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Surface Contamination of Cyclophosphamide Packaging and Surface Contamination with Antineoplastic Drugs in a Hospital Pharmacy in Sweden

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Workplaces, e.g. hospital pharmacies and hospital departments, where antineoplastic drugs are handled might be contaminated with these drugs, and pharmacy personnel and health care workers may be exposed. In this study potential sources for exposure of antineoplastic drugs were investigated. Unbroken drug vials and tablet blister packages, both containing cyclophosphamide (CP) and their outer packaging were wipe sampled. Analysis was performed by liquid chromatography combined with tandem mass spectrometry (LC-MS/MS). The result showed that almost every part of the primary packaging was contaminated with CP and ifosfamide (IF). However, the amounts of CP and IF were low, and most likely not harmful for the personnel handling these packaging in association with drug preparation. The contamination must originate from the pharmaceutical manufacturer. Different surfaces in the preparation unit of a Swedish hospital pharmacy were also investigated at two different occasions by wipe sampling. In the preparation unit CP and IF were found as contaminants on the majority of the investigated surfaces. After the first measurement the hospital pharmacy improved its routines. Lower amounts of CP and IF were detected at the second measurement. A low degree of contamination with CP and IF was also detected on the floor outside the preparation unit and this indicated a small distribution of antineoplastic drugs to the surroundings.

Keywords: antineoplastic drugs; contamination; cyclophosphamide; environmental monitoring; ifosfamide; packaging; pharmacy

INTRODUCTION

Antineoplastic drugs are very commonly used for the treatment of cancer. Many of these drugs are classified as carcinogenic, mutagenic or teratogenic to humans. Workers at hospital pharmacies and hospital departments handling antineoplastic drugs may be exposed, e.g. during preparation of infusion mixtures or administration of these. Antineoplastic drugs might be absorbed cutaneously or via inhalation, but absorption can also occur accidentally via the gastro-intestinal system. Antineoplastic drugs have been found in urine (Ensslin *et al.*, 1994; Turci *et al.*, 2002; Pethran *et al.*, 2003) and blood (Nygren and Lundgren, 1997) from pharmacy and hospital personnel handling these drugs, indicating contamination in the work environment. It is of great importance to identify the sources of contamination. Potential sources for exposure include contamination on different surfaces in work environments. Monitoring of such exposure can preferably be performed by wipe sampling. Several studies (Sessink *et al.*, 1992; Minoia *et al.*, 1998; Connor *et al.*, 1999; Schmaus *et al.*, 2002) have found contamination with antineoplastic drugs, e.g. on working trays, floors, surfaces inside biological safety cabinets (BSCs), door handles and storage shelves. Another potential source of exposure may be contamination of

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primary packaging of antineoplastic drugs delivered from the pharmaceutical manufacturers.

Cyclophosphamide (2-[bis(2-chloroethyl)amino]-tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide; CP) and ifosfamide (3-(2-chloroethyl)-2-[(2-chloroethyl)-amino]tetrahydro-2H-1,3,2- oxazaphosphorine 2-oxide; IF) are two commonly used oxazaphosphorines. The alkylating agents CP and IF are prodrugs and require biotransformation before their metabolites can cause cell death by interacting with DNA. CP but not IF is classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC, 1981, 1987).

Previous studies of primary packaging containing CP have only studied contamination on the outer wall of drug vials and outside the caps (Sessink *et al.*, 1992; Ros *et al.*, 1997; Pethran *et al.*, 2001; Favier *et al.*, 2003; Mason *et al.*, 2003; Connor *et al.*, 2005). No studies have yet investigated such contamination on primary packaging containing tablets (blister packages) and outer packaging of drug vials. We have recently published a method based on liquid chromatography tandem mass spectrometry (LC-MS/MS) for the determination of surface contamination of CP (Hedmer *et al.*, 2004).

There is a lack of knowledge about the contamination levels on surfaces in preparation units at Swedish hospital pharmacies. Furthermore, there is no knowledge of whether the contamination is distributed to the surrounding work environment. Also, the information on possibilities to reduce the surface contaminations by changes and improvements in the routines of handling of antineoplastic drugs or in the cleaning routines is scarce.

This paper presents an investigation of external contamination on drug vials and tablet blister packages containing CP. An investigation of contamination of CP and IF on different surfaces in a preparation unit at a Swedish hospital pharmacy was also performed on two different occasions.

MATERIALS AND METHODS

Chemicals and materials

Cyclophosphamide monohydrate (purity 99.5%) was from Sigma-Aldrich Chemie (Schnelldorf, Germany). IF, (Holoxan®) with purity >98%, was obtained from ASTA Medica (Frankfurt am Main, Germany). $^{2}H_{6}$-labelled CP (CP-D6), with purity of 97%, was purchased from Phychem (Bergisch Gladbach, Germany) and was used as an internal standard. Ethyl acetate (HPLC 99.8%) was from Lab-Scan (Dublin, Ireland). Acetic acid glacial (p.a. >99.8%) and sodium hydroxide (p.a. >99.0%) were from Merck (Darmstadt, Germany). The water was purified in a Milli-RQ Water Purifier from Millipore (Billerica, MA, USA).

Wipe tissues for collection of wipe samples were non-woven swabs with a size of 5 × 5 cm (Hartmann-ScandiCare, Anderstorp, Sweden). Polyethylene bottles (50 ml) with wide mouth (Kautex Textron, Bonn, Germany) were used for storage of wipe samples.

Wipe sampling of primary packaging

Primary packaging of CP (Sendoxan®), commercially available on the Swedish market, was investigated in the study. The Sendoxan packaging was manufactured by Baxter Medical (Halle, Germany) and three package sizes of CP were investigated. Two packagings of tablets containing 50 mg CP (batch 1L713A) and 10 of each drug vial containing 200 mg CP (batch 3A105D) and 1000 mg CP (batch 2K107B) in powder form were chosen and wipe sampled. The primary packaging was delivered from the Swedish distributor to a hospital pharmacy in Sweden. The Sendoxan packaging was in unbroken plastic packages and they were supplied directly from the hospital pharmacy.

Antineoplastic drugs had never circulated in the room where all the wipe sampling was performed. Before the wipe sampling, the outside of the primary packaging was visually inspected and no signs of damage were detected on the outside of the chosen primary packaging. All wipe sampling of the drug packages was performed by the same person. A new pair of gloves was used for each wipe sample. Wipe samples were collected using a uniform sampling procedure by thoroughly wiping in two different directions (up and down, right and left) on the surfaces. Two wipe tissues, one in each direction, were used in each sampling procedure. Each wipe tissue was moistened with 1 ml of 0.03 M sodium hydroxide solution. After the sampling the two wipe tissues from each sample were placed in polyethylene bottles and kept in a freezer. The storage time from sampling until work-up procedure was ∼4 weeks.

The sampling locations on the packaging can be seen in Fig. 1. The outer packaging for both drug vials and tablet blister packages were made of cardboard. The outside and inside of each outer packaging were sampled. The outside of the outer packaging was first wiped. Then it was cut open and wiped inside. The pair of scissors was thoroughly cleaned between each packaging. Each tablet packaging contained 10 blister packages and those were numbered (1–10) and each blister package was thoroughly wiped on both sides. The primary packaging of drug vials contained a package leaflet and it was also wiped with two new tissues. There were no package leaflets in the tablet packaging. The outside of the drug vials and the vial cap covers, the inside of vial cap covers and the rubber membrane of the drug vials were all wipe sampled. Blanks ($N = 24$) were prepared by placing

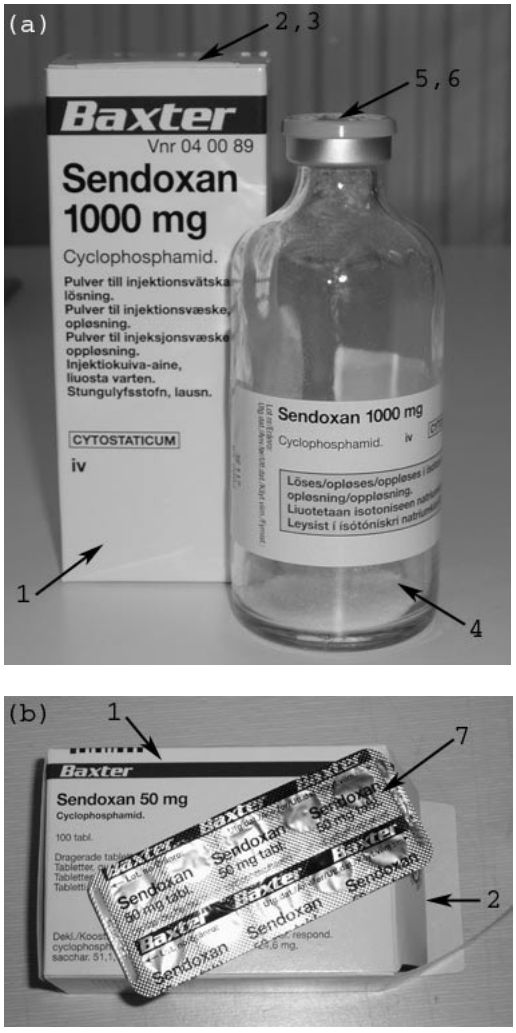

Fig. 1. An overview of the different parts that were wipe sampled on CP primary packaging of (a) drug vials and (b) tablets. The investigated parts were (1) the outside of the outer packaging, (2) the inside of the outer packaging, (3) the package leaflet, (4) the outside of the drug vial and vial cap cover, (5) the inside of the vial cap cover, (6) the rubber membrane and (7) the blister package.

two wipe tissues wetted with sodium hydroxide solution in a bottle.

Wipe sampling in a preparation unit at a hospital pharmacy

Measurement of contamination of antineoplastic drugs on different surfaces was performed at a Swedish university hospital pharmacy on two different occasions. The preparation unit in the hospital pharmacy consisted of two preparation rooms with two BSCs each, a room for storage and checking of prepared drugs, an office, two dressing rooms and a delivery room in which the prepared drugs were delivered to clients through a sluice. The hospital pharmacy prepared antineoplastic drugs for all departments at the university hospital and the drugs were handled according to the ordinance from the Swedish Work Environment Authority (1999). All antineoplastic drugs were prepared inside BSC class II with a vertical laminar air flow (danLAF®-o-matic VFRS 1206 E, Claus Damm, Humlebæk, Denmark) and the pressure inside the preparation unit was below the atmospheric pressure. Personal protective equipment was used such as specially adapted protective clothing and double protective gloves made of latex and vinyl. Preparation of infusion mixtures containing CP or IF entails dissolving the powder and transfer into infusion bags. A defined volume of CP or IF was transferred from a stock solution into an infusion bag containing 0.9% sodium chloride solution. The hospital pharmacy used CODAN Spike (CODAN Medizinische Geräte, Lensahn, Germany) containing a filter with a pore size of 0.2 μm to prevent the formation of aerosols in the BSC during drug preparation. Disposable absorbent sheets (75 × 50 cm; LamiDrape-S, Finess Hygiene, Kisa, Sweden) that were plastic-coated underneath were also used in preparation of antineoplastic drugs. An absorbent sheet was placed on the working area in the BSC. The sheet almost covered the whole working area. A new sheet was used for each preparation. All preparations of infusion mixtures and dissolving of stock solutions were performed on these sheets. The absorbent sheet was removed from the working area in the BSC before the wipe samples were collected. The working area in the BSC was then cleaned with sterile water and ethanol.

Wipe sampling was performed according to the procedure described in a recent paper (Hedmer *et al.*, 2004). Surface areas of 400 cm^2, defined by a plastic frame with internal size of 20 × 20 cm, were sampled on floors and working areas. The frame was thoroughly cleaned between each wipe sampling. Other objects such as handles and boxes had well-defined areas. All wipe samples were collected by the same person. A new pair of gloves was used for each wipe sample. The daily cleaning of the preparation unit took place every morning before work began. At the first measurement all CP and IF preparations were done in the same BSC. Wipe samples were collected at two random spots on the working area in the BSC after each preparation of infusion mixtures containing either CP or IF. At the end of the workday, wipe samples were collected at different spots in the preparation unit, e.g. at working areas and benches, floors, handgrips, door handles, bottom of a shaker used to prepare stock solutions of CP, a plastic folder and bottom of a refrigerator box. The selected spots were judged to be surface areas with potential contamination. The second measurement was performed 5 months later, after the end of the workday. Several of the surface areas that were wipe sampled at the first measurement were sampled again, e.g. floor

in the preparation and dressing room, bottom of a shaker, a plastic folder and bottom of a refrigerator box. However, at this measurement other surface areas such as different door handles, floor of the corridor outside the preparation unit and a box in a delivery closet were also wipe sampled. This was performed to investigate if contamination also could be detected on surfaces outside the preparation unit. Wipe tissues were also collected as blanks ($N = 6$) in the investigated work place by wetting two wipe tissues with sodium hydroxide and putting them into a bottle. All the wipe samples were placed in 50 ml bottles and kept in a freezer for ~3 weeks, until work-up procedure.

Preparation of standards

Stock solutions of CP and IF were prepared by dissolving weighed amounts in water. Several working solutions were made from these stock solutions by further dilution in water. A stock solution of CP-D6 was prepared by dissolving weighed amounts in water, which was further diluted in water.

Work-up procedure

Aliquots of 20 ml ethyl acetate and 100 µl internal standard (1.0 µg CP-D6 ml^{-1} water) were added to each bottle containing wipe tissues. Then, the bottles were shaken upright for 30 min with a shake apparatus 4010 Multi-Tube Vortexer (Corning, Medfield, MA, USA). Aliquots of 10 ml of the extracts were transferred into glass test tubes. The samples were evaporated to dryness under a stream of nitrogen gas at room temperature. Then, 0.15 ml of 0.5% acetic acid was added to each sample. The samples were then sonicated for 5 min and transferred into microvials, and were kept in a refrigerator until the analysis.

Standards of CP and IF were prepared by adding 100 µl aliquots of the working solution to 1 ml sodium hydroxide solution (0.03 M). Quality control (QC) samples were prepared by adding aliquots of 100 µl with 5 or 500 ng of CP and 5 or 500 ng of IF to two moistened wipe tissues. Two QC samples were prepared and analysed with each sample batch.

Analytical procedure

The wipe samples were analysed in a randomized order using a Perkin-Elmer Series 200 liquid chromatography (LC) system with a Series 200 autosampler (Applied Biosystems, Norfolk, CT, USA). The column was a Genesis C_{18} (50 × 2.1 mm) with a particle size of 4 µm (Jones Chromatography, Lakewood, CO, USA). The column outlet was coupled to an API 3000 triple quadropole mass spectrometer (Applied Biosystems/MDS-SCIEX, Toronto, Canada; MS/MS) equipped with an electrospray ionization (ESI) source.

The mobile phase consisted of water (A) and methanol (B), both containing 0.5% acetic acid. The separation was performed using gradient elution. Initially, the mobile phase started with A:B, 60:40 isocratic elution for 6 min, followed by a 2 min gradient to A:B, 0:100. Then, during 0.1 min the eluents returned to A:B, 60:40. At 60:40 the column was re-conditioned for 2.9 min. The mobile flow rate was 0.2 ml min^{-1} and sample aliquots of 20 µl were injected.

The analyses were performed using ESI with an ion spray voltage of 3000 V and temperature of 400°C. The instrument operated in a positive ion mode using multiple reaction monitoring at *m/z* 263.1/142.1 for CP, *m/z* 261.0/92.2 for IF and *m/z* 267.1/140.3 for CP-D6. As control fragments, *m/z* 261.0/140.3 for CP and *m/z* 261.0/154.1 for IF were used. Declustering potential for CP, IF and CP-D6 was 40, 41 and 44 V, respectively. Collision energy was 31 V for CP, 35 V for IF and 34 V for CP-D6, respectively. Declustering potential and collision energy for the control fragments was 42 and 31 V, respectively, for CP and 42 and 33 V, respectively, for IF. Peak-area ratios between the analyte and the internal standard were used for quantification. The ratio between the analyte and control fragments of the samples were compared with the ratio between the analyte and control fragments of the standard samples, and this was not allowed to exceed 20%. If a larger deviation was observed, the lowest value was reported and this occurred very rarely.

Quantitative analysis

Standards containing CP and IF in a range between 0.1 and 2000 ng per sample were prepared. Calibration curves were obtained by linear regression with $1/x$ weighing. Calibration curves with correlation coefficients (r) >0.99 were always obtained. The limit of detection was determined to 0.02 ng per sample for CP (0.05 pg cm^{-2} for 400 cm^2 area) and 0.05 ng per sample for IF (0.1 pg cm^{-2} for 400 cm^2 area) in wipe samples. The limit of quantitation was defined as the concentration at which the precision was 15% and determined to be 0.04 ng per sample for CP (0.2 pg cm^{-2} for 400 cm^2 area) and 0.08 ng per sample for IF (0.1 pg cm^{-2} for 400 cm^2 area). The extraction recovery rate was >82 and >81% for CP and IF, respectively. In total, eight QC samples were analysed in association with the study of primary packaging and the precision of these was 4% for CP. In association with the analysis of samples from the study of the preparation unit six QC samples containing amounts of 5 ng CP and IF were also analysed. The precision was 9% both for CP and IF. Recovery and coefficient of variation (CV) of CP and IF from spiked wipe tissues were found to be 82 and 81%, and 5 and 4%, respectively. Wipe sampling of 5 ng evaporated IF spillage on different surfaces

Table 1. Median amounts of CP and IF detected on different parts of the primary packaging of vials containing 200 mg CP

Sampled surface	Median contamination		Range		Surfaces contaminated above the limit of detection (%)	
	CP per sample[a] (ng)	IF per sample[a] (ng)	CP	IF	CP	IF
Outside outer packaging	0.5	ND[b]	0.2–1.2	—	100	0
Inside outer packaging	3.2	10	1.4–6.7	3.4–25	100	100
Package leaflet	0.06	ND	ND−0.1	ND–1.7	90	10
Outside drug vial and vial cap cover	13	24	4.9–24	ND–59	100	90
Inside vial cap cover	ND	ND	ND–0.6	ND–0.4	20	20
Rubber membrane	ND	ND	ND–0.1	—	10	0

[a]Median of 10 samples.
[b]Not detected.

Table 2. Median amounts of CP and IF detected on different parts of the primary packaging of vials containing 1000 mg CP

Sampled surface	Median contamination		Range		Surfaces contaminated above the limit of detection (%)	
	CP per sample[a] (ng)	IF per sample[a] (ng)	CP	IF	CP	IF
Outside outer packaging	1.0	—[b]	0.5–5.1	ND[c]–0.08	100	50
Inside outer packaging	2.8	0.7	1.8–7.1	0.4–0.9	100	100
Package leaflet	0.6	ND	0.1–7.4	ND–0.09	100	40
Outside drug vial and vial cap cover	19	1.6	4.8–130	1.0–2.8	100	100
Inside vial cap cover	—[d]	ND	ND–9.0	ND–0.2	50	10
Rubber membrane	0.4	ND	ND–190	—	80	0

[a]Median of 10 samples.
[b]The median value was <0.05 ng.
[c]Not detected.
[d]The median value was <0.02 ng.

made of laminate, stainless steel and plastic flooring material resulted in relative recoveries between 84–94% and the CV ranged between 4–8%.

RESULTS

Wipe samples from primary packaging

The results from the study of the primary packaging of Sendoxan are presented in Tables 1–3.

CP was found on the outside of all outer packagings of Sendoxan (50, 200 and 1000 mg). Amounts of CP between 0.2–5.1 ng per sample were found. The outer packaging of Sendoxan 50, 200 and 1000 mg had a size of 200, 130 and 240 cm^2, respectively. There were very small amounts of IF (up to 0.08 ng) detected on the outside of five outer packagings of Sendoxan 1000 mg.

CP was also quantified in all wipe samples taken from the inside of the outer packaging. The highest median contamination inside the outer packaging, 3.2 ng, was quantified at Sendoxan 200 mg. Up to 25 ng IF was detected on the inside of the outer packaging of Sendoxan 200 mg. Quantities of CP (up to 7.4 ng per sample) and IF (up to 1.7 ng per sample) were detected on the package leaflets belonging to Sendoxan 1000 and 200 mg, respectively. The package leaflets had an area of 630 cm^2.

Table 3. Median amounts of CP detected on different parts of the primary packaging containing 50 mg CP

Sampled surface	Median contamination by CP per sample (ng)	Range	Surfaces contaminated above the limit of detection (%)
Outside outer packaging	2.6[a]	1.8–3.3	100
Inside outer packaging	1.9[a]	1.8–2.0	100
Blister package	0.5[b]	0.2–3.5	100

No amounts of IF above the limit of detection were quantified and in these packaging there were no package leaflets.
[a]Median of 2 samples.
[b]Median of 20 samples.

CP was detected on the outside of all the drug vials and vial cap covers. The median contamination of Sendoxan 200 and 1000 mg were 13 and 19 ng CP

Table 4. Results from wipe samples taken at different surface areas (400 cm^2) in the hospital pharmacy at two different occasions

Location	No. of wipe samples	Median amount of CP quantified (pg cm^{-2})	Range	Median amount of IF quantified (pg cm^{-2})	Range
First measurement					
Floor in preparation room[a]	8	200	110–260	7.4	1.2–78
Floor in dressing room[a]	4	520	130–870	78	0.3–180
Floor in office	2	2.6	2.2–2.9	ND[b]	—
Working surfaces in BSC	15	9.2	2.7–200	21	1.9–740
Different working surfaces in preparation unit	8	18	2.4–54	11	2.5–38
Second measurement					
Floor in preparation room[a]	2	46	46–46	7.2	7.1–7.3
Floor in dressing room[a]	5	59	29–170	1.2	0.3–87
Floor in delivery room	1	59	—	110	—
Floor in corridor outside preparation unit	4	17	2.5–34	44	5.2–100

After the first measurement, the pharmacy changed several cleaning routines. The second measurement was performed several months after the new routines were implemented and the floors in the preparation and dressing room were investigated again.
[a]Sampled at both occasions.
[b]Not detected.

per wipe sample, respectively. The corresponding values for IF were 24 and 1.6 ng per wipe sample, respectively. Amounts up to 130 ng CP per sample and 59 ng IF per sample could be found on the outside of Sendoxan drug vials.

Only small amounts of CP and IF were found inside the vial cap covers. Amounts up to 190 ng CP per sample were detected on the rubber membranes at Sendoxan 1000 mg, but mostly small amounts of CP were present on the membranes. IF was not detected in any of these samples.

CP was quantified in all wipe samples from the blister packages. The amounts detected were within the range 0.2–3.5 ng per sample (median 0.5 ng). From this result it was not possible to see any pattern of contamination on the numbered blister packages.

The total amount of CP on the primary packaging of the drug vials varied between 6.5–28 ng (Sendoxan 200 mg: median 17 ng) and 10–216 ng (Sendoxan 1000 mg: median 38 ng). The corresponding values for IF were 3.5–85 ng (Sendoxan 200: median 35 ng) and 1.5–4.0 ng (Sendoxan 1000: median 2.4 ng). The contamination on the two investigated outer packaging (inside and outside) of tablets was found to be 3.8 and 5.1 ng CP, respectively. The total CP contamination on the entire tablet packaging was 8.6 and 15 ng CP, respectively. No IF was detected on the tablet outer packaging or on the blister packages.

In 22 out of 24 blanks no amounts of CP and IF detected, but small amounts of CP, 0.03 and 0.4 ng, were detected in two blanks.

Wipe samples from the preparation unit

Wipe sampling was performed twice in the preparation unit at the hospital pharmacy with several months between the measurements. On the first occasion 4 infusion mixtures and 10 stock solutions of CP were prepared and in total 13.8 g CP was handled in the BSC during the measurement. Also, two infusion mixtures containing 4.1 g IF in total were prepared. The second measurement was performed after a normal workday and, altogether, infusion mixtures containing 8.1 g CP and 18.8 g IF had been prepared.

During these two measurements normal working conditions prevailed and many different antineoplastic drugs were prepared in the preparation unit, but only CP and IF were studied. During the first measurement, in association with preparation of an infusion mixture containing IF, a small volume of liquid that had been spilled was visually seen on the absorbent sheet.

Results from the measurements on the two different occasions are presented in Tables 4 and 5. CP was quantified in all wipe samples collected from different working areas and from floors in the preparation unit. IF was quantified in the majority of these samples (96%). In the first measurement, the median contamination of CP on floors in the preparation room, dressing room and office was 200, 520 and 2.6 pg cm^{-2}, respectively. The corresponding median amounts for IF were 7.4, 78 and <0.1 pg cm^{-2}. The highest amounts of CP and IF on the floor were quantified in the dressing room. Median amounts of CP and IF in samples from the working area in the BSC and from other working areas in the preparation unit were found to be 9.2 and 21 pg cm^{-2} and 18 and 11 pg cm^{-2}, respectively. Amounts of CP up to 200 pg cm^{-2} and amounts of IF up to 740 pg cm^{-2} were found on the working area in the BSC.

At the second measurement the floors in the preparation and dressing room were sampled again and the results this time showed lower median amounts of CP, 46 and 59 pg cm^{-2}, respectively. The corresponding median amounts for IF were 7.2 and 1.2 pg cm^{-2}. The sample with the highest amount of CP

Table 5. Amounts of CP and IF detected in wipe samples taken at different locations in connection with the hospital pharmacy, before and after changed cleaning routines

Location	Amounts detected in wipe samples (ng per sample)	
	CP	IF
First measurement		
Bottom of shake apparatus[a]	89	5.3
Bottom of box in refrigerator[a]	2100	ND[b]
Plastic folder[a]	32	20
Handle on bottle	0.6	5.7
Door handle on refrigerator	11	9.6
Door handle on delivery closet/ sluice (inside preparation unit)	17	5.0
Sterilization bench	94	25
Second measurement		
Bottom of shake apparatus[a]	37	0.9
Bottom of box in refrigerator[a]	20	0.3
Plastic folder[a]	17	4.8
Door handle in delivery room	ND	ND
Door handle in delivery closet/sluice (clients side)	1.3	0.3
Box in delivery closet	3.1	2.2
Door handle in preparation unit	0.9	ND

[a]Sampled at both occasions.
[b]Not detected.

(170 pg cm^{-2}) quantified in the dressing room was wiped under the waste box. Only a small amount of IF was found (2.1 pg cm^{-2}) there. The floor in the delivery room showed amounts of CP and IF of 59 and 110 pg cm^{-2}, and 1.3 ng CP and 0.3 ng IF were detected on the door handle to the delivery closet. On the floor in the corridor outside the preparation unit median amounts of 17 pg CP per cm^2 and 44 pg IF per cm^2 were found. However, no CP and IF were detected on the door handle located on the inside of the door that leads from the delivery room to the corridor outside the preparation unit.

Amounts of CP and IF were also quantified on several other locations (Table 5). The highest amount of CP, 2100 ng, was detected in a refrigerator box (size of 45 × 20 cm) used to store CP stock solutions. The highest amount of IF, 25 ng, was detected in a wipe sample from a sterilization bench located in the office. The highest amounts of CP and IF were detected during the first measurement. No CP and IF was detected in the blanks.

DISCUSSION

This study demonstrated that only small amounts of CP were found on the investigated primary packaging. Our results indicate that the manufacturing and cleaning processes used by the manufacturer are effective for preventing contamination with antineoplastic drugs at hazardous levels. On most parts of the Sendoxan packaging used in this study small amounts of IF were also detected. The highest median amounts of CP and IF were found on the outside on the drug vials and vial cap covers. The level of the detected contamination of CP on drug vials and vial cap covers corresponds to what earlier investigators also have found (Sessink *et al.*, 1992; Favier *et al.*, 2003), but is much lower than Connor *et al.* (2005) reported. The median contamination of CP on the 10 blister packages in Sendoxan 50 mg packaging was found to be higher than the contamination on the other parts of the tablet packaging.

The detected contamination on the CP packaging must originate from the manufacture or packaging process at the pharmaceutical manufacturer, e.g. dusting may occur during the filling process of drug powder into drug vials or the vials might be improperly washed. In an exposure measurement by Pyy *et al.* (1988), in a drug production plant for CP the highest concentrations of CP in air were measured in the tablet production department, but in this study the primary packaging containing tablet blister packages were the least contaminated primary packaging. According to Wilken (1997) the origin of the external contamination of 5-fluorouracil drug vials may be caused by splashing and foaming during the filling process of liquid to the drug vials. The environments in drug plants may be contaminated with the drugs produced in the plant. The recent paper by Mason *et al.* (2003) reported that two wipe samples from 1000 mg vials of CP were contaminated with amounts of both CP and IF. That finding was most likely due to the fact that the two drugs were manufactured within the same drug plant. Our results point out the need for a proper cleaning of manufacturing equipments and departments, although the levels of contamination in our study were low. The amounts of IF on the tablet packaging were below the limit of detection. The packaging process of the CP tablets may be performed in another department of the drug production plant where no IF has been handled.

The results from this study have shown contamination of CP and IF on the outer packaging. However, the detected amounts of CP and IF are very low, the highest amount of CP was 216 ng. In a cancer risk assessment based on data from an animal study and with an estimated uptake of CP between 3.6 and 18 μg per day over a period of 40 years the lifetime cancer risks were found to be 100–600 per million (Sessink *et al.*, 1995). The absorbed doses during handling of primary packaging are very far from 100% and are most likely not harmful to personnel handling and preparing antineoplastic drugs.

It is hard to explain the presence of small amounts of CP found in two blanks. The blanks were prepared in new bottles in an environment where CP had never been handled before. The contamination cannot be explained by carry over effects in the LC during the

analysis. The contamination of the blanks originates probably either from a mix up of the samples or from contamination during the work-up procedure.

CP and IF were found in almost all wipe samples from both exposure measurements in the hospital pharmacy. In an investigation of six pharmacies Connor *et al*. (1999) it was also reported that CP was found in 100% of wipe samples and IF in 75% of the samples. The amounts of CP and IF quantified as a contaminant on different surface areas vary, but highest amounts of CP and IF were detected at the first measurement. CP is a more commonly used antineoplastic drug than IF. The hospital pharmacy handled annually larger amounts of CP than IF, and this was also seen in the results from the wipe sampling as higher amounts of CP were generally detected on the surface areas.

The preparation unit was cleaned every morning before work began by a trained cleaner. Surfaces such as handles, chairs and working areas were cleaned every day with both a basic detergent solution and ethanol. The floors were cleaned with the detergent solution every day. Working areas in the BSCs and the refrigerator box were cleaned by the pharmacy personnel. The detected contamination on surfaces, such as floors, working areas and handles, must occur from the drug leakage during the working day as these surfaces were thoroughly cleaned every day. It has previously been demonstrated that a basic solution efficiently cleans different surface materials (Hedmer *et al.*, 2004). But in the working place there were surfaces that were cleaned more rarely (e.g. refrigerator box), and drug contamination on these surfaces may occur from drug leakage that occurred several days before.

New routines for cleaning of the refrigerator box and shake apparatus were introduced. The box was previously cleaned once a month and with the new routine once a week instead. All vials containing stock solutions of CP were enclosed in two plastic bags instead of one before they were stored in the refrigerator box. Earlier there was no cleaning routine for the shake apparatus, but at the time of the second measurement it was cleaned once a week. A new routine for handling of waste bags, containing waste contaminated with antineoplastic drugs, was also introduced. Earlier the waste bags were placed directly on the floor in the dressing room in association with the transport from the preparation unit to the garbage room. Wipe samples taken on the floor in the dressing room showed, at the first measurement, a much higher level of contamination than the floor in the preparation room. According to the new routine the waste bags were placed in a waste box on a small trolley. To improve the work environment the hospital pharmacy changed and improved their cleaning routines after the first measurement. The hospital pharmacy also renewed all its plastic folders.

The second measurement was performed several months after the new routines were implemented. Repeated wipe sampling on some of the surface areas, e.g. floors and refrigerator box, indicated that the contamination levels of CP and IF had decreased. The reduced contamination on surfaces decreases the potential dermal exposure of CP and IF. During the second measurement extended wipe sampling was also performed on surface areas outside the preparation unit. Accordingly, a low degree of contamination of CP and IF was detected on the floor outside the preparation unit. This indicated a small distribution of antineoplastic drugs to the surrounding work environment.

In comparison with previous studies, the contamination levels on the floors in the preparation unit in this Swedish hospital pharmacy were in the same order as found by Connor *et al.* (1999), but lower than the levels found by Minoia *et al.* (1998). The contamination levels of CP on the working area inside BSC were low due to the use of adsorbent sheets, but the levels of IF on the working area inside BSC were elevated due to the spillage. The IF spillage was not cleaned enough efficiently, but was instead spread out on the working area in the BSC. During the workday at the first measurement three times as much CP than IF was handled and at the second measurement twice as much IF was handled.

The knowledge of how to interpret the results obtained from the study of surface contamination of antineoplastic drugs is limited and there is no knowledge of how the levels of surface contamination may vary over time. There is a need to study how the levels of surface contamination varies over time in workplaces that handle antineoplastic drugs. Repeated measurements of defined surface areas in the same workplace are requested. In this paper, the wipe sampling was performed by two persons, one wipe sampled the primary packaging and one sampled surface areas in the hospital pharmacy. But there is no knowledge about how the results may be affected when the wipe sampling is performed by different persons. Information about this is also requested.

Workplaces that handle antineoplastic drugs must be considered as contaminated environments although most of the investigated surfaces were thoroughly cleaned every day. The surface contamination was probably caused by direct contact with contaminated gloves or clothes, other materials or by spillage. The handling of contaminated primary packaging contributed probably only to a small portion of the detected drug contamination in the investigated preparation unit. In this investigation only two different antineoplastic drugs were analysed, but it is realistic to presume that the surfaces in the hospital pharmacy are contaminated with all the different antineoplastic drugs handled in the hospital pharmacy. During work in these environments it is important to handle

antineoplastic drugs inside the BSC, use protective clothing, often change gloves and if possible use closed-system device to minimize the contamination levels and thereby the exposure.

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