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Cutaneous Leishmaniasis in US Military, 2002-2003

ABSTRACT & COMMENTARY

Synopsis: *As a result of the recent military conflicts, cutaneous leishmaniasis has emerged as a significant disease among US troops deployed in Iraq, Afghanistan, and Kuwait. Physicians should consider the possibility of cutaneous leishmaniasis in persons with chronic skin lesions who have traveled to or been deployed within areas where leishmaniasis is endemic.*

Source: Cutaneous leishmaniasis in US military personnel—Southwest/Central Asia, 2002-2003. *MMWR Morb Mortal Wkly Rep*. 2003;52(42):1009-1012.

DURING AUGUST 2002 THROUGH SEPTEMBER 2003, THE WALTER REED ARMY Medical Center (WRAMC) identified 22 cases of cutaneous leishmaniasis (CL) among military personal involved in Operation Iraqi and Enduring Freedom. Of these 22 cases that were parasitologically confirmed, 21 (95%) were males with a median age of 29 years. The cases emerged from within multiple branches of the US military, including the Active Force, Reserve, and National Guard components of the Army, Air Force, and Marine Corps. Eighteen of the 22 cases were most likely infected in Iraq—apparently in the urban and periurban areas of An Nasiriyah and Baghdad. Two cases were probably infected in areas of Kuwait adjacent to Iraq, and the remaining 2 cases were infected in Afghanistan. As of October 20, 2003, those skin cultures with sufficient organisms for species identification were found to contain *Leishmania major*.

Upon initial evaluation at WRAMC, these 22 cases had a median of 3 skin lesions, ranging in size from 3 mm to 44 mm and were more often located on the upper (39%) or lower (32%) extremities than on the trunk/back (16%) or face/neck (13%). As is typical of CL, the lesions were most often painless, had enlarged slowly with eventual central ulceration, and were sometimes covered by an eschar, surrounded by an erythematous, indurated border. None of the cases had systemic symptoms to suggest either classic visceral leishmaniasis, or the so-called viscerotropic leishmaniasis caused by *L tropica* described after Operations Desert Storm and Shield during 1990-1991.

As of October 7, 2003, approximately 24,000 female phlebotomine sand flies, the vectors of leishmanial parasites, were collected in Iraq, using light traps, then tested for leishmania organisms by fluorogenic PCR; about 1 in 70 sand flies carried the parasite (1.4%). Many of the US military have reported numerous bites from sand flies, with some personnel reporting more than 100 bites in a single night.

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Sodium stibogluconate (Pentostam, 20 mg/kg/d IV for 20 days) was used to treat all 22 patients, and their lesions responded to treatment. Side effects that are well known to be reversible, yet associated with Pentostam, occurred. They included headache, fatigue, myalgias, arthalgias, and chemical pancreatitis.

COMMENT BY MARY-LOUISE SCULLY, MD

The most notable clinical syndromes of leishmaniasis may include visceral, cutaneous, and mucosal disease, resulting from the replication of the parasite within macrophages of the mononuclear phagocyte system, dermis, and naso-oropharyngeal mucosa, respectively. About 21 different leishmanial species, transmitted by more than 30 species of phlebotomine sand flies, account for the diversity and complexity of this disease and its treatment.[1]

For CL, one important component of the decision to treat is assessing the patient's risk for developing mucosal disease, a disfiguring potential complication of New World cutaneous leishmaniasis. Other considerations include the location of the lesions (ie, the face), the number of lesions, or their persistence. Old World cutaneous leishmaniasis, such as disease from *L major*, can heal slowly even without any specific treatment.

There is no ideal therapy identified for all CL, but 2 pentavalent antimonials, either sodium stibogluconate (Pentostam) or meglumine antimoniate (Glucantime), remain the mainstays of treatment. Antimonials must be given parentally; they may be associated with QT prolongation and EKG abnormalities, and have reversible hepatic, renal, and hematologic side effects. Toxicity to pentavalent antimonials usually is cumulative but side effects such as nausea can occur earlier. Myalgias, arthralgias, fatigue, headache, and chemical pancreatitis can occur as well.

There is a plethora of studies regarding other potential treatments of CL, but the studies are often small, uncontrolled, or based on anecdotal data. Therefore, one should be cautious in interpreting these studies and extrapolating the results to other leishmania species in different geographic settings. One randomized, double-blind, placebo-controlled trial of *L major* in Saudi Arabia assessed the efficacy of 200 mg of fluconazole daily for 6 weeks vs placebo.[2] Despite some *in vitro* studies showing poor activity of fluconazole against various leishmania species, including *L major*, the authors felt that the long half-life of fluconazole, its high solubility in water and a concentration in skin that is 10 times that of plasma, made it a worthwhile drug to evaluate. The results did show a significantly quicker time to healing in the fluconazole group (8.5 weeks vs 11.2 weeks in controls). Again, this study evaluated CL caused only by *L major* in Saudi Arabia, and CL lesions of *L major* do eventually heal without treatment.

Studies of potential treatments have also included itraconazole,[3] ketoconazole,[4] topical paramomycin, liposomal amphotericin,[5] and even thermotherapy;[5] all with varying degrees of success. The British have experienced good success rates in many cases of Old World CL using *intralesional* stibogluconate (personal communication, D. Lockwood). In the United States, the standard remains parenteral Pentostam. However, even Pentostam treatment can result in cases of clinical failure or relapses of New World CL.[6] Clearly, this is a disease in need of more straightforward and efficacious treatment.

The World Health Organization estimates that 1.5 million cases of CL occur each year. The military troops returning from Iraq comprise a group at risk for CL. Since this published report a month ago, there have been more than 140 cases of CL reported in the military and this number is expected to rise. In addition, the expanding tourist industry with travel to Costa Rica, Belize, and other parts of Central America, has led to an increase in cases of New World CL in civilian travelers to these areas. CL can occur following relatively short stays in leishmaniasis-endemic areas, and pretravel consultation should include advice to travelers to these destinations to use personal protection measures for the prevention of leishmaniasis. Both the WRAMC and the CDC provide diagnostic services and will provide the sodium stibogluconate for treatment. Health care providers should contact WRAMC (202-782-6740) for treatment of the military or their families, or the CDC's drug service (404-639-3670) for treatment of civilians. ■

References

1. Herwaldt B. Leishmaniasis. *Lancet*. 1999;354: 1191-1199.
2. Alrajhi AA, et al. Fluconazole for the treatment of cutaneous leishmaniasis caused by *Leishmania major*. *N Engl J Med*. 2002;346:891-895.
3. Momeni AZ. Treatment of cutaneous leishmaniasis with itraconazole. Randomized double-blind study. *Arch Dermatol*. 1996;132:784-786.
4. Saenz RE. Efficacy of ketoconazole against *Leishmania braziliensis* panamensis cutaneous leishmaniasis. *Am J Med*. 1990;89(2):147-155.
5. Berman J. Current treatment approaches to leishmaniasis. *Curr Opin Infect Dis*. 2003;16(5):397-401.
6. Reithinger R, et al. *Am Jour Trop Med Hyg*. 2003;69(3):548-549(Abstract # 776).
7. Lawn SD, et al. *Am Jour Trop Med Hyg*. 2003;69(3):264 (Abstract # 165).

Insects, Malaria, and Children

ABSTRACT & COMMENTARY

Synopsis: *Families traveling with infants and children should be aggressive about malaria prevention using DEET, permethrin, and chemoprophylaxis. Both this review and that of associate editor, Lin Chen, MD, in this issue underscore the importance of bednets and repellents as critical components of malaria prophylaxis*

Source: Stauffer WM, et al. Traveling with infants and children. Part IV: Insect avoidance and malaria prevention. *J Travel Med*. 2003;10:225-240.

Traveling children are at risk for insect bites and insect-born diseases. Children should be dressed with clothes covering arms and legs and should avoid the use of products with flowery scents. Spending dusk to dawn indoors behind screened windows or in air-conditioned areas decreases the risk of insect bites. Mosquito netting impregnated with permethrin or deltamethrine should be used. DEET (N,N-diethyl-meta-toluamide) is the safest, most thoroughly studied, and most effective chemical repellent currently available and should be applied to exposed skin, while avoiding potential contact with the eyes or mouth. Age and weight, as well as itinerary, figure into the choice of a chemoprophylactic agent.

COMMENT BY PHILIP R. FISCHER, MD, DTM&H

Preparation for international travel with infants and children can be stressful. What is a family to do? What is a travel medicine practitioner to do? Once again, Stauffer and colleagues have provided practically relevant, academically sound guidance to facilitate safe and healthy travel for infants, children, and adolescents. Previous review articles dealt with general anticipatory guidance,[1] immunizations,[2] and travelers' diarrhea.[3] Now, the last segment of this helpful series is a well-documented (125 references) overview of insect avoidance and malaria prevention.

Personal Protection Barriers

Personal protective measures are appropriate for all travelers to malarial areas and are the primary prevention strategy for infants. Without independent mobility during the first several months of life, babies are directly dependent on the microenvironment established by their parents and adult traveling companions. Insect-free areas can be provided through the use of physical barriers. Permethrin-impregnated netting can be spread over car seats, cribs, playpens, strollers, and even backpacks. Self-supporting netted "tents" are easily portable for use in a variety of settings.

Older children and adolescents can also choose to avoid outdoor activities between dusk and dawn. They can participate in the selection of comfortable clothing that covers most of their skin. The use of bed nets, screened windows, or air conditioning should be encouraged during sleeping times for travelers of all ages.

Chemical Barriers

A variety of chemical agents are used for children, but efficacy varies. While other agents might be considered in settings where mosquito bites are merely a nuisance, Stauffer's group suggests that DEET is the only repellent currently available that should be recommended for use with infants and children in malarious areas. A 30-35% solution is preferred. DEET is safe when used appropriately. Apply first to hands of caregivers and then to the child; avoid application to eyes or parts of hands that might come into contact with eyes or mouths; use only on intact exposed skin, and rinse off when returning to a protected environment. Adverse events have been very rarely reported in children using DEET, but there is no evidence that the risk for adverse events of correctly used DEET is linked to age.

Picaridin (LBR3023, Bayrepel) is available in some countries for use in children older than 2 years of age but does not seem to have any distinct advantage over DEET. Other "repellents," such as those containing citronella, provide only modest protection for short periods of time. Toxicity has rarely been reported with citronella.

Permethrin is a safe and effective contact insecticide. It can be applied to clothes and bednets and may be air-dried and then used 4 or more hours after the application. Permethrin is safe for use on clothes and nets of children of all ages.

Chemoprophylaxis

The itinerary-based indications for malaria chemoprophylaxis are the same for children as for adults. Age-specific and weight-based dosing considerations, however, are important. For instance, doxycycline is not advised for children younger than 8 years of age, and the combination of atovaquone and proguanil is not officially recommended for children weighing less than 11 kg.

Chloroquine is still appropriate chemoprophylaxis in a few areas of the world. It is given in a weekly oral dose of 5 mg base per kg body weight (maximum of 300 mg base per weekly dose) beginning 1 week prior to travel and continuing until the child has been out of the malaria area for 4 weeks. The bitter-tasting tablets can be crushed

and mixed with a palatable food for use in children. A liquid formulation is available in Europe and some other parts of the world.

Mefloquine is similarly used in a bitter-tasting 5 mg/kg weekly oral dose (maximum, 250 mg) beginning 1-2 weeks before travel and continuing until 4 weeks after leaving the malaria area. As with chloroquine, compounding pharmacies can help prepare exact doses for infants, and older children may approximate the dose upward to the nearest quarter pill. Side effects seem to be less common and less bothersome in children than in adults, but specific data are lacking. As for adults, children are not advised to use prophylactic mefloquine if they have an active seizure disorder, psychiatric illness, or cardiac conduction abnormalities. Mefloquine would not be contraindicated in children with a remote (but not recent) history of febrile seizures and in children with isolated attention deficit disorders.

Atovaquone-proguanil provides effective malarial prophylaxis in children. It is given daily, beginning 1-2 days prior to arrival in a malarial area and continuing for 7 days after leaving the malarial area in a weight-adjusted dose ("pediatric pills" contain 62.5 mg atovaquone and 25 mg proguanil; 1 pill daily if 11-20 kg, 2 if 21-30 kg, 3 if 31-40 kg, 4 or an equivalent single "adult pill" if more than 40 kg). It is less bitter than chloroquine and mefloquine but is not available in a liquid form. Emerging data suggest safety and efficacy in small infants, but it is not yet routinely advised for children weighing less than 11 kg. Doxycycline can cause cosmetically important dental staining if used in children younger than 8 years of age. Otherwise, it is used as for adults with a 2 mg/kg daily dose up to the adult 100-mg dose limit.

The use of "standby treatment" when symptoms of malaria begin is controversial in children. Ideally, a febrile child who has been exposed to malaria should be immediately provided with good medical care. If that is not possible, atovaquone-proguanil could be a preferred agent for *presumptive* treatment while en route to medical care.

Lactating mothers on prophylaxis do pass some medicine on to nursing children. The amount of medication, however, is not felt to be harmful to the child. Conversely, the amount transferred does not confer adequate protection to the child. Infants should receive standard chemoprophylaxis dosing, whether they are nursing or not.

Indeed, giving pretravel advice to families traveling with children can be a daunting task. Stauffer et al have helpfully contributed another useful review to the literature. This gives travel medicine practitioners specific, directed guidance in helping traveling families prevent insect bites and malaria in children. Implementing this information should help increase family comfort and decrease pediatric morbidity. ■

References

1. Stauffer WM, et al. Traveling with infants and young children. Part I: Anticipatory guidance: Travel preparation and preventive health advice. *J Travel Med*. 2001;8:254-259.
2. Stauffer WM, Kamat D. Traveling with infants and children. Part 2: immunizations. *J Travel Med*. 2002;9:82-90.
3. Stauffer WM, et al. Traveling with infants and young children. Part III: travelers' diarrhea. *J Travel Med*. 2002;9:141-150.

Bed Nets and Decreased *Plasmodium falciparum* Resistance

ABSTRACT & COMMENTARY

Synopsis: *A village in Tanzania has been found to have a decreased prevalence of* P falciparum *infections and an increased prevalence of wild type dihydrofolate reductase malaria parasites following the widespread use of permethrin-treated bed nets. The use of insecticide-treated bed nets is known to be an effective measure in the control of malaria; its possible role in reversing the trend toward increasing drug resistance is both encouraging and warrants further evaluation. Travel medicine providers should be aware of the ecological implications of their recommendations for malaria prevention.*

Source: Alifrangis M, et al. Increasing prevalence of wild types in the dihydrofolate reductase gene of *Plasmodium falciparum* in an area with high levels of sulfadoxine/pyrimethamine resistance after introduction of treated bed nets. *Am J Trop Med Hyg*. 2003;69(3):238-243.

Two villages in northeastern Tanzania with intense malaria transmission were monitored for resistance to sulfadoxine/pyrimethamine from 1998 to 2000. The 2 villages, Magoda and Mpapayu, are located 2 kilometers apart. Permethrin-treated bed nets were distributed to all households in Magoda village in 1998, while deltamethrin-treated bed nets were distributed to Mpapayu village during 2001. Study subjects were between 6 months and 5 years of age. Blood samples were collected during microscopic examination for malaria parasites, clonality assessment of *P falciparum*

by PCR typing of merozoite surface protein 1 (msp1) and msp2 genes, and dihydrofolate/dihydropteroate synthetase (*dhfr/dhps*) genotyping.

The prevalence of *P falciparum* infections decreased significantly in both villages between 1998 and 1999, when assessed by microscopy; this was attributed to a decrease in rainfall in 1999. The *P falciparum* density (measured as parasites/mL) was lower in Magoda compared to Mpapayu in 1999 and 2000. The estimated mean number of clones per infection showed a greater decrease in Magoda from 1998 to 2000 when compared to Mpapayu.

In Magoda, the prevalence of wild dhfr genotypes at codons 51, 59, and 108 increased from 1998 to 2000, while in Mpapayu, the prevalence of wild genotypes remained constant. The prevalence of wild dhps genotypes at codon 540 increased more in Magoda than Mpapayu in 2000. However, such changes did not occur at codons 436 and 437. In fact, there was an increase in the prevalence of mutant type infections at codon 437 in Magoda in 2000.

Insecticide-treated bed nets appeared to favor wild *dhfr* genotype parasites as well as to reduce parasite density and the prevalence of *P falciparum* infections. Alifrangis and colleagues suggest that insecticide-treated bed nets lowered malaria transmission, reduced the prevalence of infections, and led to less frequent use of sulfadoxine/pyrimethamine. As a result, the sulfadoxine/pyrimethamine drug pressure decreased, which may have led to the selection of wild type parasites sensitive to sulfadoxine/pyrimethamine.

COMMENT BY LIN H. CHEN, MD

P falciparum drug resistance continues to spread. Tanzania has changed its first-line antimalarial therapy from chloroquine to sulfadoxine/pyrimethamine because of widespread chloroquine resistance. However, sulfadoxine-pyrimethamine resistance is well documented. Point mutations in the *dhfr* and *dhps* genes result in reduced drug-binding affinities for dihydrofolate reductase and dihydropteroate synthetase, respectively.[1] As the authors have summarized, mutations in codons 51, 59, 108, and 164 in the *dhfr* gene lead to pyrimethamine resistance, and mutations in codons 436, 437, 540, 581, and 613 of the *dhps* gene lead to sulfadoxine resistance.

The study by Alifrangis et al is intriguing in showing the different trends of *P falciparum* infection prevalence, parasite density, clone multiplicity, and *dhfr/dhps* genotypes between the 2 villages that are only 2 kilometers apart. The use of insecticide-treated bed nets appears to have a positive effect in reducing the prevalence of infection and parasite density as well as selecting for wild *dhfr* genotype parasites. The results suggest that it may be possible to reverse the drug resistance in some areas by reducing antimalarial drug pressures.

Numerous studies have supported the efficacy of insecticide-treated bed nets in the control of malaria. In addition to reduced numbers of mosquito bites experienced by the individual net user, the use of insecticide-treated bed nets is associated with a reduction in mosquito bites outside of nets due to mass killing of mosquitoes.[2,3] Therefore, in villages where nets are widely used, entire communities benefit from an overall reduction in malaria.[2,3] The Alifrangis study illustrates the reduction in malaria prevalence. Moreover, the results support the selection for wild *dhfr* genotypes over mutant genotypes when insecticide-treated bed nets are used, possibly because of reduced drug pressure. The reversal of drug resistance trends may be an additional reason to promote the widespread use of insecticide-treated bed nets, but further studies are needed to confirm this finding.

It is also of concern that there is emerging resistance to insecticides. Pyrethroid resistance has been reported from Asia, Africa, and South America, although the resistance is more likely to arise from agricultural insecticide use than insecticide-treated nets.[4] In Africa, pyrethroid resistance has been found among *Anopheles gambiae* sensu lato mosquitos in Côte d'Ivoire, Benin, and Burkina Faso, but not in Cameroon, Senegal, and Botswana.[5] Some studies have indicated protection against malaria when untreated bed nets in good condition are used.[6] It is possible that the physical barrier of nets, even untreated, may contribute to the reduction of infection with *P falciparum* and the increase in the wild type parasites in the Alifrangis study. This issue also needs further exploration. ■

References

1. Wongsrichanalai C, et al. Epidemiology of drug-resistant malaria. *Lancet Infect Dis*. 2002;2:209-218.
2. Maxwell CA, et al. Effect of community-wide use of insecticide-treated nets for 3-4 years on malarial morbidity in Tanzania. *Trop Med Int Health*. 2002; 7(12):1003-1008.
3. Howard SC, et al. Evidence for a mass community effect of insecticide-treated bednets on the incidence of malaria on the Kenyan coast. *Trans Royal Soc Trop Med Hyg*. 2000;94:357-360.
4. Takken W. Do insecticide-treated bednets have an effect on malaria vectors? *Trop Med Int Health*. 2002;7(12):1022-1030.
5. Chandre F, et al. Status of pyrethroid resistance in *Anopheles gambiae* sensu lato. *Bull World Health Organ*. 1999;77(3):230-234.
6. Clarke SE, et al. Do untreated bednets protect against malaria? *Trans Royal Soc Trop Med Hyg*. 2001;95: 457-462.

Infants in Airplanes: Safety Seats, Statistics, and Common Sense

ABSTRACT & COMMENTARY

Synopsis: *Despite widespread debate and broad recommendations from professional organizations, careful risk and cost analyses do not support policies mandating the use of infant safety seats on commercial aircraft.*

Source: Newman TB, et al. Effects and costs of requiring child-restraint systems for young children traveling on commercial airplanes. *Arch Pediatr Adolesc Med*. 2003;157: 969-974.

WOULD LIVES BE SAVED AT A REASONABLE COST IF it were required that all infants be restrained in safety seats while on airplanes? Using carefully planned and explained assumptions and calculations, Newman and colleagues found that there would be about 0.4 (range from 0.05 to 1.6 depending on the specifics of the assumptions made) deaths of young children prevented each year in the United States by the use of restraint systems. However, it is postulated that the increased cost for airfare required for children, who would otherwise ride "free" in a companion's lap, might stimulate some families to choose road travel, thus incurring greater risk of death in traffic accidents. The break-even point for which safety seat use would actually prevent overall deaths would be if 1% of children were diverted from air to car travel because of the cost or hassle of using safety seats onboard. If more than 1% of families responded to a safety seat requirement by choosing road over air travel, the legislation could actually promote more infant deaths.

But, what if no children were diverted from air to road travel? In that case, lives would be saved—at a cost. Estimating that the additional cost per child traveler for ticketing of the aircraft seat and for the safety seat was only $200 (a conservative underestimation), it would still cost about $43 million for each life-year saved and $1.3 billion for each life saved. Newman et al poignantly conclude by saying that: "Unless space for young children in restraint seats can be provided at low cost to families, with little or no diversion to automobile travel, a policy requiring restraint seat use could cause a net increase in deaths. Even excluding this possibility, the cost of the proposed policy per death prevented is high."

COMMENT BY PHILIP R. FISCHER, MD, DTM&H

Tragically, some children die a preventable death when they are incompletely restrained in crashing airplanes. In fact, it has been suggested that an American child's life would be saved every 2 years by requiring the use of child restraint systems on aircraft. In 1995, the US Federal Aviation Administration (FAA) suggested that these saved lives might be costly. In fact, the FAA calculated that the increased cost of air travel, when ticketed seats would be needed for restrained children, would prompt enough children (likely 5-10%) to divert from air to road travel and that an additional 10 children would die each year due to automobile crashes.

Consumer advocates Ralph Nader and Wesley Smith wrote that the FAA position was "unreasonable on its face and ridiculous in its justification." Also disagreeing with the FAA calculations, the US National Transportation Safety Board has for 3 years wanted to mandate the use of safety seats for children traveling by air. Two years ago, the American Academy of Pediatrics acknowledged a lack of data about the risk of diverting air travelers to more dangerous road routes but urged a requirement for air safety systems anyway. The AAP said that "all children need their own seats on airplanes—and children under the age of 2 or weighing less than 40 pounds, should be securely fastened in child restraint seats on planes." Now, as the FAA is planning to implement a new regulation requiring children younger than 2 years to ride in approved child-restraint seats on airplanes, Newman et al finally provide convincing data that could serve as an evidence base from which to refute such legislation.

Karl Neumann, in some senses the "father of pediatric travel medicine," presented practical advice during the Pediatric Travel Symposium at the recent annual meeting of the American Society of Tropical Medicine and Hygiene in Philadelphia. He made several relevant comments as he discussed the safety of traveling by air. First, "safety is no accident." Families should prepare wisely for safe air travel. Second, children "are the only things on planes that are not restrained." We should want to keep children restrained appropriately. Finally, though, Neumann said "ground transportation is very much more dangerous" and noted that requiring safety seats could indeed increase overall childhood deaths.

So, what is a travel medicine practitioner to do? None of us wants to allow a child to die in a survivable airplane crash. We should encourage families traveling with children to appropriately restrain their children. For infants, this would involve using an FAA-approved restraint (and not all car seats are appropriate for airplanes) in a ticketed seat. Families deterred by the cost, however, should be reminded that even restrained car travel is riskier than unrestrained air travel; they should not increase a child's

risk by driving unnecessarily. However, if aircraft restraints are legislated we must study the outcomes of such legislation. If Newman's statement proves to be correct, we should be willing to change the requirement later if, indeed, it seems that more children are dying. At the same time, we should not hesitate to implement readily available, simpler, proven cost-effective interventions (such as car seats, malaria prevention, and vaccination) without which many traveling children already are suffering and dying unnecessarily. ■

Suggested Reading

1. American Academy of Pediatrics. Restraint use on aircraft. *Pediatrics*. 2001;108:1218-1221; and www.aap.org/advocacy/archives/novair.htm.
2. Bishai D. Hearts and minds and child restraints in airplanes. *Arch Pediatr Adolesc Med*. 2003;157:953-954.
3. Neumann K. Practical preparation of pediatric patients for foreign travel. Symposium 49: Pediatric Travel Medicine, 52nd Annual Meeting of the American Society of Tropical Medicine and Hygiene, Philadelphia, December 6, 2003.

A Fluoroquinolone Alert for Travelers with Type II Diabetes

BY MICHELE BARRY, MD

Synopsis: *The July 2003 edition of the Canadian Adverse Reaction Newsletter had received spontaneous reports of hypoglycemia (9) and hyperglycemia (7) associated with use of the fluoroquinolone, gatifloxacin (Tequin).*

Source: *Med Lett Drugs Ther*. 2003;45(1162):64.

A STUDY OF VARIOUS QUINOLONE AGENTS HAS BEEN shown in rats to increase insulin release from pancreatic islet cells.[1] Several cases of severe hypoglycemia associated with gatifloxacin use have been published. In 1 report, severe hypoglycemia in 3 elderly patients was refractory to IV dextrose.[2] Most of the patients in these reports have experienced hypoglycemia as seen in type 2 diabetics while taking oral hypoglycemic agents. No pharmacokinetic interactions between gatifloxacin and oral hypoglycemic agents have been reported. Of interest, 2 elderly patients with no history of diabetes died from hypoglycemia while receiving gatifloxacin. The cause of their hypoglycemia was unknown.

Of all the fluoroquinolones in current usage, gatifloxacin has had the most adverse reports with respect to alterations in glucose metabolism. A study of gatifloxacin's effect on glucose metabolism in patients with type 2 diabetes, who were not taking oral hypoglycemics, showed a modest reduction of blood glucose levels and elevations of insulin levels in the first 6 hours after a single dose.[3] Perhaps we need to warn our type 2 diabetics taking fluoroquinolones, especially gatifloxacin (Tequin) for travelers' diarrhea, to watch their glucose levels more carefully for hypoglycemia. Often appetites are reduced with a traveler's diarrheal illness leading to an even higher predisposition to hypoglycemia.

And Another Reminder of Potential Fluoroquinolone Toxicity in Travelers

A 60-year-old woman was traveling to Nepal when she was diagnosed as having dermatomal herpes zoster. She was prescribed acyclovir tablets, acyclovir cream, cetirizine, and sparfloxacin. She subsequently developed a phototoxic reaction with severe "sunburn" blistering and bullae formation in sun-exposed areas. Her trip was canceled and she was started on corticosteroids.[4]

Sparfloxacin is a fluoroquinolone known to have significant phototoxic potential. Despite having been removed from markets in the west, it is freely available in South Asia. Clearly this traveler received over-treatment for her case of shingles since prophylactic antibiotics are not indicated. Cave and colleagues emphasize how inappropriate antibiotic treatment is common in developing countries. In a study they quote from India, drug use was unnecessary in 47% of the prescriptions and hazardous in 11%.[5] Travelers to South Asia should be advised about prescribing habits in the region. In a review of quinolones and side-effects levofloxacin has had the lowest rate of phototoxicity.[6] ■

References

1. Maeda N, et al. Increase in insulin release from rat pancreatic islets by quinolone antibiotics. *Br J Pharmacol*. 1996;117:372-376.
2. Menzies DJ, et al. Severe and persistent hypoglycemia due to gatifloxacin interaction with oral hypoglycemic agents. *Am J Med*. 2002;113:232-234.
3. Gajjar DA, et al. Effect of multiple-dose gatifloxacin or ciprofloxacin on glucose homeostasis and insulin production in patients with noninsulin-dependent diabetes mellitus maintained with diet and exercise. *Pharmacotherapy*. 2000;20(6 Pt 2) suppl:76S-86S.
4. Cave W, et al. Irrational prescribing in South Asia: A case of fluoroquinolone-associated phototoxicity. *J Travel Med*. 2003;10:290-292.
5. Phakde AR. The quality of prescribing in an Indian dis-

trict. *Nat Med J India*. 1996;9(2):60-65.
6. Rubenstein E. History of quinolones and their side effects. *Chemotherapy*. 2001;47(Suppl 3):3-8.

CME Questions

16. Which one of the following statements about cutaneous leishmaniasis is *incorrect*?

a. Appropriate treatment depends on accurate knowledge of the infecting Leishmania species and the geographic area where the disease was acquired.
b. New World cutaneous leishmaniasis has the potential to progress to disfiguring mucosal disease.
c. Pentavalent antimonials remain a mainstay of treatment despite their need for parenteral administration.
d. Old World cutaneous leishmaniasis, such as *L major*, can heal without drug treatment.
e. Azole drugs, such as fluconazole, have not shown efficacy against any form of cutaneous leishmaniasis.

17. Which of the following would *not* be appropriate for use in a 9-month-old visiting a malarious area?

a. 30% DEET
b. Permethrin-impregnated bed netting
c. Mefloquine
d. Doxycycline
e. Atovaquone/proguanin

18. Which one of the following statements is true?

a. *Plasmodium falciparum* parasites in Tanzania are still generally sensitive to sulfadoxine/pyrimethamine and chloroquine.
b. Drug resistance in malaria parasites arises from chromosomal mutations.
c. Sulfadoxine/pyrimethamine are still universally effective against *Plasmodium falciparum* parasites.
d. The mosquito vectors of malaria have not shown resistance to insecticides to date.
e. Bed nets have not been shown to be useful in preventing resistant forms of malaria.

19. Legislation requiring safety restraint systems for all young children traveling by air:

a. is the subject of extensive debate.
b. is currently in force in the United States.
c. would potentially prevent scores of American children from dying in survivable crashes each year.
d. would be cost-effective when compared to other preventive health interventions.
e. has already been shown to save at least 10 lives per million pediatric air miles traveled.

Answers: 16.(e); 17.(d); 18.(b); 19.(a)

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Travel Medicine Advisor*. Send your questions to: Robin Mason, *Travel Medicine Advisor*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Travel Medicine Advisor* via the internet by sending e-mail to robin.mason@ahcpub.com. ■