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Original Article

Reduction in Surface Contamination With Cyclophosphamide in 30 US Hospital Pharmacies Following Implementation of a Closed-System Drug Transfer Device

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Abstract

Purpose: In a follow-up to a previous study, surface contamination with the antineoplastic drug cyclophosphamide was compared in 30 US hospital pharmacies from 2004 to 2010 following preparation with standard drug preparation techniques or the *PhaSeal* closed system drug transfer device (CSTD).

Methods: Wipe samples were taken from biological safety cabinet (BSC) surfaces, BSC airfoils (the front leading edge of the BSC), floors in front of BSCs, and countertops in the pharmacy, and they were analyzed for contamination with cyclophosphamide. Contamination was reassessed after a minimum of 6 months following the implementation of the CSTD. Surface contamination (ng/cm^2) was compared between the 2 techniques and between the previous and current test periods and evaluated with the Kruskal-Wallis test.

Results: With the use of CSTD compared to the standard preparation techniques, a significant reduction in levels of contamination with cyclophosphamide was observed ($P < .0001$). Median values for surface contamination with cyclophosphamide were reduced by 86% compared to 95% in the previous study.

Conclusions: The CSTD significantly reduced, but did not totally eliminate, surface contamination with cyclophosphamide. In addition to other protective measures, increased usage of CSTDs should be employed to help protect health care workers from exposure to hazardous drugs.

Key Words—antineoplastic agents, closed system drug transfer device, cyclophosphamide, drug preparation, hospital pharmacies, surface contamination

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Antineoplastic and other hazardous drugs may cause adverse health effects in health care workers who handle them.[1-21] Therefore, efforts to reduce or eliminate exposure to these drugs are essential to the health care community. To achieve this, class II biological safety cabinets (BSCs) and personal protection were introduced several decades ago.[22,23] Despite these measures, environmental contamination with antineoplastic drugs in hospital pharmacies is still observed and health care workers are still exposed.[24-29]

In 2004, the National Institute for Occupational Safety and Health (NIOSH) published an Alert on hazardous drugs used in health care settings.[30] Based on the Alert, the American Society of Health-System Pharmacists (ASHP) published updated guidelines on the safe handling of hazardous drugs in 2006,[31] and safe handling of hazardous drugs is included in *United States Pharmacopeia* (USP) Chapter <797>.[32]

In the NIOSH Alert, the ASHP guidelines, and in USP <797>, recommendations were presented to reduce environmental contamination and exposure of health care workers to these drugs. One recommendation was to consider the use of closed system drug transfer devices (CSTDs) in addition to engineering controls. Since the

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publication of the NIOSH Alert, several devices described as CSTDs have been introduced on the market.[26,28,33-47] However, for most devices, long-term clinical studies demonstrating the effectiveness of CSTDs in terms of reduction of environmental contamination and exposure of health care workers are lacking.

In addition to other published studies, a study was published recently showing that the use of the *PhaSeal* CSTD (Carmel Pharma ab, Gothenburg, Sweden) significantly reduces surface contamination when preparing cyclophosphamide, ifosfamide, and 5-fluorouracil as compared to standard drug preparation techniques using a needle and syringe.[28] The study was performed in 22 US hospital pharmacies from June 2000 until May 2005. A disadvantage of the study is that the data were collected about 5 to 10 years ago and are not current. Therefore, the study was repeated in 30 additional US hospital pharmacies covering the period August 2004 until November 2010. To compare the results, the same study design was followed as in the previous study, except the present study only monitored contamination with cyclophosphamide. In all hospital pharmacies, the same types of surfaces were wiped 2 times. The surfaces were sampled the first time after handling with the traditional technique and the second time after several months of preparation with the *PhaSeal* CSTD. Surface contamination results were compared between the 2 techniques and between the 2 studies. Up-to-date contamination data enable the evaluation of the effect of the CSTD recommendations found in the NIOSH Alert, ASHP updated guidelines, and USP <797> on surface contamination frequency and contamination levels.

METHODS

Study Design and Sample Collection

This study was conducted in 30 US hospital pharmacies from August 2004 until November 2010. Surface contamination was assessed by taking wipe samples from BSC surfaces, BSC airfoils (the front leading edge of the BSC), floors in front of BSCs, and countertops in the immediate area; this procedure was comparable to the previous study. If multiple BSCs and countertops were present, more than one BSC surface, airfoil, floor, or counter was tested. If surfaces were not identified as being used for handling cyclophosphamide, wipe samples were not collected for that surface. *Cyto Wipe Kits* (Exposure Control Sweden AB, Bohus-Björkö, Sweden) were used for wipe sampling.

After the first series of wipe samples were taken, the *PhaSeal* CSTD was introduced into the hospitals. At least 6 months after implementation of the CSTD, wipe samples were taken from the same surfaces and contamination was reassessed.

The wipe samples were analyzed for cyclophosphamide. Cyclophosphamide was selected for monitoring, because this drug was frequently used at the hospitals and was evaluated in the previous study. The same procedure as in the previous study was followed concerning storage and transport of the samples.[28]

Sample Preparation and Analysis

Sample preparation and analysis of cyclophosphamide were identical to the previous study and were performed according to published procedures.[28,48-50] The analytical detection limit for cyclophosphamide was 0.10 ng/mL of extract. The coefficient of variation as a measure of the interassay precision was 18%. Drug recovery from the surfaces was >80%.

Statistical Methods

Amounts of contamination per cm^2 were compared between the 4 surfaces, the 2 techniques, and the 2 studies using the Kruskal-Wallis test. *P* values of .05 or less were deemed significant. Data were characterized by median and range. For amounts below the detection limit, half of the detection limit was used for statistical calculations.

RESULTS

Present Study

During the study period, 143 samples were collected from 30 hospitals. The results of surface contamination with cyclophosphamide are presented in **Table 1**. The results were separated into preparation according to standard preparation techniques and preparation with the CSTD. Measurements reported for each site are single measurements.

Using the standard preparation techniques, 83% of the wipe samples of the 4 surfaces tested positive for cyclophosphamide contamination (87% for the BSC surfaces, 97% for the BSC airfoils, 82% for the floors in front of the BSCs, and 69% for the countertops). A significant difference in contamination between the 4 surfaces was observed showing the BSC airfoils to be the most heavily contaminated ($P = .001$).

Using the CSTD, contamination with cyclophosphamide was still observed and the percentage of positive samples for the 4 surfaces showed little to no change compared to the standard preparation techniques. Eighty percent of the wipe samples of the 4 surfaces tested positive for cyclophosphamide contamination (77% for the BSC surfaces, 87% for the BSC airfoils, 89% for the floors in front of the BSCs, and

Table 1. Contamination with cyclophosphamide (CP) on BSC surfaces, BSC airfoils, floors in front of BSCs, and counters in 30 US hospital pharmacies (ng/cm^2)

Site, state, and test periods				BSC surface		BSC airfoil		Floor in front of BSC		Counter	
Site	State	Test −[a]	Test +[a]	Test −	Test +	Test −	Test +	Test −	Test +	Test −	Test +
1	NC	Mar-09	May-10	0.10	0.01	3.40	0.15	0.31	1.01	<0.01	0.19
2	NC	Mar-09	Dec-09	1.02	<0.01	20.48	0.78	1.65	<0.01	1.15	0.03
3	HI	Aug-09	Nov-10	<0.01	0.03	0.35	<0.01	0.03	0.01	ns	ns
4	IL	Feb-08	Sep-09	0.96	<0.05	ns	ns	14.24	0.85	0.15	<0.01
5	IL	Mar-09	Dec-09	1.27	0.02	ns	ns	ns	ns	0.14	0.03
				0.07	0.01					<0.01	0.02
										<0.01	0.01
										<0.01	0.01
6	OH	Feb-07	Sep-07	0.01	<0.01	ns	ns	0.01	0.02	<0.01	<0.01
								0.45	0.01		
7	KS	Apr-09	Apr-10	0.02	<0.01	ns	ns	0.02	0.02	0.08	<0.01
8	IN	Oct-09	Apr-10	0.01	0.01	0.42	0.29	0.08	0.13	0.03	<0.01
9	MO	Feb-09	Mar-10	4.63	0.07	ns	ns	1.20	0.08	0.52	0.01
10	CA	May-09	Oct-09	0.67	0.09	0.39	0.39	<0.01	0.01	0.04	0.03
11	AZ	May-08	Sep-09	3.42	<0.01	0.16	0.20	<0.01	<0.01	<0.01	<0.01
										0.05	<0.01
12	TX	Oct-08	Jun-09	<0.01	0.32	0.01	3.95	<0.01	0.39	0.01	0.05
13	NV	Oct-08	May-09	0.30	<0.01	1.75	4.23	0.26	0.22	<0.01	<0.01
										<0.01	<0.01
14	IL	Sep-08	Mar-09	0.05	0.01	2.03	0.57	0.01	0.55	0.02	<0.01
15	PA	Nov-06	Oct-07	44.17	8.35	35.32	25.49	3.67	0.11	3.15	4.13
				38.08	38.59						
16	MA	Jul-08	Mar-09	ns	ns	0.02	<0.01	0.08	0.02	0.04	<0.01
17	NC	Jan-08	Nov-08	2.49	0.01	0.27	0.11	0.08	0.01	0.02	<0.01
				<0.01	<0.01	0.02	<0.01	0.58	0.01	0.01	0.01
				29.40	1.20	2.92	6.84	13.38	4.13	10.56	0.70
				5.50	0.24	5.86	1.51	6.87	2.75	4.60	1.82
18	FL	Jun-07	Oct-08	<0.01	0.01	<0.01	<0.01	<0.01	0.01	<0.01	0.01
				0.01	<0.01	0.16	0.02	<0.01	0.01	<0.01	0.01
19	MI	Apr-05	Feb-07	0.55	0.26	5.60	1.75	1.83	2.20	ns	ns
				<0.01	0.06	3.94	0.90	2.07	1.29		
20	WA	Mar-07	Nov-07	0.19	0.05	ns	ns	0.02	0.04	ns	ns
21	VA	Jun-07	Aug-08	19.42	2.66	1.63	12.56	2.19	0.98	0.47	0.24
				0.02	0.02	0.07	0.17	2.49	0.06		
22	CA	Nov-07	Jul-08	8.13	0.02	0.62	0.38	<0.01	0.02	0.01	0.19
23	IL	May-07	Apr-08	0.22	0.03	3.32	0.19	1.38	1.02	ns	ns
24	PA	Jul-07	Mar-08	0.05	0.01	2.94	3.44	0.94	0.28	0.15	0.04
25	IN	Oct-07	Apr-08	0.01	0.01	0.09	0.06	0.35	1.30	ns	ns
26	VA	Jun-06	May-07	0.01	<0.01	0.44	0.04	0.02	<0.01	0.01	<0.01

(continued)

Table 1. Contamination with cyclophosphamide (CP) on BSC surfaces, BSC airfoils, floors in front of BSCs, and counters in 30 US hospital pharmacies (ng/cm²) (CONT.)

Site, state, and test periods				BSC surface		BSC airfoil		Floor in front of BSC		Counter	
Site	State	Test −[a]	Test +[a]	Test −	Test +	Test −	Test +	Test −	Test +	Test −	Test +
27	OH	Nov-07	May-08	1.18	0.01	5.76	0.34	2.94	0.34	1.04	0.07
28	NJ	Aug-04	Feb-05	1.60	0.02	ns	ns	0.02	0.01	<0.01	0.02
				2.47	0.02			<0.01	0.01	0.10	0.03
29	NE	May-06	Dec-06	2.58	0.05	8.78	11.61	26.79	0.12	19.69	0.08
30	MI	Apr-05	Feb-07	0.76	0.01	8.29	11.23	1.98	0.08	2.90	0.01
				0.20	0.70	24.60	1.77	0.05	<0.01	0.12	0.01
Median				0.30	0.02	1.69	0.39	0.29	0.08	0.04	0.01
Min				<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Max				44.17	38.59	35.32	25.49	26.79	4.13	19.69	4.13

Note: BSC = biological safety cabinet; ns = not sampled (the surface was not used for drug handling).
[a]–Preparation according to standard preparation techniques; + preparation with the closed system drug transfer device (CSTD).

67% for the countertops). However, compared to the standard preparation techniques, a significant reduction in levels of contamination was observed for all surfaces ($P < .0001$). Median values for surface contamination with cyclophosphamide were reduced from 0.22 to 0.03 ng/cm², a reduction of 86%. A significant difference in contamination between the 4 surfaces was observed, showing again that the BSC airfoils were the most heavily contaminated ($P < .0001$) and the countertops were the least contaminated.

Comparison With the Previous Study

Surface contamination with cyclophosphamide on the 4 surfaces was compared between the 2 studies. For both the standard preparation technique and the use of the CSTD, no differences were found between the 2 studies ($P = .84$ and $P = .19$, respectively). In addition, the observed reduction in cyclophosphamide contamination was the same quantitatively in both studies ($P = .43$). The results indicate that the levels of cyclophosphamide contamination were not different in both studies for the standard preparation technique and for the CSTD and in both studies the same reduction was found. In fact, the results of the present and the previous study are identical.

DISCUSSION

The results show a substantial reduction in environmental contamination with cyclophosphamide after implementation of the CSTD. It is remarkable that the results are identical compared to the previous study. Levels of contamination following standard preparation techniques over the period from 2000 to 2005 were the same as over the period 2004 to 2010. This suggests that the updated ASHP guidelines and USP <797> following the NIOSH Alert did not have a substantial impact on the reduction of environmental contamination of at least one drug, cyclophosphamide, and probably other antineoplastic drugs. In the previously reported study[28] and the current one, a reduction of the cyclophosphamide contamination of 86% to 95% was found with the use of the CSTD. Considering the substantial decrease in contamination, the use of a CSTD should be more accentuated when antineoplastic and other hazardous drugs are being prepared and administered to patients. To achieve this, the ASHP guidelines and USP <797> should be adhered to in all aspects.

After implementation of the CSTD, contamination was still observed in both studies similar to other published studies. Where does the residual contamination come from? Is the contamination acceptable in terms of health risk for the health care workers?

Several published clinical studies have reported on the effectiveness of CSTDs in reducing environmental contamination in actual hospital pharmacy settings (**Table 2**). Several studies have also been published that looked at other CSTDs in nonhospital settings and/or with surrogates for antineoplastic drugs.[35,37,40,42,44,45,47] These studies usually compared the use of standard techniques using a needle and syringe versus the implementation of a CSTD. All published clinical studies examined *PhaSeal*, because it has been on the market longer than other CSTDs. Studies have reported a reduction in environmental contamination when the

Table 2. Published clinical studies on the effectiveness of a closed system drug transfer device (CSTD) in reducing environmental contamination

CSTD	Drugs	Site(s)	Conditions	No. of wipe samples	Outcome	Reference
PhaSeal	CP, 5FU	Swedish hospital pharmacy	No BSC 1 year use of CSTD in new pharmacy	15	14/15 <LOD for CP 15/15 <LOD for 5FU	Sessink et al, 1999[33]
PhaSeal	CP	Belgian hospital pharmacy	Pre-implementation with standard procedure, cleaning, implementation of CSTD, standard procedure (17 months)	11/sampling period	Decrease of contamination with CSTD >10-fold increase in contamination without CSTD	Vandenbroucke & Robays, 2001[34]
PhaSeal	CP, IF, 5FU	US hospital pharmacy	Pre-implementation of CSTD Post-implementation (CP and IF only) of CSTD 6 times at 4-week intervals	18	Lower levels of contamination with CP and IF compared to 5FU	Connor et al, 2002[35]
PhaSeal	CP, IF	US hospital pharmacy	Pre-implementation of CSTD 6 months post-implementation of CSTD	Pre = 17 Post = 21	Pre 17/17 >LOD for CP and 11/17 >LOD for IF Post 7/21 >LOD for CP and 15/21 >LOD for IF	Wick et al, 2003[36]
PhaSeal	CP, 5FU	3 US hospital pharmacies	Standard procedure (12 weeks) CSTD (12 weeks: 5FU on counter top) Standard procedure (6 weeks)	124 per cycle	Significant reduction in contamination with CSTD No significant increase in contamination when 5FU prepared on counter top with CSTD	Harrison et al, 2006[37]
PhaSeal	CP, IF	US hospital pharmacy	Historical data 6 months post-implementation of CSTD	Historical = 21 Post = 34	Historical 7/21 >LOD for CP and 15/21 >LOD for IF Post 7/34 >LOD for CP and 4/34 >LOD for IF	Nyman et al, 2007[38]
PhaSeal	CP	Japanese hospital pharmacy	Pre-implementation of CSTD 4 weeks post-implementation	Pre-implementation = 127 Post-implementation = 136	Pre 100% >LOD Post 75% >LOD Significant difference between pre- and post implementation of CSTD	Yoshida et al, 2009[39]
PhaSeal	CP	2 Australian hospital pharmacies	Pre-implementation of CSTD 5 and 12 months post-implementation of CSTD (12 months 1 hospital pharmacy)	22	24% reduction at 5 months post-implementation of CSTD (2 hospitals) 68% reduction at 12 months post-implementation of CSTD (1 hospital)	Siderov et al, 2010[26]

(continued)

Table 2. Published clinical studies on the effectiveness of a closed system drug transfer device (CSTD) in reducing environmental contamination (CONT.)

CSTD	Drugs	Site(s)	Conditions	No. of wipe samples	Outcome	Reference
PhaSeal	CP, IF, 5FU	22 US hospital pharmacies	Stand procedure vs CSTD ~6 months post-implementation CSTD	144	Surface contamination reduced 95% (CP), 90% (IF), and 65% (5FU) Significant reduction in levels of contamination with CSTD for 3 drugs	Sessink et al, 2010[28]
PhaSeal	Platinum	German veterinary hospital	Pre-implementation of CSTD 3,6 and 9 months post-implementation of CSTD	7 per time period	Increase at 3 months Decrease at 6 and 9 months	Kandel-Tschiederer et al, 2010[40]

Note: CP = cyclophosphamide; IF = ifosfamide; 5FU = 5-fluorouracil; LOD = limit of detection.

CSTD was used, typically measured by wipe sampling of surfaces impacted by drug preparation. The parameters evaluated are either the reduction in the percentage of samples that are above the limit of detection (LOD) and/or the reduction in the levels of surface contamination. Even though reductions in surface contamination have been reported in all studies, some level of residual surface contamination is always present. Reports from the United States and other countries document the continued problem with environmental contamination with antineoplastic drugs in health care settings.[51-84] Regarding the remaining contamination, it may be caused by leakages from mishaps and accidents and the potential for stable drugs to remain on surfaces for several months. Connor et al[85] reported residual surface contamination with cyclophosphamide 6 months after a broken drug vial. In addition, this contamination may be due, in part, to the presence of drug contamination on the outside of the drug vials.[85,86] Although attempts have been made to alleviate the contamination by washing and/or coating the vials in a plastic film, vial contamination is an ongoing source of drug residue in the pharmacy that needs to be eliminated.

Many studies have documented the uptake of these drugs, as indicated by the excretion of the parent drug and/or its metabolites in the urine of health care workers; low level exposure to these drugs will be common in health care facilities. Whether or not the remaining observed environmental contamination after the implementation of the CSTD is acceptable in terms of health risk for the health care workers is difficult to answer.[87,88] Recently, a preliminary model has been presented demonstrating that environmental contamination with cyclophosphamide lower than 0.1 ng/cm^2 is a safe reference value.[89] About one-third of the sites monitored in the current study meet this value after implementation of the CSTD (**Table 1**). This implies that additional steps have to be set at the other sites.

CONCLUSIONS

The results of the current study support the findings of the earlier study and again demonstrate the possibility of reducing environmental contamination with cyclophosphamide and other hazardous drugs in hospital pharmacies using a CSTD. Although all published studies on CSTDs have shown some residual contamination, these studies have documented a significant reduction in surface contamination with cyclophosphamide and other antineoplastic drugs. The implementation of CSTDs and the elimination of the drug contamination on the outside of vials would greatly reduce environmental contamination leading to potential exposure of health care workers by these drugs.

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