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Original Article

Hazardous Drug Residue on Exterior Vial Surfaces: Evaluation of a Commercial Manufacturing Process

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ABSTRACT

Purpose: Hazardous drug residue on the exterior surface of drug vials poses a potential risk for exposure of health care workers involved in handling these products. The purpose of this article is to heighten the awareness of this serious issue and to evaluate a commercial manufacturing process for removing and containing hazardous drug (HD) residue on exterior vial surfaces. Additionally, findings from this study are interpreted, incorporated into the current body of evidence, and discussed by experts in this field.

Methods: This study includes separate evaluations for the presence or absence of surface drug contamination on the vials of 3 HD products: 5-fluorouracil, cisplatin, and methotrexate. The drug products were packaged in vials using a patented prewashing/decontamination method, application of a polyvinylchloride (PVC) base, and use of clear glass vials. An additional step of encasing the vial in a shrink-wrapped sheath was used for 5-fluorouracil and cisplatin.

Results: Of all 5-fluorouracil (110 vials), methotrexate (60 vials), and cisplatin (60 vials) tested, only 2 had detectable amounts of surface residue. One 5-fluorouracil vial was found to have approximately 4 mg of 5-fluorouracil on the surface of the vial. The second contaminated vial was cisplatin, which was discovered to have 131 ng of platinum, equal to 200 ng of cisplatin or 0.2 µL of cisplatin solution, on the vial sheath.

Conclusion: Using validated extraction and analytic methods, all but 2 of the 230 tested vials were found to be free of surface drug contamination. Pharmacy leaders need to take an active role in promoting the need for clean HD vials. Manufacturers should be required to provide their clients with data derived from externally validated analytic studies, reporting the level of HD contamination on the exterior of their vial products.

Key Words—clean vials, hazardous drugs, safe handling, vial contamination

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The term *hazardous drugs* was first introduced more than 20 years ago by the American Society of Health-System Pharmacists (ASHP) as a way to more accurately depict therapeutic drugs with adverse effects that could endanger health care workers.[1] This term and the proposed criteria used to evaluate drugs were adopted by the Occupational Safety and Health Administration (OSHA) in 1995.[2] The National Institute for Occupational Health and Safety (NIOSH) modified the criteria in 2004 to reflect a hierarchy of concerns that would encompass future drug modalities.[3] The United States Pharmacopeia (USP) also adopted the term in its 2007 revision to USP General Chapter <797>.[4]

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A hazardous drug (HD) is generally defined as any agent for which "studies in animals or humans indicate that exposures to them have a potential for causing cancer, developmental or reproductive toxicity, or harm to organs."[3] Drugs are characterized as hazardous due to their inherent toxicity.

Concern with occupational exposure to HDs has been expressed after reports and studies of adverse effects in health care workers. Acute symptoms, such as rashes, have been reported primarily due to inadvertent skin contact.[5,6] A systematic review and meta-analysis conducted in 2005 examined reports of increased risks of cancer, reproductive complications, and acute toxic events in health care workers who were exposed to HDs and identified an association between exposure to chemotherapy and spontaneous abortions.[7] Reports of liver damage, bladder cancer, and breast cancer were not found to be suitable for statistical pooling in this 2005 study, which thereby limited the study of cancer risks.[7] A 2010 study, however, described evidence of drug uptake and chromosomal changes in oncology workers.[8] The damaged chromosomes in which changes were discovered are the same as those that are associated with therapy-related myelodysplastic syndrome (t-MDS) and therapy-related acute myeloid leukemia (t-AML); this points to a relationship between HD exposure in workers and an increased possibility of cancer.[8] Similar to the 2005 meta-analysis, a 2012 study reported adverse reproductive events in nurses exposed to HDs in the workplace and noted a 2-fold increased risk of spontaneous abortion.[7,9]

GUIDELINES

Since it was first recognized that occupational exposure to these agents posed a potential health risk to workers, various groups, institutions, and agencies around the world have developed and published guidelines or recommendations for handling HDs in the health care setting. In 2000, NIOSH assembled a Working Group on Hazardous Drugs and later published the group's findings as the 2004 NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings.[3] A number of guidelines that integrated the content of the alert were published or updated following its publication. Examples include the ASHP 2006 guidelines on handling hazardous drugs,[10] the 2007 International Society of Oncology Pharmacy Practitioners practice standards,[11] and the 2009 Oncology Nursing Society's chemotherapy and biotherapy guidelines and recommendations for practice.[12]

Despite guideline development and implementation of safe handling precautions, environmental studies in a number of countries continue to report measurable concentrations of HDs on various surfaces in health care areas.[13-28] Numerous studies report HDs in the urine of health care workers who handle, prepare, or administer them.[13,15,19,22-25,28-33]

Environmental contamination with HDs can occur when receiving and storing these agents and during all phases of their preparation, administration, and waste disposal. Strategies to reduce the risk of contamination and occupational exposure in the workplace when HDs are being handled, such as primary engineering controls (biologic safety cabinets and compounding aseptic containment isolators), personal protective equipment, and closed system drug transfer devices, are widely employed.

Studies have demonstrated the presence of drug residue on the exterior surfaces of drug vials, indicating that contamination occurs during the manufacturing process.[34-41] The reasons for this contamination have not been fully revealed, but it could be associated with leakage during filling, improper and inadequate vial cleaning after filling, or accidental leakage during transport and distribution. Contamination on the exterior surface of vials containing HDs represents a major safety concern in hospital settings worldwide, and there are no effective strategies to contain or limit environmental contamination from this source.

Although many of the guidelines promote clean HD vials, external vial contamination continues to exist.[40] Pharmacy staff who unpack and store drug orders are at risk for exposure, as contamination can spread in the environment from the unpacking and storage areas to the preparation area. Several published articles call for distributors, manufacturers, purchasing groups, professional societies, and all other pertinent parties to make the manufacturers of HDs aware of the issue of contamination and its unacceptability.[34,37,42,43] In response, several pharmaceutical manufacturers have improved their cleaning processes and have changed the presentation of their hazardous products.[44]

The extensive literature that documents surface contamination on HD vials when they are shipped and received into the clinical oncology settings should be of concern to all pharmacy practitioners. Although some manufacturers of HD products, especially in Europe, are moving toward applying special outer coverings to the vials in response to concerns about both surface drug contamination and environmental

exposure, this practice is inconsistent. In addition, there is a question as to whether manufacturers who "shield" the drug vials actually examine whether the drug residue has been eliminated from the vial surface. Such information is necessary in order to validate that improved cleaning processes and the use of outer coverings are actually effective.

The current study was undertaken to examine whether the decontamination method (used on all 3 products) and a protective sheathing/sleeve (used on 2 of the 3 products) initiated by a North American manufacturer of HD products was effective in eliminating surface drug residue on the drug vials. A validated protocol from an independent analytical laboratory with extensive expertise in detecting HD residue on the outer vial surfaces was utilized. No control was used, because the goal of this investigation was to demonstrate an absence of contamination, not reductions compared to a control group.

MATERIALS AND METHODS

This study includes separate evaluations for the presence or absence of surface drug contamination on the vials of 3 HD products: 5-fluorouracil, cisplatin, and methotrexate. The first 2 steps of this investigation included 5-fluorouracil and cisplatin that were packaged in vials using the complete *Onco-Tain* system (Hospira, Lake Forest, IL) (**Figure 1**). This patented process includes prewashing/decontamination, encasing the vials in a shrink-wrapped sheath, applying a polyvinylchloride (PVC) base, and using clear glass vials. The prewashing/decontamination process involves a complex series of multiple nozzles for vial washing, brushing, rinsing, and drying. Once vials have been washed and dried, they are transferred to a separate sterile facility for labeling and application of the sheath to provide surface protection and act as a barrier against surface drug residue. The PVC base prevents the glass vials from shattering. The glass allows for an easier inspection of the vials as a final safety check prior to dose preparation. This decontamination process is validated for the absence of active substance on vials, with documentation at the manufacturing site.

Published literature suggests that adding a sheath or sleeve reduces the contamination levels, but at varying degrees.[37] To isolate the contribution of the sheath in the reduction of contamination, the last step of this investigation analyzed methotrexate vials that were packaged using the same decontamination process as described previously except without the application of the shrink-wrapped sheath.

Figure 1. Photo of vial with decontamination packaging.

5-Fluorouracil Vials

Protocol Validation Phase

In March 2009, 10 vials of 5-fluorouracil 5 g/100 mL with *Onco-Tain* packaging were sent from the manufacturer's Canadian warehouse to the lab of Exposure Control Sweden AB (EC) in The Netherlands. Each was packed in a separate 330 mL polypropylene container (*Securitainer*; Fisher Scientific, Landsmeer, The Netherlands). At EC, each container was opened and 140 mL 0.03 M NaOH was added. The vials were totally immersed and then subjected to ultrasonic vibration for 60 minutes.

Phase 1

In April 2009, 10 vials of 5-fluorouracil 5 g/100 mL with *Onco-Tain* packaging were packaged and sent as stated in the protocol validation phase. At EC, each container was opened and the sheath-covered vial was wiped with 2 special tissues that were pre-wetted with 5 mL of 0.03 M NaOH. One tissue was used for the removed plastic cap and the aluminium seal under the cap. The other tissue was used for the sheath covering the vial itself. The 2 tissues were collected separately in different 175 mL polyethylene containers (*Nalgene Nunc*; Fisher Scientific, Landsmeer, The Netherlands) to which 140 mL 0.03 M NaOH was added, allowing the tissues to soak. The tissues were prepared for analysis according to standard procedures.[45,46] Finally, the removed plastic cap and the vial were placed back into the original 330 mL container. One hundred mL of 0.03 M NaOH was added to totally immerse the vials, and the container was sealed and subjected to ultrasonic vibration for 60 minutes. Additionally,

2 blank control samples containing a tissue and 145 mL 0.03 M NaOH were prepared and analyzed for 5-fluorouracil to verify the analytical procedure.

Phase 2

In June 2009, 90 vials of 5-fluorouracil 5 g/100 mL with *Onco-Tain* packaging were packaged and sent as stated in the protocol validation phase. Sample preparation was identical to phase 1. No blank samples were collected.

Analysis

The NaOH extracts were analyzed for 5-fluorouracil on a high-performance liquid chromatography (HPLC) system with ultraviolet (UV) detection using previously published methodology with a detection limit of 20 ng 5-fluorouracil/mL NaOH.[45,46] The contamination on the outside sheathing of the drug vials was calculated assuming 100% extraction recovery and wipe efficiency from all surfaces of the sheath covering the vial, cap, and seal, rendering all results as underestimates.

Cisplatin Vials

Phase 1

In September 2012, 10 vials of cisplatin 50 mg/50 mL with *Onco-Tain* packaging, including the sheathing, were sent from an independent Canadian warehouse to the lab of EC in The Netherlands. Vials were packed individually in cartons, as they are normally sent to customers. The packaging was opened and placed in a separate coded 265 mL polypropylene container (*Securitainer*). One hundred sixty mL of 0.5 M HCl solution was added to the container to totally immerse each cisplatin vial; the container was sealed and then subjected to ultrasonic vibration for 60 minutes.

Phase 2

In October 2012, 50 vials of cisplatin 50 mg/50 mL with *Onco-Tain* packaging, including the sheathing, were packaged and sent as stated in phase 1. Sample preparation was identical to phase 1.

Analysis

Platinum analysis was performed with stripping voltammetry according to standard procedures.[47] One-half mL of the extract was destructed using hydrogen peroxide, hydrochloric acid, and UV light, resulting in the formation of platinum ions. Finally, the platinum ions were analyzed instead of the platinum-containing cytotoxic drug. Samples were analyzed in duplicate, including destruction. Mean values were reported. Due to background levels of platinum, the limit of quantification was set at 0.50 ng/mL HCl. Five blank samples were prepared and analyzed to correct for background levels of platinum. The surface contamination on the sheath covering the outside of the drug vials was calculated assuming 100% extraction recovery, rendering all results as underestimates.

Methotrexate Vials

Phase 1

In September 2012, 10 vials of methotrexate 500 mg/20 mL manufactured with the same decontamination process for the *Onco-Tain* system, but without the sheath, were sent from an independent Canadian warehouse to EC. Each was packed in a separate 80 mL polypropylene container (*Securitainer*). Thirty-five mL of 0.03 M NaOH solution was added to each container to totally immerse the methotrexate vial, and then the sealed container was subjected to ultrasonic vibration for 60 minutes.

Phase 2

In October 2012, 50 vials of methotrexate 500 mg/20 mL manufactured with the same decontamination process for the *Onco-Tain* system, but without the sheath, were packaged and sent as described in phase 1. Sample preparation was identical to phase 1.

Analysis

The entire methotrexate extract was further processed according to standard procedures using an HPLC system with UV detection with a detection limit of 3 ng/mL NaOH. [45,46] The surface contamination of the drug vials was calculated assuming 100% extraction recovery, rendering all results as underestimates.

RESULTS

5-Fluorouracil Vials

During the protocol validation phase of this trial, 4.318 mg of 5-fluorouracil was detected on the surface of 1 vial (**Table 1**). This corresponds to about 0.09 mL of the 5-fluorouracil solution (50 mg/mL).

The results of the analysis of 5-fluorouracil on the sheath covering the 10 vials of 5-fluorouracil during phase 1 and the 90 vials during phase 2 revealed no detectable 5-fluorouracil on the vials. No 5-fluorouracil was detected on the blank samples (**Table 2**).

Table 1. Protocol validation phase: Vial contamination with 5-fluorouracil (5-FU)

Vial code	Total volume NaOH, mL	5-FU, ng/mL NaOH	5-FU, mg
1, 3-10	100	ND	--
2	100	43180	4.318

Note: ND = not detected: 5-FU < 20 ng/mL NaOH.

Table 2. Vial contamination with 5-fluorouracil (5-FU)

Phase	Vial code	Total volume NaOH, mL			5-FU, ng/mL NaOH		
		Cap + Alu	Glass part	Total	Cap + Alu	Glass part	Total
1	1-10	145	145	100	ND	ND	ND
2	1-90	145	145	100	ND	ND	ND
1	Blank 1 [a]		145			ND	
1	Blank 2 [a]		145			ND	

Note: Alu = aluminium around cap; ND = not detected: 5-FU < 20 ng/mL NaOH.

[a]Blank sample contains a tissue and 145 mL NaOH.

Cisplatin Vials

Phase 1 analysis of platinum on the outside of the sheath of the 10 vials of cisplatin revealed that platinum was not detected on any of the vials. During phase 2, platinum was not detected on the outside of the *Onco-Tain* sheath on 49 of the 50 vials, however, 131 ng platinum was detected on the *Onco-Tain* sheath of 1 vial. This corresponds to about 200 ng cisplatin or 0.2 µL cisplatin solution (1 mg/mL) (**Table 3**).

Methotrexate Vials

Phase 1 and phase 2 analysis of methotrexate on the 10 and 50 vials, respectively, of methotrexate revealed no detectable methotrexate on any of the total 60 vials (**Table 4**).

DISCUSSION

In the protocol validation phase, the results show contamination with 5-fluorouracil on the outside of

Table 3. Vial contamination with platinum (PT)

Phase	Vial code	Total volume HCl, mL	PT, ng/mL HCl	PT, ng
1	1-10	160	ND	--
2	11-21, 23-60	160	ND	--
2	22	160	0.82	131

Note: ND = not detected: PT < 0.50 ng/mL HCl.

Table 4. Vial contamination with methotrexate (MTX)

Phase	Vial code	Total volume NaOH, mL	MTX, ng/mL NaOH
1	1-10	35	ND
2	11-60	35	ND

Note: ND = not detected: MTX < 3 ng/mL NaOH.

one vial. This could be caused by real contamination on the vial, but it is more likely due to damage of the vial during transportation to the lab as the vials were transported unprotected. Damage was not observed by visual inspection. Another explanation could be that the sheath was damaged by the aggressive extraction methods, where the extraction liquid could have dissolved drug residue between the glass and the sheath in the positive sample.

Due to the high concentration found during the protocol validation phase, phase 1 was performed, ensuring vials were transported to the lab in protective bubble wrap. A testing process for contamination of separate parts of the vials, which was conducted in addition to the whole vial extraction, was identical to the protocol validation phase. No contamination was detected on any of the parts of the 10 vials in phase 1. The results were again confirmed in phase 2 with no contamination detected on any of the parts of the 90 vials.

The observed contamination in the protocol validation phase seems to be an exceptional occurrence based on the overall results: No contamination was detected on 109 out of 110 vials. Additionally, if the source of the detected drug contamination was located between the vials and the protective film, the contamination would not have resulted in any HD exposure, possibly demonstrating the importance of external sheathing.

In phase 1, the results show no contamination on the outside of the sheaths of 5-fluorouracil and cisplatin vials nor on the outside of the methotrexate vials. In phase 2, no contamination was observed with the 5-flourouracil and the methotrexate vials. Contamination with platinum was observed on 1 out of 50 vials of cisplatin. The origin of contamination on the surface of 1 cisplatin vial at just above the detection limit of the analytical method is not known. It is not possible to assess what the results would have been if the cisplatin vials had not been externally sheathed during the *Onco-Tain* process, as previous studies have shown higher numbers of contaminated vials and/or higher levels of contamination on the outside of drug vials that do not have protective coverings.[34-38,48]

As noted previously, at the time of this investigation, the methotrexate vials did not include the application of a sheath. Sampling the un-sheathed vials allowed validation of the prewashing/ decontamination method independent of the sheathing process. While the washing process proved to be effective in reducing external vial contamination, the sheathing was shown to provide additional protection against contamination resulting from damage during handling and transport. Methotrexate vials are now manufactured with the complete decontamination process, which includes the external sheath.

CONCLUSION

HD residue on the exterior surface of drug vials poses a potential risk for exposure of health care workers involved in handling these products. This type of HD contamination can easily spread throughout the workplace as drug vials are moved between receiving, storage, preparation, and waste disposal areas. It is important to educate staff that the potential for surface contamination exists and to require them to follow appropriate handling precautions (eg, personal protective equipment, regular decontamination of surfaces, use of separate storage areas).

Pharmacy leaders need to take an active role in promoting clean HD vials. Manufacturers should be required to provide their clients with data derived from externally validated analytic studies, reporting the level of HD contamination on the exterior of their vial products. Studies analyzing HDs need to be specific to each manufacturing process and should be performed with each change in manufacturing process. The detection of drug residue on vial surfaces must prompt manufacturers to implement processes of eliminating (eg, washing) and properly containing (eg, shielding) surface contamination and then to follow-up with re-analysis to demonstrate the efficacy of the new processes.

In this study, HD vials from one manufacturer using a patented process designed to remove and contain exterior drug residue were tested for surface drug contamination. Using validated extraction and analytic methods, the tested vials were found to be free of surface drug contamination.

This analytic study of surface drug contamination from one manufacturer's HD vial products is an important example of the responsibility to document and report the level of surface drug contamination after implementation of an enhanced manufacturing process. Individuals or groups (eg, group purchasing organizations) responsible for contracting and/or purchasing HD products for use in the health care workplace should request and review this information. Preferential consideration should be given to those vial products for which manufacturing processes have been implemented to minimize surface contamination and breakage and, further yet, to those where validated information exists to support clean vial distribution.

The NIOSH alert reinvigorated concerns about occupational exposure to HDs. There are many steps and responsibilities, involving many individuals and groups, that need to be taken when working toward elimination of HD exposure in the workplace. Clean vials, which are free of HD surface residue, are a very important step in achieving this goal.

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