



Evaluation of Chemotherapy Contamination Following the Implementation of Closed System Transfer Devices

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Abstract

This study compared the contamination of the chemotherapeutic agent cyclophosphamide between using a conventional admixing procedure and closed system transfer devices (CSTDs). Surface wipes and urine samples were collected for two weeks before and two weeks after the CSTDs were used. The surface wipe samples were collected from critical areas in an aseptic dispensary unit and a chemotherapy patient care unit. The urine samples were collected from healthcare workers. Contamination from cyclophosphamide in the surface wipe samples was detected in fewer areas following the implementation of CSTDs. The median cyclophosphamide concentration in aseptic dispensary unit areas following the usage of CSTDs was significantly lower than what was detected when the conventional method ($p=0.036$, Mann-Whitney's U-test) was used. Cyclophosphamide contamination was not detected in critical areas of the patient care unit following the use of the CSTDs. This study demonstrates the potential advantages of utilizing CSTDs to reduce contamination from chemotherapeutic agents in a work setting.

Keywords: Closed system transfer device; antineoplastic drug; chemotherapeutic agent; healthcare worker; contamination

Introduction

Antineoplastic drugs have proven to be effective in the treatment of various malignancies providing positive outcomes among cancer patients. Nonetheless, there is a concern about the toxic effects that may occur from handling these chemotherapeutic agents. During the preparation process, antineoplastic drugs are diluted and subsequently mixed into an infusion fluid by healthcare personnel prior to administration to patients. In such a process, contamination can occur via airborne particles or accidental spillage in working areas, on clothes, and/ or on medical equipment. Increased hair loss, skin rashes, infertility, miscarriage, genotoxicity leading leukemia or other secondary cancers have been reported among healthcare providers exposed to antineoplastic drugs [1, 2, 3, 4, 5]. Occupational exposure to cytotoxic drugs has significantly increased the risk for leukemia (RR = 10.65 [1.29-38.5]) among these workers [4]. The safe handling guidelines for antineoplastic drugs issued by the National Institute for Occupational Safety and Health (NIOSH) and the United States Pharmacopoeia (USP) Chapter <797> recommend the required use of a biological safety cabinet (BSC) during the preparation of antineoplastic drugs [6, 7]. Currently, all hospital settings involved in preparing cytotoxic drugs should have designated BSC to prevent contamination during the preparation of cytotoxic drugs. In Thailand, the preparation of cytotoxic drugs has been conducted in BSC according to the standard safe handling procedure. As of yet, there has been no systematic quantitative study on the degree of the contamination caused by cytotoxic drugs in the environment and to healthcare personnel at work. Moreover, CSTDs are not routinely used for the preparation and administration of antineoplastic drugs. The present investigation evaluates the contamination caused by chemotherapeutic agents in the environment and to healthcare workers by comparing the degrees

of contamination prior to and following the implementation of CSTDs during the preparation and administration of cyclophosphamide.

Methods

The study was conducted from October to November 2011 to evaluate the amount of chemotherapy contamination by chemotherapeutic agents in the working environment and among healthcare workers at Sapsithiprasong Hospital, a tertiary care hospital in Ubon Ratchathani, Thailand. The study protocol was approved by the ethics committees of the Faculty of Pharmaceutical Sciences, Prince of Songkla University (reference no.0521.1.07/1064, approved on June 16, 2011) and Sappasithiprasong Hospital (reference no.022/2554 approved on August 8, 2011). All participants provided their written informed consent. The study was divided into three phases. During Phase 1, before the initiation of the study, we provided a two-week CSTDs run-in as a training period for the pharmacists and pharmacy technicians in order for them to become familiar with the CSTDs technique. During Phase 2, which occurred over the following two weeks, conventional methods utilizing a BSC alone were performed by the pharmacy personnel when preparing cytotoxic drugs. During Phase 3, the last two-week period, the CSTDs method (using a CSTD in conjunction with a BSC) was subsequently applied during the preparation of cytotoxic drugs.

Phaseal CSTDs were used in the present study. A PhaSeal system consists of a protector equipped with an expansion chamber, a membrane and air cannula and an injector luer lock equipped with a membrane, a safety latch, a luer and a specially cut cannula. The connection of the protector and injector luer lock was covered with a membrane. When the protector was connected with the injector luer lock, the membrane of the protector adhered tightly to the membrane of the injector, so the specially cut cannula of the injector luer lock could be inserted into the vial

without exposure to the outside air. When air was injected from the syringe into the vial, the expansion chamber equalized the pressure of the vial by transferring the air from the vial to the chamber. When the drug solution was extracted from the vial into the syringe, the expansion chamber equalized the pressure in the vial by transferring air from the chamber into the vial. Because a CSTDs seals the cannula and equalizes the pressure of the vial, spills can be prevented [8].

To determine the amount of cyclophosphamide contamination to the environment, Cyto Wipe Kits were used to collect all samples in 13 critical areas of the aseptic dispensary unit (five areas on transferring carts, five areas on countertops, one floor area inside the BSC, one floor area in front of the BSC and one floor area inside the pass box) and five areas in the chemotherapy patient care unit (on countertops) [9, 10]. This kit consists of tissue paper, a dropper prefilled with 17 ml of 0.03 M sodium hydroxide (NaOH) and a container for collecting the completed surface wipe samples. The sizes of the positions from each wiping area were subsequently measured and calculated to account for the actual amount of cyclophosphamide in each area. The sampling process occurred before and after the use of a CSTD for a period of two weeks. Sample collection was performed at 4 pm on a Friday during each sampling week, as it was the last day of the work week, to ensure maximum cumulative exposure to chemotherapeutic agents. The surface wipe samples were collected by dripping the 0.03 M NaOH solution over the targeted sampling surface. The entire targeted areas were then wiped thoroughly with the tissues provided in the Cyto Wipe Kits and collected in the designated containers. Exposure to cyclophosphamide by the healthcare workers was subsequently evaluated by measuring the concentrations of cyclophosphamide in the urine from five pharmacy technicians, five compounding pharmacists and one clinical pharmacist. Twenty-

four-hour urine collections were taken each sampling week from 8 am Thursday to 8 am Friday. Samples were collected twice during the two weeks prior to commencing with the CSTDs method and two weeks when the CSTDs method. Subsequently, 30 ml of each of the urine samples was analysed for its cyclophosphamide concentration.

The surface wipe and urine samples were shipped for analysis by gas chromatography coupled with tandem mass spectrometry (GC-MSMS) at the laboratory of Exposure Control Sweden AB, Nijmegen, the Netherlands. During transportation, all samples were stored at -8 degrees Celsius at all times prior to analysis. Each surface wipe sample was prepared by adding a 0.03 M NaOH solution, which increased the total volume up to 160 ml. After extraction, a part of the extract was further cleaned up according to standard procedures including a derivatisation with trifluoroacetic anhydride [11, 12]. Five ml of the urine was extracted with diethylether following the same procedure [11, 12]. The limit of detection was 0.10 ng/ml extract for the wipe samples and 0.01 ng/ml urine for the urine samples. This allowed a detection of 16 nanograms (ng) per cyclophosphamide per sampling surface. Recovery from surfaces was > 80%. MSMS detection of N-trifluoroacetylated cyclophosphamide was performed on the daughter ion mass $m/z = 212$ abstracted from the parent ion mass $m/z = 307$ [13, 14, 15].

The continuous variables were compared by means of a Student's t-test or a Mann-Whitney's U-test, as appropriate with a 95% confidence interval and p value of 0.05. The data were analyzed by using IBM SPSS version 22.0 for Windows. The lower limit of detection was used for the undetectable cyclophosphamide levels.

Results

Cyclophosphamide contamination as determined by the surface wipe samples was detected in fewer areas when the CSTDs method was applied as compared to when the conventional

method was used (Table 1 & Table 2). As shown in Table 3, about half the amount of cyclophosphamide contamination in the surface wipe samples was detected following the use of CSTDs. Moreover, the median of the cyclophosphamide concentration detected for the conventional method decreased from 0.20 ng/cm² to non-detectable after the CSTDs method was implemented ($p = 0.009$). The highest concentration of cyclophosphamide contamination was detected on the floor inside the BSC (5.57 ng/cm²), followed by the floor in front of the BSC (0.40 ng/cm²).

With the exception of the preparation areas, the median cyclophosphamide concentration detected in the aseptic dispensary unit significantly decreased from 0.03 ng/cm² to 0.01 ng/cm² ($p=0.036$) after the CSTDs method was employed. The use of the CSTDs significantly reduced cyclophosphamide contamination on countertops located in the aseptic dispensary unit ($p=0.035$). Furthermore, no surface contamination was detected following the use of CSTDs in the chemotherapy patient care unit. Cyclophosphamide was undetectable in all urine samples of the 11 healthcare workers and this hypothetically implied that there was no measurable uptake by the healthcare workers.

Table 1 Concentration of cyclophosphamide on the surface wipe samples (ng/cm²) from the environmental surfaces of the aseptic dispensary unit

Wipe sampling from critical areas in the aseptic dispensary unit	n	Conventional method (only BSC)				Closed system device method (BSC and CSTDs)				P value ^a
		mean ^b	median ^b	range ^b	detection rate (%)	mean ^b	median ^b	range ^b	detection rate (%)	
1.1 Preparation areas	3	2.08	0.4	0.08-5.57	100	1.59	0.14	0-4.64	67	0.27
- Floor inside pass box	1	-	0.28	-	-	-	0	-	-	-
- Floor inside BSC	1	-	5.57	-	-	-	4.64	-	-	-
- Floor in front of BSC	1	-	0.40	-	-	-	0.14	-	-	-
1.2 Other areas	10	0.05	0.03	0-0.16	90	0.01	0.01	0-0.02	60	0.036^c
- Transferring carts	5	0.04	0.01	0-0.16	80	0.10	0.01	0-0.02	60	0.381
- Countertops	5	0.05	0.06	0.01-0.08	100	0.12	0.01	0-0.02	60	0.035 ^c

^a = Mann–Whitney's U-test, ^b = cyclophosphamide concentration (ng/cm²) and the lower limit of detection = 0.10 ng/ml sample, ^c = significant at a p value of less than 0.05

Table 2 Concentration of cyclophosphamide on the surface wipe samples (ng/cm²) from the environmental surfaces of the chemotherapy patient care unit.

Wipe sampling from nurse station areas in the chemotherapy patient care unit	n	Conventional method (only BSC)				Closed system device method (BSC and CSTDs)				P value ^a
		mean ^b	median ^b	range ^b	detection rate (%)	mean ^b	median ^b	range ^b	detection rate (%)	
Countertops	5	0.052	0.20	0-0.20	60	0	0	0	0	0.054

^a = Mann–Whitney's U-test, ^b = cyclophosphamide concentration (ng/cm²) and the lower limit of detection = 0.10 ng/ml sample, ^c = significant at a p value of less than 0.05

Table 3 Concentration of cyclophosphamide on the surface wipe samples (ng/cm²) from the aseptic dispensary unit and the chemotherapy patient care unit.

Wipe sampling points	n	Conventional method (only BSC)				Closed system device method (BSC and CSTDs)				P value ^a
		mean ^b	median ^b	range ^b	detection rate (%)	mean ^b	median ^b	range ^b	detection rate (%)	
The aseptic dispensary unit and chemotherapy patient care unit	18	0.38	0.20	0-5.57	83	0.27	0	0-4.64	44	0.009 ^c

^a = Mann–Whitney's U-test, ^b = cyclophosphamide concentration (ng/cm²) and the lower limit of detection = 0.10 ng/ml sample, ^c = significant at a p value of less than 0.05

Discussion

Antineoplastic drugs are clearly beneficial in the treatment of patients with cancer but there are several concerns about the associated health risks to the personnel involved with handling the products. The evidence from this study has demonstrated that having a designated BSC installed for use in chemotherapy preparation insufficiently prevents chemotherapy contamination in the working environment [9]. Recently, USP <797> has adopted the use of CSTDs as an essential step in the preparation and administration of antineoplastic drugs to minimize the risk of exposure while using a BSC [7]. In Thailand, there has been no official study to date on the degree of contamination by chemotherapeutic agents in the working environment or to the healthcare personnel who use the standard safe handling practice in a BSC. In addition, CSTDs are not consistently used or accessible for the preparation and administration of antineoplastic drugs in hospital settings.

This study has evaluated the contamination by chemotherapeutic agents of the environment and healthcare workers by comparing the effects resulting from the added use of CSTDs to the conventional admixing method. The preliminary results demonstrate that contamination with cyclophosphamide was primarily identified in most areas of the aseptic dispensary unit. The highest concentration level of contamination was identified on the floor inside the BSC, because this area was directly exposed to cyclo-

phosphamide spillage, which can occur during the admixing process. After implementing the CSTDs method for drug preparation and administration, reductions in the cyclophosphamide concentrations occurred in most of the tested areas. The median cyclophosphamide contamination concentration was significantly reduced following the use of CSTDs in all the tested areas.

These results are consistent with previous reports that have evaluated the cyclophosphamide contamination in a similar manner. It has been reported that the areas inside the aseptic dispensary unit tended to be the most contaminated [11, 12, 16]. The observed areas of contamination were mainly on the floor inside the BSC and on the floor in the BSC installed room. This implies that some spillage had occurred during the admixing procedure. Spillage of chemotherapeutic agents should be limited as much as possible to foster a safe environment for the personnel responsible for preparing and administering antineoplastic drugs.

The current study also measured the cyclophosphamide contamination in the urine of the healthcare workers working in the aseptic dispensary unit. Although the chemical half-life of cyclophosphamide seems to be short, varying from 3 to 12 hours, cyclophosphamide contamination has been detected in the urine of healthcare workers several months after exposure [17, 18]. All of the participants in the current study are full-time workers and had at least one

year of experience working in the unit. During the collection, the volumes of the 24-hour urine samples sent for analysis appeared to be in the normal range of urine production for human adults (1-2 L/person). It can be ensured that the cyclophosphamide concentrations detected in the study were not affected by urine volume. In the present study, no cyclophosphamide was detected in the urine samples. This could be attributed to dilution, which may have occurred as the 24-hour urine samples were collected and analyzed. Dilution would not have occurred if individual spot samples had been collected within the 24-hour period and analyzed separately. The results seen are similar to those of a previous report [10]. Nonetheless, some reports have identified the excretion of cyclophosphamide in the urine of pharmacists and pharmacy technicians, implying that contamination could have occurred among staff who had not realized the importance of safe handling during preparation procedures. Some workers might not have strictly followed the established guidelines such as declining to wear masks or implement other precautionary measures [12, 19, 20, 21, 22]. Some were working or handling the drug vials without proper gloving, which would have prevented accidental contact exposure. With regard to the difference between the background contamination patterns, these high levels of background contamination were related to spillage from breakage, leakage or preexisting contamination in the environment. These have led to increased chances for exposure to the chemotherapeutic agent, which subsequently absorbs systemically so as to be detected in healthcare workers' urine [12, 19, 20, 21, 22]. In contrast, there was no measureable uptake of the chemotherapeutic agent among those certified workers who handled the agent who according to the safe handling guidelines [10]. At the current research site, the staff were certified and re-certified every six months to ensure all proper techniques were used during the preparation for chemotherapy.

In the present study, the highest level of contamination was found on the floor inside the BSC and the floor in front of the BSC. To prevent contamination by cyclophosphamide, special attention and decontamination procedures should be given to these critical areas where the healthcare workers may accidentally be exposed. For a future study, the standard preparation procedures and effective cleaning methods need to be evaluated to remove the remaining contamination and to avoid the introduction of new contamination. Frequent cleaning will remove the remaining contamination in most areas. Floor cleaning is known to be very challenging, but effective cleaning will further reduce contamination after frequent cleaning for the next 6 to 12 months with a cationic soap solution, followed by a diluted bleach solution, followed again by a cationic soap solution and a final alcohol wipe [10, 23, 24].

Conclusion

This research has compared the traditional method with the use of CSTDs and demonstrated the advantages of using the CSTD method to reduce contamination by cytotoxic agents. The levels of contamination have been dramatically reduced in all areas of the aseptic dispensary unit including the transferring carts, countertops, floor inside the BSC, floor in front of the BSC, and floor inside the pass box. In the tested areas of the chemotherapy patient care unit, including countertops at the nurses' supply areas, surface contamination did not exist after CSTDs were used.

This study did not detect contamination in the urine samples of the healthcare workers who handled chemotherapeutic drugs. However, nursing staff members who could have potentially been contaminated by antineoplastic drugs were not included in the current study. Moreover, there remains a small possibility that the concentrations of cyclophosphamide in the urine samples were lower than the limit of detection of the analysis method used. The staff members who

participated in this research strictly followed the safe handling practices to ensure a reduction in their chances of exposure to cyclophosphamide. Thereby, in other aseptic dispensary units where safe handling practices are not strictly followed, greater contamination may be present. Prospective future studies could be conducted in areas where safe handling practices are not emphasized and also oncology nurses should be included to assess the magnitude of increased contamination and perhaps systematical uptake. Such results may better reflect the actual exposure of healthcare workers in Thai hospital settings to cyclophosphamide contamination. Nevertheless, the results from the surface wipe samples demonstrate that there was some cyclophosphamide contamination in the aseptic dispensary unit and to a lesser extent in the chemotherapy patient care unit. Although the levels of contamination were small due to the brief study period, cumulative drug exposure could possibly be an issue. Spillage and subsequent contamination should be proactively prevented and precautions need to be addressed by all levels of healthcare personnel who deal with chemotherapy.

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