin against aerobic bacteria are not significantly affected by culture medium composition or by changes in inoculum size in the range 10^3 to 10^6 cfu/spot (Table 2). In one study with 37 enterobacteria in Mueller-Hinton agar, increases in MIC values of norfloxacin at 10^8 cfu/spot were 2- to 4-fold higher than at 10^6 cfu/spot.

MICs of 4- to 33-fold higher were seen when representative enterobacteria were tested simultaneously in Diagnostic Sensitivity Test (DST) agar at pH 5.5 (MIC range = 0.12 to 32 mg/L), and at pH 7.2 (MIC = 0.015 to 4). This reduction in antibacterial activity suggests a pH effect (Table 2). In pooled human urine agar at pH 6.5 the observed MICs ranged from 0.06 to 16 mg/L. The magnesium content of urine could account for the reduced activity of norfloxacin and other quinolones in pooled human urine agar.

Generally, minimal bactericidal concentrations (MBCs) for norfloxacin are 1 to 4 times the MICs against susceptible bacteria. At these concentrations, norfloxacin is bactericidal, even with bacteria in their stationary phase of growth.

TABLE 1

CUMULATIVE PERCENT OF STRAINS INHIBITED AT THE INDICATED CONCENTRATIONS OF NORFLOXACIN

		(mg/L)																
Organism	**No./Strains**	**0.002**	**0.004**	**0.008**	**0.016**	**0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**
Achromobacter xylosoxidans	(30)											3	7	13		37	60	73
Acinetobacter calcoaceticus	(122)								1	7	20	38	62	91	96	100		
Alcaligenes faecalis	(23)											4		9	22	70	91	
Citrobacter freundii	(27)					26	48	74	93	96	100							
Citrobacter spp.	(15)						60		80	87		100						
Enterobacter cloacae	(76)					3	28	50	92	96		97	100					
Enterobacter spp.	(67)						33	55	87	91	96	97	100					
Escherichia coli	(417)					0.5	47	77	93	95	97	99	99	100				
Klebsiella pneumoniae	(50)						6	30	64	84	88	94	98	100				
Klebsiella spp.	(138)						24	56	77	84	95	99	99	100				
Morganella morganii	(52)					2	25	79	87		94	100						
Neisseria gonorrhoeae	(589)*	0.5	2	14	56	82	95	99	99	99				100				
Proteus mirabilis	(115)						51	63	74	93	100							
Proteus vulgaris	(58)					10	26	67	93	98		100						
Proteus spp., indole [+]	(10)						90	100										
Proteus spp.	(27)							52	93	100								
Providencia rettgeri	(111)					10	23	43	66	74	80	85	87	93	100			
Providencia stuartii	(16)				6	32	63	76	82	88		94			100			
Providencia spp.	(20)							80	85	95	95	100						
Pseudomonas aeruginosa	(245)							1	8	36	64	84	92	98		100		
Pseudomonas cepacia	(17)												6		71	100		
Pseudomonas maltophilia	(43)												2	9	49	84	95	100
Pseudomonas spp.	(112)							10	12	58	81	86	90	96	99	100		
Salmonella spp.	(11)						55		91		100							
Serratia marcescens	(87)							6	44	67	79	85	90	93	99	100		
Serratia spp.	(20)						15	95	100									
Shigella spp.	(3)								100[x]									
Staphylococcus aureus	(111)							1	2	8	42	76	95	99	100			
Staphylococcus epidermidis	(75)							3	15	41	81	95	97	100				
Staphylococcus saprophyticus	(15)								13	13	87	100						
Streptococcus agalactiae	(10)										10	90	100					
Streptococcus bovis	(15)								20	20	33	53	80	87	100			
Streptococcus faecalis	(67)										3	52	91	100				
Ureaplasma urealyticum	(20)												15	50	90	100		

* Includes 303 penicillinase-producing strains.

[x] Only three strains.

TABLE 2

EFFECT OF CULTURE MEDIUM COMPOSITION, pH, AND INOCULUM SIZE ON ANTIBACTERIAL ACTIVITY OF NORFLOXACIN

		MIC (mg/L)										
		Culture Medium[a]				pH[b]			Inoculum Size (cfu)[c]			
Organism/Strain		**TSA**	**NA**	**MH**	**BHI**	**6**	**7**	**8**	**10^3**	**10^4**	**10^5**	**10^6**
Staphylococcus aureus	2868	0.125	1.0	0.5	2	4	2	1	2	2	2	2
Escherichia coli	4391	0.03	0.06	0.06	0.06	1	0.06	0.06	0.03	0.03	0.03	0.03
Klebsiella pneumoniae	4005	0.06	0.06	0.06	0.06	ND	ND	ND	0.03	0.06	0.06	0.06
Escherichia coli	4392	0.25	0.25	0.25	0.5	8	0.5	0.25	0.5	0.25	0.25	0.5
Proteus mirabilis	3125	0.125	0.25	0.125	0.25	2	0.5	0.125	0.03	0.125	0.03	0.125
Serratia marcescens	2854	0.25	0.5	0.125	0.25	ND	ND	ND	0.125	0.125	0.06	0.125
Pseudomonas aeruginosa	2835	1	1	1	2	4	1.0	0.5	1	1	0.5	0.5

[a] TSA = trypticase soy agar (BBL); NA = nutrient agar (Difco); MH = Mueller Hinton agar (BBL); BHI = brain heart infusion (Difco); 10^6 cfu, pH 7.3

[b] Trypticase soy broth, 10^5 cfu/mL; ND = not done

[c] TSA (BBL), pH 7.3

Development of Resistance

A progressive increase in MIC of norfloxacin was demonstrated in five bacterial isolates by daily passage in subinhibitory concentrations of drug (Table 3). Cross-resistance with other quinolone antibacterial agents has also been observed.

TABLE 3

COMPARATIVE NORFLOXACIN MIC OF PARENT AND DERIVATIVE STRAINS

		Norfloxacin MICs (mg/L)[x]		
Organism/Strain		**Parent Strain**	**R3**	**R5**
Escherichia coli	2891	0.25	0.25	0.5
Klebsiella pneumoniae	4354	0.25	4	8
Proteus vulgaris	2829	0.25	0.5	4
Pseudomonas aeruginosa	2835	0.5	2	8
Staphylococcus aureus	4310	1	4	32

[x] Broth dilution test, inoculum 10^6 cfu/mL, trypticase soy broth.

R 3 = parent strain after 3 transfers.

R 5 = parent strain after 5 transfers.

The frequency with which resistant mutants arise varies among genera (Table 4), is greatest for *P. aeruginosa* and least for *E. coli*. In concentrations within two dilutions of the MIC, mutants of *P. aeruginosa* can be isolated rather frequently (10^{-4} to 10^{-6}), whereas those of *E. coli* are relatively uncommon (10^{-8}). Increasing amounts of norfloxacin resulted in lower frequency of mutants (Table 4).

TABLE 4

FREQUENCY OF NORFLOXACIN-RESISTANT MUTANTS AMONG VARIOUS SPECIES OF *ENTEROBACTERIACEAE, PSEUDOMONAS AERUGINOSA*, AND *STAPHYLOCOCCUS AUREUS*

		Norfloxacin (mg/L)[x]		
Organism/Strain		**0.15**	**0.45**	**1.5**
Escherichia coli	3773	1.1×10^{-8}	ND	ND
Klebsiella oxytoca	4007	7.5×10^{-7}	1.5×10^{-7}	ND
Klebsiella pneumoniae	3972	2.2×10^{-7}	5.1×10^{-8}	ND
Enterobacter cloacae	301	2.3×10^{-8}	ND	ND
Serratia marcescens	1581	4.6×10^{-7}	2.8×10^{-7}	1.3×10^{-9}
Citrobacter freundii	2301	5.0×10^{-8}	ND	ND
Proteus vulgaris	J 17	1.2×10^{-6}	ND	ND
Morganella morganii	2481	1.3×10^{-7}	ND	ND

		Norfloxacin (mg/L)		
Organism/Strain		**2**	**8**	**24**
Pseudomonas aeruginosa	1404	8.9×10^{-5}	7.3×10^{-9}	ND
Pseudomonas aeruginosa	976	4.6×10^{-7}	ND	ND
Pseudomonas aeruginosa	526	1.3×10^{-6}	ND	ND
Pseudomonas aeruginosa	380	ND	ND	ND
Pseudomonas aeruginosa	133	4.6×10^{-4}	ND	ND
Pseudomonas aeruginosa	89	5.4×10^{-7}	ND	ND
Staphylococcus aureus	51	ND	ND	--
Staphylococcus aureus	105	ND	ND	--
Staphylococcus aureus	137	4.1×10^{-9}	ND	--

[x] Overnight cultures in trypticase soy broth (Oxoid) were plated in 10- and 100-fold dilutions on CLED agar (Oxoid) containing various concentrations of norfloxacin.

ND = not detectable, frequency of resistant mutants < 10^{-10}.

Nalidixic acid-resistant urinary isolates have been reported to demonstrate higher MICs to norfloxacin than nalidixic acid-susceptible strains. In one study, nalidixic acid-resistant strains of enterobacteria (MIC $\geq$128 mg/L) showed an MIC range for norfloxacin of 0.06 - 16 mg/L (Table 5), or 4-16 times that for the nalidixic acid-susceptible strains tested (MIC range of 0.015 - 1.0 mg/L). Thus, induced resistance to nalidixic acid was associated with cross-resistance to norfloxacin.

TABLE 5

NORFLOXACIN MICs AGAINST NALIDIXIC ACID-SUSCEPTIBLE AND-RESISTANT URINARY ENTEROBACTERIA

Organisms (# of strains tested)	MIC Range (mg/L)[x]
Nalidixic acid-susceptible[a] (59)	
DST agar (Oxoid) (pH 7.2)	0.015 - 0.12
urine agar (pH 6.5)	0.06 - 1.0
Nalidixic acid-resistant[b] (44)	
DST agar (pH 7.2)	0.06 - 4.0
urine agar (pH 6.5)	0.25 - 16.0

[x] The inoculum was applied with a multipoint inoculator, at approximately 10^2 cfu/spot.
[a] MIC $\leq$ 32 mg/L
[b] MIC $\geq$ 128 mg/L

Nalidixic acid-resistant organisms were inhibited by norfloxacin at a concentration of 16 mg/L or less for approximately 90% of the isolates investigated. Norfloxacin is active *in vitro* against *Enterobacteriaceae* and nonfermentative gram-negative bacilli (*Pseudomonas aeruginosa, Acinetobacter* spp.) resistant to ampicillin, carbenicillin, trimethoprim and aminoglycosides. Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

Susceptibility Testing

The standardized disc (1-3) susceptibility test [formerly, Kirby-Bauer] (using the 10 µg NOROXIN® disc of 6-mm diameter) or dilution susceptibility should be used.

Organisms should be tested with NOROXIN® discs, since norfloxacin has been shown by *in vitro* tests to be active against genera and strains of bacteria known to be or determined to be resistant when nalidixic acid discs are used.

TABLE 6

INTERPRETATION OF SUSCEPTIBILITY CRITERIA OF NORFLOXACIN (FOR MILD OR MODERATE INFECTIONS OF THE URINARY TRACT)

	Zone Diameter (10 µg norfloxacin disc) (mm)	Approximate MIC Correlation (µg/mL)
Susceptible	≥17	≤4
Intermediate	13 - 16	8
Resistant	≤12	≥16

These susceptibility criteria apply only to organisms isolated from urine (urinary tract).

There is a lack of clinical data to indicate if these same susceptibility criteria will be appropriate for the treatment of severe urinary tract infections suitable for oral therapy.

Proposed control limits for monitoring susceptibility tests are given in Table 7.

TABLE 7

CONTROL LIMITS FOR MONITORING NORFLOXACIN SUSCEPTIBILITY TESTS

Organism	Zone Diameter (mm)	MIC (mg/L)
E. coli ATCC* 25922	28-35	0.03 - 0.12
S. aureus ATCC* 25923	17 - 28	
S. aureus ATCC* 29213		0.5 - 2.0
S. faecalis ATCC* 29212		2.0 - 8.0
P. aeruginosa ATCC* 27853	22 - 29	1.0 - 4.0

* Trademark of American Type Culture Collection

PHARMACOLOGY

Animal Pharmacology

Central Nervous System

Norfloxacin (0.1-1.0 g/kg p.o.) showed no significant influences on behavior or in various pharmacological tests of central nervous system activity in either mice or rats. Similarly, norfloxacin (10 mg/kg I.V.) produced no changes in the central nervous system of rabbits implanted with recording electrodes.

Peripheral Nervous System

Intravenous administration of norfloxacin (10 mg/kg) modestly reduced (30%) contractions of the cat nictitating membrane elicited by both pre- and post-ganglionic nerve stimulation. Nerve stimulated contractions of the rabbit tibialis muscle, however, were unaffected by similar doses of norfloxacin.

Using *in vitro* smooth muscle preparations (guinea pig ileum and trachea), norfloxacin (100-300 mg/L) exhibited no anticholinergic, antiserotonergic or

antihistaminergic activity. Likewise, norfloxacin did not alter the intrinsic muscle tone of the above preparations. In the isolated rat vas deferens, norfloxacin did alter responses to norepinephrine (slightly enhancing low concentrations and reducing high concentrations) though no alteration in epinephrine responses were observed in the guinea pig ileum and trachea. Norfloxacin (100 mg/L) slightly reduced the amplitude of spontaneous contractions of the pregnant and nonpregnant rat uterus and rabbit ileum *in vitro*. However, *in vivo* norfloxacin (10 mg/kg I.V.) was without significant effect on spontaneous contractions of the stomach, intestine, bladder and uterus of rabbits. Similarly, gastrointestinal motility in mice was unaffected by 1.0 g/kg p.o. of norfloxacin.

Cardiovascular and Respiratory Systems

Norfloxacin (1.0 mg bolus) slightly increased (10 ± 3%) coronary flow and decreased heart rate (7 ± 2%) while modestly depressing contractile force (45 ± 4%) of isolated, perfused guinea pig hearts. In the isolated rabbit ear artery, a similar 1 mg bolus of norfloxacin produced a weak, transient decrease followed by an increase in blood flow. *In vivo*, norfloxacin administered intravenously increased by about 20% the respiratory rate in urethane anesthetized rabbits (30 mg of norfloxacin/kg) and barbiturate anesthetized dogs (10 mg of norfloxacin/kg). In these animals blood pressure tended to be reduced without significant changes in heart rate. The decrease of blood pressure in rabbits (approximately 15%) and particularly dogs, was marked by considerable animal variation (3/6 dogs had decreases of 90-100 mmHg). Infusion of norfloxacin (180 mg/hour I.V.) produced an elevation in the respiratory rate (60% increase) with a decrease (about 10%) in blood pressure and no change in heart rate in dogs. In urethane anesthetized rats a reduction of about 20% in blood pressure was caused by norfloxacin (200 mg/kg I.V.). This reduction was inhibited by diphenhydramine but unaffected by atropine, propranolol or phentolamine. Oral administration of norfloxacin (1.0 g/kg) did not alter the blood pressure of unanesthetized rats.

Other Systems

Norfloxacin (1.0 g/kg p.o.) did not change blood sugar levels or coagulation time in rats and did not exhibit any antiinflammatory activity in rats. Similarly, norfloxacin (300 mg/kg p.o.) was unable to prevent cold stress-induced ulcers in rats. Subcutaneous administration of norfloxacin (200 mg/kg) significantly reduced by about 90% gastric acid secretion while doses as high as 1.0 g/kg p.o. failed to alter bile secretion in rats. Norfloxacin (1.0 g/kg p.o.) significantly reduced urinary volume (30% decrease) over 24 hours and reduced urinary Na^+ excretion (ca. 25%) and significantly increased urinary K^+ excretion (ca. 30%) over this time period. None of these effects were observed at doses of 100 mg/kg p.o.

Animal Pharmacokinetics

The absorption, distribution, and excretion of norfloxacin has been studied in rats, dogs, monkeys, mice, and rabbits. Absorption is rapid in all species following oral administration, ranging from 10-12% in rats, mice and rabbits to 20-25% in monkeys and 70% in beagle dogs. Serum levels of norfloxacin measured for 0.5 to 4 hours after oral drug administration to monkeys (25 mg/kg) ranged from 0.3 to 2.35 µg/mL. In rats, dogs, and monkeys, 8%, 39%, and 17% of respective oral doses of norfloxacin was excreted in urine, chiefly as unchanged drug (>75%), but also as various combinations of six metabolites, all with modifications in the piperazine ring.

Human Pharmacology

Pharmacokinetics

In fifteen healthy fasting male volunteers aged 22 to 52 years (mean age: 34.1 ± 9.2 years), the mean peak serum concentrations of norfloxacin was 0.8 ± 0.3 (0.4-1.5) and 1.5 ± 0.6 (0.6-2.7) mg/L occurring within 1-1.5 hours of oral administration of 200 mg and 400 mg doses, respectively (see Figure 1).

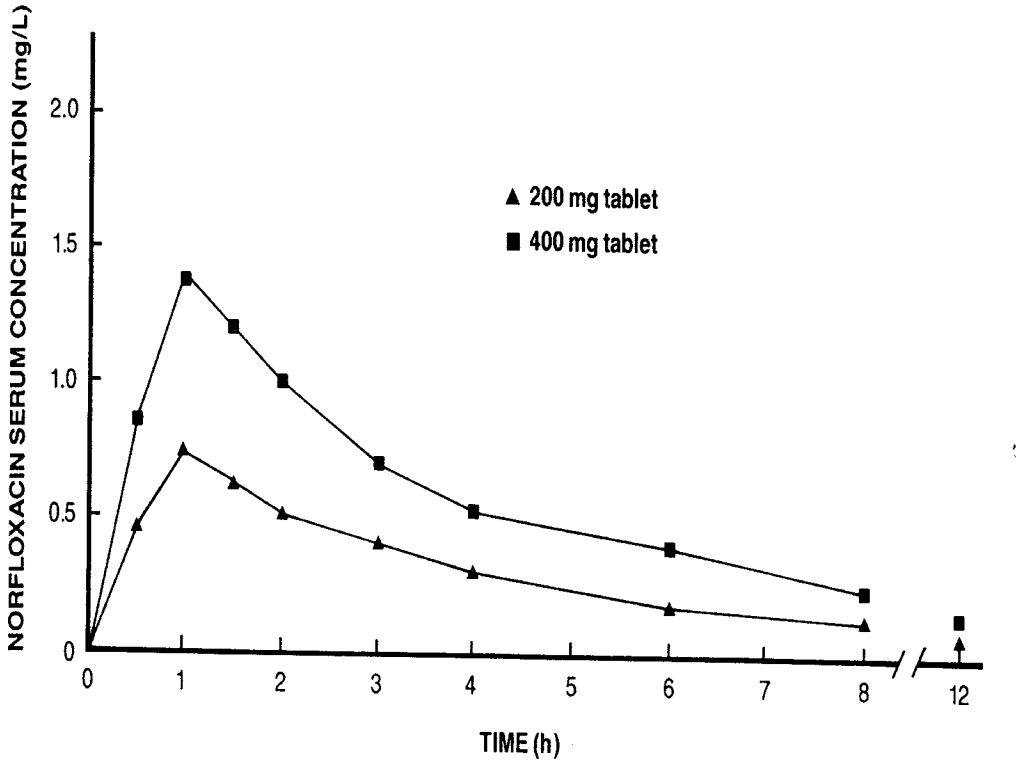


FIGURE 1 Mean norfloxacin serum concentrations after single oral doses

The mean elimination half-life of norfloxacin was approximately 3 hours (2.3 - 4.5). Therefore, as was noted in another group of twenty-six healthy male (23) and female (3) volunteers aged 19 to 50 years (mean age: 28.6 ± 9.1 years), norfloxacin regimens of 400 mg given every 12 hours produced slight accumulation (see Figure 2).

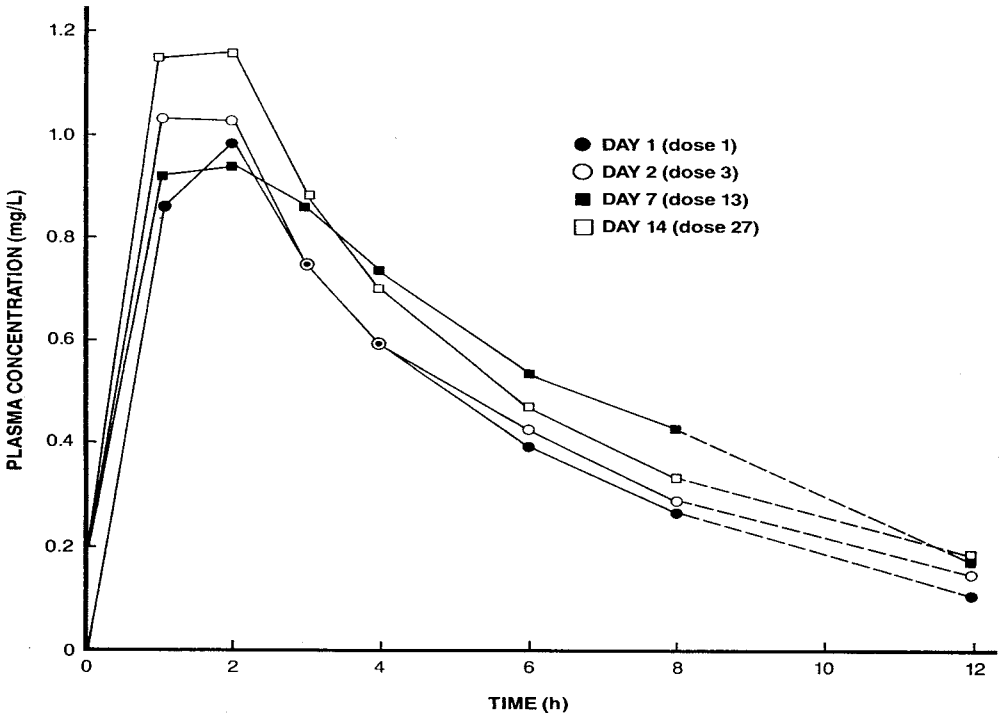


FIGURE 2 Mean norfloxacin plasma concentrations after 400 mg doses given every 12 hours.

Theoretically it could be expected that steady state concentrations of norfloxacin will be attained after 2 days of recommended dosage.

Pharmacokinetic information for healthy normal volunteers is given in Table 9.

Excretion and Metabolism:

Following oral administration to fifteen healthy fasting male volunteers, aged 22 to 52 years (mean age: 34.1 ± 9.2 years), 25%-30% of a norfloxacin dose was recovered unchanged in urine within 48 hours (see Table 8).

TABLE 8

MEAN URINARY EXCRETION OF NORFLOXACIN

	Hours After Administration									
	0-1	**1-2**	**2-3**	**3-4**	**4-6**	**6-8**	**8-12**	**12-24**	**24-48**	**Total**
	Urine Concentration, µg/mL (±S.D.)									
200 mg dose	37.7 (31.3)	139.1 (159.9)	65.7 (88.3)	44.5 (54.8)	19.1 (10.7)	19.2 (9.9)	16.5 (10.5)	7.3 (6.4)	1.0 (1.7)	--
400 mg dose	138.6 (206.0)	392.7 (302.0)	244.6 (300.9)	141.0 (182.9)	57.0 (60.5)	42.2 (26.4)	36.0 (24.1)	13.7 (9.9)	1.5 (2.0)	--
400 mg dose elderly	100.6 (100.8)	154.1 (85.1)	148.3 (74.0)	67.8 (77.5)	101.8 (59.5)	43.0 (23.1)	30.5 (11.0)	12.8 (7.0)	--	--
	Amount Excreted, mg (±S.D.)									
200 mg dose	3.2 (2.4)	14.2 (6.6)	8.2 (2.6)	5.0 (2.0)	6.5 (3.7)	3.9 (1.6)	5.0 (3.3)	5.3 (3.2)	0.9 (1.3)	52.2 (18.6)
400 mg dose	7.5 (6.4)	22.6 (9.9)	19.7 (12.9)	12.5 (6.6)	14.2 (6.4)	8.8 (3.4)	10.2 (4.3)	8.3 (4.3)	1.3 (1.8)	105.1 (36.2)
400 mg dose elderly	9.0 (3.3)	19.0 (9.0)	16.0 (9.0)	6.3 (3.7)	8.7 (5.9)	8.3 (7.1)	8.7 (4.2)	7.1 (3.2)	--	83.2 (31.6)

During the same period of time, an additional 8-10% of the dose is recovered as six metabolites with modifications on the piperazine ring. The two major metabolites are the 3-oxo-piperazinyl derivative and the 7-ethylenediamine derivative. The 3-oxo-piperazinyl predominates and no glucuronide conjugates were detected. Norfloxacin and these metabolites were detected in bile. The concentration of norfloxacin in bile was 5 µg/mL collected 1-2 hours after oral administration of a 200 mg dose to one patient with choledocholithiasis. A similar distribution ratio of the same six metabolites was in both bile and urine. These data suggest that 30-40% of an oral dose of norfloxacin is absorbed. After a single 400 mg dose of NOROXIN® (norfloxacin), mean antimicrobial activities equivalent to 164 (±202), 338 (±220), 632 (±688), and 126 (±123) µg of norfloxacin/g of feces were recovered over 0-12, 12-24, and 24-36, and 36-48 hours, respectively.

Renal excretion of norfloxacin occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance 4.58±1.18 mL/s (range: 2.68 - 7.07) [275±71 mL/min (range: 161 - 424)]. Two to three hours after a single 400 mg dose, mean urinary concentrations of 200 mg/L or more were obtained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 mg/L for at least 12 hours following a 400 mg dose (see Table 8).

Factors Influencing the Pharmacokinetics:

Food

Food slightly reduces the absorption of norfloxacin as evidenced by a reduction of approximately 30% in peak serum concentration and of approximately 35% in peak urine concentration.

Age (elderly)

In 4 females and 2 males, 67 to 74 years old with normal renal function for their age i.e., creatinine clearance 1.52±0.23 mL/s/1.73 m^2 (91±14 mL/min/1.73 m^2), norfloxacin was eliminated more slowly because of their slightly decreased renal function causing a small increase in plasma concentrations of drug (see Figure 3).

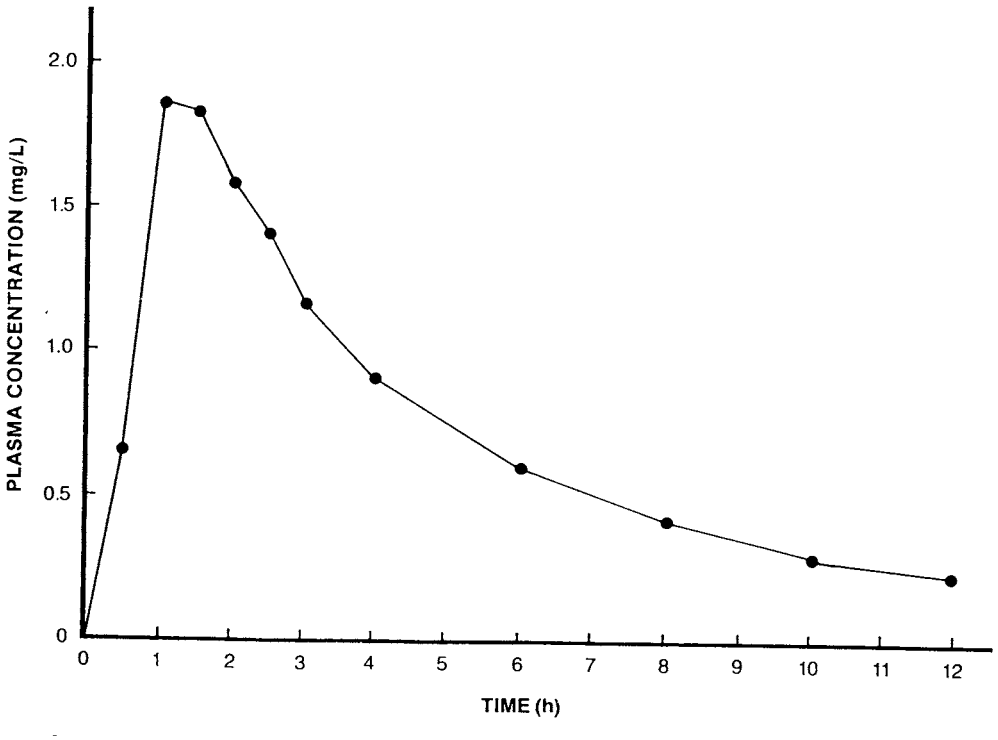


Figure 3. Mean norfloxacin plasma concentrations following a single 400 mg dose given to healthy elderly subjects.

Approximately 22% of the norfloxacin dose was recovered unchanged in urine (see Table 8). The renal clearance of drug was 2.57 mL/s (154 mL/min). The maximum plasma concentration of norfloxacin was approximately 2 mg/L, occurring 1.3 hours after drug administration. The plasma half-life of norfloxacin in these individuals was 4 hours (see Table 9).

Table 9

COMPARISON OF PHARMACOKINETIC PARAMETERS BETWEEN HEALTHY ELDERLY VOLUNTEERS AND HEALTHY YOUNGER VOLUNTEERS FOLLOWING A SINGLE 400 MG ORAL DOSE

Parameter	Elderly Volunteers	Younger Volunteers
C_{max}, mg/L	2.0 (± 0.8)	1.5 (± 0.6)
T_{max}, h	1.3 (± 0.4)	1.0 (± 0.4)
Half-life, h[x]	3.9	3.2
Total (AUC), mg·h/L	9.8 (±2.8)	6.6 (± 3.3)
Renal clearance, mL/min	154 (± 16)	299 (± 95)
Renal clearance, mL/s.	2.57(± 0.27)	4.98 (± 1.58)
%-Dose Urinary Recovery	22(± 7)	27(± 9)

[x] Harmonic mean

Impaired renal function

Excretion of norfloxacin in patients with creatinine clearance (C_{cr}) greater than 0.50 mL/s/1.73 m^2 (30 mL/min/1.73 m^2), was similar to that of healthy volunteers. In patients with C_{cr} less than 0.50 mL/s/1.73 m^2 (30 mL/min/1.73 m^2) but greater than 0.11 mL/s/1.73 m^2 (6.6 mL/min/1.73 m^2), less than 10% of an oral dose was excreted in urine. The mean elimination half-life of norfloxacin in serum increased to 6.5 hours in these patients (see Table 10 and Figure 4).

TABLE 10

MEAN PHARMACOKINETIC PARAMETERS FOR NORFLOXACIN FOLLOWING A SINGLE 400 MG ORAL DOSE IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH VARYING DEGREES OF RENAL INSUFFICIENCY

	Parameter						
Group	**Creatinine Clearance [mL/s/1.73 m^2] (mL/min/1.73 m^2)**	**C_{max} (mg/L)**	**T_{max} (h)**	**Half-Life[x] (h)**	**Total (AUC) (mg·h/L)**	**Renal Clearance (mL/min)**	**%-Dose Urinary Recovery**
I	[≥1.5] ≥90	1.51 (±0.56)	1.4 (±0.4)	3.47	6.94 (±2.73)	297.2 (±117.4)	28.2 (±12.8)
II	[0.52-1.48] 31-89	1.91 (±0.71)	1.3 (±0.4)	3.38	9.53 (±2.47)	264.5 (±83.2)	35.3 (±9.2)
III	[0.17-0.50] 10-30	1.70 (±0.43)	1.8 (±1.1)	6.57	24.01 (±13.49)	17.8 (±4.4)	6.7 (±4.1)
IV	[0.11-0.15] 6.6-9	1.70 (±0.92)	1.8 (±1.2)	6.40	16.46 (±14.52)	14.7 (±8.4)	2.4 (±1.1)

[x] Harmonic mean

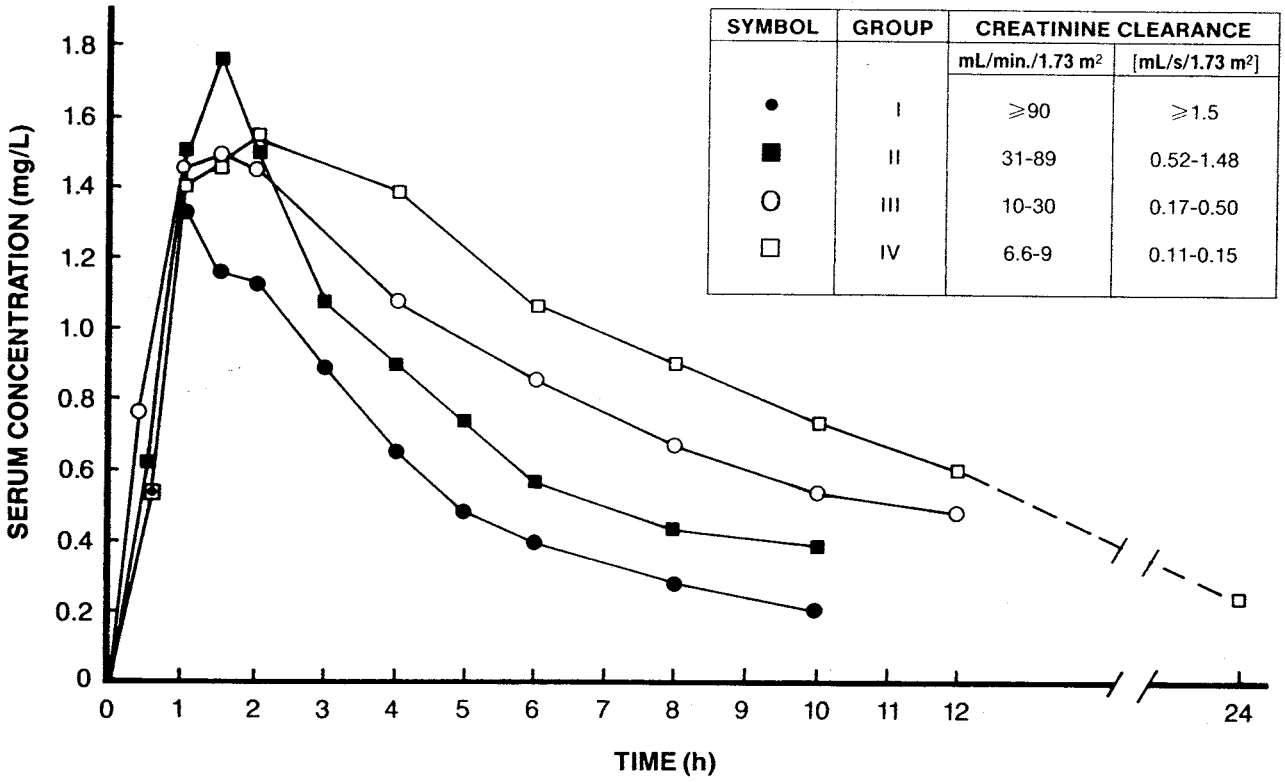


Figure 4 Mean norfloxacin serum concentrations following a single 400 mg dose given to healthy volunteers and to patients with varying degrees of renal insufficiency.

Probenecid

The 12-hour urinary excretion of norfloxacin following a 200 mg dose was diminished from 28% of the dose to 14% of the dose by the coadministration of probenecid.

Serum Protein Binding

At a serum concentration of 2.5 mg/L the human serum protein binding is 10-15%.

Tissue Concentrations

Concurrent norfloxacin concentrations in serum, tissues and body fluids are given in Table 11.

TABLE 11

NORFLOXACIN CONCENTRATIONS IN HUMAN TISSUES AND BODY FLUIDS

Tissue/Fluid	No. of subjects	Dose of norfloxacin (mg)	Sampling time (h after dose)	Concentration (±S.D.)	
				Tissue/Fluid (mg/L or mg/kg)	Serum (µg/mL)
Liver	2	200 mg	2 h	3.40	0.10
				1.66	0.52
Gall bladder	2	200 mg	2.5 h	<0.2	-
				0.48	-
Gall bladder bile	2	200 mg	2 h	0.15	0.10
				4.46	0.52
	20	400 mg	2 h	10.3 (± 2.7)	1.25 (± 0.3)
Bile in common bile duct	2	200 mg	2.5 h	0.41	-
				4.19	-
	20	400 mg	2 h	8.8 (± 1.4)	1.25 (± 0.3)
Bile	1	100 mg	4 h	3.16	0.65
			6 h	5.68	0.48
	3	400 mg	2 h	0.13 - 0.70	0.18 - 1.2
			3 h	2.72 - 6.0	0.53 - 1.1
			4 h	2.60 - 4.20	0.6 - 0.83
			6 h	1.4 - 2.5	0.30 - 0.70
Prostate	15	800 mg[+]	3 - 4 h	0.93 (± 0.66)	1.17 (± 0.55)
	10	800 mg[x]	1 - 2 h	<0.25 - 4.65	<0.25 - 5.30
Kidney[xx]	3	800 mg[x]	2 h	16.2	4.30
			3 h	15.1	4.00
			6.5 h	3.9	0.32

[+] One 400 mg tablet at time zero the evening before surgery and again 11h later.

[x] One 400 mg tablet given between 21h and 22h the night before surgery and a second 400 mg tablet one hour before surgery.

[xx] The serum levels in 2 out of 3 patients were higher than expected and consequently kidney concentrations may also have been higher than expected.

TOXICOLOGY

Acute Toxicology

SPECIES	SEX	ROUTE	LD_{50} mg/kg (95% confidence limits)
Mouse	Male	p.o.	>4,000
Mouse	Male	Subcutaneous	>1,500
Mouse	Male	Intramuscular	470(405-545)
Mouse	Male	Intravenous	220(209-232)
Mouse	Female	p.o.	>4,000
Mouse	Female	Subcutaneous	>1,500
Mouse	Female	Intramuscular	480(429-538)
Mouse	Female	Intravenous	237(226-248)
Rat	Male	p.o.	>4,000
Rat	Male	Subcutaneous	>1,500
Rat	Male	Intramuscular	> 500
Rat	Male	Intravenous	270(233-313)
Rat	Female	p.o.	>4,000
Rat	Female	Subcutaneous	>1,500
Rat	Female	Intramuscular	> 500
Rat	Female	Intravenous	245(211-284)

The six metabolites were also tested orally for their acute toxicity in rats and mice. The LD_{50} values were estimated to be greater than 2,000 mg/kg.

Subacute Toxicity Studies

One month oral toxicity studies were carried out in rats (250, 500 and 1,000 mg/kg/day, 10 males and 10 females per group), dogs (50, 100 and 200 mg/kg/day, one male and one female per group; or 25, 50 and 100 mg/kg, b.i.d., 6 days per week, 3 males and 3 females per group) and monkeys (25, 50, 100 mg/kg, b.i.d., 6 days per week, 2 males per group). In all studies similar size groups served as controls and received sterile distilled water.

A slight increase in urinary potassium excretion was seen in female rats dosed at 500 and 1,000 mg/kg/day. There was, however, no concurrent decrease in serum potassium level. A slight enlargement of cecum was observed in 3 of 10 male rats at 1000 mg/kg/day. Liver glucose-6-phosphatase activity was slightly increased at all dose levels in the dog study in which norfloxacin was given at doses of 25, 50 or 100 mg/kg b.i.d.

Chronic Toxicity Studies

Rat

A six-month oral toxicity study in rats at norfloxacin doses of 0, 125, 250 and 500 mg/kg/day (10 rats/sex/group) revealed only minimal effects as evidenced by slight body weight retardation in male rats in the 250 and 500 mg/kg/day groups.

A similar study was carried out in rats (15 rats/sex/group) at norfloxacin doses of 0, 50, 200 and 600 mg/kg/day orally. There was a slight, but not statistically significant, decrease in body weight gain at 600 mg/kg/day in males. In addition, crystalluria consisting of the dihydrate and the magnesium salt of norfloxacin occurred in rats from the 200 and 600 mg/kg/day groups. The crystalluria was most frequent in males given 600 mg/kg/day. A high incidence of cecal enlargement was seen at all dose levels. Gray feces were observed in all treated groups and a very slight but statistically significant decrease in serum proteins were observed in males dosed at 600 mg/kg/day.

Dog

Four chronic oral toxicity studies were performed to evaluate the potential toxicity of norfloxacin in dogs following chronic administration for 20 weeks to 13 months. The doses used were: 0, 25, 50 and 100/200 mg/kg/day (the dose was increased due to lack of drug-induced effect, 6 days per week, 4 males and 4 females per group); 0, 50, 150 and 300 mg/kg/day (7 days per week, 3 males and 3 females per group); 0, 25, 50 and 100 mg/kg/day, (7 days per week, 1 male and 1 female per group); 0, 50, 100 and 150 mg/kg/day (7 days per week, 4 males and 4 females per group). Crystalluria was evident in one of these studies where

dogs were given the drug at 50, 150 and 300 mg/kg/day for 26 weeks. The incidence was dose related. Four dogs, (1 and 3 in the 150 and 300 mg/kg/day dosage groups, respectively), were found dead or were sacrificed due to urinary obstruction from drug crystals. It was postulated that crystalluria in dogs and rats is the result of low solubility of norfloxacin in alkaline urine. This was supported by the observation of a significant decrease in the incidence of crystalluria and the absence of urinary obstruction in dogs in a separate study at 50, 150 and 300 mg/kg/day orally to 3 dogs/sex/group for three months where the urine was acidified by the administration of ammonium chloride. The pH after urine acidification was generally 6.0 or below whereas the urinary pH of dogs where drug crystals were formed was between 6.86 and 8.28.

Other frequently observed changes in the 150 and 300 mg/kg/day groups consisted of a dose-related incidence of emesis, grey or clay-coloured feces (due to unabsorbed drug) and retardation of body weight gain. There were also changes in the haematologic and serum biochemical parameters (leukocytosis, elevated serum urea nitrogen and creatinine) that are compatible with uremia and pyelonephritis secondary to intrarenal or urethral obstruction.

Reproduction Studies

Fertility

The effect of norfloxacin on fertility was assessed in male and female mice. Norfloxacin was administered orally at dosage levels of 0, 125, 250, 500 mg/kg/day (20 per sex per group) for 61 days before mating and during mating to male mice and for 15 days before mating until the sixth day of pregnancy to female mice. There were no treatment-related effects on the reproductive performances of the adults or differences in growth and characteristics of the fetuses.

Teratology

Mice

In mice oral doses of 0, 125, 250 or 500 mg/kg/day (31 mice/group) given on days 6 to 15 of gestation did not have any adverse effect on the pregnant mother or F_1 or F_2 fetuses.

Rats

In rats, oral doses of 0, 50, 200 or 800 mg/kg/day (administered b.i.d. to 20 rats/group) given on days 6 to 17 of gestation did not adversely affect the progress or outcome of pregnancy.

Rabbits

In an oral teratology study, rabbits were given 0, 25, 50 or 100 mg/kg/day of norfloxacin orally (12 or 13 rabbits per group) from day 6 to 18 of gestation. In this study, rabbits in the 100 mg/kg/day group showed decreased activity, reduced appetite, diarrhea, and reduced body weight gain. Embryotoxicity (i.e., abortion and fetal resorption) was also observed at this dosage level. An additional study comparing the maternal and fetal toxicity of norfloxacin administered orally at doses of 100 mg/kg/day with that administered subcutaneously at doses of 20 mg/kg/day (which resulted in approximately 5-fold higher maximum plasma drug levels) was carried out. There was no evidence of embryotoxicity in the group that received norfloxacin at a dose of 20 mg/kg/day by the subcutaneous route. This suggested that the embryotoxicity of norfloxacin in rabbits did not correlate with drug levels in blood.

Monkeys

In an oral teratology study in cynomolgus monkeys, norfloxacin was given at doses of 0, 50, 100, 150 or 300/200 mg/kg/day (the dose was reduced because of emesis) in single or divided doses from days 20 to 50 of gestation. There were at least 10 female monkeys in each group. Doses of 200 mg/kg/day and greater were maternotoxic and produced vomiting, reduced appetite, and body weight loss. In the 150 and 300/200 mg/kg/day groups, 3 of 10 and 11 of 16 monkeys lost their embryos. There was no evidence of a teratogenic effect in surviving fetuses. Doses of 100 mg/kg/day did not result in any increase in embryonic losses relative to controls.

Gestation and Postnatal Development

The effect of norfloxacin during gestation and postnatal period was studied in mice at doses of 0, 125, 250 and 500 mg/kg/day (21 mice per group). Female mice were dosed orally from Day 15 of gestation to Day 21 postpartum. No significant difference was observed with newborn of the treated groups as compared to controls.

Mutagenicity

Norfloxacin was negative in a dominant lethal test in mice (300 or 800 mg/kg administered as a single dose), an *in vivo* chromosome aberration test in rats (1000 mg/kg/day for 38 days) and hamsters (250 or 500 mg/kg, one dose), and various *in vitro* genotoxicity studies including an Ames test, chromosomal aberration test, sister chromatid exchange assay, unscheduled DNA synthesis assay and V-79 mammalian cell mutagenesis assay. Norfloxacin was weakly positive in a test for DNA repair (rec assay), however, this was considered to be of questionable biological significance since a more sensitive test for DNA repair (V-79 mammalian cell mutagenesis assay) was negative.

Carcinogenicity

A 19-month chronic oral toxicity study was done in rats (50 per sex per group). The rats were autopsied after a 12 to 14 week withdrawal period. Norfloxacin was given in the diet at 0.05 or 0.2% in the feed. The estimated drug intake was 18-35 mg/kg/day for the low dose group and 70-140 mg/kg/day for the high-dose group. No drug related neoplastic changes were reported as compared to control animals. The highest dose was below the maximum tolerated dose (approximately 600 mg/kg/day).

Special Toxicity Studies

Arthropathy

Three to five month old dogs were treated orally with norfloxacin for seven days at doses of 0, 30, 60, 100, 250 or 500 mg/kg/day or for 99 days at a dose of 0 or 200 mg/kg/day (2 or 3 dogs per group). Similarly, 8-10 week old rabbits were treated orally for seven days at 0, 250 or 300 mg/kg/day or for 21 days at 0, 100 or 150 mg/kg/day (5-11 rabbits/group). Nalidixic acid (30, 60 and 100 mg/kg/day) and pipemidic acid (30, 60, 100, 200 and 500 mg/kg/day) were used as positive controls. Clinical signs of lameness appeared from the second day in dogs given doses greater than 60 mg/kg/day of norfloxacin and persisted through the duration of the seven day study. Similar signs of lameness were seen in dogs given oral doses greater than 30 mg/kg/day of nalidixic acid and pipemidic acid. No clinical signs of lameness were seen in rabbits treated with any of these test compounds. In dogs, lameness was associated with joint lesions that were characterized by increased amount of synovial fluid and blister formation and sometimes erosions on the articular cartilage. There was recovery from clinical signs within six to eight weeks after initiation of the study, but lesions remained. In the rabbits, there was blister formation on the articular cartilage at doses of 250 mg/kg/day or greater for seven days. There were no clinical signs of lameness.

The arthropathogenic effects of norfloxacin were limited to young animals. There was no evidence of lameness or gross changes in the joints of dogs that were 8

to 10 months of age at the start of the study and given oral doses of norfloxacin up to 100 to 150 mg/kg/day for 22 weeks to 13 months.

Antigenicity

Antigenicity of norfloxacin was studied by examining its potential to induce delayed hypersensitivity and anaphylactic reaction in guinea pigs (0.8% and 0.5% respectively) and specific antibodies in rabbits (30 mg/mL - 1 mL, 2 injections). Norfloxacin elicited no delayed hypersensitivity reaction on the skin of guinea pigs. Anaphylactic reaction was not observed in guinea pigs sensitized with norfloxacin alone or a mixture of norfloxacin and Freund's complete adjuvant. Serum from guinea pigs sensitized with norfloxacin failed to induce passive cutaneous anaphylaxis in recipient guinea pigs. Specific antibodies against norfloxacin were not detected in sera of rabbits immunized with norfloxacin conjugated with bovine gammaglobulin and Freund's complete adjuvant.

Retina

No evidence of retinal toxicity was seen in cats given oral doses up to 200 mg/kg/day for two weeks as measured by electroretinogram and histopathology.

Auditory System

Norfloxacin administered to rats at a rate of 500 mg/kg/day orally for six months did not have any adverse effect on the auditory or vestibular function or on the histology of the organ of Corti.

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