

Health Matters July 2006; Volume 1, Issue 1

Promethazine and Pediatric Alert by YenLinh Bui

Promethazine, a histamine H1 antagonist, is used as an antiemetic for motion sickness, sedation, postoperative pain and various allergic conditions.¹ Marketed by Wyeth under the brand name Phenergan®, it has recently received attention for reports of respiratory depression in the pediatric population.² Wyeth has sent out notification to healthcare professionals of the changes in its warning label and a Food and Drug Administration (FDA) Alert was posted April 2006. These alerts repeat the warning for its use in children under 2 years of age and remind healthcare professionals of the label changes. These labeling changes apply to all promethazine products including syrups, suppositories, tablets, or injectables.

In December 2004, the FDA added a “boxed warning” for promethazine use in children under 2 years of age due the number of adverse events that were reported.³ During this period between 1969 and 2003, the FDA received reports on 125 cases of life-threatening and fatal respiratory depression in children. Of these, 22 involved

patients 2 years of age and under and 7 deaths occurred to due respiratory depression.

The black boxed warning placed on the label of all promethazine products warns against its use in children less than 2 years of age due to the potential for death from respiratory depression. It also cautions the use in children 2 years and older, especially when co-administered with other drugs that may also have CNS depressive effects such as alcohol, sedatives/hypnotics, narcotics and tranquilizers. When used in the children over 2 years, the lowest effective dose should be used.⁴

A review conducted by Cote *et al.* looked at 118 case reports of adverse drug events from the FDA, US Pharmacopoeia, and the results from a survey of pediatric specialists on drugs that are used for sedation in pediatrics. Their study found that medications with long plasma half-lives, including promethazine, chloral hydrate, promazine, chlorpromazine and pentobarbital, led to the highest death and injury rates after being discharged from the hospital.⁵ With promethazine, respiratory depression was seen at a wide range of doses, from 0.45 to 6.4 mg/kg.³

It is necessary that all healthcare professionals taking care of the pediatric population be made aware of these adverse events and labeling changes for all promethazine products in order to prevent adverse events from continuing to occur.

References

1. Lacy CF, Armstrong LL, Goldman MP, Lance LL, editors. Drug Information Handbook, 13th Edition. Hudson, Ohio, Lexi-Comp, Inc.; 2005: 1257-1259.
2. FDA Information for Healthcare Professionals. Promethazine Hydrochloride. [cited 2006 June 12]. Available from: <http://www.fda.gov/cder/drug/infopage/promethazine/default.htm>
3. Starke PR, Weaver J, Chowdhury BA. Boxed warning added to promethazine labeling for pediatric use. N Engl J Med. 2005; 352 (25):2653.
4. Wyeth Pharmaceuticals Inc. Phenergan® package insert. Philadelphia, PA: revised December 2004.
5. Cote CJ, Karl HW, Notterman DA, Weinberg JA, McCloskey C. Adverse sedation events in pediatrics: Analysis of medications

Inside this issue:

Promethazine and Pediatric Alert	1
Tysabri® Returns to the Market	1
New Guidelines on Prevention and Treatment of Peripheral Artery Disease Released by the AHA and ACC	2
Varenicline tartrate (Chantix®): New Medication for Smoking Cessation	3
Remicade® in Pediatric Patients with Crohn's disease	3
Evista® and Breast Cancer	4
Recommendations For Mumps Control and Elimination	5

Tysabri® Returns to the Market by Kelly Pham

The FDA (Food and Drug Administration) announced in June of 2006 that marketing of Tysabri® (natalizumab) for the treatment of relapsing forms of multiple sclerosis would resume under a new dispensing program. In February of 2005, manufacturer Biogen-Idec voluntarily withdrew natalizumab from pharmacy shelves. The FDA also halted clinical trials on the drug at this time. These actions followed a report received by the FDA from Biogen-Idec that three patients from clinical trials of natalizumab had developed progressive multifocal leukoencephalopathy (PML).^{1,2} PML is a progressive, neurologic disease that is characterized by the destruction of myelin in patches throughout the central nervous system.³ Two of those patients died as a result.

Natalizumab, a monoclonal antibody, was approved for the treatment of relapsing multiple

sclerosis by the FDA in November 2004 via an accelerated application.² Natalizumab functions by binding to $\alpha 4$ integrins, resulting in the inhibition of the interaction between adhesion molecules and their counter-receptors on endothelial cell walls (such as vascular cell adhesion molecule-1—or VCAM-1—and mucosal addressin cell adhesion molecule-1—abbreviated MadCAM-1).^{4,5} This diminishes the ability of leukocytes to bind to their counter-receptors and migrate across the endothelium. How this mechanism functions in the treatment of multiple sclerosis has not been clearly defined as of yet. It is believed that the halting of inflammatory cells across the blood-brain barrier prevents them from causing the destructive lesions characteristic of multiple sclerosis.⁴

See pg. 2 Tysabri Story Continued

Tysabri Story Continued

Following the removal of natalizumab from the market, Biogen-Idec performed a follow-up assessment of the original trials' patients and found no new incidents of PML.¹ The FDA then allowed the manufacturer to resume clinical studies. Biogen-Idec eventually developed and proposed to the FDA its guidelines for a Risk Minimization Plan for the distribution of Tysabri®. Called TOUCH™, the plan requires that prescribers, infusion centers, dispensing pharmacies, and patients who are involved with the use of natalizumab be enrolled in the program.¹ Patients are to be screened via magnetic resonance imaging prior to beginning therapy in order to assess the future risk of developing PML.¹ Once therapy has been initi-

ated, patients are to follow-up with a health-care provider at 3 months, 6 months and then every 6 months.¹ The findings from these follow-up visits will be reported to Biogen-Idec.

The approval of TOUCH™ by the FDA allowed marketing of natalizumab to resume in June of 2006, again providing another option in the treatment of multiple sclerosis.

References

1. FDA News: FDA approves resumed marketing of Tysabri under a special distribution program. Available from: <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01380.html>
2. FDA News: FDA issues public health advisory on Tysabri, a new drug for MS.

Available from: <http://www.fda.gov/bbs/topics/news/2005/NEW01158.html>

3. Harrison's Principles of Internal Medicine. 16th edition

4. Biogen-Idec. *Tysabri*® package insert. Cambridge, MA: 2006

5. Niino M, Bodner C, Simard ML, Alatab S, Gano D, Kim HJ, et al. Natalizumab effects on immune sponses Sclerosis. *Neurology* 2006;59:754



cell re-
in Multiple
Annals of
Neurology
(5): 748-

New Guidelines on Prevention and Treatment of Peripheral Artery Disease Released by the AHA and ACC by Louis Stites

Peripheral Artery Disease (PAD) affects somewhere between 12 and 20 million people in the United States. In December 2005, a new set of guidelines by the American Heart Association (AHA) and the American College of Cardiology (ACC) were released to help physicians diagnose and help prevent Peripheral Artery Disease.¹

PAD refers to vascular diseases caused by atherosclerosis or thromboembolic events that alter the aorta and arteries of the lower extremities. PAD is typically caused by fatty deposits collecting on the walls of the arteries, leading to an impedance of blood flow and potential further complications. Early signs and symptoms are lower-extremity cramps and fatigue, especially after walking or other physical activity¹.

The guidelines list the six major risk factors for PAD as:

- Age less than 50 with diabetes and one other atherosclerotic risk factor
- Age 50-69 who smokes or has diabetes
- Age older than 70
- Leg symptoms upon exertion or ischemic rest pain.
- Abnormal lower extremity pulse
- Existing atherosclerotic, carotid, or renal arterial disease.²

It is recommended that patients at risk should receive a vascular physical examination. The physical should include blood pressure measurements, an inspection of

the feet, a test for impaired walking, abdomen palpitation, and palpitation of the carotid.

It is important to obtain an early diagnosis of PAD to help prevent further complications PAD can lead to a difficulty in walking, increased blood pressure, a rupture in the aorta, failure of the kidneys or amputation. The fatty deposits that are seen in the peripheral arteries can sometimes be found in the vessels of the brain and heart, which greatly increases the chance of stroke and myocardial infarct¹.

In the treatment of PAD, there is evidence that includes the use of a statin drug to help reduce patients LDL cholesterol below 100 mg/dL. Also antihypertensive medications should be used in patients with blood pressure that exceed 140 systolic and 90 diastolic, in diabetics the blood pressure goal should be set at 130 mg/dL systolic and 80 mg/dL diastolic. This will help reduce the risks of heart disease and stroke. Beta blockers and ACE inhibitors can be used for hypertensive therapies in patients with PAD.¹

The American Heart Association and the American College of Cardiology, have issued these guidelines to assist in preemptively diagnosing patients in which therapy can be beneficial and improve health, ensuring a higher quality of life.¹ For more specific information on these guidelines, please contact the Drug Information Center at 402-280-

5100.

References

- 1) Hirsh A, Haskal Z, Hertzner N, Bakal C, Creager M, Halperin J, et al. ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). [cited 2006 June 13]. Available from <http://www.americanheart.org/downloadable/heart/1133899967030PAExecSumm.pdf>.
- 2) Peck P. Peripheral arterial disease guidelines push early diagnosis. Medpage Today. December 7, 2005. [cited 2006 June 13] <http://www.medpagetoday.com/Cardiology/PeripheralArteryDisease/tb/2277?pf=101&spc=230>.



Varenicline tartrate (Chantix®): New Medication for Smoking Cessation by Jaclyn Waters

On May 11th, 2006, the Food and Drug Administration (FDA) has approved Pfizer's new smoking cessation aid, varenicline (Chantix®), the first anti-smoking drug to come to the market in almost a decade. New options in the battle against smoking are needed because tobacco use is the single most preventable cause of death in the United States¹. The average smoker will attempt to quit smoking 11 times over 19 years before they actually quit for good². That results in 95% of quit attempts that end in relapse. Before the release of varenicline, the first line therapies available for smoking cessation were nicotine replacement therapies (NRT) such as gum, lozenges, inhalers, nasal sprays, and patches and bupropion (Zyban®), the only other oral product. Varenicline offers a new way to combat the withdrawal symptoms of smoking cessation by acting as a partial agonist at the $\alpha_4\beta_2$ nicotinic receptor. Craving relief is provided by partially agonizing this receptor and inhibiting dopaminergic activity that normally provides a reward response to the brain when someone smokes³.

The efficacy of varenicline has been tested in six clinical trials. Two identical trials showed the superiority of varenicline, which quadrupled the likelihood of quitting smoking, over bupropion, which doubled the patient's likelihood of quitting⁴. These results emphasize the importance of the release of this new medication. Using varenicline can be beneficial at any time because, as soon as the patient stops smoking, the risk to their health immediately declines.

Varenicline is available in 0.5mg and 1mg

strengths. It is dosed starting at 0.5mg orally once a day for the first 3 days of treatment followed up an upward titration to 0.5mg twice daily on days 4-7 and then 1mg twice daily until the end of treatment. Patients should set a date to quit smoking one week after the start of varenicline treatment and continue the treatment for 12 weeks. If the patient has successfully stopped smoking at the end of the 12 week period, then varenicline should be continued for an additional 12 weeks to sustain abstinence. Patients who do not quit smoking during the initial 12 weeks of therapy or if they relapse after treatment, should be encouraged to attempt treatment with varenicline again once factors contributing to the failed attempt have been identified and resolved⁵. Patients should take their varenicline dose after eating a meal and with a full glass of water. Dose adjustments do need to be made for patients with renal dysfunction, with a maximum dose of 0.5mg twice daily⁴.

Overall, varenicline is well tolerated. The most common adverse effects when taking varenicline are nausea, sleep disturbance, constipation, flatulence and vomiting which occur at an incidence greater than 5% and twice the rate of placebo. Nausea, the most common adverse effect, is generally mild to moderate in severity and is dose dependent. The incidence of nausea is reported as 30% 1mg twice daily and 16% on 0.5mg twice daily⁵.

If smoking cessation is achieved, a health care provider should re-evaluate doses of the patient's other medications. Smoking is an inducer of drug metabolism, so dose reductions may be needed for some medications including

insulin, warfarin, and theophylline. Varenicline is in pregnancy Category C and its use with other smoking cessation products has not been evaluated⁴.

There are various considerations when choosing the right nicotine cessation product for a patient. Preference of delivery route, medical conditions, compliance to drug regimens, and cost should all be discussed with the patient before a treatment is selected. Overall, health care providers should be aware that smoking is a chronic condition that is often associated with many relapses, but now varenicline is one more option in the fight against this deadly addiction².

References

1. U.S. Food and Drug Administration, Press Release. FDA approves novel medication for smoking cessation. May 11, 2006. Retrieved from: <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01370.html>
 2. Corelli R, Hudmon K. Pharmacological interventions for smoking cessation. *Crit Care Nurs Clin N Am* 2006 (18): 39-51.
 3. Coe J, Brooks P, Vetelino M, Wirtz M, Arnold E, et al. Varenicline: an $\alpha_4\beta_2$ nicotinic receptor partial agonist for smoking cessation. *J Med Chem* 2005 (48): 3474-3477.
 4. Pfizer Pharmaceuticals, News Release. Pfizer's smoking cessation medication Chantix™ (Varenicline) receives FDA approval. May 11, 2006. Retrieved from: http://mediaroom.pfizer.com/index.php?s=press_releases&items=57
- Pfizer Pharmaceuticals Inc. Chantix™ package insert. New York, NY: May 2006.

Remicade in Pediatric Patients with Crohn's disease by Jared Snively

Remicade (infliximab) is the first tumor necrosis factor (TNF)-alpha monoclonal antibody approved for use in treating pediatric Crohn's disease. It was approved in May 2006 by the FDA for use in moderate to severe active Crohn's disease in pediatric patients older than 6 years of age.¹ Infliximab underwent an accelerated review process because of its orphan drug status.^{2,3} Approximately 100,000 children under the age of 18 are affected by Crohn's disease.³ According to PRNewswire, in a recent phase III trial 112 patients were enrolled to receive 5 mg/kg of infliximab at 0, 2 and 6 weeks. After 10 weeks these patients were then randomized for maintenance therapy for 8 or 12 week intervals. The results showed an

88% clinical response in 10 weeks. For the 8 week and 12 week maintenance groups, 56% and 24% respectively remained in remission at one year. The results of this trial dubbed REACH (A Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF Monoclonal Antibody Remicade in Pediatric Subjects with Moderate to Severe Crohn's Disease) are not yet available for public evaluation.²

Infliximab is a chimeric monoclonal antibody that attaches to TNF-alpha and works to neutralize it to prevent the inflammatory cascade. TNF-alpha neutralization reduces adhesion and infiltration of neutrophils, macrophages

and other inflammatory cells.⁴ Infliximab is administered intravenously at a recommended dose of 5 mg/kg at 0, 2 and 6 weeks for induction therapy and then maintenance doses every 8 weeks for pediatric patients 6-17 years of age.² Common adverse effects of infliximab therapy include: nausea and vomiting, abdominal pain, fatigue, arthralgia and pruritus. The most serious adverse effect is the increase risk of infection. Patients with an increased chance of tuberculosis, histoplasmosis, listeriosis, or pneumocytosis should evaluate the benefit versus risk of infection. Infliximab can also increase the chance of optic neuritis, seizure, and the risk for lymphomas.⁴

See pg. 4 Remicade Story Continued

Remicade Story Continued

The FDA maintains that infliximab should only be used in children with active moderate or severe disease, and those not responding to established therapies such as 6-MP, azathioprine, or methotrexate.⁵ The safety and efficacy has not been evaluated sufficiently for children less than 6 years of age and is not recommended for this population.⁶ Like any new therapy it is uncertain what infliximab's role is for long-term therapy but it may be another option for pediatric patients with Crohn's disease.

References

1. FDA News May 19, 2006; FDA approves remicade for children with Crohn's Disease. Available from: <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01376.html> downloaded, June 14, 2006

2. PR Newswire Association LLC Oct. 25 2005; Remicade data show promise for children afflicted with Crohn's Disease; Remicade receives fast track designation for the treatment of pediatric Crohn's Disease. Available Academic Universe at: http://web.lexis-nexis.com/universe/document?m=741573f6a1948596020c06a70cbb27e5&_docnum=4&wchp=dGLbVlz-zSkVA&_md5=6d7726c36052e0af7e9c9af04d971994. downloaded June 14, 2006

3. Genomics & Genetics Weekly, May 5, 2006 Available at Academic Universe: http://web.lexis-nexis.com/universe/document?m=741573f6a1948596020c06a70cbb27e5&_docnum=7&wchp=dGLbVlz-zSkVA&_md5=07a19f1a0f4d7e378a5d261a96b63e08

4. Centocor Inc. Remicade.package insert. Malvern, PA City: Feb 2002

5. Stenson WF. Chapter 142 Inflammatory Bowel Disease. Goldman L, Ausiello D editors. Cecil Textbook of Medicine 22nd edition. Saunders, Philadelphia PA, 2004. pg 861-868

6. Questions and Answers on Remicade/ FDA Action, May 19,2006; <http://www.fda.gov/cder/drug/infopage/infliximab/qa.htm> downloaded, June 14, 2006



Evista and Breast Cancer by Sarah Bentley

Since its approval by the FDA in December of 1997, raloxifene (Evista®) has been indicated for the prevention and treatment of osteoporosis in post-menopausal women. Recently, however, raloxifene has shown efficacy in the prevention of breast cancer in post-menopausal women at an increase risk. Raloxifene is a selective estrogen receptor modulator (SERM) or "anti-estrogen".¹ Tamoxifen, another "anti-estrogen" or SERM, approved by the FDA more than 20 years ago to help fight breast cancer, was approved more recently in 1998 for use by women who had not had breast cancer, but were at high risk. Tamoxifen has shown to reduce the risks of breast cancer in women who were at high risk by 49%.² With each drug, however, comes side effects, and in the case of tamoxifen, potentially serious adverse effects. Serious adverse effects of tamoxifen are uterine cancer, blood clots, strokes, and cataracts. Raloxifene's known, serious side effect is blood clots, however, long-term effects have not been



assessed as extensively.² Pulmonary embolisms and deep vein thrombosis (DVT) are risks with both medications, but have been found to be markedly less common in patients taking raloxifene.³

Previous trials conducted, the Multiple Outcomes of Raloxifene (MORE) and the Continuing Outcomes Relevant to Evista (CORE), were designed to determine whether raloxifene reduced the incidence/risks of breast cancer. Results from both of these trials concluded that in fact raloxifene does reduce the risk of breast cancer.² A new trial was designed in 1999, the Study of Tamoxifen and Raloxifene (STAR) trial, to see how raloxifene compares with tamoxifen in reducing the incidence of breast cancer in post-menopausal women who are at risk. The STAR trial is one of the largest trials conducted on breast cancer prevention and enrolled almost 20,000 women from 1999-2004. Recently, initial results have been released showing that raloxifene is as effective as tamoxifen in reducing the risk of developing invasive breast cancer in post-menopausal women, with fewer side effects. Both drugs reduced the risk of developing invasive breast cancer by approximately 50%. Women receiving raloxifene developed, on average, about 36% fewer uterine cancers and 29% fewer blood clots than patients receiving tamoxifen.^{3,4} These results are preliminary, but a significant and optimistic step in the prevention of breast cancer. Additional results will be presented and published throughout the year.

The initial results of the STAR study may represent a major step in breast cancer prevention and will continue to be researched. Raloxifene may begin to become more commonly used and accepted by women because it does, in fact, reduce the risks of two major concerns of women: osteoporosis and breast cancer. This will give post-menopausal women a choice, with possibly less side effects, in the prevention of invasive breast cancer.

References

1. Eli Lilly and Company. Package literature for raloxifene (Evista®). Indianapolis, IN: December 1997. <http://www.evista.com/index.jsp>.

References

2. Kalidas M, Hilsenbeck S. Defining the role of raloxifene for the prevention of breast cancer [editorial]. J Natl Cancer Inst 2004;96(23):1731-32.

3. National Cancer Institute [homepage on the Internet]. Bethesda [cited 2006 June 16]. The study of tamoxifen and raloxifene (STAR) trial. Available from: <http://www.cancer.gov/clinicaltrials/digestpage/STAR>.

4. WebMD [homepage on the Internet]. 2005-2006. [cited 2006 June 19]. WebMD Evista for breast cancer prevention? Available from: <http://www.webmd.com/content/article/121/114102.htm>

Recommendations For Mumps Control and Elimination

by Michael Lueth

In May 2006, the Advisory Committee on Immunization Practices (ACIP) issued a statement recommending updates in the current measles, mumps, and rubella (MMR) vaccination guidelines.¹ Using studies done over the last two decades and spurred on by the recent epidemic of mumps seen in at least eleven states, the committee has decided to make changes to the previous guidelines from 1998. The epidemic has exposed possible shortcomings of earlier policies in relation to the prevention and control of mumps outbreaks in health care and high risk settings, especially college students and other populations whose age-group (18-24) represented 80% of the most recent mumps outbreak.^{2,3} After reviewing data from the current outbreak and previous evidence on mumps vaccine effectiveness and transmission, ACIP issued these new recommendations for mumps vaccination with the intention of increasing protection to the groups most likely to be at risk during a mumps outbreak.

The guidelines address changing the presumptive evidence of immunity for mumps and also call for routine vaccination for

health care workers. According to ACIP, acceptable presumptive evidence of immunity is considered: (one of the following)

- documentation of adequate vaccination
- laboratory evidence of immunity
- birth before 1957, or
- documented case of physician-diagnosed mumps.¹

Adequate vaccination requires one dose of a live mumps vaccine for preschool-aged children and adults not at high risk, and two doses for school-aged children (grades K-12) and for high risk adults, which include healthcare workers, international travelers, and college students.¹ Specifically related to healthcare workers, if a person has no history of vaccination or other evidence of immunity, they should receive two doses of vaccine at a minimum interval of 28 days between doses. If they have received only one dose, they should still receive a second. Even though most people born before 1957 actually contracted the illness, ACIP considers this only presumptive evidence of immunity and now suggests that healthcare facilities consider inoculating this age group with at least one dose of mumps vaccine.¹

The new recommendations should help fill gaps that now exist in the prevention and control of mumps. Still, it must be remembered that no vaccination series will guarantee 100% effectiveness in all populations; there will still be some who are susceptible. To help reduce the risk that still exists, precautions will need to be taken where cases of mumps exist so the disease can be controlled as much as possible.

References

- 1) CDC. Notice to Readers: updated recommendations of the advisory committee on immunization practices (ACIP) for the control and elimination of mumps. June 1, 2006;55(Early Release):1-2.
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm55e601a1.htm>
- 2) CDC. Mumps Epidemic—Iowa, 2006. MMWR Weekly April 7, 2006;55:(13):366-368.
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5513a3.htm>
- 3) CDC. Update: Multistate Outbreak of Mumps-United States, January 1-May 2, 2006. MMWR Weekly May 26, 2006;55(20):559-563.



Health Matters July 2006; Issue 1, Volume 1

Our Mission...

To serve the health care professional community by providing evidence-based, timely and unbiased information in an effort to contribute to comprehensive patient-based care. We also strive to provide excellent training and foundational skills to prepare our students to competently meet the challenges of providing such information throughout their careers.

Creighton University Drug Information Center
2500 California Plaza
Omaha, NE 68178

We're on the web!!
<http://druginformation.creighton.edu>

Contact us:

Telephone: 402-280-5100
800-561-3728

Fax: 402-280-5149

Email: druginfo@creighton.edu



Faculty:

Amy Friedman Wilson, PharmD. Director of Drug Information Services

Philip J. Gregory, PharmD. Assistant Professor, Pharmacy Practice

Linda K. Ohri, PharmD. Associate Professor, Pharmacy Practice

Edited by Drug Information Clerkship Students, Creighton University
Pharmacy Class of 2007

Sarah Bentley	Kelly Pham
YenLinh Bui	Jared Snavely
Michael Lueth	Louis Stites
Thythu Luu	Jaelyn Waters

