

**OREGON HEALTH AUTHORITY
PUBLIC HEALTH DIVISION
ACUTE AND COMMUNICABLE DISEASE
PREVENTION SECTION**

**Model Standing Order for
Antimicrobial Prophylaxis in Setting of Exposure to
Yersinia pestis Aerosol or to a Patient with Pneumonic Plague**

I. OREGON MODEL STANDING ORDER

1. Follow the nursing assessment of individuals presenting for prophylactic treatment against a known or potentially harmful biological agent.
2. Provide people information about plague and the preventive antibiotics prior to administration, answering any questions
3. Dispense antibiotic prophylaxis in accordance with prophylactic treatment guidelines (Table 1) and within the restrictions of the guidelines of the Centers for Disease Control and Prevention (CDC) Medical Countermeasures Program.

<http://www.cdc.gov/phpr/stockpile/stockpile.htm>

Signature, Health Officer

Date

II. People for whom prophylaxis may be ordered

1. People who have a confirmed or highly suspect exposure to *Yersinia pestis*, as determined by the Local Health Officer, either through an intentional aerosol release or through contact with a person who has pneumonic plague.
2. People in a group for which the State Health Officer has activated the Health and Medical Annex (Annex F) of the State of Oregon Emergency Operations Plan and recommended plague post-exposure prophylaxis.

Table 1: Post-exposure prophylaxis (PEP)^{1,2}

Post-exposure prophylaxis is indicated in persons with known exposure to a person with pneumonic plague or to an aerosol release. Duration of post-exposure prophylaxis to prevent plague is 7 days. The recommended antibiotic regimens for PEP are as follows:

	Preferred agents	Dose	Route of administration
Adults	Doxycycline	100 mg twice daily	PO
	Ciprofloxacin	500 mg twice daily	PO
Children	Doxycycline (for children ≥ 8 years)	Weight < 45 kg: 2.2 mg/kg twice daily (maximum daily dose, 200 mg) Weight ≥ 45 kg: same as adult dose	PO
	Ciprofloxacin	20 mg/kg twice daily (maximum daily dose, 1 g)	PO
Pregnant women	Doxycycline ¹	100 mg twice daily	PO
	Ciprofloxacin ¹	500 mg twice daily	PO

¹Adapted from: Inglesby TV, Dennis DT, Henderson DA, et al. [Plague as a biological weapon: medical and public health management](#). Working Group on Civilian Biodefense. JAMA. 2000 May 3;283(17):2281-90. Accessed 22 July 2015.

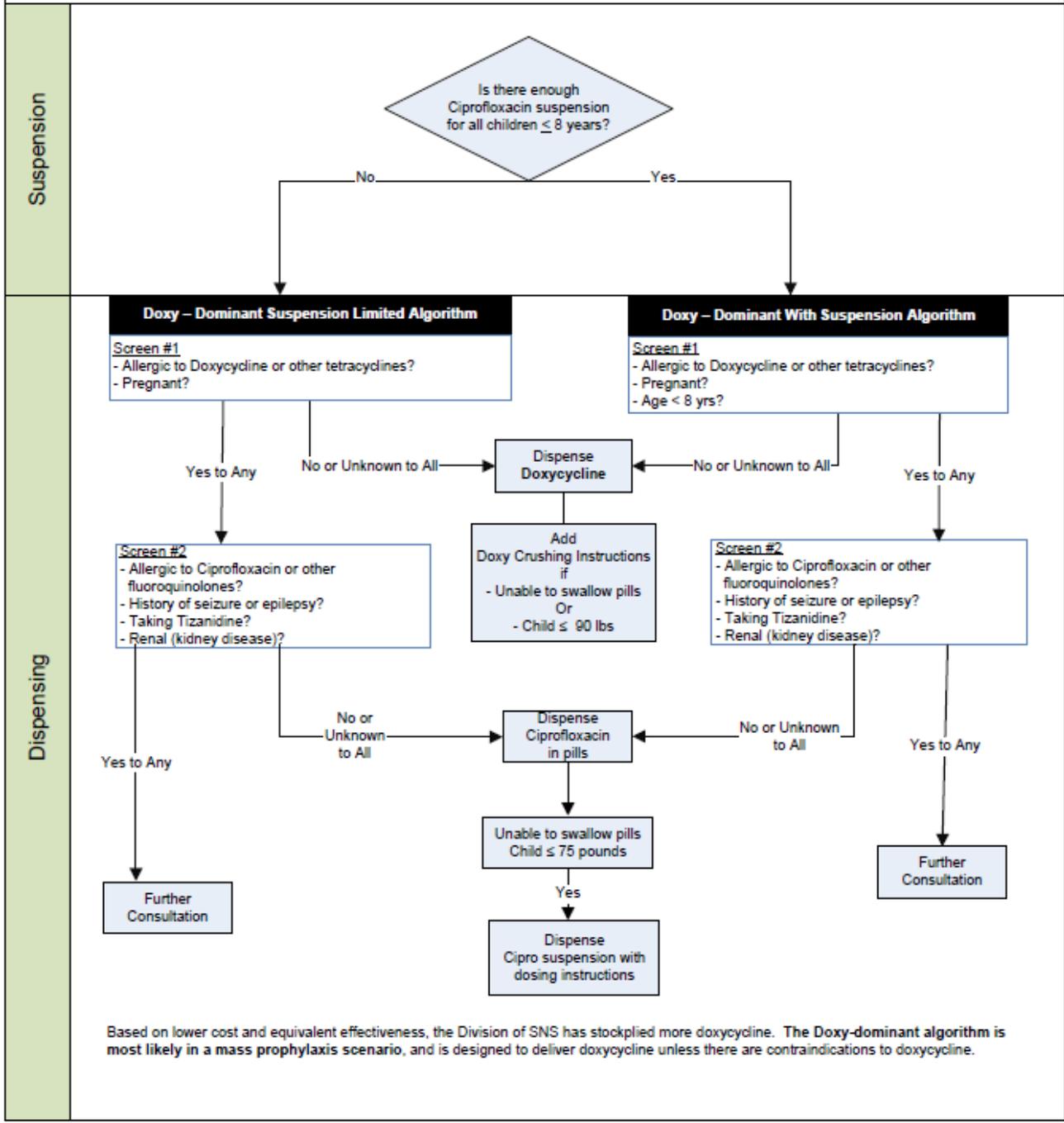
²Doxycycline and ciprofloxacin are pregnancy categories D and C, respectively. PEP should be given only when the benefits outweigh the risk. Available at: <http://www.cdc.gov/plague/healthcare/clinicians.html>. Accessed 22 July 2015.

Plague Post-exposure Prophylaxis Dispensing Algorithm

The following diagram and these footnotes describe drug selection and dosing information for people requiring post-exposure prophylaxis or preventive treatment after exposure to *Yersinia pestis*, the bacterium that causes plague. Recommendations follow those of the Working Group on Civilian Biodefense.¹

Algorithm for Post-Exposure Prophylaxis: Use for Mass Prophylaxis in Setting of Suspected or Confirmed Release of Plague Aerosol

OR
 Focused Prophylaxis in setting of Exposure to a Person with Pneumonic Plague



Based on lower cost and equivalent effectiveness, the Division of SNS has stockpiled more doxycycline. The Doxy-dominant algorithm is most likely in a mass prophylaxis scenario, and is designed to deliver doxycycline unless there are contraindications to doxycycline.

Until antibiotic susceptibility results of the implicated strain are available, initial prophylaxis for prevention of plague after exposure to *Y. pestis* is doxycycline with ciprofloxacin as an alternative option.¹ Following an intentional release, if susceptibility testing suggests resistance to doxycycline, Oregon Health Authority will specify whether another regimen is indicated for prophylaxis. All people who have been potentially exposed to *Y. pestis* should receive a 7-day course of drug therapy.

Recommendations for prophylaxis against plague must balance risks associated with treatment against those posed by the illness. Children aged 9 years or older generally can be treated with tetracycline antibiotics safely. However, in children younger than 9 years*, tetracycline antibiotics may cause discolored teeth, and rare instances of retarded skeletal growth have been reported in infants. The assessment of the Working Group is that the potential benefits of these antimicrobials in the treatment of pneumonic plague infection substantially outweigh the risks. The Working Group specifically recommends that doxycycline be used for post-exposure prophylaxis in children.¹ If the child is unable to take doxycycline or the medication is unavailable, ciprofloxacin would be recommended.

To prevent serious medical consequences associated with hypersensitivity reactions and drug interactions, the Oregon Health Authority recommends that people be medically evaluated as described in this document prior to dispensing. In the event that this is not possible due to extreme time constraints, following a non-medical model may be necessary.

*See table 1 on page 2 for dosing of children younger than 9 years.

Plague Post-Exposure Prophylaxis Dispensing Algorithm **Doxycycline Designated as Primary Drug**

All persons to receive post-exposure prophylaxis start in the “express” line. Anyone answering “yes” to any of the following questions should be routed to a medical screener for evaluation.

1. Has the patient ever had an allergic reaction to any medication in the tetracycline class?

Allergic reactions may include: hives, redness of the skin, rash, difficulty breathing, or worsening of lupus after taking one of the tetracycline class drugs, including demeclocycline (Declomycin[®]); doxycycline (Adoxa[®], Bio-Tab[®], Doryx[®], Doxy[®], Monodox[®], Periostat[®], Vibra-Tabs[®], Vibramycin[®]); minocycline (Arestin[®], Dynacin[®], Minocin[®], Vectrin[®]); oxytetracycline (Terak[®], Terra-Cortril[®], Terramycin[®], Urobiotic-[®]250[®]); or tetracycline (Achromycin V[®], Sumycin[®], Topicycline[®], Helidac).^{3,4}

Patients who are allergic to any medication in the tetracycline class should be referred to a medical screener and receive another form of therapy such as ciprofloxacin.

2. If the patient is female, is she pregnant or breast-feeding?

The assessment of the Working Group is that the potential benefits of ciprofloxacin and doxycycline in the prevention and treatment of pneumonic tularemia infection substantially outweigh the risks in pregnant women.¹

Women who are pregnant or breastfeeding should be referred to a medical screener for counseling regarding these recommendations.

3. Does this person weight less than 99 pounds (45 kilograms)?

People weighing less than 99 pounds (45 kilograms) should be referred to a medical screener to be weighed. They will receive a 7 day supply of doxycycline, 2.2 mg/kg (as described in Table 2) by mouth every 12 hours.

Table 2

Weight (lbs)	Weight (kg)	Dose (mg)	Available Dosage Forms of Doxycycline				
			20 mg Tablet	50 mg tablet Or capsule	100mg tablet* or capsule	25mg/5mL suspension*	50mg/5mL syrup
5-10	2-5	10				2mL	1mL
11-20	6-9	20	1			4mL	2mL
21-30	10-14	30				6mL	3mL
31-40	15-19	40	2			8mL	4mL
41-50	20-22	50		1	1/2	10mL	5mL
51-60	23-27	60	3			12mL	6mL
61-70	28-32	70				14mL	7mL
71-80	32-26	80	4			16mL	8mL
81-90	37-41	90				18mL	9mL
91-200	≥42	100	5	2	1	20mL	10mL

*Dosage Forms available through the CDC National Pharmaceutical Stockpile Program
<http://www.cdc.gov/phpr/stockpile/stockpile.htm>

4. Is this person younger than 9 years?

Doxycycline and other tetracyclines are not normally recommended for children and pregnant women due to the risk of dental staining of the primary teeth, concerns about possible depressed bone growth, defective dental enamel, and rare liver toxicity. Therefore, children and pregnant and lactating women will not normally receive doxycycline.

Due to the risk of teeth discoloration associated with tetracyclines, children without a quinolone allergy, who don't have all of their permanent teeth, should be prescribed ciprofloxacin. Since the age at which a child obtains his/her permanent teeth varies, it is possible for children under the age of 9

years to receive doxycycline. The parent or guardian of the child should be asked whether the child has a full set of permanent teeth.

5. People answering “no” to all of the above questions.

People answering “no” to all medical screening questions should receive doxycycline as described in Table 1. Duration of post-exposure prophylaxis to prevent pneumonic plague infection is 7 days.

Plague Post-exposure Prophylaxis if Ciprofloxacin is Designated as Alternative Primary Drug

All people to receive post-exposure prophylaxis start in the “express” line. Anyone answering “yes” to any of the following questions should be routed to a medical screener for evaluation.

1. Has this person ever had an allergic reaction to any medication in the quinolone class?

Allergic reactions may include: difficulty breathing, rash, itching, hives, yellowing of the eyes or skin, swelling of the face or neck, cardiovascular collapse, loss of consciousness, hepatic necrosis (death of liver cells), or Stevens-Johnson Disease (a rare but severe skin reaction) after taking a quinolone class drug, including: acrosoxacin or rosoxacin (Eradacil); cinoxacin (Cinobac); ciprofloxacin (Cipro, Ciloxan); gatifloxacin (Tequin); grepafloxacin (Raxar); levofloxacin (Levaquin, Quixin); lomefloxacin (Maxaquin); moxifloxacin (Avelox, ABC Pak); nadifloxacin (Aquatim); norfloxacin (Chibroxin, Noroxin); nalidixic acid (NegGram); ofloxacin (Floxin, Ocuflox); oxolinic acid; pefloxacin (Peflacin); rufloxacin; sparfloxacin (Zagam, Respipac); temafloxacin; trovafloxacin or alatrofloxacin (Trovan).⁴

People who have had an allergic reaction to any medication in the quinolone class should be referred to a medical screener and receive another form of therapy such as doxycycline.

2. If the patient is female, is she pregnant or breast-feeding?

The assessment of the Working Group is that the potential benefits of ciprofloxacin and doxycycline in the prevention and treatment of pneumonic tularemia infection substantially outweigh the risks in pregnant women.¹

Women who are pregnant or breastfeeding should be referred to a medical screener for counseling regarding these recommendations.

3. Does the patient have known kidney problems?

Patients with kidney problems include those receiving dialysis, with known kidney failure (end-stage renal disease) or who have reduced kidney function. Patients who have chronic kidney infections or kidney stones do not need an adjusted dose, unless they have been told by a healthcare professional that they have kidney damage.

4. Is person with kidney problems 73 pounds (33 kilograms) or greater?

Use the chart⁵ below to determine the dose of ciprofloxacin when creatinine clearance is known or can be determined. If creatinine clearance is unknown, give ciprofloxacin 500 mg by mouth ONCE a day, and refer the person to a physician for further assessment. Give all patients a 7-day supply of medication.

Table 3⁵

Kidney Function	Ciprofloxacin Dose
Creatinine Clearance >50mL/min	500 mg every 12 hours
Creatinine Clearance = 30–50mL/min	250 mg every 12 hours
Creatinine Clearance = 5–29mL/min	250 mg every 18 hours
Hemodialysis	250 mg every 24 hours

If person with kidney problems weighs less than 73 pounds, refer for medical consultation.

5. Does this person weigh less than 73 pounds (33 kilograms)?

Patients who weigh less than 73 pounds (33 kilograms) should receive a 7-day supply of ciprofloxacin 20mg/kg (as described in the chart below) by mouth every 12 hours.

Table 4

Weight (lbs)	Weight (kg)	Dose (mg)	Available Dosage Forms of Ciprofloxacin				
			100mg Tablet	250mg Tablet	500mg Tablet*	250/5mL Suspension*	500mg/5mL suspension
7-12 lbs	3-5kg	50mg PO BID	1/2	1/4		1mL (1 bottle)	0.5mL (1 bottle)
13-22 lbs	6-10kg	100mg PO BID	1			2mL (1 bottle)	1mL (1 bottle)
18-28 lbs	8-13kg	125mg PO BID		1/2		2.5mL (1 bottle)	1.25mL (1 bottle)
22-33 lbs	10-15kg	150mg PO BID	1 1/2			3mL (1 bottle)	1.5mL (1 bottle)
29-44 lbs	13-20kg	200mg PO BID	2			4mL (1 bottle)	2mL (1 bottle)
36-56 lbs	16-25kg	250mg PO BID		1		5mL (1 bottle)	2.5mL (1 bottle)
55-83 lbs	25-37kg	375mg PO BID		1 1/2		7.5mL 2(bottles)	3.75mL (1 bottle)
≥73 lbs	≥33kg	500mg PO BID		2		10mL (2 bottles)	5mL (1 bottle)

*Dosage Forms available through the CDC National Pharmaceutical Stockpile Program
<http://www.cdc.gov/phpr/stockpile/stockpile.htm>

6. Does this person have a history of seizures or neurologic problems?

People with a history of seizures should avoid use of ciprofloxacin if alternative antibiotics are available. Send to a medical screener to assess for use of doxycycline.

7. Is this person taking any prescription medications, over-the-counter antacids, anti-inflammatory drugs, or Tizanidine?

People who are taking any medications or over-the-counter antacids, anti-inflammatory drugs or Tizanidine should be referred to a medical screener for the review of the person's medical and drug history, as these drugs can have interactions with antibiotics used for plague prophylaxis. See Attachment 2 for drug interactions with ciprofloxacin.

8. People answering “no” to all of the above questions

People >73 pounds (33 kilograms) should receive ciprofloxacin 500 mg by mouth every 12 hours for 7 days as described in Table 1 on page 2.

Attachment 1 Tetracycline Drug Interactions⁶

Other Drug	Effect	Recommendation
Antacids (containing aluminum, calcium or magnesium salts) Iron salts Zinc salts	Tetracyclines administered with aluminum, calcium, magnesium, iron or zinc salts form an insoluble chelate, thereby decreasing the absorption and serum levels of the tetracycline.	Administer tetracyclines 1 hour before or 2 hours after these agents
Barbiturates – Phenobarbital, amobarbital, aprobarbital, butabarbital, secobarbital (various brand names)	Barbiturates increase the hepatic metabolism of doxycycline, thereby decreasing doxycycline's half-life and serum levels.	Adjust doxycycline dose as needed. Consider using an alternative tetracycline.
Bismuth salts	Co-administration of bismuth salts in liquid formulations may decrease the serum levels of tetracyclines.	Give the bismuth salt 2 hours after the tetracycline.
Carbamazepine (Atretol [®] , Epitol [®] , Tegretol [®] , Carbatrol [®]) anticonvulsant	Carbamazepine may decrease the half-life and serum levels of doxycycline due to increased hepatic metabolism.	Adjust doxycycline dose as needed. Consider using an alternative tetracycline.
Cholestyramine (LoCHOLEST [®] , Questran [®] , Prevalite [®]) Colestipol (Colestid [®]) treatment for hyperlipidemia	Co-administration may decrease or delay the absorption of tetracyclines, therefore decreasing the serum concentrations.	Adjust the tetracycline dose if needed.
Contraceptives, oral	Tetracyclines may interfere with the enterohepatic recirculation of certain contraceptive steroids, leading to reduced efficacy. Although infrequently reported,	Counsel patient regarding use of alternative contraceptives while taking tetracyclines.

⁶ Adapted from Drug Facts and Comparison, 2013, 68th Edition. Lippincott Williams & Wilkins

Attachment 1 Cont. Tetracycline Drug Interactions⁶

Other Drug	Effect	Recommendation
Digoxin (Lanoxin [®] , Lanoxicaps [®]) cardiac glycoside	Co-administration may result in increased serum levels of digoxin in a small subset of patients (~10%).	Monitor digoxin levels and signs of toxicity.
Insulin	The ability of insulin to produce hypoglycemia may be potentiated.	In diabetic patients, monitor blood glucose concentrations closely and tailor the insulin regimen as needed.
Isotretinoin (Accutane [®] , Claravis [®]) acne treatment	Isotretinoin use has been associated with a number of cases of pseudotumor cerebri, some of which involved co-administration of tetracyclines.	Avoid concomitant use.
Methoxyflurane (Penthrane [®]) general anesthetic	Co-administration may enhance the risk for renal toxicity; deaths have been reported.	Do not co-administer.
Penicillins (various brand names)	The bacteriostatic action of tetracyclines may interfere with the bactericidal activity of penicillins.	Consider avoiding this combination, if at all possible.
Phenytoin (Dilantin [®]) anticonvulsant	Phenytoin appears to induce the metabolism of doxycycline causing the half-life to be significantly decreased.	Increased doxycycline dosage may be needed.
Rifamycins – Rifampin, rifabutin, rifapentin	Rifamycins appear to induce the metabolism of doxycycline causing the half-life to be significantly decreased.	Increased doxycycline dosage may be needed.

⁶Adapted from Drug Facts and Comparison, 2013, 68th Edition. Lippincott Williams & Wilkins

Attachment 1 Cont. Tetracycline Drug Interactions⁶

Other Drug	Effect	Recommendation
Theophylline (various brand names) bronchodilator	The incidence of adverse reactions to theophyllines may be increased.	Monitor theophylline levels and adjust dose as needed.
Urinary alkalinizers (e.g., sodium lactate, potassium citrate)	Co-administration may result in increased excretion of the tetracyclines and decreased serum levels.	Separate administration by 3 to 4 hours; however, this may not be effective, and an increase in tetracycline dose may be necessary if the pH of the urine remains increased.
Warfarin, (Coumadin [®]) anticoagulants	The action of oral anticoagulants may be increased because of the elimination of vitamin K-producing gut bacteria by tetracyclines.	Monitor coagulation parameters and adjust anticoagulant dose as needed.

⁶ Adapted from Drug Facts and Comparison, 2013, 68th Edition. Lippincott Williams & Wilkins

Attachment 2 Ciprofloxacin Drug Interactions⁶

Other Drug	Effect	Recommendation
Antacids	Decreased GI absorption of quinolones resulting in decreased serum levels. Bioavailability of ciprofloxacin may be reduced by as much as 90%.	Avoid simultaneous use.
Caffeine	The hepatic metabolism of caffeine is decreased by certain quinolones; therefore, the pharmacologic effects of caffeine may be increased.	
Cyclosporine (various brand names) immunosuppressant	Increased cyclosporine toxicity. The mechanism is unknown.	
Cimetidine (Tagamet [®]) ulcer treatment	Cimetidine may interfere with the elimination of the fluoroquinolones.	
Dairy products	Reduce the absorption of ciprofloxacin.	Ciprofloxacin should not be taken with dairy products.
Didanosine (Videx [®]) Antiretroviral agent	The magnesium and aluminum cations in the buffers present in didanosine tablets decrease the GI absorption of quinolones via chelation.	Avoid simultaneous use.
Iron salts	GI absorption of certain quinolones may be decreased by formation of an iron-quinolone complex.	Avoid co-administration of these drugs.
NSAIDs Nonsteroidal anti-inflammatory drugs	Concurrent administration of NSAIDs with a quinolone may increase the risk of CNS stimulation and convulsive seizures.	

⁶ Adapted from Drug Facts and Comparison, 2013, 68th Edition. Lippincott Williams & Wilkins

Attachment 2 Cont. Ciprofloxacin Drug Interactions⁶

Other Drug	Effect	Recommendation
Probenecid Gout treatment	Diminished urinary excretion of the quinolones has been reported during concomitant administration with probenecid.	Due to the interaction between probenecid and ciprofloxacin, probenecid should be temporarily stopped.
Sucralfate (Carafate [®]) ulcer treatment	Decreased GI absorption of quinolones.	Avoid simultaneous use; administer sucralfate \geq 6 hours after the quinolone.
Theophylline (various brand names) bronchodilator	Administration of theophylline with ciprofloxacin has decreased theophylline clearance and increased plasma levels and symptoms of toxicity, including seizures.	Use an alternative antibiotic or decrease the dose of theophylline by 50%.
Tizanidine (Zanaflex Capsules [™]), (Zanaflex [®] Tablets)	Ciprofloxacin strongly potentiates the action of tizanidine, resulting in low blood pressure and CNS depression. Patients should be advised not to stop tizanidine suddenly as rebound hypertension and tachycardia may occur.	Patients requiring tizanidine should use Doxycycline whenever possible.
Warfarin, (Coumadin [®]) anticoagulants	Quinolones decrease the clearance of the R-warfarin, the less active isomer of racemic warfarin. The clearance of the active S-isomer is not affected, and changes in clotting time have not been observed.	Monitor prothrombin times when given concomitantly.

⁶ Adapted from Drug Facts and Comparison, 2013, 68th Edition. Lippincott Williams & Wilkins

References

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