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Special Bioterrorism Watch supplement enclosed

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Pharmaceutical Care Across the Continuum

IN THIS ISSUE

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Urgency for bioterrorism response plan increases during anthrax scare

Pharmacists should become part of a larger response network

The confirmed cases of anthrax may still be isolated, but the growing panic across the country is not. Pharmacists need to prepare now to meet any possible bioterrorism situation that may arise, advocates say. **(To learn about potential threats and their treatments, see chart, p. 83.)**

"The key message is to be prepared," says **Mitchel Rothholz**, RPh, vice president for professional practice of the American Pharmaceutical Association in Washington, DC.

"Have a plan in place. If you don't have stock [of antibiotics that treat biological agents] on hand, you are going to have to answer questions from patients."

One of the best ways to prepare is to become part of a larger response network, says **Joe Deffenbaugh**, MPH, professional practice associate at the American Society of Health-System Pharmacists (ASHP) in Bethesda, MD. "Pharmacists should work through their hospital safety officers to find out if they are in one of the 120 metropolitan medical response systems identified by the Public Health Service." The total metropolitan medical response systems will be increasing to 200 in the next two years. Hospitals that are not in major metropolitan areas should find out what is going on in their state, he says.

Pharmacists should get involved in the planning activities around pharmaceutical availability and distribution, he says. "That would include what products to have on hand and how those products would be on hand among all of the health care facilities within a particular geographic area."

Otherwise, pharmacists are left to face the million-dollar question on their own: What stock do you need on hand? "That's the hardest question to answer, not knowing what kind of hit hospitals are going to take," Rothholz says. **(See checklist for assessing your pharmaceutical and equipment inventory, enclosed in this issue.)**

The question of having enough drugs to get you through the initial stages is going to be a new

(Continued on p. 84.)

APhA develops Pharmacist Response Center web site

In light of the Sept. 11 terrorist attacks and more recent anthrax exposure threats, the American Pharmaceutical Association (APhA) in Washington, DC, has created a comprehensive Bioterrorism Action Center on its web site (www.aphanet.org/pharmcare/ResponseCenter.htm). APhA suggests these guidelines when preparing your own facility for possible future problems:

- Tell local and state public health and emergency medical officials that you want to be a part of your community's emergency response team.
- Create a disaster response team within your practice setting.
- Check with your state board of pharmacy, if needed, to determine if an emergency dispensing provision exists within your state practice act. If one does not exist, discuss such an option with your state pharmacy association.
- Consult with the administrators of the major prescription drug benefit programs you serve (such as Medicaid, pharmacy benefit managers, etc.) to determine if a protocol exists for emergency refills.
- Work with wholesalers to establish storage sites for drugs, biologicals, and supplies received after a disaster, if your facility is not equipped or is nonoperational.
- Compile a handbook with contact information for wholesalers, suppliers, manufacturers, communication companies, and other resources that could assist you in obtaining pharmaceuticals, medical supplies, communication links, etc. Also include a plan for utilization of your practice's vehicles to transport health care professionals and deliver supplies.
- Develop a list of drugs, biological supplies, nutritional products, or other items for emergency shelters or health departments in time of a disaster.
- Create a list of local representatives who can be contacted to assist in obtaining necessary drugs and supplies.
- Obtain training in the area of immunizations, first aid, and disaster preparedness.
- Keep up with the latest developments and recent findings in emergency preparedness within your community. Serve as a resource within your community to ensure correct information is disseminated to the public.
- Create a list of pharmacists to call upon for assistance. Identify a lead pharmacist to coordinate activities within your practice. Make all staff aware of your disaster procedures. ■

COMING IN FUTURE MONTHS

- The questions surrounding placebo-controlled trials
- Drug company mergers squeeze drug availability
- A cost-cutting success story
- Telepharmacy gives 24x7 pharmacist call center support
- Multitasking in community pharmacies

Treatment of Biological Agent Exposure

AGENT	CLINICAL SIGNS AND SYMPTOMS	TREATMENT	OTHER	SECONDARY TRANSMISSION
Anthrax (spore)	Fever, malaise, non-productive cough, progressing to dyspnea, stridor, shock. Incubation 1-6 days.	Prophylaxis/treatment: ciprofloxin, doxycycline, PCN licensed vaccine. IV therapy: ciprofloxin doxycycline, PCN licensed vaccine.	High mortality (>90%) even with treatment.	None except aerosolized body fluids.
Pneumonic Plague (bacteria)	High fever, chills, headache, hemophysis, toxemia, dyspnea, stridor, bleeding diathesis. Incubation 2-3 days.	Prophylaxis/treatment: vaccine, doxycycline, TMP/sulfamethoxazole. IV therapy: streptomycin (>1 yo), gentamicin, chloramphenicol.	Antibiotic treatment effective if begun early.	Strict isolation needed. Isolation mandatory for at least the first 48 hours of treatment.
Tularemia (bacteria)	Regional lymphademepathy, fever, chills, headache, malaise, cutaneous ulcers. Incubation 2-10 days.	Streptomycin, gentamicin. Adult prophylaxis: doxycycline.	Low mortality (about 5%).	Rare, body fluid precautions only.
Q Fever (bacteria)	Fever, cough, pleuritic chest pain. Incubation 10+ days.	Tetracycline, doxycycline.	Low mortality.	Does not require universal precautions.
Smallpox (virus)	Malaise, fever, rigors, vomiting, headache, backache; 2-3 days later lesions appear and quickly progress from macules to papules to pustular vesicles. Incubation 16-17 days.	Supportive — vaccine available from CDC. Immune globulin may be available from CDC. No antiviral medication available.	Supposed to be extinct (doubtful).	Highly contagious.
Viral Equine Encephalitis	Supportive. No antiviral medication exists.	Ribaviron, supportive care.	Isolate patients in single room with an adjoining anteroom stocked with PPE. Negative air pressure if possible.	Body fluids. Otherwise infectious by vector (mosquitoes).
Viral Hemorrhagic Fevers	Fever, malaise, myalgias, headache, vomiting, diarrhea, easy bleeding, petechiae, shock.	Ribaviron, intensive care, convalescent plasma (Argentine HF), vaccine (yellow fever), blood replacement products for DIC.	Decontaminate with hypochlorite or phenolic disinfectants.	Transmitted by bodily fluids. Strict barrier-nursing techniques. Limit patient transfers: may increase risk for secondary transmission.
Botulism (toxin)	Ptosis, weakness, dizziness, dry mouth, blurred vision, diplopia, descending paralysis. Incubation 24-36 hours.	Several antitoxins are available and effective if administered early. CDC vaccine good only for A and B.	Disinfect with hypochlorite and/or soap and water. Supportive long-term mechanical ventilation.	None.
Ricin (toxin)	Weakness, fever, cough, pulmonary edema, incubation 18-24 hours.	Supportive — oxygenation and hydration. No antitoxin or vaccine available.	Disinfect with hypochlorite and/or soap and water.	None. Derived from caster beans.
Staphylococcal Enterotoxin B (toxin)	Fever, headache, chills, myalgias, cough, nausea, vomiting, diarrhea. Incubation 3-12 hours.	Supportive — oxygenation and hydration. Ventilator support may be required.	Disinfect with hypochlorite. Most victims recover.	Use PPE.

Source: Robert Suter, DO, MHA, FACEP, Questcare Emergency Services, Plano, TX.

(Continued from p. 82.)

discussion topic around the pharmacy and therapeutics tables of each institution, he says. "There will be some hierarchy of decisions depending upon the agent — what is the treatment of choice? In terms of anthrax, you can use the Cipro [ciprofloxacin] or doxycycline. You have some variety. In some cases, depending upon the strain, penicillin would work."

In a chemical situation, pharmacists would need atropine, he says. "Do hospitals have enough on hand? Is there a shortage? Potentially there could be. There will be a lot of discussion about this."

Rothholz also suggests working with the emergency response system. Some hospitals are allowing the emergency response system to rotate or maintain their stock, he says. Most hospitals would struggle with ordering additional doses and having it sit on their shelves. "No system can afford to have it sit and not be productive inventory."

Jumping the gun and stockpiling antibiotics is one of the worst things pharmacists can do, says Deffenbaugh. "They shouldn't go out and try to buy a lot of ciprofloxacin or any of the drugs that have been recommended for the treatment of any of these biological agents. That would be premature and is not going to be useful — and would contribute to a potential shortage of those items."

Working out a mechanism to obtain supplies in case of a run on the drug treatments is another primary recommendation, Rothholz says. "One of the fears now is that people stockpiling the drugs will cause a disproportionate distribution of the necessary antibiotics and other medications."

Smaller hospitals have more of a challenge in getting enough stock in case of a problem, he says. "They don't carry a larger inventory, and they are farther away from some distribution centers than hospitals in the city. They also have less opportunity for sharing among institutions depending upon what's happening."

Pharmacists need to remember that between community pharmacies and hospitals, there is a distribution of supply that can be tapped into, he explains. "Unless the roads are all torn up, the National Guard may be used to move [drugs] from one pharmacy to another."

Pharmacists also have to consider access points if they need to get someone treated, Rothholz adds. "The community pharmacies, the parking lot, and the hospitals can all be tapped into as delivery sites."

The problem of panic

One problem threatening the antibiotic supply is the increasing number of regular citizens who are afraid of getting anthrax and who are obtaining prescriptions for antibiotics from their physicians. This might result in other health problems down the road, Rothholz says.

"The biggest concern we have right now in the whole health care system is, if patients start taking Cipro or other antibiotics, will this exacerbate the situation of antibiotic resistance? We may not see patients dying of anthrax, but they may die of other infectious diseases that we don't have antibiotics to treat."

In the community setting, pharmacists should take special care with the patients who have obtained a prescription for ciprofloxacin because they are worried about a bioterrorist attack, says Deffenbaugh. "Pharmacists should use [their interaction] as an opportunity to educate patients about the inappropriateness of doing that. But that's hard because everyone is panicking."

Pharmacists also need to ensure that they are educated about the biological agents so they are on alert in their own facilities. With situations involving agents such as anthrax, people don't suddenly start dropping, Rothholz says. "They are going to come into pharmacies with symptoms on the fly and try to medicate themselves. Your stockpeople may notice they are stocking a lot more of antidiarrheal or cough-and-cold products."

That could be a sign, he says. "That's where your staff can really come into play."

The infectious disease personnel in your facility are good sources for education about these biological agents. Pharmacists should work with them to develop guidelines for what they would do in the event of an attack. Pharmacists also should obtain the Working Group on Civilian Biodefense articles that deal with the five most likely biological agents: anthrax, smallpox, plague, botulinum toxin, and tularemia, says Deffenbaugh. (The articles are available free on the *Journal of the American Medical Association* web site — jama.ama-assn.org/ — and also are referenced on the ASHP site.)

The Center for Civilian Biodefense Studies at John's Hopkins University offers fact sheets on those five biological entities, too. (This web site can be found at www.hopkins-biodefense.org.) Pharmacists should periodically check the Centers for Disease Control and Prevention's web site at www.cdc.gov/ for updated information on the biological agents and treatment, as well.

(Editor's note: Another resource for bioterrorism preparedness is ASHP's Emergency Preparedness — Counterterrorism Resource Center. This information can be accessed at www.ashp.org/public/proad/emergency/em_prep.html.) ■

Eptifibatide has long-term benefit, cost-efficiency

ESPRIT trial changed coronary-stent practices

Several months have passed since the release of the six-month results of the ESPRIT (Enhanced Suppression of the Platelet Receptor glycoprotein IIb/IIIa using Integrilin Therapy) trial. During this time, many physicians have switched from abciximab (ReoPro) to eptifibatide (Integrilin) as their primary GP IIb/IIIa inhibitor in the setting of coronary intervention during stenting, says one of the trial's principal investigators. And more are considering it, he suggests.

A look at the trial

ESPRIT was a randomized, placebo-controlled trial designed to assess whether a novel, double-bolus dose of eptifibatide could improve the outcomes of patients undergoing coronary stenting. The trial involved 2,064 patients undergoing stent implantation in a native coronary artery.

The trial was stopped prematurely in February 2000 when results showed a highly significant 37% reduction in the endpoint complications by 48 hours between the placebo group and the eptifibatide group. The 30-day secondary endpoint, which was a composite of death, myocardial infarction (MI), or urgent target vessel revascularization (TVR), also was reduced significantly.

By six months, the composite endpoint of death or MI had occurred in 7.5% of eptifibatide-treated patients and in 11.5% of placebo-treated patients, a difference of 35%. The composite of death, MI, or TVR was 14.2% in eptifibatide-treated patients vs. 18.3% in placebo-treated patients. Most of this benefit accrued early (less than 48 hours after initiation of therapy) and was maintained through six months. Six-month mortality in the eptifibatide group was 0.8% vs. 1.4% in the placebo group, and TVR occurred in 8.6% of the eptifibatide group vs. 9.4% of the placebo group.

"The fact that we have a durable result that is very highly statistically significant reinforces the result of using this class of drugs, in particular eptifibatide, in the setting of coronary intervention during stenting," says **James E. Tcheng**, MD, FACC, FSCAI, associate professor of medicine at the Duke Clinical Research Institute at Duke University Medical Center in Durham, NC.

The ESPRIT investigators were hoping that the absolute risk reduction would stay the same between 30 days and six months, Tcheng says. "We saw the absolute risk reduction increase between 30 days and six months. That means that there is not only a durable benefit, but that the benefit continues to increase with time."

The implication of these results is profound, he continues. "This means that something we are doing for a very short period of time — the drug is only given for 18-24 hours — is having long-lasting effects that continue to make a difference with the passage of time."

Eptifibatide vs. abciximab

The ESPRIT results are basically the same as the results that have been seen in trials of other IIb/IIIa inhibitors, in particular ReoPro, given the same type of study design, Tcheng says. "The relative risk reduction and the absolute risk reduction are what we had predicted, what we had expected, and are entirely consistent with those that have been seen with the others."

However, some researchers have questioned whether ReoPro has more benefit to diabetics than Integrilin. The discussion stems from one analysis of one trial of ReoPro — EPISTENT (Evaluation of IIb/IIIa Platelet Inhibitor for Stenting trial), Tcheng says. EPISTENT evaluated three strategies in reducing the primary endpoint of death, heart attack, and urgent repeat procedures at 30 days (coronary stenting alone, coronary stent with ReoPro, and conventional angioplasty plus ReoPro). Compared with patients receiving a stent alone, those receiving angioplasty and ReoPro had a 36% reduction in the primary endpoint, while those receiving both a stent and ReoPro had a 51% reduction.

The EPISTENT trial showed a greater than 50% relative reduction in the rate of restenosis at six months after the procedure in the diabetic subgroup. From that, the conclusion has been reached that ReoPro has magical benefits in the setting of diabetes, Tcheng says. He disagrees with this conclusion for several reasons.

"In the ESPRIT trial, the risk reduction wasn't 50%; it was about 11% with regard to restenosis," he says. "But we would have expected that the rate reduction in the diabetics was the same as that in the nondiabetics." This is what the researchers found. "So from a statistical standpoint, the results we saw in the ESPRIT trial make more sense. It's not that there isn't a benefit. It's just that the benefit is basically the same between the diabetics and the nondiabetics."

Tcheng also is concerned that this result has not been duplicated in other trials. "There is actually an increase in restenosis in the diabetic population in other trials of ReoPro. There is no statistical consistency from one trial to the next, which makes you think that it may have been a play of chance."

He says the rate of restenosis in the diabetics who received ReoPro in the TARGET trial (Do Tirofiban and ReoPro Give Similar Efficacy Trial) was higher than in the group that did not receive ReoPro. TARGET compared two GP IIb/IIIa inhibitors, tirofiban (Aggrastat) and ReoPro; it randomized 4,809 patients who were undergoing percutaneous coronary revascularization with stenting to either ReoPro or Aggrastat. The 30-day results showed a significant benefit with ReoPro. The six-month results, however, show that the benefit of ReoPro has become much smaller over time, and at six months there was no significant difference for TVR or mortality between the two drugs. Most importantly, the reduction in MI seen with abciximab at 30 days has not translated into a reduction in mortality at six months.

Because of the other trials and a myriad of other reasons, Tcheng basically makes no discrimination between the diabetics and the nondiabetics — they should all receive a GP IIb/IIIa inhibitor, he says. "The choice of IIb/IIIa is up to the institution. I would make a strong argument that the diabetics are benefited by both Integrilin and ReoPro."

Duke had primarily been choosing ReoPro during coronary stent implantation until it saw the results of the ESPRIT trial, Tcheng says. "In February/March 2000 before the trial was terminated prematurely, we were using a IIb/IIIa agent in about 85% of our patients, about 90% of which was ReoPro. After the 30-day results were released in April 2000, we switched to about 50/50. After the six-month results were released, we went to the opposite: 90% Integrilin and 10% ReoPro."

He claims that three-quarters or more of institutions have made the switch from ReoPro to Integrilin as their primary IIb/IIIa antagonist, and that many more are considering it. A primary reason for making the switch is the difference in price of the drugs. "[Integrilin] costs about $350 per treatment as opposed to ReoPro, which is about $1,500 per treatment," he says. "The economics so strongly favor the use of Integrilin. That's one of the reasons why our lab has switched from using ReoPro to Integrilin in our angioplasty procedures. Another is that the drug works.

"If you think about [these savings] across the whole health care economy of the United States, you are talking about hundreds of millions of dollars," he continues. "At the same time, it is not only saving money, but it also is saving lives and creating better outcomes." ■

FDA charges drug makers with misleading marketing

Several pharmaceutical companies received letters in early October from the Food and Drug Administration (FDA) charging that they made misleading marketing claims:

• The FDA has charged Merck and Co. with misleading doctors about its arthritis painkiller rofecoxib (Vioxx) with promotions that downplayed a possible risk of heart attacks. The agency took issue with statements made during company-sponsored audio conferences, in a May 22 press release, and by sales representatives at two medical meetings.

The FDA said the promotions minimized results of the VIGOR (Vioxx Gastrointestinal Outcomes Research) trial, which showed a higher rate of heart attacks among people treated with Vioxx compared with the nonsteroidal anti-inflammatory drug naproxen. Additionally, the FDA said Merck's materials downplayed a potentially dangerous interaction between Vioxx and the anticlotting drug Coumadin, known generically as warfarin.

In a Sept. 17 warning letter, the FDA ordered the company to stop using some promotional

materials and to send a letter to health care providers to correct any false impressions.

• The FDA has ordered Novartis to immediately stop using the "Extend the Reach Patient Starter Kit," which included a patient survey and promotional material about entacapone tablets (Comtan), its Parkinson's disease treatment.

Some statements in the starter kit "imply that Comtan therapy impacts patient quality of life, overall well-being, and mood, where these outcomes have not been demonstrated with substantial evidence," a letter from the FDA said.

Novartis said in a statement that it thought the claims were appropriate and that the company was working with the FDA to resolve the issue.

• The FDA charged that AstraZeneca made misleading claims in a promotional brochure about the effectiveness of its migraine treatment zolmitriptan (Zomig). The FDA said the brochure included "claims that broaden the efficacy" of Zomig and "imply superiority ... over competitive therapies." Those claims were "not supported by substantial evidence," the agency said in a letter to the company.

These claims included statements such as "reliable in recurrent migraine headaches" and "consistent attack after attack." Another statement said a majority of patients thought Zomig was similar to or better than previously tried migraine therapies.

• The FDA objected to Galderma Laboratories' dissemination of "violative" promotional materials for adapalene gel (Differin) 0.1%. The ads consisted of two television commercials that the FDA said lacked fair balance because "the communication of important risk information associated with the use of Differin is inadequate." ▼

Antidepressants may raise bleeding risk

In September, Canadian scientists warned that the latest generation of antidepressants could cause stomach and intestinal bleeding in the elderly.

Carl van Walraven, MD, and researchers at Ottawa Hospital say people in their 80s and those with previous bleeding problems face the highest risk from the drugs, known as serotonin re-uptake inhibitors (SSRIs).

"The risk of upper gastrointestinal bleeding in elderly and depressed patients increases with antidepressants having the greatest extent of inhibition of serotonin re-uptake," reported van Walraven in the *British Medical Journal.*

Van Walraven and his team compared data on 314,000 people older than age 65 who had been taking SSRIs between 1992 and 1998 and hospital admissions for stomach bleeding. They found that the more powerful the drug, the greater the chance of bleeding. People with peptic ulcers had the highest risks.

Van Walraven says this research supports a study by Spanish scientists who also linked SSRIs with an increased risk of bleeding. ▼

Questions about drug cards

The Bush administration says it will fight a federal court decision that blocked Medicare's plans to promote private pharmacy discount cards. **Tom Scully**, administrator of the Centers

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Editorial Questions

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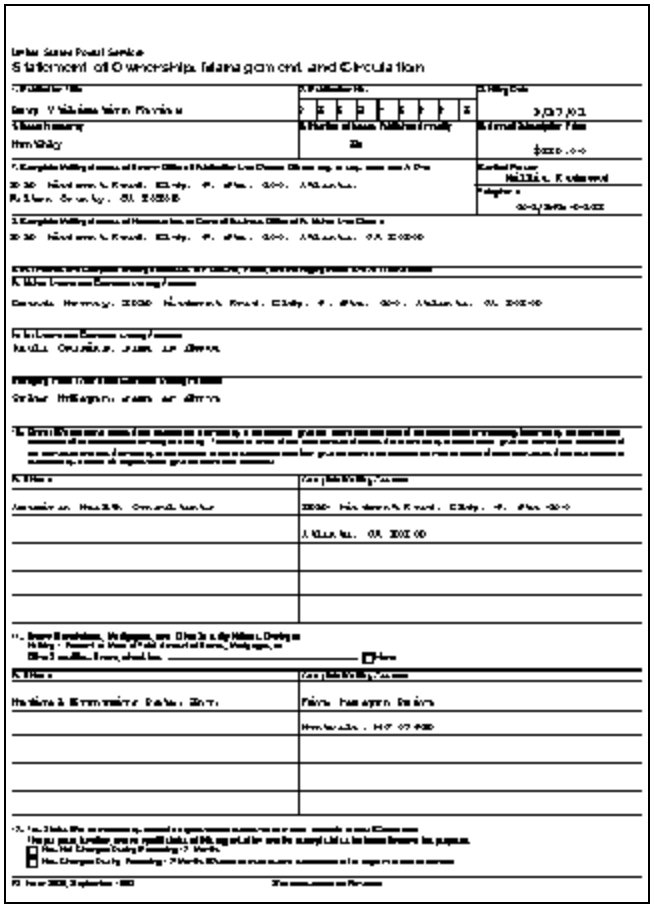
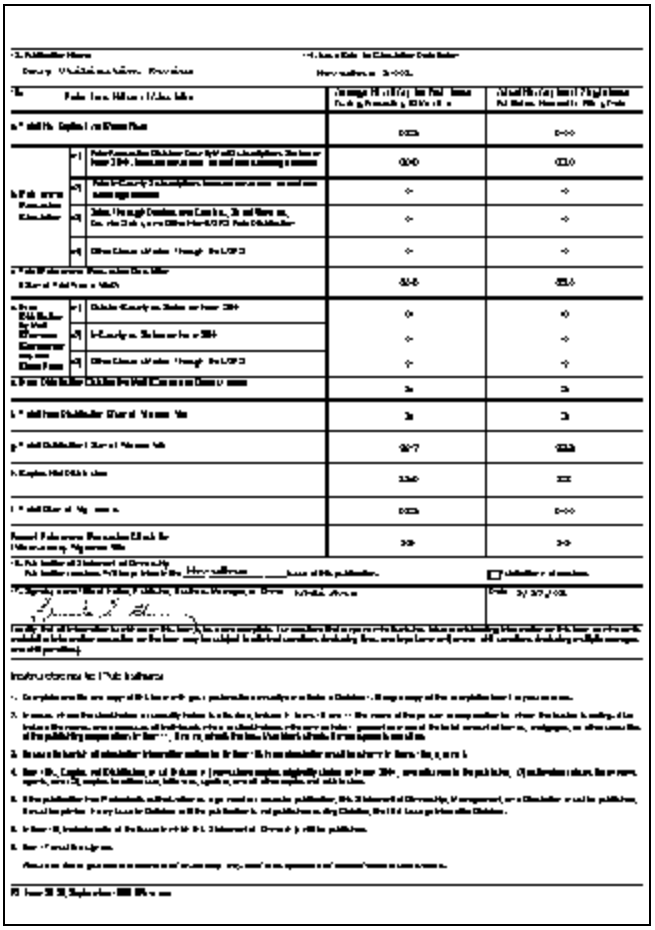
for Medicare and Medicaid, says the government will appeal the injunction, which prevented the fall launch of the program. Bush officials say the promotional program would help millions of cash-strapped seniors get cheaper medicines.

"We are determined to get a prescription drug benefit to seniors,'' says Scully. "We should be actively looking at anything that works."

In July, the National Association of Chain Drug Stores and the National Community Pharmacists Association filed a suit against Secretary of Health and Human Services Tommy Thompson and Scully. The lawsuit argued the plan did not clearly outline who must subsidize the lower prices. It also questioned whether federal officials had the power to promote the cards without Congress' approval. U.S. District Judge Paul Friedman blocked the start of the program.

Some lawmakers promised to support a bill that would make the plan a permanent law. Scully told a group of health care professionals that he is confident that Congress might consider such a bill, even with a social policy schedule severely limited by the Sept. 11 terrorist attacks. ■





DRUG CRITERIA & OUTCOMES™

Pantoprazole intravenous

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Introduction

Since the U.S. market approval of omeprazole 12 years ago, a growing number of drugs have been added to the benzimidazole proton pump inhibitor (PPI) class. Currently, five agents have U.S. Food and Drug Administration (FDA) approval for oral use (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole). Of that group, only pantoprazole (Protonix IV) also is FDA-approved for intravenous (IV) use.

Oral (PO) PPIs have become very widely used over the past decade and now represent a multi-billion-dollar market in the United States alone.

The market introduction of IV pantoprazole offers clinicians the potential for additional therapeutic flexibility. Injectable omeprazole (and to a lesser extent lansoprazole) has been studied extensively in world-wide clinical trials with success. These agents have not been introduced to the U.S. market to date, in spite of their clinical promise, likely due to pharmaceutical (e.g., stability and formulation) challenges.

The introduction of an injectable form of a PPI has created considerable interest among hospital pharmacists and other clinicians. The challenge for pharmacy and therapeutics (P&T) committees everywhere will be to carefully manage the use of IV pantoprazole through proper identification of acceptable indications and durations of treatment (both in the absence of optimal clinical information). The issue of the optimal route of PPI administration (i.e., IV vs. PO vs. nasogastric [NG]) also will be the subject of considerable P&T committee debate due to both efficacy and cost implications.

Pharmacokinetics

Pantoprazole demonstrates linear kinetics between dosing and peak serum concentration (C_{MAX}) or serum concentration under the curve (C_{AUC}) in the dosage range of 10-80 mg. Following the infusion of a 40 mg dose, the C_{MAX} is 4.6-5.5 mcg / mL and the C_{AUC} is 5.4 mcg-h / mL. Time to peak concentration is achieved at the end of the infusion.

Distribution. The apparent volume of distribution of pantoprazole is approximately 11-23.6 L with limited tissue distribution. Plasma protein binding of pantoprzole is ~ 98%, primarily to albumin.

Metabolism. Pantoprazole is extensively metabolized by the liver via cytochrome P-450-mediated oxidation followed by sulfate conjugation. The main metabolic pathway is CYP 2C19. In patients with mild-to-moderate hepatic impairment, metabolism is impaired; however, dosage adjustment may not be required because peak plasma concentration is elevated marginally. Pantoprazole does not appear to cause any induction or inhibition of the cytochrome P-450 enzyme system.

Elimination. Seventy-one percent of the dose is excreted in the urine as metabolites and 18% is excreted in the feces through biliary excretion. Hemodialysis and renal impairment do not have clinically significant effects on elimination. Pantoprazole has an average half-life of 1.9 hours (0.8-5.1 hours). The half-life is prolonged to 7-9 hours in patients with hepatic cirrhosis or among slow metabolizers. Caution should be

exercised when administered IV pantoprazole in these populations.

Pharmacodynamics

Mechanism of action. As with the other drugs in the PPI class, pantoprazole reduces gastric acid secretion through inhibition of the proton pump on the gastric parietal cell. In the strongly acidic environment (i.e., pH $\leq$ 3), pantoprazole (a weak base, pKa = 3.9) is converted rapidly to an active form, a cation cyclic sulfonamide, which binds covalently to cysteine residues on the surface of parietal H+/K+ ATPase, thereby causing irreversible inhibition of the proton pump function. As H+/K+ ATPase represents the final step in the secretory process, inhibition of this enzyme suppresses gastric acid secretion regardless of the primary stimulus.

Effects on gastric secretions. Suppression of the 24-hour accumulative pentagastrin-stimulated acid output (PSAO) of single-dose pantoprazole is dose-related over the range of 20-80 mg. Complete suppression was achieved with 80 mg dosing; no further inhibition was observed with higher doses (120 mg). As noted with other antisecretory agents, serum gastrin level was elevated three- to four-fold compared with placebo following the administration of multiple pantoprazole doses. Gastric level came back to normal range 24 hours following the administration of the last dose.

Other effects. Unlike cimetidine or omeprazole, pantoprzole does not interfere with cortisol synthesis. It also is reported to not significantly affect basal plasma thyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteotrophic hormone, prolactin, or somatotrophic hormone levels.

Adverse reactions

IV pantoprazole has been very well-tolerated in clinical trials of gastroesophageal reflux disease (GERD) patients and healthy volunteers. The most frequent adverse effects potentially related to IV pantoprazole therapy include abdominal pain (12%), chest pain (6%), rash (6%), and pruritis (4%). Injection site reactions also have been reported. The adverse effects of pantoprazole were equally tolerated relative to cimetidine or ranitidine in the "German pantoprazole phase IV program."

Drug interactions

Of all the proton pump inhibitors available, pantoprazole has the lowest affinity for the hepatic cytochrome P-450 enzyme system in animal studies. In contrast to omeprazole and cimetidine, pantoprazole does not show remarkable interactions with substrates for the CYP-450 1A, 2C, and 3A subfamilies of the isoenzyme.

In healthy volunteers, pantoprazole has shown a lack of clinically significant interactions with

Table 1

Potential Therapeutic Uses	FDA Approval	Comparison with Existing Therapies
Treatment of GERD in patients who are unable to tolerate PO therapy.	Yes	Equivalent acid suppression with equivalent doses.
Treatment of acute peptic ulcer bleeding.	No	Studies are being conducted with high-dose therapy: 80 mg bolus dose plus constant infusion of 8 mg/hr for up to 72 hours.
Treatment of hypersecretory disorders (e.g., Zollinger-Ellison syndrome).	No	Rare disorder.
Treatment of pyloric channel ulcers that lead to gastric outlet obstruction.	No	80-120 mg q 8-12 hours may be required.
Prophylaxis for stress-related mucosal disease.	No	Studies currently are ongoing to help differentiate efficacy between PPIs and H2As.
Treatment of critically ill patients when PO and/or NG administration of a PPI is not feasible.	No	H2A IV or sulcralfate offer equivalent therapeutic options.
Perioperative use as prophylaxis for acid aspiration syndrome during induction of anesthesia.	No	More data are required to formulate recommendations.
Diagnostic test for patients with non-cardiac chest pain.	No	More data are required to formulate recommendations.

diazepam, digoxin, theophylline, carbamazepine, diclofenac, warfarin, nifedipine, caffein, metoprolol, or ethanol.

Potential therapeutic uses

A survey of the clinical literature identifies a variety of potential therapeutic uses for IV pantoprazole. The positioning of this agent within the institution will depend upon its efficacy and cost relative to other existing therapeutic options (e.g., histamine-2 receptor antagonists [H2A]). A summary of the potential therapeutic uses for IV pantoprazole is found in **Table 1, p. 2**.

Dosage and administration

Pantoprazole is available in an injectable dosage form as a freeze-dried powder in a glass vial. When treating GERD, each vial (40 mg) should be reconstituted with 10 mL of 0.9% sodium chloride for injection and further diluted with 100 mL of solution (0.9% sodium chloride, dextrose 5% in water, or lactated Ringer's) for a final concentration of 0.4 mg / mL. The dose should be administered IV once daily for 7-10 days. The drug should be infused over 15 minutes (at a rate not to exceed 3 mg / min) with a filter to remove the precipitate that may form when the reconstituted drug is diluted.

No dosing adjustments are required in patients with renal insufficiency (including those undergoing hemodialysis), mild or moderate hepatic insufficiency, or the elderly. The pharmacokinetics of IV pantoprazole have not been well characterized in patients with severe hepatic impairment.

There is little consensus to support any particular dosing strategy with regard to IV pantoprazole in non-FDA approved clinical situations. It is likely that clinicians will develop a feel for optimal dosing through clinical experience before FDA-approved labeling is available. The P&T committee can play an important role in the accumulation of data related to non-FDA approved indications.

Conclusions and formulary considerations

Pantoprazole is the only PPI commercially available in an IV dosage form; as a result, it should be available on the hospital formulary for use in selected patients. The specific patient population(s) targeted should be determined based on an ongoing evaluation of clinical literature and through discussions among pharmacists, gastroenterologists, and intensivists.

To date, there is considerably more published clinical information available for IV omeprazole (on the market in Europe and Asia) than for IV pantoprazole. P&T committees will likely need to extrapolate IV omeprazole data in some cases as policy decisions are made. It may be particularly difficult at the current time to come to a consensus on dosing guidelines for the various clinical situations.

For reasons of efficacy and cost, IV pantoprazole should be used only when the PO and / or NG route of administration is not feasible or an H2A IV is not an equivalent therapeutic option.

Given the dynamic nature of the U.S. PPI market, very interesting contract scenarios are being promoted for the PO agents. The ultimate cost of IV pantoprazole to the institution may be greatly influenced by the decisions made relative to the PO PPI formulary.

Table 2, below, summarizes the various actions P&T committees should consider when evaluating IV pantoprazole for formulary purposes.

Resources

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Table 2

Potential P&T Committee Actions
1. Consider various control mechanisms (e.g., restriction policies, usage criteria, drug protocols, care maps) to ensure appropriate patient selection and duration of therapy of IV pantoprazole.
2. Monitor use of IV pantoprazole concurrently and report performance regularly to P&T Committee. Focus should include a determination of optimal dosing and duration of treatment.
3. Review clinical literature on an ongoing basis to follow evolving standards of care relative to IV PPIs.
4. Develop criteria to distinguish among candidates for IV, PO, and NG administration of PPIs.
5. Review available contract options carefully to accurately project cost impact of IV PPI use.

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CroFab: A treatment for snakebites

By **Mary Juanita Meeks**, PharmD*
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* Written as a PharmD candidate at Samford University

Crotalidae Polyvalent Immune Fab-Ovine (CroFab) is an antivenom that was approved for the treatment of snakebites in October 2000. CroFab is indicated for patients with minimal or moderate North American crotalid envenomation. Early use (defined as within six hours of the envenomation) is recommended to prevent deterioration and systemic coagulation abnormalities.

Wyeth-Ayerst announced its decision to stop the production of its polyvalent antivenin once CroFab became available. For years, Wyeth's polyvalent product was the principal snakebite antivenom to treat snakebites related to the continental United States. This polyvalent antivenin was manufactured from horse serum, which contributes to a high rate of serum sickness reactions. CroFab is manufactured from sheep serum, and the chemical moiety in horse serum that contributed to serum sickness reaction is absent in the newer product.

The active part is a Fab fragment of immunoglobulin G that binds and neutralizes venom toxins to prevent the destruction in target tissues. This makes CroFab less likely to cause serum sickness, although the possibility still exists. The lack of moiety allows physicians to treat patients who normally would not be treated (i.e., in patients who risk possible side effects that are more severe than the snakebite effect itself). This is especially true with copperhead bites that tend not to be as severe.

There are limited data comparing CroFab to other antivenoms. Only two clinical trials using CroFab have been completed so far, but other trials are planned or in progress. One benefit noticed during a clinical trial was that patients who had developed thrombocytopenia before treatment with CroFab had much faster normalization of platelet count after CroFab administration and clinical stabilization. The platelet count recovery normally takes several hours to several days after a patient has been bitten.

Papaya is used to cleave the whole antibody into its active garments; thus, traces of papaya may be found in CroFab. Therefore, CroFab should not be administered to patients who have a known hypersensitivity to papaya or papain unless the benefits outweigh the risks.

Caution also should be used if administering CroFab to nursing women, as CroFab may appear in breast milk. Geriatric and pediatric studies have not been conducted, although the weight-based dose required for children is believed to be the same as in adults. The product must be refrigerated and used within four hours of reconstitution.

Snakebite coverage for CroFab includes:

- Western diamondback rattlesnake;
- Eastern diamondback rattlesnake;
- Mojave rattlesnake; and
- cottonmouth or water moccasin.

CroFab also is believed to cover certain species closely related to those listed above. ■

EPS and sedation with phenothiazines reviewed

By **Jenni Ball**, PharmD
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The phenothiazines prochlorperazine (Compazine) and promethazine (Phenergan) are low-cost antiemetics that commonly are prescribed at Huntsville Hospital. They are effective at reducing nausea and vomiting due to their ability to block the D2 dopaminergic receptors of the chemoreceptor trigger zone.

However, they also block histamine receptors and cholinergic receptors, which can lead to certain side effects. Although the common side effects are reported to include extrapyramidal symptoms (EPS) and sedation, the overall incidence rate of these side effects remains low compared to the number of doses administered.

Extrapyramidal reactions are classified as either acute or chronic reactions. Acute EPS develop within days or weeks of beginning therapy and include dystonic reactions, akathisia, and parkinsonian symptoms. Chronic EPS, such as tardive dyskinesia, usually occur after months of therapy, are not dose-related, and may persist after the drug is discontinued.

This article will focus on acute EPS due to prochlorperazine and promethazine, which are more common in the hospital setting than chronic EPS.

By blocking dopamine receptors, phenothiazines leave the excitatory actions of cholinergic neurons unopposed, and this leads to acute EPS. These reactions often are dose-related and occur early in therapy, sometimes after only a single dose.

If acute EPS do occur, they may subside with a decrease in dosage. An anticholinergic drug also may be used for treatment. For example, diphenhydramine 1-2 mg/kg (maximum 50 mg) can be given PO, IM, or IV and followed by a maintenance dose for 2-3 days. If diphenhydramine is ineffective, benztropine 1-2 mg PO, IM, or IV may be used. With these agents, the EPS usually improve within 2-5 minutes. If it is necessary to use the phenothiazine at a later time, the medication should be instituted at a low dose.

Certain patient populations are at increased risk for developing EPS. Three important risk factors include large doses, IV therapy, and a history of previous reactions to phenothiazines. In addition, both pediatric and geriatric patients experience a higher rate of EPS with phenothiazines. Another risk factor is concurrent use of other drugs that can cause EPS such as haloperidol, fluphenazine, or metoclopramide. The use of these agents is cautioned in patients with a history of seizures and Parkinson's disease. The incidence of EPS also is increased in patients experiencing acute infections or dehydration.

Sedation is one of the antihistaminic effects that can occur with phenothiazines. Sedation often is dose-related and is most prevalent in the first two weeks of treatment. If a patient is experiencing excessive sedation, a dose reduction may be necessary. There are several patient populations that are at increased risk of experiencing this side effect. For example, patients who are taking other medications that can cause sedation (e.g., CNS depressants, antihistamines, or tricyclic antidepressants) are more likely to experience sedation when taking a phenothiazine.

Sedation also is seen when phenothiazines are combined with other antiemetic agents (e.g., droperidol or dolasetron) after chemotherapy and when they are used after surgery in a patient who also is taking a narcotic analgesic. As with EPS, the elderly may be particularly susceptible to this side effect.

When considering the use of a phenothiazine, there are several steps a health care provider can take to minimize the occurrence of side effects:

- Identify patients at increased risk for EPS and sedation and monitor each patient carefully.
- Avoid the use of phenothiazines in high-risk patients such as parkinsonian patients or those with a history of seizures.
- Use the lowest dose necessary.
- Switch from IV to PO as soon as possible.
- Discontinue the drug in a reasonable amount of time.
- Avoid specific drug combinations such as promethazine with codeine, and avoid phenothiazines prescribed with drugs such as metoclopramide, haloperidol, or amitriptyline. ■

IN THE PIPELINE

• Biomira's subsidiary, Biomira USA, has initiated a Phase Ib clinical research trial to test safety and immunogenicity of an autologous vaccine strategy for the treatment of **B-cell lymphoma**. This program, carried out under a Collaborative Research and Development Agreement with the U.S. National Cancer Institute, is the second step in the investigation of an autologous vaccine strategy based on a liposomal formulation.

• Novartis has launched NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research), the largest-ever diabetes prevention clinical trial to date. The trial aims to determine whether long-term administration of nateglinide (Starlix) or valsartan (Diovan) reduces or delays the development of **Type 2 diabetes** and **cardiovascular disease** (CV) in people who have impaired glucose tolerance (IGT) and who are at high cardiovascular risk. Recent studies suggest that people with IGT are 34% more likely to die from CV disease than people with normal blood glucose control.

• La Jolla Pharmaceutical Co. has filed an Investigational New Drug application with the FDA to begin a Phase I/II clinical trial of LJP 1082, its clinical candidate for the treatment of **antibody-mediated thrombosis**. The normal regulatory review has been completed, and the company is preparing to begin the clinical study.

• MedImmune has begun dosing **psoriasis** patients with siplizumab (MEDI-507) in a large Phase II clinical trial. This trial, which is to enroll approximately 400 patients at 50 sites in the United States and Canada, is a part of MedImmune's development program for siplizumab. By the end of 2001, MedImmune expects to have enrolled approximately 750 patients in seven clinical studies with siplizumab.

• Aventis Behring will initiate a multinational pivotal clinical trial during the first quarter of 2002 for an inhaleable form of Alpha1-Antitrypsin [Human] (AAT) for the treatment of **hereditary emphysema**. This therapy uses the Inhance pulmonary delivery technology, a proprietary drug delivery solution from Inhale Therapeutic Systems, Aventis Behring's development partner.

• Immunex Corp. and Wyeth-Ayerst Laboratories have announced that the FDA granted "priority review" status for Immunex's supplemental Biologics License Application to use etanercept (Enbrel) in the treatment of psoriatic arthritis. Enbrel is the first product reviewed by the FDA to treat the signs and symptoms of **psoriatic arthritis**.

• Vical has completed enrollment of 200 patients in a randomized, controlled Phase III registration trial to evaluate the safety and efficacy of Allovectin-7 for the treatment of chemotherapy-naive patients with **metastatic melanoma**. The company chose to complete enrollment at 200 patients based on discussions with the FDA in March 2001.

• Sepracor has announced that (R,R)-formoterol inhalation solution has advanced into Phase III studies for the treatment of **bronchospasm** in patients with obstructive airway disease. Results of Sepracor's (R,R)-formoterol Phase II program demonstrated a significant improvement in FEV_1 immediately after dosing and a duration of action of up to 24 hours. Currently marketed long-acting beta-agonists require twice-a-day dosing and currently are not available as an inhalation solution.

• Human Genome Sciences has completed patient enrollment in two Phase II clinical trials evaluating mirostipen (Myeloid Progenitor Inhibitory Factor — MPIF) as a treatment for **chemotherapy-induced neutropenia and thrombocytopenia**. The studies are designed to evaluate the safety, optimal dosing schedule, and preliminary efficacy of mirostipen in this indication.

• NeoTherapeutics' NeoOncoRx oncology subsidiary will initiate two Phase II studies during the fourth quarter of 2001 of Neotrofin in patients with **chemotherapy-induced neuropathy**. Both studies will include 50 patients for six months of treatment at the NYU Medical Center. One study will look at Neotrofin's ability to protect patients from chemotherapy-induced neuropathy, and the second will study the drug's efficacy in treating neuropathy resulting from chemotherapy.

• Human Genome Sciences has completed enrollment in a Phase IIa clinical trial evaluating repifermin (keratinocyte growth factor-2, KGF-2) as a systemically administered treatment for **cancer therapy-induced mucositis**. The double-blind, placebo-controlled, dose-escalation Phase IIa human clinical study of repifermin is designed to determine repifermin's safety, preliminary efficacy, and optimal dosing.

• Atrix Laboratories has submitted a New

Drug Application to the FDA for Leuprogel Three-Month Depot, 22.5 mg leuprolide acetate, for the treatment of **advanced prostate cancer**. Atrix is in late-stage development of three Leuprogel products that release leuprolide acetate over a period of one-, three-, and four-months using Atrix's Atrigel Depot drug delivery system.

• Genelabs Technologies has initiated a Phase II clinical trial of an investigational new vaccine for prevention of disease caused by **hepatitis E virus**. The trial is being conducted by the Walter Reed Army Institute of Research in collaboration with the Medical Department of the Royal Nepal Army, the U.S. National Institutes of Health, and Genelabs' licensee GlaxoSmithKline Biologicals.

• Ribozyme Pharmaceuticals has started the third clinical trial of the antiangiogenic drug Angiozyme in cancer patients. The current study will evaluate Angiozyme as a treatment for **cancer patients who currently are taking carboplatin and paclitaxel therapy**.

• Forest Laboratories has submitted a New Drug Application with the FDA to market lercanidipine for the treatment of **hypertension**. Lercanidipine is a member of the dihydropyridine calcium channel blocker class of drugs.

• Nastech Pharmaceutical Co. has commenced a Phase I clinical trial in the United States to evaluate the nasal administration of somatropin (recombinant human growth hormone, or rhGH). The objective of the Phase I study is to determine nasal absorption, tolerance, and safety of somatropin in healthy volunteers. Somatropin is indicated for the long-term treatment of children with **growth failure** due to lack of adequate endogenous growth hormone secretion.

• Genmab A/S has initiated a Phase I/II clinical trial with its fully human antibody HuMax(TM)-IL15 to treat patients with active **rheumatoid arthritis**. This multi-center, placebo-controlled study will test up to six dose levels and include approximately 30 patients. It is designed to provide safety data about both single and multiple doses of HuMax-IL15, with a secondary goal of gathering information about the efficacy of the antibody.

• Ribozyme Pharmaceuticals has begun a multicenter Phase II clinical trial using Heptazyme for the treatment of patients with **chronic hepatitis C**. The study is designed to evaluate Heptazyme safety and efficacy when administered alone and in combination with interferon.

• Texas Biotechnology Corp. has announced that its marketing partner, GlaxoSmithKline (GSK), has initiated a Phase II trial evaluating Argatroban as a treatment for patients undergoing **percutaneous coronary interventions**. The 100-patient, open-label clinical trial is designed to assess the safety and efficacy of Argatroban as an alternative to heparin in patients undergoing PCI and in combination with GPIIb/IIIa receptor antagonists.

• Nastech Pharmaceutical Co. has commenced enrollment in a Phase II clinical trial in the United States to evaluate the efficacy and safety of a patent-protected nasal formulation of morphine gluconate for the treatment of **breakthrough pain in opioid-tolerant cancer patients**. A total of 20 qualified cancer patients will receive the study medication as part of an open-label, single-site study.

• Hollis-Eden Pharmaceuticals has received approval to initiate a Phase II clinical trial in **Hepatitis B**-infected patients with the company's lead investigational drug, HE2000, at Mt. Elizabeth Medical Centre in Singapore. The clinical study will evaluate the safety, tolerance, and clinical and biological effects of HE2000, an immune regulating hormone, in young chronic HBV-infected patients.

• AtheroGenics has announced that it has begun a Phase I clinical trial with AGIX-4207 IV as an intravenous treatment for people with **rheumatoid arthritis**. The trial is designed to assess the safety and tolerability of AGIX-4207 IV in healthy volunteers. ■

New FDA Approvals

These drugs recently received final approval from the Food and Drug Administration (FDA):

• *Cefditoren pivoxil (Spectracef) by TAP Pharmaceutical Products.* The FDA has approved a new cephalosporin antibiotic, Spectracef (cefditoren pivoxil). Spectracef is indicated for the treatment of the following: **mild-to-moderate infections** in adults and adolescents (12 years of age or older), **acute exacerbations of chronic bronchitis, pharyngitis/tonsillitis,** and **uncomplicated skin and skin structure infections**.

• *Zoledronic acid for injection (Zometa 4 mg) by Novartis.* The FDA has approved zoledronic acid for injection (Zometa 4 mg) for the treatment of **hypercalcemia of malignancy**, a common life-threatening metabolic complication associated with cancer. Zometa is an intravenous bisphosphonate that works by inhibiting the breakdown of bone (resorption).

• *Zolmitriptan Orally Disintegrating Tablet by AstraZeneca.* The FDA announced the approval of a new 5 mg strength zolmitriptan (Zomig-ZMT) Orally Disintegrating Tablet for the treatment of **migraine** in adults, following the recent approval of Zomig-ZMT 2.5 mg. Zomig-ZMT 5 mg, like the 2.5 mg, is an orange-flavored tablet that dissolves on the tongue in seconds without the need for additional liquids.

• *Budesonide (Entocort EC) capsules by AstraZeneca.* The FDA has approved budesonide (Entocort EC) capsules for the treatment of mild-to-moderate active **Crohn's disease** involving certain sections of the small and large intestines. Entocort EC is an orally administered steroid that is released in the intestine, where it works locally and topically to decrease inflammation. Unlike other steroids used to treat Crohn's disease, most of Entocort EC is not absorbed into the body.

• *Etonogestrel/ethinyl estradiol vaginal ring (NuvaRing) by Organon.* The FDA has given approval to market etonogestrel/ethinyl estradiol vaginal ring (NuvaRing), the first monthly vaginal ring for **birth control**. NuvaRing is a flexible, transparent ring that provides month-long contraceptive protection and can be discretely administered by a woman in her own home. The product works by releasing a continuous low dose of estrogen and progestin, on average 0.120 mg of etonogestrel and 0.015 mg of ethinyl estradiol, per day over a 21-day period of use. ■

Voluntary Micronase recall

The U.S. Food and Drug Administration has announced a voluntary recall of Micronase lots 84DWB (1.25 mg, bottle of 100); 91DYR (2.5 mg, bottle of 100); 67FPP (5 mg, bottle of 100); and 42 different lots of Greenstone brand Glyburide tablets. Fungal organisms have been detected in some lots, traced to a raw material used in the formulation. For more information, see this web site: www.fda.gov/medwatch/SAFETY/2001/safety01.htm#glybur. ■

Topamax warnings stronger

The U.S. Food and Drug Administration and drug maker Ortho-McNeil have strengthened the warnings and precautions sections in the label of Topamax tablets and Sprinkle capsules, indicated as adjunctive therapy for adults and pediatric patients ages 2-16 years with seizure disorders. Cases of secondary angle closure glaucoma characterized by ocular pain, acute myopia, and increased intraocular pressure were reported in pediatric and adult populations. The primary treatment is discontinuation of Topamax. If left untreated, serious sequelae, including permanent vision loss, may occur. Patients taking Topamax should be told to seek immediate medical attention if they experience blurred vision or periorbital pain. Web site: www.fda.gov/medwatch/safety/2001/safety01.htm#topama. ■

BIOTERRORISM WATCH
Preparing for and responding to biological, chemical and natural disasters

Clinicians must be voice of reason, reassurance now that bioterrorism battle has been joined

The threat is real, but we are far from defenseless

A new era of bioterrorism has begun with the intentional anthrax scares that have left several people dead and many more exposed as this issue went to press.

But amid the shrill coverage of the widening anthrax investigations, the scramble for gas masks and the expected hoarding of Cipro, there must be a voice of calm and reason. That voice must be your own.

Infection control professionals, hospital epidemiologists, and other key clinicians involved in health care bioterrorism readiness and response must set the tone for a panicky public and an uneasy health care work force, emphasizes veteran epidemiologist **William Schaffner**, MD, chairman of preventive medicine at Vanderbilt University School of Medicine in Nashville.

"We have to re-instill a sense of confidence for people who work in the health care system," he says. "Start with the doctors. They are the ones who are going to be more panicked than the nurses."

Restoring calm to health care community

The current situation is reminiscent of the early stages of the HIV epidemic, when there was much anxiety about the communicability of the disease and whether even casual contact would spell a death sentence for health care workers.

In that chilling time of alarmist reactions and burning mattresses, Schaffner recalls that ICPs, epidemiologists, and other clinicians, stepped into the fray to provide calming confidence and accurate risk data.

"I'm beginning to think that we may be in a similar position now," he says. "We could have a very powerful educational and reassuring effect. Everybody's anxious about this, but I think we can diminish the level of anxiety," Schaffner adds.

Infection control methods in place

Health care workers must be educated about bioterrorism agents and provided reassurance that the patient isolation precautions developed by the Centers for Disease Control and Prevention (CDC) are extremely effective, urges Schaffner.[1]

"The barrier precautions are going to work for bioterrorism. Once you get to chemical [weapons] then you get into the whole 'moon suit' issue. But for bioterrorism, we don't need that," he says.

For example, systems of barrier precautions such as gloves, gowns, and masks to isolate patients infected with all manner of infectious diseases are already in place in virtually all U.S. hospitals.

"They work," he says. "Look, we all know pulmonary tuberculosis is communicable. I'm an infectious disease doctor, have been for 30 years. I've seen a lot of patients with tuberculosis, but I have also been meticulous about my use of [face masks and respirators]. My tuberculin test continues to be negative."

This supplement was prepared by Gary Evans, editor of *Hospital Infection Control.* Telephone: (706) 742-2515. E-mail: gary.evans@ahcpub.com.

A Bioterrorism Time Line

1155 Barbarossa uses the bodies of dead soldiers to poison the wells at the battle of Tortona.

1346 Mongols catapult corpses of plague victims into the city of Kaffa to infect the defenders.

1763 British commander Sir Jeffrey Amherst ordered the transfers of blankets used by British smallpox victims to Native American tribes, ostensibly as a gesture of goodwill, with the intention of inducing illness.

1970 The United States ends its programs of developing biological agents for use in warfare. The offensive use of such weapons was forbidden by U.S. policy under executive orders of President Richard Nixon.

1972 Soviet Union signs off on Biological and Toxin Weapons Convention, but continues a high-intensity program to develop and produce biological weapons at least through the early 1990s. Hundreds of tons of weaponized anthrax spores are stockpiled, along with dozens of tons of smallpox and plague. Many of these agents are reputed to have been specifically designed to be resistant to common antibiotics.

1984 Members of the Rajneesh cult contaminated salad bars in Oregon with salmonella, resulting in the infection of 751 people. The Paris Police raided a residence suspected of being a safe house for the German Red Army Faction. During the search, they found documentation and a bathtub filled with flasks containing *Clostridium Botulinum.*

1990s Japan's Aum Shinrykyo cult plans attacks using biological agents, specifically, anthrax and botulinum toxin. While these biological attacks were not successful, cult members later implemented the release of sarin nerve gas in the Tokyo subway system.

1995 A U.S. microbiologist with right-wing ties orders bubonic plague cultures by mail. The ease with which he obtained these cultures prompts new legislation to ensure that biologic materials are destined for legitimate medical and scientific purposes.

1998 A variety of feigned exposures to anthrax spores occurred in several U.S. cities including Indianapolis, where a full-scale response by emergency services and public health occurred before the episode was found to be a hoax.

Sources

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And anthrax, of course, is not communicable from person to person, reminds Schaffner, who investigated a case of occupational anthrax in an animal-hide worker when he was a epidemiologist for the CDC in the late 1960s.

"The bacteria do not cause a conventional pneumonia," he says. "They replicate locally and then release toxins. Because the bacteria never replicate to very high numbers the person is not communicable. It is not so much an infection as it is an intoxication."

Inordinate fear of anthrax could cause another problem — hoarding and misuse of Ciprofloxacin and other antibiotics. That tactic eventually could contribute to emerging resistance in pathogens such as *Streptococcus pneumoniae,* Schaffner notes.

"It is one thing for a hospital and the health department to develop an inventory in the event of an emergency," he says. "I do not recommend that individuals do that. I'm quite concerned that with antibiotics in their medicine cabinets there will be a temptation to just use it now and again for inadequate reasons in inadequate doses. If there was a recipe for antibiotic resistance — that's it."

More terror than toll

While the anthrax mailing campaign now under way sends out another shock wave with every news report, the tactic will likely result in more terror than actual toll. The rapid administration of antibiotics has offset illness following exposures, the disease is not communicable from those actually infected, and everyone is now on high alert for suspicious mailings.

Indeed, if the wave of anthrax mailings continues, postal-treatment technologies may become a growth industry.

Regardless, anthrax is problematic as a bioweapon because only a certain micron size of the inhaled spore will lodge in the upper lungs where it can release its toxins, says **Allan J. Morrison Jr.**, MD, MSc, FACP, a bioterrorism expert and health care epidemiologist for the Inova Health System in Washington, DC.

"If it is too large, it won't go in," says Morrison, a former member of the U.S. Army Special Forces. "If it's too small, it goes in and moves about freely without ever lodging. This is not as easy as getting a culture, growing it in your home, and the next day having infectious microbes.

"The sizing, preparation, and ability to deliver such a weapon are extremely difficult," he adds.

The Aum Shinrykyo cult in Tokyo attempted at least eight releases of anthrax or botulism during 1990 to 1995 without getting any casualties, he recalls. **(See time line, p. 2.)** Variables such as humidity can come into play, clumping up spores even if they are perfectly sized for inhalation. Anthrax spores bound for human targets are also at the whims of ultraviolet light, rain, and wind dispersal patterns, Morrison says.

"It is a very hostile climate for microbes on planet earth." Morrison says. "The intent may be widespread, but the ability to deliver weapons grade agents is going to be restricted to a very small subgroup. And even among them, they still will require optimal climatic conditions to carry it out. There will be causalities, as in war, but the distinction here is that there has not been widespread infection."

While anthrax is the current weapon of choice, the direst scenarios usually turn to the most feared weapon in the potential arsenal of bioterrorism: smallpox.

"Invariably, I have seen smallpox described as 'highly infectious,'" Schaffner says. "It's not. That is erroneous." For example, during the global eradication efforts in the 1960s, African natives infected with smallpox were often found living with extended families in huts, he adds. "It would usually take two to three incubation periods for smallpox to move through an extended family."

"It doesn't happen all it once. This was a critical concept in the strategy to eradicate smallpox. If you could find smallpox, you could vaccinate around that case and prevent further transmission. If it had been a frighteningly [rapid] communicable disease, that strategy would never have worked," Schaffner explains.

In addition, some medical observers question the certitude of the general consensus that all those vaccinated decades ago are again susceptible to smallpox. They argue that those immunized during the eradication campaign may at least have some greater protection against fatal infection.[2]

Regardless, rather than dropping like flies, as many as 70% of those infected with smallpox actually survive and then have lifelong immunity.

While there are many other agents to discuss and prevention plans to outline in the weeks and months ahead, perhaps the greatest protective factor is the unprecedented level of awareness in the health care system. The world has changed so much since Sept. 11th that hospitals are probably more prepared for bioterrorism than they have ever been. Everywhere, lines of communication have been opened with health departments and affiliated clinics, emergency plans have been reviewed and hot-button phone numbers posted on the wall.

"We're on alert," says **Fran Slater**, RN, MBA, CIC, CPHQ administrative director of performance improvement at Methodist Hospital in Houston. "We are *all* on alert."

References

1. Garner JS, the Centers for Disease Control and Prevention Hospital Infection Control Practices Advisory Committee. *Guideline for Isolation Precautions in Hospitals. Web site: http://www.cdc.gov/ncidod/hip/ISOLAT/isolat.htm.*
2. Bosker G. Bioterrorism: An update for clinicians, pharmacists, and emergency management planners. *Emergency Medicine Reports* (in press) 2001. ■

Should clinicians get smallpox vaccinations?

Questions arise, stockpile expansion fast-tracked

The recent decision to accelerate production of a new smallpox vaccine is raising the complex question of whether health care workers — front-line soldiers in the war against bioterrorism — should be immunized against the disease.

As opposed to the current anthrax attacks, a biological release of smallpox would result in incoming patients with an infectious disease. Even health care workers directly exposed to anthrax could be treated with ciprofloxacin and several other antibiotics, so the anthrax vaccine is not a likely candidate for health care.

On the other hand, legitimate questions have been raised about whether health care workers will stay on the job during a smallpox outbreak unless they and their families are rapidly vaccinated. The only known stocks of smallpox virus are held by the United States and Russia, but many bioterrorism experts have warned for years that another nation or group might have secret stocks.

"I think if smallpox [vaccine] became available, we should definitely immunize all the health care workers," says **Martin Evans**, MD, hospital epidemiologist at the University of Kentucky Chandler Medical Center in Lexington. "A lot of people think [health care workers] ought to

be high on the list because they are part of the response team if there was an outbreak in the community. Not to sound self-serving, but I think we ought to immunize the medical community."

But the question currently is somewhat moot because the Centers for Disease Control and Prevention (CDC) is not wavering from its established policy of mobilizing the available vaccine only if smallpox is released. "I'm sure CDC wants to conserve its current stocks for dealing with an outbreak so it could immunize contacts," Evans says. "If [the agency has] already used [its stock] by immunizing all the health care workers in the country, then it won't be able to respond."

15 million doses stockpiled

Currently, there are some 15 million doses of the old smallpox vaccine available, according to Secretary of Health and Human Services **Tommy Thompson,** who recently announced plans to accelerate production of a new smallpox vaccine. Forty million new doses of vaccine are expected to be available by mid-to-late 2002, moving the project up considerably from its original completion date of 2004 or 2005.

The manufacturer of the new vaccine is Acambis Inc. (formerly OraVax) — based in Cambridge, UK, and Cambridge and Canton, MA. The new vaccine will be a purified derivative of the same strain of cowpox virus (vaccinia) that was used in the United States previously, because the old vaccine's efficacy was clearly demonstrated by direct exposures to those infected. While the method of immunization through scarification will be essentially the same, the new vaccine will be produced in a mammalian cell culture that contains no animal protein.

Acambis stated on its web site that it would have no other comment on the project other than to confirm it has "accelerated" its production plans. But when the project was first announced in 2000, company officials said they had the ability to scale up production well beyond the requested 40 million doses. They were even scouting for other global markets. That means the capability to produce smallpox vaccine in abundance is on the horizon, and the question of immunizing health care workers will invariably arise. *Bioterrorism Watch* was unable to get a CDC response on the question as this issue went to press, but CDC director **Jeffrey Koplan**, MD, MPH, outlined the agency's position in an Oct. 2, 2001 Health Alert posted on a CDC web site.

"Smallpox vaccination is not recommended and, as you know, the vaccine is not available to health providers or the public," Koplan said. "In the absence of a confirmed case of smallpox anywhere in the world, there is no need to be vaccinated against smallpox. There also can be severe side effects to the smallpox vaccine, which is another reason we do not recommend vaccination. In the event of an outbreak, the CDC has clear guidelines to swiftly provide vaccine to people exposed to this disease. The vaccine is securely stored for use in the case of an outbreak."

One factor in favor of the CDC's position to rapidly deploy the vaccine — rather than do widespread vaccinations — is that immunization should still be effective several days after a smallpox exposure. In the smallpox global eradication campaign, epidemiologists found they could give vaccine two to three days after an exposure and still protect against the disease. Even at four and five days out, immunization might prevent death. Still, though the new vaccine will be improved in many ways, the hazards and risk factors of introducing cowpox into the human body are expected to be roughly the same as those documented with the old vaccine.

"We are looking at probably about one death per million primary vaccinations," says **D.A. Henderson**, MD, director of the Center for Civilian Biodefense Studies at Johns Hopkins University in Baltimore. "We are looking at one in 300,000 developing post-vaccinal encephalitis — an inflammation of the brain, which occasionally is fatal and sometimes can leave people permanently impaired."

Based on those estimates, if the new stockpile of 40 million doses is eventually rolled out, approximately 40 of those immunized will die, and another 133 will develop encephalitis. In addition to those severe outcomes, the arm lesion created during inoculation can be very large and painful, serving as a reservoir to self-inoculate the eyes or even infect immune-compromised patients.

The downside is real, but as more vaccine becomes available immunization will certainly be discussed at hospitals in previously targeted areas such as New York City and Washington, DC. If they are not immunized in advance, health care workers are going to want vaccine very quickly if they are expected to take care of smallpox patients, says **Allan J. Morrison Jr.**, MD, MSc, FACP, health care epidemiologist for the Inova Health System in Washington, DC. "Forget about smallpox patients. We're talking about taking care of any patients." ■

Use this bioterrorism checklist to assess inventory

American Hospital Association provides guidance on chemical and bioterrorism preparedness

The recent anthrax threats have prompted the American Hospital Association (AHA) in Chicago to offer guidance materials to help hospitals respond to any bioterrorism or chemical emergency. For example, the AHA has advised hospitals to revise their disaster readiness plans, increase coordination with local emergency agencies, expand training, and review inventory levels of drugs.

Part of its guidance materials includes a Chemical and Bioterrorism Preparedness Checklist. Here is the portion of the checklist that specifically addresses pharmaceuticals and equipment:

6.0 Pharmaceuticals and equipment:

6.1 Has your facility/system assessed its pharmaceutical inventory to determine whether it could support the treatment and provide prophylaxis for mass numbers of patients exposed to biological or chemical agents?

6.2 Has your facility/system identified an emergency pharmaceutical supply system via local pharmacies for pharmaceuticals related to treatment/prophylaxis for exposure to biological or chemical agents?

6.3 Has your facility/system identified an emergency pharmaceutical supply system via pharmaceutical vendors related to the prophylaxis and treatment for exposure to biological or chemical agents?

6.4 Does your facility/system have protocols for the following medication distribution scenarios for an incident in the event of limited supplies?

Rank order in terms of precedent for care	**1 highest – 5 lowest**
6.4.1 Prophylaxis of patient family members	_____
6.4.2 Patients with known exposure/no symptoms	_____
6.4.3 Prophylaxis of providers/staff members	_____
6.4.4 Symptomatic patients	_____
6.4.5 Prophylaxis of staff/provider family members	_____
6.4.6 Prophylaxis of community emergency response personnel	_____

6.5 Does the pharmaceutical and equipment inventory of your facility/system contain the following items? **(If yes, indicate the approximate average amount on hand):**

6.5.1 **Bacterial agents:**		**# on hand**		
Ciprofloxacin	NA	_____	Yes	No
Doxycycline	NA	_____	Yes	No
Penicillin	NA	_____	Yes	No
Chloramphenicol	NA	_____	Yes	No
Azithromycin	NA	_____	Yes	No
Rifampin	NA	_____	Yes	No
Streptomycin	NA	_____	Yes	No
Gentamicin	NA	_____	Yes	No
6.5.2 **Botulism toxin:**				
Mechanical respiratory ventilators	NA	_____	Yes	No
Other associated supplies	NA	_____	Yes	No

6.5.3 **Cyanides:**				
Cyanide antidote kits containing amyl nitrite, sodium nitrite, sodium thiosulfate	NA	_____	Yes	No
6.5.4 **Lewisite:**				
British Anti-Lewisite	NA	_____	Yes	No
6.5.5 **Nerve agents:**				
Atropine	NA	_____	Yes	No
Pralidoxime chloride	NA	_____	Yes	No
Diazepam (or lorazepam)	NA	_____	Yes	No
6.5.6 **Pulmonary agents:**				
Oxygen ventilators	NA	_____	Yes	No
Respiratory care supplies	NA	_____	Yes	No
6.5.7 **All agents:**				
Resuscitation equipment and supplies	NA	_____	Yes	No
Vasopressors	NA	_____	Yes	No

6.6 Does your facility/system have access to dosage requirements for antidotes and therapies for patients (adult and pediatric) who are exposed to biological or chemical agents?

6.7 Is the necessary drug administering equipment available for the on-hand quantities of antidotes and therapies?

6.8 Does your facility/system have a staff member designated to accept deliveries from the National Pharmaceutical Stockpile in the event of a bioterrorism event?

To see the full checklist, see http://www.aha.org/Emergency/Content/MaAtChecklistB1003.doc/.