Monitoring method for surface contamination caused by selected antineoplastic agents

R. R. LARSON, M. B. KHAZAELI, AND H. KENNETH DILLON

Abstract: A method of evaluating surface contamination caused by selected antineoplastic agents was studied.

The antineoplastic agents tested were cyclophosphamide, ifosfamide, doxorubicin hydrochloride, fluorouracil, and paclitaxel. Each agent was reconstituted and prepared as a stock solution. A 0.1-mL portion of each solution was spread evenly over a 600-cm^2 area of a stainless steel surface, a resin countertop surface, and a vinyl flooring surface. After drying, the surfaces were wiped with each of two types of commercially available wiping materials (Whatman no. 42 filters and Kimberly-Clark Kimwipes). A blend of methanol, acetonitrile, and buffered water was used both as the wetting agent for wiping the surfaces and as a desorbing solution. The desorbate was analyzed for drug concentration by reverse-phase high-performance liquid chromatography (HPLC).

Mean ± S.D. percent total recovery ranged from 72.4% ± 17.6% to 95.3% ± 2.9% for the vinyl surface wiped with filters, 91.5% ± 5.4% to 104.7% ± 0.8% for the resin surface wiped with filters, 73.9% ± 2.3% to 95.3% ± 1.7% for the stainless steel surface wiped with filters, and 18.2% ± 1.4% to 372.8% ± 8.0% for the stainless steel surface wiped with Kimwipes. Results were best for ifosfamide and cyclophosphamide. Kimwipes were deemed ineffective for this monitoring method because an ingredient interfered with the quantitative analytical tests.

A wipe-sampling, desorption, and HPLC method for monitoring surface contamination by selected antineoplastic agents was sufficiently accurate and sensitive to evaluate surfaces typically found in both the pharmacy and drug administration areas of oncology treatment facilities.

Index terms: Antineoplastic agents; Chromatography, liquid; Contamination; Cyclophosphamide; Doxorubicin hydrochloride; Fluorouracil; Ifosfamide; Methodology; Paclitaxel; Solvents; Tests

Am J Health-Syst Pharm. 2002; 59:270-7

Biological evidence of absorption through the skin exists for several antineoplastic agents. For example, Hirst et al.[1] detected cyclophosphamide in the urine of two nurses who handled the agent, thereby documenting absorption. Hirst et al. also documented skin absorption in human volunteers by using gas chromatography after topical application of the drug. It has been reported that dermal and ingestive routes of entry are more significant than inhalation for a number of these agents.[2] Many are cytostatic drugs that have pharmacologic properties linked to potential genotoxic hazards. Because the mechanisms of interaction of these drugs frequently involve DNA, RNA, or protein synthesis, many have carcinogenic or mutagenic effects.[3-7] Thus, when conducting a hazard analysis at work sites where antineoplastic agents are used, it is important to assess the presence of surface contaminants, just as it is to evaluate airborne contaminants.

Wipe sampling is a common method of evaluating surfaces for the presence of potentially hazardous agents.[8-14] This method is also used to evaluate the effectiveness of personal protective equipment (PPE), housekeeping, and decontamination programs. Terms like "swipe sampling" and "smear sampling" are synonymous with wipe sampling, and they all describe the techniques used to assess surface contamination, wheth-

R. R. LARSON, CIH, PH.D., at the time of this study, was Ph.D. degree candidate, Department of Environmental Health Sciences, School of Public Health; M. B. KHAZAELI, Ph.D., is Professor, Division of Hematology/Oncology, Department of Medicine; and H. KENNETH DILLON, PH.D., is Associate Professor, Department of Environmental Health Sciences, School of Public Health, The University of Alabama at Birmingham.

Address correspondence to Dr. Larson at the Department of Environmental Health Sciences, School of Public Health, The University of Alabama at Birmingham, RPHB 317, 1530 3rd Avenue South, Birmingham, AL 35294-0022.

er it be on work surfaces, PPE surfaces, or skin.

The objective of this study was to identify an acceptable method of evaluating surfaces for contamination by certain antineoplastic agents. The method had to be able to identify an effective material for wiping surfaces of various types; have acceptable absorption and desorption capabilities, especially for cyclophosphamide (because it is a known carcinogen); and have sufficient sensitivity to detect the agent of interest at low concentrations.

Methods

Antineoplastic agents. The antineoplastic agents tested were cyclophosphamide, ifosfamide, doxorubicin hydrochloride, fluorouracil, and paclitaxel (Table 1). Brand-name products were used for each antineoplastic except paclitaxel. Taxol (paclitaxel, Bristol-Myers Squibb) was found to interfere with the drug assay used.

Each of the five agents was first reconstituted with distilled water as applicable and in accordance with the manufacturer's instructions, then prepared as a stock solution by dilution in a mixture of 50% methanol and 50% Milli-Q equivalent water (analytical grade, distilled, deionized). Any subsequent dilutions used to prepare standards of a desired concentration were obtained by mixing the stock solution with the water.

Surfaces tested. Surfaces commonly found in pharmacies and oncology clinics consist of stainless steel (e.g., biological safety cabinets [BSC]), resins (e.g., countertops), and vinyl (e.g., flooring). Portions of each type of surface were obtained: 2000-cm^2 sheets of stainless steel, 2400-cm^2 sections of resin countertops, and 12×12 in (929-cm^2) vinyl flooring squares. Each type of surface to be used for contamination monitoring was marked to indicate 600-cm^2 test areas.

Wipe materials. A variety of wipe materials are available for collecting samples of surface contaminants. Wipes may vary in type of material, surface area, type of solution used for wetting, and volume of solution for desorption.

Two types of wipes were selected for the study, a 55-mm-diameter ashless cellulose circle filter (Whatman no. 42, Whatman Inc., Ann Arbor, MI) and an 11.4×21.6 cm analytical wipe of 100% virgin wood fiber (nearly all cellulose) (Kimberly-Clark Corporation, Irving, TX). Both types of wipes were selected after discussions with technical services representatives at the two companies. Whatman no. 1 55-mm-diameter filters have been used for some surface contamination-monitoring methods.[15]

One requirement for the wipes selected was uniform size and weight for ensuring consistent performance with respect to absorption and desorption of contaminants. The Whatman no. 42 filters were known to provide acceptable consistency, but such information was not readily available for the Kimwipes. Therefore, a test was conducted. The first 5 wipes in a new box of Kimwipes were removed and discarded, and then 10 wipes were consecutively removed and individually weighed on a precision balance (Mettler Balance, Mettler Toledo, Columbus, OH). The mean ± S.D. weight was 466.7 ± 9.8 mg (coefficient of variation, 2.1%; variation within the range of 5.0% is usually considered acceptable for consistency in weight measurements).

Desorption solution. Initially, desorption solutions of methanol and water (50:50 methanol:water, 60:40 methanol:water, and 70:30 methanol:water) were evaluated. Desorption of ifosfamide from the wipe materials was moderate (~70%), but desorption of cyclophosphamide was low (~50%) when using methanol and water. Therefore, a solution of 50:50 acetonitrile:water was evaluated. Recovery was about 50% for ifosfamide and the same for cyclophosphamide, but the results were much better for doxorubicin, fluorouracil, and paclitaxel (an average recovery of nearly 100% for each). Because of the variation in the physical characteristics of the agents of interest and the different polarities of the molecules in this study, both methanol and acetonitrile were used for desorption. Tests of various blends showed that the most effective desorption solution was a mixture of 10% acetonitrile, 25% methanol, and 65% Milli-Q water, with the water

Table 1.
Drugs Tested

Drug	Brand Name	Manufacturer(s)	Lot(s)	Expiration Date(s)
Fluorouracil 50 mg/mL	Adricil injection	Pharmacia & Upjohn	FFA221	06/2001
Ifosfamide 50 mg/mL	Ifex injection	Meade-Johnson (Bristol-Myers Squibb)	KCS99	03/2002
Cyclophosphamide 20 mg/mL	Cytoxan injection	Meade-Johnson (Bristol-Myers Squibb)	9G22823	07/2001
Doxorubicin hydrochloride 2 mg/mL	Doxorubicin hydrochloride injection	Novaplus Bedford	123200A 93592	12/2001 06/2001
Paclitaxel	. . .[a]	Sigma	NA[b]	NA

[a]The brand-name product, Taxol (Bristol-Myers Squibb), was not used because it interfered with the drug assay.
[b]NA = not available.

buffered to pH 6.0 by blending 10 mM monobasic potassium phosphate with dibasic potassium phosphate. Buffering to pH 6.0 was chosen because of the pH used in existing collection and analysis methods for cyclophosphamide.[15,16] This mixture provided desorption rates of nearly 100% for cyclophosphamide, ifosfamide, fluorouracil, and paclitaxel; the rate for doxorubicin was ~60%.

Surface-sampling procedures. Initial solutions of the standards for the individual antineoplastic agents to be tested on each surface were prepared at concentrations of 400–1000 μg/mL for fluorouracil, ifosfamide, cyclophosphamide, and doxorubicin hydrochloride. A higher concentration (1000 μg/mL) was applied on the vinyl surface because of concerns for other chemicals present in this material. Initial samples for paclitaxel were prepared at 120 μg/mL for the tests using Whatman wipes and 200 μg/mL for the tests with Kimwipe wipes. From each of these solutions, 0.1 mL was removed with a 1.0-mL syringe and spread evenly over the 600-cm^2 areas marked on each type of surface. This yielded an equivalent of 40 μg or 100 μg for each of fluorouracil, ifosfamide, cyclophosphamide, and doxorubicin and an equivalent of 20 or 12 μg for paclitaxel. While the surfaces were being treated with the agents, wipes were spiked with the same quantity of each agent. These spiked wipes served as analytical controls. Desorbing the spiked wipes in 4.0 mL of solvent would be expected to yield a 10-μg/mL result for fluorouracil, ifosfamide, cyclophosphamide, and doxorubicin and a 3-μg/mL finding for paclitaxel.

After each surface was treated with each antineoplastic agent, drying was accomplished in a laboratory with fluorescent lighting, 60% relative humidity, and a temperature of 72 °F. Drying was usually allowed to occur over at least four hours. The investigators then donned latex gloves and conducted testing as follows.

Whatman filters. One-half milliliter of the desorbing solvent was spread with a syringe over the 600-cm^2 area of the surface to be wiped. The test area was then wiped thoroughly with a single Whatman filter, which was placed in a disposable Petri plate to dry. This step was repeated with a second Whatman filter, which was placed in a separate Petri plate. Drying occurred under the same conditions as for the surfaces. When both filters were dry (a minimum of four hours), they were placed together in a single covered Petri plate and considered as the "first wipe." Four milliliters of desorbing solution was injected onto the surface of the two filters. The desorption solvent was the same as that used in collecting the surface samples (10% acetonitrile, 25% methanol, and 65% Milli-Q water buffered to pH 6.0). After the solvent was added, the closed plates were placed on an orbital shaker and shaken for 30 minutes at 100 rpm. The desorbate was removed with a syringe equipped with a filter (Gelman 25-mm Acrodisc LC PVDF syringe filter, 0.2-μm pore size, Waters, Milford, MA). This filtration was necessary for both the Whatman filters and Kimwipe wipes in order to remove fiber particulates so that they would not affect the quantitative analysis. Samples of standards were also filtered to determine if the filtering caused any interference with the analytical results; no interferences were identified. The filtered desorbate was placed into a 15-mL test tube (disposable nonpyrogenic polypropylene centrifuge tube with flat screw cap, Corning, Corning, NY) until it could be analyzed. Subsequent wipes with a Whatman filter over the same surface area (usually three additional wipes) were conducted to better determine the overall effectiveness of removal and recovery of the surface contamination. All subsequent wipes were individually desorbed.

Kimwipes. The Kimwipes were used like the Whatman filters, except that a larger volume (1.5 mL) of desorbing solvent was spread over the area to be wiped and only a single wipe was used for the first and subsequent wiping, since the size of a Kimwipe was larger than a Whatman filter. After wiping, the Kimwipes were allowed to dry, folded, and placed in a clear 10-mL glass vial with a screw cap and septum (Microvial, Kimble Glass, Inc., Vineland, NJ). Desorbing was accomplished by injecting 4.0 mL of the desorbing solvent into the vial. The vials were placed on an orbital shaker and shaken for 30 minutes at 150 rpm. After shaking, the desorbate was removed with a syringe equipped with a filter (13-mm PVDF syringe filter, 0.2-μm pore size, sterile and nonpyrogenic, Whatman) and placed into a 15-mL disposable tube with a screw cap. Analysis of the desorbate involved the same analytical method as used for the Whatman filter desorbate.

Analysis of drugs. The analytical method involved a reverse-phase high performance liquid chromatography (HPLC) system equipped with a model 1790 programmable ultraviolet–visible light (UV–vis) monitor (Bio-Rad, Hercules, CA). The system had a 500-μL injection loop and a 150 × 4.6 mm C_{18} column with 5.0-μm particles (Symmetry, Waters, Milford, MA).

The agents were scanned with a spectrophotometer (DU-600, Beckman, Fullerton, CA) to determine their individual UV wavelength ranges in nanometers for UV detection. The optimum UV range for detecting all five agents with the same analysis was 190–200 nm (individual ranges were 195–210 nm for fluorouracil, 190–195 nm for ifosfamide and cyclophosphamide, 190–195 and 230–235 nm for doxorubicin, and 190–210 nm for paclitaxel). Thus, a wavelength of 195 nm was used.

A combination isocratic and gradient method was found to be acceptable for the detection of all five agents with a single analysis. The mobile phase was 22.75% acetonitrile in Milli-Q water buffered with potassium phosphate to pH 6.0 and filtered through a 0.20-μm filter under vacuum. Analysis was conducted in isocratic phase for the first 20 minutes, followed by a 25-minute gradient phase to 70% acetonitrile in buffered water. At the end of the gradient phase, the analysis was returned to isocratic at 22.75% acetonitrile over 5 more minutes; a 10-minute final period was provided for a complete return to the normal baseline. Gas formation from the acetonitrile was minimized by first degassing any solutions containing acetonitrile.

The selectivity of the assay (separation of peaks) was confirmed by the calibration curves constructed from the analysis of freshly prepared reference standards. These standards were prepared from the stock solution of each agent and varied from containing a single agent at a specific concentration to containing all five agents at various concentrations. The selectivity of the method was verified by analyzing blank and spiked samples.

Results

Percent recovery with Whatman filters for each of the five agents is indicated in Tables 2 (the vinyl surface), 3 (the resin surface), and 4 (the stainless steel surface). Percent recovery with Kimwipe wipes for each of the five agents on the stainless steel surface is shown in Table 5. The wipes were not tested on other surfaces once we discovered that an additive in the wipes interferes with the peak for ifosfamide in the chromatogram.

Recovery of cyclophosphamide with Whatman filters was found to be acceptable for the vinyl surface and very good for the resin and stainless steel surfaces (Table 6). Similar results were seen in the evaluation of ifosfamide recovery. The method showed good precision and accuracy in detecting this agent on resin and stainless steel surfaces. Less, but still acceptable, precision and accuracy were observed for ifosfamide on vinyl tile, probably because of the presence of a variety of other chemicals in floor tiles and the wax surface treatment.

Fluorouracil recovery was fully evaluated for the resin and stainless steel surfaces wiped with Whatman filters but not the vinyl surface. This was due in part to the need to change the sensitivity (absorbance unit full-scale [AUFS]) settings on the chromatograph and reconduct the analyses to evaluate the chromatographic peak. At the AUFS settings used for the other agents, the fluorouracil peak was obscured by the solvent front.

Doxorubicin was detected on each surface, but recovery with the first wipe was poor (generally less than 40%). Overall recovery was also generally poor. Paclitaxel could also be detected, but the results varied substantially, and recovery was generally less than 50% for the first wipe.

The goal for this method was to detect a minimum drug concentration of at least 10 ng/cm^2, equivalent to 1.0 μg per 100 cm^2 (100 cm^2 is the area typically wiped to detect antineoplastic agents in other studies). The minimum concentration detected with the Whatman filters ranged from 0.2 to 4.0 ng/cm^2 (equivalent to 0.02 to 0.4 μg per 100 cm^2), which is acceptable for the evaluation of surface contamination on the types of surfaces tested (Table 7). The precision and accuracy of the method were generally very good for detection on resin and stainless steel surfaces (S.D., typically ≤1.2%) and acceptable for detection on vinyl floor tiles (S.D., 7.3% for ifosfamide and cyclophosphamide).

Discussion

Kimwipes were evaluated on stainless steel for all five agents, but what appears to be one of the additives used in the manufacture of these wipes eluted at the same time as ifosfamide in the HPLC. Therefore, Kimwipes were judged not to be acceptable as a monitoring medium for the antineoplastics in this study. The Whatman filters, on the other hand, appeared to provide an appropriate material.

For evaluating contamination by fluorouracil, the filter–solvent–HPLC method required reanalysis of the sample desorbate with a reduction in instrument sensitivity. The reduced sensitivity of the assay

Table 2.
Recovery of Antineoplastic Agents from Vinyl Surface Wiped with Whatman Filters

Agent	Quantity Applied to Surface (μg)	Mean ± S.D. % Recovery				
		Wipe 1	Wipe 2	Wipe 3	Wipe 4	Total
Fluorouracil	100	...[a]	...	...	...	...
Ifosfamide	100	56.7 ± 7.3	14.0 ± 1.7	13.0 ± 2.8	6.5 ± 1.5	90.2 ± 12.5
Cyclophosphamide	100	57.2 ± 7.3	13.3 ± 1.7	10.9 ± 2.8	6.3 ± 1.5	87.7 ± 15.3
Doxorubicin hydrochloride	100	39.6 ± 14.0	15.6 ± 2.7	10.4 ± 4.5	6.8 ± 1.8	72.4 ± 17.6
Paclitaxel	12	49.2 ± 0.7	27.1 ± 0.8	13.5 ± 1.1	5.6 ± 0.5	95.3 ± 2.9

[a]The fluorouracil peak was obscured by the solvent front and could not be analyzed.

Table 3.
Recovery of Antineoplastic Agents from Resin Surface Wiped with Whatman Filters

Agent	Quantity Applied to Surface (μg)	Mean ± S.D. % Recovery				
		Wipe 1	Wipe 2	Wipe 3	Wipe 4	Total
Fluorouracil	40	48.2 ± 0.6	29.1 ± 1.9	19.8 ± 1.3	<10.0	97.0 ± 5.1
Ifosfamide	40	88.2 ± 0.7	11.9 ± 0.4	4.7 ± 0.1	<3.75	104.7 ± 0.8
Cyclophosphamide	40	88.0 ± 1.0	8.3 ± 0.6	2.9 ± 0.2	<2.5	99.2 ± 0.5
Doxorubicin hydrochloride	40	50.2 ± 7.4	38.4 ± 2.0	3.0 ± 2.0	NA[a]	91.5 ± 5.4
Paclitaxel	12	53.1 ± 8.7	46.4 ± 8.7	13.4 ± 1.9	8.0 ± 1.2	95.3 ± 2.9

[a]NA = not available (no wipe performed).

Table 4.
Recovery of Antineoplastic Agents from Stainless Steel Surface Wiped with Whatman Filters

Agent	Quantity Applied to Surface (μg)	Mean ± S.D. % Recovery				
		Wipe 1	Wipe 2	Wipe 3	Wipe 4	Total
Fluorouracil	50	66.7 ± 0.0	13.4 ± 1.8	7.0 ± 0.6	<4.0	87.0 ± 1.6
Ifosfamide	40	78.0 ± 0.5	9.8 ± 1.4	7.6 ± 0.2	<1.3	95.3 ± 1.7
Cyclophosphamide	40	76.8 ± 1.2	8.6 ± 0.4	5.4 ± 1.0	<1.3	90.8 ± 1.7
Doxorubicin hydrochloride	40	42.2 ± 1.5	34.8 ± 1.4	<5.0	NA[a]	77.0 ± 0.5
Paclitaxel	12	38.2 ± 0.6	21.0 ± 0.6	10.4 ± 0.9	4.3 ± 0.4	73.9 ± 2.3

[a]NA = not available (no wipe performed).

Table 5.
Recovery of Antineoplastic Agents from Stainless Steel Surface Wiped with Kimwipe Wipes

Agent	Quantity Applied to Surface (μg)	Mean ± S.D. % Recovery				
		Wipe 1	Wipe 2	Wipe 3	Wipe 4	Total
Fluorouracil	50	. . .[a]	. . .	16.6 ± 1.1	7.6 ± 0.9	N.Appl.[b]
Ifosfamide	40	112.4 ± 0.9	95.0 ± 1.1	82.4 ± 3.5	83.0 ± 3.6	372.8 ± 8.0[c]
Cyclophosphamide	40	62.4 ± 8.3	13.6 ± 0.6	7.6 ± 0.4	<1.25	83.6 ± 7.4
Doxorubicin hydrochloride	40	4.2 ± 1.7	6.4 ± 0.3	3.0 ± 1.1	NA[d]	18.2 ± 1.4
Paclitaxel	20	29.8 ± 0.5	30.7 ± 0.8	18.0 ± 2.0	<5.0	85.9 ± 3.1

[a]The fluorouracil peak was obscured by the solvent front and could not be analyzed.
[b]N.Appl. = not applicable.
[c]Total recovery of ifosfamide was significantly higher than the amount applied because of a confounding chemical in the Kimwipes.
[d]NA = not available (no wipe performed).

Table 6.
Recovery of Cyclophosphamide from Test Surfaces Wiped with Whatman Filters

Surface	Mean ± S.D. % Recovery	
	After One Wipe	After Four Wipes
Vinyl	57.2 ± 7.3	87.7 ± 15.3
Resin	88.0 ± 1.0	99.2 ± 0.5
Stainless steel	76.8 ± 1.2	90.8 ± 1.7

was a likely explanation for the higher minimum concentration of detection and lower overall recovery for fluorouracil relative to the other agents on the same surface types.

Sensitivity and recovery were excellent for ifosfamide and cyclophosphamide, given that total recovery (the sum of four wipe analyses) was at least 85% (and generally >90%) for each agent on all three surfaces.

Average recovery was lowest for doxorubicin, perhaps in part because of the drug's decomposition on the test surfaces. In an acidic pH (the standards were in a buffered solution with a pH of 6), the glycosidic bond in doxorubicin splits and produces water-insoluble aglycone (adriamycinone) and a water-soluble, basic, reducing aminosugar (daunosamine).[17] However, the limit of detec-

Table 7.
Minimum Concentrations of Antineoplastic Agents Detected with Whatman Filters

Surface	Minimum Concentration Detected (ng/cm²)				
	Fluorouracil	Ifosfamide	Cyclophosphamide	Doxorubicin Hydrochloride	Paclitaxel
Vinyl	. . .[a]	3.3	3.3	2.0	0.2
Resin	4.0	2.5	1.7	2.0	0.3
Stainless steel	2.0	0.8	0.8	2.0	0.2

[a]The fluorouracil peak was obscured by the solvent front and could not be analyzed.

tion of this method exceeds that obtained with a visible-light method developed by Van Raalte et al.[18] for testing doxorubicin on skin and other surfaces. That method is based on measuring the fluorescence of doxorubicin and can detect a minimum concentration of 20 ng on an 80-mm^2 surface or 0.25 ng/mm^2 (25 ng/cm^2). The filter–solvent–HPLC method detected a minimum concentration of 0.02 ng/mm^2.

The lower limit of detection for paclitaxel was very good. The presence of a confounding agent, such as another taxane,[19] and the low solubility of paclitaxel may have contributed to the variation observed. Paclitaxel has limited solubility in aqueous solutions and can form a white precipitate. It also degrades in the presence of light. It was very difficult to dissolve paclitaxel in the standards prepared for this study; this low solubility may have been a factor in the recovery of paclitaxel from the surfaces tested. In one literature method for monitoring paclitaxel, a mixture of 200 μL of glacial acetic acid and methanol is used to make 1 L of acidified methanol reagent for dissolving paclitaxel.[20] However, this mixture would not be acceptable in this method for dissolving and recovering the other agents.

One concern in using Whatman filters for sampling is their durability. Some disintegration of these filters did occur during use, but it was minimal and did not interfere with analysis as long as appropriate syringe filters were used to remove the desorbate from the desorbing vials.

When the sensitivity of the filter–solvent–HPLC method is compared with that of more sensitive methods and adjusted for the difference in surface area, the lower limit of detection is much closer than might be expected. For example, when the 1.7-ng/cm^2 minimum concentration of cyclophosphamide detected for a 600-cm^2 (~0.65-ft^2) resin surface wiped with a Whatman filter is adjusted for wiping the area of 4900 cm^2 (~760 in^2, or ~5.3 ft^2) used in the method of Connor et al.[10] and the same quantity of agent is recovered, it equals ~0.1 ng/cm^2. The method of Connor et al. is more sensitive for the same area at a lower limit of detection of ~0.01 ng/cm^2, but it involves an extraction step followed by analysis with gas chromatography in tandem with mass spectroscopy–mass spectroscopy (GC-MS-MS).

The advantages of the filter–solvent–HPLC method include its ease of use, its ability to detect five agents simultaneously, and the fact that it requires less analytical time than a GC-MS-MS method. Furthermore, although GC-MS-MS analysis does have high specificity and high sensitivity, it requires a derivatization step, such as use of trifluoroacetic anhydride for derivatization of ifosfamide and cyclophosphamide.[21] Also, relatively expensive and complex analytical instruments are needed, and there is less ability to conduct simultaneous analyses for multiple agents.

The study results confirm the effectiveness of using a mixed solvent for both the wipe procedure and sample desorbing for detection. This method may be able to detect other cytostatic drugs on similar surfaces (e.g., methotrexate).

Recent surface-contamination studies indicate that antineoplastic agents may be detected in areas adjacent to where they are handled and that some BSCs do not effectively control environmental contamination by some cytostatic drugs. Specifically, a class II, type A BSC recirculates approximately 70% of cabinet air through high-efficiency particulate air (HEPA) filters back into the cabinet; the rest is discharged through a HEPA filter into the preparation room. It has been reported that cyclophosphamide particles sublimated from a HEPA filter and returned to the work area.[22] This report is supported by observations in six cancer treatment centers of contamination in places adjacent to work areas.[10] Thus, in evaluating the pharmacy and administration areas of an oncology treatment area for potential exposure of the health care workers, monitoring should be conducted in adjacent areas, as well as in the admixture and administration areas. This is especially important when cyclophosphamide and ifosfamide are reconstituted in a class II, type A BSC.

Wipe sampling can be very useful in identifying areas where additional decontamination of surfaces or the use of PPE may be necessary. Wipe sampling can also be applied in evaluating the effectiveness of PPE.

Areas where antineoplastic agents are used generally require special cleaning and decontamination procedures.[2] Frequently, cleaning re-

quires the use of a detergent for polar compounds, a solvent for nonpolar compounds, and the combination when both polar and nonpolar compounds are likely to be present. This is usually followed by a decontamination step, which frequently involves the use of a 10% bleach solution (5.25% sodium hypochlorite diluted 10:1 with water to ~0.5%). The final step is repeating the wipe sampling to verify that the cleaning and decontamination were effective.

The Occupational Safety and Health Administration indicates classic wiping techniques and media for use in the collection of samples from surfaces.[2] Mixed cellulose ester filter disks and smear tabs are most often recommended. However, squares of a gauze material are sometimes used because they are more durable than filter media, especially when wiping rough surfaces. Either the mixed cellulose ester or the gauze material may be used dry or wetted with an appropriate solvent (usually a 50% solution of isopropyl alcohol in water).

A method described by Sessink et al.[9] involved the use of 20 × 21 cm tissues (Kleenex Professional Wipes, Kimberly-Clark Corporation, Koblenz, Germany) for sampling. The tissue was wetted with a 0.03 M sodium hydroxide solution, and the spots and objects were wiped clean. For packings, boxes, chamber pots, and urinals, two tissues and 5 mL of sodium hydroxide solution were used. Floors, hood work trays, tables, and sinks were cleaned with four tissues and 10 mL of sodium hydroxide solution. For wipe samples taken from the floor, the tissues were not wetted, but the solution was pipetted onto the floor. The minimum drug concentrations detected by using this wipe-sampling method were as follows:

- Cyclophosphamide 0.02 ng/cm^2 and fluorouracil 0.1 ng/cm^2 on a 0.7 × 0.7 m area (27.6 × 27.6 in, or ~5.3 ft^2) of floor and tables,
- Cyclophosphamide 0.01 ng/cm^2 and fluorouracil 0.04 ng/cm^2 on a 1.9 × 0.8 m area (74.8 × 31.5 in, or 16.36 ft^2) of work trays of two hoods, and
- Cyclophosphamide 0.06 ng/cm^2 and fluorouracil 0.3 ng/cm^2 on boxes and 9 cyclophosphamide drug vials and 20 fluorouracil ampuls before, and 76 packings after, preparation of drugs.

In the method used by Connor et al.,[10] an area of 4900 cm^2 is spread with a solution of 0.03 M sodium hydroxide by using a pipette (typically 20 mL) and one or two Scott 130 roll towels (Kimberly-Clark Corporation, Northrop, United Kingdom) to wipe the measured surface. The towels are stored in a coded, 125-mL plastic screw-top container. All samples were extracted and analyzed by GC-MS-MS. Minimum concentrations detected were similar to those identified in the method of Sessink et al.[9]

The filter–solvent–HPLC method for monitoring surface contamination is recommended because it is relatively easy and cost-effective and has very good precision and accuracy for ifosfamide and cyclophosphamide.[23] It can be useful in identifying these agents on the types of surfaces tested, determining the level of exposure risk, and evaluating the effectiveness of methods used to remove these agents from such surfaces.

Conclusion

A wipe-sampling, desorption, and HPLC method for monitoring surface contamination by selected antineoplastic agents was sufficiently accurate and sensitive to evaluate surfaces typically found in both the pharmacy and drug administration areas of oncology treatment facilities.

References

1. Hirst M, Tse S, Mills DG et al. Occupational exposure to cyclophosphamide. *Lancet*. 1984; 1:186-8.
2. OSHA technical manual. Section II, chapter 2. Sampling for surface contamination. Washington, DC: Occupational Safety and Health Administration; 1996.
3. Kolmodin-Hedman B, Hartvig P, Sorsa M et al. Occupational handling of cytostatic drugs. *Arch Toxicol*. 1983; 54:25-33.
4. Hemminki K, Kyyrönen P, Lindbohm M. Spontaneous abortions and malformations in the offspring of nurses exposed to anesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. *J Epidemiol Commun Health*. 1985; 39:141-7.
5. Skov T, Maarup B, Olsen J et al. Leukaemia and reproductive outcome among nurses handling antineoplastic drugs. *Br J Ind Med*. 1992; 49:855-61.
6. OSHA instruction TED 1.15, section II, chapter 2. Directorate of technical support. Controlling occupational exposure to hazardous drugs. Washington, DC: Occupational Safety and Health Administration; 1999.
7. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: overall evaluations of carcinogenicity: and updating of IARC monographs vols. 1 to 42. Lyon, France: International Agency for Research on Cancer; 1997.
8. Sessink PJ, Boer KA, Scheefhals AP et al. Occupational exposure to antineoplastic agents at several departments in a hospital: environmental contamination and excretion of cyclophosphamide and ifosphamide in urine of exposed workers. *Int Arch Occup Environ Health*. 1992; 64: 105-12.
9. Sessink PJ, Anzion RB, van den Broek PH et al. Detection of contamination with antineoplastic agents in a hospital pharmacy department. *Pharm Weekbl Sci*. 1992; 14:16-22.
10. Connor TH, Anderson RW, Sessink PJ et al. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health-Syst Pharm*. 1999; 56:1427-32.
11. McDevitt JJ, Lees PSJ, McDiarmid MA. Exposure of hospital pharmacists and nurses to antineoplastic agents. *J Occup Med*. 1993; 35:57-60.
12. Robbins MC. OSHA's wipe sampling policies and procedures. Sampling and analysis of toxic organics in the atmosphere, ASTMS STP 721. West Conshohocken, PA: American Society for Testing Materials; 1980:48-55.
13. Floridia L, Pietropaolo AM, Tavazzani M et al. Measurement of surface contamination from nucleoside analogue antineoplastic drugs by high-performance liquid chromatography in occupational hygiene studies of oncologic hospital departments. *J Chromatogr B Biomed Sci Appl*. 1990; 724:325-34.
14. Wheeler JP, Stancliffe JD. Comparison of methods for monitoring solid particulate surface contamination in the workplace. *Ann Occup Hyg*. 1998; 42:477-88.
15. Method for the evaluation of cyclophos-

phamide in swab samples. Evansville, IN: Bristol-Myers Squibb Pharmaceutical and Mead Johnson Nutritional Group; 1994.
16. Reverse-phase HPLC for determination of cyclophosphamide collected on Teflon filters. New Brunswick, NJ: Bristol-Myers Squibb Pharmaceutical Group; 1993.
17. Di Marco A, Gaetani M, Scarpinato B. Adriamycin (NSC-123,127): a new antibiotic with antitumor activity. *Cancer Chemother Rep.* 1969; 53:33-7.
18. Van Raalte J, Rice C, Moss CE. Visible-light system for detecting doxorubicin contamination on skin and surfaces. *Am J Hosp Pharm*. 1990; 47:1067-74.
19. Volk KJ, Hill SE, Kerns EH et al. Profiling degradants of paclitaxel using liquid chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry substructural techniques. *J Chromatogr B Biomed Sci Appl*. 1997; 696:99-115.
20. Reverse-phase HPLC for determination of Taxol in dust samples collected on Teflon filters. New Brunswick, NJ: Bristol-Myers Squibb Pharmaceutical Group; 1993.
21. Sessink PJ, Bos RP. Drugs hazardous to healthcare workers. *Drug Saf.* 1999; 20: 347-59.
22. Clark C. Occupational exposure to cytotoxic drugs. *Pharm J.* 1999; 263:65-8.
23. Pyy L, Sorsa M, Hakala E. Ambient monitoring of cyclophosphamide in manufacture and hospitals. *Am Ind Hyg Assoc J.* 1988; 49:314-7.