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Mercury Levels after Vaccination with Thimerosal-containing Vaccines

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD

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Dr. Jenson is on the speaker's bureau for Merck. This article originally appeared in the April 2008 issue of Infectious Disease Alert. *It was peer reviewed by Connie Price, MD, Assistant Professor, University of Colorado School of Medicine. Dr. Price reports no financial relationship relevant to this field of study.*

Synopsis: *Increased mercury levels following vaccination with thimerosal-containing vaccines were detected in blood with a peak at 0.5 to 1 day post-vaccination. The half-life was 3.7 days, with return to prevaccination levels by 30 days post-vaccination.*

Source: Pichichero ME, et al. Mercury levels in newborns and infants after receipt of thimerosal-containing vaccines. *Pediatrics*. 2008;121:e208-e214.

A PROSPECTIVE, OBSERVATIONAL STUDY WAS CONDUCTED IN BUENOS AIRES, Argentina, during 2003-2004 among 216 healthy infants > 32 weeks gestation who received age-appropriate immunizations, as routinely administered in Argentina. There were 3 groups: 72 newborns (group 1); 72 infants 2 months of age (group 2); and 72 infants 6 months of age (group 3). Total mercury levels were measured by atomic absorption in blood, stool, and urine samples taken before vaccination and, at one time, at a randomly assigned time point following vaccination. Half-life estimates were based on a 1-compartment, first-order pharmacokinetics model adjusted for the dosage of thimerosal in the vaccines and weight and age effects on volume and clearance.

Blood levels of mercury were detected at highest concentration in the samples immediately following vaccination. For groups 1, 2, and 3, respectively, the maximal mean + SD blood mercury levels were 5.0 ± 1.3, 3.6 ± 1.5, and 2.8 ± 0.9 ng/mL occurring at 0.5 days (group 1) to 1 day (groups 2 and 3) post-vaccination. Maximal mean + SD stool mercury levels were 19.1 ± 11.8, 37.0 ± 27.4, and 44.3 ± 23.9 ng/g occurring on day 5 post-vaccination. The blood mercury half-life was calculated to be 3.7 days for newborns, 2.0 days for 2-month-old infants, and 2.2 for 6-month-old infants; these half-lives were not significantly different. Blood mercury levels returned to prevaccination levels by 30 days post-vaccination.

Mercury as inorganic mercury was detected in most stool samples, and increased significantly after vaccination in all three groups. Mercury was not detected in urine. There was no elevation of urine GGT levels, a sensitive indi-

cator of damage to proximal renal tubules.

COMMENTARY

Thimerosal (sodium ethyl mercury thiosalicylate) has been used as a preservative in vaccines and other biologicals since the 1930s. Its antibacterial properties are attributed to the ethyl mercury that dissociates from the thimerosal molecule. The biology of ethyl mercury (CH3 CH2 Hg+) is poorly understood, and most exposure guidelines, such as from the US Environmental Protection Agency, are based on data of methyl mercury (CH3 Hg+). Both forms are readily transported to all tissues, and ethyl mercury has a shorter half-life.

In this study, mercury levels were relatively low in all age groups and were highest at 0.5 to 1 day post-vaccination. The increase in stool mercury in all three groups following vaccination suggests enterohepatic excretion of ethyl mercury, similar to methyl mercury. There was no evidence of urinary excretion, also similar to methyl mercury.

Based on the recommended childhood vaccination schedule in 1999, children in the United States could have potentially received up to 187.5 ug of ethyl mercury during the first 6 months of life from thimerosal-containing vaccines. This led to the recommendation in 1999 by the American Academy of Pediatrics that thimerosal be removed from all vaccines administered to infants in the United States. Because of the presence of ethyl mercury, the use of thimerosal in vaccines has been suggested by some, especially in the lay media and among anti-vaccine activists, to cause pervasive developmental disorders and autism, which has not been supported by epidemiologic studies. This study provides quantitative evidence of the perceived risk of thimerosal as a preservative in vaccines. The low, and very transient, levels of mercury found in this study are reassuring, and suggest that there is a very low risk, if any, for toxicity from mercury exposure from thimerosal-containing vaccines. ■

U.S. Virgin Islands and Caribbean HIV Epidemic Needs More Attention, Researchers Say

HIV infection rate is high among sex workers

By Melinda Young

This article originally appeared in the April 2208 issue of AIDS Alert. *It was reviewed by Morris Harper, MD, AAHIVS, Vice President, Chief Medical Officer, HIV/AIDS & Hepatitis Associates, Waynesburg, PA. Dr. Morris reports consulting work with Agouron Pharmaceuticals, Gilead Sciences, Abbott Pharmaceuticals, GlaxoSmithKline, and Bristol-Myers Squibb.*

THE CARIBBEAN RECEIVES SCANT ATTENTION FROM HIV researchers and public health officials, and this has resulted in an epidemic that is poorly understood, an investigator says.

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"I sometimes feel the Caribbean is somewhat neglected as far as HIV research," says Hilary Surratt, PhD, scientist with the Center for Drug & Alcohol Studies of the University of Delaware in Coral Gables, FL.

This is especially true with the English-speaking Caribbean, which is very diverse culturally, Surratt says.

"Chiefly, the incidence of HIV/AIDS in the English-speaking Caribbean is very high, but there hasn't been a significant focus of research in the region," Surratt says.

Funding is the issue. HIV research funds are spent in areas where the HIV epidemic is greater in scope, she notes.

"That's understandable, but from a U.S. perspective, there should be greater focus in the area because that's our neighbor," Surratt says.

Surratt characterizes the Caribbean's HIV epidemic as primarily heterosexual in nature, although it's associated with non-injection substance use and men who have sex with men (MSM).

"Sometimes those [heterosexual transmission] features are not as exciting to people in terms of research dollars, and that's why there's not a history of research being done here," she says.

Surratt found in her own research that drug-using migrant sex workers are particularly vulnerable to HIV infection and transmission throughout the Caribbean.[1]

"The sex workers are servicing, to a great extent, tourists from the United States, Canada, and other parts of the world," Surratt says. "They work the cruise ship routes and bars, and that's their target much more heavily than the local population."

Lindsey Wolf, another investigator who has focused on the Caribbean, agrees that the region needs more research attention.

"A big challenge in the Caribbean is identifying all of those who actually need treatment, and that will involve HIV screening expansion," says Wolf, who is a medical student at the University of California in San Francisco, and who was working as a senior research analyst with the Cost Effectiveness of Preventing AIDS Complications Group at Massachusetts General Hospital in Boston, MA, when she conducted a study on HIV and the Caribbean.

The UNAIDS' 2007 AIDS Epidemic Update states that the primary mode of HIV transmission in the region is unprotected sex between sex workers and clients, the UNAIDS report says.[2]

HIV prevalence among female sex workers in Guyana is 31 percent; in Jamaica it's 9 percent, and in the Dominican Republic it's 3.5 percent.[2]

"Unsafe injecting drug use is responsible for a minority of HIV infections, and contributes significantly to the spread of HIV only in Bermuda and Puerto Rico," the report states.[2]

While men who have sex with men (MSM) transmission also is a significant factor, it is hidden because of stigma, the report adds.[2]

Stigma also plays a role in suppression of efforts to get sex workers and others to be tested for HIV, Surratt says.

"Honestly, the challenges are tremendous and not just with the sex workers," she says. "It goes back to a sense that this is a small, close-knit community, and HIV still carries a stigma in the community."

People are reluctant to be tested for HIV because they're afraid they'll be seen by someone they know, Surratt says.

"Going to the HIV clinic is something nobody wants to be involved with because within five minutes everybody on the island will know that so-and-so was going to this particular location," she explains. "There are tremendous barriers for people to talk about HIV, much less being tested for HIV."

Surratt did not provide HIV testing as part of her study, mostly for this reason.

Wolf saw the stigma first-hand when she worked on the English-speaking island of St. Lucia as a health educator for children at a boys' technical school.

"People who have an HIV diagnosis haven't told people about it, not even their families because they don't want the word to get out," Wolf says. "The number of identified HIV cases is very low compared with the World Health Organization's projection of how many people are infected in the region."

The stigma needs to be addressed, and health care professionals should come up with strategies for screening for HIV, Wolf says.

"Basically, everyone should be tested, and those who need treatment should get treatment," Wolf adds.

Universal testing might even be feasible since the island populations are small, she notes.

"We looked into what we could do to break down these barriers, to see what would make people more likely to be HIV tested," Surratt says. "People told us very often that if you want people to be HIV tested, make the location not identified with HIV testing."

For example, an HIV testing site should offer other health care screenings, such as blood pressure checks, and a variety of services.

"If we had a mobile unit with an array of services, that would be ideal," Surratt says. "But, honestly, the resources are not there to do something like that."

Even folding HIV testing into the existing medical clinics wouldn't be feasible because these established

sites are resource-strapped, and the staff might worry about being associated with HIV testing, she adds.

Some of the other factors that increase risk of HIV transmission in the English-speaking Caribbean involve the tendency of island residents to have a young initiation of sexual intercourse and young women engaging in sexual activity with older men, Surratt says.

"There is really broad acceptance of alcohol consumption, which is endemic to many parts of the Caribbean," Surratt says. "There is a broad acceptance of men having many different female sexual partners, and many of these factors drive the heterosexual epidemic."

In Surratt's study, she found a strong relationship between the sex workers' use of illicit drugs and their engaging in riskier levels of HIV behaviors.[1]

"Among the non-substance-using sex workers, we found that protected sex was very common," Surratt adds. "So their HIV risk was significantly less if they were non-using women, but if they were drunk or high then they'd forget about using condoms or could be convinced not to use condoms." ■

References:

1. Surratt H. Sex work in the Caribbean Basin: patterns of substance use and HIV risk among migrant sex workers in the US Virgin Islands. *AIDS Care*. 2007;19(10):1274-1282.
2. UNAIDS/WHO. 2007 AIDS Epidemic Update. Dec. 2007: available online at www.unaids.org.

CME Objectives

•To present the latest data regarding the diagnosis and treatment of various travel-related diseases;

•To present new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world; and

•To alert the readers to recent disease outbreaks and epidemics. ■

PHARMACOLOGY WATCH

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

FDA Drug Approval to Change its Ways?

In This Issue: FDA drug approval to change? Urinary incontinence in women; how metabolism of certain drugs can be predicted by genetic analysis; bowel preps may compromise renal function especially in the elderly according to a new study; FDA Actions.

Should the FDA change the way it approves drugs? With the number of drug withdrawals and black box warnings in the last 10 years, the FDA's approval process has come under scrutiny. Many have focused on the Prescription Drug User Fee Act (PDUFA), originally enacted in 1992 which transformed the FDA's drug approval process. At that time the FDA was underfunded and understaffed. PDUFA was negotiated with the pharmaceutical industry to help defray the cost of new drug approvals. Under this plan drug manufacturers would pay a user fee for each drug review to help cover the costs of FDA staff; however the FDA would be required to make a decision on each application within a fixed date after submission. Some have argued that this arrangement makes the FDA too beholden to the industry that it regulates. There has also been concern that the required deadline for approval has accelerated the approval process, perhaps at the expense of drug safety. A new study from Harvard in the March 27 *New England Journal of Medicine* looks at the relationship between drug review deadlines and safety issues—specifically whether drugs approved immediately before their deadlines are associated with a higher rate of post-marketing safety problems. As compared with drugs approved at other times, drugs approved within the two months before their PDUFA deadlines were more likely to be withdrawn for safety reasons (odds ratio 5.5; 95% CI, 1.3 to 27.8), and more likely to carry a subsequent black box warning (OR 4.4; 95% CI, 1.2 to 20.5), and more likely to have one or more dosage forms voluntarily discontinued by the manufacturer (OR 3.3; 95% CI, 1.5 to 7.5). The authors conclude that PDUFA deadlines have appreciably changed the approval decisions of the FDA, and drugs approved immediately before their deadline are more likely to have subsequent safety problems. They also state, "A plausible hypothesis is that relying more on staffing and less on deadlines could result in the same degree of review efficiency without increasing the risk (and resulting greater cost) of unanticipated drug-safety problems." (NEJM 2008; 358:1354-1361).

Help for Women with Urinary Incontinence

Urinary incontinence is a common problem in women, affecting one third of women over the age of 65, and up to 25% of younger women. The NIH has published a systematic review of nonsurgical treatments for urinary incontinence in women, reviewing the most commonly used modalities. Pelvic floor muscle training (Kegel exercises) plus bladder training resolved urinary incontinence

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: iris.young@ahcmedia.com.

compared with regular care. Different injectable blocking agents and medical devices all had similar improvement rates, while electrical stimulation failed to resolve urinary incontinence. Oral hormone administration improved urinary continence, however transdermal or vaginal estrogen results were inconsistent. Adrenergic drugs were ineffective. Oxybutynin (Ditropan) and tolterodine (Detrol) were both effective at resolving urinary incontinence compared with placebo, however duloxetine improved but did not resolve incontinence. The authors conclude that pelvic floor muscle training and bladder training are effective interventions for women with incontinence as are oxybutynin and tolterodine. Duloxetine improved but did not resolve incontinence and electrostimulation, medical devices, injectable blocking agents, and local estrogen therapy were inconsistent (*Annals Int Med.* 2008; 148: 459-473).

Human Genome Study Affects Pharmacology

Phamacogenetics and pharmacogenomics are terms that practicing physicians will have to get use to the next few years. The study of the human genome has led to many breakthroughs, not the least of which is the realization that metabolism of certain drugs can be predicted by genetic analysis. The FDA has recently altered the labels of both warfarin and carbamazepine to incorporate language encouraging health professionals to consider pharmacokinetic testing prior to prescribing these drugs in some situations. Some are calling this personalized medicine, but there are concerns ranging from the cost/benefit of these analyses to the potential for abuse of this information, including genetic discrimination. The March 19 issue of *JAMA* is entirely devoted to medical genomics (the study of how genes interact and influence the biology and physical characteristics of living things) and includes articles reviewing genetic analysis for cardiovascular risk, osteoporosis, post-traumatic stress disorder, deep venous thrombosis, and cancer. The issue includes a patient page "Genetics: the Basics" with a glossary of terms (good for patients and doctors alike!).

Bowel Preps and Renal Function in Elderly

Oral sodium phosphate solution (OSPS) bowel preps may compromise renal function especially in the elderly according to a new study. Researchers in Texas retrospectively reviewed 286 patients who received phosphorus containing bowel preps (Fleet Phospho-Soda, Accu-Prep, Visicol) for colonoscopy or sigmoidoscopy and 125 controls. Both groups had similar baseline characteristics, the mean age was 68, 85% were white, and 64% female. In patients treated with OSPS, the baseline glomerular filtration rate was 79 mL/min/1.73 m2 which declined to 73 mL/min/1.73 m2 at 6 months after exposure to OSPS. The GFR in the control group was stable at six months. A drop in GFR in the treatment group was still present one year later although to a lesser degree. Concomitant use of ACEIs or ARBs or the presence of diabetes were significant determinants of the fall in GFR after OSPS preps. The authors conclude that use of oral sodium phosphate solution bowel preps is an under-diagnosed cause of acute kidney injury and that if patients are to receive these preps, physicians should focus on adequate hydration and avoidance of ACEIs and ARBs, especially in diabetic patients (*Arch Int Med.* 2008; 168:593-597). The authors state that their health-care system has banned the routine use of OSPS as bowel cleansing agents for colonoscopies and has switched to polyethylene glycol agents for any patient with stage 3-5 CKD. An accompanying editorial points out that of the two most commonly used methods for colon preps, oral sodium phosphate solutions are often preferred over polyethylene glycol because of the lower volume and better tolerability. Oral phosphate solutions however have been associated with hypokalemia, hypophosphatemia, hypernatremia, and hypocalcemia. Although these are generally transient, acute phosphate nephropathy has also been described with OSPS. Based on the findings, caution should be exercised using phosphorus preps especially in those patients who are risk for renal failure (*Arch Int Med.* 2008; 168:565-567).

FDA Actions

The FDA has issued in early communication about an ongoing safety review of tiotropium (Spiriva), Boehringer Ingelheim's inhaler for bronchospasm associated with COPD. Ongoing safety monitoring has identified a possible increased risk of stroke associated with use of Spiriva. Based on data from 29 placebo-controlled studies the risk of stroke was 8 patients per 1000 treated for one year with Spiriva vs 6 patients per 1000 treated with placebo. The FDA has not confirmed this analysis and recommends the patient should not stop taking Spiriva before talking to their doctor.

The FDA has approved desvenlafaxine for the treatment of depression. The drug is a metabolite of venlafaxine (Effexor) which has recently gone generic in some formulations. Desvenlafaxine is a serotonin-norepinephrine inhibitor which may have less drug-drug interactions than venlafaxine. The drug will be marketed by Wyeth as "Pristiq." ■