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New Money, Old Parasite

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EVERY YEAR ABOUT THIS TIME, I SEE A COUPLE OF UNHAPPY LOCAL RESIDENTS WHO PRESENT with an intensely pruritic, erythematous papular mystery rash. In contrast to flea bites, which are simple raised papules, the lesions seem umbilicated or have a central bite mark. The patient typically is floored when I explain they have rat mite bites, and they need to go home and set traps — I mean, this is Palo Alto! It is estimated that half the homes in this area have resident roof rats, or *Rattus norvegicus*, especially at this time of year, when they are looking for a warm, dry place to nest. The spiny rat mite, *Laelaps echidnina*, is the most common ectoparasite found in large rodents.

Chiggers and mites are frequent causes of dermatosis in patients referred to the ID clinic, especially in travelers,[1] in whom the rash must be distinguished from those of sand flies and other parasites. Chiggers and non-human mites typically cause an intensely pruritic, red, bumpy rash. Non-human mite dermatosis can result from animal or plant infestations, including animal habitats, dens, bird nests, fruits, trees, and furniture. Mites cannot jump, but they can crawl about 1 inch per hour on warm dry skin. Just like scabies, female mites burrow under the skin, where they lay their eggs. A sampler of different mites is as follows:

• Chiggers are free-living ectoparasites, meaning the larvae feed for a few hours and then drop to the ground, before maturing into nymphs (including the trombiculid chigger species Leptotrombidium, which can transmit scrub typhus). Chigger bites are initially painless but, within hours, become intensely pruritic, followed by an erythematous papular eruption, called prurigo, which lasts a day or two. The bites are commonly found in areas where clothing is tighter, such as around waistbands, underwear, thighs, and ankles.

• Zoonotic (or non-human) scabies from any number of mammalian and bird species can infect humans, who are essentially dead-end hosts; the larvae never develop in humans, although symptomatic infection from mites burrowing under the skin may still

respond to 5% pyrethrine or ivermectin. Common mites in this category include the poultry mite (seen in poultry handlers, typically on the hands); bird mites (in bird fanciers, breeders, and pet shop owners), various rodent mites, such as the rat mite and the common house mouse mite (the latter can transmit Rickettsialpox [*R. akari*], resulting in a typical eschar). Pigeon mites have been known to cause infestations in apartment buildings, where they roost outside of windows — and one hospital experienced a nosocomial outbreak of pigeon mites in patients and nurses.[2] Bird-mite bites are usually self-limited and can be managed with antihistamines and topical corticosteroids.

• Plant mites are more unusual, but include the North American and European straw itch mites, which can cause infestations in caned furniture, straw baskets, and straw rugs; they are most typically seen after hay rides in the fall. A characteristic "comet tail" has been described, which is literally the track of the mite moving away from the bite site. Other Pyemotes (plant mites) relatives can occasionally cause outbreaks, such as a large outbreak of North American oak leaf gall mite in residents in Pittsburg, KS. Plant insect mites can also occur in back packers, campers, and resort-goers, especially during the summer months, when mites breed and feed.

In travelers, chigger and mite bites must be distinguished from sand flea bites, such as those from *Tunga penetrans* (found in sub-Saharan Africa and South America) and *Tunga trimamillata* (found in Ecuador and Peru), which infect both animals and humans. The pregnant sand flea females burrow under the skin, causing inflammation and ulceration — the legs and feet can become so that walking becomes painful. A recent consult was just this — a young woman who took a brief Easter jaunt to Machu Pichu and presented with severe tungiasis with dramatic lower-extremity swelling and multiple small black eschars just above her sock line — quite different from mite bites.

Patients never seem as excited or intrigued as I am when they present with one of these dermatoses, but at least they are relieved to have an answer, even it means going home and setting rat traps. ■

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Rifaximin Tablets (Xifaxan®)

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

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A RIFAMYCIN ANTIBACTERIAL AGENT HAS BEEN APPROVED for treating patients with hepatic encephalopathy (HE). Rifaximin is a minimally absorbed oral antimicrobial that was originally approved in 2004 for the treatment of travelers' diarrhea caused by *Escherichia coli*. It is marketed by Salix Pharmaceuticals as Xifaxan®.

Indications

Rifaximin is indicated to reduce the risk of hepatic encephalopathy recurrence in adult patients who are in remission.[1]

Dosage

The recommended dose is one 550 mg tablet twice daily. The drug may be taken with or without food. Rifaximin is available as 200 mg and 550 mg tablets.

Potential Advantages

Rifaximin reduces the risk of an episode of hepatic encephalopathy and the risk of hospitalization involving hepatic encephalopathy.[1,2]

Potential Disadvantages

More than 90% of study subjects in the clinical trial were using lactulose. The effectiveness of rifaximin is not known if given without lactulose. In the pivotal trial that led to the approval for this indication, 2 of 140 patients in the treatment group developed *C. difficile* infections as compared 0 of 159 patients in the control group.[2]

Comments

Rifaximin is an orally administered nonsystemic antibacterial agent. Its efficacy was shown in a double-blind, international, randomized, placebo-controlled trial in patients who had at least two episodes of hepatic encephalopathy in the previous 6 months but were in remission. Study participants were randomized to rifaximin (550 mg twice daily; n = 140) or placebo (n = 159) for 6 months. The incidence of HE was 22% in the rifaximin group and 46% in the placebo group (hazard ratio [HR] 0.42; 95% confidence interval [CI], 0.28-0.64; $P < 0.001$). The rates of hospitalization involving HE were 13.6% and 22.6%, respectively (HR 0.50; 95% CI, 0.29-0.87; $P = 0.01$). Ninety-one percent of subjects had concomitant therapy with lactulose. The incidence of adverse events was similar between the two groups; however, a higher frequency (compared to placebo) occurred for peripheral edema (15% vs 8%), dizziness (13% vs 8%), and anemia (8% vs 4%). The two patients who developed *C. difficile* infection continued rifaximin therapy along with concomitant treatment for the infection and fully recovered. Rifaximin has also been reported to be effective as acute treatment for HE compared to non-absorbable disaccharides and antibiotics.[3,4]

Clinical Implications

More than 5 million Americans have hepatic cirrhosis. Hepatic encephalopathy is a complication of hepatic cirrhosis that is severely debilitating and often results in hospitalization. It is characterized by cognitive deficit that can vary from mild lack of awareness to coma.[5] The pathophysiology appears to be multifactorial, but ammonia produced by gut flora is most commonly implicated. Current therapy includes lactulose and oral antibiotics such as neomycin. Rifaximin is a nonsystemic antibacterial with broad-spectrum activity against gram-positive, gram-negative, and anaerobic enteric bacteria. It has been shown to reduce the risk of HE and hospitalization involving HE. ■

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Reintroduction of TB Meds Following Hepatotoxicity

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Source: Sharma SK, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. *Clin Infect Dis*. 2010;50:833-839.

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DRUG-RELATED HEPATOTOXICITY DURING TREATMENT FOR TUBERculosis is a common barrier to initiation of antimycobacterial. While most hepatotoxicity results in minimal to no gastrointestinal complaints, some patients experience significant nausea, anorexia, vomiting, or abdominal pain. While there are several proposed methods for reintroducing TB therapy in these patients, there is no consensus as to how to proceed. Our local public health department strongly discourages the stepwise reintroduction of medications based on concerns about the potentiation of resistance, although this approach has been recommended by both the American Thoracic Society and the British Thoracic Society.

These investigators selected 237 consecutive patients with clinical and laboratory evidence of hepatotoxicity occurring during antimycobacterial treatment, and prospectively evaluated the risk of recurrent hepatotoxicity upon reintroduction of TB therapy over a three-month period. Hepatotoxicity was defined as $\geq$ 3 times the upper limit of normal transaminases on three consecutive occasions, $\geq$ 5 times the ULN transaminase on one occasion, or any elevation in transaminase associated with nausea, vomiting, anorexia, and jaundice. Patients were screened for other contributing causes of hepatotoxicity, such as hepatitis, HIV, and alcohol use; based on this, 58 patients were excluded from the analysis and four patients died.

Treatment was not reintroduced until normalization of liver function test results. The median time to normalization of liver test results was 18 days (range, 14 to 28 days), and the median time to reintroduction of medications was 23 days (range, 14 to 44 days).

Patients were randomly assigned to one of three retreatment strategies: the simultaneous reintroduction of all three meds (isoniazid, rifampin, and pyrazinamide) at maximal dosages at day one; the stepwise reintroduction of medications at full dosages with rifampin at day one, INH at day eight, and PZA at day 15 (similar to the ATS recommendations); and the stepwise reintroduction of medications with dose-escalation beginning with INH 100 mg/day at day one, increasing to full dose by day four, then rifampin 150 mg/day at day eight, increasing to full dose by day 11, and finally PZA at 500 mg/day at day 15, increasing to maximal dose by day 18 (according to the BTS guidelines).

Nineteen (10.9%) patients had recurrent treatment-related hepatotoxicity. The frequency of recurrent hepatotoxicity was similar (13.8% vs. 10.2% vs. 8.6%), (p = .69), respectively, for each of the three groups outlined above. In addition, the peak bilirubin and transaminase values were similar between the three groups. The median number of days to recurrence of hepatotoxicity was similar (14 for group 1 vs. 21 days for the other two groups, with a maximum of 35 days). No deaths were observed. The only risk factor associated with recurrent hepatoxicity was lower pre-treatment albumin levels.

These data support the simultaneous reintroduction of full-dose TB medications in patients who have experienced hepatoxicity. The severity of the initial hepatotoxicity did not appear to predict the risk of recurrent hepatotoxicity, nor the severity of symptoms if recurrent hepatotoxicity occurred. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

PPIs, *Clostridium difficile*, and Bone Fractures

In this issue: *New reports about proton pump inhibitors and the effects of gastric suppression, pioglitazone vs vitamin E for non-alcoholic steatohepatitis, metformin and vitamin B12 deficiency, and FDA Actions.*

PPIs, C. difficile, and bone fractures

Since H2 antagonists were introduced 30 years ago followed by proton pump inhibitors (PPIs) 20 years ago, there has been speculation whether long-term gastric acid suppression might have adverse effects. Billions of doses later, there is new evidence that chronic PPI use may lead to infections, especially *Clostridium difficile* infection (CDI), and may also contribute to bone fractures.

In the first of several studies published in the May 10 issue of *Archives of Internal Medicine*, researchers looked at more than 101,796 discharges from a tertiary care medical center during a five-year period, reviewing the level of acid suppression therapy and its relationship to CDI. As the level of acid suppression increased, the risk of CDI increased from 0.3% in patients not receiving acid suppressive therapy to 0.6% in those receiving H2 antagonists to 0.9% in those receiving daily PPIs and finally 1.4% in those receiving high-dose PPI therapy. After adjustment for a number of factors including comorbid conditions, age, and antibiotic use, the odds ratio for CDI infections were: 1 with no acid suppressing treatment, 1.53 (95% confidence interval [CI], 1.12-2.10) with H2 antagonist, 1.74 (95% CI, 1.39-2.13) with PPIs, and 2.36 (95% CI, 1.12-2.10) with high-dose PPI therapy. The authors conclude that increasing levels of pharmacologic acid suppression are associated with increased risk of nosocomial *C. difficile* infections, and the risk increases with more aggressive acid suppression (*Arch Intern Med* 2010;170: 784-790).

In a second study from the same journal, researchers from the VA system in Massachusetts performed a retrospective, cohort study of 1166 inpatients and outpatients with CDI to determine if PPI use affected recurrence rates. During treatment for CDI, 45% of patients received a PPI while 55% did not. Recurrent CDI was more common in those exposed to PPIs than in those not exposed (25.2% vs 18.2%). The hazard ratio for recurrent CDI in those exposed to PPIs was 1.42 (95% CI, 1.11-1.82). The risk was higher in patients older than 80 years and in patients exposed to antibiotics not targeted to CDI infections The authors conclude that PPI use during treatment for CDI was associated with a 42% increased risk of recurrence (*Arch Intern Med* 2010;170:772-778).

It has also been postulated that suppressing gastric acid may affect digestion and absorption of certain nutrients, specifically calcium. Although this has never been definitively proven, multiple studies have shown that chronic PPI use is associated with bone fractures. The most recent study, also published in the May 10 issue of *Archives of Internal Medicine*, was a prospective analysis of more than 160,000 women enrolled in the

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Women's Health Initiative study. In more than 1 million person-years of follow-up, there were 1500 hip fractures, 4881 forearm or wrist fractures, 2315 clinical spine fractures, and more than 21,000 total fractures. The multivariate-adjusted hazard ratios for current PPI use was 1 for hip fracture, 1.47 (95% CI, 1.18-1.82) for clinical spine fracture, 1.26 (95% CI, 1.05-1.51) for forearm or wrist fractures, and 1.25 (95% CI, 1.15-1.36) for total fractures. Bone mineral density did not vary between PPI users and non-users. The authors conclude that use of PPIs in women was not associated with hip fractures but was modestly associated with clinical spine, forearm or wrist, and total fractures (*Arch Intern Med* 2010;170:765-771). This study confirms the findings of several large epidemiological studies that suggest that PPI use is associated with increased osteoporotic fracture risk. On May 25, the FDA issued a warning regarding the possible fracture risk associated with high-dose long-term use of PPIs. The Agency will require labeling changes to describe the possible risk.

As noted in these studies, PPI use is associated with risk of osteoporotic fractures and *Clostridium difficile* infections. Other studies have linked the PPIs to a higher risk of hospital- and community-acquired pneumonia, as well as enteric infection such as *Salmonella* and *Campylobacter* gastroenteritis. In an editorial in the May 10 issue of *Archives of Internal Medicine*, Mitchell Katz, MD, notes that of the more than 110 million prescriptions for proton pump inhibitors filled each year, many are for inappropriate indications, making PPIs one of the most overprescribed medication classes in the world. He suggests that "for most patients the adverse effects of PPIs outweigh the benefits" and urges physicians to offer other treatments for dyspepsia, prescribe shorter courses, and consider a trial of discontinuing PPIs in patients who are asymptomatic (*Arch Intern Med* 2010;170:747-748). ■

Pioglitazone vs vitamin E for NASH

Non-alcoholic steatohepatitis (NASH) is a common liver disease that is difficult to treat and often progresses to cirrhosis. A new study compares the thiazolidinedione pioglitazone (30 mg daily) to vitamin E (800 IU daily) in a placebo-controlled trial for 96 weeks in 247 nondiabetic NASH patients. The primary outcomes were standardized scores for steatosis, lobar inflammation, hepatocellular ballooning, and fibrosis as determined by liver biopsy. Vitamin E therapy was associated with a significant improvement in non-alcoholic steatohepatitis (43% vs 19%; $P = 0.001$), but pioglitazone did not show statistical improvement (34% vs 19%; $P = 0.04$). Serum transaminases improved with both treatments, and both reduced hepatic steatosis and lobular inflammation, but neither improved fibrosis. Pioglitazone caused significant weight gain compared to vitamin E or placebo. The authors conclude that vitamin E was superior to placebo for the treatment of NASH in adults without diabetes (*N Engl J Med* 2010;362:1675-1685). ■

Metformin and vitamin B12 deficiency

Monitor your patients on metformin for vitamin B12 deficiency. This is the message of a recent study from the Netherlands. The study enrolled 390 patients with type 2 diabetes on insulin and initiated metformin 850 mg three times a day or placebo for an average of 4.3 years. Metformin treatment was associated with a mean decrease in vitamin B12 concentrations of 19% ($P < 0.001$) and an increase in homocysteine concentrations of 5% ($P = 0.091$). Longer-term treatment with metformin was associated with larger declines in vitamin B12 levels. The authors conclude that metformin likely causes malabsorption of vitamin B12 and recommends routine monitoring of vitamin B12 levels in patients who are treated with metformin (*BMJ* 2010;340:c2181). ■

FDA actions

The FDA has approved a new formulation of oxycodone (OxyContin®) that is designed to discourage chewing, crushing, or dissolving the drug. The FDA admits, however, that although the new formulation reduces the risk of snorting or injecting the drug, it can still be abused by simply ingesting larger doses than recommended. Vocal critics have called for oxycodone's withdrawal from the market due to an explosion in abuse of the drug nationwide and calls this new formulation "too little too late."

The FDA has recommended resuming use of Rotarix® rotavirus vaccine and to continue using RotaTeq® rotavirus vaccine. Rotarix was found to have elements of the porcine circovirus 1 (PCV1) in March, which resulted in an advisory to clinicians to stop using the vaccine. Subsequently, DNA from PCV1 and PCV2 was discovered in the RotaTeq vaccine. The FDA now says that there is no evidence that PCV causes illness or infection in humans while the benefits of the vaccine are substantial. ■