

Deaths From Intravenous Colchicine Resulting From a Compounding Pharmacy Error—Oregon and Washington, 2007

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Colchicine for injection has been available in the United States since the 1950s. Although not approved by the Food and Drug Administration (FDA), intravenous (IV) colchicine has been an accepted treatment for acute gout symptoms. Several additional IV uses have been studied, including treatment of familial Mediterranean fever, pericarditis, primary biliary cirrhosis, amyloidosis, and Behçet's syndrome.¹⁻³ More recently, outpatient use of IV administration for chronic back pain has been advocated by alternative medicine providers but is not an accepted practice. Colchicine has well-known toxicities that limit its safe therapeutic use. IV doses that exceed the standard single-use therapeutic dose of 2-4 mg per episode of gout have resulted in life-threatening toxicity.² In March 2007, two persons from Washington and Oregon died after receiving IV colchicine for back pain from an alternative medicine clinic in Oregon. This report describes the investigation, which determined that a measuring error by a Texas compounding pharmacy resulted in a fatal colchicine concentration that was eight times greater than the recognized standard level. A subsequent review of medical records revealed that a third death from colchicine toxicity in a patient treated at the Oregon clinic also occurred in March and likely was associated with the same compounding error. These deaths highlight the potential risk from use of IV colchicine for back pain and the possibly fatal consequences of measuring errors in compounding pharmacy products.

Investigation and Control Measures

Investigation into the causes of death of the two patients and a suspected third patient indicated that they each received IV colchicine infusions obtained from the same alternative medicine clinic in Oregon. The clinic had purchased the drug from a Texas compounding pharmacy.

The Washington case occurred when an employee in the clinic gave colchicine from the implicated lot to her relative (patient A) to take home. The patient had received previous infusions from different lots and had not become ill, but the infusion from the new lot resulted in sudden onset of symptoms on March 19. The unusual circumstances of the woman's death were discussed on March 26 at a weekly

Oregon-Washington poison center teleconference, alerting toxicologists and poison centers in three states.

On March 30, the Oregon patient (patient B) was treated at the same alternative medicine clinic as patient A. On April 2, when staff members at the Oregon Poison Center were consulted about patient B, they notified the county public health department of the two cases. The Oregon Board of Naturopathic Examiners was notified and voluntarily posted a warning on its website the same day.

Investigators from the Oregon office of the state medical examiner learned that the deaths both occurred after the patients had received colchicine supplied by the Oregon clinic. The medical examiner's office confiscated from the clinic approximately 70 remaining vials of the colchicine, which were from several lots. Toxicology tests of colchicine vials from the same lot used to treat the patients indicated a concentration of 4 mg/mL. However, the vial labels indicated a concentration of 0.5 mg/mL; therefore, each intended infusion of a 2-mg dose of colchicine was actually 16 mg. The clinic supplied its medical records, including records of a third patient who was treated the same day as patient B and who also died. The clinic closed voluntarily in April 2007 and subsequently ceased operations.

The third suspected case occurred in a man aged 55 years who received a colchicine infusion on March 30 (the same day as patient B). He experienced severe vomiting, diarrhea, and chest pain within 1 hour of infusion and sought treatment at an ED. Because he had a history of coronary heart disease and recently had received a cardiac stent, his initial evaluation included a coronary catheterization, which was normal. He died within 24 hours of receipt of his last colchicine infusion; his death was attributed initially to cardiac causes. Media coverage of the deaths associated with the Oregon clinic prompted a nurse who had treated this man to call the poison center and report possible colchicine toxicity. After the investigation, the medical examiner reissued the man's death certificate, listing colchicine toxicity as cause of death. Although an autopsy was performed, no body fluids were available to confirm colchicine toxicity.

After the drug concentration in the colchicine vials used was determined to be eight times the labeled concentration, investigators attributed the deaths to an error at the Texas compounding pharmacy. On April 30, in coordination with FDA, the Texas State Board of Pharmacy issued a recall of all colchicine that had been sold or produced by the compounding pharmacy within the last year and shipped throughout the United States. No other cases have since been linked to this product.

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CDC Editorial Note:

FDA policy allows an ingredient from an FDA-approved drug to be compounded to fill a prescription from a licensed practitioner for use by a specifically named patient. Compounding pharmacies are either registered or licensed by state pharmacy boards. Compounded drugs are not evaluated for safety and efficacy and, unlike pharmaceutical manufacturers, traditional compounding pharmacies are not inspected by FDA to ensure that they have the capacity to consistently produce high-quality drugs. However, certain compounding pharmacies that engage in large-scale manufacturing are subject to regulations that FDA imposes on pharmaceutical manufacturers.

Although FDA has approved drugs that contain a combination of colchicine and probenecid for oral use, no FDA-approved colchicine products for IV use exist. The Texas State Board of Pharmacy and the Texas attorney general are investigating the deaths described in this report; the Oregon attorney general has issued an injunction against the Texas pharmacy from doing business in Oregon.

Colchicine, a naturally occurring alkaloid derivative of the autumn crocus *Colchicum autumnale* and the glory lily *Gloriosa superba*, has been used to treat gout for centuries. The drug has a narrow therapeutic range; in toxic levels, colchicine can disproportionately affect rapidly dividing cells and have substantial effects on multiple organ systems. In 2005, the American Association of Poison Control Centers Toxic Exposure Surveillance System reported 312 exposures and four deaths related to colchicine,⁵ annual totals that had remained stable during the preceding 15 years.⁶ A review of FDA Adverse Event Reporting System data from 1983 to 2000 indicated that IV administration of colchicine in amounts that exceeded the maximum recognized dose resulted in 20 deaths from colchicine toxicity, 17 of these during treatment for gout.² In 2001, an incident involving an error of 10 times the standard therapeutic dose occurred in Pennsylvania and resulted in an FDA recall from an Arizona compounding pharmacy.⁷

The recognized maximum cumulative IV dose is 4 mg for a single course of therapy, with a 7-day colchicine-free interval after each full IV course.⁸ However, deaths have been reported with cumulative doses as low as 5.5 mg.² Older adults, patients with preexisting renal and hepatic failure, and patients with concomitant use of nonsteroidal antiinflammatory drugs or oral colchicine might have a higher risk for toxicity and death.²

Use of colchicine for treatment of low back pain and intervertebral disc herniation was described initially in the 1970s. A single case series in 1979 suggested some effectiveness with low doses of oral and IV colchicine in reducing pain⁹; subsequent prospective double-blind studies showed no improvement over placebo with oral use¹⁰ and only short-lived improvement with IV therapy.³ Nevertheless, numerous Internet sources continue to recommend use of IV colchicine for back pain, referencing these early studies as evidence of the drug's effectiveness.

The cases described in this report highlight the risk for serious health consequences from use of IV colchicine for back pain. Although no FDA-approved indication for use of IV colchicine exists, multiple clinics continue to offer such therapy for various musculoskeletal disorders. These deaths underscore the potentially fatal ramifications of errors by compounding pharmacies, which generally are not subject to the same oversight and manufacturing practices as pharmaceutical manufacturers. The public health response to these drug-related deaths and the sharing of public health information among several states, which included poison control centers, medical examiners' offices, and county health departments, likely prevented additional deaths.

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