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INSIDE

New Antibiotics Appear Effective Against Multiply Resistant Bacteria

By William T. Elliott, MD, FACP

Two new antibiotic classes appear to be effective against multiply resistant bacteria, including vancomycin-resistant enterococci and staph. The FDA recently approved **Rhone-Poulenc Rorer's** two-drug combination of **quinupristin** and **dalfopristin**, both members of the new class of antibiotics known as **streptogramins**. The two agents work synergistically to inhibit bacterial protein synthesis. The parenteral drug combination, which was approved for the treatment of complicated skin infections as well as infections caused by vancomycin-resistant *Enterococcus faecium*, will be marketed under the name **Synercid**. **Pharmacia & Upjohn** is seeking approval for its own new drug, **linezolid**, the first of a new class of antibiotics known as **oxazolidinones**. Linezolid also appears to be effective against vancomycin-resistant gram-positive organisms. It is active as both an intravenous and oral preparation. The drug is in the final regulatory stages with approval expected within the next six months.

Does growth hormone benefit critically ill patients? Two recent studies from Europe raise doubts. In controlled, double-blind studies of more than 500 intensive care patients, the in-hospital mortality rate was higher for patients treated with growth hormone (*N Engl J Med* 1999;341:785-792), contradicting the findings of earlier American studies. In an accompanying editorial, the reasons for the negative findings are considered, including the possibility that the drug may have been given too late in the hospitalization or that it is not effective for patients with respiratory failure, the major diagnosis in the European studies. Growth hormone also causes an increase in metabolism and is pro-inflammatory, both reasons why the drug may worsen mortality in patients with inflammatory conditions.

Phen-fen may have been given a bad rap—at least with regard to the weight loss drug combination's propensity for causing heart valve abnormalities. The combination of **phentermine** and **fenfluramine** was implicated in the development of valvular insufficiency, eventually leading to the removal of fenfluramine (and later dexfenfluramine) from the market. But several recent studies have questioned whether the echocardiograms that showed the valvular regurgitation in the original studies may have been overread. The most recent study from Harvard/Beth Israel reviewed echocardiograms in 226 patients who were treated with phen-fen as part of a clinical study in the mid-90s. The prevalence of valvular abnormalities

was found to be no higher in the phen-fen treated patients than the general population (*J Am Coll Cardiol* 1999;34:1153-1162). This study, and others seriously question the validity of the original studies that led to the withdrawal of these drugs.

Expect an unprecedented marketing push this winter for **Glaxo's zanamivir** (**Relenza**) (*see page 20*), the recently approved anti-influenza drug, and **Roche's oseltamivir** (**Tamiflu**) whose FDA approval is expected before the flu season starts. Both will be heavily promoted directly to flu sufferers. According to the *Wall Street Journal*, the marketing departments of both companies plan to track flu outbreaks around the country, then descend upon affected areas with a blitz of TV, radio, and print ads directed at consumers as well as aggressive marketing to physicians. The goal is to convince consumers that the flu is now a treatable condition and, in the process, generate more than $1 billion in revenues. In order to avoid just such a scenario, the United Kingdom's national health program will probably not cover the cost of zanamivir. A national committee of experts responsible for advising the government on how it should spend the national health budget has recommended rejecting the flu drug. Managed pharmacy plans in this country are also struggling with the relatively modest benefits of the drug vs. the price tag of $44 per treatment course.

The FDA has approved **raloxifene** (**Evista—Eli Lilly**) for the treatment of postmenopausal osteoporosis. Previously, the drug had only been approved for prevention of osteoporosis. Sales of raloxifene have been below expectations, partially due to competition from **Merck's alendronate** (**Fosamax**). Alendronate works by inhibiting bone resorption by osteoclasts, similar to the way estrogens (and drugs like raloxifene) work. In related news, a new study sponsored by Merck suggests that the effects of alendronate and hormone replacement therapy (HRT) are additive. In a multicenter, randomized trial of nearly 430 women, the combination of alendronate and HRT significantly increased bone density in the lumbar, spine, and hip, but not the femoral neck, compared to HRT alone (*J Clin Endocrinol Metab* 1999;84:3076-3081).

"Head lice from hell" is the way some pediatricians feel about a wave of resistant pediculosis sweeping across the country. The high treatment rate in the United States may be partially to blame for the prevalence of **permethrin-resistant pediculosis**. Researchers from Harvard recently tested permethrin resistance in lice from children in Idaho, Massachusetts, and Borneo (where pediculosis is often tolerated and not treated). All the lice from Borneo were immobilized by increasing doses of permethrin, but a percentage of head lice from the U.S. sites were resistant to all doses of the permethrin (*Arch Pediatr Adolesc Med* 1999;153:969-973). Parents are resorting to a number of home remedies including salad dressing and mayonnaise, but a better option may be coming back. **Medicis' Ovide pediculicide**, which contains **malathion**, is being brought back after poor sales and safety concerns forced it off the market. The product kills lice and eggs, but it is flammable, needs to be left on for 8-12 hours, and has a distinct odor.

The antidepressant **mirtazapine** (**Remeron-Organon**) may have a new and unexpected use. A report in *Neurology* of five patients with movement disorders (Parkinsonism, action tremor, and levodopa-induced dyskinesias) who were incidentally treated with mirtazapine for depression showed marked improvement in tremor soon after the drug was started (*Neurology* 1999;53:1154). Two patients stopped the drug temporarily with a return of the preexisting tremor. The drug acts on both serotonergic and noradrenergic neurons, and has been touted as an antidepressant with limited sexual and gastrointestinal side effects. The authors of these case reports recommend a further study of mirtzapine for the treatment of tremors. ■

Rabeprazole Delayed Release Tablets

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

The fda has approved a third proton pump inhibitor (PPI) for the treatment of duodenal ulcers and gastroesophageal reflux disease (GERD). Rabeprazole (Aciphex) joins omeprazole (Prilosec) and lansoprazole (Prevacid) in this competitive, $3 billion worldwide market. Rabeprazole will be comarketed in this country by Eisai Inc and Janssen Pharmaceutica. The drug is a pyridyl methysulfinyl benzaminidazole, chemically similar to omeprazole. The PPIs inhibit gastric acid secretion by inhibiting the proton pump (H+/K+ ATPase) in the canalicular membrane of gastric parietal cells.[1]

Indications

Rabeprazole is approved for the healing of duodenal ulcers and erosive or ulcerative gastroesophageal reflux disease (GERD). It is also indicated for the maintenance or healing of erosive or ulcerative GERD and the treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome).

Dosage

For duodenal ulcers, rabeprazole is dosed at 20 mg once daily after the morning meal for up to four weeks (a few patients may require longer therapy). The same dose is given for erosive or ulcerative gastrointestinal reflux disease, 20 mg once daily, but for 4-8 weeks. If healing has not been achieved, an additional eight-week course may be considered. A dose of 20 mg once daily may also be given long term for maintenance or healing of erosive or ulcerative gastrointestinal reflux disease. Higher doses are required for pathological hypersecretory conditions: 60 mg once daily initially with dosage and duration adjustments as appropriate up to 100 mg daily or 60 mg twice daily.[6]

The tablets should be taken whole and not chewed, crushed, or split. No dosage adjustment is necessary in the elderly, patients with renal impairment, or patients with mild to moderate hepatic impairment. Rabeprazole is supplied as 20 mg delayed-release enteric coated tablets.

Potential Advantages

In two European comparative trials between rabeprazole (20 mg daily) and omeprazole (20 mg daily), one with gastric ulcer (n = 227) and one with duodenal ulcer (n = 205), the rabeprazole treated groups had a significantly higher percentage of patients showing improvement in daytime pain symptom relief at the three- or four-week end point respectively, but no difference in healing rates.[4,5] In addition to daytime pain symptom relief, rabeprazole-treated patients with gastric ulcers also had a significantly higher percentage of patients reporting reduction in pain frequency and complete resolution of night pain at six weeks.[4] Symptom improvements are secondary end points based on patient diaries using five-point scales.[4,5]

Clinically significant drug interactions involving the cytochrome P450 system have not been reported with rabeprazole even though the drug is metabolized by this enzyme system.[6]

Rabeprazole has been shown in animal studies to increase mucin synthesis in gastric mucosa, while omeprazole decreases synthesis and lansoprazole has no effect.[2] Rabeprazole has also been reported to have greater antimicrobial activity against *H. pylori* than omeprazole and lansoprazole.[2] Rabeprazole is apparently a noncompetitive irreversible inhibitor for bacterial urease.[3]

Potential Disadvantages

Rabeprazole decreases the bioavailability of ketoconazole and coadministration is not recommended.[2] Headache is the most commonly reported side effect with an incidence of 2.4% vs. 1.6% for placebo.[6] Rabeprazole has not been approved by the FDA for the treatment of gastric ulcers.

Comments

Rabeprazole is a potent proton pump inhibitor similar to omprazole and lansoprazole. It differs from these other agents by being a "reversible" inhibitor that results in shorter duration of action.[2] The duration of action is about two days for rabeprazole compared to four days for omeprazole.[2] Clinical trials indicate that rabeprazole was reported to be well tolerated and as efficacious as omeprazole and more efficacious than ranitidine in promoting the healing of erosive or ulcerative gastrointestinal reflux disease (GERD).[7,9] The drugs were comparable in relief of heartburn symptoms.[5] Rabeprazole and omeprazole also produced comparable healing in duodenal and gastric ulcers, although certain symptom relief end points were reported to be in favor of rabeprazole.[4,5] Rabeprazole has also been reported to be effective when used in combination with antibiotics for the eradication of *H. pylori*.[8]

The cost of rabeprazole is slightly less than that of omeprazole ($3.70 vs $3.99) and similar to that of lansoprazole 15 mg ($3.66) and lansoprazole 30 mg ($3.73).

Clinical Implications

Rabeprazole provides an alternative to omeprazole and lansoprazole. Results from clinical trials suggest that rabeprazole may provide better symptom relief than omeprazole in patients with duodenal or gastric ulcers. However, these were observed for only certain secondary symptom end points, one out of six for duodenal ulcers and three out of six for gastric ulcers. In addition, no differences were reported for patients with GERD. ■

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Zanamivir for Inhalation (Relenza—Glaxo Wellcome)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Just in time for the 1999 flu season, the fda has approved Glaxo Wellcome's zanamivir (Relenza) for the treatment of influenza A and B. Zanamivir is the first of a new class of antiviral drugs, the sialic acid analogs, which were developed through computer-assisted design. These drugs are believed to inhibit viral replication by inhibiting the viral surface enzyme, neuraminidase.[1] Zanamivir is formulated as an inhaled product that is delivered through a breath activated device.

Indications

Zanamivir is indicated for the treatment of uncomplicated acute illness due to influenza virus (A and B) in adults and adolescents (≥ 12 years of age). Patients should be symptomatic for two days or less.[2]

Dosage

The recommended dose is two inhalations at 5 mg each twice daily, about 12 hours apart, for five days. Two doses should be administered on the first day of treatment (at least 2 hours apart). Treatment should be initiated within two days after onset of symptoms. Patients should be instructed in the proper use of the delivery device and advised to complete the five-day course.[1]

Zanamivir is supplied as powder for inhalation. Each foil pack contains four blisters—each contain 5 mg of zanamivir and 20 mg of lactose. The contents of each blister is inhaled using a Diskhaler.

Potential Advantages

In contrast to amantadine and rimantadine, which are effective against influenza A only, zanamivir is active against influenza A and B although in the clinical trials patients were predominately infected with influenza A.[1] The drug is well tolerated and is generally free of systemic side effects.[2-4] One placebo-controlled study (n = 455) conducted in Australia, New Zealand, and South Africa reported a significant reduction in median time to the symptom relief of 1.5 days (6.0-4.5 days) in patients who initiated therapy within 36 hours of onset based on intent-to-treat analysis. In patients who were influenza positive and febrile, the median reduction was two days (6.5-4.5 days).[3] A small number of high-risk patients (n = 79) had a statistically significant reduction in median time to alleviation of symptoms of 2.5 days (8.0-5.5 days).[3] In influenza-positive patients, zanamivir-treated patients also reported less sleep disturbance and earlier return to normal activity.[3]

Potential Disadvantages

The administration of the drug requires two inhalations of zanamivir powder twice daily. The FDA had some concerns that this delivery system may be cumbersome for some patients and may require some initial training. Patients with underlying respiratory disease may experience bronchospasm and/or decline in pulmonary function after use of the drug.[2] These patients should have a short-acting beta agonist available when treated with zanamivir.[2] Therapy should be initiated within 48 hours after onset of influenza symptoms, and preferably within 36 hours.

Comments

Zanamivir is the first of a new class of antivirals, the selective neuraminidase inhibitors. Neuraminidase, also referred to as sialidase, is a surface glycoprotein essential for the replication of both influenza A and B viruses.[5] The speculated roles of this enzyme include promotion of the release of virions from infected host cells, prevention of viral inactivation by respiratory mucus, and inducing the elaboration of certain cytokines (e.g., tissue necrosis factor).[5] Animal models indicated that zanamivir reduces viral replication.[1] The clinical benefit of zanamivir is modest. In a study conducted in the Southern Hemisphere (n = 455), zanamivir reduced the median time to symptom relief by 1.5 days when patients initiated treatment within 36 hours.[3] However, in studies conducted in North America (n = > 600), zanamivir reduced the median time to symptom relief by only one day when patients initiated treatment within 48 hours and statistical significance was not achieved.[2] Time-to-symptom improvement was defined as improvement in major symptoms: resolution of fever, headache, myalgia, cough, and sore throat.[2] Findings from clinical trials did not show any difference in the rate of development of complications between treatment groups.

The drug has not been adequately studied in patients with high-risk underlying medical conditions. Zanamivir is currently FDA approved for the treatment of uncomplicated acute illness due in influenza. It is not approved for the prevention of illness, although a recent randomized, controlled trial showed the drug to be efficacious in

healthy young adults.[4]

Zanamivir-resistant strains have been isolated in vitro; however they have been reported to be less infectious.[1,2,7] The wholesale cost for a treatment course of zanamivir (5 days) is $44.

Clinical Implications

Prior to the approval of zanamivir, only amantadine and rimantadine have been approved for the treatment of influenza. The use of these agents was limited by inactivity against influenza B, rapid development of resistance, and CNS and gastrointestinal side effects. In contrast, zanamivir is active against influenza A and influenza B. It is well tolerated but should be used with caution in patients with underlying respiratory disease. Drug-resistant viruses can appear in about one-third of patients treated with amantadine or rimantadine.[6] In clinical trials of zanamivir, drug-resistant strains have not been a problem.[1,4]

The benefit of zanamivir is modest. North American data showed that initiation of therapy within 48 hours failed to produce a statistically different reduction in median time to symptom improvement. Initiation of therapy within 36 hours may improve the efficacy, although it is unlikely that most adults will seek medical care or receive a definative diagnosis of influenza within 36 hours of onset of symptoms. The delivery system may also represent an obstacle to appropriate use in early stages of the illness. An orally active neuraminidase inhibitor is currently in the FDA pipeline.

There are no indications that the drug can reduce complications of influenza illness in patients at risk for these events. Vaccination remains the primary prophylactic means of controlling influenza and preventing sequelae. Patients should not eschew vaccination in favor of treatment after infection. The chemoprophylactic use of zanamivir has not been FDA approved, but neuraminidase inhibitors, especially orally active ones, may eventually have a role in managing influenza outbreaks particularly involving variant strains not covered by the vaccine. ■

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Oral Therapy for Febrile, Neutropenic Patients

Sources: *Freifeld A, et al. N Engl J Med 1999;341:305-311; Kern WV, et al. N Engl J Med 1999;341:312-318.*

Freifeld and colleagues conducted a randomized, double-blind, placebo-controlled trial comparing oral ciprofloxacin (750 mg q 8 h) and amoxicillin/clavulanate (500 mg q 8 h) with intravenous ceftazidime (2 g q 8 h) for the empiric treatment of febrile neutropenic cancer patients. All patients were hospitalized during the period of fever and neutropenia. Neutropenia was expected to last for no more than 10 days, and patients were free of serious other medical conditions, abdominal symptoms, signs of catheter-related infection, and new pulmonary infiltrates. Criteria for changes in the initial regimen were prospectively defined. Empirical therapy was considered successful if the patients survived the episode of fever and neutropenia without modification of the regimen or evidence of active infection at resolution.

There were a total of 116 episodes in each treatment group. Infection was documented in approximately one-third of episodes; most were soft tissue or mucosal infections. There were five bacteremias in the oral therapy group and 12 in the intravenous therapy group. Treatment efficacy was similar in both groups (71% in the oral therapy group, 67% in the intravenous therapy group). Failure in the intravenous therapy group was more likely to have been due to the need to add anti-infective agents (32%) than in the oral therapy group (13%). Failure in the oral therapy group was more likely to be due to intolerance of the regimen (16%). Fever resolved by day 5 in 90% of all episodes. There were no deaths.

In a similar, but unblinded study, Kern and colleagues randomized patients to receive either oral ciprofloxacin (750 mg q 12 h) plus amoxicillin/clavulanate (625 mg q 8 h) or ceftriaxone (2 g daily) plus amikacin (20 mg/kg daily). The anticipated duration of neutropenia was 10 days or less, and patients with serious complicating illness or evidence of catheter infection were excluded. Patients were hospitalized for the duration of the fever. Successful empiric therapy required resolution of therapy for three consecutive days, resolution of signs of infection if pre-

sent on entry, eradication of the original pathogen, and lack of recurrence for one week after the end of therapy. The success rate of evaluable patients assigned to oral therapy was 86% (138/161); the success rate of patients receiving intravenous therapy was 84% (127/151). Twelve percent of the patients were bacteremic. There were six deaths due to infection, two in the oral therapy group and four in the intravenous therapy group. Rates of secondary infection and adverse events were similar in the two treatment groups. Patients in the oral therapy group had a high rate of gastrointestinal symptoms (26%), while only patients receiving IV therapy experienced nephrotoxicity (4%) or catheter-related complications (11%).

Comment by Robert Muder, MD

The current standard of treatment for cancer patients with fever and neutropenia consists of administration of broad-spectrum intravenous antibiotic therapy.[1] However, previous studies have indicated that certain febrile, neutropenic cancer patients are at relatively low risk for serious complications.[2] These include ambulatory patients who are free of serious comorbid illness or uncontrolled malignancy. Preliminary trials have indicated that these patients might be successfully managed with oral therapy. These two recent randomized trials confirm that empiric oral therapy is as safe and effective as standard, broad spectrum intravenous therapy. Although the two studies used somewhat different study designs and drug regimens, the patient populations studied and the results were quite similar.

Several important cautions are in order, however. The patients in both trials were carefully selected for limited, anticipated duration of neutropenia, and for the absence of complicating medical conditions. Further, patients were hospitalized until resolution of fever in one trial, and resolution of fever and neutropenia in the other. Patients could be carefully monitored for signs of clinical deterioration or drug toxicity, and appropriate changes in regimen or institution of supportive care could be undertaken. Because oral therapy is less expensive than intravenous therapy, and because oral therapy can be given as an outpatient, one can easily envision pressure by insurers or HMOs to treat low-risk episodes of febrile neutropenia on a purely outpatient basis. This would be premature, and potentially unsafe. In the study of Freifeld et al, for example, 4% of patients suffered a serious adverse event such as hypotension or cecitis. All survived; however, any delay in recognition or treatment might well have been disastrous.

It may be that certain febrile neutropenic patients can, with appropriate careful monitoring, be managed with oral therapy on an outpatient basis. Identification of appropriate patients and regimens will require additional well-designed trials. Until these are completed, I agree with the authors of the accompanying editorial[3] that management of episodes of febrile neutropenia should occur in the inpatient setting. ■

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Route of Analgesia and Pain Perception

Source: *Schwartz NA, et al. Acad Emerg Med 1999;6:505.*

The purpose of this prospective, randomized, double-blind study was to compare the analgesic effects of IM vs. PO placebo. A convenience sample of 77 patients with acute musculoskeletal pain was given 800 mg of ibuprofen in an orange flavored drink. Thirty-nine of the subjects then received a physiologically inactive tablet resembling ibuprofen and the remaining thirty-eight subjects received a physiologically inactive IM injection resembling ketorolac 60 mg. Subjects then rated the intensity of their pain on a 100 mm visual analog scale (VAS) at baseline and 30, 60, 90, and 120 minutes after treatment.

A total of 64 patients completed the study, giving the authors the ability to detect a 20% difference in VAS score between the two groups with 90% power. After two hours, the mean VAS score had decreased from 60 to 26 for the IM group and from 59 to 27 in the PO group. There were no significant differences in the VAS scores at baseline or at each subsequent interval.

Comment by Stephanie Abbuhl, MD, FACEP

I suspect that all of us have thought, at one time or another, that at least some of the benefit from a parenteral analgesic was due to the placebo effect of the perception of a "stronger medication." The authors of this clever, but small, study have provided some initial evidence to refute this commonly held belief. Instinctively, I like this study

because it reminds us of our tendency as physicians to think that pain management is more of a subjective game of manipulation than part of objective disease management. We may have again underestimated our patients.

Admittedly, it is possible that larger studies will expose some placebo effect from parenteral analgesia. In addition, there may also be clinically important differences in patient-assigned VAS scores at less than a 20% difference.[1] Finally, it is also possible that certain subgroups of patients will gain a significant placebo effect from parenteral analgesics. ■

Dr. Abbuhl is Medical Director, Department of Emergency Medicine, The Hospital of the University of Pennsylvania; Associate Professor of Emergency Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA.

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Two Measles Doses are Better Than One

Source: *Vitek CR, et al. Pediatr Infect Dis J 1999;18:620-623.*

A measles outbreak of 62 confirmed cases in 1994 in Mesa County, Colo., was investigated to evaluate measles vaccine effectiveness. The attack rate in unvaccinated children (7/16, 44%) was higher than those with one dose (10/320, 3%) or two doses (0/289, 0%). Two doses of measles vaccines provided 100% protection, compared to 92% for one dose (P = 0.003).

Comment by Hal B. Jenson, MD, FAAP

Between 1984 and 1988, an average of 3700 cases of measles were reported annually in the United States, with a sharp rise in 1989 that continued in 1990 when 27,786 cases of measles were reported. In 1989, the American Academy of Pediatrics and the Advisory Committee on Immunization Practices (ACIP) of the CDC recommended that a second measles dose be given (as MMR). The current recommendations are for the first dose at 12-15 months of age, and the second dose routinely at 4-6 years of age, although the second dose can be administered at any visit if at least one month has elapsed since receipt of the first dose and both doses are administered at or after 12 months of age. Children who have not previously received the first dose should complete the schedule no later than the routine visit at 11-12 years of age. Since this recommendation, the annual number of cases of measles in the United States has dropped below 100, suggesting, but not proving, that this policy has been effective. The age distribution of children with measles in this outbreak was interesting. The age groups with cases included young children who had not received two doses of measles vaccine, and older children (15-18 years of age) beyond statutory requirements for two doses of measles vaccine. There were no cases of measles among children 12-14 years of age, for whom state law had required two doses of measles vaccine. This suggests that we should be diligent to make sure all children receive two doses, and don't assume that age is protective.

This study is the first that evaluates the effectiveness of the two-dose measles policy in an outbreak, which is the setting in which we are most likely to encounter measles in the United States today. The results convincingly demonstrate the importance and the effectiveness of the second dose in preventing measles, and substantiate the current recommendations for a second dose of measles vaccine for all children. ■

Dr. Jenson is Chief, Pediatric Infectious Diseases, University of Texas Health Science Center, San Antonio, TX.

Therapeutics & Drugs Briefs

Rotavirus Vaccine on Hold

Source: *MMWR Morb Mortal Wkly Rep 1999;48:577-581.*

Based on concerns of a possible association between the administration of rotavirus vaccine (Rotashield) and an increased risk of intussusception in children, the American Academy of Pediatrics and the CDC are recommending that the use of this vaccine be suspended until the availability of additional safety data. Children scheduled to receive this vaccine, including those who have already begun the series, should not receive it until further notice. Any child who has recently received the vaccine and who develops gastrointestinal symptoms, including persistent vomiting, abdominal distention, severe abdominal pain, and black or bloody stools, should be urgently evaluated. Clinicians should be aware of this possible adverse event and are urged to report this or any other postvaccination event to the Vaccine Adverse Event Reporting System at http://www.nip.gov/nip/vaers. htm (1-800-822-7967). Data from an ongoing case-control study should be available by November 1999. ■

Terbinafine Superior to Itra in Toenails

Source: *Evans EG, et al. BMJ 1999;318:1031-1035.*

Because therapeutic concentrations of itraconazole persist in the nail bed for several days, some experts advocate that, for the treatment of onychomycosis, the administration of this azole should be cycled. In contrast to itraconazole, which is fungistatic, terbinafine is a newer allylamine antifungal agent that has cidal activity against most dermatophytes. In a double-blind, randomized, controlled trial, 496 patients with onychomycosis were randomized to receive either continuous terbinafine 250 mg daily for either 12 or 16 weeks or itraconazole 400 mg daily for one week of every month for 12 or 16 weeks. Eligible patients had distal subungual or total dystrophic nail disease confirmed by culture as well as KOH.

Continuous terbinafine was substantially better, resulting in clinical cures (defined as 100% toenail clearing) in 54% of patients at 12 weeks and 60% of patients at 16 weeks. In contrast, only 32% of patients receiving itraconazole were clinically cured. Mycological cures were achieved in 76-80% of patients receiving terbinafine and 38-49% receiving itraconazole. Both drugs were well tolerated and the frequency of side effects was similar. While daily terbinafine is superior to intermittent itraconazole in the treatment of onychomycosis, clinicians should keep in mind that 20-40% of patients may fail three to four months of therapy and require a longer course of treatment. ■

The Therapeutics & Drugs Briefs were written by Carol A. Kemper, MD, FACP, Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases; Santa Clara Valley Medical Center.

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CME questions

Testing form inserted in the January 2000 issue

28. Which of the following statements about zanamivir is *not* true?

a. It should be started as early as possible.
b. It is approved for preventing influenza.
c. It is an oral inhaler.
d. It treats influenza A and B.

29. Which of the following statements about Rabeprazole is *false*?

a. It is given once a day.
b. It may be chewed or split.
c. Symptom relief in peptic ulcers is at least as effective as omeprazole.
d. It may be more effective for treatment of *H. pylori* than omeprazole and lansoprazole.

30. All of the following are true about measles vaccination *except*:

a. The first dose is recommended at 12-15 months.
b. The second dose is recommended at 4-6 years of age.
c. Clinical measles occur largely in children who have received only one dose.
d. A second dose is not recommended for children older than 15 years of age.

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