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Bayer Pulls Cerivastatin Due to Worldwide Deaths

By William T. Elliott, MD, FACP

Bayer has withdrawn cerivastatin (baycol) from the worldwide market after as many as 52 deaths have been attributed to the drug. The deaths were caused by **rhabdomyolysis**. Most of the deaths were in older patients on high doses of the drug, and many of these patients were also taking **gemfibrozil**, a drug known to increase the risk of **myositis** with all statins. While statins are known to cause myositis in a small minority of patients, the rate and the severity of the disorder with cerivastatin was excessive, accounting for more than half of the cases of rhabdomyolysis reported for all statins. The effect of the withdrawal has been disastrous for Bayer, and may force the company to sell its pharmaceutical unit or partner with another company. Meanwhile, manufacturers of other statins are relooking at their own data, and reissuing warnings about the use of statins with gemfibrozil. The FDA is also dealing with a petition from the watchdog group Public Citizen to put "Black Box" warnings on all statins, concerning the risk of rhabdomyolysis. But a disaster for one company is a marketing opportunity for another, so statin manufacturers are aggressively stepping into the lost cerivastatin market with offers of free drugs and other enticements to patients willing to switch.

COX-2 Inhibitors

Do COX-2 inhibitors promote cardiovascular events? A recent meta-analysis from the Cleveland Clinic tries to answer this question. The theory that COX-2s may lead to prothrombotic activity by decreasing **vasodilatory** and **antiaggregatory prostacyclin production** is the source of this concern. The study looked at the VIGOR trial that compared **rofecoxib** with **naproxen**, the CLASS trial comparing **celecoxib** with **ibuprofen**, and 2 smaller studies of the COX-2 drugs. While the VIGOR trial showed an increase in cardiovascular events with rofecoxib, the CLASS trial did not. However, when the CLASS data, and data from the smaller COX-2 studies were combined and compared to rates of cardiovascular events from other studies, the rates of cardiovascular events were higher than expected in users of COX-2 inhibitors. Mukherjee and colleagues admit that this study is far from conclusive, but it does raise a "cautionary flag" about the risk of cardiovascular events associated with the use of COX-2 inhibitors (Mukherjee D, et al. *JAMA*. 2001;286:954-959).

Oxycontin Abuse

Oxycontin has become a favorite drug of abuse, especially in rural America.

INSIDE

Now Purdue Pharma, the manufacturer of the drug, is working to prevent street use of the drug in a rather ingenious fashion. The time-released drug is crushed by abusers, defeating the time-release properties. After crushing, the powder is then injected or snorted. The company is working on combining an **opiate antagonist** with oxycodone. The antagonist would be inert when taken orally, but would be activated if the capsule is crushed, potentially triggering opiate withdrawal symptoms in abusers. Purdue Pharma is applying for an international patent for this new formulation.

Ventricular Tachycardia

Drugs are ineffective for preventing **ventricular tachycardia** (VT) according to the Multicenter UnSustained Tachycardia Trial (MUSTT) trial. More than 700 patients with a history nonsustained VT were randomized to PVS-guided antiarrhythmic therapy or no drug therapy. There was no benefit found to drug therapy despite looking at several different end points. Several antiarrhythmic drugs were evaluated, but none was found to be superior to the others. The one positive outcome was seen with PVS-guided **implantable defibrillators,** which were found to significantly improve outcomes (Wyse D, et al. *J Am Coll Cardiol.* 2001;38:344-351).

Hepatitis C

The FDA has approved a new treatment for **hepatitis C**. Schering's **peginterferon alfa-2b** (Peg-Intron) has been approved for use with **ribavirin** (Rebetol) for patients with chronic hepatitis C with compensated liver disease who have not previously been treated with **interferon**. Pegelated interferon was developed using a **polyethylene glycol molecule** (PEG) and combining it with interferon to form an injectable form that can be given once a week instead of 3 times a week as was the case with interferon alpha-2b (Intron-A). Ribavirin, which is also a Schering product, was previously approved for use with Intron-A. Along with being more convenient, peginterferon/ribavirin is more effective than interferon/ribavirin in treating chronic hepatitis C according to documentation filed with the FDA. Hoffman-LaRoche has developed their own pegelated interferon product, **peginterferon alpha-2a** (Pegasys). The 2 companies recently reached a long-term co-marketing agreement on the 2 products which may allow ribavirin to be used in combination with Pegasys as well.

Hormone Replacement

Several studies published in August focus on the use of **hormone replacement** for various clinical entities. **Estrogen** given in high doses by skin patch may improve some cognitive skills in women with **Alzheimer's disease**. Twenty women with Alzheimer's disease were randomized to receive **estradiol** or placebo. The estradiol treated women improved in tests of selective attention as well as verbal and visual memory compared to placebo treated patients (Astana S, et al. *Neurology*. 2001;57:605-612). These findings seem to contradict recent studies that have not shown cognitive improvement with estrogen replacement. In related research, older women who take hormone replacement therapy (HRT) have smaller increases in systolic blood pressure over time than women who do not take hormones. In a longitudinal study of 226 women in Baltimore, women who did not take HRT were found to have an 18.7 mm Hg increase in systolic blood pressure over 10 years, while women who took hormones were noted to only show a 7.6 mm Hg increase over the same time period (Scuteri A, et al. *Ann Intern Med.* 2001;135:229-238). HRT has also been shown to increase bone mineral density in the frail elderly. Bone-related outcomes were measured in 67 women age 75 and older who were deemed frail. HRT of conjugated estrogen and **medroxyprogesterone** significantly increased bone mineral density of the lumbar spine and hip compared to placebo over the 9 months of the study (Villareal D, et al. *JAMA.* 2001;286:815-820). Finally, HRT may improve glycemic control in women with **type 2 diabetes**. Over 15,000 women from Northern California, followed in the Kaiser Permanente Diabetes Registry were followed for 24 months. Diabetic women on HRT (25% of the sample group) were found to have significantly lower mean HbA1c levels (average 0.5 points lower) than diabetic women not on HRT (Ferrara A, et al. *Diabetes Care*. 2001;24:1144-1150). ■

Twinrix—A New Vaccine for Hepatitis A and B

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

The fda recently approved a vaccine that provides dual protection against hepatitis A and B. Marketed as Twinrix by GlaxoSmithKline Pharmaceuticals, the vaccine combines inactivated hepatitis A vaccine with hepatitis B recombinant vaccine, the antigenic components in Havrix and Engerix B, respectively. The combination reduces the number of

injections needed to immunize patients to both viruses from 5 to 3. An exact release date is expected soon.

Indications

Twinrix is indicated for the active immunization of adults (18 years of age or older) against disease caused by hepatitis A virus and infections by all known subtypes of hepatitis B virus.[1]

Dosage

The primary immunization for adults is 1 mL given intramuscularly in 3 doses at 0, 1, and 6 months. The injection should be given in the deltoid region, not in the gluteal region. Administration in the gluteal region may result in a suboptimal response.[1] Each 1 mL dose of Twinrix contains 720 ELISA units (EL.U) of inactivated hepatitis A virus and 20 mcg of recombinant hepatitis B surface antigen (HbsAg).

Potential Advantages

The combined vaccine offers more convenience and potentially better compliance. Twinrix requires 3 injections and 3 sites compared to 5 injections and 5 injection sites (2 for hepatitis A and 3 for hepatitis B).

Potential Disadvantages

Safety and effectiveness of Twinrix have not been established in pediatric patients. The effectiveness in patients age 65 years and older has also not been established.[1]

Comments

The immunogenicity and safety of Twinrix has been demonstrated in more than 1500 subjects. After the completion of the 3-dose regimen, seroconversion was detected in more than 98% of subjects against both hepatitis A and B.[1,2] In a comparative trial, Twinrix was at least as effective as Havrix and Engerix-B administered separately.1 The antibody titers achieved with Twinrix were actually higher than that achieved with Havrix. This may be attributed to a difference in dosing. Twinrix is given as 3 doses of 720 EL.U at 0, 1, and 6 months while Havrix is given as 2 doses of 1440 EL.U at 0 and 6 months.

The most frequent reported side effects are local soreness and headache or fatigue. These were similar to that reported with Havrix or Engerix-B.[1]

Clinical Implications

Hepatitis B is a viral infection with serious consequences including acute hepatic necrosis, chronic active hepatitis, and cirrhosis of the liver. Chronic hepatitis B infection has been linked to hepatocellular carcinoma. The main modes of transmission are parenteral drug abuse, unprotected sex, visits to high-prevalence countries, exposure to infected body fluids, and high-risk occupations or settings. The CDC estimates that there are 1-1.25 million chronic carriers of hepatitis B in the United States. These persons can infect others in the community. Currently, vaccination is routine in children. This strategy will not only protect persons from infection but reduce disease incidence by reducing transmission.

Hepatitis A is one of the most frequently reported vaccine preventable diseases and is considered a major public health problem.[3] The main mode of transmission is fecal-oral. Contaminated food or water or infected food handlers are a major source of transmission. Unlike hepatitis B, there is no routine childhood vaccination for hepatitis A. Twinrix offers a vaccine for adults who have not been vaccinated with either hepatitis A or B, and is recommended for those at risk of exposure to these viruses. These include travelers to endemic areas (who often are immunized against hepatitis A but rarely against hepatitis B), those with chronic liver disease, high-risk workers (laboratory, sanitation workers, medical personnel), employees of day-care centers, correctional facilities, persons with at-risk behavior (homosexuals, parenteral drug users), military personnel, persons with clotting-factor disease (eg, hemophiliacs), and those in close contact with individuals with hepatitis A.

Twinrix provides a convenient vaccine for the immunization against preventable diseases caused by hepatitis A and B in adults. The duration of protection is at least 4 years.[1] ■

References

1. Twinrix Product Labeling. GlaxoSmithKline Pharmaceuticals. May 2001.
2. Thoelen S, et al. *Vaccine*. 1999;17:1657-1662.
3. CDC. *MMWR Morb Mortal Wkly Rep*. 1999;48 (no. RR-12):18-29.

IV Pantoprazole—The First Parenteral PPI

By William T. Elliott, MD, FACP, and James Chan PharmD, PhD

The first parenteral proton pump inhibitor (PPI) is now available in this country. Wyeth Laboratories' pantoprazole, which has been marketed for more than a year under the trade name

Protonix, will soon be available as an injectable for use in hospitals. Although this is the first PPI available in a parenteral form in this country, several others are currently available in Europe.

Indications

Pantoprazole sodium IV is indicated for short-term treatment (7-10 days) of gastroesophageal reflux disease (GERD) in patients in whom oral therapy is not appropriate.[1]

Dosage

The recommended dose of pantoprazole sodium is 40 mg daily for 7-10 days. It should be administered over a period of 15 minutes at a rate not faster than 3 mg/min. No dosage adjustment is required in patients with mild, moderate, or severe renal impairment, or mild or moderate hepatic impairment.[1] Pantoprazole sodium is supplied as a freeze dried powder containing 40 mg of pantoprazole.

Potential Advantages

Pantoprazole is the first PPI to be available in parenteral form. The oral and intravenous forms of pantoprazole appeared to be equipotent. No change in dosage is required when switching from one formulation to the other.[2,3] Pantoprazole has low potential for drug-drug interactions involving the cytochrome P450 isoenzymes.[1]

Potential Disadvantages

Postmarket spontaneous reported adverse events involving intravenous or oral pantoprazole have included anaphylaxis, angioedema, anterior ischemic optic neuropathy, severe dematologic reactions (eg, erythemia multiforme, Steven-Johnson syndrome, toxic epidermal necrosis, and hepatocellular damage).[1]

Comments

Pantoprazole sodium is the first PPI to be available in an injectable form. For patients temporarily unable to take oral PPI initiating therapy with parenteral pantoprazole for 5-7 days followed by oral pantoprazole for 8 weeks has been shown to be effective in the healing of moderate or severe (stage II and stage III) GERD.[4] Complete healing was achieved in 77% of patients in 4 weeks and 85% in 8 weeks based on intent-to-treat analysis and 87% and 95%, respectively, per protocol. Parenteral pantoprazole (160-240 mg/d) has also been reported to be effective in controlling acid output in patients with Zollinger-Ellison syndrome.[5] Pantoprazole costs about $24 per 40 mg vial.

Clinical Implications

Pantoprazole sodium is the first parenteral PPI approved in the United States. Only histamine 2 receptor antagonists such as ranitidine, famotidine, and cimetidine are currently available in parenteral form. When a PPI has been needed in patients unable to swallow the oral dosage form, the drug has been administered by mixing it with a liquid and injecting it through the nasogastric tube. The parenteral form would facilitate administration in this setting. Although the drug is only approved for GERD, other potential uses of parenteral PPIs include Zollinger-Ellison syndrome, prevention of stress ulcer, acid-induced lung injury, and bleeding peptic ulcers.[6] ■

References

1. Protonix IV Product Information. Wyeth Laboratories. May 2001.
2. Pisegna JR. *J Clin Gastroenterol.* 2001;32(1):27-32.
3. Hartmann M, et al. *Aliment Pharmacol Ther*. 1998; 12(10):1027-1032.
4. Wurzer H, et al. *Hepatogastroenterology*. 1999;46(27): 1809-1815.
5. Lew EA, et al. *Gastroenterology.* 2000;118(4):696-704.
6. Metz DC. *Digestion.* 2000;62(2-3):73-81.

Effect of Hormone Replacement Therapy in Breast Cancer Patients

Source: *O'Meara ES, et al. J Natl Cancer Inst. 2001;93:754-762.*

The medical records of 400,000 group health Cooperative of Puget Sound HMO patients were searched for women with primary invasive breast cancer from 1977 to 1994, and 2755 were identified. Only those women without distant metastatic disease were selected. HMO pharmacy data were used to determine which subjects in the study group used HRT. Other factors, including parity, gravidity, age at first full-term pregnancy, age at menarche, age at and reason for cessation of menses, menopausal symptoms, hysterectomy, oophorectomy, smoking history, family history, height, weight, details of breast cancer treatment, and tumor characteristics were also extracted from the patients' records. An HRT user was defined as any woman who filled 2 or more HRT prescriptions within any 6-month period after breast

cancer diagnosis and prior to diagnosis of a recurrence.

There were 175 women who were classified as HRT users and were evaluable. Forty-three percent used vaginal preparations exclusively, 41% used only oral agents, and 16% used both. Adherence to the prescribed HRT regimen was assumed. Dose-equivalents of conjugated estrogen were calculated for esterified estrogen and ethinyl estradiol. Tubes of vaginal HRT were counted. Four non-HRT users from a pool of 698 women were then matched to each user based on age, year of diagnosis, and stage at diagnosis. Nonusers were still included even if they subsequently began HRT at some date later than that date chosen to match a user's interval from the time of their breast cancer diagnosis to the entry point in the study. HRT was used before diagnosis by 68% of HRT users after diagnosis and by 48% of nonusers. Patients were followed for a median of 3.7 years for recurrence and 4.6 years for mortality.

Recurrences were diagnosed in 16 HRT users (9%) and 101 nonusers (15%). The unadjusted relative risk (RR) was 0.58, and the RR after adjusting for potential confounding features such as those mentioned above, was 0.50. Analysis by type of hormone replacement did not change the RR results. Five HRT users (3%) and 59 nonusers (8%) died during the follow-up period. The unadjusted RR was 0.31, and the adjusted RR was 0.34.

O'Meara and colleagues concluded from their results that women who used HRT after a diagnosis of breast cancer had lower risks of recurrence and death than nonusers. They stated that their results should be interpreted with caution given the limitations of the study.

Comment By Edward J. Kaplan, MD

Menopausal symptoms can result in significant discomfort and impaired quality of life for sufferers. Symptoms can be severe and prolonged. No agents offer efficacy equivalent to HRT with regard to amelioration of these symptoms. Given that estrogen has been associated with an increased risk of breast cancer, and tamoxifen, with its antiestrogen properties, has been shown to decrease breast cancer recurrences, there is great concern over whether HRT in breast cancer survivors is wise. For the most part, HRT is discouraged in the latter group. However, data are very limited. O'Meara et al used a detailed, meticulous approach in their case-control study and determined that HRT does not put breast cancer survivors at increased risk of new events. On the contrary, HRT appeared to offer a protective effect.

In an accompanying editorial, Cuzick suggests that, even if HRT is found to be neutral with respect to an effect on breast cancer prognosis, it would represent an important advance in patient management.[1] Potentially, it would enable physicians to treat patients' menopausal symptoms without fear of provoking breast cancer into recurring.

Col and associates from Brigham and Women's Hospital in Boston performed a MEDLINE search for studies published from 1966 to 1999 and calculated RR values for 11 papers reporting on HRT following a diagnosis of breast cancer. Their objective was to combine all the existing data to establish the effect of HRT in this patient cohort. Their results coincided with the findings of O'Meara et al in that no significant increase in the risk of breast cancer recurrence was identified. O'Meara et al suggested that, although not conclusive, their results indicated that any risk associated with HRT must be of a limited magnitude.

Despite the data showing the absence of a deleterious effect of HRT on outcomes in breast cancer survivors, clinicians must continue to proceed with caution when counseling patients regarding the use of estrogens or estrogen derivatives. We are awaiting the results of 2 randomized trials that may offer further insights into this vexing issue.[3,4] ■

References

1. Cuzick J. *J Natl Cancer Inst*. 2001;93:733-734.
2 Col NF, et al. *J Clin Oncol*. 2001;19:2357-2363.
3 Marsden J, et al. *Acta Obstet Gynecol Scand.* 1997; 76(abstract suppl):22.
4 Vassilopoulou-Sellin R, et al. *J Natl Cancer Inst.* 1994;6: 153-159.

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Maybe We Should Put Statins in the Water

Source: *Ray JG, et al. Arch Intern Med. 2001;161:1405-1410.*

This paper is actually 2 retrospective analyses of large cohorts of individuals at risk for deep venous thrombosis (DVT). In the first analysis, they calculated the hazard ratio for new DVT development in 125,862 Ontarians who were free of documented atherosclerosis, venous thromboembolism, or cancer in

the prior 3 years. The mean age of participants was 72.9 years, and the observation period was 1.4 years. Of these patients, 77,993 were statin users and had a hazard ratio of 0.78 (CI, 0.69-0.87) for new DVT development compared with those who used thyroid replacement therapy. These findings were controlled for age, gender, prior hospitalization, new cancer, and treatment with aspirin, coumadin, or estrogen. Those individuals who used nonstatin lipid-lowering agents did not show a similar reduction in DVT risk. In the second analysis of 89,508 women, Ray and colleagues found that those women who were taking estrogen replacement therapy (n = 29,165) were at increased risk for DVT (hazard ratio, 1.16; CI, 1.01-1.33) compared with those who were not. Statins appeared to lower that risk (hazard ratio 0.68; CI 0.59-0.79) compared with those receiving thyroid replacement therapy. This reduction was not seen with nonstatin lipid-lowering agents.

Comment by Barbara A. Phillips, MD, MSPH

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are in widespread use to prevent cardiovascular disease in people with elevated lipid levels. Ray et al undertook the current study because the Heart Estrogen Replacement Study (HERS) suggested a 50% risk reduction of venous thromboembolism in women who used statins.[1] Because the HERS study was not designed to evaluate this effect of statins, further specific investigation of their effects on DVT development is warranted. This study is an important step in that direction.

Ray et al make several interesting observations in their discussion. First, the rate of spontaneous discontinuation of lipid-lowering medications by patients is very high; at least half of patients stop taking these meds within a year of the initial prescription, most within the first 3 months.[2,3] This may not be true in Ontario, where, as Ray et al proudly proclaim, "The Ontario Health Insurance Plan covers all medical care and prescription drug costs for every Ontario Senior Citizen." Second, the rate of DVT development in older women on estrogen replacement therapy may be much higher than previously recognized. In this study, the rate of DVT and pulmonary embolism in women on estrogen was 12.6 per 1000 person years, twice that seen in the HERS study.[1] Ray et al point out that the women in the HERS study were younger and were more likely to be on aspirin or lipid-lowering agents because they were known to have coronary heart disease. For me, the take home messages are to lower the threshold to prescribe statins, particularly in women on estrogen replacement therapy, and to regularly encourage their use. ■

References

1. Grady D, et al. *Ann Intern Med.* 2000;132:689-696.
2. Simons LA, Levis G, Simons J. *Med J Aust.* 1996;164: 208-211.
3. Avorn J, et al. *JAMA.* 1998;279:1458-1462.

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Does Pravastatin Prevent the Development of Diabetes Mellitus?

Source: *Freeman DJ, et al. Circulation. 2001;103:357-362.*

Most previous investigations into the relationship of pravastatin and glucose tolerance had been equivocal and have yielded inconclusive results.2-3 The West of Scotland Coronary Prevention Study (WOSCOPS) database, however, has now provided us with sufficient information to prospectively determine the effects of pravastatin therapy on the risk of developing diabetes mellitus (DM) in a specific population with follow-up data ranging from 3.5 to 6.1 years.[1] Freeman and colleagues evaluated the effects of pravastatin therapy and the risk of developing DM in a total of 5974 men aged 45-64 years. During this study 139 subjects became diabetic and it was determined that, in this population, pravastatin therapy resulted in a 30% reduction in the hazard of developing DM.

Comment by Harold L. Karpman, MD, FACC, FACP

Freeman et al have determined that pravastatin was effective in preventing the onset of DM with a P value of 0.42 in the WOSCOPS cohort consisting of 5974 men. It should be noted that such therapy was effective on a long-term basis and that the subjects had, on average, normal triglyceride levels at baseline. The mechanism by which pravastatin reduces a subject's risk of developing DM is not clear, however, the beneficial effects of pravastatin therapy on glucose-intolerant subjects had previously been

shown in the CARE trial in which significant reductions in cardiovascular risks occurred in the pravastatin-treated subjects.[4]

Three known effects of pravastatin therapy may have played a primary role either individually or collectively in preventing the development of DM in the WOSCOPS subjects. Pravastatin therapy reduced triglycerides by an average of 12%, and since it has been known for many years that elevated triglyceride levels are associated with the development of DM,[5] it is quite possible that a treatment effect mediated through a change in plasma triglyceride levels may have prevented the onset of glucose intolerance in these subjects. However, it should be noted that other lipid-lowering drugs do not appear to improve insulin resistance suggesting that triglyceride lowering in itself probably does not explain the observed effect.[6] Second, pravastatin has been demonstrated to have anti-inflammatory effects and it has been postulated that the drug may interrupt the natural progression from central obesity to insulin resistance by reducing cytokine production which may be responsible for the metabolic syndrome associated with insulin resistance. Finally, improvement in endothial function seen in patients on pravastatin therapy has been shown to result in diminished capillary recruitment which may significantly influence selective tissue perfusion and thereby benefit glucose and insulin transport.[7]

Regardless of the exact mechanisms involved, it would appear that pravastatin therapy may have reduced the propensity of the subjects within the WOSCOPS to develop DM; this effect may have been one of the important mechanisms which contributed significantly to the observed positive cardiovascular benefits of the drug. The forthcoming results of the Prospective Study of Pravastatin in the Elderly Risk (PROSPER) trial will attempt to prospectively determine if pravastatin truly reduces the risk of developing DM in an elderly population.[7] ■

References

1. Sheperd J, et al. *N Engl J Med*. 1995;333:1301-1307.
2. Sheu WH, et al. *Am Heart J*. 1994;127:331-336.
3. Baba T, et al. *Diabetes Care*. 1993;16:402-404.
4. Goldberg RB, et al. *Circulation*. 1998;98:2513-2519.
5. Haffner SM, et al. *JAMA*. 1990;263:2893-2898.
6. Sane T, et al. *Metabolism*. 1995;44:589-596.
7. Sheperd J, et al. *Am J Cardiol*. 1999;84:1192-1197.

Dr. Karpman is Clinical Professor of Medicine, UCLA School of Medicine, Los Angeles, Calif.

Antibiotic Rotation—Worthwhile or Not?

Source: *Vecchione A. Hospital Pharmacist Report. 2001;6:31-32.*

This special report reviews the concept of antibiotic rotation (also known as antibiotic cycling) and its role in reducing antibiotic resistance. The theory is that by restricting certain antibiotics for preset periods of time, the lessened exposure of microbes to those antibiotics should lessen the likelihood of resistance. Unfortunately, there is little support for this concept in the literature, and few hospitals have actually implemented antibiotic rotation programs.

Of the few studies performed, one of the largest that looked at antibiotic rotation was in the 1980s at the Veterans Administration Medical Center in Minnesota. Due to a problem they were having with gentamicin resistant organisms, they switched from gentamicin to another agent and the gentamicin resistance disappeared.

In order to shed some light on this concept, the Centers for Disease Control and Prevention (CDC) have initiated a 3-year study with 3 academic medical centers to evaluate the efficacy of a scheduled rotation of antibiotics in the intensive care unit. Participating in the study are the Washington University in St. Louis, Mo, the University of Virginia in Charlottesville, and the Rush-Presbyterian-St. Luke's Medical Center in Chicago, Ill. In this study, certain antibiotics will be rotated every 3-4 months. One of the key elements of this study will be to insure that patient care is not compromised as a result of antibiotic cycling. As a result, patient outcomes will be closely monitored to insure that length of stay and mortality do not trend in a negative direction. Other elements being studied are the cost factors associated with the cyclic rotation of antibiotics.

Comment by Thomas G. Schleis, MS, RPh

Antibiotic cycling has always been an interesting concept, but no one has actually investigated it in enough detail to garner any wide-range support. That is why the CDC study is desperately needed to help answer many of these questions.

Antibiotic formularies at most hospitals are driven by acquisition cost, with the primary goal being to lower overall antibiotic expenditures. Often I have heard the term

"antibiotic cycling" as an enticement to change formulary items to a less expensive antibiotic. Unfortunately, there is no really good science at this time to support this. In fact, should antibiotic rotation be recommended, I feel most hospital pharmacists would be concerned over the potential formulary cost increases. Cost increases would result when more expensive antibiotics are used in the "rotation," the loss of contract pricing because of lack of ability to commit to volume and market share, and the increased personnel time needed to implement rotations and provide educational support. Pharmacists will need to look "outside the box" to evaluate the overall cost of patient care—the cost of antibiotic rotation and the cost of antibiotic resistance—in order to decide whether implementation of such a program at their institution is warranted.

While most experts agree that antibiotic rotation may not be the complete solution to the resistance problem, they support studies such as the one being conducted by the CDC. It is hoped that this study will help determine if antibiotic rotation has merit and when and where it should be performed. (*Editor's Note: As this issue went to press, Puzniak and colleagues reported failure of scheduled antibiotic rotation to reduce the rate of acquisition of enteric vancomycin-resistant enterococci in an ICU [Puzniak LA, et al. Clin Infect Dis. 2001;33:151-157].*) ■

Dr. Schleis is Director of Pharmacy Services, Infections Limited, Tacoma, Wash.

CME questions

Testing form inserted in the January 2002 issue

4. **Statins:**
   a. have no effect on the development of DVT.
   b. reduce the development of DVT to the same degree as do nonstatin lipid-lowering agents.
   c. reduce the risk of DVT in men, but not in women.
   d. reduce the risk of DVT in both men and women, and reduce the rate of development of DVT related to estrogen therapy.
   e. have no measurable effect of development of DVT, but appear to be associated with reduced risk of pulmonary embolism, especially in men.

5. **Which statement is *false* about pantoprazole injection?**
   a. No dose adjustment is needed in renal failure.
   b. It is given once a day.
   c. Drug/drug interactions are common.
   d. It is approved for the treatment of GERD.

6. **Which is *not* true about Twinrix?**
   a. It is less effective than both vaccines given individually
   b. It is not approved for children
   c. It requires 3 injections
   d. It is given at 0, 1, and 6 months

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