

## Health Matters October 2007; Volume 2, Issue 4

### New FDA MedWatch Warnings—Codeine and Thiazolidinediones

by Kristi Yanemoto

In August 2007, the U.S. Food and Drug Administration (FDA) issued two new alerts concerning 1) the use of codeine in breastfeeding women, and 2) an update on the labeling of all thiazolidinediones.

Physicians are advised to prescribe the lowest effective dose of codeine-containing products for the shortest period of time to mothers who are breastfeeding. An incident has been reported whereby a 13-month old baby died of a morphine overdose when its nursing mother was taking codeine for pain relief. Codeine is metabolized to morphine, which is excreted in breast milk. If a breastfeeding woman is in the population of people who are genetically rapid metabolizers, the codeine she ingests may be transmitted as a large amount of morphine to the infant, leading to life-threatening adverse effects. It is recommended that mothers on codeine and their nursing infant be carefully monitored for signs or morphine overdose, including: fatigue, shortness of breath, difficulty breastfeeding, or limpness.

Due to the amount of adverse events previously reported, the FDA has recommended manufacturers of all thiazolidinediones (Avandia, Actos, Avandaryl, Avandamet, and Duetact) to update their labeling with a boxed warning. The warning contains information about the risk of causing or worsening heart failure while on therapy with a thiazolidinedione. Patients started on therapy should be closely monitored for signs and symptoms of heart failure including rapid and excessive weight gain, shortness of breath, and edema. Any of these symptoms should be treated appropriately and continuation of therapy re-evaluated. Reports have shown outcomes to be poor if therapy is continued. The warning also includes a contraindication for use in patients with established NYHA Class III or IV heart failure. The boxed warning is intended to emphasize the increased risk of heart failure associated with this class of drugs, and to recommend close monitoring while patients are treated with any thiazolidinedione.

Reference:

FDA MedWatch 2007 Safety Alerts. Available from <http://www.fda.gov/medwatch/safety/2007/safety07.htm>. Accessed September 2007.

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## **New Warning—Ceftriaxone and Calcium-Containing Products** by Karin Wedeking

The FDA issued an alert on September 11, 2007, regarding the CONTRAINDICATIONS, WARNINGS, and DOSAGE and ADMINISTRATION sections of the prescribing information for Rocephin®<sup>1,2</sup> due to reports of ceftriaxone-calcium precipitates in the lungs of neonates (age ≤ 28 days). The updated sections in the prescribing information extend this warning to adults as well, although there have been no case reports of adults suffering from ceftriaxone-calcium precipitation in the lungs. A recommendation by the manufacturer states that intravenous (IV) ceftriaxone should not be administered concomitantly with calcium containing IV products. Ceftriaxone should not be mixed with calcium-containing products and should not be administered via the same or different IV line. Patients should not receive ceftriaxone and calcium-containing products within 48 hours of each other. At this time there is no information available on whether there is an interaction between intramuscular (IM) ceftriaxone and calcium products, or if there is an interaction between ceftriaxone and oral calcium products.<sup>1,2</sup>

Ceftriaxone has been found to be incompatible at concentrations of 10 to 40 mg/mL with Ringer's injection and lactated Ringer's injection, as rapid precipitation occurs.<sup>3</sup> Per the manufacturer, diluents containing calcium, such as Lactated Ringer's or Hartmann's solution should not be used for the reconstitution of ceftriaxone.<sup>1,2</sup>

Ceftriaxone has been associated with biliary pseudolithiasis (biliary sludge) and nephrolithiasis. A study in the Archives of Disease in Childhood reported that normal or high dose ceftriaxone therapy may result in biliary sludge or renal stones.<sup>4</sup> Calcium may potentially be implicated in the development of this adverse effect.

Ceftriaxone has bacteriocidal activity and is effective for gram-negative and gram-positive bacteria in the presence of beta-lactamases, penicillinases, or cephalosporinases. Ceftriaxone is indicated for use in infections caused by susceptible organisms in lower respiratory tract infections, acute bacterial otitis media, skin and skin structure infections, urinary tract infections, uncomplicated gonorrhea, pelvic inflammatory disease, bacterial septicemia, bone and joint infections, intra-abdominal infections, meningitis, and for surgical prophylaxis.<sup>5</sup> Caution should be used when considering using ceftriaxone concomitantly with calcium-containing products in both neonates and adults until more evidence is found on this issue.

### References:

1. Information for Healthcare Professionals: Ceftriaxone. Food and Drug Administration Web site. Available at: <http://www.fda.gov/cder/drug/InfoSheets/HCP/ceftriaxone.htm>. Accessed September 17, 2007.
2. Roche Laboratories Inc., Dear Healthcare Professional Letter. Food and Drug Administration Web site. Available at: [http://www.fda.gov/medwatch/safety/2007/Rocephin\\_HCP\\_august2007.pdf](http://www.fda.gov/medwatch/safety/2007/Rocephin_HCP_august2007.pdf). Accessed September 17, 2007.
3. Trissel LA. *Handbook on Injectable Drugs*. 14<sup>th</sup> ed. Bethesda, MD: American Society of Health-System Pharmacists; 2007:334-342.
4. Avci Z, Koktener A, Uras N, et al. Nephrolithiasis associated with ceftriaxone therapy: a prospective study in 51 children. *Arch Dis Child*. 2004;89:1069-1072.
5. Rocephin [package insert]. Nutley, NJ: Roche Laboratories Inc.; 2007.

## **Prevention of Varicella: New Recommendation from ACIP** by Jocelyn Suchor

The Advisory Committee on Immunization Practices (ACIP) has updated recommendations for the prevention of varicella in children, adolescents, and adults. The new recommendations have been published in this year's June 22 issue of the Morbidity and Mortality Weekly Report.

The new recommendations are in response to increasing reports of varicella outbreaks among highly vaccinated populations. In preparing these recommendations, the ACIP workgroup reviewed data on the impact of the one-dose varicella vaccination program. Studies demonstrated that one dose of single-antigen varicella vaccine is approximately 85% effective in preventing varicella and its use has greatly reduced morbidity and mortality associated with varicella. However, its success has not been sufficient to prevent varicella outbreaks, which have continued to occur in highly vaccinated school populations. Therefore, in 2006, a routine 2-dose vaccination schedule was adopted for children. The rationale for the second dose of varicella vaccine for children is to further decrease varicella disease and its complications in the United States.

Randomized clinical trials have directly compared vaccine efficacy between the one-dose regimen and the two-dose regimen. Ten-year vaccine efficacy after 2 doses of single-antigen varicella vaccine in children (98.3%) was significantly higher than that after one dose (94.4%). The risk for breakthrough disease was 3.3-fold lower among children who received 2 doses than it was among children who received one dose. A second dose of varicella vaccine in children was found to improve immunologic response, which correlates with improved protection.

**Varicella vaccine continued on page 3**

## Varicella vaccine, continued from page 2

A summary of the updated ACIP recommendations for prevention of varicella can be found in Table 1. There are several changes between the original recommendations and the new report, but the main difference is the recommendation for a routine 2-dose vaccination schedule for children. **Healthy children aged 12 months through 12 years should receive 2 doses of varicella vaccine**, with the first dose administered at age 12-15 months and the second dose at age 4-6 years. The recommended age for the second dose is supported by the current epidemiology of varicella, with a higher incidence and more outbreaks among elementary-school aged children. Routine vaccination of all healthy persons aged 13 years or older without evidence of immunity is also now recommended with two doses of varicella vaccine, 4-8 weeks apart. At this time, ACIP has also approved criteria for evidence of immunity to varicella.

Reference:

1. CDC. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007;56 (No. RR-4).

**Table 1. Summary of ACIP recommendations for prevention of varicella – United States, 1999,2007<sup>1</sup>**

Category	1999 recommendations	2007 recommendations
Routine childhood schedules	1 dose recommended at age 12-18 months	2 doses recommended ✦ 1 <sup>st</sup> dose at age 12-25 months ✦ 2 <sup>nd</sup> dose at age 4-6 years
Adults and adolescents aged $\geq 13$ years	Recommended for susceptible persons who have close contact with persons at high risk for serious complications (Health-care workers, family contacts of immunocompromised persons)  Recommended for susceptible persons at high risk for exposure or transmission (Persons who live or work in environments in which transmission of VZV is likely, in which transmission can occur; nonpregnant women of childbearing age; international travelers; adolescents and adults living in households with children)  Is desirable for other susceptible adolescents	Recommended for all adolescents and adults without evidence of immunity.
Catch-up vaccination	1 dose recommended for all susceptible children aged 19 months – 12 years (i.e. those with no history of varicella or vaccination)	2 <sup>nd</sup> dose recommended for all persons who received 1 dose previously
HIV-infected persons	2 doses, 3 months apart  Should be considered for asymptomatic or mildly symptomatic HIV-infected children in CDC immunologic and clinical categories N1 or A1 with age-specific CD4+ T-lymphocyte percentages $\geq 25\%$	2 doses, 3 months apart  Should be considered for HIV-infected children with age-specific CD4+ T-lymphocyte percentages $\geq 15\%$  May be considered for adolescents and adults with CD4 counts $>200 /\mu\text{L}$
Antenatal screening	None	Recommended prenatal assessment and postpartum vaccination
Outbreak control vaccination	Should be considered	Recommend 2-dose vaccination policy
Postexposure vaccination	Recommended within 3-5 days	No change
Vaccination requirements	Recommended for children without evidence of immunity attending child care centers and entering elementary school  Should be considered for middle school and junior high school students without other evidence of immunity	Recommended for children attending child care centers, students in all grade levels, and persons attending college or other post-secondary educational institutions.

## New CAP Joint Guidelines from IDSA and ATS by Megan Sell

In an effort to ease confusion and improve care for adults with community acquired pneumonia (CAP) the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) have worked together to issue joint CAP guidelines. Their major recommendations for empirical treatment are outlined in the table below. It is essential to recognize the need to adapt these guidelines at the local level due to differences in antibiotic susceptibility patterns and in order to improve processes and clinical outcomes.<sup>1</sup> These guidelines make empirical recommendations based upon the pathogens that are most likely to cause CAP.<sup>1</sup> However, it is important to keep in mind that numerous other pathogens can cause CAP and risk factors for more infrequent pathogens should not be overlooked.<sup>1</sup> Examples of people at risk for uncommon pathogens include alcoholics, smokers and those with COPD, HIV infection, recent travel and exposure to bat or bird droppings.<sup>1</sup> It is recommended that CAP patients be treated for a minimum of five days, be afebrile for 48-72 hours and have no more than one of the following signs of instability: Temperature  $\geq 37.8^{\circ}\text{C}$ , Heart Rate  $\geq 100$  beats/min, Respiratory rate  $\geq 24$  breaths/min, Systolic Blood Pressure  $\leq 90$  mm Hg, Arterial oxygen saturation  $\leq 90\%$  or  $\text{pO}_2 \leq 60$  mmHg on room air, inability to maintain adequate oral intake, altered mental status when discontinuing therapy.<sup>1</sup> Patients can be switched from IV to PO therapy when they are hemodynamically stable, improving clinically and have a normally functioning GI tract.<sup>1</sup> Prevention of pneumonia is an important consideration. Vaccinations against pneumococcal disease and influenza, smoking cessation, and good hygiene are all important steps in the prevention of pneumonia.<sup>1</sup> The full guidelines can be accessed online at <http://www.journals.uchicago.edu/CID/journal/issues/v44nS2/41620/41620.web.pdf>.

<b>Empirical Antibiotics for CAP Treatment</b>	
<b>Outpatient</b>	<b>Treatment</b>
Previously healthy and no antimicrobial use in last 3 months	Macrolide <sup>a</sup> (level 1 evidence) OR Doxycycline (level 3 evidence)
Presence of Comorbidities: chronic heart, lung, liver, or renal disease; diabetes mellitus, alcoholism, malignancies, asplenia and other immunosuppressing conditions OR use of antibiotics within the previous three months (use alternative from different drug class)	Respiratory fluoroquinolone <sup>b</sup> (level 1 evidence) OR A $\beta$ -lactam <sup>c</sup> <b>plus</b> a macrolide <sup>a,d</sup> (level 1 evidence)
Regions with a high rate (>25%) of macrolide resistant <i>Streptococcus pneumoniae</i> (MIC $\geq 16\mu\text{g/mL}$ )	Consider use of above regimen (outpatient with presence of comorbidities) and include patients without the presence of comorbidities (level 3 evidence)
<b>Inpatient</b>	<b>Treatment</b>
Non-Intensive Care Unit	Respiratory fluoroquinolone <sup>b</sup> (level 1 evidence) OR A $\beta$ -lactam <sup>e</sup> <b>plus</b> a macrolide <sup>a,f</sup> (level 1 evidence)
Intensive Care Unit	A $\beta$ -lactam <sup>g</sup> <b>plus</b> respiratory fluoroquinolone <sup>b</sup> (level 1 evidence) OR A $\beta$ -lactam <sup>g</sup> <b>plus</b> azithromycin (level 2 evidence) <b>PCN allergic:</b> respiratory fluoroquinolone <sup>b</sup> <b>plus</b> aztreonam
Pseudomonas is a concern (risks for pseudomonas infection include chronic oral steroid use, severe bronchopulmonary disease, and frequent antibiotic therapy)	Antipneumococcal, antipseudomonal $\beta$ -lactam <sup>h</sup> <b>plus</b> either ciprofloxacin or levofloxacin 750mg OR Above $\beta$ -lactam <b>plus</b> aminoglycoside <b>plus</b> azithromycin OR Above $\beta$ -lactam <b>plus</b> aminoglycoside <b>plus</b> ciprofloxacin or levofloxacin 750mg <b>PCN allergic:</b> substitute aztreonam for $\beta$ -lactam
If community-acquired MRSA is a concern	Add vancomycin or linezolid (level 3 evidence)

a: macrolide: azithromycin, clarithromycin or erythromycin

b: respiratory fluoroquinolone: moxifloxacin, gemifloxacin or levofloxacin[750mg]

c: preferred  $\beta$ -lactams: high dose amoxicillin (1g TID) or high dose amoxicillin-clavulanate (2g BID); alternatives for preferred  $\beta$ -lactam include ceftriaxone, cefpodoxime and cefuroxime

d: alternative for macrolide is doxycycline (level 2 evidence)

e: preferred  $\beta$ -lactams: cefotaxime, ceftriaxone and ampicillin; ertapenem for selected patients, use respiratory FQ for PCN allergic

f: alternative for macrolide is doxycycline (level 3 evidence)

g: cefotaxime, ceftriaxone, or ampicillin-sulbactam

h: piperacillin-tazobactam, cefepime, imipenem, or meropenem

### Reference:

1. Mandell L, Wunderink R, Anzueto A, Bartlett J, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clinical Infectious Diseases*, 44(Supl 2) S27-S72. Retrieved September 17, 2007 from <http://www.journals.uchicago.edu/CID/journal/issues/v44nS2/41620/41620.web.pdf>



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