TRAVEL MEDICINE ADVISOR

This Month's Compendium of Articles from Other Thomson American Health Consultants Publications

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Volume 14, No. 11
November 2004

Travel Medicine Advisor® is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd. NE, Six Piedmont Center, Suite 400, Atlanta, GA 30305. Periodicals postage paid at Atlanta, GA. POSTMASTER: Send address changes to *Travel Medicine Advisor®*, P.O. Box 740059, Atlanta, GA 30374.
Customer Service:
1-800-688-2421.
Subscription Information:
Travel Medicine Advisor® Update is a bimonthly supplement to *Travel Medicine Advisor®* looseleaf service. Price: $429 (includes *Travel Medicine Advisor* looseleaf reference manual plus one-year subscription to *Travel Medicine Advisor® Update*.) To subscribe, **call 1-800-688-2421.**

Azithromycin for Typhoid Fever

ABSTRACT & COMMENTARY

Synopsis: *Five days of oral treatment with azithromycin appeared to be at least as effective as a similar duration of treatment with ceftriaxone for children in Cairo with typhoid fever.*

Source: Frenck RW Jr., et al. Short-Course Azithromycin for the Treatment of Uncomplicated Typhoid Fever in Children and Adolescents. *Clin Infect Dis*. 2004;38:951-957.

Frenck and colleagues randomized 68 children in Cairo with typhoid fever to treatment with either orally administered azithromycin (20 mg/kg po daily) or ceftriaxone (75 mg/kg IV daily), each for 5 days. The maximum daily doses allowed were 1000 mg and 2500 mg, respectively.

Both treatments were highly effective, with 94% of azithromycin and 97% of ceftriaxone recipients achieving clinical cure by day 7. The 2 clinical failures in the azithromycin group were due to mild gastrointestinal symptoms that resolved by 7 days without further intervention, and the single clinical failure in the ceftriaxone group was due to persisting fever, which also resolved without changes in management. The mean time to defervescence was 4.5 ± 1.9 days for azithromycin recipients and 3.6 ± 1.6 days for ceftriaxone recipients, a difference that was not statistically significant.

Only 1 patient, a ceftriaxone recipient, failed to achieve microbiologic cure. None of the isolates demonstrated in vitro resistance to ceftriaxone. The azithromycin MIC_{90} was 6 mcg/mL, with 7 isolates having an MIC > 8 mcg/mL, and thus considered resistant. Four of these 7 were recovered from patients randomized to receive azithromyin and, despite the in vitro results, all 4 were successfully treated with this azalide antibiotic.

Blood culture after 3 days of therapy was still positive in 12 of 31 (37.5%) patients treated with azithromycin, but in none of the 36 given ceftriaxone ($P = 0.0001$). Blood isolates from all 12 of those bacteremia persisting to day 3 on azithromycin remained susceptible to this antibiotic. All 12 patients were asymptomatic by the time the results of the blood culture were known. The only positive blood culture at day 8 was in a ceftriaxone recipient.

Bacteremic relapse after hospital discharge was detected in 5 patients, all of whom had been treated with ceftriaxone; each isolate remained susceptible in vitro to this antibiotic. Stool cultures were negative in all patients examined at a follow-up visit at 1 month. Both treatments were well tolerated.

COMMENT BY STAN DERESINSKI, MD, FACP

It is estimated that 16 million cases of typhoid fever occur each year in the

world. Unfortunately, many strains of *Salmonella enterica* serovar Typhi have acquired resistance to a number of antibiotics commonly used for treatment of this infection, resulting in the emergence of multidrug resistance (although this problem appears to be inexplicably receding in some areas).[1] Such isolates are commonly resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. Of great concern, is the decreasing susceptibility to fluoroquinolones.

While frank in vitro resistance (the NCCLS breakpoint is 4 mcg/mL) to fluoroquinolones among *S. enterica* serovar Typhi remains uncommon, reduced susceptibility is increasingly common. In 1998, 19% of isolates had an MIC to ciprofloxacin ≥ 0.25 mcg/mL; most were from the Indian subcontinent.[2] While these would be reported as susceptible, most are resistant to nalidixic acid, providing a clue to reduced fluoroquinolone susceptibility.

Treatment of typhoid fever due to infection with such isolates as ciprofloxacin has been associated with an increase in time to defervescence and a need for prolongation of therapy and, in some cases, with frank therapeutic failure.

The Sanford guide currently recommends treatment of typhoid fever with either ciprofloxacin or ceftriaxone, listing azithromycin as an alternative choice. Ceftriaxone of course, can only be administered parenterally.

The current study confirms, previous studies that used a longer duration of antibiotic administration, that azithromycin is an excellent choice for the treatment of typhoid fever. In this study, clinical cure rates did not differ between azithromycin and ceftriaxone recipients, despite a longer duration of bacteremia in the former group. On the other hand, no bacteremic relapses were detected among the azithromycin recipients, in contrast to a 14% relapse rate in ceftriaxone recipients, a finding seen in previous evaluations of this antibiotic.

The longer duration of bacteremia in azithromycin recipients may be due to a number of factors, including the relatively low serum concentrations achieved with this drug and the presumed more rapid bactericidal activity of ceftriaxone. The absence of relapses in azithromycin recipients may be related to the extraordinarily high intracellular concentrations achieved with this drug, and the fact that Salmonella is an intracellular pathogen. These high intracellular concentrations may also account for the success of therapy in a number of cases, despite in vitro susceptibility test results that are interpreted by NCCLS standards as indicating resistance.

The increasing resistance of bacterial enteric pathogens to fluoroquinolones in some parts of the world, including the Indian subcontinent and southeast Asia, raises concern regarding the optimal self-treatment for travelers' diarrhea. The recent FDA approval of rifaximin provides a novel

Travel Medicine Advisor is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd. NE, Six Piedmont Center, Suite 400, Atlanta, GA 30305.
POSTMASTER: Send address changes to *Travel Medicine Advisor,* P.O. Box 740059, Atlanta, GA 30374.
Customer Service: 1-800-688-2421.

Subscription Information: *Travel Medicine Advisor* is a monthly supplement to *Travel Medicine Advisor* looseleaf service. Price: $429 (includes *Travel Medicine Advisor* looseleaf reference manual plus one-year subscription to *Travel Medicine Advisor Update*.) To subscribe, **call 1-800-688-2421.**

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Bia is a consultant for GlaxoSmithKline and Bristol Myers Squibb. Dr. Barry is a consultant with the Ford Foundation and receives funds from Johnson & Johnson for academic programs. Dr. Hill reports a speaker's bureau relationship with Chiron and Merck. Dr. Jong is a consultant with Berna-Vaccines, is on the speaker's bureau of Aventis and GlaxoSmithKline, and is involved in research with Merck. Dr. Keystone is a consultant for Merck, on the speaker's bureau of GlaxoSmithKline and is involved in research with Roche. Dr. Mileno is a consultant with GlaxoSmithKline and is involved in research with Merck. Dr. Chen, Dr. Fischer, Dr. Scully, and Ms. Hynes report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

alternative, but this rifampin derivative has a more limited antibacterial spectrum and is poorly absorbed from the gastrointestinal tract.[3] Azithromycin may prove a better choice in some instances, and would have the potential to abort cases of typhoid fever in travelers. ■

This article was published in the October 2004 issue of Infectious Disease Alert.

References

1. Parry CM. Typhoid Fever. *Curr Infect Dis Reports*. 2004;6:27-33.
2. Threlfall EJ, et al. Ciprofloxacin-Resistant Salmonella typhi and Treatment Failure. *Lancet*. 1999;353: 1590-1591.
3. Rifaximin (Xifaxan) for Travelers' Diarrhea. *Med Lett*. 2004;46:74-75.

Treatment of Latent TB: A High Priority

By Carol A. Kemper, MD, FACP

Source: Horsburgh CR Jr. *N Engl J Med*. 2004;350: 2060-2067.

Reduction in the number of cases of TB in the United States is one of the United States Public Health Department's highest priorities. In order to achieve this goal, the numbers of patients who undergo testing and treatment for latent TB must be increased. Dr. Horsburgh says he's always encouraged patients to accept treatment by providing a rough estimate of their lifetime risk of reactivation (~5-10%), but specifically encourages 3 groups of patients, irrespective of age, to accept treatment: those with 1) recent skin test conversion, 2) evidence of old healed disease on chest radiograph, or 3) those with immunosuppression, corticosteroid use, or HIV. Of course, any infant or child < 5 years of age with household exposure should be presumptively treated with INH; such patients are at high risk for primary progressive disease, and it is too late to wait for skin test conversion.

It has always been assumed that the risk of reactivation is generally greatest in the 2-3 years following conversion, then begins to decrease over the next decade, and remains fairly stable at low levels thereafter. Recent data suggests that ~10% of patients lose their tuberculin reactivity each decade; these individuals do not contribute to the overall risk of reactivation TB. Therefore, estimates of the risk of reactivation may actually be lower than previously assumed especially in younger persons, but the effect of this statistical finding on risk diminishes as patients age.

Believing that more precise information on the risk of reactivation can allow clinicians to target groups at highest risk, Dr. Horsburgh constructed a risk model based on age, degree of induration on tuberculin skin test, and whether there was recent conversion, evidence of old healed TB, immunosuppressive therapy, or HIV. Five groups at significant lifetime risk for reactivation TB were identified: 1) children ≤5 years of age with ≥ 10 mm of induration have a 10-20% risk; 2) younger persons ≤35 years of age with ≥ 15 mm of induration and recent conversion have a 10-20% risk; 3) younger persons ≤35 years of age with ≥ 15 mm of induration receiving immunosuppressive therapy have a 10-20% risk; 4) persons with ≥ 10 mm of induration and evidence of old healed TB have ≥ 20% risk.

Interestingly, in Horsburgh's model, persons > 66 years of age have < 10% risk of reactivation under any circumstance (except HIV infection); this suggests that it may be reasonable to defer treatment in persons over the age of 65.

Dr. Horsburgh suspects the reason that too few patients are treated for latent TB is because clinicians still have 3 bad rules stuck in their heads: these include patients with a history of a positive test for many years do not need treatment, a history of BCG means you don't need treatment, you have a false-positive PPD, and anyone older than 35 is at higher risk for side effects and should not be treated. This backwards approach ensures that immigrants from a country endemic for TB (especially one where BCG is common), and anyone over the age of 35, is less likely to receive treatment for latent TB, even if they have risk factors. Confronting these fallacies, convincing clinicians that the benefits of INH prophylaxis outweigh the risks, disregarding a history of BCG, and keeping the rules of who should be treated as simple as possible may ensure that more patients receive treatment for latent TB. ■

This article was published in the October 2004 issue of Infectious Disease Alert.

Ground Castor Beans Put in Tampered Baby Food Jars

Domestic terror scare does not involve refined ricin.

In what appears to be a relatively crude attempt at domestic bioterrorism, ground-up remnants of castor beans were found in 2 baby food jars in Irvine, CA.

Although ricin can be purified through chemical extraction processes from castor beans, the material found in these jars was far less toxic than purified ricin, the Food and Drug Administration (FDA) reported.

Contrary to the impression given by some early reports, the FDA did not find purified ricin in the baby food jars, the agency stressed in a news release posted on its web site.

To date, no injuries have been reported, and the prob-

lems seem to be isolated within the immediate Irvine area. Nevertheless, consumers who find anything suspicious concerning the packaging or contents of baby food products should not feed it to anyone, but instead notify their local FDA office.

Look for Lid Safety

As with all baby foods, caregivers should carefully examine all food product packaging, including such anti-tampering devices as lid safety buttons. According to a published report in the Orange County Register, a 47-year-old transient man was being sought for questioning in the case. Two sets of parents found threatening notes inside jars of Gerber Banana Yogurt Dessert fed to their infants. A third jar containing the same note couldn't be tested because 1 father washed out the food after his 11-month-old son had eaten some. The boy, and a 9-month-old girl who ate from a separate jar, were not harmed.

Notes inside the jars, purchased May 31 and June 16 at an Irvine supermarket, were wrapped in cellophane. They implied that an Irvine police officer had planted the message. Confirmation of the mashed castor beans took weeks because the food was sent to the Orange County Crime Lab for forensic analysis and then to the FDA to test for chemical contents, officials said.

For more information on food tampering, go to FDAs web page at www.cfsan.fda.gov/~dms/ fstamper.html. ■

This article was published in the September 2004 issue of Bioterrorism Watch.

Nitazoxanide Tablets for Giardiasis

By Stan Deresinski, MD, FACP

NITAZOXANIDE (ALINIA™) IS A BROAD SPECTRUM antiparasitic agent, previously approved for use as an oral suspension for the treatment of cryptosporidiosis and giardiasis in children.[1] It has now received FDA approval as a 500 tablet for the treatment of giardiasis in adolescents and adults.[2]

Clinical response rates to treatment with nitazoxanide tablets in a double-blind, controlled trial in Peru and Egypt, with diarrhea caused by *Giardia duodenalis* lamblia, was 85% (46/54) compared to 44% (12/27) in placebo recipients. Cysts persisted in the stools of some clinical responders, however. Response rates to the oral suspension in children have been similar.[2]

Nitazoxanide, a nitrothiazolyl-salicylamide derivative, is a prodrug that is rapidly hydrolyzed to tizoxanide (desacetyl-nitazoxonide), which is then glucuronidated, with both metabolites being the active forms of the drug.[4] Tizoxanide, which is > 99% bound to plasma proteins, appears to not have an inhibitory effect on cytochrome P450 enzymes.

The tablet and oral suspensions are not bioequivalent; the latter has only 70% relative bioavailability. Administration of the tablets with food is associated with an almost 2-fold increase in AUC and approximately 50% increase in Cmax of the active metabolites; the food effect is significantly less with the oral suspension. Overall, approximatley two-thirds of an oral dose of nitazoxanide is excreted as its metabolites in feces, and one-third in urine. In adults greater than 17 years of age, the Cmax of tizoxanide and tizoxanide glucuronide after administration of a singly 500 mg table with food is 10.6 ± 2.0 mcg/mL and 10.5 ± 1.4 mcg/mL, respectively. The pharmacokinetics of nitazoxanide have not been evaluated in patients with impaired renal or hepatic function.

The active metabolites of nitazoxanide are believed to interfere with the pyruvate:ferredoxin oxidoreductase enzyme-dependent electron transfer reaction. Other undefined pathways may also important. Nitazoxanide appears to be well tolerated, and is a Pregnancy Category B drug.

Other drugs available for the treatment of giardiasis include metronidazole (which has never received FDA approval for this indication), paromomycin (also not FDA-approved for this infection), and furazolidone. Quinacrine is available through some compounding pharmacies. Tinidazole had recently received approval as a single 2 gram dose for treatment of giardiasis in adults. Albendazole also has activity in patients with giardiasis.[5] The most recent recommendations of *The Medical Letter,* for the treatment of giardiasis in adults, list 3 drugs of choice: metronidazole (250 mg tid x 5d), nitazoxanide (500 mg bid x 3d), and tinidazole (2 grams once) (ML).[6] Three alternatives are listed: paromomycin, furazolidone, and quinacrine.

Overall, nitazoxanide is an useful, albeit expensive, addition to our therapeutic options in the management of patients with giardiasis. ■

This article was published in the October 2004 issue of Infectious Disease Alert.

References

1. Kemper CA. New FDA-Approved Agent for Cryptosporidiosis. *Infect Dis Alert*. June 15, 2002.
2. Alinia. http://www.fda.gov.
3. Nitazoxanide. *Med Lett*. 2003;45:29-31.
4. Bailey JM, et al. Nitazoxanide Treatment for Giardiasis and Cryptosporidiosis in Children. *Ann Pharmacother*. 2004;38:634-640.
5. Karabay O, et al. Albendazole vs Metronidazole Treatment of Adult Giardiasis: An Open Randomized Study. *World J Gastroenterol*. 2004;10:1215-1217.
6. Drugs for Parasitic Infections. *Med Lett*. August 2004.