Serious Adverse Events Attributed to Nevirapine Regimens for Postexposure Prophylaxis After HIV Exposures—Worldwide, 1997-2000

MMWR. 2001;49:1153-1156

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IN SEPTEMBER 2000, TWO INSTANCES OF life-threatening hepatotoxicity were reported in health-care workers taking nevirapine (NVP) for postexposure prophylaxis (PEP) after occupational human immunodeficiency virus (HIV) exposure. In one case, a 43-year-old female health-care worker required liver transplantation after developing fulminant hepatitis and end-stage hepatic failure while taking NVP, zidovudine, and lamivudine as PEP following a needlestick injury. In the second case, a 38-year-old male physician was hospitalized with life-threatening fulminant hepatitis while taking NVP, zidovudine, and lamivudine as PEP following a mucous membrane exposure. To characterize NVP-associated hepatotoxicity, CDC and the Food and Drug Administration (FDA) reviewed MedWatch reports of serious adverse events in persons taking NVP for PEP received by FDA. This report summarizes the results of that analysis and indicates that healthy persons taking abbreviated 4-week NVP regimens for PEP are at risk for serious adverse events. Clinicians should use recommended PEP guidelines and dosing instructions to reduce the risk for serious adverse events.

MedWatch is a voluntary reporting system for adverse events and problems with drugs, medical devices, biologics, and special nutritional products. For this analysis, a serious adverse event was defined as any event that was life-threatening, permanently disabling, required or prolonged hospitalization, required intervention to prevent permanent impairment or damage, or any other event that required medical attention.

Including the two case reports of fulminant hepatitis, FDA received reports of 22 cases of serious adverse events related to NVP taken for PEP from March 1997 through September 2000. These 22 events included hepatotoxicity (12), skin reaction (14), and rhabdomyolysis (one); four cases involved both hepatotoxicity and skin reaction, and one case involved both rhabdomyolysis and skin reaction. The median age of affected persons was 36.5 years (range: 12-50 years; age was not reported for four cases); 12 were female, and 12 occurred in the United States. Reasons for administration of PEP were occupational needlestick or other sharps injury (12), other occupational exposure (four), sexual exposure (three), nonoccupational (pediatric) needlestick injury (one), other nonoccupational exposure (one), and unknown (one).

Nine persons took a maximum NVP dose of 200 mg per day, and 12 persons took a maximum dose of 200 mg twice per day (the dose of NVP was not recorded for one person). Among the 12 persons taking a maximum dose of 200 mg twice daily, six were first given a lead-in dose of 200 mg per day for 3-14 days. Concomitant antiretroviral agents used with NVP for PEP included zidovudine and lamivudine (10); stavudine and lamivudine (three); zidovudine and didanosine (two); stavudine and didanosine (one); stavudine and indinavir (one); didanosine and indinavir (one); stavudine, didanosine, and ritonavir (one); lamivudine, didanosine, and nelfinavir (one); stavudine, lamivudine, nelfinavir, and saquinavir (one); and none (one). Among the 12 persons with hepatotoxic reactions, one developed liver failure (requiring liver transplantation), seven had clinical hepatitis (e.g., jaundice, fever, nausea, vomiting, abdominal pain, and/or hepatomegaly), and four had elevations in serum liver enzymes (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) without reports of clinical hepatitis.

Baseline liver function tests were reported for six patients and were within normal limits. Abnormal liver function tests were reported during PEP for 10 patients; median peak ALT was 215 U/L (range: 182-2790 U/L; normal: 10-34 U/L), median peak AST was 375 U/L (range: 96-2370 U/L; normal: 10-34 U/L), and median peak total bilirubin was 7.5 mg/dL (range: 2.0-33.7 mg/dL; normal: 0.2-1.0 mg/dL). The median time from initiation of NVP use to first abnormal liver function tests was 21 days (range: 13-36 days). In six cases, hepatitis A, B, and C serologies were reported; all were negative. Eleven persons reported symptoms, including fever, malaise, and abdominal pain. The median onset of these symptoms was 14 days after beginning NVP for PEP (range: 3-36 days). The 14 reports of skin rash included one documented and two possible cases of Stevens-Johnson syndrome. The median onset of rash occurred 9 days after beginning PEP (range: 6-36 days).

REPORTED BY: D Boxwell, Pharm D, Office of Postmarketing Drug Risk Assessment; H Haverkos, MD, S Kukich, MD, K Struble, Pharm D, H Jolson, MD, Div of Anti-Viral Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration. Prevention and Evaluation Br, Div of Healthcare Quality Promotion [proposed], National Center for Infectious Diseases, CDC.

CDC Editorial Note: Severe, life-threatening, and fatal cases of hepatotoxicity and skin reactions have occurred among HIV-infected patients treated with NVP, and are described in a box warning on the NVP label (ViramuneTM [package insert], † Boehringer Ingelheim/
Roxane Laboratories, Inc., Ridgefield, Connecticut, 1998). This report suggests that persons taking NVP regimens for PEP after HIV exposures also are at risk for serious adverse events.

In 1996, the U.S. Public Health Service (PHS) first recommended PEP after certain occupational exposures to HIV. These recommendations, updated in 1998, are being revised to include other antiretroviral agents that have been approved by FDA for use in HIV-infected persons. NVP is not recommended for basic or expanded PEP regimens. However, data on the safe and effective use of single-dose NVP to prevent perinatal HIV transmission and a theoretical advantage of more rapid activity (i.e., NVP does not require phosphorylation for activation) have prompted clinicians to include NVP in PEP regimens following HIV exposures. In the HIV PEP registry, which collected data on occupational HIV PEP use from October 1995 through March 1999, six cases of serious adverse events related to PEP were reported among 492 registered participants; a severe skin reaction occurred in one of 11 healthcare workers taking a regimen that included NVP.

Because most occupational HIV exposures do not result in transmission of HIV, clinicians considering prescribing PEP for exposed persons must balance the risk for HIV transmission represented by the exposure and the exposure source against the potential toxicity of the specific agent(s) used. In many circumstances, the risks associated with NVP as part of a PEP regimen outweigh the anticipated benefits. When PEP is prescribed, the manufacturer’s package insert should be consulted for dosing instructions, possible side effects, and potential drug interactions.

The findings in this report are subject to at least three limitations. First, MedWatch is a voluntary, passive reporting system, and it is unlikely that all serious adverse events in persons taking NVP for PEP have been reported. Second, data about administration of a lead-in dose and results of baseline liver function tests and hepatitis serologies were not included in all reports. In six cases, the initial dose of NVP was 200 mg twice daily without the recommended 2-week dose escalation, which may have increased the likelihood of adverse events. Third, available denominator data about the use of NVP for PEP were insufficient to calculate accurate rates of adverse events.

The findings in this report do not apply to NVP use in other settings. Single-dose NVP is one of the regimens recommended by PHS for prevention of perinatal HIV transmission. No serious toxicity has been reported among mother-infant pairs using this regimen. Combination antiretroviral regimens containing NVP may be used in HIV-infected persons after weighing the risks and benefits and monitoring adverse reactions.

Health-care providers and the public can assist in monitoring the safety of antiretrovirals and other agents by reporting adverse reactions to the FDA MedWatch program: telephone, (800) 332-1088, fax, (800) 332-0178, WorldWideWeb, http://www.FDA.gov/medwatch, or mail, MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

REFERENCES

5. CDC. Public Health Service guidelines for the management of health-care worker exposures to HIV and recommendations for postexposure prophylaxis. MMWR 1998;47(no. RR-7).
<82% genetic similarity to OPV. The differences in nucleotide sequences among the outbreak isolates suggest that the virus has been circulating for approximately 2 years in an area where vaccination coverage is very low and that the virus had accumulated genetic changes that restored the essential properties of wild poliovirus.

The ministries of health of the Dominican Republic and Haiti, with the assistance of the Pan American Health Organization and CDC, are investigating the outbreak to determine the extent of spread, evaluate the reasons for the outbreak, and initiate appropriate control measures. The Dominican Republic has started a nationwide mass vaccination campaign with OPV, and three nationwide vaccination rounds with OPV are planned for January, February, and March 2001 in Haiti.

Circulation of OPV-derived polioviruses in areas with very low OPV coverage has been documented in one other setting—type 2 OPV-derived virus circulating in Egypt for an estimated 10 years (1983-1993) and was associated with >30 reported cases. Vaccination coverage was very low in the affected areas, and circulation of a vaccine-derived poliovirus stopped when OPV coverage increased. The key factor in controlling circulating OPV-derived viruses and wild polioviruses is achieving and maintaining high vaccination coverage. No evidence for circulation of OPV-derived virus has been found in areas with high coverage.

Since 1991, no cases of polio attributed to wild poliovirus have been detected in the Western Hemisphere. The current outbreak underscores the need for polio-free areas to maintain high coverage with polio vaccine until global polio eradication has been achieved. OPV is safe and effective and recommended for the eradication of polio. All countries should maintain high quality AFP and poliovirus surveillance and accelerate current activities to complete the global eradication of wild polioviruses.

Health-care providers should consider polio as a diagnosis in case-patients with a history of travel to other countries of the Western Hemisphere from the Dominican Republic and Haiti who present with AFP usually accompanied by fever. These possible cases should be investigated properly, including collection of stool samples. Suspected cases should be reported immediately to state and local health departments.

Travelers to the Dominican Republic and Haiti who are not vaccinated adequately should be considered at risk for polio. All travelers should be vaccinated fully against polio according to national vaccination policies.

**References**

*Current recommendations for children in the United States include a 4-dose vaccination series with inactivated poliovirus vaccine (IPV) at ages 2, 4, 6-18 months, and 4-6 years. Unvaccinated adults should receive three doses of IPV, the first two doses at intervals of 4-8 weeks and the third dose 6-12 months after the second. If three doses cannot be administered within the recommended intervals before protection is needed, alternative schedules are proposed. For incompletely vaccinated persons, additional IPV doses are recommended to complete a series. Booster doses of IPV may be considered for persons who previously have completed a primary series of polio vaccination and who may be traveling to areas where polio is endemic.*

**Recommendations From Meeting on Strategies for Improving Global Measles Control, May 11-12, 2000**

MMWR. 2000;49:1116-1118

**During May 11-12, 2000, World Health Organization (WHO), United Nations Children’s Fund (UNICEF), and CDC co-sponsored a technical working group meeting to review the status of global measles control and regional elimination efforts and to formulate recommendations to accelerate control activities, particularly in countries and regions with a high disease burden.**

After reviewing the epidemiologic data by WHO region and by selected countries, participants concluded that vaccination coverage of >90% is required to achieve measles control and that a one-dose measles policy is insufficient to achieve and sustain measles control targets. The average seroconversion rate of 85% following one dose at age 9 months, the recommended strategy for routine vaccination in developing countries, leaves many children susceptible. The routine delivery system in many countries also fails to reach many children with a dose at 9 months. Therefore, in addition to the first dose at age 9 months, meeting participants recommended that a second opportunity for measles immunization is essential to protect those children previously missed by routine services and for those children who failed to respond to their first dose of measles vaccine. The second opportunity can be provided through routine programs, supplemental campaigns, or a combination of both.

Meeting participants developed recommendations for accelerating measles control by improving routine and supplemental vaccination, measles surveillance, and vitamin A supplementation. Selected key recommendations follow. The full text of the recommendations is available at http://www.who.int/wer/75_27_52.html.

**Action Plans for Accelerating Measles Control**

- Action plans to reduce measles mortality through increasing vaccination coverage should be part of each country's comprehensive long-term vaccination strategy and should be incorporated into the 3-5 year Expanded Program on Immunization plans of action.
- Action plans should specify tasks and budgets for all recommended strat-
egies for measles control such as improving vaccination (i.e., two opportunities for measles vaccination), intensifying surveillance, managing measles cases, and providing vitamin A supplements.

- Countries that qualify for support from the Global Alliance for Vaccines and Immunization (GAVI) should be encouraged to use these resources for measles control activities.
- In collaboration with its partners, the GAVI board should support measles control and mortality reduction through strengthening vaccination services.

Routine and Supplemental Vaccination

- Countries and donor agencies should assess the reasons for low coverage and should improve routine coverage using appropriate strategies (i.e., fixed posts, outreach services, door-to-door canvassing, and regular pulse vaccination§).
- Management of vaccination services should be strengthened at all levels. WHO should support the development of training courses and tools that cover such topics as reducing missed opportunities and dropout rates, canvassing door-to-door, conducting outreach, and periodic supplementary campaigns.
- When well implemented, mass measles vaccination campaigns are an effective strategy to control measles. Depending on the coverage achieved during the campaign and routine coverage, mass campaigns will need to be repeated at regular intervals. Preliminary data suggest that targeted urban campaigns have limited impact on measles transmission either in cities or in neighboring rural areas. Campaigns should target large populations (entire nations or large regions) and should achieve ≥90% coverage using safe injection practices.
- The target age group for mass campaigns should be based on the susceptibility profile of the population, which can be determined from the history of measles vaccination coverage, age-specific disease incidence data, and seroprevalence studies.

Measles Surveillance

- Measles surveillance should include measles case counts by month and geographic area, age and vaccination status of case-patients and deaths by area, and timeliness and completeness of reporting.
- In countries and regions that have implemented elimination strategies, proposed methods for monitoring interruption of indigenous transmission of measles virus (e.g., percentage imported cases, average outbreak size, number of chains of transmission) should be applied to assess their usefulness.

Vitamin A

- In countries in which vitamin A deficiency is a significant public health problem, vaccination visits and measles campaigns should be used to provide vitamin A supplements.

REFERENCES


The World Health Assembly in 1989 set targets for measles morbidity and mortality reduction of 90% and 95%, respectively, compared with prevaccine era levels.

On March 31, student health services at a university in the District of Columbia (DC) notified the DC health department that an increased number of students had become ill with acute gastroenteritis beginning March 29. Some ill students reported eating tuna or chicken salad sandwiches from dining hall A on campus. On March 31, the DC health department initiated an outbreak investigation. This report summarizes results of the investigation, which indicated that group A rotavirus transmitted by food was the cause of the outbreak.

Telephone interviews were conducted with students who reported illness to student health services, with additional ill students who were identified during interviews, and with healthy controls selected randomly from the university registry of students residing on campus. A case of gastroenteritis was defined as three or more episodes of diarrhea and/or two or more episodes of vomiting within a 24-hour period in a student with onset on or after March 20.
Controls and case-patients whose illness onset occurred during March 27-31 were questioned about food history, residence and dining hall, source of water, use of a public access computer or sports equipment at the university gym, and attendance at social or athletic events. Electronic records of student meal attendance were available for 49 case-patients with illness onset during March 27-31 and for 55 control subjects.

Twenty-three (79%) of 29 employees of dining hall A were interviewed to identify their work duties and determine whether they were ill. Stool specimens were collected during March 29-April 10 from six ill students and 21 dining hall A employees. Samples were screened for bacterial and parasitic pathogens at a commercial laboratory and for viral pathogens at CDC.

The outbreak among students began March 27 and peaked at 19 cases on March 31. A total of 108 students (55 were identified by telephone interviews and 53 were self-reported) had gastrointestinal symptoms during March 26-April 11; 85 (79%) had illness that met the case definition. The attack rate among students residing on campus was 5% (77 of 1641), with no significant differences in attack rates by sex, occupancy of residence hall, or grade level. Eight case-patients resided off campus (attack rate: 0.02%). Among the 83 case-patients for whom a complete list of symptoms was reported, 77 (93%) had diarrhea, 75 (90%) abdominal pain or discomfort, 69 (83%) loss of appetite, 67 (81%) nausea, 64 (77%) fatigue, 56 (67%) vomiting, 49 (59%) headache, 48 (58%) chills, 48 (58%) subjective or low-grade fever, and 42 (51%) myalgia. Sore throat, cough, and/or congestion were reported by six case-patients with onset on or after April 2. The median duration of illness was 4 days (range: 1-8 days). Nine (11%) case-patients received intravenous fluids to treat dehydration.

Of those who completed the telephone interview, 40 (91%) of 44 case-patients and 27 (68%) of 40 controls ate at least one deli sandwich from campus dining hall A during March 27-30 (p=0.017; odds ratio [OR] = 4.8; 95% confidence interval [CI] = 1.3-22.1). During March 27-30, four (8%) of 49 case-patients ate four or more meals at dining hall B compared with 18 (33%) of 55 controls (p=0.005; OR=0.2; 95% CI=0.04-0.6). Food histories of employees were not recorded; however, six employees reported illness.

Stool specimens of students and employees were negative for bacterial and parasitic pathogens and for Norwalk-like viruses. Using electron microscopy, enzyme immunoenzymoassay, and reverse transcriptase-polymerase chain reaction (RT-PCR), nine (33%) of 27 specimens were positive for group A rotavirus. Rotavirus positive stool specimens from four students and three employees were identified as genotype combination P[4],G2 by RT-PCR. Two of the three P[4],G2-positive employees were line cooks who reported having symptoms of gastroenteritis on March 27 and April 2, respectively, while the third positive employee, a deli server, reported no illness.

Reported by: M Fletcher, PhD, ME Levy, MD, Bur of Epidemiology and Disease Control, District of Columbia Dept of Health. DD Griffin, Oak Ridge Institute for Science and Education, Oak Ridge Associate Univs, US Dept of Energy. Viral Gastroenteritis Section, Respiratory and Enterovirus Br, Div of Viral and Rickettsial Diseases, National Center for Infectious Diseases, CDC.

CDC Editorial Note: Group A rotavirus is the most common cause of childhood diarrhea worldwide, infecting >90% of children by age 3 years. Because rotavirus immunity develops early in life, disease among older children and adults is uncommon. Although the role of rotavirus in diarrhea outbreaks in adults has not been well studied, it has been documented as the cause of adult diarrhea outbreaks in hospitals, nursing homes, isolated communities, and in travelers. Also, parents of children infected with rotavirus have been reported to experience acute gastroenteritis. However, the rotavirus G and P protein-type combinations, the proteins that elicit an immune response in humans, were not characterized in most of these reports.

The rapid increase and gradual decline of the campus outbreak suggest that the infection was foodborne during the first week and was spread person-to-person during the following week. During the first week, illness was associated with eating sandwiches at dining hall A and was associated inversely with eating frequently at dining hall B. The employee who prepared sandwich fillings did not report illness and tested negative for rotavirus. None of the three deli servers who assembled and served sandwiches reported illness; however, one was rotavirus P[4],G2 positive. It is unknown whether the deli server who tested positive was infected before the outbreak among students.

This rotavirus serotype G2 outbreak was unusual for two reasons; food was implicated as the source of infection and the adults affected should have been immune. During April 2000, a gastroenteritis outbreak among adults in Japan also was caused by foodborne transmission of group A rotavirus serotype G2. These adults should not have been susceptible to severe rotavirus illness. G2 strains often are found combined with serotype P[4]. The G and P neutralization antigens of serotype G2 strains may allow G2 strains to escape immunity induced by the more common G1, G3, and G4 strains. In addition, G2 has been associated with more severe dehydration during diarrheal episodes in children than other common strains. These outbreaks of rotavirus gastroenteritis in adults in the United States and Japan raise questions about the persistence of immunity to rotavirus and the virulence of G2 strains. Investigators and clinicians should consider rotavirus as a possible cause of acute gastroenteritis in adults.

REFERENCES

9 available