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CASE STUDIES IN TOXICOLOGY
Series Editor: **Lewis S. Nelson, MD**

Intrathecal Administration Errors

Intrathecal administration of an agent not intended for this route can have catastrophic results. Two cases illustrate the potential damage.

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CASE 1: Intrathecal Chemotherapy

A 16-year-old boy with acute lymphoblastic leukemia (ALL) is receiving his seventh weekly prophylactic intrathecal chemotherapeutic treatment with methotrexate 15 mg, cytarabine 50 mg, and hydrocortisone 50 mg. During the intrathecal injection, he complains of burning pain in both legs, prompting abrupt cessation of administration. The patient's neurologic exam does not reveal any motor weakness or abnormal rectal tone. The symptoms subside within approximately 20 minutes. Shortly thereafter, it is discovered that the cytarabine and methotrexate were unintentionally dissolved in bacteriostatic water, which contains 0.9% benzyl alcohol, instead of in preservative-free water.

CASE 2: Intraventricular Chemotherapy

A 52-year-old woman with central nervous system (CNS) lymphoma presents for her scheduled infusions of IV vincristine and intracerebroventricular methotrexate. The patient correctly receives methotrexate through an Ommaya reservoir (Figure 1), but the vincristine (2 mg), which was intended for IV administration, is also infused into the Ommaya reservoir.

What is the benefit of intrathecal pharmacotherapy?

Intrathecal administration is the injection or infusion of a xenobiotic into the cerebrospinal fluid (CSF) at any level of the cerebrospinal axis, including into the cerebral ventricles (eg, Ommaya reservoir). The intrathecal route of administration has several advantages when compared to other routes. It delivers medication directly to the CNS, bypassing the blood-brain barrier; causes fewer side effects; and allows appropriate CNS drug concentrations to be attained with lower doses. Intrathecal medications are typically administered though an indwelling lumbar catheter or spinal/epidural needle. Medication classes that are commonly administered intrathecally include antibiotics, chemotherapeutics, local anesthetics, and analgesics.

Although the intrathecal route of administration is used less commonly than most other routes and is associated with fewer complications, when problems do occur, they can be catastrophic. Incorrect dosing, improper compounding, and delivery of medications not intended for intrathecal administration (eg, vincristine, benzyl alcohol) are examples of errors associated with such complications.

What adverse events are associated with benzyl alcohol (benzene methanol)?

Benzyl alcohol (Figure 2) is a colorless liquid with a mild aromatic odor that is used as a solvent due to its polarity and low vapor pressure. It is also commonly added to pharmaceuticals as a bacteriostatic agent. Benzyl alcohol is present in IV medications such as lorazepam, vecuronium, and diazepam in concentrations that range from 0.9% to 2%.[1]

Benzyl alcohol is oxidized to benzoic acid and subsequently conjugated with glycine in the liver to form hippuric acid, which is then renally eliminated. In the 1980s, a "gasping" syndrome was described in low birth weight infants who received either IV pharmaceuticals containing benzyl alcohol or flushes with bacteriostatic saline/water containing 0.9% benzyl alcohol. This syndrome consisted of bradycardia, hypotension, gasping respirations, acidosis, seizures, and death. Preterm infants lack the ability to properly

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conjugate benzoic acid (perhaps due to glycine deficiency), resulting in the bioaccumulation of benzoic acid.[1]

Intrathecal chemotherapeutics diluted in solutions containing benzyl alcohol preservative are reported to cause transient paraplegia. Evidence from animal studies in which benzyl alcohol was applied to dorsal nerve roots suggests this acute effect is caused by nerve conduction blockade, akin to that occurring with a local anesthetic.[1] Chronic exposure to benzyl alcohol results in patchy demyelination that may be irreversible, resulting in neuronal death.[1] Treatment of patients who have received intrathecal benzyl alcohol injection is typically supportive, but significant exposures may require aggressive CSF exchange and lavage, as described below. Several case reports demonstrate neurotoxicity after intrathecal exposure to bacteriostatic preservative.[2]

Why should vincristine never be administered intrathecally?

Vincristine is derived from the Madagascar rosy periwinkle plant (*Catharanthus roseus*) and was initially thought to have a role in the treatment of diabetes.[3] Investigations failed to prove any antidiabetic effects of vincristine, but they did reveal its ability to cause severe bone marrow suppression. Vincristine and other vinca alkaloids (eg, vinblastine) bind tubulin, causing tubulin to depolymerize, and disrupting the formation of microtubules, which are responsible for many critical cell functions.[3] Microtubule dysfunction leads to cell division arrest in metaphase, resulting in rapid cell death.[4] Rapidly dividing cells, such as those that are cancerous, intestinal, epithelial, and hematopoietic in origin, are most affected. This accounts for the use of vincristine to treat lymphoma, leukemia, and certain solid tumors.

Vincristine used intravenously causes well-recognized dose-limiting neurotoxicity, which often manifests as peripheral neuropathy.[5] Findings include sensory and motor deficits, ocular palsies, and bowel dysfunction and are due to failure of axonal transport processes, which are mediated by microtubules. These effects are often reversible with discontinuation of the drug. Under normal circumstances, CNS toxicity does not occur with IV administration because vincristine does not penetrate the blood-brain barrier.

It is never appropriate to administer vincristine directly into the cerebrospinal compartment by either the intrathecal or intracerebroventricular route. The first case report of intrathecal administration of vin-

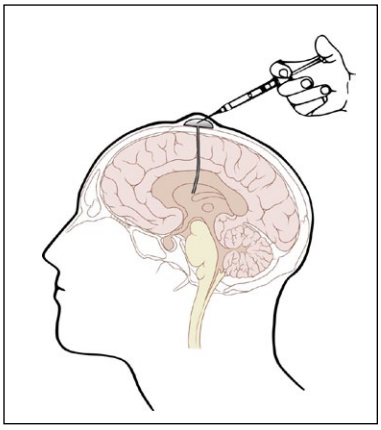

FIGURE 1. Ommaya reservoir.

This device consists of a small balloon (reservoir) that is inserted underneath the scalp and connected to tubing that traverses the skull into an intracranial cavity, such as the ventricular space. The reservoir allows easy access to the cerebrospinal fluid for sampling or administration of an intracerebroventricular infusion of chemotherapeutics. Artwork by Patrick J. Lynch.

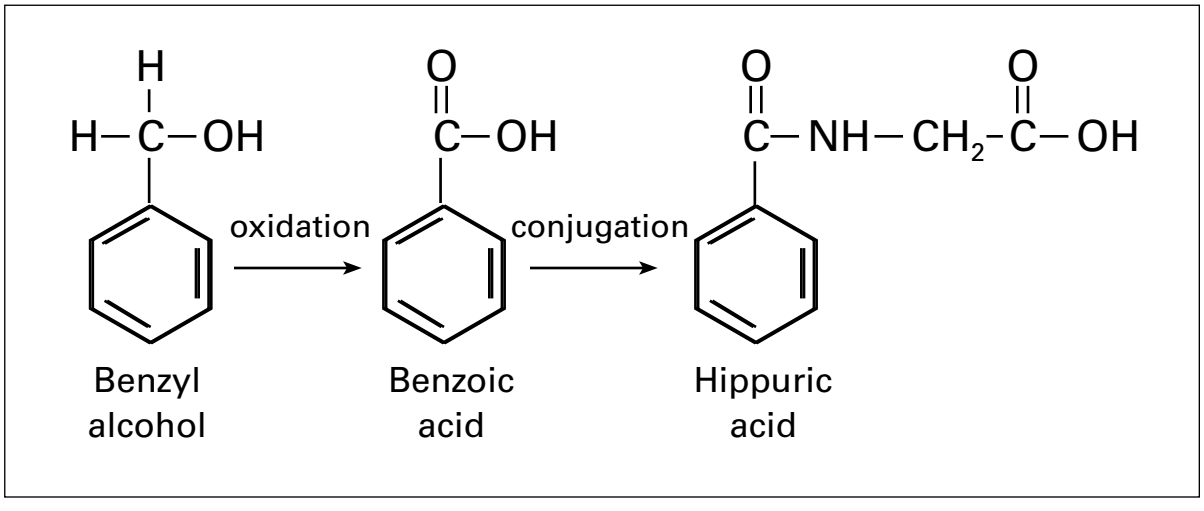

FIGURE 2. Benzyl alcohol metabolism.

cristine was published in 1968, and there have since been more than 55 cases reported worldwide.[3] When vincristine is inadvertently administered in this manner, the fatality rate approaches 100%.[3,4] It is believed that there are only five reported long-term survivors of intrathecal vincristine exposure, all of whom sustained significant permanent neurologic deficits.[3] The effects may be seen within the first few hours after exposure, but they are often delayed for 24 to 72 hours. Clinical toxicity after intrathecal injection generally follows a predictable course, manifesting as a progressive ascending myeloencephalopathy.[3,6] Initial signs and symptoms include distal lower extremity weakness, paresthesias, pain, and loss of tendon reflexes. Neurologic deficits begin at the lumbosacral level of exposure and ascend superiorly, spreading across other levels of the spinal cord and finally to the brain. The neurologic damage then rises to involve the trunk and upper extremities, with concurrent autonomic dysfunction of the bladder, bowel, and other organs. CNS effects usually follow, including chemical meningitis, headache, altered mental status, central respiratory failure, and coma.[7] At autopsy, CNS lesions of patients exposed to intrathecal vincristine show ascending chemical leptomeningitis and ventriculitis, with underlying necrosis of the spinal cord, brain stem, and cerebellum.[6]

How should errors in dosing or direct CNS exposure to drugs not intended for this route be managed?

The following are general management guidelines for inadvertent intrathecal exposure to excess methotrexate or unintended administration of vincristine. These guidelines cannot be considered as truly evidence-based, given the infrequent and variable nature of such exposures. Individual cases, depending on the drug and dose, warrant varying levels of intervention. After intrathecal or intracerebroventricular exposure to vincristine, the most aggressive measures should be taken. The most important intervention that may impact survival is the immediate aspiration of local CSF to retrieve as much drug as possible. Time is extremely critical, as the amount of drug recovered falls dramatically within the first few hours. In human case reports of intrathecal methotrexate overdose, 10 mL of CSF aspirate recovered 94% of the drug at 30 minutes after exposure, but only 10% was recovered at 180 minutes.[7] Placing the patient in the upright position immediately, if possible, is also a common intervention after intrathecal administration errors, using gravity to delay the ascent of the drug to the brain. In the case reported here, vincristine was injected directly into the ventricle of the brain; thus, immediate cerebral exposure has already occurred, and it is unclear whether such positioning after intracerebroventricular exposure provides any benefit.

Subsequent to positioning and aspiration, CSF should be removed sequentially in 20- to 75-mL aliquots in adults and in 10- to 20-mL aliquots in children.[7] Each disposed amount of CSF should be replaced by sterile technique with equal amounts of normal saline or lactated Ringer's solution. Following critical exposures such as to vincristine, while CSF exchange is under way, the patient can be prepared for CSF lavage. Commonly, a ventriculostomy is performed or a cervical spinal catheter and a lumbar drain are inserted, allowing fluid (eg, normal saline) to be infused through the brain or upper spinal cord, respectively, and drained out of the lumbar region. In case 2 and other previous reports, the Ommaya reservoir allowed infusion of fluid, so that only the placement of a lumbar drain was needed. Fresh frozen plasma (FFP) should be added to the isotonic fluid because it binds vincristine.[7,8] Generally, 15 to 25 mL of FFP is added to 1 L of lactated Ringer's solution, and the rate of lavage should approach a goal of 150 mL/hour; this rate is reasonable but is based on little data.[7] It is recommended that CSF lavage be performed for a minimum of 24 hours, but this is based on case reports and the understanding that most drugs, including vincristine, will no longer be present in the CSF after 24 hours.[8]

Are there other adjuncts or interventions that may be used specifically for intrathecal vincristine exposure?

There are four adjuncts that have been used in cases of intrathecal or intracerebroventricular vincristine exposure (Table). Dexamethasone is given to prevent and treat meningeal inflammation.[7] Glutamic acid, pyridoxine, and folinic acid are also used in cases of neuraxial exposure because of data suggesting their benefit in treating the neurotoxicity of IV vincristine.[7] Glutamic acid and vincristine share a common cellular transport mechanism; therefore, glutamic acid may competitively inhibit vincristine entry into the cell. In addition, glutamic acid appears to stabilize tu-

bulin structure and promote microtubule formation. Human and animal data demonstrate that glutamic acid may prevent peripheral neuropathy from IV vincristine.[7] In an animal model, pyridoxine reduced neurotoxicity from vincristine, but in a human trial it failed to show a benefit.[9] Folinic acid (leucovorin) has also been used to treat vincristine-associated peripheral neuropathy and myelosuppression, because vincristine may also inhibit dihydrofolate reductase and thymidylate synthetase.[7] An antibody to vinca alkaloids has shown limited benefit for IV vincristine overdose, but there is no evidence for its role following intrathecal exposure.[10]

How can intrathecal errors be prevented?

Because errors in intrathecal administration of chemotherapeutics are potentially devastating, with significant morbidity and mortality, prevention is critical. Errors may result from failures that occur in several steps along the process of ordering, preparation, labeling, and administration. Intrathecal errors should never occur; they are often due to poorly designed or absent safety checks. The Joint Commission issued a sentinel event alert in 2005 regarding vincristine administration errors to provide guidance to all hospitals, chemotherapeutic infusion centers, and other facilities where intrathecal injections or infusions are given.[11] Reason's human error theory recommends the implementation of systems that support front-line workers by both simplifying the practice and complicating error production.[12] Practical procedures need to be implemented at all levels—pharmacy, transport, nursing, and physicians—to prevent such errors.

Table. Suggested Dosing of Adjuncts Given After Intrathecal Vincristine Exposure

Adjunct	Dosage Regimen
Dexamethasone	4 mg/m^2 IV q 6 h
Glutamic acid	10 g IV over 24 h or 500 mg PO tid
Pyridoxine	50 mg IV q 8 h
Folinic acid	25 mg IV q 6 h

Data extracted from Wang.[7]

In case 1, an error occurred in the pharmacy, where bacteriostatic water was inadvertently used in an intrathecal preparation. In case 2, intrathecal vincristine administration occurred because both an intrathecal and an IV drug were at the patient's bedside concurrently, and there were no specific policies or procedures in place for intrathecal administration.

Following are a few recommendations that may help to prevent these intrathecal errors[13,14]: Create dedicated locations in the pharmacy and in the hospital ward for the preparation and administration of intrathecal medications (IT zones)—within which no other activities are performed (this may prove impractical in most pharmacies, where the volume of intrathecal medication preparation is low); label the vincristine syringe "For intravenous use only—fatal if given by other routes"[15]; allow transport of intrathecal medications only by a dedicated messenger or by the administering/verifying clinician, who delivers the drugs directly to the IT zone at the scheduled time of administration. Designate the IT zone exclusively for the intrathecal agent; no IV medications should be permitted in the space. It may be far more important to deliver IV vincristine *only* to areas where intrathecal medications are *not* being administered. It is advisable to always use the term *IV vincristine* when discussing use of vincristine with intrathecal administration of other agents such as methotrexate. This will help prevent incorrect association of the term *intrathecal* with the term *vincristine*. Some facilities have established (and the Institute for Safe Medication Practices supports) policies whereby patients who are on a regimen of intrathecal and IV chemotherapy receive medications via these two different routes on two separate days or in physically separate locations solely to prevent such errors. In pediatric cases where sedation or general anesthesia is used, the IT zone (eg, dedicated Mayo stand) should ideally be outside of the anesthesiologist's area to prevent inadvertent placement of another drug in the zone. A "time out" procedure should be performed using a dual-person check that involves the administering clinician; this should include a specific confirmation that the intrathecal label on the syringe is visible. It has also been suggested that preparing vincristine as a small-volume infusion only, rather than in a syringe, can prevent confusion, as most intrathecal agents are given by syringe only.[16] Ideally, the labels and connectors for the tubing and catheters involved in the

various routes of administration would be designed to adequately warn or frankly prevent delivery of a medication by an incorrect route. Such a technological solution is not currently available.

CASE 1: Resolution

The patient was placed in an upright position and interventional radiology was consulted for possible placement of a lumbar drain. He was admitted for observation, no lumbar drain was placed, and he did not develop any further neurologic sequelae.

CASE 2: Resolution

Approximately 15 minutes after the injection of vincristine into the Ommaya reservoir, the clinicians realized the error, and 30 mL of CSF was aspirated from the reservoir. The patient was transferred to the neurosurgical ICU for CSF exchange and ventriculolumbar lavage. FFP was added to the perfusate, and dexamethasone, glutamic acid, pyridoxine, and folinic acid were administered intravenously at the recommended doses discussed earlier. The patient had no complaints or neurologic deficits until day 3, when she began to have subtle hearing loss, headache, and mild left lower extremity weakness. Her symptoms progressed rapidly, with ascending paralysis, autonomic dysfunction, respiratory failure, and coma, and she died on day 12.

CONCLUSION

The limited utility of rescue measures after the administration of an incorrect agent intrathecally underscores the need for absolute adherence to safety requirements. While the majority of reported errors involve chemotherapeutic agents, the potential for a misadministration event exists with any agent. Should a misadministration occur, critical actions in the management of intrathecal errors include promptly recognizing the error, maintaining access to the lumbosacral space and immediately withdrawing the CSF, and replacing the CSF with isotonic fluid. Unless the toxicity of the agent is known, all intrathecal errors should be assumed to be potentially fatal, and aggressive and timely treatment should be initiated. □

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