

Auburn Healthlink

A Newsletter of the Auburn University School of Pharmacy

Drug Information News

INFLUENZA 2000-2001: DEALING WITH THE DELAY

Flu season is upon us, and we continue to face the issue of delayed vaccine supply. Health care facilities throughout the country are dealing with difficulties in influenza vaccine acquisition. Although a portion of the supply is delayed, the remaining doses were scheduled for distribution throughout December and January. The estimated distribution of doses for the season is 75 million, approximately the same amount utilized last year.¹ On December 4th, the CDC reported that 77% of the 66 million initial doses had been distributed leaving approximately 15 million doses.² This number does not include the additional nine million doses that the CDC contracted Aventis-Pasteur to produce in an effort to help health care providers vaccinate high-risk individuals. The delay in production this year was reportedly due to manufacturing problems and difficulty growing one of the three viral components of the vaccine.

In the face of a delayed vaccine supply, we are fortunate that thus far, influenza activity in the United States has been lower than that of previous years. In the last 18 years, flu season has reached its peak in mid-January or later the majority of the time (Season peaked in December four years, January four years, February seven years, and March three years). Flu season generally begins in November and continues through April. Timely vaccination can prevent illness and death due to influenza. Development of antibodies, and therefore protection against the virus, occurs seven to fourteen days after administration of the vaccine. Hence, vaccination is recommended from October to mid-November, in order to provide protection prior to or at the onset of flu season. Due to delays in vaccine supply this year, optimum vaccination goals have not been met. However, vaccination is beneficial any time before exposure to influenza occurs.

Administration of vaccine should continue through January and beyond as vaccine becomes available.

Approximately 20,000 deaths and 110,000 hospitalizations each year are due to influenza infections. A substantial delay in the distribution of vaccine could greatly impact these numbers. The CDC and the Advisory Committee on Immunization Practices (ACIP) have updated the vaccination recommendations in an effort to minimize the adverse impact of this season's delay on high-risk individuals. Realization of the recommendations requires a dedicated practitioner effort in the identification, recruitment, and vaccination of high-risk individuals. The CDC and ACIP issued the following recommendations in the October 6th Morbidity and Mortality Weekly Report. **Updated recommendations from the CDC and ACIP for the 2000-2001 influenza season³:**

(Continued on page 4)

Therapeutic Issues

DARVOCET®: WHAT PRACTITIONERS SHOULD KNOW

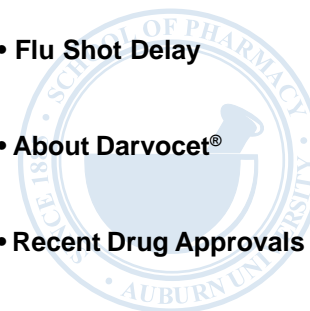
The 21st century brings hope of new medical technology and information. However, we should still celebrate the advances made in the last century. Among these advances are the evolution medicine has made from a theory-based practice to one of scientific or evidenced-based. The amount of information available has grown by astronomical proportions. This expansion has brought recognition to the importance of scrutinizing study designs and statistical analyses, a practice that has made its way into the curriculum of medical and pharmacy schools, alike. Today, theory leads to experimentation. It no longer guides treatment when scientific evidence, derived from a proper study design, suggests otherwise.

(Continued on page 2)

Inside . . .

- Flu Shot Delay
- About Darvocet®
- Recent Drug Approvals

. . . This Issue



(DARVO CET[®], Continued from page 1)

In a time where medical practice is subjected to such scrutiny, it is hard to imagine one of the most commonly prescribed pain medications may actually be no better than placebo.

The narcotic analgesic propoxyphene, is most often prescribed in combination with acetaminophen, (i.e. Darvocet N-100[®], 650mg of acetaminophen and 100 mg of propoxyphene). A critical review of propoxyphene, published as far back as 1970, pointed out that in 16 published studies comparing propoxyphene to placebo, 7 reported placebo to be more effective.¹ In a single-dose crossover design, the effects of several pain medications were compared in 57 cancer patients.² There was no difference between placebo and 65 mg of propoxyphene in regards to the percentage of patients achieving greater than a 50% improvement, nor when total percentages of pain relief were compared. When patients were asked to rank the analgesic effect of each drug, propoxyphene finished sixth. Drugs reported to be more effective included aspirin, acetaminophen, and codeine, while placebo was reported as the least effective of the nine drugs.

Four studies have evaluated the use of propoxyphene in the treatment of pain associated with episiotomy.³⁻⁶ Hopkinson et al compared the effects of 650 mg of acetaminophen, 65 mg of propoxyphene, the combination of acetaminophen and propoxyphene, and placebo.³ Two hundred patients were randomized to one of the four treatment groups. Based on a global evaluation of pain relief, acetaminophen alone was more effective than both propoxyphene alone and placebo. The difference between propoxyphene alone and placebo was not statistically significant, nor was the difference between acetaminophen alone and the combination of acetaminophen with propoxyphene.

A study conducted by Smith et al reported 1000 mg of acetaminophen to be more effective than both Darvon Compound-650 (propoxyphene 65 mg, acetylsalicylic acid 227 mg, phenacetin 162 mg, caffeine 32.4 mg) and placebo in regards to both pain intensity and relief of pain.⁴ The difference between Darvon-compound and placebo was not statistically significant for total relief of pain, but Darvon-compound was reported to be more effective than placebo for decreasing pain intensity. It was also noted that the onset of action was more rapid with acetaminophen. Acetaminophen was more effective at each time of evaluation and the duration of action was longer than that of the propoxyphene combination.

A similar study conducted by Berry et al evaluated the effectiveness of acetaminophen 1000 mg, propoxyphene 65 mg, and placebo in 225 females suffering from pain of episiotomy.⁵ Again, acetaminophen was found to be superior to

propoxyphene, with 82% of patients in the acetaminophen group experiencing “good” to “excellent” pain control compared to only 35% of patients receiving propoxyphene. However, in this study, propoxyphene was found to be significantly superior to placebo.

The fourth trial conducted in episiotomy patients evaluated the effects of acetaminophen alone, placebo alone, and the most commonly prescribed combination of the two drugs; propoxyphene 100 mg with acetaminophen 650 mg.⁶ In 224 patients evaluated, the 1000 mg dose of acetaminophen alone was found to be superior to the combination product, yet both acetaminophen and the combination were superior to placebo ($p < 0.01$). Reductions in the mean intensity of pain were reported as 60% for acetaminophen, 50% for the combination, and 29% for the placebo group.

Studies conducted in patients experiencing dental pain report different conclusions concerning the effectiveness of propoxyphene. A study by Liashek et al compared the effectiveness of acetaminophen, propoxyphene, the combination, and placebo in 45 patients treated before and after the removal of an impacted molar.⁷ Only a minimal difference was seen between propoxyphene and the combination, yet both were found to be significantly more effective than acetaminophen and placebo. The investigators argue that the delayed onset of propoxyphene has been responsible for previous results that have suggested acetaminophen, and in some instances placebo, to be more effective. However, in this trial they did not show a difference between acetaminophen and placebo, in contrast to numerous prior studies.

Forbes et al evaluated the effects of diflunisal, a nonsteroidal anti-inflammatory agent, in comparison to propoxyphene alone and in combination with acetaminophen and placebo.⁸ Results based upon the evaluation of 132 patients with impacted molar removal showed propoxyphene to be superior to placebo, but not until the third hour of observation. The combination of propoxyphene and acetaminophen was shown to be more effective than propoxyphene alone, however acetaminophen alone was not tested. In this trial however, the nonsteroidal was shown to be the most effective treatment.

Liashek et al make a valid point that studies have not been designed to evaluate the benefits of propoxyphene after multiple dosing. If their theory is correct, propoxyphene could have a place in the treatment of chronic pain. However at present, data is lacking to support this claim. There is sufficient evidence to argue that propoxyphene is not the best agent for the treatment of acute pain when a faster onset of action is desired.

(Continued on next page)

FDA Update

RECENT DRUG APPROVALS

Letrozole (Femara®)

In early January, the FDA approved letrozole (Femara®) as first line treatment for postmenopausal women with hormone receptor positive or hormone receptor unknown, advanced or metastatic breast cancer. Letrozole was approved for treatment of advanced breast cancer in 1997 in women whose cancer had not responded to antiestrogen drugs. In a randomized, double-blinded, comparative trial, letrozole was superior to tamoxifen in delaying time to progression of disease (9.4 months compared to 6 months).

Bivalirudin (Angiomax®)

On December 15, 2000, the FDA approved bivalirudin (Angiomax®), an injectable anticoagulant, for use in

conjunction with aspirin in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). Bivalirudin is a direct inhibitor of thrombin and is a synthetic analogue of recombinant hirudin.

Nateglinide (Starlix®)

The FDA approved Novartis' nateglinide (Starlix®) as monotherapy to lower blood glucose in patients with Type 2 diabetes whose hyperglycemia cannot be adequately controlled by diet and exercise. Nateglinide is also indicated for use in combination with metformin in patients whose hyperglycemia is inadequately controlled with metformin. The recommended starting and maintenance dose of nateglinide, alone or in combination with metformin, is 120 mg three times daily 1-30 minutes before meals.

(DARVO CET®, Continued from page 2)

Regardless of the preferred treatment of acute versus chronic pain, Darvocet® should not be prescribed merely as a reflex reaction. Pain is a complex topic with many causes. The source or type of pain should always be investigated and treated accordingly. Pain associated with inflammation can initially be treated with nonsteroidal agents. Pain associated with muscle strains can often be treated effectively with central and non-central acting muscle relaxants. Fibromyalgia and neuropathic pain have been found to respond to therapy with antidepressants and anticonvulsants, respectively. Many pharmacological choices for pain management exist, and the effectiveness of alternative or adjuvant therapies are continuing to be investigated. However, even if an opioid is considered necessary, propoxyphene is still only one of several choices. An argument could be made for propoxyphene if, among the opioids, there was a smaller degree of dependence associated with its use; however, this is not the case.

In the drug selection process, benefits are always weighed against risks. Propoxyphene has the potential for significant adverse reactions, particularly in the elderly. Elderly patients commonly have some degree of renal impairment and propoxyphene can accumulate to dangerous levels in these patients. Studies have shown that propoxyphene is associated with an increased risk of falls and hip fractures in elderly patients. Despite this evidence, propoxyphene is one of the top 20 drugs prescribed inappropriately in elderly patients.

Considering the wide spread use of propoxyphene in various types of pain syndromes, it is important that we critically evaluate the ways in which we use this drug. Would patients benefit just as well from acetaminophen alone, or

should agents more capable of relieving acute pain be selected instead of Darvocet®? Are we using Darvocet® without considering the type of pain, and in situations where adjuvant therapy may be more appropriate? Is Darvocet® being used in lieu of other opioids because of a false sense that propoxyphene does not result in dependence? Questions remain to be answered. Physicians should be aware of the facts, and Darvocet® should not be prescribed based on the theory that it is effective. Evidence should continue to guide therapy, not historical or common practice.

By: Lori Hornsby, Pharm.D.

References

1. Miller R, Feingold A, Powers J. Propoxyphene hydrochloride, a critical review. *JAMA* 1970;213:996.
2. Moertel C, Ahmann D, Taylor W, Schwartzau N. A comparative evaluation of marketed analgesic drugs. *JAMA* 1972;286(15):813-5.
3. Hopkins J, Bartlett F, Steffens A, McGlumphy T, Macht E, Smith M. Acetaminophen versus propoxyphene hydrochloride for relief of pain in episiotomy patients. *J Clin Pharm* 1973 July;251-63.
4. Smith M, Levin H, Bare W. Acetaminophen extra strength capsules versus propoxyphene compound-65 versus placebo: a double-blind study of effectiveness and safety. *Curr Therap Res* 1975;17(5):452-9.
5. Berry N, Miller J, Levin H, Bare W, Hopkinson J, Feldman A. Relief of severe pain with acetaminophen in a new dose formulation versus propoxyphene hydrochloride 65 mg and placebo: a comparative double-blind study. *Curr Therap Res* 1975;17(4):361-8.
6. Hopkins J, Blatt G, Levin H, Berry N, Cohn H. Effective pain relief: comparative results with acetaminophen in a new dose formulation, propoxyphene napsylate acetaminophen combination, and placebo. *Curr Therap Res* 1976;19(6):622-30.
7. Liashek P, Desjardins P, Triplett R. Effect of pretreatment with acetaminophen-propoxyphene for oral surgery pain. *J Oral Maxillofac Surg* 1987;45:99-103.
8. Forbes J, Foor V, Bowser M, Calderazzo J, Shackelford R, Beaver W. A 12-hour evaluation of the analgesic efficacy of diflunisal, propoxyphene, propoxyphene-acetaminophen combination, and placebo in postoperative oral surgery pain. *Pharmacotherapy* 1982;2:43-9.

Auburn HealthLink

Volume 2, Number 1

Jan/Feb 2001

Contributing Editor,

Shauna Buring, Pharm.D., Dir. of DILRC

Dean,

Auburn University School of Pharmacy

R. Lee Evans, Pharm.D.

This publication is produced by the Drug Information and Learning Resource Center of the Auburn University School of Pharmacy.

The *Auburn HealthLink* is a service of the Auburn University School of Pharmacy. Its purpose is to disseminate information on drug therapy, current excerpts from the literature regarding drug usage, FDA warnings, and adverse reaction. The inclusion of a product name in this publication, or information on a products should not be construed as an endorsement of that product. Material in this publication may not be reprinted without written permission of the Auburn University School of Pharmacy.

The publication of this newsletter is supported by an unrestricted educational grant from Pfizer, Inc.

Auburn University School of Pharmacy
Drug information & Learning Resources Center
105 Walker Building
Auburn, AL 36849-5502

Non-Profit Org.
 U.S. Postage
 PAID
 Permit No. 9
 Auburn, AL
 36830

(FLU, Continued from page 1)

- Administer currently available vaccine to high-risk individuals and the health care workers who care for them first.
- Persons at high risk for complications from influenza include:
 - Persons aged 65 years or greater;
 - Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
 - Children and adults who have chronic disorders of the pulmonary or cardiovascular systems, including asthma;
 - Children and adults who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases including diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunosuppression (e.g.,
- caused by medications or human immunodeficiency virus);
- Persons aged 6 months to 18 years who are receiving long-term aspirin therapy and therefore might be at risk for developing Reye syndrome after influenza; and
- Women who will be in the second or third trimester of pregnancy during the influenza season.
- Use vaccine available early in the season to maximize protection of high-risk persons; continue to vaccinate high-risk persons and health care workers as vaccine becomes available December and later.
- Beginning in December, make efforts to vaccinate persons aged 50 to 64 years, including those who are not at high risk and are not household contacts of high-risk persons.
- Vaccination efforts for all groups should continue as long as influenza vaccine is available.

Although there is a delay in supply, there is not a shortage; timely vaccination of high-risk individuals can still prevent severe illness and death due to influenza infections and complications. This can be achieved through focused efforts and dedication to patient care.

By Samantha Eichner, Pharm.D.

References

1. <http://www.cdc.gov/mmwr//preview/mmwrhtml/mm4939a3.htm>
2. <http://www.cdc.gov/nip/flu-vac-supply/flusources.htm>
3. CDC. Notice to Readers: Updated Recommendations From the Advisory Committee on Immunization Practices in Response to Delays in Supply of Influenza Vaccine for the 2000-01 Season. *MMWR*2000;49:888-892.