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ORIGINAL ARTICLE

Environmental and biological monitoring of antineoplastic drugs in four workplaces in a Swedish hospital

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Abstract
Objectives Exposure to antineoplastic drugs should be avoided due to the risk of getting adverse health effects. Antineoplastic drugs such as cyclophosphamide (CP) and ifosfamide (IF) are commonly used in medical attendance. In this study the variability of surface contamination of CP and IF was investigated by repeated wipe sampling over time in four workplaces in a university hospital. The surface contamination levels were also evaluated and health care workers were biologically monitored.
Methods A hospital pharmacy, two oncology wards and one oncology outpatient department were selected. Between 10 and 13 different surface areas such as work areas, floors and handles were selected in each workplace and wiped between 7 and 8 times during 9 months. Pre- and post-shift urine samples were collected from the workers in the investigated workplaces. Analysis was performed by liquid chromatography combined with tandem mass spectrometry.
Results Measurable amounts of CP and IF were detected on the majority of the sampled surfaces. The highest concentrations were found on the floors in the patient lavatories and utility rooms (up to 95 ng cm^{-2}). In general, the surface contamination of CP and IF on floors did not vary much over time. Work areas and handles had larger variability. Neither CP nor IF were detected in any of the collected urine samples.
Conclusions The variability in surface contamination of CP and IF was rather low especially on floors. Higher concentrations of CP and IF were found on the floors compared with the work areas. The highest surface loads were found on floors (in patient lavatories and utility rooms) that were related to patient activities such as handling of patients' urine. Although high contaminations were found, the biological monitoring showed no uptake. Wipe sampling is a good method to improve the work practices.

Keywords Antineoplastic drugs · Biological monitoring · Occupational exposure · Variability · Wipe sampling

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Introduction

Occupational exposure to antineoplastic drugs can occur in hospital pharmacies and hospitals where antineoplastic drugs are prepared, administered to patients or where treated patients are nursed. Occupational exposure can also occur in other work environments such as laundries, pharmaceutical industries and veterinary clinics (Meijster et al. 2006).

Antineoplastic drugs can cause acute adverse health effects to exposed workers such as hair loss, skin rash and light-headedness (Valanis et al. 1993a, b; Krstev et al. 2003) and delayed effects on reproduction (Selevan et al. 1985; Stucker et al. 1990; Valanis et al. 1997, 1999; Dranitsaris et al. 2005; Fransman et al. 2007a). Furthermore, some antineoplastic drugs are genotoxic (Fuchs et al. 1995; Undeger et al. 1999; Burgaz et al. 2002; Cavallo et al. 2005) and could cause cancer (IARC 1981, 1987, 1990). IARC has classified ten antineoplastic drugs as group 1, carcinogenic to humans and ten as group 2A, probably carcinogenic to humans (IARC 1987, 1990). It is therefore

important to have knowledge of the potential occupational exposure to antineoplastic drugs.

At least 40 different antineoplastic drugs are handled every day with in medical treatment of neoplastic and non-neoplastic diseases (Ringborg et al. 1998). Since it is not realistic to measure all different types of antineoplastic drugs, two common antineoplastic drugs with wide application areas, cyclophosphamide (CP; group 1) and ifosfamide (IF; group 2A), were used as indicators for occupational exposure to antineoplastic drugs and in particular to alkylating agents.

There are several methods available to assess the exposure to antineoplastic drugs such as biological monitoring, air monitoring, wipe sampling and patches. One commonly used method to assess surface contamination of antineoplastic drugs is wipe sampling (Sessink et al. 1992a; Minoia et al. 1998; Connor et al. 1999a; Mason et al. 2001; Kiffmeyer et al. 2002; Schmaus et al. 2002; Hedmer et al. 2004). By performing wipe sampling it is possible to estimate the transferable surface load of antineoplastic drugs to the skin and thereby it is possible to evaluate the potential dermal exposure. Previous studies investigated surface contamination of antineoplastic drugs at one time only (Sessink et al. 1992a, b; McDevitt et al. 1993; Minoia et al. 1998; Connor et al. 1999a; Floridia et al. 1999; Rubino et al. 1999; Kiffmeyer et al. 2002; Schmaus et al. 2002; Ziegler et al. 2002; Wick et al. 2003; Turci et al. 2003; Crauste-Manciet et al. 2005; Fransman et al. 2005; Schulz et al. 2005). However, no information on how the contamination levels on the sampled surfaces varied over time was obtained with the study design used in those studies. In a study by Mason et al. (2005), two spots in a preparation room were selected and wiped during four consecutive days, but no results about the variability was reported. Without the knowledge of the variability of the surface load this can cause problem with the interpretation of the detected surface contamination. By knowing the variability it would be possible to determine if it is suitable to monitor surface contamination based on collection of single wipe samples. It is therefore important to have knowledge about the variability of surface contamination. The optimal way of performing environmental monitoring of workplaces contaminated with antineoplastic drugs is by single wipe sampling.

Personal exposure can with an advantage, be assessed by biological monitoring since there are at least two exposure routes, via skin and through inhalation. A hand to mouth contact could also contribute to an uptake. Furthermore, extensive personal protective equipment (PPE) is used. It is therefore suitable to perform biological monitoring with the biomarkers CP and IF in urine to estimate the doses that have been taken up in the body. It has previously been shown that health care workers handling antineoplastic drugs were occupationally exposed since antineoplastic agents were found in their urine (Evelo et al. 1986; Sessink et al. 1992a; Ensslin et al. 1994). Also more recent studies indicate occupational exposure despite the use of PPE such as protective clothing and special gloves, and other safety precautions e.g. biological safety cabinets (BSC) class II (Turci et al. 2002; Pethran et al. 2003; Wick et al. 2003).

Methods for wipe sampling of CP and IF on surfaces and biological monitoring of CP and IF in urine have previously been developed (Hedmer et al. 2004, 2005, 2008).

The specific aim of this investigation was to study the variability of surface contamination of CP and IF by repeated wipe sampling over time on a number of surfaces in hospital work environments where CP and IF were handled. Furthermore, the levels and trends over time regarding the surface contamination in the investigated workplaces were also evaluated. In connection with the wipe sampling, biological monitoring of health care workers was performed to assess the personal exposure.

Material and methods

Description of workplaces

Four workplaces where antineoplastic drugs were used were selected for surveillance of antineoplastic drug exposure. The workplaces were one hospital pharmacy, two oncology wards (ward A–B) and one outpatient department (ward C) located at a university hospital in Sweden. The characteristics of the workplaces are presented in Table 1. The three wards handled different amounts of CP and IF due to their specialization in treatment of different cancer diseases. Mean amounts of CP and IF handled during the sampling days and months and the annually handled amounts are specified in Table 2.

Hospital pharmacy

The preparation of antineoplastic drugs in the university hospital was centralized to the hospital pharmacy and it supplied the wards of both the university hospital and another adjacent hospital with antineoplastic drug mixtures. Thus, CP and IF were frequently handled in this workplace (Table 2). The preparation unit in the hospital pharmacy consisted of two preparation rooms. Each preparation room was equipped with two BSCs, class II with a vertical laminar air flow (danLAF®-o-matic VFRS 1206 E, Claus Damm, Humlebæk, Denmark) where the preparations were performed. Air vents (CODAN Spike, CODAN Medizinische Geräte, Lensahn, Germany) were used to prevent the formation of aerosols in the BSCs during drug preparation. The prepared drug mixtures were enclosed in

Table 1 Characteristics of the investigated workplaces

Workplace	Activity concerning antineoplastic drugs	Time of handling antineoplastic drugs	Number of beds	Daily cleaning time
Hospital pharmacy	Preparation	8 a.m.–5 p.m.[a]	–	Every morning before work
Ward A	Administration, nursing and care taking of treated patients	24 h	14–16	At noon
Ward B	Administration, nursing and caretaking of treated patients	24 h	12	Every morning
Ward C	Administration	8 a.m.–5 p.m.[b]	8	After work[c]

[a] Antineoplastic drugs were prepared mainly on weekdays

[b] Antineoplastic drugs were administered on weekdays

[c] The floor in the medicine room was cleaned at noon

Table 2 Mean of daily and monthly amounts of CP and IF handled in the hospital pharmacy and wards during the surveillance

Workplace	Mean handled amount (g)				Annually handled amounts[a] (g)	
	Sampling day		Sampling month			
	CP (range)	IF (range)	CP (range)	IF (range)	CP	IF
Hospital pharmacy	12 (1.4–20)	24 (0–50)	246 (157–375)	236 (150–342)	3,014	2,868
Ward A	0 (–)	0.7 (0–5.2)	4.3 (0–16)	36 (12–108)	84	592
Ward B	1.2 (0–5.0)	6.6 (0–20)	19 (9–27)	88 (48–116)	218	962
Ward C	2.2 (0–3.9)	0 (–)	53 (29–99)	2.6 (0–10)	648	38

The annually handled amounts are also shown

[a] During the year (2005) of sampling

self-closing plastic bags before they were taken out from the BSCs. The preparation unit also consisted of a room, called "the square" used for storage and checking of prepared drugs, an office for administrative work, two dressing rooms (one for the preparation section and one for the office section) and a room in which the prepared drugs were delivered to clients through a sluice from the "square". The air pressure in the preparation unit was below the atmospheric pressure.

Oncology ward A

Oncology ward A treated primary patients with Hodgkin's disease, malignant lymphoma, renal cancer and urinary bladder cancer. The ward had several patient rooms, a medicine room, a utility room and offices. Patients treated with IF had to collect urine in bottles to check the hydration status. In the utility room, assistant nurses weighed the bottles and the urine was then manually poured in the urinal washer. The workers at the ward handled frequently drug mixtures containing IF, but CP was handled more seldom (Table 2). The drug mixtures were stored in the medicine room before they were intravenously (i.v.) administrated to patients. The mixtures containing CP and IF required storage in a refrigerator.

Oncology ward B

Oncology ward B was mainly involved in the treatment of patients with lymphoma, sarcoma and testicular cancer. The ward handled frequently IF but also smaller quantities of CP (Table 2). The layout of the ward was similar to that of ward A.

Oncology ward C

Oncology ward C treated patients with breast cancer, malignant lymphoma and urinary bladder cancer. Ward C was an outpatient department, which consisted of two treatment rooms with the total capability to treat eight patients at a time. A medicine room, a utility room, an examination room, a patient lavatory and offices were also located in the ward. Ward C handled the largest annual amounts of CP of the wards, but also the smallest amounts of IF (Table 2).

Personal protective equipment

The workers in the investigated workplaces handled antineoplastic drugs according to the ordinance from the Swedish Work Environment Authority (2005) and to the local safety guidelines of the hospital. Pharmacy workers who

prepared antineoplastic drugs used PPE such as specially adapted overalls, hair covers, hood protections, surgical masks and two pairs of protective gloves made of vinyl and latex. Nurses who worked with administration of antineoplastic drugs to patients were specially trained and used PPE such as protective gloves of nitrile rubber and protective gowns. Assistant nurses who handled urine from IF treated patients used protective gloves of plastic or vinyl, protective gowns and surgical masks. The cleaner in the hospital pharmacy wore the same clothing as the pharmacy workers, except for the hood and mask. The cleaners in the wards wore work clothes such as short-sleeved tops, trousers and thin gloves made of vinyl.

Wipe sampling

Sampling strategy

A predetermined sampling scheme with selected surface areas was constructed. The scheme included different floors and work areas on benches in the investigated workplaces. Potential contact surfaces such as handles, balances and infusion pumps were also chosen as sampling areas. In the wards, similar surface areas were sampled to allow comparison. The used sampling strategy can be seen in Table 3. The workers in the investigated workplaces were not informed of the surface areas that were wipe sampled. At each sampling occasion, all workplaces were sampled on the same day by one person (M.H.).

The investigated floor areas were cleaned on a daily basis by cleaners while the health care workers were responsible for the cleaning of the work areas. Information about the time of cleaning can be seen in Table 1. Most of the flooring was made of plastic, except for the floors in the patient lavatory and utility room in ward A, where the floors were made of polished concrete. All work areas were made of laminate except for the one made of stainless steel (utility room in ward C). In connection with the first wipe sampling, the exact location of each sampling area was measured with measuring tape and written down. Many of the selected areas were also documented with photos.

All areas were wipe sampled once a month at randomly selected occasions during a time period of 9 months (January to September except August). During the July sampling, ward A and B were combined in the premises of ward A and ward C had been moved to the premises of ward B. No wipe sampling was performed in the wards in July since the work practice differed substantially. Approximately similar locations were chosen in the three wards (A–C) to allow comparison. In connection with the two wipe sampling occasions (February and April), floors in patient rooms and floors next to patient lavatories in ward A and B also were sampled.

Sampling areas in the hospital pharmacy

Wipe samples were taken on the following floors: on the floor in one of the preparation rooms (in the middle of the room and between the BSC and a roller table), on the floor in the doorway between the preparation room and the "square", on the floor in the dressing room on both sides of the border line separating the dressing room in two parts and on the floor in the corridor outside the preparation unit. Wipe samples were also taken on the following work areas in the "square": on a bench next to the shaker apparatus and on a bench used to check the prepared mixtures before delivery to clients. Other surface areas that were sampled were the bottom of a refrigerator box, a step over bench located on the border in the dressing room, door handles located on doors between the "square" and the dressing room ("square side"), the dressing room and the delivery room ("dressing room side") and the delivery room and the corridor ("delivery room side").

Sampling areas in the oncology ward A

Wipe samples were taken from the floor in the medicine room, the utility room and the corridor. Work areas on the benches in the medicine room and utility room were wipe sampled. Other areas that were sampled were the balance, the control panel of the infusion pump and the refrigerator handle and shelf.

Table 3 Sampling strategy used in the investigation of the workplaces

Workplace	Time of sampling	Number of sampled surfaces areas each occasion			Number of wipe sampling occasions	Total number of collected wipe samples
		Floor	Work area	Other area		
Hospital pharmacy	5.10– 6.40 p.m.[a]	6	2	5	8	104
Ward A	12.40–3.00 p.m.	3	3	5	7	77
Ward B	12.30–3.40 p.m.	3	3	6	7	84
Ward C	3.30–4.40 p.m.	5	3	2	7	70

[a] Sampling was performed after the workday

Sampling areas in the oncology ward B

The sampled surface areas corresponded to the surfaces investigated in the oncology ward A.

Sampling areas in the oncology ward C

Wipe samples were taken from the floor in the medicine room, utility room, one of the treatment rooms, patient lavatory next to the toilet and corridor. The location of the sampled work areas corresponded to the other wards. Other surface areas that were sampled in the ward were the refrigerator handle and shelf.

Wipe sampling method

Two nonwoven swabs, with a size of 5 × 5 cm (Hartmann-ScandiCare, Anderstorp, Sweden), wetted with 1 ml 0.03 M sodium hydroxide solution were used for collection of wipe samples. All wipe samples were collected according to a previously described procedure (Hedmer et al. 2004, 2005). For each collected wipe sample, a new pair of gloves was used to avoid cross-contamination. Surface areas of 400 cm^2 (20 × 20 cm cut-out interiors) defined by a plastic frame were wiped on work areas, floors and refrigerator shelves. The surface was wiped with S-shaped motions with the first swab and the second swab was wiped in the same way but with a 90°-change in wipe orientation. Wiped objects such as handles, boxes and balances were self-defined areas. The plastic frame was reused and therefore decontaminated between each wipe sample. The collected wipe samples were stored in 50 ml polyethylene bottles with wide mouth (Kautex Textron, Bonn, Germany) at −20°C until analysis. Three field blanks were collected in each workplace at each sampling occasion by wetting two wipe tissues with sodium hydroxide and putting them into a bottle. In total, 88 field blanks were collected in the investigated workplaces.

Biological monitoring

Biological monitoring was performed once at each workplace in connection with one occasion of wipe sampling. Biological monitoring was performed on health care workers who worked with CP or IF during the day of urine collection.

Urine was sampled from pharmacy workers ($N = 3$) who prepared mixtures containing CP and IF, nurses who administered infusion mixtures containing CP and IF ($N = 7$), assistant nurses involved in patient care of CP and IF treated patients ($N = 8$) and cleaners ($N = 4$) who cleaned the investigated workplaces. Prior to entry into this study, all workers received both written and oral information about the biological monitoring. The workers gave their written informed consent. This part of the study was approved by the Research Ethics Committee (LU 688–01) at Lund University (Lund, Sweden).

The biomarkers, CP in urine and IF in urine, reflect the short-term exposures, since the half-lives of CP (5 h up to 60 h after uptake) and IF (4–6 h) are relatively short (Boddy and Yule 2000; Hedmer et al. 2008).

In average, the pharmacy workers handled 16 g CP (range 2–36 g) and 13 g IF (range 0–25 g) during the biological monitoring.

Urine sampling

Spot samples of urine were collected in 250 ml polyethylene bottles (Kautex Textron, Bonn, Germany) before and after work. Totally, 44 pre- and post-urine samples were collected. The urine samples were stored at 5°C during maximum 24 h. Then, aliquots of 20 ml urine were transferred to test tubes and stored at −20°C until sample preparation. No drug spillage or accidents were reported in connection with the urine sampling.

Work-up and analytical procedure

The preparation and analysis of wipe and urine samples were performed according to the methods by Hedmer et al. (2004, 2005, 2008). Briefly, the samples were added with an internal standard $^2H_6$-labelled CP and extracted with ethyl acetate. The samples were evaporated to dryness and then dissolved in 0.5% acetic acid. The samples were blindly and randomly analyzed by liquid chromatography (LC) combined with tandem mass spectrometry in electrospray ionization mode. Duplicates of quality control (QC) samples containing 5 and 500 ng CP and IF were prepared and analyzed together with each batch of wipe samples.

Previously, limit of detection (LOD) was determined to be 0.02 ng CP per wipe sample (0.05 pg cm^{-2} for 400 cm^2 area) and 0.05 ng IF per wipe sample (0.1 pg cm^{-2} for 400 cm^2 area; Hedmer et al. 2004, 2005). Furthermore, the within-day and between-day precision was <9% for the wipe samples. For urine samples the LOD was determined to be 10 ng/l for CP and 30 ng/l for IF (Hedmer et al. 2008).

In total, 56 QC samples containing either 5 or 500 ng CP and IF were analyzed. The precision of the QC samples containing 5 ng for CP and IF 2 was 11%. The corresponding values for the QC samples containing 500 ng were 4 and 19% for CP and IF, respectively.

Statistical analysis

The computer software SPSS for Windows (version 12.0.1, 2003, SPSS Inc., Chicago, USA) was used for the statistical

analysis. According to Leidel et al. (1975), exposure measurements are generally log-normally distributed. P–P plots indicated that data were log-normally distributed, and thus all analyses were performed on log-transformed data. Exposure variability, e.g. interday environmental variability is usually expressed by geometrical standard deviation (GSD; Leidel et al. 1975; Soule 1991; Peretz et al. 1997), so geometrical mean (GM) and GSD were calculated for the data. Wipe samples taken from similar location but in different wards were considered to belong to the same group. An analysis of variance (ANOVA) considering repeated measures was performed on the log-transformed data and multivariate analysis on interacting terms was performed. The data from the hospital pharmacy were not included in the analysis of the matched surfaces since they deviated from the oncology wards. Time trends were evaluated using ANOVA with sample number as independent variable. To investigate correlations, Spearman's rank test was used. Values below the LOD were given the value of half the LOD. Statistical significance was considered at P values below 0.05.

Results

Wipe sampling

The detected surface contamination in the hospital pharmacy is presented in Table 4. The GM amounts of CP and IF on the floors in the hospital pharmacy ranged between 6.7 and 45 pg cm^{-2} and 13 and 78 pg cm^{-2}, respectively. The GM amounts of CP and IF on work areas were 2.2–6.8 and 11–14 pg cm^{-2}, respectively. Surface contamination on other objects such as handles had GM values below or close to LOD for CP and below the LOD for IF.

The surface loading data from the wards are shown in Tables 5 and 6. The GM amounts of contamination on the floors in ward A were between 8.3 and 24 pg cm^{-2} and 33 and 480 pg cm^{-2} for CP and IF, respectively. The corresponding GM values for ward B ranged between 4.4 and 21 pg cm^{-2} and 31 and 300 pg cm^{-2} for CP and IF, respectively. In ward C, the GM amounts on the floors were between 34 and 2,000 and 2.6–360 pg cm^{-2} for CP and IF, respectively.

Table 4 Results of CP and IF as surface contamination on floors, work areas and other areas in the hospital pharmacy preparation unit

Location		GM ± GSD (pg cm^{-2})[a]		Range		Percentage above LOD (%)	
		CP	IF	CP	IF	CP	IF
Floor	Preparation room[b]	35 ± 8	39 ± 2	7.0–5700	15–170	100	100
	Preparation room[c]	13 ± 1	78 ± 2	9.2–20	39–420	100	100
	Door opening[d]	12 ± 2	47 ± 2	6.7–26	23–130	100	100
	Dressing room[e]	45 ± 1	13 ± 1	32–69	8.4–23	100	100
	Dressing room[f]	18 ± 1	24 ± 1	13–30	19–36	100	100
	Corridor[g]	6.7 ± 1.2	19 ± 1	4.7–8.5	13–27	100	100
Work area	Square[h]	2.2 ± 2.7	11 ± 5	0.6–13	1.3–130	100	100
	Square[i]	6.8 ± 3.7	14 ± 8	1.7–70	1.8–260	100	100
Other area[j]	Refrigerator box	0.9 ± 3.3	0.4 ± 18	0.1–3.8	ND[k]–35	100	75
	Step-over bench	0.02 ± 3.1	0.03 ± 4.0	ND–0.2	ND–0.3	25	38
	Door handle 1[l]	0.03 ± 5.0	ND	ND–0.5	ND–0.5	38	13
	Door handle 2[m]	ND	ND	–	–	0	0
	Door handle 3[n]	ND	ND	ND–0.04	ND–0.6	13	25

[a] Based on eight samples

[b] Floor next to BSC

[c] Floor in the middle of the preparation room

[d] Doorway between preparation room and "square"

[e] Part of dressing room using the same shoes as in the preparation room and "square"

[f] Part of dressing room, entrance side

[g] Located out side the preparation unit

[h] Next to shake apparatus

[i] Work area used for checking of the preparations before delivery to clients

[j] ng sample^{-1}

[k] No amounts detected

[l] Handle inside "square" on door toward dressing room

[m] Handle inside dressing room on door toward delivery room

[n] Handle inside delivery room toward corridor

Table 5 Results of CP and IF as surface contamination on floors, work areas and other areas in the three oncology wards A–C

Location	Workplace																	
	Ward A						Ward B						Ward C					
	GM ± GSD (pg cm^{-2})[a]		Range		% >LOD		GM ± GSD (pg cm^{-2})[a]		Range		% >LOD		GM ± GSD (pg cm^{-2})[a]		Range		% >LOD	
	CP	IF	CP	IF	CP	IF	CP	IF	CP	IF	CP	IF	CP	IF	CP	IF	CP	IF
Floor																		
Medicine room	8.3 ± 1.9	33 ± 1	5.3–32	27–50	100	100	4.4 ± 1.1	31 ± 1	3.7–5.7	28–38	100	100	34 ± 2	2.6 ± 1.4	16–160	1.7–4.1	100	100
Utility room	24 ± 2	480 ± 2	10–59	170–2700	100	100	21 ± 3	300 ± 2	2.9–60	59–750	100	100	48 ± 1	9.5 ± 1.7	34–98	4.6–16	100	100
Corridor	8.8 ± 1.9	54 ± 2	4.4–23	27–120	100	100	8.3 ± 1.1	73 ± 1	7.2–10	58–99	100	100	92 ± 2	4.8 ± 1.6	62–240	1.9–8.8	100	100
Treatment room	–[b]	–	–	–	–	–	–	–	–	–	–	–	45 ± 1	2.6 ± 1.6	29–62	1.5–6.1	100	100
Patient lavatory	–	–	–	–	–	–	–	–	–	–	–	–	2000 ± 2	360 ± 2	1100–3800	200–620	100	100
Work area																		
Medicine room[c]	0.2 ± 8.0	0.5 ± 8.1	ND[d]–5.2	ND–3.0	57	71	0.5 ± 4.9	2.3 ± 2.3	ND–4.4	0.8–7.3	86	100	0.7 ± 5.4	0.1 ± 8.2	ND–3.6	ND–2.7	86	43
Medicine room	0.1 ± 9.1	0.2 ± 15	ND–3.4	ND–10	43	43	0.7 ± 2.3	4.0 ± 2.9	0.2–2.9	0.8–14	100	100	1.8 ± 2.2	0.3 ± 6.2	0.9–8.9	ND–2.4	100	71
Utility room	0.6 ± 2.7	4.9 ± 3.6	0.1–1.7	0.6–31	100	100	0.9 ± 19	33 ± 26	ND–37	ND–360	86	86	0.6 ± 5.2	0.1 ± 24	ND–3.4	ND–92	86	29
Other area[e]																		
Door handle refrigerator[f]	0.3 ± 5.8	2.3 ± 3.3	ND–2.4	0.8–22	86	100	0.04 ± 0.2	0.02 ± 0.09	ND–0.5	ND–0.3	57	29	0.7 ± 1.7	0.1 ± 6.5	0.4–1.9	ND–0.7	100	71
Refrigerator shelf	0.1 ± 6.0	0.4 ± 17	ND–0.9	ND–13	71	71	0.3 ± 2.6	6.0 ± 5.2	0.06–1.1	1.2–170	100	100	0.3 ± 5.2	0.08 ± 8.7	ND–1.5	ND–2.3	86	57
Balance	0.4 ± 6.2	3.4 ± 9.0	ND–3.1	0.04–37	86	100	0.3 ± 26	10 ± 5.2	ND–19	1.4–130	71	100	–	–	–	–	–	–
Control panel balance	0.03 ± 8.7	0.2 ± 29	ND–2.8	ND–110	29	57	1.0 ± 3.1	8.6 ± 1.9	0.3–6.3	4.9–23	100	100	–	–	–	–	–	–
Control panel infusion pump	3.4 ± 2.8	19 ± 2	1.1–15	6.6–81	100	100	0.8 ± 2.6	9.4 ± 2.2	0.3–3.6	3.8–25	100	100	–	–	–	–	–	–

[a] Based on seven samples

[b] Not sampled

[c] Area used to store infusion bags containing other antineoplastic drugs than CP and IF

[d] No amounts detected

[e] ng sample^{-1}

[f] The handle in ward B consisted of two keys

Table 6 In February and April, floors in three patient rooms and lavatories in ward A and B were sampled

Workplace	Location of floor area	Amounts of floor contamination (pg cm^{-2})	
		CP	IF
Ward A	Patient room[a]	65	710
	Patient lavatory[a]	290	95,000
Ward B	Patient room 1[a]	140	530
	Patient lavatory 1[a]	6,300	7,500
	Patient room 2[b]	44	740
	Patient lavatory 2[b]	530	5,600

These floors were only sampled once

[a] Sampled in February

[b] Sampled in April

The highest GM contamination of CP was found on the floor next to the toilet in the patient lavatory in ward C (2,000 pg cm^{-2}). The highest GM value for IF was found on the floor in the utility room in ward A (480 pg cm^{-2}). However, the highest level of surface contamination was found on the locations that were only sporadically wipe sampled (floors in patient lavatories and patient rooms in ward A and B). The maximum surface loading data of CP and IF found on floors in patient lavatories were 6,300 and 95,000 pg cm^{-2}, respectively (Table 6). Amounts of CP and IF up to 140 and 740 pg cm^{-2}, respectively, were found on floor areas in patient rooms.

The GM amounts of CP and IF detected on the investigated work areas in the wards ranged between 0.1–1.8 pg CP cm^{-2} and 0.1–33 pg IF per cm^{-2}. Generally, the GM amounts in the investigated workplaces were lower on the work areas compared with the floors.

Among the category of other surface areas, the control panel of the infusion pump in ward A had the highest GMs of CP (3.4 ng per sample) and IF (19 ng per sample). The highest amount of IF, 170 ng per sample, was detected on the refrigerator shelf in ward B.

The monthly GM surface contamination for each workplace is presented in Fig. 1. The monthly and total GM of contamination of CP and IF for each category of surfaces in the wards are presented in Table 7. Using ANOVA to evaluate the differences (using log-transformed data) between the three oncology wards showed a significant difference with respect to CP ($P = 0.04$) but not IF ($P = 0.28$). Ward C had higher levels of CP contamination on the surfaces. In the corresponding analysis, evaluating differences between surfaces regardless of ward (Table 7) both CP ($P < 0.01$) and IF ($P = 0.02$) were found to differ between the surfaces. Floors had a higher surface load of antineoplastic drugs than the other categories of surfaces. No interaction was found between the workplace and surface area. Significant trends

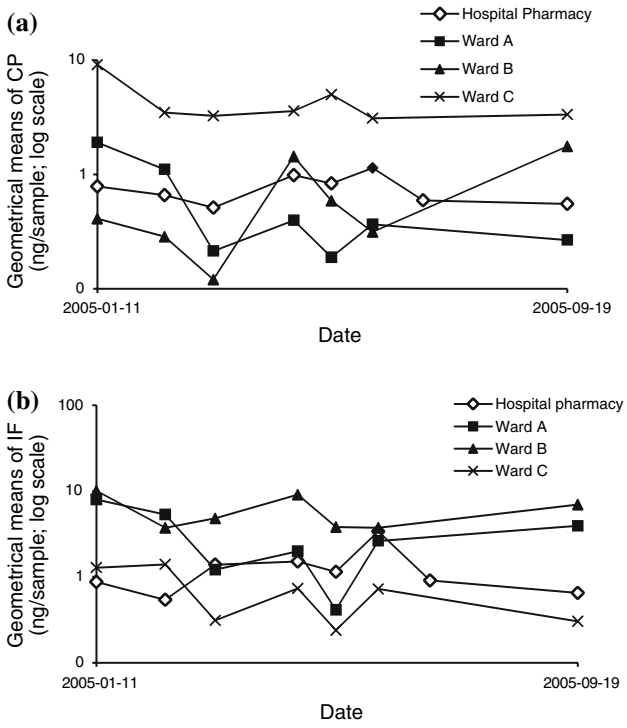

Fig. 1 Time trends of contamination of **a** CP and **b** IF based on the monthly GMs of all wiped surfaces (floors, work areas and other surfaces) in each workplace

over time of the GM surface contamination of each workplace were seen in ward A ($P = 0.02$) and ward B ($P = 0.02$) for CP. The surface contamination decreased over time in ward A while it increased in ward B (Fig. 1). No time trends were seen for the floor contamination in the four workplaces.

Ward C had the highest value of total GM surface contamination for CP (4.1 ng/sample) and the corresponding value for IF (5.6 ng/sample) was found in ward B. This is in agreement with the quantities handled among the wards as ward C and B handled the largest quantities of CP and IF, respectively. However, no correlations between the detected floor contamination of CP and IF and the daily or monthly handled amounts of CP and IF were seen in any of the investigated workplaces.

In general, high correlations were found between the surface load of CP and IF at each sampling occasion with a few exceptions. The median correlation for the hospital pharmacy was 0.7 and the median correlations for the wards A–C were 0.8, 0.9 and 0.9, respectively.

The GSDs of CP and IF of the sampled surfaces can be seen in Tables 4 and 5. The overall variability of CP and IF in the study presented as median values was 2.7 (range 1.0–26) and 2.9 (range 1.0–29), respectively. Based on the sampled surfaces in each workplace, the hospital pharmacy had the lowest variability of surface contamination, while ward A had the highest variability (Fig. 2). Ward A handled the smallest quantities of CP. Ward C handled the smallest

Table 7 Monthly and total GM of contamination of CP and IF for each type of investigated surface area in the oncology wards

Antineoplastic drug	Location	Month							Total GM amounts
		January	February	March	April	May	June	September	
CP	Floor[a]								
	Medicine room	27	12	9.6	8.2	7.3	9.3	9.6	8.0
	Utility room	44	36	20	37	25	21	26	22
	Corridor	30	24	18	16	13	13	24	14
	Work area[a]								
	Medicine room[b]	0.8	0.5	0.1	1.2	0.3	0.8	0.3	0.4
	Medicine room[c]	1.5	0.8	0.2	0.5	0.2	2.1	0.3	0.5
	Utility room	0.6	0.5	0.1	1.6	0.8	0.6	2.1	0.6
	Other area[d]								
	Door handle refrigerator	0.4	0.3	0.07	0.1	0.5	0.2	0.3	0.2
	Balance	0.5	0.1	0.1	4.4	0.1	0.1	2.3	0.4
	Control panel balance	3.1	0.1	0.1	0.3	0.3	0.1	0.1	0.2
	Control panel infusion pump	7.1	2.9	1.1	0.8	0.7	1.2	2.3	1.1
	Refrigerator shelf	0.6	0.2	0.2	0.4	0.1	0.03	0.3	0.2
IF	Floor[a]								
	Medicine room	14	17	14	14	12	12	15	12
	Utility room	86	110	70	150	97	190	100	88
	Corridor	21	37	28	27	20	32	26	22
	Work area[a]								
	Medicine room[b]	1.6	0.8	0.1	2.3	0.2	0.5	0.3	0.5
	Medicine room[c]	0.5	4.2	0.1	0.5	0.1	3.0	1.2	0.6
	Utility room	45	0.9	2.9	3.5	1.3	1.5	1.7	2.9
	Other areas[d]								
	Door handle refrigerator	1.1	0.4	0.06	0.2	0.1	0.3	0.6	0.2
	Balance	15	3.0	20	9.6	0.4	2.5	32	1.9
	Control panel balance	26	0.5	1.6	0.4	0.2	0.8	1.7	0.6
	Control panel infusion pump	11	43	15	8.9	5.4	13	19	9.8
	Refrigerator shelf	5.3	4.1	0.2	1.1	0.1	0.2	0.1	0.5

[a] pg cm^{-2}

[b] Area used to store infusion bags containing other antineoplastic drugs than CP and IF

[c] Work area

[d] ng $sample^{-1}$

quantities of IF and showed to have the highest variability regarding IF contamination on surfaces. CP and IF contaminated floors showed a lower variability compared with contaminated work areas (Fig. 3).

In 86 of 88 field blanks, no amounts of CP and IF were detected, but in one blank a small amount of 0.06 ng CP was detected and in another 1.0 ng IF was quantified.

Biological monitoring

No CP nor IF were detected in any of the collected pre- and post-shift urine samples from workers at the investigated workplaces.

Discussion

Repeated collection of wipe samples was for the first time performed during a longer time period in workplaces where antineoplastic drugs were used. In general, the variability of contamination on floors was low. The low variability of surface contamination was unexpected. Even if work practice and cleaning procedures in the investigated workplaces were similar over time, spillage of a very small volume of urine with high concentration of IF or CP could contaminate the floors with amounts that ranged over a very large magnitude. Since no surface loads were detected on some of the work areas, this resulted in a higher variability. The

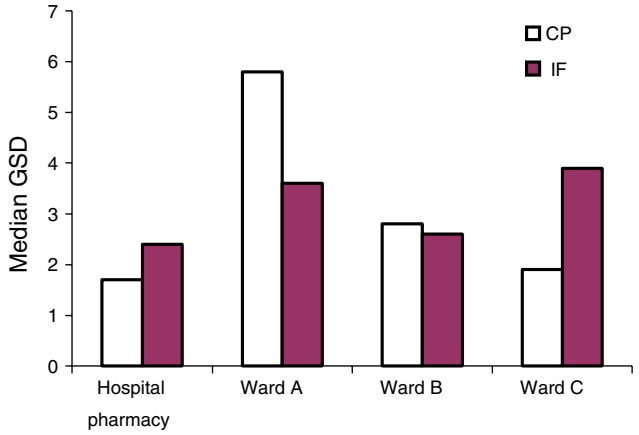

Fig. 2 Histogram of the median variability based on all sampled surfaces in each workplace

Fig. 3 Histogram of median variability of **a** CP and **b** IF for different categories of surfaces

surface load of CP and IF were higher on floors compared with work areas. The highest concentrations were found on the floors in the patient lavatories.

The contamination levels of CP and IF were generally low in the pharmacy as well as in the oncology wards. However, on the floors in the patient lavatories and in the utility rooms significant contamination was found. Frequent and widespread spillage of contaminated urine from patients has been previously reported by Kromhout et al. (2000). Patients treated with CP and IF excrete approximately 13 and <20% of the dose in urine, respectively (Sladek 1994; Boddy and Yule 2000). High concentrations of CP have been measured in urine from patients, i.v. treated with CP (Fransman et al. 2005; Hedmer et al. 2008). The high levels of antineoplastic drugs on the floors next to patient toilets probably originate from urine spillage either during the use of the toilet or from filling of the urine bottles. The floor contamination may be also caused by the aerosol formation during flushing. The contamination in the utility rooms must originate from the urine spillage or from the aerosol formation during pouring of urine into the urinal washer. Since the urine concentration of antineoplastic drugs is high, even a very small volume of urine can cause a high surface contamination. Due to patient secrecy, it was not possible to select permanent sampling areas on the floors in patient rooms and lavatories in wards A and B. Therefore, floors in the patient rooms and lavatories at these wards were only investigated a few times. In the wards, the majority of the contamination on the surfaces probably originates from treated patients excreta (urine, sweat, faeces). The widespread contaminations in the patient's area are on one hand an important finding for optimizing the work practice and on the other hand also involves a risk for visitors.

The wipe sampling was performed at randomly selected occasions since we thought that the levels of surface contamination were not dependent only on the actual drug handling on the sampling day.

CP and IF were not often used in ward A and ward C, respectively. Although these drugs were not handled in the wards in connection with the sampling days detectable amounts were found on the surfaces. Similar observations were also reported by Acampora et al. (2005). The surface load of CP and IF found on all sampled surfaces in the investigated workplaces showed to correlate very well at each sampling occasion. This covariation is interesting in the point of view that it is possible to use the most frequent handled antineoplastic drug in the workplace as a marker for antineoplastic drug contamination (at least for alkylating agents).

None of the previous investigations within this field of research had evaluated the variability of wipe sample recoveries of antineoplastic drugs (Sessink et al. 1992a, b; McDevitt et al. 1993; Minoia et al. 1998; Connor et al. 1999a; Floridia et al. 1999; Rubino et al. 1999; Kiffmeyer et al. 2002; Schmaus et al. 2002; Ziegler et al. 2002; Wick et al. 2003; Turci et al. 2003; Crauste-Manciet et al. 2005; Fransman et al. 2005; Schulz et al. 2005). There are only a

few references in the literature regarding the variability of surface contamination. Our results therefore had to be compared with the results from wipe sampling of other occupational exposures such as pesticides (Fenske et al. 1991) and mutagenic activity in dust (Vermeulen et al. 2001). Fenske et al. reported a variability of 40–60% in wipe samples taken on the same day. Our results seem to be in the same low range as reported by Fenske et al. although our sampling interval was much longer. In the study by Vermeulen et al. (2001) the variability was described to be large due to the fact that many of the wipe samples had no detectable mutagenic activity.

According to Soule (1991), variability for much industrial hygiene data GSDs range between 1.5 and 2.5 and in a summary made by Rappaport (1991), GSDs ranged from 1.2 to 9.3 with most values under 3.0. The overall median variability of CP and IF as surface contamination in this study was approximately 3. According to Buringh and Lanting (1991), small number of samples collected during surveys leads to biased estimates of the variance of the exposure distribution and there is a high likelihood of an underestimate of variance. By performing repeated measurements of surface contamination between seven and eight occasions, the assessment of variability in this study must be reliable.

The higher variability on work areas might depend on that the cleaning of these areas was performed by the pharmacy and health care workers on a more irregular basis compared with the floor areas that was cleaned on a daily basis by cleaners. There is also reason to believe that the low variability of contamination of CP and IF on floor areas might depend on insufficient removal of the drugs during cleaning. The possibility that contamination of antineoplastic drugs is still present on the surfaces after cleaning also has been considered by Turci and Minoia (2006). The detected surface contamination could also partly be due to the amount of drug desorbed from the matrix of the floor, rather than added during the working hours since the latest cleaning. The surface contamination could assumably diffuse into the pores of the flooring material and be accumulated there over longer periods since the drugs are stable and then emitted back to the surface again (V N Handlos, personal communication). However, these assumptions have to be further evaluated.

The samplings in the wards and hospital pharmacy were performed at different times, relative to the time of cleaning. Thus, the sampling time did not seem critical. According to Acampora et al. (2005), cleaning with sodium hypochloride solutions reduces the surface contamination levels of CP compared to cleaning with polyphenol or generic detergents. However, Roberts et al. (2006) reported that detergents (acid, neutral, alkali) easily and efficiently removed CP from a surface. In our study, e.g. the floors in the investigated workplaces were cleaned with different detergents. However, normal cleaning procedures may not remove the surface contamination. Improvements of the cleaning routines might be needed. Therefore, issues concerning the cleaning procedure such as type of cleaning agent and frequency should be further investigated.

From the ANOVA, it could be concluded that there were significant differences in the surface contaminations between the investigated wards within the same hospital. The reason for this probably depends on the handled amounts of CP and IF and the number of patients treated with these antineoplastic drugs. Selection of both the workplace and surface area seem to be important factors to be considered in association with future wipe sampling.

Furthermore, only time trends of GM surface contamination of CP in ward A and B were seen (Fig. 1). However, these wards handled larger amounts of IF, but no trends over time were seen for IF. This indicated that the workers in the workplaces did not change their behavior or working method during the study. A study design with repeated wipe sampling could influence the workers to improve their work practice and in that case a decrease of the surface contamination in the workplace would be seen, but this was not observed in this study. We also investigated if time trends of contamination on the floors were seen, but no trends over time were seen for any floor contamination in the investigated workplaces. Thus, floor contamination does not seem to accumulate over time in the flooring material.

The presence of CP and IF in two wipe sampling blanks is difficult to explain. The contamination cannot be explained by carry over effects in the LC during analysis. However, the blanks were prepared in workplaces, where CP and IF were handled. The contamination of the blanks probably depends on the contamination during the preparation and work-up procedures or on a mix up of samples. Still it must be emphasized that a total of 960 samples were analyzed in this study.

In the literature, much attention has been paid to workers involved in preparation and administration of antineoplastic drugs. In our study the pharmacy workers appeared to be well protected and they also showed good work practice. Also, nurses who administrated antineoplastic drugs seemed to have adequate PPE. Our study indicated that the assistant nurses and cleaners might come into direct contact with patients' excreta or indirect contact with surface contamination originating from patients excreta during their daily duties since they used inadequate gloves. Thicker gloves made of latex or nitrile rubber would better to protect them from dermal contamination (Laidlaw et al. 1984; Connor 1999b). The Swedish Work Environment Authority (2005) also recommends use of double pair gloves made of different material.

Despite the high levels of contamination of CP and IF observed in the cleaners and assistant nurses' workplaces,

we did not find any CP or IF in their urine. However, it should be emphasized that only 12 workers from these two groups were biologically monitored. Furthermore, it is likely that the exposure is intermittent or limited to certain days. This accentuates the drawback of biomarkers that only reflect the exposures of a single day.

From this study, knowledge of the contamination levels of antineoplastic drug on different surface areas in a Swedish hospital was obtained. The results provide us with a hint of the contamination levels in Swedish workplaces. However, workplaces other than university hospital need to be investigated to gain more confident assessment of the levels of surface contamination in Sweden. In comparison with previous investigators, our contamination levels of CP and IF on floor areas seem to be lower than the levels found by Minoia et al. (1998) and within the same ranges as those found by Connor 1999b, Schmaus et al. (2002), Wick et al. (2003), Mason et al. (2003, 2005) and Fransman et al. (2007b).

In conclusion, the variability in surface contamination of CP and IF was rather low especially on floors. Higher concentrations of CP and IF were found on floors compared with work areas. The highest surface loads were found on floors (in patient lavatories and utility rooms) that were related to patient activities such as handling of patients' urine. Moreover, a single wipe sample seemed to reflect the contamination levels over time rather well especially on floor areas but this should be confirmed in further studies. No correlations were seen between the surface contamination on floors and the daily or monthly handled amounts of CP and IF but the highest levels of contamination was found on the wards with the highest usage.

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