



# World of Drug Information

Volume 12, Issue 4 – December 2001

## Preventing and Treating Anthrax from Bioterrorist Attacks

CURRENT CLINICAL  
ISSUES

**Goal:** To educate healthcare practitioners about the recommended therapy for anthrax in case of a bioterrorist attack.

**Objectives:**

1. Summarize the various forms of anthrax disease.
2. Provide information on the dosage schedule of the anthrax vaccine and its side effects.
3. Provide detailed information on the currently recommended therapy for post-exposure prophylaxis and treatment of anthrax.

**Introduction:**

Bioterrorism was considered a credible threat long before September 11<sup>th</sup>. Reports of the possibility of bioterrorist attacks would appear sporadically in the newspapers, magazines and TV news shows. The list of potential bioterrorist diseases included brucellosis, plague, Q fever, tularemia, viral encephalitides, viral hemorrhagic fevers, botulinum toxins, staphylococcal enterotoxin B, anthrax and smallpox. (Franz, 1997) Experts speculated that it was not a matter of “if” it would happen but “when.” Then suddenly after September 11<sup>th</sup>, the possibility of bioterrorism seemed more real rather than a thought provoking news piece. Shortly thereafter, the first case of anthrax in Florida was announced...and then another, and another and another. So far, except for a few isolated cases, anthrax has proved to be more a time and resource consuming problem than a widespread public health problem. The potential and fear of greater consequences from

anthrax still exists. Consequently, it is imperative that healthcare professionals be aware of the current therapy and treatment options available to treat such patients.

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## **Anthrax:**

### *Inhalation*

The disease anthrax is a consequence of infection by the spores of the bacterium *Bacillus anthracis*. The three forms of anthrax disease are cutaneous, gastrointestinal and inhalation with inhalation being the most deadly. The estimated infectious dose of inhalation anthrax is 8,000-50,000 spores (CDC, Dec.15, 2000). The size of the aerosolization particles influences the infectivity of the agent. After initial aerosolization, any particles greater than 5 microns will quickly fall from the atmosphere and bond to any surface. The energy to resuspend these particles is thought to be too great to be a threat of infection by inhalation (CDC, Dec.15, 2000). Particles 1-5 microns behave as a gas and will not settle. Aerosolized anthrax spores > 5 microns will settle in the upper respiratory tract. Spores between 2 and 5 microns are able to travel much deeper, going into the alveolar ducts and alveoli. (Shafazan, 1999) While the initial point of entry is the lung, in most cases there is no infection of the lung present when the disease manifests. This is because the spores are transported by macrophages from the lower respiratory system to the lymph nodes where the spores produce the anthrax toxin which eventually disseminates into the systemic circulation. (Dixon, 1999)

The incubation period for inhalation anthrax is thought to range from 1 to 43 days and may also be inversely related to the initial dose (CDC, Dec.15, 2000). A non-productive cough, malaise, myalgia, fever and occasional feeling of retrosternal pressure are often the first symptoms lasting an average of 4 days. (Shafazan, 1999) This phase is followed by a rapid deterioration with the onset of acute respiratory distress, hypoxemia and cyanosis. Death often occurs within 24 hours of developing this second stage of disease. In 1979, residents of Sverdlovsk, a city in the

*“While the initial point of entry is the lung, in most cases there is no infection of the lung present when the disease manifests.”*

former Soviet Union, were exposed to an accidental release of anthrax spores. The mean time between onset of symptoms and death was 3 days with a range of 1 to 10 days. (Dixon, 1999)

### *Cutaneous*

The name anthrax comes from the Greek word for coal that probably refers to the black eschar that forms in cases of cutaneous anthrax. Cutaneous anthrax typically manifests 3 to 5 days after subcutaneous inoculation of anthrax spores via a cut or abrasion. (Dixon, 1999) The primary skin lesion is normally a nondescript, painless, pruritic papule. The primary lesion forms a vesicle that undergoes central necrosis and drying, forming the characteristic black eschar, edema and a number of purplish vesicles. A painful, pustular eschar combined with fever is often indicative of a secondary infection with staphylococcus or streptococcus. (Dixon, 1999)

### *Gastrointestinal*

Gastrointestinal anthrax is most commonly caused by ingesting *B. anthracis* contaminated meat from diseased animals. Symptoms of gastrointestinal anthrax begin two to five days after ingestion. (Dixon, 1999) Symptoms include fever, diffuse abdominal pain with rebound tenderness, constipation or diarrhea, blood-tinged or coffee ground appearance vomitus and ascites. (Dixon, 1999) An oropharyngeal form of the disease is characterized by lesions at the base of the tongue or tonsils, sore throat, dysphagia, fever and regional lymphadenopathy (CDC, Dec. 15, 2000).

## **Prophylaxis:**

### *Vaccination*

Anthrax vaccine adsorbed (AVA) is the only licensed human anthrax vaccine available in the United States. Information on the efficacy of the anthrax vaccine in preventing inhalation

anthrax in humans is very limited, though the vaccine has been proven efficacious in animal models. (Shafazand, 1999) The vaccine is a mixture of cellular components including the three proteins produced by *B. anthracis*; protective antigen (PA), lethal factor (LF) and edema factor (EF). (CDC, Dec. 15, 2000) The vaccine is administered in three 0.5 ml subcutaneous injections at 0, 2, and 4 weeks followed by three booster vaccinations at 6, 12, and 18 months. (Anon., 1998) An antibody level sufficient to protect against disease is usually present 7 days after the second dose of vaccine. An annual booster injection is recommended to retain immunity. Current studies are looking at the effectiveness of fewer doses and intramuscular administration as opposed to subcutaneous. (CDC, Dec.15, 2000)

Controversy about the safety of the anthrax vaccine was raised when a few American servicemen refused to be vaccinated during the vaccination of all U.S. military personnel. The vaccine is a non-infectious sterile filtrate from the culture of an attenuated strain of *B. anthracis* and it is not possible to contract anthrax from the vaccine.

(Friedlander, 1999) In prelicensure evaluations of AVA, severe local reactions occurred after 1% of vaccinations, moderate local reactions after 3% of vaccinations, and mild local reactions occurred after 20% of vaccinations. (CDC, Dec.15, 2000) From January 1, 1990 to August 31, 2000, 1,859,000 doses of AVA were distributed in the United States. During this time the Vaccine Adverse Events Reporting System (VAERS) received 1,544 reports of adverse events to AVA. (CDC, Dec. 15, 2000) Five percent of these adverse events resulted in death, hospitalization, permanent disability or was life threatening. Injection-site hypersensitivity, injection-site edema, injection-site pain, headache, arthralgia, asthenia and pruritus were the most commonly reported side effects. (CDC, Dec. 15, 2000) As of April 12, 2000, 425, 976 U.S. service men and women had received 1,620,793 doses of anthrax vaccine. (CDC, April 28, 2000) Six thousand

*“Antibiotics are only effective against the germinating or vegetative *B. anthracis* and are not effective against the nonvegetative or spore form of the organism.”*

eight hundred seventy-nine questionnaires regarding AVA vaccination were completed by military personnel in Korea from September-October 1998. Higher rates of adverse reactions were reported by female service members. (CDC, April 28, 2000) Most adverse events reported by both men and women were localized, minor, self-limited and did not lead to impaired work performance, lost work time beyond that required to seek care, and/or a clinic visit or hospitalization. In another survey of 603 military personnel receiving anthrax vaccine, 47 (7.9%) of 595 reported seeking medical advice and/or taking time off work for an adverse effect after the first dose; after the second dose, 30 (5.1%) of 585 after the third dose 16 (3.0%) and after the fourth dose 17 (3.1%) of 536. (CDC, April 28, 2000)

### *Post-exposure prophylaxis and treatment*

“Persons with an exposure or contact with an item or environment known, or suspected to be contaminated with *B. anthracis*—regardless of laboratory tests results—should be offered

antimicrobial prophylaxis. Exposure or contact, not laboratory test results, is the basis for initiating such treatment.” (CDC, October 26, 2001) Antibiotics are only effective against the germinating or vegetative *B. anthracis* and are not effective against the nonvegetative or spore form of the organism. (CDC, Dec.15, 2000) Consequently, prolonged sustained antibiotic levels must be maintained to ensure the eradication of the *B. anthracis* organism. Isolates of *B. anthracis* from the recent cases in Florida, New York City and Washington, D.C. were found to be susceptible to ciprofloxacin, doxycycline, chloramphenicol, clindamycin, tetracycline, rifampin, vancomycin, penicillin, and amoxicillin. (CDC, October 26, 2001) The recommendation from the Center for Disease Control (CDC) for prevention of inhalation anthrax is the use of ciprofloxacin OR doxycycline. The October 31, 2001 CDC Health Advisory states that there is no evidence showing ciprofloxacin to be more or less

effective than doxycycline in preventing inhalation anthrax. (CDC Health Advisory, October 31, 2001) For prophylaxis of inhalation anthrax, the recommended therapy for adults (including immunocompromised individuals but excluding pregnant women) is ciprofloxacin 500 mg po BID or doxycycline 100 mg po BID for 60 days. (CDC, October 19, 2001) For pregnant women, ciprofloxacin 500 mg po BID for 60 days is the recommended antibiotic. (CDC, Nov. 2, 2001) Doxycycline is not recommended in pregnant patients because of the potential fetal effects. Doxycycline should only be used in pregnant patients if other antibiotics are contraindicated. If the organism proves to be susceptible to penicillin, pregnant patients may be switched to amoxicillin 500 mg po TID for 60 days. For children, the recommended prophylactic doses are: ciprofloxacin 10-15 mg/kg po q 12 hours for 60 days (not to exceed 1 gm/day) or doxycycline 100 mg po bid (>8 years and >45 kg); 2.2 mg/kg po bid (>8 years and <= 45 kg) or 2.2 mg/kg po bid (<= 8 years) for 60 days. (CDC, October 19, 2001) Because of the potential side effects of fluoroquinolones and tetracyclines in children, if the organism is found to be susceptible to penicillin, children should be switched to oral amoxicillin 80 mg/kg/day divided into 3 doses every 8 hours (not to exceed 500 mg tid).

For symptomatic cases of inhalation anthrax and gastrointestinal anthrax in adults (including pregnant and immunocompromised patients), the CDC recommends therapy with IV ciprofloxacin 400 mg q 12 hours or IV doxycycline 100 mg q 12 hours in conjunction with one or two other antibiotics with *in vitro* activity. (CDC, October 26, 2001) Therapy should continue for 60 days though patients may be switched from IV to oral therapy when clinically appropriate. While penicillin is indicated for the treatment of anthrax, penicillin or ampicillin should not be used alone to treat systemic anthrax as there has been *in vitro* data

*“The October 31, 2001 CDC Health Advisory states that there is no evidence showing ciprofloxacin to be more or less effective than doxycycline in preventing inhalation anthrax.”*

showing an increasing resistance of *B. anthracis* when exposed to semisynthetic penicillins. (CDC, October 26, 2001) It is acceptable, however, to use penicillins alone in a prophylactic setting as the number of vegetative anthrax organisms is substantially less.

Doxycycline and ciprofloxacin are also first line treatments for cutaneous anthrax. The same dosage schedule for adults and children applies as for prophylaxis of inhalation anthrax. (CDC, October 26, 2001) Intravenous therapy with a multi-antibiotic therapy should be used in cases of cutaneous anthrax with signs of systemic involvement, extensive edema or lesions on the head or neck. Previous guidelines suggested treatment for 7 to 10 days, but in cases where patients may have also inhaled the *B. anthracis*, therapy should continue for 60 days. (CDC, October 26, 2001) Patients may also be switched to oral amoxicillin once there has been clinical improvement.

## Conclusion:

Fortunately, therapeutic options exist for treating and preventing the various forms of anthrax. The effectiveness of antibiotics, however, is a race against time. The fulminant course of the disease demands rapid diagnosis and initiation of therapy and notification of others who were potentially exposed. Any delays in diagnosis or beginning appropriate therapy or prophylaxis can have catastrophic effects. And while there is an anthrax vaccine, it is in very limited supply, under tight governmental control and unavailable to the general public. Anthrax is a rare disease for which there previously was little information concerning its treatment and prevention. Since the advent of the anthrax cases in the U.S., much more information has become available and the CDC has been updating their recommendations regularly as more is learned.

*“The fulminant course of the disease demands rapid diagnosis and initiation of therapy and notification of others who were potentially exposed.”*

For the most up-to-date information on the treatment and prevention of anthrax, healthcare professionals would do well to monitor the CDC's website for the latest information regarding anthrax (<http://www.cdc.gov>).

## References:

1. Anon. Anthrax vaccine. *Med Lett Drug Ther.* 1998; 40:52-53. (IDIS Article Number 404350)
2. CDC. Surveillance for adverse events associated with anthrax vaccination – U.S. Department of Defense, 1998-2000. *MMWR* April 28, 2000;49:341-345. (IDIS Article Number 445558)
3. CDC. Use of anthrax vaccine in the United States: Recommendations of the advisory committee on immunization practices. *MMWR* December 15, 2000;49:1-20. (IDIS Article Number 458443)
4. CDC. Updated recommendations for antimicrobial prophylaxis among asymptomatic pregnant women after exposure to bacillus anthracis. *MMWR* November 2, 2001;50:960.
5. CDC. Update: Investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR* October 26, 2001;50:909-919.
6. CDC. Update: Investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. *MMWR* October 19, 2001; 50:889-893. (IDIS Article Number 471389)
7. Cieslak T J, Christopher G W, Kortepeter M G, et al. Immunization against potential biological warfare agents. *Clin Infect Dis.*2000;30:843-850. (IDIS Article Number 451516).
8. Dixon T C, Meselson M, Guillemin J, Hanna P C. Anthrax. *N Engl J Med.*1999;341:815-826. (IDIS Article Number 432452).
9. Franz D R; Jahrling P B; Friedlander A M; McClain D J; et al. Clinical recognition and management of patients exposed to biological warfare agents *JAMA.* 1997;278:399-411. (IDIS Article Number 389093)
10. Friedlander A M, Pittman P R, Parker G W. Anthrax vaccine: evidence for safety and efficacy against inhalational anthrax. *JAMA.*1999;282:2104-2106. (IDIS Article Number 437427).
11. Shafazand S, Doyle R, Ruoss S, et al. Inhalational anthrax: epidemiology, diagnosis, and management. *Chest* 1999;166:1369-1376. (IDIS Article Number 438686).
12. Official CDC Health Advisory. Use of ciprofloxacin or doxycycline for postexposure prophylaxis for prevention of inhalation anthrax, October 31, 2001. <http://www.bt.cdc.gov/CodumentsApp/Anthrax/10312001/han49asp>. Accessed November 6, 2001.



## Accreditation Information

The University of Iowa College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. The ACPE program number is 020-000-02-001-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation, and return to Iowa Drug Information Service with a \$5.00 check for the processing fee, made out to the College of Pharmacy. A certificate will be awarded upon achieving a passing grade of 70% or better. Pharmacists must complete this program by October 1, 2002 to receive credit.



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# Assessment Questions:

Circle the most appropriate answer:

- Bacillus anthracis* is a spore forming:
  - Bacteria
  - Fungus
  - Virus
  - Yeast
- The minimum number of inhaled *B. anthracis* spores most likely needed to induce inhalation anthrax would be:
  - 100
  - 1,000
  - 10,000
  - 100,000
- Cutaneous anthrax lesions are often painless unless secondary infection is present.
  - True
  - False
- An antibody level sufficient to protect against anthrax disease is thought to be present 7 days after the \_\_\_\_\_ of anthrax vaccine.
  - first dose
  - third dose
  - fifth dose
  - second dose
- From January 1, 1990 to August 31, 2000 1,859,000 doses of AVA were distributed in the United States. During this time the Vaccine Adverse Events Reporting System (VAERS) received 1,544 reports of adverse events to AVA. What percent of these reports resulted in death, hospitalization, permanent disability or was life threatening?
  - .5%
  - 1%
  - 2%
  - 5%
- According to a recommendation from the MMWR, "Persons with an exposure or contact with an item or environment known, or suspected to be contaminated with *B. anthracis*—regardless of laboratory tests results—should be \_\_\_\_\_."
  - quarantined
  - started on double antibiotic therapy
  - observed until symptoms appear before starting therapy
  - offered antimicrobial prophylaxis
- Recommended initial therapy for post-exposure inhalation anthrax prophylaxis in pregnant women is:
  - Ciprofloxacin 500 mg po bid
  - Doxycycline 100 mg po bid
  - Amoxicillin 500 mg po tid
  - Ciprofloxacin 500 mg po bid and clindamycin 300 mg po qid
- For the majority of patients, the CDC recommends initial post-exposure prevention of inhalation anthrax with ciprofloxacin or \_\_\_\_\_.
  - tetracycline
  - azithromycin
  - penicillin v
  - doxycycline
- The recommended duration of antibiotic therapy for cutaneous anthrax in which the possibility of inhalation of anthrax spores exists is:
  - 2 ½ months
  - 2 months
  - 1 ½ months
  - 1 month
- Children who have been potentially exposed to airborne anthrax spores should be started on ciprofloxacin or doxycycline. If the *B. anthracis* proves to be susceptible to penicillins, the recommendation is to switch children to therapy with:
  - ampicillin
  - ceftriaxone
  - penicillin V
  - amoxicillin

## Directions

Select the most appropriate answer for each of the following questions and circle the corresponding letter on the answer sheet.

To receive one hour of continuing education credit (0.1 CEU) for successful completion of this program, you must:

- Complete the answer sheet.
- Print or type your name, address, social security number and pharmacy license number(s) in the space provided on the CE registration form.
- Complete the program evaluation.

Mail a \$5.00 check made out to the College of Pharmacy and your completed answer sheet/registration form/evaluation to:

Iowa Drug Information Service  
ATTN: Donna Brus  
The University of Iowa  
100 Oakdale Campus N330 OH  
Iowa City, IA 52242-5000

Certificates will be issued to those who score 70% or higher. Those who score below 70% will be notified and no credit will be recorded. Please allow four weeks for processing.

**ANSWER SHEET**

- |    |   |   |   |   |     |   |   |   |   |
|----|---|---|---|---|-----|---|---|---|---|
| 1. | a | b | c | d | 6.  | a | b | c | d |
| 2. | a | b | c | d | 7.  | a | b | c | d |
| 3. | a | b | c | d | 8.  | a | b | c | d |
| 4. | a | b | c | d | 9.  | a | b | c | d |
| 5. | a | b | c | d | 10. | a | b | c | d |

**CE REGISTRATION**

(please print)

**ACPE Program #020-000-02-001-H01**

Title of Educational Activity (Article) Preventing and Treating Anthrax from Bioterrorist Attacks

Name \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

Social Security Number \* \_\_\_\_\_

Pharmacy License Number(s)\* \_\_\_\_\_

\*The University of Iowa College of Pharmacy requests this information for the purpose of processing your registration. No persons outside The University of Iowa College of Pharmacy are routinely provided this information.

*I hereby certify that I have taken this test:*

\_\_\_\_\_  
*Signature*

\_\_\_\_\_  
*Date*

**PROGRAM EVALUATION**

	Excellent				Poor
Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
	Agree				Disagree
Important to pharmacists	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me \_\_\_\_\_ hours and \_\_\_\_\_ minutes to read this article and complete the assessment questions.



# ***IDIS* Database: Herbal Recap**

The use of alternative medicine in the United States has increased from 33 percent in 1990 to 42 percent in 1997(1). Four out of ten Americans use alternative therapy. According to an article published in *JAMA* in 1998, 64 percent of the medical schools in the US offered courses involving complementary and alternative medicine as part of their curriculum. Is *IDIS* coverage of herbal medicine literature keeping up?

## **What percentage of the *IDIS* database pertains to herbal medicine?**

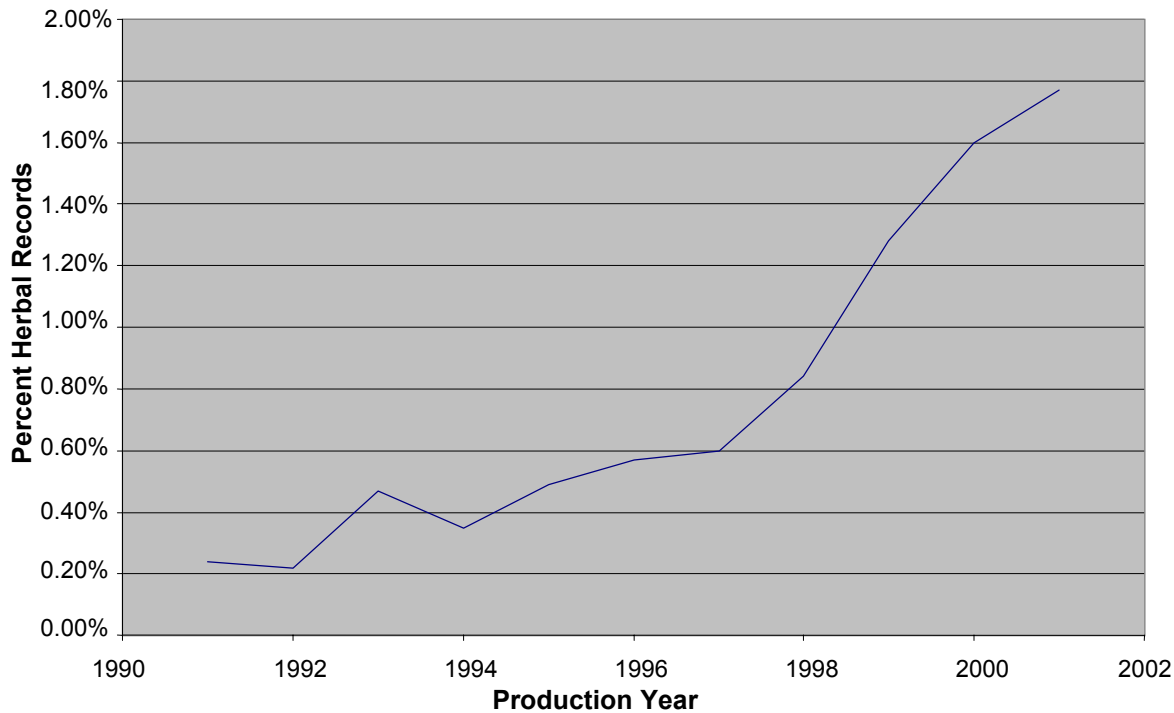
The number of records generated by searching "92510\*" (the herbal drug category) over the last eleven publication years compared with the total annual number of

records shows that *IDIS* herbal coverage increased from 0.24% in 1991 to 1.77% in 2001. The greatest and most consistent increase occurred during the late 1990's.

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001*
All Records	16,788	13,865	13,725	18,558	20,293	20,764	21,331	22,851	21,154	17,954	11,807
92510*	40	31	64	68	99	118	129	191	270	287	209
Percentage	0.24%	0.22%	0.47%	0.35%	0.49%	0.57%	0.6%	0.84%	1.28%	1.60%	1.77%

\* January-October 2001 Update

***IDIS* Herbal Coverage**



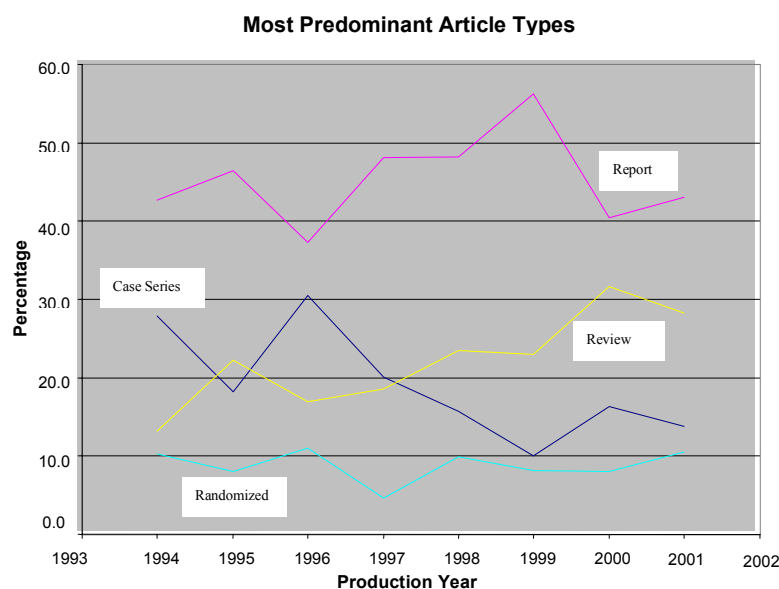
## What is the most prevalent article type found in *IDIS* herbal literature?

A search conducted with “92510\*” combined with specific study type descriptors shows that over the years, “report” is consistently the predominant article type found in herbal literature. Herbal review articles outnumber

herbal case series. Review articles constitute 31.7% of all herbal records found in 2000. The percentage of randomized studies remains stable, hovering between 8% and 11%.

Article Type	1994		1995		1996		1997		1998		1999		2000		2001*	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Case series	19	28.	18	18.2	36	30.5	26	20.1	30	15.7	27	10.	47	16.4	29	13.9
Report	29	42.6	46	46.5	44	37.3	62	48.1	92	48.2	152	56.3	116	40.4	90	43.1
Review	9	13.2	22	22.2	20	16.9	24	18.6	45	23.6	62	23.0	91	31.7	59	28.2
Case Control	1	1.5	0	0	1	.9	1	.8	0	0	0	0	0	0	1	.5
Cohort	2	2.9	1	1.	2	1.7	9	7.	4	2.1	5	1.9	8	2.8	6	2.9
Randomized	7	10.3	8	8.1	13	11.0	6	4.6	19	9.9	22	8.1	23	8.0	22	10.5
Non-Clinical	1	1.5	4	4.0	2	1.7	1	0.8	1	0.5	2	0.7	2	0.7	2	0.9
<b>Total</b>	<b>68</b>	<b>100</b>	<b>99</b>	<b>100</b>	<b>118</b>	<b>100</b>	<b>129</b>	<b>100</b>	<b>191</b>	<b>100</b>	<b>270</b>	<b>100</b>	<b>287</b>	<b>100</b>	<b>209</b>	<b>100</b>

\* January-October 2001 Update



As of November 2001, *IDIS* database contains:

- approximately 2000 herbal citations (indexed from ten alternative medicine publications and other journals)
- approximately 150 specific valid herbal drug terms
- approximately 600 cross-referenced herbal drug terms

The renewed interest in herbals as potential therapeutic treatment for various diseases is evident.

The recent addition of journals, valid and cross-referenced drug terms in the area of herbal medicine and the creation of HerbaLinks web site, <http://www.uiowa.edu/~idis/herbalinks/>, provide up-to-date information to support the pharmacist in finding the best source of herbal information.

(1) National Center for Complementary and Alternative Medicine. For consumers and practitioners. Frequently asked questions. (resource on World Wide Web). URL: (<http://nccam.nih.gov/an/general/#camsgrowing>). Available from the Internet. Accessed 2001 November 11.



ThaiBinh TonThat, R.Ph., Pharm.D.

## FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) <i>Trade Name</i>	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number ( <i>IDIS</i> Citations)*	Indication/Use	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
<b>Cefditoren Pivoxil</b> (1S)** <i>Spectracef</i>	Tap Pharmaceutical Products, Inc. (Aug. 29)	CEFDITOREN 8120672 (4 citations)	For the treatment of acute bacterial exacerbation of chronic bronchitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections.	Pharyngitis, Acute 462. Tonsillitis, Acute 463. Bronchitis, Chronic NEC 491.
<b>Darbepoetin Alfa</b> (NA)*** <i>Aranesp</i>	Amgen, Inc. (Sept. 17))	DARBEPOETIN ALFA 20040006 (2 citations)	For the treatment of anemia associated with chronic renal failure, including patients on dialysis and patient not on dialysis.	Anemia, Renal Origin 285.21
<b>Ethinyl Estradiol/ Etonogestrel</b> (1S) <i>Nuvaring</i>	Organon, Inc. (Oct. 3)	ETONOGESTREL 68320029 (6 citations) ETHINYL ESTRADIOL 68160008 (2126 citations)	For the prevention of pregnancy in women who elect to use this product as a method of contraception.	Contraceptive Management V25.
<b>Tenofovir Disoproxil Fumarate</b> (1P)**** <i>Viread</i>	Gilead Sciences, Inc. (Oct. 26)	TENOFOVIR 8180816 (6 citations)	For the treatment of HIV-1 infection in combination with other antiretroviral agents.	Syn-Acq Immune Deficiency 042. Infection, HIV, Asymptomatic V08.
<b>Zoledronic Acid</b> (1P) <i>Zometa</i>	Novartis (Aug. 20)	ZOLEDRONIC ACID 92000239 (22 citations)	For the treatment of hypercalcemia of malignancy.	Disorder, Calcium Metabolism 275.4 Neop, Mgn-NEC 199.

\* Through November 2001 Update. Complete bibliographic citations will be provided upon request.

\*\* New molecular entity given standard review by FDA.

\*\*\* Not applicable.

\*\*\*\* New molecular entity given priority review by FDA.

# New Drug Selected Bibliography

This new drug selected bibliography provides a selection of key clinical studies and reviews of new drugs approved by the FDA August 11 through October, 2001. *IDIS/CD-ROM* was searched to retrieve key articles relevant to the new drugs and their approved uses.

## Cefditoren

Kuti JL and Quintiliani R. Cefditoren pivoxil: a novel broad-spectrum oral cephalosporin. *Formulary* 2001;36:265-275. (*IDIS* Article Number 462723). *This article is a comprehensive review of cefditoren pivoxil.*

## Darbepoetin alfa

Joy MS. Novel erythropoiesis-stimulating protein: an erythropoietin analogue with an extended half-life and less frequent dosing. *Formulary* 2001;36:19-25. (*IDIS* Article Number 459281). *This article is a comprehensive review of darbepoetin alfa.*

## Tenofovir Disoproxil Fumarate

Barditch-Crovo P, Deeks SG, Collier A et al. Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. *Antimicrob Agts Chemother* 2001;45:2733-9. (*IDIS* Article Number 469675). *In a randomized, double-blind, placebo-controlled, escalating-dose (75, 150, 300 or 600 mg given once daily for 28 days) study, investigators evaluated the activity, safety and pharmacokinetics of oral tenofovir disoproxil fumarate in 49 patients with documented HIV-1 infection.*

## Zoledronic Acid

Major P, Lortholary A, Hon J et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001;19:558-567. (*IDIS* Article Number 460631). *Two identical, concurrent, parallel, multicenter, randomized, double-blind, double-dummy trials were conducted to investigate the clinical efficacy and safety of zoledronic acid (4 or 8 mg via a five minute infusion) compared to 90 mg pamidronate via a two-hour infusion in 278 patients with hypercalcemia of malignancy.*



Ruth Calloway, R.Ph., M.S.



## SUBSCRIPTION RENEWAL REMINDER

**Current subscriptions to the Iowa Drug Information Service expire with the December 2001 update.** Renewal materials for the 2002 subscription period were mailed to subscribers in September and November. We urge you to notify us of your renewal intentions as soon as possible. **To avoid any interruption in service, we must receive your 2002 renewal order by January.**

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# Perspective from an *IDIS* Subscriber



## Re: Safety of 130 mg of Propoxyphene HCl q 6h?

**DATA:** ALLERGIES — penicillin, SULFONAMIDES; ADVERSE DRUG REACTIONS — simvastatin - ↑ LIVER FUNCTION TESTS, ASPIRIN – GI bleed, 83 Year-old Female; 60 inches/145 lbs; CALCULATED CREATININE CLEARANCE — 29 mL/min (09/11/01), LIVER FUNCTION TESTS — within reference range (09/11/01), VITALS — BLOOD PRESSURE 131/93, PULSE — 62 irregularly irregular, RESPIRATION RATE — 18, TEMPERATURE — 97.6F, THYROID STIMULATING HORMONE — 2.06 (09/07/01).

### HISTORY OF PRESENT ILLNESS:

Admitted with extreme swelling of her left leg and exacerbation of heart failure. Transferred from Medical Service status post Deep Vein Thrombosis (DVT) (2<sup>nd</sup> episode) of her left lower extremity to complete a course of enoxaparin and begin several months of warfarin therapy.

### PREVIOUS MEDICAL HISTORY:

Coronary Artery Disease (CAD) with a history of myocardial infarction (MI), stent placement in circumflex coronary artery (3/00), heart failure New York Heart Association class II-ejection fraction 55%, chronic atrial fibrillation, mild mitral and tricuspid regurgitation, history of cerebrovascular accident x 3, status post pacemaker insertion for tachybrady syndrome (7/99), hyperlipidemia, gouty arthritis of the hands, hypothyroidism (not on thyroid medication), history of surgery for carcinoma of the rectum, glaucoma, history of anemia-etiology unclear.

**SOCIAL HISTORY:** Lives with daughter. Never drank alcohol, quit smoking 50 years ago, denies illicit drug use.

**MEDICATIONS:** On admission: Beclomethasone nasal 2 puffs bid, brimonidine 0.2% one drop in each eye bid, clopidogrel 75mg qd, diltiazem 60 mg qd, enoxaparin 70 mg q 12h, fosinopril 40 mg hs, furosemide 40 mg qd (since 09/14/01), ipratropium 0.02% nebulizer treatment qid, isosorbide dinitrate SA 40 mg tid, latanoprost

0.005% one drop each eye hs, metoprolol 50 mg bid, nitroglycerin sublingual 0.4 mg q 5 minutes prn,

potassium chloride 16mEq bid, propoxyphene HCL 65 mg q 6h prn, quinine 325mg hs, ranitidine 150mg hs, temazepam 15 hs prn

New propoxyphene orders: Take 65mg q 6h prn pain, for unrelieved pain take 130 mg q 6h prn.

### TREATMENT PLAN:

Continue her maintenance on medications, establish a stable warfarin regimen, begin her functional rehabilitation program with the goal of returning her to independent living.

During the current admission she was begun on Percocet 1-2 tablets q 4h prn for an acute right wrist pain syndrome. She did not tolerate the Percocet and her propoxyphene was restarted in a q 6h prn schedule.

### LITERATURE: (Background)

Propoxyphene (Darvon™) is an opiate structurally related to methadone. It was first marketed in the United States as an analgesic in 1957. It was promoted by Lilly as a non-narcotic analgesic equal in potency to codeine, but without addiction or abuse potential. (Eli Lilly & Company, 1979). Like other narcotics propoxyphene can produce respiratory depression with devastating rapidity. Effective marketing by Lilly combined with physician's need for an intermediate analgesic product between aspirin and narcotics, led to the widespread use of propoxyphene. Traditionally propoxyphene has been thought of as an analgesic of moderate potency, which was unlikely to result in dependence in standard doses or present other risks

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to the patient. Propoxyphene, unlike other opiates, was considered suitable for treatment of chronic or recurrent pain syndromes.

Concerns about the safety of propoxyphene have focused on deaths associated with its use or abuse, not its side effect profile. The first published fatality attributed to propoxyphene involved a 15 year-old female who ingested 40 thirty-two milligram capsules which had been prescribed for menstrual cramps. (McCarthy, 1974) Within an hour of the ingestion she presented to an emergency room in El Paso. She was in a deep coma within 2 hours and required ventilator support 13 hours after the ingestion. She died on the fifth hospital day. They described her course as follows: rapid loss of consciousness, respiratory depression, followed by generalized seizures, hypoxia and ultimately cardiovascular collapse. Staff at Lilly Research Laboratories reported that an almost identical pattern was noted in animal experiments.

During the 1970's several case series were published on intentional and unintentional overdoses with propoxyphene, particularly when combined with alcohol or other CNS depressants. (Sturner, Garriott, 1973) (Young, 1972) (Hudson, 1977) (Wetli, Bednarczyk 1980)

By 1977, propoxyphene ranked second only to the barbiturates as the leading prescription drug implicated in an estimated 1,000-2,000 overdose deaths per year in the United States. Although the majority of the cases involved deliberate suicide attempts, in many others there was no hint of suicidal intent. In a substantial minority of these cases, the amount of propoxyphene ingested was only slightly higher than the normal therapeutic dose. In many of the lower dose cases, propoxyphene was combined with alcohol or other sedatives. The majority of these overdose cases were from the medical population, rather than illegal drug abusers. Because of the growing problem of "abuse" propoxyphene was reclassified as a Schedule IV Controlled Substance in 1977.

By the Spring of 1978, the FDA notified physicians for the first time of the possibility of accidental deaths associated with propoxyphene through the *FDA Drug Bulletin*. (Anon, 1978) Over 5,000 drug abuse cases involving propoxyphene were reported in the Drug Abuse Warning Network (DAWN) between May 1976 and April 1977. Only half of the cases involved suicide attempts.

Only eleven months later the FDA considered it necessary to issue another statement on the growing problem of accidental death associated with propoxyphene use. (Anon, 1979) Several major hazards were described with propoxyphene use:

- deaths due to suicide attempts with propoxyphene alone or combined with other drugs;
- accidental deaths some of which occurred in drug abusers who took high doses of propoxyphene with other drugs or alcohol to get a "high";
- other accidental deaths in people who were not drug abusers and who apparently took propoxyphene in conjunction with tranquilizers, alcohol, or sedatives without understanding the danger.

By this time there was increasing evidence that some of these accidental deaths might have occurred at propoxyphene doses only slightly higher than the upper limits of the recommended dose. Pharmacists were advised to warn people not to take propoxyphene with alcohol, tranquilizers, or sedative-hypnotics.

Later in 1979 the FDA added a major new boxed warning on the risk of death associated with the use of propoxyphene. Included for the first time is a voluntary "Patient Information Sheet", distributed from 1978-1980, with specific warnings about drug combinations, especially alcohol, and the risk of exceeding the maximum recommended daily dose. (Anon, 1979)

Almost a decade later, Soumerai and colleagues reported on prescribing trends for propoxyphene before and after the informational campaign carried out between 1978 and 1980. They found that the risk of overdose death with propoxyphene had remained about constant since 1979. In their opinion, stronger or more sustained regulatory or educational measures will be required to deal effectively with the propoxyphene problem. (Soumerai, 1987) By 1983, propoxyphene overdose was recognized to have all the features of opiate toxicity and was the subject of a review by Young. (Eli Lilly & Co., 1979)

Neither propoxyphene HCL in a generic version, nor any of the Darvon™ or Darvocet™ products were in the top 200 drug list for the year 2000 for new or total prescriptions. (IMS Health, 1984) In 1983 Darvocet-N ranked 10<sup>th</sup> in new prescriptions and 12<sup>th</sup>

in new and refill prescriptions combined (Anon, 1984)

**(Cases and subsets of cases from case series):**

The following descriptions are taken from published case series of propoxyphene deaths.

**#1)** 31 Year-old Female, with propoxyphene prescription took three pills and some beer for “rib pain,” there was no history of prior suicide attempts or any reason to believe she was suicidal. Her cause of death was listed as “unclassified.” Her blood alcohol level was 1.4 mg%. (Sturner, Garriott, 1973)

**#2)** Three patients who were taking propoxyphene alone specifically for pain relief (diabetes with leg pain, pulmonary fibrosis, and hypertension with headache) deaths were classified as accidental. There was no evidence of acute overdose, such as twelve doses at once, in any of the cases. (Wetli, 1980)

**#3)** One patient who died from the interaction of propoxyphene and alcohol, whose blood alcohol concentration was between 0.15% and 0.3% was thought to have used propoxyphene in recommended doses. She suffered from asthma, hypertension and arteriosclerotic heart disease (ASHD). (Wetli, 1980)

**#4)** Twenty-four deceased patients had carisoprodol (Soma™) in their blood. Propoxyphene was also detected in 8 of the 24 cases. Propoxyphene levels ranged from 0.13 to 7.2 mg/L and norpropoxyphene concentrations ranged from 0.47 to 7.8 mg/L. Data from the DAWN network indicated that the most common cointoxicant in cases of deaths related to carisoprodol was propoxyphene in 31% of the fatal cases. (Davis, 1996)

**#5)** Jonasson, recently reviewed the death certificates of 1782 cases with propoxyphene in their peripheral blood. Over 50% were classified as fatal propoxyphene poisoning. The manner was classified as undetermined in 38% of the cases and accidental in only 5% of cases. He concludes that accidental propoxyphene fatalities may be underestimated. (Jonasson, 1998)

(Blood levels of propoxyphene (PX) and norpropoxyphene (NPX) in chronic users and accidental deaths):

Wolfe concluded that people who chronically use propoxyphene HCL at levels up to 6 doses of 65 mg a day (the maximum recommended dose) developed

blood levels of PX of 0.28-0.75 micrograms/ml and blood levels of NPX to 0.75-3.0 micrograms/ml. People taking only twice the recommended dose, i.e. 12 doses a day develop PX blood levels of 0.52-0.78 micrograms/ml and NPX levels of 3.3-5.1 micrograms/ml. Eight published cases of accidental death associated with propoxyphene were associated with PX blood levels of 0.4 to 1.1 micrograms/ml and NPX levels of 1.1 to 5.1 micrograms/ml. In none of these cases was another drug being used and in two there was no alcohol. (Eli Lilly & Co., 1979)

**COMMENT:** The patient’s leg pain syndrome was successfully treated with propoxyphene 65mg, she reported complete pain relief lasting 6 hours. She has not taken any 130 mg propoxyphene doses because of fear of “addiction.” She has not taken any propoxyphene doses for the past week because her leg pain has subsided.

She is also on temazepam 15 hs prn which she uses several times a week which could cause additional CNS depression.

**RECOMMENDATION:** Discontinue patient’s propoxyphene order. In the future, restrict total daily propoxyphene HCL orders to no more than 390mg. (or propoxyphene napsylate to 600 mg daily). Such a restriction is important in anyone who consumes alcohol, is on other CNS depressants, or is unable to tolerate modest CNS depression. A reasonable alternative is codeine.

**EDITOR’S NOTE:** From time to time, we publish articles contributed by *IDIS* subscribers. An article from Dave Mace, B.S.Pharm., is included in this issue. Dave Mace is from an institution that is a long-standing *IDIS* subscriber, utilizing the database on a regular basis. His consult illustrates *IDIS* database use contributing directly to patient care outcomes. The responsibility for errors is the author’s alone. The consult does not necessarily represent hospital views and recommendations. We hope you find the information interesting and useful and welcome comments. If you are interested in sharing your experiences using the *IDIS* database, please contact [donna-brus@uiowa.edu](mailto:donna-brus@uiowa.edu).



**Donna Brus, Editor**

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To obtain application materials contact one of the Co-directors. The application deadline is February 1, 2002.

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*World of Drug Information* is published quarterly (March, June, September, December) by the Division of Drug Information Service.

Editor ..... Donna Brus  
Production/Design Coordinator ..... Julie Tomash  
Photographer ..... David Luck

ISSN# 1529-4331

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