Intrathecal Methotrexate Containing the Preservative Benzyl Alcohol Erroneously Administered in Pediatric Leukemia Patients: Clinical Course and Preventive Process

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Administration of intrathecal chemotherapy for leukemia is a common procedure in pediatric oncology. The direct delivery of drug into the cerebral spinal fluid requires that no preservative be used. Preserved drugs administered in error can result in significant neurotoxicity. A case series is described where preservative-containing methotrexate was incidentally administered intrathecally. All patients were treated at Children's Hospitals and Clinics of Minnesota. Medical records of the patients affected were reviewed and abstracted for this report. Four children with acute lymphoblastic leukemia received 1 dose of intrathecal methotrexate that contained 0.07% benzyl alcohol in January 2019. Overall, minimal to no symptoms were seen after dosing. The error was traced to a drug shortage in which benzyl alcohol-containing methotrexate was obtained and incorrectly stocked. A novel replacement drug procurement process was developed within our institution. The process includes sequestered queues where a drug awaits evaluation and independent double check of entry accuracy in the electronic health record and pharmacy parenteral dose preparation software prior to release and use. In contrast to IV administration, intrathecal benzyl alcohol at concentrations $\geq 0.9\%$ can cause significant neurotoxicity. Although minimal, if any, neurotoxicity was seen in patients who received a 10-fold lower concentration of benzyl alcohol than previously associated with complications, all institutions should recognize the potential for this error and implement similar safety precautions to ensure that this type of error will not occur.

ABBREVIATIONS ALL, acute lymphoblastic leukemia; BSA, body surface area; COG, Children's Oncology Group; IT, intrathecal; IV, intravenous

KEYWORDS acute lymphoblastic leukemia; benzyl alcohol; drug-procurement; drug shortage; intrathecal; medication safety; methotrexate; pediatric; preservative

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Introduction

Therapy for acute lymphoblastic leukemia (ALL) requires central nervous system-directed therapy through the administration of intrathecal (IT) chemotherapy.¹ Common IT agents used include methotrexate, cytarabine, and corticosteroids such as hydrocortisone or methylprednisolone. Thiotepe and liposomal cytarabine are less commonly used IT agents, often reserved for relapsed or refractory patients. These agents are delivered to the subarachnoid space into the cerebrospinal fluid, usually below the second lumbar vertebra, to avoid the spinal cord. Notably, IT chemotherapy can be associated with neurotoxicity (most often associated with cytarabine and methotrexate) that can include spinal cord lesions resulting in paraplegia or cauda equina syndrome, seizures, and encephalopathy.² Sterile drug preparations, including chemotherapy agents, are commonly formulated from either non-preserved solutions suitable for single-dose use, or preserved solutions, suitable for either single-dose or multi-dose use. However, it has been documented that

preservatives can cause significant neurotoxicity when administered into the subarachnoid space. Thus, any preparation given via the IT route must be preservative-free.³ Here we describe the case of 4 children who received IT methotrexate that was formulated with the preservative benzyl alcohol because of human error. The clinical course and outcome of the patients and changes in pharmacy processes are described with the goal to prevent future errors at other institutions.

Materials and Methods

This study was reviewed and approved by the Children's Hospitals and Clinics of Minnesota Institutional Review Board. Over a 6-day period in January 2019 four children with ALL received 1 dose of IT methotrexate that contained benzyl alcohol at Children's Hospitals and Clinics of Minnesota. The error was discovered within 1 hour after 2 patients were each administered a single IT dose of benzyl alcohol-containing methotrexate. Both patients were admitted to the hospital for a 24-hour observation period. After a comprehensive

Table. Summary of Four Patients Given Intrathecal Methotrexate Containing Benzyl Alcohol											
Patient (Sex)	Diagnosis	COG Protocol	Course	Age, yr	Weight, kg	BSA, M ²	Methotrexate Dose, mg	Volume, mL	Benzyl Alcohol* Amount, mg	Benzyl Alcohol* Concentration, %	Neurologic Symptoms
1 (male)	T-ALL	AALL0434	Consolidation	7.2	30.2	1.046	12	6	4.3	0.07	Transient global weakness day +3†
2 (male)	B-ALL	AALL0932	Induction	4.2	15.1	0.639	12	6	4.3	0.07	Transient lower extremities weakness day +2, recovered day +3‡
3 (male)	B-ALL	AALL1131	Maintenance	4.0	17.2	0.690	12	6	4.3	0.07	None. Observed 24 hours
4 (female)	B-ALL	AALL1631	Delayed intensification	6.3	21.5	0.824	12	6	4.3	0.07	None. Observed 24 hours

ALL, acute lymphoblastic leukemia; BSA, body surface area; COG, Children's Oncology Group; IT, intrathecal
* The 12-mg dose of methotrexate was taken from a 25-mg/mL injection solution that contained 0.9% (9 mg/mL) benzyl alcohol, which was diluted with 0.9% normal saline in a total of 6 mL. The final concentration of benzyl alcohol was 0.07% (0.7 mg/mL).
† Patient had global weakness from steroids and vincristine, making it difficult to ascribe causation to the benzyl alcohol-containing IT methotrexate.
‡ The transient weakness of this patient was more distinct and temporally suggestive of association with benzyl alcohol-containing IT methotrexate.

safety review was conducted of previously administered IT methotrexate doses, it was then discovered that 2 additional patients each received a single dose of benzyl alcohol-containing methotrexate 6 days earlier. All parents were informed about the error by one of the authors (NPG). One of the authors (NPG) obtained consent from the parents of all 4 children for the publication of this error. Medical charts were reviewed and abstracted for this report. Patient 1 was in consolidation and was seen weekly in the clinic. Patients 2 was in the hospital when he received the IT dose of benzyl alcohol-containing methotrexate. Patients 3 and 4 were immediately admitted for 24 hours' observation on the day they received the IT dose of benzyl alcohol-containing methotrexate. All patients had subsequent visits in the clinic, which were reviewed. The neurological assessments by the clinicians and physical therapists were reviewed in this report.

Results

Four patients received IT methotrexate containing benzyl alcohol as described in the Table. The patient's ages ranged from 4 to 7.2 years, with 3 males and 1 female; 1 had Down syndrome, 3 had B-lineage ALL, and 1 had T-cell ALL. All patients were treated for ALL according to Children's Oncology Group (COG) protocols. An order was placed to administer 12-mg methotrexate IT diluted with 0.9% preservative-free normal saline in a total of 6 mL to each patient per our institutional IT chemotherapy administration guidelines. However, instead of selecting a preservative-free methotrexate preparation, the 12-mg dose of methotrexate was taken from a 25-mg/mL injection solution that also contained 0.9% (9 mg/mL) benzyl alcohol. As a result, the dose of benzyl alcohol given to each patient was 4.3 mg diluted in 6 mL, yielding a final concentration of 0.07% (0.7 mg/mL). The error was discovered after each of the patients received only 1 dose of benzyl alcohol-containing IT chemotherapy.

Patients 1 and 2 both had transient symptoms that may have been related to the benzyl alcohol-containing IT solution. Patient 1 received IT therapy on day 15 of consolidation therapy and was noted to have global weakness. The weakness was also possibly caused or exacerbated by steroid myopathy from 28 days of dexamethasone induction and neuropathy that was possibly caused or exacerbated by vincristine. Patient 2 exhibited lower extremity weakness 2 days following IT therapy that resolved within 24 hours. Patients 3 and 4 had no neurological consequences. None of the patients required any additional intervention (as determined by the treating team), so corticosteroid administration, spinal cord imaging, and cerebrospinal irrigation were all avoided.

The error was discovered by a pharmacy technician who examined the source vials closely and noticed that they contained preservative. She confirmed her

Figure. New drug procurement process.

EMR, electronic medical record; IV, intravenous

* For urgent requests, the Pharmacy Manager will engage the Pharmacy Purchaser with the drug specific need. Once received and reviewed, the Pharmacy Purchaser will shepherd the replacement drug from receiving, to EMR, to Inventory Management System, to IV Management System within 12 business hours.

** For after hours requests, pharmacist on duty will page the on-call Pharmacy Administrator. The on-call Pharmacy Administrator will engage the Pharmacy Manager to order drug, process EMR request, and process Inventory system add.

observation with the pharmacist working in the IV room. The source of the error can be traced back to our institution's drug procurement process. Historically, our pharmacy only carried preservative-free methotrexate for injection. In the context of a methotrexate shortage, our pharmacy department purchased 2-mL vials of benzyl alcohol-containing methotrexate for IV use. The 2-mL benzyl alcohol-containing methotrexate vials were unfortunately stocked into a bin in the pharmacy that was reserved for preservative-free product. As a result, the pharmacy technicians assumed the product was safe for IT use. In addition, the pharmacist reviewer failed to read the preservative warning on the vial because of the small font size. A review of all IT methotrexate dose images was conducted in the IV management system (DoseEdge, version 2.4.1, Baxter Healthcare Corporation, Deerfield, IL) as soon as the stocking error was discovered. This was when it was discovered that a total of 4 IT doses were dispensed and administered that contained benzyl alcohol.

A root cause analysis was conducted to identify factors that contributed to the error. As a result, our institution established a novel replacement drug procurement process for the pharmacy department to improve safety. The full process was mapped (Figure) to prevent errors such as this.

Discussion

Methotrexate is the most common IT chemotherapy

agent administered in pediatric ALL. Thousands of IT chemotherapy procedures are performed routinely in pediatric and adult oncology centers worldwide, with approximately 650 procedures conducted each year by our pediatric oncology service alone. It is common practice to administer methotrexate from a preservative-free preparation that includes preservative-free 0.9% sodium chloride. However, inadvertent IT administration of benzyl alcohol-preserved methotrexate may cause severe and potentially irreversible neurological damage. Hahn et al⁴ summarized 20 case reports, including their own case, showing that administration of benzyl alcohol into the central nervous system at concentrations of 0.9% to 1.5% can cause pain, anesthesia, and flaccid or spastic paraplegia (Table S1, included as Supplemental Table available only online, and appears with permission from *Neurology*). That report noted a rare ascending paralysis causing respiratory and cardiac arrest resulting in death. Application of a lumbar drain and methylprednisolone can potentially reverse these symptoms.⁴ They did observe 2 general presentations of injury including immediate flaccid areflexic paraparesis and, less common, delayed progressive spastic paraparesis with an onset weeks after IT treatments.⁴ This group also conducted experiments on nerve roots of rats, showing anesthetic effects of 0.9% benzyl alcohol on these nerves as well as irreversible effects noted after multiple exposures, including demyelination and fiber degradation.⁴

It is possible that the transient neurotoxicity exhib-

ited by 2 of our patients may have been caused by direct chemical action of benzyl alcohol on central nervous system tissues or, to some degree, by the chemotherapy itself. Regardless, the effect seen was minimal. It is possible that our patients exhibited a less severe and more transient course of symptoms because the concentration of benzyl alcohol (0.07%) used in our preparations was at least 10-fold lower than concentrations $\geq 0.9\%$, which have led to more severe and permanent symptoms seen in published reports. Notably, all our patients recovered completely.

The cause of our specific error can be traced back to the drug procurement process, which has become exceedingly more complex in the age of drug shortages. For us, the incidental purchasing of 2-mL vials of benzyl alcohol-containing methotrexate for IV use resulted in the potential harm of the 4 patients described. This is one example of a largely unreported detrimental effect of drug shortages on the health care system. The time and complexity required to constantly interchange manufacturers, vial sizes, and formulations merely to obtain drug products is a major stressor on every health care system across the world. Treatment delays, changes in regimens, and missed or suboptimal doses of chemotherapy have been previously reported.⁵ As drug shortages are becoming exceedingly more frequent this calls for increased awareness to the potential for errors in the medication use process, including medication administration that can be significant and potentially life-threatening or fatal.

Conclusion

Although this error resulted in minimal, if any neurotoxicity it is critical that all institutions recognize the potential for error and implement similar safety processes and precautions to ensure that this type of error will not occur.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent This study was approved by the Institutional Review Board for expedited review (Children's Hospitals and Clinics of Minnesota IRB# 1906-062). Altered consent and HIPAA authorization process was requested to contact parents of each patient by phone or in person. Consent was obtained from a parent of each patient by phone, and permission was obtained to use information from the patient's medical records for this research protocol. A witness was present and the process was documented in our files.

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