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Rezulin comes under fire as *LA Times* alleges more adverse reactions

FDA and manufacturer continue to counter new claims of fatality

The controversy over Rezulin (troglitazone) erupted anew in mid-December when the *Los Angeles Times* alleged 53 more deaths have been linked to the enormously popular drug used to treat the most stubborn cases of insulin resistance. Countering with a statement of its own, Warner-Lambert, manufacturer of Rezulin, announced the reports were taken out of context and accused the *LA Times* of bias and distortion.

But even before this newest round of tough press, health care professionals say they have been moving away from Rezulin out of concerns for the safety of their patients.

"It doesn't really make sense to prescribe troglitazone in light of the safety concerns and that there are two other drugs in the same class that have a similar mode of action and do not have the hepatotoxic effects," says American Diabetes Association (ADA) president **Bruce Zimmerman**, MD. He is an endocrinologist at the Mayo Clinic in Rochester, MN. Zimmerman says safety concerns about Rezulin prompted him and his endocrinology team to recommend removing the drug from Mayo's formulary several months ago. The ADA, he says, is discussing its viewpoint on the matter. "It's not where we can develop a consensus now or put a name on hard scientific evidence. We need to let more facts accumulate."

That cautious viewpoint was echoed by the ADA's chief scientific and medical officer, **Richard Kahn**, PhD. "It's hard for the ADA to make a judgment based on an article in the *Los Angeles Times*. We certainly assume the FDA is paying close attention to the safety and efficacy issues as they relate to the use of this drug." He says the ADA will most likely present evidence if the FDA decides to conduct another review of Rezulin as it did in March of last year, two years after the drug was introduced.

In practice, health care organizations are voting with their checkbooks when it comes to Rezulin.

FDA's Statement on Report of Adverse Effects from Rezulin

1. The FDA is actively monitoring these adverse reaction reports. A key element in this process is careful analysis of each report to determine whether the drug is actually a significant cause of the injury or death or whether these problems can be attributed to other factors (e.g. underlying health problems, other drug interactions, etc.). Until this analysis is done, it is impossible to conclude that the drug caused the injury or death.
2. Drugs are removed when they pose an unacceptable risk to patients — when it is established that their potential risk outweighs their potential benefit. The number of raw adverse reaction reports filed cannot determine this. Again, careful medical analyses are essential in determining whether a drug is causing injuries. Such analyses may demonstrate that a large number of reports actually reveal no link between injuries and a drug; on the other hand, analysis of a small number of reports can reveal a clear disturbing pattern that would lead to a drug's removal.
3. Since the safety of troglitazone was reviewed by the Metabolic and Endocrine Drugs Advisory Committee in March 1999, a total of nine cases of death due to liver failure that are possibly or probably related to troglitazone have occurred and have been reported to the FDA through MEDWATCH. The Agency is continuing to actively evaluate the risks and benefits of troglitazone as well as the risks and benefits of other members of this drug class that are marketed in the United States to determine whether any further regulatory actions are warranted.

Source: U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Washington, DC.

The *LA Times* reported that four major managed care organizations — Aetna Inc., Cigna Healthcare, UnitedHealthcare, and Kaiser Permanente — have either removed Rezulin from their formularies or are requiring doctors to justify the drug's use. That means patients who want to stay on the drug will find it harder to get and may have to pay the entire cost out of their own pockets. Prudential Healthcare officials removed Rezulin from their formulary last fall because of safety concerns, says **Arthur Levin**, MD, vice president for technical and clinical practice assessment for Prudential who now holds the same title for the merged company under Aetna's corporate name.

"This is disturbing," he says. "I don't think we should have to learn about this from the press. I'd certainly like to see these reports from the FDA. There should be some mechanism for informing physicians and health care organizations about what information they have received. It concerns me greatly that these data seem to be piling up at the FDA and nobody knows anything about it except the people at the FDA."

Rezulin remains on the Aetna formulary with several restrictions. The company's pharmacy and therapeutics committee is currently considering its position on the matter, Levin said.

The *LA Times* article reported the 53 cases were found by searching records gained under a federal Freedom of Information request. If these reports are substantiated, it would mean a total of 215 reported fatalities could be attributed to Rezulin use, due to incidences of liver failure occurring since the drug was introduced in March 1997.

In a written statement, the FDA disputed the figures and said it is investigating all reports of adverse effects linked to the drug. FDA spokeswoman **Crystal Wyand** says nine new cases have been received since March 1999, when the agency's Metabolic and Endocrine Drugs Advisory Committee reviewed Rezulin's status and issued directives for close monitoring of liver function for patients using the drug. She says six of those cases are "probable" Rezulin links, the other three are "possible," and there have been no new cases reported since August 1999.

At the March hearing, FDA epidemiologist David Graham testified that at least 28 people had died of liver failure associated with Rezulin use since the drug came on the market. The report says 21 of the 53 new deaths were from liver failure. During that hearing, Graham also told the panel he believed the number of incidents of liver failure associated with Rezulin had been underreported

COMING IN FUTURE MONTHS

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and suggested the number of adverse liver side effects may be as high as one in 1,800 patients using the drug. Graham also estimated Rezulin patients were 1,200 times more likely to suffer liver failure than those who take other medications.

After that review hearing, the panel said the benefits of Rezulin outweighed the risks associated with its use. However, the panel recommend Rezulin not be used as a monotherapy and said close liver function monitoring is necessary for patients using the drug.

Warner-Lambert accused the *LA Times* of providing its readers with "a biased and strongly distorted picture of Rezulin," called the reports of additional deaths "absolutely false," and said the article "represents a cynical intent to alarm the public and prescribing physicians."

A written company statement issued shortly after the article was published stated the article cites post-marketing case reports out of context and contends that the recent reports listed in the FDA's MEDWATCH explicitly warn users that reports of additional liver toxicity events "cannot be interpreted as proof of causality."

Warner-Lambert says that through November 1999, the company received reports of seven deaths or liver transplants, which were considered based on available information to be "possibly or probably related to the drug."

Rezulin use dropped dramatically between January and September, according to figures reported by the *Los Angeles Times*. In January, 488,000 prescriptions were written for the drug, and in September, 370,000 prescriptions were written. The *LA Times* reported Rezulin has generated sales of approximately $1.7 billion.

During the intervening months, not only did the FDA review Rezulin, but two other drugs in thiazolidinedione class were approved. Rosiglitazone, marketed under the brand name Avandia by SmithKline Beecham was approved in May, and pioglitazone, marketed by Eli Lilly under the brand name Actos, was approved a few weeks later. Neither of the newer drugs was associated with liver toxicity in clinical trials. Since Avandia entered the market in June, the *LA Times* reported, one death from undisclosed causes has been reported to the FDA. No deaths have been linked to Actos, which became available in August.

Experts such as Zimmerman have expressed concern that liver toxicity may increase over time with any of the medications because they are intended for long-term use and there is no means of determining their potential effects over years. ■

After the party's over: The effects of alcohol

Some may book passage on 'banana boat'

With the celebration of St. Patrick's Day this month, there will be the inevitable few who drink enough alcohol to require medical attention. Some will show up in your emergency department for treatment, but what kind of treatment should they receive?

"First and foremost is attention to respiratory support. Patients are given oxygen, if it's required, and the nurses make sure patients don't aspirate if they are vomiting. At that point, most of our intoxicated patients are given a 'banana boat,' which consists of 1 L of normal saline, with 10 mL multivitamin, and 100 mg thiamine," says **Rhonda Beene**, RPh, of Health Midwest Hospital in Lee's Summit, MO.

Reasons for IV fluids vary

Why are these patients treated with intravenous fluids? As is the frequent answer in medicine: It depends. Some would say it's to correct volume depletion and thus also correct hypotension. In the "banana boat," the components are given to correct volume depletion caused by vomiting (normal saline), help correct nutrition depleted by vomiting and/or chronic drinking (multivitamin), and prevent Wernicke's encephalopathy (thiamine). (Patients who are thiamine-deficient can experience sudden onset of Wernicke's encephalopathy following administration of glucose.) Often, if a patient receives dextrose, it's to correct hypoglycemia that alcohol can induce. Still others contend that IV fluids are administered to speed the time to sobriety by increasing the clearance of the drug.

Ethanol Content of Drinks

Light beer	2-4%
Beer	4-6%
Ale and special beers	up to 12%
Wine	10-20%
Distilled drinks (e.g., rum, whiskey, liqueurs)	35-55% or as much as 95%

Source: Adapted from *Applied Therapeutics*, 5th ed.[1]

In a study conducted by J Li and colleagues,[2] five men and five women ages 23 to 36 were given ethanol sufficient to cause blood alcohol levels of 150 mg / dL. These same healthy volunteers served as their own controls in a crossover design when, four days later, the subjects underwent the same exercise. This time, subjects were given 1 L of normal saline "wide open" immediately after ingesting the ethanol. A comparison of results showed no difference between groups in the clearance rate of ethanol. Therefore, Li et al. concluded that administration of IV fluids does not affect the clearance rate of ethanol.

Certainly, IV fluids are appropriate in some intoxicated patients. However, not all of those patients require it. Although the cost to supply the drug is not great in this case, the cost of supplies and personnel required to give an IV is enough to make the health care team consider whether every intoxicated patient needs an IV.

Ethanol is oxidized at an approximate rate of 15 mg / dL / h in men and 18 mg / dL / h in women.[1] It takes time to "sober up," and time might just be what the doctor ordered. Pharmacists can help review and evaluate IV use in their hospitals. While some intoxicated patients may require a good deal more care than described here, still others may not even require a "banana boat."

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From the Editor

Keep a brain in your pocket

By **Ruth Noland**, PharmD
Editor
Drug Utilization Review

Many a time, my second "brain" I kept in a pocket provided me the information I needed while walking the halls or sitting at my desk as a pharmacy resident. The brain I refer to is not the one inside the skull, but rather, a 3"× 5" notebook nestled in my lab coat. As a resident, I found it invaluable to clip important formulas, conversion charts, and other assorted pearls of wisdom and insert them into my pocket brain.

In an effort to keep my brain growing and to help you grow yours, short pocket-size (yet very important) information will appear in this section in coming issues for you to cut and paste into your second brain. I encourage you to start such a brain if you currently rely solely on the one in your head.

Please e-mail related pearls you find useful to ruthnoland@hotmail.com so I may share them with your colleagues in future issues of *Drug Utilization Review.* ■

Tyramine-containing Foods

Tyramine, a component of various foods, can cause a hypertensive reaction in patients taking monoamine oxidase inhibitors, or MAOIs. (Adapted from MicroMedex.)

Cheeses

Alcoholic beverages (one to two drinks/day OK):
ale, beer (especially unpasteurized), chianti, cognac, red wine, vermouth

Fish
camlin, caviar, cod, herring, snails

Fruits/vegetables
avocados, bananas, beans (broad, green, Italian flat), Chinese pea pods, eggplant, canned figs, oranges (one/day OK), papayas, red plums, raisins, raspberries, tomatoes

Meat
aged meat/game/poultry, canned meat, liver, sausage

Miscellaneous
bread or crackers with cheese, caffeine (>2 cups), chocolate (large amounts only), commercial gravies, licorice, marmite, meat extracts and tenderizers, MSG, peanut butter, peanuts, pickles, sauerkraut, canned soup, soup cubes, spoiled sour cream, soy sauce, tofu, vanilla, yeast breads/extracts and products, spoiled yogurt

NEWS BRIEFS

New FDA Web site

Buying drugs and medical products on-line

The FDA has launched a new Web site to educate consumers about the risks of buying prescription drugs and medical products on-line. Risks present themselves to consumers when Web sites masquerading as legitimate pharmacies turn out to be fraudulent.

While consumers enjoy the convenience of the Internet, they also need to know the risks associated with obtaining prescriptions and drugs there and the actions they can take to protect themselves.

By going to the FDA Web site at www.fda.gov and clicking on "Buying Medical Products Online?" consumers can learn:

- how to protect themselves from dangers of buying medications on-line;
- about FDA's enforcement efforts;
- how to discern a health fraud;
- answers to commonly asked questions about Internet drug sales;
- how to report suspicion or knowledge of illegal on-line sales of drug and drug-related products directly to the FDA. ▼

Surgeon General reveals new health strategy

Surgeon General David Satcher, MD, has announced a 10-year health plan for Americans. The plan focuses on:

- getting kids into better shape;
- getting people to stop smoking;
- cutting drug use;
- encouraging teens to either abstain from sex or use condoms.

As part of the Healthy People 2010 plan, the Surgeon General hopes to see 30% of Americans exercise for 30 minutes each day. Currently, only 15% of us do so. Healthy People 2010 is the first plan of its kind to establish measurements. Data will be collected from state and local health agencies as well as federal agencies that compile health statistics. Eliminating racial disparities is also among the Surgeon General's goals. While Americans of all backgrounds are, in general, healthier now than they were 10 years ago, disparities still exist between races, Satcher says. ▼

Propulsid warning emphasized

Prescribing information for Propulsid, which is marketed by Janssen Pharmaceutica, has been updated to include a requirement for physicians to conduct certain tests to identify patients who are not appropriate candidates for the drug. An initial electrocardiogram must be conducted to exclude patients with cardiac abnormalities, Janssen reports, along with an assessment of electrolytes and creatinine, which is excreted by the kidneys. Caution also is advised, Janssen notes, regarding Propulsid's use in the elderly because many elderly patients use contraindicated medications or have contraindicated conditions. Propulsid is for symptoms of nighttime heartburn in adults with gastroesophageal reflux disease. ▼

More diabetes trouble for older women

Older women with diabetes tend to demonstrate lower levels of cognitive function and more rapid rates of decline than do nondiabetic older women, according to a study by Edward W. Gregg and colleagues reported in the *Archives of Internal Medicine.*

In addition, "The odds of cognitive impairment and major cognitive decline increased with the duration of diabetes," the authors write. Older diabetic women in the study had as much as a twofold increased risk of cognitive impairment and a 74% increased risk of cognitive decline than did older nondiabetic women.

(For more information, read Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Arch Intern Med *2000; 160:174-180.)* ▼

HHS' year 2000 report: No stockpiling of drugs

Health and Human Services Secretary Donna E. Shalala recently announced that monitoring efforts indicate no significant Y2K-related problem with the supply of pharmaceuticals in the United States. Fears that many consumers would stockpile drugs in preparation for Y2K proved unfounded.

In addition to monitoring by the FDA, the Pharmaceutical Alliance for Y2K Readiness, a group comprising leading drug manufacturers, pharmacies, and health care practitioners, met regularly during 1999 to monitor pharmaceutical production and distribution patterns.

Analysis of those reports showed no notable problems with the nation's drug supply, nor any production or distribution problems associated with Y2K.

The audit reports are: "Report on the Evaluation of Manufacturers' Activities to Assess the Year 2000 Compliance Status of Their Medical Devices," "Report on the Y2K Readiness Survey of Manufacturers of Essential Medical Supplies," "Assessment of Biologics Industries' Readiness for Year 2000: Interim Report," and "Assessment of Pharmaceutical Industries' Readiness for Year 2000: Interim Report." You may view the findings at www.fda.gov/oc/y2k/. ▼

FDA issues call for wise prescribing of antivirals

This year's flu season has seen a high level of prescribing of new antiviral drugs targeting influenza. Indeed, consumers have been reminded over and again of the availability of these new agents through advertising by the manufacturers.

In January, the FDA issued a public health advisory to health care workers to remind prescribers that judicious prescribing is necessary in patients with apparent influenza. It is important to identify patients appropriate to receive one of the antivirals available for influenza, the FDA noted, advising that the following items be considered:

1. "Vaccination remains the primary method of preventing and controlling influenza."

2. "Always consider the possibility of primary or concomitant bacterial infection when making treatment decisions for patients with suspected influenza."

3. "Use special caution if prescribing Relenza to patients with underlying asthma or chronic obstructive pulmonary disease."

Health care workers are encouraged to report serious adverse events to the FDA MedWatch program at (800) FDA-1088 [fax: (800) FDA-0178] or to the appropriate manufacturer:

- Flumadine (rimantadine), Forest Pharmaceuticals, (800) 678-1605;
- Relenza (zanamivir), Glaxo Wellcome, (800) 825-5249;
- Symmetrel (amantadine; also generic), Endo Pharmaceuticals, (800) 462-3636;
- Tamiflu (oseltamivir), Roche Laboratories, (800) 526-6367.

(For more details, see www.fda.gov/cder/drug/advisory/influenza.htm.) ▼

Help prevent diabetes: Reach for those tennies

The prevalence of diabetes type 2 has continued to increase over past years. Recent evaluation of data shows that its incidence is reduced by being physically active. In a recent paper, Aaron Folsom et al. examined whether the "incidence of type 2 diabetes was lower over 12 years in physically active women compared with inactive women."

The 41,836 older women (ages 55 to 69 years upon first contact) who participated in the Iowa Women's Health Study responded to an initial questionnaire from Folsom and his colleagues that assessed tobacco and alcohol use, estrogen replacement, height, weight, and family history of diabetes.

An analysis of the data shows that postmenopausal women who partake of any type of regular exercise are approximately half as likely, in a 12-year period, to develop type 2 diabetes as are inactive women. Those findings were strengthened when results were adjusted for body mass index and waist-to-hip ratio.

(The findings can be seen in Am J Public Health *2000; 90:134-138.)* ▼

Time to bone up on alendronate treatment

Results published in the *Annals of Internal Medicine* show that four years of "alendronate treatment prevented postmenopausal bone loss at the spine, hip, and total body and was more effective than two years of alendronate treatment followed by 2 years of placebo."

The 1,609 postmenopausal women who participated in the Early Postmenopausal Intervention Cohort Study were assigned to either alendronate, placebo, or open-label estrogen-progestin combination. Subjects receiving alendronate were given either 2.5 mg / day or 5 mg / day orally for two years, followed by two years of placebo or continued alendronate. Bone mineral density was more greatly affected by four years of the 5 mg dose of alendronate than by the 2.5 mg dose over the same time frame ($P < 0.01$).

(See Ravn P, Bidstrup M, Wasnich RD, et al. Alendronate and estrogen-progestin in the long-term prevention of bone loss: Four-year results from the early postmenopausal intervention cohort study. Ann Intern Med *1999; 131:935-942.)* ▼

CDC stresses guidelines for *S. aureus* testing

Upon receiving a fourth report of an *S. aureus* infection with reduced susceptibility to vancomycin, the Centers for Disease Control and Prevention (CDC) in Atlanta is stressing the importance of CDC guidelines for testing for those resistant bacteria. The CDC has expressed concern that many U.S. labs may not be testing properly for antibiotic-resistant bacterial strains.

This recent report of recent bacteria and the death associated with it points again to the important role of the pharmacist in making recommendations for appropriate antibiotic use. Swift and accurate culture and sensitivity determination is important in antibiotic selection. Close work between pharmacists and their labs can expedite the application of lab results in making decisions concerning antibiotic selection and dosing.

(See MMWR *2000; 48:1,165-1,171.)* ■

Change is good, right?

Greg Fulton, editor of *Drug Utilization Review* for the past two years, has left his editorial post to pursue other career opportunities. We thank Greg for his excellent work during his tenure as *DUR* editor.

His departure also means the opening of an opportunity for me, your new editor. As a pharmacist myself, I hope to enrich *DUR* by applying my pharmacy degree and the contacts I've made with the many wonderful people I've met thus far in my pharmacy career. Knowing how small the world of pharmacy is, I may well contact you as a source of information or ideas.

Motivational speakers and bosses like to tell us that "change is good." I anticipate that it will be good for all involved. You can let me know as we grow and learn together by contacting me at ruthnoland@hotmail.com. I value your input and ideas.

Sincerely,
Ruth Noland, PharmD

New FDA Approvals

These drugs and/or new indications have received final approval from the U.S. Food and Drug Administration:

✔ **Immunosuppressive agent azathioprine tablets, by Mylan Laboratories.** As generic equivalent to Glaxo Wellcome's Imuran. Azathioprine is first of several generic products to receive FDA approval under a collaborative effort between Mylan Laboratories and Genpharm.

✔ **Migraine treatment Maxalt (rizatriptan) by Merck.** A 5HT1 agonist indicated for acute treatment of migraine attacks with or without aura. Not intended for prophylactic use. Available in 5 mg and 10 mg tablets.

✔ **Onychomycosis treatment Penlac Nail Lacquer (ciclopirox): Topical Solution 8% by Aventis Pharmaceuticals.** A synthetic broad-spectrum antifungal agent indicated for use as a component of a comprehensive management program for the topical treatment in immunocompetent patients

with mild to moderate onychomycosis of fingernails and toenails without lunula involvement, due to *Trichophyton rubrum.* The comprehensive management program should include removal of any unattached, infected nails as often as monthly by a health care professional. Solution is applied once daily with an applicator brush to affected nails and adjacent skin.

✔ **Surfactant Curosurf (poractant alfa) Intratracheal Suspension by Dey Laboratories.** A nonpyrogenic pulmonary surfactant indicated for the treatment (rescue) of Respiratory Distress Syndrome in premature infants. The drug is supplied in ready-to-use rubber-stoppered glass vials containing 1.5 mL (120 mg phospholipids) or 3 mL (240 mg phospholipids) of suspension.

✔ **Carnitor (levocarnitine) Injection by Sigma-Tau Pharmaceuticals.** Carnitor has been approved for the prevention and treatment of carnitine deficiency in patients with end stage renal disease who are undergoing dialysis. It is available as 200 mg/mL in 2.5 mL and 5 mL ampoules.

✔ **Breast cancer agent Aromasin7 (exemestane) tablets by Pharmacia & Upjohn.** The new drug application was approved for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. The drug is available in a 25 mg dose.

✔ **Oral cephalosporin Omnicef (cefdinir) capsules by Parke-Davis.** The FDA has approved the capsules for a five-day dosing regimen (300 mg bid) for the treatment of acute exacerbations of chronic bronchitis.

✔ **Sedative Precedex (dexmedetomidine HCl) by Abbott Laboratories.** Precedex is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Precedex should be administered by continuous infusion not to exceed 24 hours.

✔ **Combination antiplatelet agent Aggrenox (aspirin/extended-release dipyridamole) capsules by Boehringer Ingelheim Pharmaceuticals.** Aggrenox received FDA approval to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis. The drug is available as a capsule containing 25 mg aspirin and 200 mg dipyridamole in an extended-release form. ■

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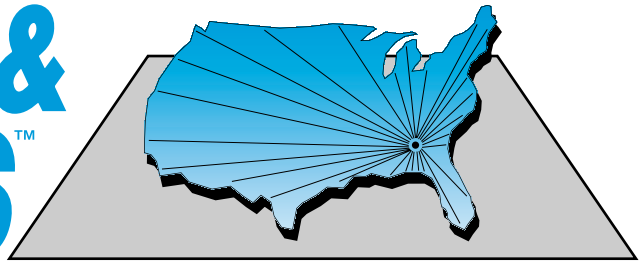

A pox on chickenpox: A guide to treating children

By **Ruth Noland**, PharmD
Editor, *Drug Utilization Review*

Varicella zoster virus (VZV) may cause varicella (chickenpox) or herpes zoster (shingles). Chickenpox manifests as an itchy vesicular skin eruption, accompanied by headache, fever, and malaise. VZV remains dormant in sensory-nerve ganglia and may be reactivated at a later time, thus presenting shingles, which manifests as a painful rash with dermatomal distribution of sensory-nerve roots.[1,2]

There are approximately 300,000 cases of shingles in the United States each year[1] and, prior to availability of a vaccine, 4 million cases of chickenpox, 11,000 hospitalizations, and 100 deaths each year.[3] Children and adolescents represent 80% of the annual varicella-related hospitalizations. Varicella complications that lead to hospitalization include bacterial skin infections, pneumonia, encephalitis, dehydration, and hepatitis.[2]

VZV is spread by airborne particles, usually requiring face-to-face exposure, but it also can be contracted by susceptible people through indirect air exposure. The period during which the virus is contagious is thought to be between two days before and four days after the appearance of vesicles, or until the vesicles have crusted over.[1,2,4]

Nearly all people who live in the United States develop varicella. Ninety percent of cases of chickenpox occur in patients under age 15; more than 90% of adults are immune to VZV.[3] Illness after re-exposure is rare but may occur with immunocompromised individuals. Re-exposure to wild-type VZV in an otherwise healthy person often boosts antibodies without clinical signs of disease.[2] Infection caused by VZV typically confers lifetime immunity.[2]

In 1995, the FDA granted approval for Varivax (varicella virus vaccine, Merck), a live attenuated vaccine, for individuals 12 months and older who have not had varicella. Among 6,889 susceptible children ages 12 months to 12 years, a single 0.5 mL dose of the vaccine given subcutaneously (SC) has resulted in seroconversion in >97% of vaccinated people. Antibodies were found in 97% of Japanese children seven to 10 years after they were given the vaccine.

Follow-up at 20 years showed antibody levels even higher than those seen 10 years earlier, presumably due to boosting of immunity from the vaccine by subsequent exposure to wild-type VZV.[2]

Among those vaccinated at age 13 or older, 78% of subjects seroconverted with one dose of vaccine; 99% seroconverted following a second dose four to eight weeks later.[2]

VZV vaccine should be given to children 12 months to 12 years old and should be routine in children 12 to 18 months old. Children with a history of chickenpox are considered immune.[2,5] Adolescents and adults without a history of chickenpox also should be vaccinated, especially health care workers, day care workers, teachers,

VZV vaccination

Susceptible* children 12 months to 12 years old
1 SC dose (0.5 mL)

Susceptible* individuals (13 and older)
2 SC doses (0.5 mL each) at least 4 weeks apart

*Those lacking a reliable history of chickenpox who have not been immunized.

Types of vaccines

Active: Antigen is introduced so that the individual's immune system is stimulated to make the appropriate antibodies.
Passive: Preformed protective antibodies are transferred.

Those who should be vaccinated

- ✔ Children 12 months to 12 years old (routinely at 12 to 18 months of age)
- ✔ Adolescents and adults without history of chickenpox, especially:
- Health care workers
- Day care workers
- Teachers
- College students
- Military personnel
- Prisoners
- Nonpregnant women of childbearing age
- International travelers
- Family contacts of immunocompromised patients

college students, military personnel, prisoners, non-pregnant women of childbearing age, international travelers, and family contacts of immunocompromised people.[1-2]

The varicella vaccine should not be given routinely to immunocompromised people or to pregnant women.[6]

Approximately 15% of people will have shingles during their lifetimes. Shingles occurs most often in the immunocompromised and the elderly.[2] Octogenarians have a one in 100 chance per year of developing shingles.[1] Importantly, shingles occurs less frequently in vaccinated persons than in those who experienced wild-type varicella.[6]

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6. Klein JO. "Immunization of Children and Adults." In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases.* 2nd ed. Philadelphia: W.B. Saunders Company; 1998, p. 448. ■

Varicella vaccine opens shelter doors

The effectiveness of vaccinating children and adults following exposure to varicella was elucidated at a homeless shelter for women and children in Philadelphia in 1998. Barbara Watson and colleagues describe the scenario in their paper in the January 2000 issue of *Pediatrics*.[1]

Following the eruption of two cases of varicella in a 27-year-old mother (case A) and her 11-month-old son (case B), the shelter director notified the Philadelphia Department of Public Health's Division of Disease Control of the cases. Both patients had been prescribed antiviral medication when they were seen in the emergency department, but they failed to have the prescriptions filled due to cost of the drug. Instead, they returned to the shelter and the restrooms and common area for classes, recreation, and eating they shared with the other residents.

Assume exposure

Because all residents use the common room and had been in that room with the identified mother and child for the two-day period before diagnosis of the cases, it was assumed that all residents had been exposed to the virus. Upon notification, staff at the Division of Disease Control offered varicella vaccine to all susceptible residents of the shelter. At that time, the shelter was at its full capacity of 154 residents and no new (i.e., unexposed) residents were allowed into the shelter.

Within a 36-hour period, all susceptible residents were offered the varicella vaccine free of charge. First, Watson and colleagues interviewed all the residents to determine susceptibility by history of chickenpox and of varicella vaccination. "All unvaccinated persons with negative or unknown varicella history status were considered susceptible," the authors wrote. "Although a specific postexposure recommendation was not in force at the time, this practice was, nonetheless,

consistent with varicella vaccination recommendations of both ACIP [the Advisory Committee on Immunization Practices] and the American Academy of Pediatrics."[1]

Within 36 hours, 67 individuals (25 women, 42 children <13 years old) were vaccinated. Ten children determined to be susceptible were not vaccinated; nine were under the age of 12 months, and one remained unvaccinated due to an inaccurate reporting of history followed by development of chickenpox before the child could be vaccinated.

Two children developed a vesicular rash 12 days after administration of vaccines; both children were sons of case A and were considered to have had longer initial exposure to the virus. Both of the cases in children who received the vaccine were mild in intensity (<50 skin lesions). No other cases of chickenpox developed from the initial exposure.

"Using an attack rate of 100% in the 1 unvaccinated child," the authors wrote, "the vaccine was 95.2% (95% CI, 81.6%-98.8%) effective in preventing all disease and 100% effective in preventing moderate and severe disease."[1]

Residents were monitored for up to 42 days after the last diagnosed case of chickenpox. Though still monitored, the shelter was reopened just six weeks after diagnosis of the initial case of chickenpox with no susceptible individuals in residence. On the other hand, a varicella outbreak in another shelter in Philadelphia caused the second shelter to close its doors for six months. Therefore, the varicella vaccine was effective not only in protecting individuals from infection, but in opening the shelter to newcomers earlier than previously reported.

The authors conclude that use of the varicella vaccine postexposure "and for outbreak control should limit the spread of varicella, prevent its associated complications and dramatically shorten outbreaks."[1]

Reference

1. Watson B, Seward J, Yang A, et al. Postexposure effectiveness of varicella vaccine. *Pediatrics* 2000; 105:84-88. ■

ACIP recommends vaccine postexposure

A growing amount of data from household, hospital, and community settings shows that administration of the varicella vaccine postexposure is effective in preventing illness or decreasing severity of infection when given within three — and possibly as many as five — days following exposure. Based on those data, the Advisory Committee on Immunization Practices now recommends use of the vaccine in susceptible individuals following exposure to the virus.

When initial exposure to the virus does not cause infection, the vaccine will provide protection from development of infection associated with future exposure. When initial exposure does lead to infection, no evidence suggests that the vaccine will worsen side effects or increase likelihood of those effects. In fact, evidence suggests just the opposite.

Transmission of the vaccine virus has been documented in only three cases of 15 million doses of vaccine. All three of the cases were mild and without complications.

[For details, see MMWR *1999; 48(RR-6).]* ■

Varivax: Background of a vaccine

The varicella virus vaccine Varivax (Merck) comes from the Oka / Merck strain of live, attenuated virus. The original virus was obtained from a child with natural varicella.

According to the package insert, the varicella vaccine should not be given to anyone with known hypersensitivity to any of its components, including gelatin and neomycin.[1] It is further contraindicated in individuals with blood dyscrasia, leukemia, lymphomas of any type, and other malignant neoplasms affecting bone marrow or lymphatic systems.

Patients on concomitant immunosuppressive therapy and those with primary and acquired immunodeficiency states should not be given the vaccine. Additionally, those with active untreated tuberculosis or any febrile respiratory illness or infection should not be administered the vaccine.

Varivax is contraindicated in pregnant women; caution should be exercised when giving the vaccine to women who are lactating. Women are advised to avoid pregnancy for three months after vaccination, the Merck package insert notes.

The duration of immunity is currently unknown, and thus guidelines for boosters are undetermined, Merck says. However, elevated antibody titers have been observed in several

vaccinated persons following exposure to wild-type varicella and following a booster of varicella vaccine four to six years after initial vaccination. In a population that is highly vaccinated against varicella virus, lack of exposure to the virus may cause immunity to wane. Postmarketing surveillance continues to evaluate the potential need for and timing of booster doses.

Patients should avoid use of salicylates after vaccination for a period of six weeks as Reye's syndrome has been reported following the use of salicylates during the natural course of varicella, the package insert notes.

In clinical trials, adverse events reported at a significantly greater rate in vaccinated subjects than in placebo subjects were pain and redness at the site of injection, Merck reports.

Reference

1. Varivax [package insert]. West Point, PA: Merck & Co; 1995. ■

Changes in immunization schedule published

Publication cites vaccine changes

The Advisory Committee on Immunization Practices (ACIP), American Academy of Pediatrics (AAP), and American Academy of Family Physicians have approved a new recommended childhood immunization schedule for the United States. Changes include:

1. withdrawal of rotavirus vaccine;

2. use of inactivated poliovirus vaccine for all four doses of polio vaccine;

3. combination acellular pertussis vaccine with diphtheria and tetanus toxoids for pertussis vaccination (followed by boosters of tetanus and diphtheria toxoids every 10 years);

4. Hepatitis A vaccination only in certain states or regions (contact local health authorities to determine need for your area).

(For more details on the recommendations, see Pediatrics *2000; 105:148-151. Or visit AAP at www.aap.org or ACIP at www.cdc.gov/nip.)* ■

Pharmacists and VAERS: Unearthing the adverse

A decade with the vaccine reporting system

Pharmacists play an important role in reporting any kind of adverse reaction to a medication, and vaccines are no exception.

The importance of post-marketing surveillance is undisputed. Even large clinical trials of > 10,000 subjects are inadequate to reveal very rare but often serious adverse events of a drug. In addition, subjects in controlled clinical trials are in very controlled environments. Once a drug is approved and administered to the general population, however, recipients are of vastly divergent demographics, medical histories, medical problems, and concomitant medications. Often, rare side effects do not appear in patients until a drug is administered to a diverse population. It is important then that adverse events be reported in order to further evaluate the safety of a drug.

In 1990, the U.S. Department of Health and Human Services established the Vaccine Adverse Event Reporting System (VAERS). The FDA and Centers for Disease Control and Prevention work together in accepting all VAERS reports.

VAERS is a passive surveillance system for monitoring vaccine safety. All reports of adverse events associated with vaccines — whether submitted by health care professionals, vaccine manufacturers, or those receiving vaccines — end up in the VAERS database. The final destination of those reports is with the VAERS database, whether originally submitted to local or state health authorities, manufacturers, or directly to VAERS. ■

More VAERS information enclosed in this issue

Enclosed in this issue of *Drug Utilization Review* is an outline of post-marketing surveillance systems and a sample of the Vaccine Adverse Event Reporting System form in a special insert. There are extensive instructions on the proper way to fill out the form and file it; therefore, readers are advised to go to on-line for the entire 19-page document. The World Wide Web address is www.fda.gov/cber/vaers/vaers.htm. Click on "How to Report." ■