Journal of Oncology Pharmacy Practice

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J Oncol Pharm Pract published online 28 June 2010
DOI: 10.1177/1078155210374673

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J Oncol Pharm Pract OnlineFirst, published on August 12, 2010 as doi:10.1177/1078155210374673

Journal of Oncology Pharmacy Practice

Research Paper

J Oncol Pharm Practice
0(0) 1–7

DOI: 10.1177/1078155210374673
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Evaluation of surface contamination with cyclophosphamide following simulated hazardous drug preparation activities using two closed-system products

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Abstract

Purpose. A preliminary investigation was conducted to evaluate and compare the effectiveness of two closed-system products in preventing contamination of typical pharmacy workplace surfaces with cyclophosphamide during simulated hazardous drug preparation activities in a controlled laboratory setting.

Methods. Two separate trials simulating hazardous drug compounding using cyclophosphamide were performed with two different closed-system products. Prior to each trial, work area surfaces of the biological safety cabinet (BSC) workbench, the BSC airfoil and front grill, and the floor below the BSC were cleaned, and wipe samples were collected and analyzed to determine, if present, levels of cyclophosphamide. Following each trial, wipe samples were collected from the work area surfaces to determine the hazardous drug containment effectiveness of each closed-system product.

Results. Cyclophosphamide was not detected on work area surfaces prior to each trial. Low levels were detected on the BSC workbench surface following both trials.

Discussion. Based on the limited number of samples obtained during this preliminary study and the determination of the presence of the chemical of interest on the drug vials, no statistical evaluation was performed to compare the relative effectiveness of the two systems tested. Work practices and procedures regarding product operation may affect hazardous drug containment and worker safety. Further study and statistical analyses are needed.

Keywords
hazardous drug, surface contamination, effectiveness, containment, closed-system, cyclophosphamide

Introduction

Worldwide, cancer is the leading cause of death with an estimated 7.9 million deaths in 2007.[1] These numbers are expected to double before 2030.[1] Given the increase in the number of patients, the increasing numbers of new agents being developed to treat cancer and the increasing complexity of chemotherapy combination therapy, there will be a dramatic increase in the number of healthcare workers exposed to hazardous drugs from the current estimate of 5.5 million workers per year.[2]

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Handling of chemotherapy drugs has been recognized since the 1970s as a potential health hazard to workers. In the early 1990s, the American Society of Health-System Pharmacists was the first organization to formally define 'hazardous drugs'.[3] Drugs are classified as hazardous if 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] Both the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health (NIOSH) have adopted the aforementioned definition.[4,5] NIOSH expands the definition to consider a drug hazardous if it exhibits one or more of the following six characteristics:

1. Carcinogenicity;
2. teratogenicity;
3. reproductive toxicity;
4. organ toxicity at low doses;
5. genotoxicity; and
6. structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria.

NIOSH and The United States Pharmacopeia's General Chapter 797 (USP 797) recommend using a closed-system transfer device to minimize occupational exposures to antineoplastic and other hazardous drugs.[5,6] The NIOSH definition of a closed system is one that mechanically prevents the transfer of environmental contaminants into the system and the escape of drug or vapor out of the system. Some studies have shown the benefits of a closed system in reducing hazardous drug surface contamination when compared to traditional preparation techniques in the clinical setting.[7–9]

This study was conducted to evaluate and compare two closed-system products during simulated hazardous drug preparation activities using a known amount of cyclophosphamide in a laboratory setting. Attempts were made to control, minimize, and evaluate other known sources of environmental contamination which may be found in clinical settings to help focus on the closed-system products' efficiencies in minimizing contamination of typical pharmacy workplace surfaces.

Methods

The study site was an experimental laboratory setting. A Class 100 clean room and a Class II Biological Safety Cabinet (BSC) vented to the outdoors were utilized. There was no knowledge of prior use or handling of cyclophosphamide in the clean room or BSC at the study site.

Two closed-system products which appeared to be commonly used in health care settings were evaluated. Both products include vial and intravenous (IV) bag adaptors and connectors that were designed to prevent hazardous drug release. The first was ChemoCLAVE™ Oncology Preparation and Delivery System (ICU Medical, Inc.) which include the Genie™ Closed Vial Access Device (REF CH-77), the Spiros™ Closed Male Connector (REF CH2000); (Figure 1), and the Access Device, IV Bag, Clave Connector (REF CH-10). Once the Spiros was attached to a syringe and the Genie was attached to a vial, three user steps were required for fluid transfer. The needle-free Spiros was connected to the Genie Closed Vial Access Device by inserting the male end of the Spiros into the female end of the Genie, pressing, and twisting. Disconnection required twisting in the opposite direction and withdrawing from the Genie. Access to the IV Access Device was identical.

The second product was PhaSeal® (Carmel Pharma), which included the Protector™ vial access device (REF

Figure 1. ChemoCLAVE™ System: Genie Closed Vial Access Device with internal balloon and Spiros Closed Male Connector.

P50), the Injector™ Luer Lock male connector (REF N31); Figure 2), and the Infusion Adaptor (REF C100). Once the Injector Luer Lock was attached to a syringe and the (Protector was attached to a vial, five user steps were required for fluid transfer. The Injector, with a contained needle, was connected to the Protector by inserting the male end of the Injector into the female end of the Protector, pressing, twisting, lifting a lever on the Injector (to release a needle cap), and pushing the needle into the vial. Disconnection was achieved by pulling the needle out of the vial, twisting in the opposite direction, and withdrawing from the Protector. Access to the Infusion Adaptor was identical.

A certified pharmacy technician specializing in oncology preparations performed all simulated compounding duties using standard aseptic and hazardous drug preparation techniques and personal protective equipment. The technician had approximately 1 year experience working with ChemoCLAVE and approximately 7 years experience working with PhaSeal.

Figure 2. PhaSeal® Protector 50 vial access device with external balloon and Injector Luer Lock male connector.

Cyclophosphamide was selected as a hazardous drug marker for its common use in the clinical setting and the availability of a sensitive analytical method to detect trace levels of the chemical. The analytical limit of detection for cyclophosphamide was 15.7 ng per sample. Wipe samples were collected from strategic locations and items to sample for cyclophosphamide on surfaces. All wipe samples were collected using Cyto Wipe Kits (Exposure Control B.V.).

At each sampling location(s), the surfaces were measured to determine the surface area that was to be sampled. A new pair of nitrile gloves was donned prior to the collection of each sample. Using a medicine dropper, ~17 ml of solution was applied to each surface. A paper tissue was used to spread the solution over the entire pre-measured area and the area was sampled by wiping in multiple directions using moderate hand pressure. During the sampling, emphasis was placed on sampling the surfaces in a manner as to not wipe outside of the measured surface area and to not damage the tissue. The tissue was placed in a plastic 175-ml sample bottle. A second tissue was used to completely dry the surface using unidirectional wiping techniques and was also placed in the same sample bottle.

For items that would not permit the solution to be placed on the surface, approximately one-half of the solution from the medicine dropper was placed directly on the first paper tissue. The surfaces were sampled at each location as described above, the remaining solution was placed on the second paper tissue, and the surface was wiped a second time as described above, carefully folding the tissue and completely drying the surface.

The study was performed over a 2-day period. On Day 1 of the study, the site was prepared by measuring and demarcating the surfaces to be sampled on the BSC workbench (4400 cm^2), the BSC airfoil and front grill (2000 cm^2), and the floor directly below and in front of the BSC (4400 cm^2). All of the surfaces that were selected to be sampled were cleaned using Surface Safe® (Hospira). Surface Safe is a product that was designed to inactivate cytotoxic drug substances including cyclophosphamide, and remove them from surfaces using a two-step application process. Following Surface Safe application, the surfaces were further cleaned using filtered water and lint-free towels and allowed to dry.

In a separate area of the clean room, 40 vials containing 1g of lyophilized cyclophosphamide powder (Baxter) were removed from their individual outer cardboard box packaging materials and randomly divided into two groups of 20 vials each designated as Vial Group 1 and Vial Group 2. Composite wipe

samples were collected from the exterior surfaces of the vials to determine if contamination was present on the containers in their as-received conditions from the manufacturer. All vials used during the study were sampled. Five vials were wiped for each composite wipe sample. The wipes were folded after each vial was sampled to minimize spreading possible contamination between vials during sampling.

On Day 2 of the study, the product trials were conducted. The ChemoCLAVE trial was conducted first using Vial Group 1, followed by the PhaSeal trial using Vial Group 2. Prior to each trial and after cleaning with Surface Safe, a wipe sample was collected from the demarcated surface areas of the BSC workbench, BSC airfoil/grill, and the floor to determine if the surfaces were free from cyclophosphamide contamination.

Vials were placed on protective/absorbent pads on either side of the demarcated area within the BSC to minimize possible exterior vial contamination from contacting the sampling surfaces. For each trial, the pharmacy technician donned a new pair of gloves and performed compounding activities inside the BSC over the demarcated areas. Each of the 20 cyclophosphamide vials were reconstituted using 50 ml of 0.9% sodium chloride for injection, then three individual volumes of 5 ml each were removed from each of the 20 vials and transferred to 10 IV bags (six transfers to each bag) containing closed-system connectors (totals for each trial: 60 transfers; 300 ml solution; 6 g cyclophosphamide.) The pharmacy technician was observed while performing duties during the trials. The duration of each trial was ~1h. Following each trial, wipe samples were collected from the demarcated areas of the BSC workbench, BSC airfoil/grill, and the floor, and from the pharmacy technician's gloves. A composite sample of both gloves used during the trial was collected utilizing one tissue media for each glove. All exterior surfaces of the gloves were wiped. Concentrations were reported in ng cyclophosphamide per cm^2 of surface area, or for gloves, reported as total ng cyclophosphamide per pair.

A total of five field blank samples were collected during the study for quality control purposes. The field blank samples were handled similarly to environmental wipe samples, only no surfaces were wiped. Approximately one-half of the solution was placed on each tissue media, and the tissues were folded and placed in the sample bottles.

All of the wipe samples obtained were contained in sample bottles as soon as possible after collection and were stored in an insulated container with dry ice. At the completion of the study, all samples were packaged with dry ice and shipped to Exposure Control in The Netherlands for analysis.

The wipe samples were prepared by adding 140 ml of a 0.03 M NaOH solution. After extraction, a part of the extract was subjected to laboratory 'clean up' operations.[10,11] Samples were analyzed using a gas chromatograph that was equipped with dual mass spectrometers (GC-MSMS), which is an enhancement to the original method developed for GC-MS.[12] Specificity and sensitivity are increased using GC-MSMS in place of GC-MS.[13]

Results

Vial wipe sampling results

Cyclophosphamide was detected on the exterior of some vials in Vial Group 1 (used for the ChemoCLAVE trial.) Of the four composite wipe samples collected from Vial Group 1, two samples showed detectable levels and two samples showed no cyclophosphamide contamination. No cyclophosphamide was detected on the exterior of vials intended for the PhaSeal trial (Vial Group 2). Table 1 summarizes the composite vial sample results.

Pre-trial wipe sampling results

No cyclophosphamide was detected on the BSC or floor surfaces following cleaning with Surface Safe and prior to both trials. Table 2 summarizes the pre-trial sample results.

Post-trial wipe sampling results

Following the ChemoCLAVE™ trial, no cyclophosphamide was detected on the BSC airfoil/grill or the floor. Cyclophosphamide was detected on the BSC workbench and the pharmacy technician's pair of gloves. Following the PhaSeal® trial, cyclophosphamide was detected on the BSC workbench, but not on

Table 1. Summary of vial sample results

Vial group	Composite samples[a]	Cyclophosphamide (ng)
1 (Used for ChemoCLAVE™ trial)	Sample 1	nd[b]
	Sample 2	nd
	Sample 3	2694
	Sample 4	17
2 (Used for PhaSeal® trial)	Sample 1	nd
	Sample 2	nd
	Sample 3	nd
	Sample 4	nd

[a]Each composite sample was taken from five 1g vials.
[b]nd = not detected (cyclophosphamide < 15.7 ng).

the BSC airfoil/grill, the floor, or the pharmacy technician's gloves. Table 3 summarizes the post-trial sample results.

Quality control sample results

No cyclophosphamide was detected on the field blank samples.

Discussion

Surface contamination in pharmacies and treatment areas has been a major concern. BSCs, countertops, floors in and adjacent to preparation areas, tabletops, chairs, and floors in treatment areas may have contamination with hazardous drugs when a closed-system is not used. A study examining the contamination in six sites in the US and Canada found that measurable amounts of the antineoplastic agents (cyclophosphamide, ifosfamide, fluorouracil) were detected in 75% of pharmacy samples and 65% of administration samples.[14]

Many factors may contribute to surface contamination in the clinical setting. Some studies have also shown contamination on the exterior of vials as received from manufacturers.[15,16] Unreported or inadequately cleaned spills, transport and placement of contaminated objects, patient body fluids, and spreading by hand or foot contact may contribute to surface contamination.

This study was conducted in a controlled laboratory setting, using known amounts of cyclophosphamide, while taking measures to minimize other known sources of surface levels common in the clinical setting. This approach was used to help focus on the closed-system products' efficiencies in minimizing contamination of typical pharmacy workplace surfaces.

The results from the analyses of the wipe samples collected from the BSC workbench, airfoil/grill, and the floor following cleaning with Surface Safe showed that the surfaces were free from detectable levels of cyclophosphamide prior to each trial. Cyclophosphamide was detected in low concentrations on the BSC workbench surfaces but not on the airfoil/grill or floor following both trials.

It was postulated that vial contamination may contribute to levels of cyclophosphamide on the work area surfaces following the product trials. To determine if vial contamination could have contributed to surface levels, wipe samples were collected from the vials and the technician's gloves. To help minimize possible vial contamination from contributing to surface levels, vials were placed on protective pads on either side of the demarcated area of the BSC workbench and the technician was careful not to touch or place vials on the workbench.

Although many of the vials used in the study had no detectable cyclophosphamide contamination, the results showed that some vials used for the ChemoCLAVE trial had detectable levels. The presence

Table 2. Summary of pre-trial sample results

		Prior to ChemoCLAVE™ trial		Prior to PhaSeal® trial	
Surface description	Surface area (cm^2)	Cyclophosphamide (ng)	Cyclophosphamide concentration (ng/cm^2)	Cyclophosphamide (ng)	Cyclophosphamide concentration (ng/cm^2)
Floor	4400	nd[a]	<0.004	nd	<0.004
Airfoil/grill	2000	nd	<0.008	nd	<0.008
Workbench	4400	nd	<0.004	nd	<0.004

[a]nd = not detected (cyclophosphamide < 15.7 ng).

Table 3. Summary of post-trial sample results

		Following ChemoCLAVE™ trial		Following PhaSeal® trial	
Surface description	Surface area (cm^2)	Cyclophosphamide (ng)	Cyclophosphamide concentration (ng/cm^2)	Cyclophosphamide (ng)	Cyclophosphamide concentration (ng/cm^2)
Floor	4400	nd[a]	<0.004	nd	<0.004
Airfoil/grill	2000	nd	<0.008	nd	<0.008
Workbench	4400	468	0.11	622	0.14
Gloves	2 gloves	377	na[b]	nd	na

[a]nd = not detected (cyclophosphamide < 15.7 ng).
[b]na = not applicable.

of the chemical on the vials may have contributed to the low level detected on the BSC workbench. It was observed that on two occasions during the ChemoCLAVE trial, a vial was inadvertently placed on the BSC workbench by the technician performing the simulated compounding duties. The presence of contamination on some vials and on the technician's gloves suggests that the chemical was transferred to the gloves. It is possible that contamination was spread to the workbench by contact with syringes and/or IV bags that were handled by the technician's gloves. It is assumed that vial contamination was reduced due to vial wipe sampling, and higher levels would be expected on the pharmacy technician's gloves and on surfaces if the vial wipe sampling had not been conducted.

The surface transfer of the chemical as postulated above with the ChemoCLAVE trial is an unlikely factor in the PhaSeal trial. This is because, although there was a low level of cyclophosphamide detected on the BSC workbench following the PhaSeal trial, no contamination was detected on the vials or on the pharmacy technician's gloves. It is possible that work practices and procedures regarding product operation could have contributed to surface contamination during the PhaSeal trial. On two occurrences the Injector Luer Lock protective needle caps were not retracted when withdrawn from the drug vials exposing the needle. Small droplets that normally would otherwise be contained could have possibly reached the BSC workbench. These occurrences also posed needlestick hazards.

The concentrations reported in these results were calculated with no determination of analyte recoveries and wipe efficiencies. Therefore, all results reported are estimates of the concentrations present on the surfaces sampled.

Vial contamination may have contributed to the low level of cyclophosphamide observed on the BSC workbench following the ChemoCLAVE trial. Work practices and procedures regarding product operation may have contributed to the low level of cyclophosphamide observed on the BSC workbench following the PhaSeal trial. Work practices and procedures regarding product operation appeared to be an important factor in hazardous drug containment and needle safety when using PhaSeal, but not when using ChemoCLAVE, which requires fewer user steps and it is needle free. The PhaSeal Injector Luer Lock model (REF N31) that was used for this study has been replaced by a more recent model (REF N35).

Based on the limited number of samples obtained during this preliminary study and the determination of the presence of the chemical of interest on the drug vials, no statistical evaluation was performed to compare the relative effectiveness of the two systems tested. Further study and statistical analyses are needed to investigate the containment effectiveness of the products in a controlled setting.

Acknowledgments

We would like to thank pharmacy personnel from Maine Center for Cancer Medicine for their contributions to this study. This work was supported by ICU Medical, Inc.

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