

**DEPARTMENT OF HUMAN SERVICES  
PUBLIC HEALTH DIVISION  
ACUTE AND COMMUNICABLE DISEASE PROGRAM**

**Model Standing Order for  
Anthrax Prophylaxis**

**I. ORDER**

1. Follow the nursing assessment of individuals presenting for prophylactic treatment to a known or potentially harmful biological agent.
2. Provide patient information about anthrax 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 Strategic National Stockpile program.

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Signature, Health Officer

Date

**II. Persons for whom prophylaxis may be ordered**

1. Persons who have a confirmed or highly suspect exposure to *Bacillus anthracis* as determined by the local Health Officer;
2. Persons 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.

December 22, 2006

Table 1

<b>Recommended Therapy for Inhalational Anthrax in a Mass Casualty Setting or for Postexposure Prophylaxis <sup>a</sup></b>			
<b>Category</b>	<b>Initial oral therapy</b>	<b>Alternative therapy if strain is proved susceptible</b>	<b>Duration after Exposure</b>
<b>Adults</b>	Ciprofloxacin <sup>b</sup> 500 mg orally every 12 hours	Doxycycline <sup>c</sup> 100 mg orally every 12 hours Amoxicillin <sup>d</sup> 500 mg orally every 8 hours	60 days
<b>Children</b>	Ciprofloxacin <sup>b, e</sup> 20-30 mg/kg/d orally taken in 2 daily doses, not to exceed 1 g/d	Weight $\geq$ 20 kg: Amoxicillin <sup>d</sup> 500 mg orally every 8 hours Weight <20 kg: Amoxicillin <sup>d</sup> 40 mg/kg orally in 3 doses every 8 hours	60 days
<b>Pregnant women <sup>f</sup></b>	Ciprofloxacin <sup>b</sup> 500 mg orally every 12 hours	Amoxicillin <sup>d</sup> 500 mg orally every 8 hours	60 days
<b>Immunosuppressed persons</b> : Same as for nonimmunosuppressed adults and children			
<p><sup>a</sup> Some of these recommendations are based on animal studies or in vitro studies and are not approved by the US Food and Drug Administration.</p> <p><sup>b</sup> In vitro studies suggest ofloxacin (400 mg orally every 12 hours) or levofloxacin (500 mg orally every 24 hours) could be substituted for ciprofloxacin.</p> <p><sup>c</sup> In vitro studies suggest that 500 mg of tetracycline orally every 6 hours could be substituted for doxycycline. In addition, 400 mg of gatifloxacin or monifloxacin, both fluoroquinolones like ciprofloxacin, taken orally daily could be substituted.</p> <p><sup>d</sup> According to the Centers for Disease Control and Prevention recommendations, amoxicillin is suitable for post exposure prophylaxis only after 10 to 14 days of fluoroquinolone or doxycycline, and then only if there are contraindications to these 2 classes of medications (e.g., pregnancy, lactating mother, age &lt;18 years or intolerance of other antibiotics).</p> <p><sup>e</sup> Doxycycline could also be used if antibiotic susceptibility testing, exhaustion of drug supplies, adverse reactions preclude use of ciprofloxacin. For children heavier than 45 kg, adult dosage should be used. For children lighter than 45 kg, 2.2 mg/kg of doxycycline orally every 12 hours should be used.</p> <p><sup>f</sup> See "Management of Special Groups" section of Inglesby, et al, for details.</p>			

## Reference:

Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a Biological Weapon, 2002: Updated Recommendations for Management. JAMA 2002; 287:2236-2252.

## Anthrax Postexposure Prophylaxis

Reports have been published of engineered strains of tetracycline-resistant and quinolone-resistant *Bacillus anthracis*.<sup>1,2</sup> There is also a possibility for resistance to penicillins through induction of beta-lactamase enzymes. For these reasons, public health officials will test the antibiotic susceptibility of clinical isolates, to determine drug selection. Based upon these susceptibility results, the most widely available, efficacious, and least toxic antibiotic will be dispensed for postexposure prophylaxis.<sup>1</sup>

Until antibiotic susceptibility results of the implicated strain are available, initial therapy for postexposure prophylaxis for prevention of anthrax after intentional exposure of *Bacillus anthracis* is doxycycline or ciprofloxacin.<sup>3</sup> Following a terrorist attack, public health officials of the Oregon Department of Human Services will designate which of these two drugs will be the primary drug to use for prophylaxis.

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.

Ciprofloxacin and other quinolones are not normally recommended in children and pregnant women due to the risk of arthropathy.<sup>1,4,5</sup> This recommendation is based on studies in animals. Data in humans have not confirmed this risk. The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice recommend the use of ciprofloxacin in pregnant or lactating women for postexposure prophylaxis for prevention of anthrax after intentional exposure of *Bacillus anthracis*.<sup>6</sup> Children and pregnant and lactating women without an allergy to quinolones should receive ciprofloxacin according to this algorithm. The risks associated with the serious and life-threatening complications from anthrax outweigh any risks from taking ciprofloxacin. If susceptibility to penicillin is confirmed, prophylactic therapy for children and pregnant women should be changed to amoxicillin.<sup>3</sup>

All patients who have been potentially exposed to anthrax should receive an initial 10-day supply of drug. Public health officials will advise people to return for follow-up in 7-10 days to obtain an additional supply (50 days) of medication to complete a full course of therapy (60 days). At the follow-up visit, susceptibility data will be available, and drugs may be changed.

To prevent serious medical consequences associated with hypersensitivity reactions and drug interactions, The Oregon Department of Human Services recommends that patients 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.

The use of postexposure use of anthrax vaccine in combination with antibiotics has been shown to be effective at preventing disease in nonhuman primates after exposure to *B. anthracis* spores.<sup>7</sup> Use of anthrax vaccine is not discussed in this document. However, it is possible that once the release of anthrax has been confirmed the vaccine will be made available to the affected population. If so, Department of Human Services will provide guidelines for administration.

## **Anthrax Postexposure Prophylaxis** **Ciprofloxacin Designated as Primary Drug**

All patients to receive postexposure prophylaxis start in the “express” line. Anyone answering “yes” to any of the following questions will be routed to a medical screener.

### **1. Has the patient 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 Steven-Johnson Disease (a rare skin disease) after taking a quinolone class drug, including: acrosoxacin or rosoxacin (Eradacil); cinoxacin (Cinobac); ciprofloxacin (Aeroseb-Dex, Ciloxan, Cipro, Cipro Cystitis Pack, Cipro HC Cipro XR); gatifloxacin (Tequin, Zymar); grepafloxacin (Raxar); levofloxacin (Levaquin, Quixin); lomefloxacin (Maxaquin); moxifloxacin (Avelox, ABC Pak, Vigamox); nadifloxacin (Acuatim); norfloxacin (Chibroxin, Noroxin); nalidixic acid (NegGram); ofloxacin (Floxin, Ocuflax); oxolinic acid (Utibid); pefloxacin (Peflacin, Uroquina); rosoxacin (Eradacil); rufloxacin (Ruflox); sparfloxacin (Zagam, Respipac); temafloxacin (Omniflox); trovafloxacin or alatrofloxacin (Trovan).<sup>8</sup>

Patients 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.

For people who have allergic reactions to drugs in the quinolone and tetracycline classes, other options for prophylactic therapy include: amoxicillin/clavulanate, clindamycin, rifampin, imipenem, aminoglycosides, chloramphenicol, vancomycin, cefazolin, tetracycline, linezolid, or a macrolide (clarithromycin, erythromycin).<sup>1,9</sup> These other drugs are not approved by the Food and Drug Administration for prevention of anthrax and require individual prescribing by a medical doctor or dispensing under an investigational new drug application.

### **2. Does the patient weigh less than 73 pounds (33 kilograms)?**

Ciprofloxacin and other quinolones are not normally recommended in children and pregnant women due to the risk of arthropathy.<sup>1,4,5</sup> This recommendation is based on studies in animals. Data in humans have not confirmed this risk. Therefore, children and pregnant and lactating women without an allergy to

quinolones should receive ciprofloxacin as described in Tables 1 and 2. The risks associated with the serious and life-threatening complications from anthrax outweigh any risks from taking ciprofloxacin.

People weighing less than 73 pounds (33 kilograms) should be referred to a medical screener, where they will receive the appropriate dose of ciprofloxacin for their weight. Ciprofloxacin dosage should not exceed 1 g/day in children.

Patients less than 73 pounds (33 kilograms) should receive a 10-day supply of ciprofloxacin, 10-15 mg/kg (as described in Table 2) by mouth every 12 hours with a mandatory follow-up appointment in 7-10 days. At that time, information about the effectiveness of certain medications in preventing anthrax will be available, and the drug may be changed. A minimum of 60 days of drug therapy is necessary for the full protective effect.<sup>3</sup> Table 2 purposefully reflects more than one dose for a particular weight to permit flexibility in dosing based upon the products that are available at the time of dispensing. These doses are within the recommended ranges for ciprofloxacin: 10-15 mg/kg.

Table 2

Weight (pounds)	Weight (kilogram)	Dose (mg)	Available Dosage Forms of Ciprofloxacin				
			100mg tablet	250mg tablet	500mg tablet*	250mg/5mL suspension*	500mg/5mL suspension
7-12 lbs	3-5 kg	50 mg PO BID	½	¼		1 mL (1 bottle)	0.5 mL (1 bottle)
13-22 lbs	6-10 kg	100 mg PO BID	1			2 mL (1 bottle)	1 mL (1 bottle)
18-28 lbs	8-13 kg	125 mg PO BID		½	¼	2.5 mL (1 bottle)	1.25 mL (1 bottle)
22-33 lbs	10-15 kg	150 mg PO BID	1½			3 mL (1 bottle)	1.5 mL (1 bottle)
29-44 lbs	13-20 kg	200 mg PO BID	2			4 mL (1 bottle)	2 mL (1 bottle)
36-56 lbs	16-25 kg	250 mg PO BID		1	½	5 mL (1 bottle)	2.5 mL (1 bottle)
55-83 lbs	25-37 kg	375 mg PO BID		1½	¾	7.5 mL (2 bottles)	3.75 mL (1 bottle)
≥73 lbs	≥ 33 kg	500 mg PO BID		2	1	10 mL (2 bottles)	5 mL (1 bottle)

\* Dosage Forms available through the CDC National Pharmaceutical Stockpile Program.

### 3. Is the patient pregnant or breastfeeding?

Ciprofloxacin and other quinolones are not normally recommended in children and pregnant women due to the risk of arthropathy.<sup>1,4,5</sup> This recommendation is based on studies in animals. Data in humans have not confirmed this risk. The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice recommend the use of

ciprofloxacin in pregnant or lactating women for postexposure prophylaxis for prevention of anthrax after intentional exposure of *Bacillus anthracis*.<sup>6</sup> Children and pregnant and lactating women without an allergy to quinolones should receive ciprofloxacin as described in Tables 1 and 2. The risks associated with the serious and life-threatening complications from anthrax outweigh any risks from taking ciprofloxacin. If susceptibility to penicillin is confirmed, prophylactic therapy for children and pregnant women should be changed to amoxicillin.<sup>3</sup>

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

#### 4. Does the patient have 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 health care professional that they have kidney damage.

Patients with kidney problems who weigh less than 73 pounds should be referred to a medical screener.

Give patients  $\geq 73$  pounds (33 kilograms) with kidney problems ciprofloxacin 500 mg by mouth ONCE a day, and refer them to a physician for further assessment. Use the Table 3<sup>10</sup> to determine the dose of ciprofloxacin required for patients with kidney problems when creatinine clearance is known or can be determined. Give all patients an initial 10-day supply of medication, and schedule a follow-up appointment within 10 days. At that time, information about the effectiveness of certain medications in preventing anthrax will be available, and the drug may be changed. A minimum of 60 days of drug therapy is necessary for the full protective effect.<sup>3</sup>

Table 3

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

**5. Does the patient 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.

**6. Is the patient taking any prescription medications or over-the-counter antacids or anti-inflammatory drugs?**

People who are taking any medications or over-the-counter antacids or anti-inflammatory drugs 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 anthrax prophylaxis. See Attachment 1 for drug interactions with ciprofloxacin.

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

Patients  $\geq 73$  pounds (33 kilograms) should receive ciprofloxacin 500 mg by mouth every 12 hours for 10 days (as described in Table 1), with a mandatory follow-up appointment within 10 days. At that time, information about the effectiveness of certain medications in preventing anthrax will be available, and the drug may be changed. A full course of therapy (60 days) is necessary for the full protective effect.<sup>3</sup>

## **Anthrax Postexposure Prophylaxis** **Doxycycline Designated as Primary Drug**

All patients to receive postexposure prophylaxis start in the “express” line. Anyone answering “yes” to any of the following five questions will be routed to a medical screener.

### **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); tetracycline (Achromycin V, Sumycin, Topicycline, Helidac).<sup>8,11</sup>

Patients who are allergic to any medication in the tetracycline class should receive another form of therapy such as ciprofloxacin.

For people who have allergic reactions to drugs in the quinolone and tetracycline classes, other options for prophylactic therapy include: amoxicillin/clavulanate, clindamycin, rifampin, imipenem, aminoglycosides, chloramphenicol, vancomycin, cefazolin, tetracycline, linezolid, or a macrolide (clarithromycin, erythromycin).<sup>1,9</sup> These other drugs are not approved by the Food and Drug Administration for prevention of anthrax and require individual prescribing by a medical doctor or dispensing under an investigational new drug application.

### **2. Does the patient weight less than 99 pounds (45 kilograms)?**

Patients weighing less than 99 pounds (45 kilograms), should be referred to a medical screener to be weighed. 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. The American College of Obstetricians and Gynecologists’ Committee on Obstetric Practice recommend the use of ciprofloxacin in pregnant or lactating women for postexposure prophylaxis for prevention of anthrax after intentional exposure of *Bacillus anthracis*.<sup>6</sup> Therefore, children and pregnant and lactating women will not normally receive doxycycline. If

susceptibility to penicillin is confirmed, prophylactic therapy for children and pregnant women should be changed to amoxicillin.<sup>3</sup>

Patients weighing less than 99 pounds (45 kilograms), should be referred to a medical screener to be weighed. They will receive an initial 10-day supply of doxycycline 2.2 mg/kg (as described in Table 4) by mouth every 12 hours with a mandatory follow-up appointment within 10 days. At that time, information about the effectiveness of certain medications in preventing anthrax will be available, and the drug may be changed. A minimum of 60 days of drug therapy is necessary for the full protective effect.<sup>3</sup>

Table 4

Weight (lbs)	Weight (kg)	Dose (mg)	Available Dosage Forms of Doxycycline				
			20 mg tablet	50mg tablet or capsule	100mg tablet* or capsule	25mg/5mL suspension*	50mg/5mL syrup
5-10	2-5	10				2 mL	1 mL
11-20	6-9	20	1			4 mL	2 mL
21-30	10-14	30				6 mL	3 mL
31-40	15-19	40	2			8 mL	4 mL
41-50	20-22	50		1	½	10 mL	5 mL
51-60	23-27	60	3			12 mL	6 mL
61-70	28-32	70				14 mL	7 mL
71-80	33-36	80	4			16 mL	8 mL
81-90	37-41	90				18 mL	9 mL
91-100	> 42	100	5	2	1	20 mL	10 mL

\*Dosage Forms available through the CDC National Pharmaceutical Stockpile Program

### 3. Is the patient 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 have not received 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.

**4. Is the patient pregnant or breast-feeding?**

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. The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice recommend the use of ciprofloxacin in pregnant or lactating women for postexposure prophylaxis for prevention of anthrax after intentional exposure of *Bacillus anthracis*.<sup>6</sup> If susceptibility to penicillin is confirmed, prophylactic therapy for children and pregnant women should be changed to amoxicillin.<sup>3</sup>

**5. Is the person taking any prescription medications or over-the-counter antacids or anti-inflammatory drugs?**

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

**6. People answering "no" to all of the above questions**

Patients weighing  $\geq 99$  pounds should receive an initial 10-day supply of doxycycline 100 mg by mouth every 12 hours (as described in Table 1) with a mandatory follow-up appointment within 10 days. At that time, information about the effectiveness of certain medications in preventing anthrax will be available, and the drug may be changed. A minimum of 60 days of drug therapy is necessary for the full protective effect.<sup>3</sup>

## References

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**Attachment 1****Ciprofloxacin Drug Interactions<sup>1</sup>**

<b>Other Drug</b>	<b>Effect</b>	<b>Recommendation</b>
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%.
Sucralfate (Carafate <sup>®</sup> ) ulcer treatment	Decreased GI absorption of quinolones.	Avoid simultaneous use; administer sucralfate $\geq$ 6 hours after the quinolone.
Iron salts	GI absorption of certain quinolones may be decreased by formation of an iron-quinolone complex.	Avoid coadministration of these drugs.
Didanosine (Videx <sup>®</sup> ) 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.
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.	

<sup>1</sup> Adapted from Drug Facts and Comparison, 2004 Edition.

<b>Other Drug</b>	<b>Effect</b>	<b>Recommendation</b>
Cimetidine (Tagamet <sup>®</sup> ) ulcer treatment	Cimetidine may interfere with the elimination of the fluoroquinolones.	
Probenecid Gout treatment	Diminished urinary excretion of the quinolones have been reported during concomitant administration with probenecid.	Due to the interaction between probenecid and ciprofloxacin, probenecid should be temporarily stopped.
Warfarin, (Coumadin <sup>®</sup> ) 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.
NSAIDs Nonsteroidal anti-inflammatory drugs	Concurrent administration of NSAIDs with a quinolone may increase the risk of CNS stimulation and convulsive seizures.	
Dairy products	Reduce the absorption of ciprofloxacin.	Ciprofloxacin should not be taken with dairy products.

## Attachment 2 Tetracycline Drug Interactions<sup>2</sup>

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, butobarbital, 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	Coadministration of bismuth salts in liquid formulations may decrease the serum levels of tetracyclines.	Give the bismuth salt 2 hours after the tetracycline.
Carbamazepine (Atretol <sup>®</sup> , Epitol <sup>®</sup> , Tegretol <sup>®</sup> , Carbatrol <sup>®</sup> ) 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 <sup>®</sup> , Questran <sup>®</sup> , Prevalite <sup>®</sup> ) Colestipol (Colestid <sup>®</sup> ) treatment for hyperlipidemia	Coadministration may decrease or delay the absorption of tetracyclines, therefore decreasing the serum concentrations.	Adjust the tetracycline dose if needed.
Phenytoin (Dilantin <sup>®</sup> ) anticonvulsant	Phenytoin appears to induce the metabolism of doxycycline causing the half-life to be significantly decreased.	Increased doxycycline dosage may be needed.

<sup>2</sup> Adapted from Drug Facts and Comparison, 2004 Edition.

Other Drug	Effect	Recommendation
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.
Urinary alkalinizers (e.g., sodium lactate, potassium citrate)	Coadministration 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 <sup>®</sup> ) 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.
Contraceptives, oral	Tetracyclines may interfere with the enterohepatic recirculation of certain contraceptive steroids, leading to reduced efficacy. Although infrequently reported, contraceptive failure is possible.	Counsel patient regarding use of alternative contraceptives while taking tetracyclines.
Digoxin (Lanoxin <sup>®</sup> , Lanoxicaps <sup>®</sup> ) cardiac glycoside	Coadministration 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 <sup>®</sup> , Claravis <sup>®</sup> ) acne treatment	Isotretinoin use has been associated with a number of cases of pseudotumor cerebri, some of which involved coadministration of tetracyclines.	Avoid concomitant use.

<b>Other Drug</b>	<b>Effect</b>	<b>Recommendation</b>
Methoxyflurane (Penthrane <sup>®</sup> ) general anesthetic	Coadministration may enhance the risk for renal toxicity; deaths have been reported.	Do not coadminister.
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.
Theophylline (various brand names) bronchodilator	The incidence of adverse reactions to theophyllines may be increased.	Monitor theophylline levels and adjust dose as needed.