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TRAVEL MEDICINE ADVISOR

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

THOMSON
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INSIDE

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Be Alert for Ricin Poison Cases After Deadly Toxin Used in Threat

Look for epidemiologic clues to detect clusters

CLINICIANS SHOULD BE ALERT FOR POSSIBLE CASES OF RICIN POISONING because the easily available toxin was used recently to make a terrorist threat at a mail processing center in Greenville, SC, public health investigators warn.

Ricin poisoning might resemble typical gastroenteritis or respiratory illness, making it difficult to discern from other infections and exposures. Thus, suspicion of cases should occur in conjunction with epidemiologic clues suggestive of a chemical release, the Centers for Disease Control and Prevention (CDC) recommends.[1] For example, a ricin attack may lead to an unusual increase in the number of patients seeking care or an unexpected progression of symptoms in a group of patients. With a broad panoply of symptoms somewhat dependent on how the poison was delivered, a ricin attack could go undetected until an astute epidemiologist identifies a cluster of cases, says Martin Belson, MD, a medical toxicologist in the CDC national center for environmental health.

"It's really difficult because [it] depends on the route that you were exposed," he says. "If you breathe it in, you basically can have flulike symptoms. If you ingest it, it will be like a stomach virus. Of course, it is going to depend again on how much [ricin] and the grade of it. If you start seeing a lot of people with these types of symptoms, especially if they progress beyond your typical viral infection, then you need to be [suspicious]. You have to at least think about it if you see a cluster of people who have similar disease. Of course, with this particular threat associated with it, that has got to raise the bar even more."

The Greenville incident is the most recent example among several documented instances of ricin used as a criminal or terrorist weapon. On October 15, 2003, an envelope with a threatening note and a sealed container was received at a mail processing and distribution facility. Laboratory testing at the CDC confirmed that the substance in the container was ricin. The accompanying note threatened to poison water supplies if demands were not met.

According to published reports, the threat specifically related to new federal regulations over the trucking industry.

"This is someone supposedly domestic [who] is making this threat," Belson says. "We have known for a long time that countries like Iraq have

produced ricin. Before this event, it has always been thought of as some way-off potential. This brings to light that this is a commonly available [material], and it can be very toxic if used in the wrong way in the wrong hands."

Poison From a Common Plant

Ricin is a biologic toxin derived from the innocuous castor bean plant *Ricinus communis*. Ricin is one of several toxalbumins that create toxicity in the body by inhibiting protein synthesis in eukaryotic cells. Castor beans are processed throughout the world to make castor oil, and ricin is part of the waste "mash" produced when the oil is processed. The plant is not uncommon.

"I saw one the other day in somebody's yard driving home." Belson says. "The castor bean is something you can get a hold of rather easily. You can produce it very crudely just by crushing the beans, and apparently this [Greenville case] was fairly crude-looking. It did not look like a purified sample of ricin. But there is not a capability at this time—hopefully, there will be in the near future—to actually detect how purified it is. It is more [a matter of] looking at it visually."

Indeed, no methods are available for the detection of ricin in biologic fluids. Ricinine is a separate compound from ricin present in the castor bean and might be more feasible to monitor in those exposed to ricin-containing plant material, the CDC advises. Treatment for ricin toxicity is primarily supportive, including intravenous fluids, vasopressors, respiratory support, and cardiac monitoring. No specific antidotal therapy exists, and ricin cannot be removed by dialysis. Prophylactic vaccine and immunotherapy are not available. The same general guidelines for gastrointestinal decontamination employed for other ingested toxins should be applied to ricin, the CDC recommends.[2]

A single dose of activated charcoal should be administered as soon as possible if the patient is suspected of ricin ingestion and is not vomiting. Skin decontamination—preferably in a designated area outside the main emergency department (ED)—should be performed if a powder or similar substance is found on the ricin-exposed patient.

Casting a Wide Net

In the Greenville case, CDC investigators closed the facility for investigation, but found no evidence of environmental contamination and no cases of ricin-associated illness. The CDC cast a wide net, asking area EDs, clinicians, health departments, and the local postal facility to report any cases consistent with ricin exposure. State poison control center records and intensive care unit charts at 7 hospitals in the Greenville, Spartanburg, and Anderson areas were reviewed daily for illness consistent with ricin exposure. Investigators interviewed all 36 workers at the postal facility to identify ricin-related illnesses.

The CDC conducted environmental assessment and sampling at the postal facility, taking 70 wipe samples and 5 surface dust samples. Wipe samples were collected from specific surfaces in the facility, including storage bins, surfaces, conveyor belts, and sorting tables that had been in contact with the letter. All environmental samples were negative for ricin.

In addition, investigators monitored call volumes at 62 of the 63 poison control centers in the United States for clinical effects consistent with ricin poisoning and for cases referring to the specific product code ("contaminated water") because water had been stated as the target by the note in the package. The postal facility was reopened after the environmental samples for ricin were found to be negative and all of the workers were confirmed to be well. In regard to the specific threat in the Greenville case, poisoning a large water reservoir would be no small undertaking, but an attack on the "end-user" water supply would be less subject to dilution. "It would be difficult, but it depends on how much ricin, the purity of the ricin, and the water supply you are talking about," Belson says.

Ricin poisoning is not contagious, and person-to-person transmission does not occur. However, it would be a mistake to underestimate its potential as a bioterrorism weapon, Belson warns.

"Certainly it is psychological, but it is a real threat, too," he says. "This is a compound that is relatively water soluble, and if you really had it refined, you could put it in food or water. It doesn't have much taste, and it is very toxic."

Large Amount Needed for Mass Attack

Routes of exposure to ricin include ingestion, inhalation, injection, skin, and eyes. However, systemic toxicity has been described in humans only after ingestion or injection. Ricin is considered to be a much more potent toxin when inhaled or injected compared with other routes of exposure. Processed and purified ricin can be disseminated by aerosol, contami-

nation of food or water, or injection, the CDC reports. No inhalational cases occurred at the postal facility, in part, because the ricin apparently never escaped the container.

"This was not like [anthrax] powder that was being spread to other letters," Belson says. "The ricin material itself was in a sealed container, which was within the envelope with a threat letter."

Airborne spread would be possible if ricin were processed to a small particle size. Ricin particles of less than 5 μ have been used for aerosol dispersion in animal studies and can stay suspended in undisturbed air for several hours, the CDC reports.

"It certainly would be possible," Belson says. "There are a lot of factors, probably most importantly, how pure the ricin is and the size of the particles. Just crushing castor beans would make exposure by aerosolization very unlikely. Ingestion is typically the more concerning route when you just crush beans. You would have to have your act together to disperse it broadly and aerosolize it into a large population."

Bioterrorism researchers have found that a large amount of ricin is necessary to produce the desired effect of a mass casualty weapon. For example, the amount of ricin necessary to cover a 100 km^2 area and cause 50% lethality, assuming aerosol toxicity of 3 μg/kg and optimum dispersal conditions, is approximately 4 metric tons. Only 1 kg of *Bacillus anthracis* is required for the same effect.[3]

"Ricin, however, would have efficacy as a disabling agent," the researchers note. "Its use as a food and water contaminant easily could incapacitate many and overwhelm local health care resources." ■

References

1 Centers for Disease Control and Prevention. Investigation of a ricin-containing envelope at a postal facility—South Carolina. *MMWR Morb Mortal Wkly Rep*. 2003;52(46):1,129-1,131.

2. Chyka PA, Seger D. Position statement: Single-dose activated charcoal. American Academy of Clinical Toxicol-ogy; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 2000; 38:721-741.

3. Mirarchi FL, Allswede M. CBRNE Ricin. www.emedicine.com.

Gary Evans is the editor of BioTerrorism Watch. *This article was published in the January 2004 issue.*

Antiviral Drug Resistance: Implications for Post-Exposure Prophylaxis in Health Care Workers with Occupational HIV Exposure

ABSTRACT & COMMENTARY

Synopsis: *In a multicenter study of occupational HIV exposures, 38% of source patients had genotype mutations associated with resistance to antiretroviral drugs. Recent antiretroviral treatment history was highly associated with resistance.*

Source: Beltrami EL, et al. Antiretroviral drug resistance in human immunodeficiency virus-infected source patients for occupational exposures to healthcare workers. *Infect Control Hosp Epidemiol*. 2003;24:724-730.

Beltrami and colleagues enrolled health care workers with percutaneous exposure to HIV, along with the source patients for the exposures, in tertiary care medical centers in 5 US cities. They collected antiretroviral treatment histories from source patients. In addition, they collected source patients' blood for RNA viral load. HIV-1 isolates were submitted for genotyping in order to identify mutations associated with primary drug resistance.

They enrolled a total of 64 HCW-patient pairs. Fourteen patients had undetectable viral loads, and thus virus was not available for genotyping. Of the 50 isolates genotyped, 19 (38%) had 1 or more (range, 1-6) mutations associated with primary drug resistance. Of the 50 patients, 26 had taken and 23 had not taken antiretroviral agents within the 3 months prior to the exposure incident. No drug treatment history was available from 1 patient. Of the 26 isolates from patients having received antiretroviral therapy, 16 (26%) had at least 1 primary drug resistance mutation. Of the 23 isolates from patients without recent antiretroviral treatment, 3 (13%) had at least 1 primary drug resistance mutation.

Multivariate analysis was performed on 5 drugs that are included in the CDC's current postexposure prophylaxis regimens: lamivudine, zidovudine, efavirenz, nevirapine, and nelfinavir.[1] *Resistance to a specific drug was related to current or previous (within 3 months) use of that drug or of another drug of the same class.* The results were similar when agents used within the preced-

ing year were analyzed.

Beltrami et al recommend that when a health care worker sustains a percutaneous exposure from a source patient known to be HIV positive, postexposure prophylaxis should include 1 or more agents with which the source patient has not been treated. If that is not possible, an attempt should be made to select agents with which the source patient has not been treated within the preceding 3 months.

COMMENT BY ROBERT MUDER, MD

Although a health care worker's risk of acquiring HIV infection after a percutaneous exposure to blood from an HIV-positive source patient is low (0.3%), the US Public Health Service recommends the initiation of postexposure prophylaxis (PEP) in order to reduce the risk further.[1] Although there are no controlled trials of PEP, the estimated efficacy is approximately 80%, based on indirect evidence and animal models. The recommended regimes contain 2 or 3 antiretroviral drugs; ideally, PEP should be started within 24 hours of exposure. The relatively high prevalence of primary drug resistance mutations in HIV from patients who have received antiretroviral therapy could potentially compromise the efficacy of antiretroviral therapy. At the time of a percutaneous exposure incident, the viral genotype of the source patient is likely to be unavailable, and the appropriate testing can't be performed within the 24-hour window in which PEP should be initiated.

Beltrami et al show evidence that the source patient's recent history of antiretroviral therapy is highly correlated with the presence of primary drug resistance mutations. It's not perfect; for example, 13% of treatment-naïve patients had virus with drug resistance mutations. Nevertheless, treatment history is likely to be obtainable in a timely fashion and offers at least a rational basis for adjusting the agents used in PEP. Whether such an approach will reduce the incidence of occupationally acquired HIV infection will probably never be demonstrated by a clinical trial, but at present it seems to be a highly logical approach. ■

Reference

1. Centers for Disease Control and Prevention. Updated US Public Health Service guidelines for the management of occupational exposures to HBV, HCV and HIV and recommendations for postexposure prophylaxis. *MMWR Morb Mortal Wkly Rep*. 2001;50(RR11):1-52.

Dr. Muder is a hospital epidemiologist at Pittsburgh VA Medical Center.

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