

Fourth Year of Medical School May Need a Redo

BY M. ALEXANDER OTTO

FROM THE ANNUAL CONGRESS OF DELEGATES OF THE AMERICAN ACADEMY OF FAMILY PHYSICIANS

DENVER – The fourth year of medical school needs a curriculum brush-up to better prepare students for residencies, based on discussions raised at the congress.

“In many meetings over the past 2

years, I’ve heard residency directors say first-year residents today are less well prepared than in the past. If it’s true, this is a serious matter for all of us,” said Dr. Douglas Henley, the CEO of the AAFP, who noted that his group’s education committee plans to look into the issue.

A recent study of 30 residency directors in 10 fields – including family medicine and pediatrics – said that common problems with interns include the need

for greater medical knowledge, professionalism, self-reflection, and organizational skill (Acad. Med. 2009;84:823-9).

With health care delivery evolving toward patient-centered medical homes and other newer models, the concerns are particularly pressing, Dr. Perry Pugno, director of the AAFP’s division of medical education, said in an interview.

The changes will place a premium on teamwork, solid primary care skills, and

good communication skills – all skills that could be fostered in the fourth year.

Instead, “many medical schools allow a large portion of the fourth year to be elective, and students use it to hone their resumes for specialties, not their skills. They [develop] an extensive knowledge base of esoteric stuff, but don’t learn how to talk to people,” Dr. Pugno said.

With so much emphasis on technology and careerism, the arts of diagnosis and patient communication are not valued, he said.

The study’s senior author, Dr. Michael Harper, observed in an interview that “there’s a lot of medical tourism in the fourth year.” Students often end up acting as “an appendage to in-patient consult services. They often are not integrated. The primary care role [of students’ making decisions under supervision] seems to be missing.”

Dr. Harper of the department of medicine and director of the geriatrics fellowship program at the University of California, San Francisco, said that UCSF is brainstorming solutions.

One possible step is extended ambulatory care rotations – in which students are typically more involved with patients – to “allow for ongoing authentic roles in patient care.” Another fourth-year concept is individual learning plans that are tailored to fill gaps in students’ skills. ■

NEXIUM® (esomeprazole magnesium)

Delayed-Release Capsules (20, 40 mg) and for Oral Suspension (10, 20, 40 mg)

BRIEF SUMMARY of Prescribing Information.

INDICATIONS AND USAGE

Treatment of GERD NEXIUM is indicated for the short-term treatment (4 to 8 weeks) for healing and symptomatic resolution and maintenance (controlled studies do not extend beyond 6 months) of confirmed erosive esophagitis (EE); the treatment of heartburn and other symptoms associated with GERD; **Risk Reduction of NSAID-Associated Gastric Ulcer; H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence; Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome.**

DOSE AND ADMINISTRATION

Please see full Prescribing Information for recommended dosages, dosage adjustments, and administration options for **Special Populations. Information for Patients** NEXIUM is available as a delayed-release capsule or for delayed-release oral suspension. NEXIUM should be taken at least one hour before meals. Administration Options: 1) NEXIUM Delayed Release Capsules should be swallowed whole. For patients who have difficulty swallowing capsules, open the capsule and mix the granules with one tablespoon of applesauce. Swallow immediately without chewing or crushing. Do not store for future use. The applesauce should not be hot. 2) NEXIUM For Delayed-Release Oral Suspension: Stir the contents of a packet with 1 tablespoon (15 mL) of water. Leave 2 to 3 minutes to thicken. Stir and drink within 30 minutes. If any material remains after drinking, add more water, stir, and drink immediately. Antacids may be used while taking NEXIUM.

CONTRAINDICATIONS

NEXIUM is contraindicated in patients with known hypersensitivity to any component of the formulation [see **Description** (11) in full Prescribing Information] or to substituted benzimidazoles. Hypersensitivity reactions, e.g., angioedema and anaphylactic reaction/shock, have been reported with NEXIUM use.

WARNINGS AND PRECAUTIONS

Concurrent Gastric Malignancy Symptomatic response to therapy with NEXIUM does not preclude the presence of gastric malignancy.

Atrophic Gastritis Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which NEXIUM is an enantiomer.

Bone Fracture Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

Risks of Amoxicillin (as Part of H. pylori Triple Therapy) [See Warnings and Precautions in the prescribing information for amoxicillin for complete information.] Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions that have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis.” After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Risks of Clarithromycin (as Part of H. pylori Triple Therapy) [See Warnings and Precautions in the prescribing information for clarithromycin for complete information.] Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking clarithromycin, the patient should be apprised of the potential hazard to the fetus. Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, terfenadine, ergotamine, or dihydroergotamine is contraindicated.

ADVERSE REACTIONS

Clinical Studies Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of NEXIUM was evaluated in over 15,000 patients (aged 18 to 84 years) in clinical trials worldwide including over 8,500 patients in the United States and over 6,500 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, NEXIUM was well tolerated in both short and long-term clinical trials. The safety of NEXIUM was evaluated in 316 pediatric and adolescent patients aged 1 to 17 years in four clinical trials for the treatment of symptomatic GERD [see **Clinical Studies** (14.2) in full Prescribing Information]. In 109 pediatric patients aged 1 to 11 years, the most frequently reported ($\geq 1\%$) treatment related adverse reactions were diarrhea (2.8%), headache (1.9%) and somnolence (1.9%). In 149 pediatric patients aged 12 to 17

years the most frequently reported ($\geq 2\%$) treatment related adverse reactions were headache (8.1%), abdominal pain (2.7%), diarrhea (2%) and nausea (2%). No new safety concerns were identified in pediatric patients. Safety in the treatment of healing EE was assessed in 4 randomized comparative clinical trials (1,240 patients on NEXIUM 20 mg, 2,434 patients on NEXIUM 40 mg, and 3,008 patients on omeprazole 20 mg daily). The most frequent adverse events ($\geq 1\%$) in all 3 groups were headache (5.5, 5.0, and 3.8, respectively) and diarrhea (no difference among all groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates in those taking NEXIUM or omeprazole. Additional adverse reactions reported as possibly related to NEXIUM with an incidence $< 1\%$ are listed by body system: **Body as a Whole:** abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, substernal chest pain, edema (facial, leg, peripheral or generalized), hot flushes, fatigue, fever, flu-like disorder, malaise, pain, rigors; **Cardiovascular:** flushing, hypertension, tachycardia; **Endocrine:** goiter; **Gastrointestinal:** bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting; **Hearing:** earache, tinnitus; **Hematologic:** anemia, anemia hypochromic, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia; **Hepatic:** bilirubinemia, hepatic function abnormal, SGOT and SGPT increased; **Metabolic/Nutritional:** glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight change; **Musculoskeletal:** arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica; **Nervous System/Psychiatric:** anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertension, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; **Reproductive:** dysmenorrhea, menstrual disorder, vaginitis; **Respiratory:** asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis; **Skin/Appendages:** acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculopapular, skin inflammation, sweating increased, urticaria; **Special Senses:** otitis media, parosmia, taste loss, taste perversion; **Urogenital:** abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria; **Visual:** conjunctivitis, vision abnormal. Endoscopic findings that were reported as adverse events include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett’s esophagus, and mucosal discoloration. In two placebo-controlled studies, 710 patients were treated for symptomatic GERD and the most common adverse events possibly or probably related to NEXIUM were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Postmarketing Experience The following adverse reactions have been identified during post-approval use of NEXIUM. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system: **Blood:** agranulocytosis, pancytopenia; **Eye:** blurred vision; **Gastro-intestinal:** pancreatitis, stomatitis; **Hepatobiliary:** hepatic failure, hepatitis with or without jaundice; **Immune System:** anaphylactic reaction/shock; **Infections:** GI candidiasis; **Musculoskeletal:** muscular weakness, myalgia; **Nervous System:** hepatic encephalopathy, taste disturbance; **Psychiatric:** aggression, agitation, depression, hallucination; **Renal:** interstitial nephritis; **Reproductive/Breast:** gynecomastia; **Respiratory:** bronchospasm; **Skin:** alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (ten, some fatal).

DRUG INTERACTIONS

Interference with Antiretroviral Therapy Concomitant use of atazanavir and nelfinavir with proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. Co-administration of saquinavir with proton pump inhibitors is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. **Reduced concentrations of atazanavir and nelfinavir** For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg daily), AUC was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75% respectively for nelfinavir and M8. Following multiple doses of atazanavir (400 mg, daily) and omeprazole (40 mg, daily, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended. **Increased concentrations of saquinavir** For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported, with an increase in AUC by 82%, in C_{max} by 75%, and in C_{min} by 106%, following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily co-administered days 11 to 15. Therefore, clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with NEXIUM. Dose reduction of saquinavir should be considered from the safety perspective for individual patients. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Drugs for Which Gastric pH Can Affect Bioavailability Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, atazanavir, iron salts, and digoxin).

Effects on Hepatic Metabolism/Cytochrome P-450 Pathways Esomeprazole is extensively metabolized in the liver by CYP 2C19 and CYP 3A4. *In vitro* and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin. However, post-marketing reports of changes in prothrombin measures have been received

among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. Esomeprazole may potentially interfere with CYP 2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole 30 mg and diazepam, a CYP 2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Concomitant administration of esomeprazole and a combined inhibitor of CYP 2C19 and CYP 3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-Ellison’s Syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered. Omeprazole acts as an inhibitor of CYP 2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased C_{max} and AUC of clobazepam by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydroclobazepam, which has 4-7 times the activity of clobazepam, were increased by 29% and 69% respectively. Co-administration of clobazepam with esomeprazole is expected to increase concentrations of clobazepam and its above mentioned active metabolite. Therefore a dose reduction of clobazepam from 100 mg b.i.d. to 50 mg b.i.d. should be considered.

Combination Therapy with Clarithromycin Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin [see **Clinical Pharmacology** (12.4) in full Prescribing Information]. Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, terfenadine, ergotamine, or dihydroergotamine is contraindicated [see prescribing information for clarithromycin].

USE IN SPECIFIC POPULATIONS

Pregnancy *Pregnancy Category B* There are no adequate, well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Sporadic reports have been received of congenital abnormalities in infants born to women who received omeprazole during pregnancy [see **USE IN SPECIFIC POPULATIONS, Pregnancy** (8.1) in full Prescribing Information]. **Nursing Mothers** Omeprazole concentrations have been measured in breast milk of one woman taking omeprazole 20 mg per day. However, the excretion of esomeprazole in milk has not been studied. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for NEXIUM in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of NEXIUM have been established in pediatric patients 1 to 17 years of age for short-term treatment (up to eight weeks) of GERD. However, effectiveness has not been demonstrated in patients less than 1 year of age. Use of NEXIUM in 1 to 17 year olds is supported by extrapolation from well-controlled adult studies and safety and pharmacokinetic studies in pediatric and adolescent patients [see **CLINICAL PHARMACOLOGY, Pediatric** (12.3) in full Prescribing Information]. The safety and effectiveness of NEXIUM for other pediatric uses have not been established. *Neonates to less than one year of age* There was no statistically significant difference between NEXIUM and placebo in the rate of discontinuation in a multicenter, randomized, double-blind, controlled, treatment- withdrawal study of patients ages 1 to 11 months, inclusive. Patients were enrolled if they had either a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. All patients received NEXIUM Delayed-Release Oral Suspension once daily during a two-week, open-label phase of the study. There were 80 patients who attained a pre-specified level of symptom improvement and who entered the double-blind phase, in which they were randomized in equal proportions to receive NEXIUM or placebo for the next four weeks. Efficacy was assessed by observing the time from randomization to study discontinuation due to symptom worsening during the four-week, treatment withdrawal phase. The following pharmacokinetic and pharmacodynamic information was obtained in pediatric patients with GERD aged birth to less than one year of age. In neonates (< 1 month old) given NEXIUM 0.5 mg/kg once daily, the percent time with intragastric pH > 4 over the 24-hour dosing period increased from 44% at baseline to 83% on Day 7. In infants (1 to 11 months old, inclusive) given NEXIUM 1.0 mg/kg once daily, the percent time with intragastric pH > 4 increased from 29% at baseline to 69% on Day 7, which is similar to the pharmacodynamic effect in adults [see **Clinical Pharmacology** (12.2) in full Prescribing Information]. Apparent clearance (CL/F) increases with age in pediatric patients from birth to 2 years of age. Because NEXIUM was not shown to be effective in the randomized, placebo-controlled study for this age group, the use of NEXIUM in patients less than 1 year of age is not indicated. **Geriatric Use** No differences between elderly and younger patients in safety and efficacy were observed or reported, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

A single oral dose of NEXIUM at 510 mg/kg (about 103 times the human dose on a BSA basis) was lethal to rats. Major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions. Symptoms with deliberate NEXIUM overdose (limited experience of doses > 240 mg/day) are transient. Single 80 mg doses of NEXIUM were uneventful. Reports of overdose with omeprazole (up to 2,400 mg, 120 times the usual dose) in humans may be relevant. Manifestations varied, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and others seen in normal clinical experience (see omeprazole package insert-*Adverse Reactions*). No specific antidote for NEXIUM is known. Since NEXIUM is extensively protein bound, it is not expected to be removed by dialysis. Treatment of overdose should be symptomatic and supportive and the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose contact a Poison Control Center at 1-800-222-1222.

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