Evaluation of the Efficacy of Additional Measures Introduced for the Protection of Healthcare Personnel Handling Antineoplastic Drugs

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Objectives: Due to their adverse effects, antineoplastic drugs are considered as a potential health risk to healthcare personnel. The objective of the study was to compare the surface contamination level of the conventional preparation room and outpatient clinic before and after the implementation of a set of additional protective measures.

Methods: The measures were targeted at eliminating potential sources of environmental contamination, and modification of the cleaning procedure. The measures introduced into the preparation room consisted of (i) the introduction of manual cleaning of drug vials before they enter the preparation room, (ii) the modification of the routine cleaning procedure performed at the end of each working day (i.e. shifting the cleaning of the isolators as the most contaminated objects from the beginning of the cleaning process to the end), and (iii) the introduction of regular cleaning of the work table every 2h. The measures introduced into the outpatient clinic consisted of (i) replacement of the standard infusion sets with multichannel sets for safe drug administration, (ii) the introduction of self-cleaning seats to the patient lavatories supporting hygienic and contamination-free seated urination, and (iii) replacement of standard infusion stands with wall-mounted stands, supporting the regular and proper cleaning of the floor beneath. To determine the surface contamination level with antineoplastic drugs, cyclophosphamide and platinum were determined in wipe samples with high performance liquid chromatography with tandem mass spectrometry and inductively coupled plasma mass spectrometry.

Results: In the preparation room, depending on the sampling spot and analyte, median concentrations ranged from 5 to 267 pg cm−2 and from 2 to 368 pg cm−2 before and after implementation of the measures, respectively. In the outpatient clinic, median concentrations ranged from 5 to 5310 pg cm−2 and from <0.2 to 574 pg cm−2 before and after implementation of the measures, respectively. Depending on the sampling spot, median contamination of the outpatient clinic with cyclophosphamide and platinum was reduced by 57–99% and 61–98%, respectively.

Conclusions: The measures implemented in the outpatient clinic were shown to reduce workplace contamination effectively. Therefore, they can be recommended also for other workplaces where antineoplastic drugs are administered. In contrast, measures implemented in the preparation room, where relatively strict regulations had already been adopted before the study, were less effective. To decrease the actual contamination of the preparation room, other protective measures (e.g. closed-system transfer devices) should be considered.

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IntrODuctIOn

This study addresses the surface contamination of the hospital working environment with antineoplastic drugs (ADs), which have been shown to have many hazardous properties such as genotoxicity, cancerogenicity, and reproductive toxicity (Ensslin et al., 1997; Sessink and Bos, 1999; Schneider et al., 2000; Hessel et al., 2001; Pethran et al., 2003; Turci et al., 2003; Yoshida et al., 2006). With respect to these effects, the occupational exposure of healthcare workers should be avoided. For the purpose of enhancing occupational safety, several policy and technical improvements have been incorporated into drug handling practice since the 1980s. However, recent studies still demonstrate that workers continue to be exposed to these hazardous drugs (Soutar et al., 2000; Nygren et al., 2002; Connor et al., 2010).

Considering the possible routes of exposure, surface contamination and dermal exposure seem to be of major importance (McDevitt et al., 1993; Sessink et al., 1994a,b; Kromhout et al., 2000). This was also supported by our previous study, which investigated surface and airborne contamination with cyclophosphamide in the Masaryk Memorial Cancer Institute (Brno, Czech Republic). The study determined diffuse surface contamination throughout the hospital pharmacy and the outpatient clinic. In contrast, airborne contamination occurred only sporadically and in low concentrations; gaseous cyclophosphamide concentrations up to 4.3 ng m⁻³ were determined only in the outpatient clinic (Odraska et al., 2011). This study extends the previous investigation by evaluating the efficiency of additional protective measures implemented to reduce the surface contamination observed in the preparation room and the outpatient clinic.

The Masaryk Memorial Cancer Institute is one of the biggest of 13 complex oncology centres in the Czech Republic. Preparation of ADs is centralized in the hospital pharmacy, where strict protective measures are applied according to valid international standards and national legislation (R.Lgs._n.84, 11 March 2008). Drug preparation is carried out in two negative pressure isolators using needles and Luer lock syringes. The pharmacy prepares 150–180 chemotherapies per day. Most of these are transferred to the outpatient clinic, where ADs are administered to patients. Total capacity of the outpatient clinic is 20 patients at a time (corresponding to app. 120 patients per day). Administration of ADs is performed using intravenous bolus injection or continuous infusion. Connection of administration sets to infusion bags is performed exclusively by pharmacy technicians in the isolators immediately after the admixing activities. Reuse of the administration sets is forbidden. Floors, sinks, door handles, phone receivers, and other objects frequently touched by workers’ hands are cleaned every day after the work shift using common detergents and disinfectants.

Despite regular cleaning, frequent surface contamination was determined in a previous study (Odraska et al., 2011). To reduce the surface contamination, additional protective measures were suggested and implemented. In general, the measures were workplace specific and were tailored to minimize potential sources of contamination.

In the preparation room, the following three distinct measures were implemented. Firstly, the outer surfaces of vials delivered from the manufacturers were repeatedly shown to be contaminated with traces of ADs (Nygren et al., 2002; Mason et al., 2003; Connor et al., 2005; Schierl et al., 2010) and therefore manual decontamination of the vials before they entered the preparation room was implemented. Secondly, to prevent the spread of surface contamination from the inside of the isolators to the preparation room during the daily cleaning procedure, the cleaning of the isolators was shifted from the beginning to the end of the routine cleaning procedure. Thirdly, as the outer surfaces of infusion bags and bolus syringes are known to be frequently contaminated during the preparation process (Crauste-Manciet et al., 2005), regular cleaning of the work table where the ADs are placed after preparation was implemented.

In the outpatient clinic, another three distinct measures were implemented. Firstly, with the aim of eliminating possible spillages of ADs during the disconnection of the administration sets from the cannula, standard single-channel administration sets were replaced with special multichannel sets that enable the rinsing of ADs from the
set after the application of ADs is completed. Secondly, to vacate the floor under the infusion stands, which would make it accessible for regular routine cleaning, standard stands were replaced with wall-mounted stands. Thirdly, with the aim of reducing surface contamination of the laboratories used by oncology patients, an information campaign promoting hygienic use of the toilets (i.e. seated urination) was launched. In addition, conventional toilet seats were replaced with automatic self-cleaning seats which enhanced the hygienic standard of the lavatories and made them more comfortable for the patients.

The main objective of the study was to determine the effect of the additional protective measures on surface contamination in the preparation room and the outpatient clinic. For this purpose, cyclophosphamide (CP) and platinum (Pt) contamination levels in both workplaces were determined before implementation (BI) and after implementation (AI) of the measures. CP and Pt were selected as markers of contamination because they are among the most widely used ADs. In addition, CP has been shown to have high toxicological importance as it has been classified as carcinogenic to humans by the International Agency for Research of Cancer (IARC, 1981, 1987).

METHODS

Experimental design

Sampling strategy. The efficacy of the measures was evaluated by comparing contamination levels determined in the preparation room and the outpatient clinic. For this purpose, cyclophosphamide (CP) and platinum (Pt) contamination levels in both workplaces were determined before implementation (BI) and after implementation (AI) of the measures. CP and Pt were selected as markers of contamination because they are among the most widely used ADs. In addition, CP has been shown to have high toxicological importance as it has been classified as carcinogenic to humans by the International Agency for Research of Cancer (IARC, 1981, 1987).

Vial decontamination. The decontamination of vials was carried out by the pharmacy staff in the material anteroom before the vials were sent to the preparation room. The decontamination was performed manually using commercially available prewetted single-use surface cleaners (Meliseptol HBV Tissues, 13.5 × 22 cm, B. Braun Melsungen AG, Germany). One new towel was used for each vial. The towels contain 50% 1-propanol in water as an active agent for parallel surface cleaning and microbial decontamination.

Modification of the routine cleaning procedure. The preparation room is routinely cleaned daily at the end of the work shift using a solution containing common detergent and disinfectant. BI, the surfaces of the preparation room were cleaned in the following order: (i) inner space of isolators (walls and airfoil inside), (ii) work table and pushcarts, and (iii) floor and walls of the preparation room. Although different towels and clean solvent were used in each step, the spread of contamination from the isolators to the preparation room via cleaner’s gloves and suits could not be neglected. To prevent this, cleaning of the isolators was
shifted from the beginning to the end of the cleaning procedure.

**Cleaning of the work table.** The work table where infusion bags and bolus injections are placed after preparation began to be cleaned regularly every 2 h. The cleaning was performed by pharmacy personnel using the same prewetted towels as used for vial decontamination (Meliseptol HBV Tissues, 13.5 × 22 cm, B. Braun Melsungen AG, Germany). For each cleaning procedure two towels were used.

**Multichannel administration sets.** To prevent the possible release of ADs during the disconnection of intravenous administration sets from intravenous cannulae, conventional single-channel sets were replaced with multichannel sets (Cyto-Set, B. Braun Melsungen AG, Germany). These sets enable the central administration link to be rinsed with neutral solution before the set is disconnected. Regardless of the study period (BI versus AI), the sets were preflushed with neutral solution and connected to the infusion bags in the preparation room. At the end of AD application, the infusion bag is discarded together with the administration set as an intact system.

**Wall-mounted stands.** To vacate the floor under the infusion stand and open it up for proper everyday cleaning, conventional infusion stands were replaced with wall-mounted stands (Danisevsky LLC, Czech Republic).

**Support of seated urination.** To reduce surface contamination of the lavatories with urine from patients containing ADs, pictograms showing the hygienic use of the toilets (i.e. the adoption of sitting position) were placed on the walls in front of the toilets. In addition, this educative campaign was supported by the replacement of conventional toilet seats with automatic self-cleaning seats (CWS CleanSeat Universal, HTS Internationally Trading AG, Baar, Switzerland), making the toilet more comfortable for use in the proposed way.

**Chemical analyses**

**Chemicals.** Cyclophosphamide monohydrate (purity 99.5%) was purchased from Sigma–Aldrich Chemie (Steinheim, Germany) and ²H₄-labelled cyclophosphamide (CP-D4; purity 97%) was obtained from Niomech (Bielefeld, Germany). Methanol [high performance liquid chromatography (HPLC) gradient grade 99.9%], acetonitrile (HPLC gradient grade 99.9%), acetic acid [per analysis, eluent additive for liquid chromatography-mass spectrometry (MS)], and ammonium acetate (per analysis for HPLC 99%) were all from Sigma–Aldrich Chemie (Steinheim, Germany). Water was purified in a Milli-Q Water Purifier (Millipore, Billerica, MA, USA). Calibration solutions (Pt) and internal standard solution (200 ng ml⁻¹ Re and Bi in 1% hydrochloric acid) were prepared by dilution of Pt, Re, and Bi stock standard solutions Astasol (1 g l⁻¹, Analytika Prague, Czech Republic). Hydrochloric acid (37% for analysis EMSURE® ACS, ISO, Reag. Ph Eur) was purchased from Merck (Darmstadt, Germany). 18.2 MΩ-cm water (Simplicity 185, Millipore, USA) was used throughout the experiments.

**Sampling and work-up procedure.** Surfaces were wiped by Mesoft nonwoven swabs (7.5 × 7.5 cm; Mönlycke Health Care AB, Göteborg, Sweden) moistened with 0.75 ml acetic acid buffer (20mM, pH = 4). All wipe samples were collected with a standardized sampling procedure (three repeated wipes varying in direction by one swab folded in half after each wipe). A clean pair of gloves was used for the collection of each sample. After sampling, the swab was placed into a polypropylene syringe (60 ml; Terumo Europe N.V., Leuven, Belgium) and stored at −20°C until the work-up procedure. To control sampling quality (i.e. correct sample handling without cross-contamination during the sampling process), a field blank was prepared at the end of each sampling occasion (i.e. on each sampling day at each workplace) as follows: a clean wipe was moistened with 0.75 ml acetic acid buffer and placed directly into the polypropylene syringe. Field blanks were processed (stored and worked up) together with wipe samples. Before the quantitative analyses, samples were extracted with 25 ml acetic acid buffer (20 mM, pH = 4) in an ultrasonic bath for 30 min. After sample extraction, aliquot of 1 ml was diluted with 14 ml 1% hydrochloric acid.

**Liquid chromatography/tandem mass spectrometry.** The samples were analysed by an HPLC-MS/MS system Agilent 1200 coupled with a 6410 Triple-Quad MS (Agilent Technologies Inc., USA), with an electrospray interface operating in negative ion mode. To correct for injection volume errors and matrix effects on MS detection, internal standard (CP-4D in methanol solution, c = 2.5 μg ml⁻¹) was added to samples to a concentration of 25 ng ml⁻¹. Separation was achieved on a Zorbax SB-C18 column (2.1 × 30 mm, 3.5 μm; Agilent Technologies Inc., Wilmington, DE, USA) at 30°C with a flow rate of 0.3 ml min⁻¹. The separation was performed under the gradient elution
(linear gradient 10–25% B during 0–6 min, then ramped from 25% to 80% B in the period 6–7 min and kept at 80% B for another 3 min, before the next injection column was equilibrated at 10% B for a further 5 min; mobile phases—A: acetate buffer, 5 mM, pH = 4, B: acetonitrile). The mass spectrometer was operated in a multiple reaction monitoring mode with collision energy 22 eV. The capillary and cone voltage were 2000 V and 130 V, respectively. The m/z transitions 261.1–140.0 and 265.1–144.0 were monitored for a 250 ms dwell time to detect CP and CP-4D, respectively. Quantitative analyses were performed using an external calibration procedure, with an internal standard to correct the error of HPLC-MS (analyte peak area/internal standard peak area ratio versus concentration, retention time 6.1 min).

A calibration curve was prepared by determining CP in calibration solutions (0.3, 1, 4, 20, 100 ng ml⁻¹) prepared by the dilution of methanol standard solutions with acetate buffer containing CP-4D (c = 25 ng ml⁻¹).

**Inductively coupled plasma/mass spectrometry.** The samples were analysed by an Inductively coupled plasma/mass spectrometry (ICP-MS) system Agilent 7500ce (Agilent Technologies Inc., Japan). The platinum isotopes used for calculation of platinum concentrations were 194Pt and 195Pt. Internal standards (185Re, 209Bi) were applied for the diminution of matrix effects and signal drift. ICP was operated at 1500 W RF power with sample and internal standard flow rates at 0.4 and 0.125 ml min⁻¹, respectively. The integration time applied to 185Re and 209Bi measurement was 0.3 s and for platinum isotopes 1 s. Quantitative analyses were performed using an external calibration procedure, with an internal standard to correct the error of ICP-MS (analyte signal/internal standard signal versus concentration). Calibration standards (0, 0.1, 1, 10, and 100 ng ml⁻¹) were prepared by diluting stock standard to 1% hydrochloric acid.

**Method characterization**

**Selectivity of the HPLC-MS/MS method.** The selectivity of the method was evaluated by analysing the sample blanks [also called extracted matrix blanks (Boyd et al., 2008)], which were obtained by wiping the floor, work table, and door handles at the Department of Internal Medicine of the Military Hospital Brno, where ADs have never been handled. Four samples of each object were analysed and the presence of false signals were evaluated.

**Work-up procedure.** The work-up procedure was evaluated in terms of extraction efficiency and intraday and interday precision. The procedure was assessed at three different concentration levels as follows. A defined amount of the analyte in 0.5 ml of MeOH was added to a clean wipe to simulate surface contaminations of 18, 180, and 1800 pg cm⁻² of CP and 35, 175, and 150 pg cm⁻² of Pt (Pt was added in the form of cisplatin, which is the most frequently used Pt-containing drug in the hospital). Each concentration level was assessed in triplicate. The recovery was also assessed using the results of both intra- and interday experiments.

**Sampler efficiency.** In order to test the surface sampler removal efficiency, model stainless steel surfaces 30 × 30 cm were spiked at the three levels described above (the surfaces were dosed with 0.5 ml of CP or cisplatin solution in methanol). The surfaces were wiped and further processed after the solvent evaporated. The results are presented as the percentage of amount applied on the surface recovered by the method, including the sample work up.

**RESULTS**

**Analytical method**

HPLC-MS/MS analyses of CP in the samples collected in the non-oncology hospital (extracted matrix blanks, n = 12) confirmed that there were no interfering peaks in the chromatograms. However, Pt levels reached the limit of detection in one of these blanks (0.2 pg cm⁻²). Nevertheless, the natural background level of Pt is not expected to affect the results substantially.

The results of the experiments on method recovery and precision are presented in Table 1. The method showed very good precision and recovery for CP. Less, but still acceptable, precision and recovery were observed for Pt, most probably because of extraction solvent used.

The limit of detection (LOD) and lower limit of quantification (LLOQ) were determined as follows. For HPLC-MS/MS determination of CP, LOD and LLOQ were determined based on a signal to noise ratio of 3:1 and 10:1, respectively. For non-selective determination of Pt with ICP-MS, LOD and LLOQ were determined as the three-fold and ten-fold standard deviation of the concentration measured in dilution media (1% hydrochloric acid). For a standard surface area of 900 cm², LODs and LLOQs were 2 pg cm⁻² and 7 pg cm⁻² for CP and 0.2 pg cm⁻² and
In total, 100 unknown samples were collected during the study. From these, 94 and 95 samples had detectable levels of CP and Pt, respectively. Concentrations reached up to 15 500 pg cm\(^{-2}\) (CP) and 20 700 pg cm\(^{-2}\) (Pt). None of the 20 field blanks had detectable levels of CP or Pt. For each sampling spot, 5 wipe samples were collected in each sampling campaign.

Although recovery efficiencies have been shown to deviate from 100% for Pt (Table 1), corrections were not made to the results, since the recoveries for individual Pt-containing drugs can differ to some extent (Brouwers et al., 2007) and their concentrations remain unknown, as ICP-MS does not differentiate between these drugs. Furthermore, some studies have shown that the method recovery

### Table 1. Precision and recovery parameters of the method for determining cyclophosphamide (HPLC-MS/MS) and platinum (ICP-MS) in wipe samples

<table>
<thead>
<tr>
<th>Concentration (pg cm(^{-2}))</th>
<th>Cyclophosphamide</th>
<th>Platinum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1800</td>
<td>1750</td>
</tr>
<tr>
<td>Intraday precision (RSD, %, (n = 3))</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Interday precision (RSD, %, (n = 3))</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Extraction recovery (% , (n = 6))</td>
<td>90</td>
<td>62</td>
</tr>
<tr>
<td>Sampler efficiency (% , (n = 1))</td>
<td>116</td>
<td>65</td>
</tr>
</tbody>
</table>

RSD = relative standard deviation.

![Image of bar charts](image.png)

**Fig. 1.** Comparison of cyclophosphamide and platinum concentrations (median, range, \(n = 5\); logarithmic scale) in the preparation room (a) and outpatient clinic (b) before and after the introduction of specific protective measures. Statistical differences are marked with an asterisk (Mann–Whitney, \(P < 0.05\)).
can also be affected by the surface material with respect to both CP (Larson et al., 2002) and Pt (Brouwers et al., 2007). Therefore, values presented in this study can differ to some extent from the actual CP and Pt concentrations.

In the preparation room (Fig. 1a), median CP concentrations determined for different sampling spots ranged from 56 to 267 pg cm\(^{-2}\) and from 69 to 368 pg cm\(^{-2}\) BI and AI, respectively; median Pt concentrations ranged from 5 to 16 pg cm\(^{-2}\) and from 2 to 47 pg cm\(^{-2}\) BI and AI, respectively. Significant decreases in either CP or Pt levels (Mann–Whitney test, \(P < 0.05\)) were observed sporadically. In particular, CP levels were reduced significantly on the refrigerator, whereas Pt levels were reduced on the floor. For other sampling spots, non-significant changes with several non-significant increases were determined.

In the outpatient clinic, a more marked reduction in contamination was observed compared with the preparation room (Fig. 1b). Median CP concentrations at different sampling spots ranged from 175 to 5310 pg cm\(^{-2}\) and from <2 to 371 pg cm\(^{-2}\) BI and AI, respectively; median Pt concentrations ranged from 5 to 1490 pg cm\(^{-2}\) and from <0.2 to 241 pg cm\(^{-2}\) BI and AI, respectively. Median concentrations of CP and Pt were reduced by 87 and 61% (work table), 89 and 67% (floor under the infusion stand), 99 and 98% (phone receiver), 57 and 91% (infusion pump), and 95 and 84% (floor of lavatory), respectively. With two exceptions (see Fig. 1b), the observed reductions were statistically significant (Mann–Whitney, \(\alpha = 0.05\)).

Unfortunately, the workload increased at both workplaces during the course of the study. The daily use of CP and Pt in BI and AI campaigns is compared in Table 2. Although the statistical analysis (Mann–Whitney, \(\alpha = 0.05\)) did not show a significant difference for any pair of data, it should be noted that in the case of Pt, the consumption nearly doubled.

**DISCUSSION**

**Analytical method**

The method proposed for the analyses of ADs in the working environment was designed to be simple and quick, thus supporting high laboratory throughput. It uses a wiping technique to collect samples, like other methods reported in the literature (e.g. Connor et al., 1999; Hedmer et al., 2005; Brouwers et al., 2007; Schierl et al., 2010). This study used simple wipe extraction to aqueous solution and consequent HPLC-MS determination of CP and ICP-MS determination of Pt. With respect to the composition of the HPLC mobile phase, ammonium acetate was used as desorption and extraction solution. In other studies, ammonium acetate was used; for example, by Sabatini et al. (2005) for parallel determination of CP, 5-fluorouracil, and methotrexate. Furthermore, Floridia et al. (1999a,b) used acetate buffer as the desorption and extraction solution for methotrexate, 5-fluorouracil, cytarabin, and gemcitabine.

In this study, no preconcentration or purification techniques were needed to achieve sufficient sensitivities. The missing preconcentration step was compensated by the relatively large size of the sampled area (900 cm\(^2\)). As recommended by Hedmer et al. (2004), a large area should be preferred to enhance the likelihood of detecting the spillage of ADs. The LOD for CP determination (2 pg cm\(^{-2}\)) observed in our study was closely comparable to those reported by Minoia et al. (1998), Schmaus et al. (2002), and Mason et al. (2005), while the LOD for Pt determination was slightly higher compared with Brouwers et al. (2007), Nygren et al. (2002), and Schierl et al. (2009) because of the dilution of the buffered samples with high volumes of hydrochloric acid. Nevertheless, Pt concentrations below 0.092 pg cm\(^{-2}\) (Brouwers et al., 2007) and 0.2 pg cm\(^{-2}\) (Maydl et al., 2005) were reported as background levels coming from other sources such as traffic and the use of Pt catalysts, and concentrations of 0.1–0.5 pg cm\(^{-2}\) were recommended as reasonable thresholds for the determination of Pt from ADs (Maydl et al., 2005; Brouwers et al., 2007).

**Comparative study on protective measures**

The study revealed frequent surface contamination in both the preparation room and outpatient clinic. Comparison of the BI and AI

### Table 2. Daily use (g) of cyclophosphamide (CP) and platinum (Pt) in the preparation room and outpatient clinic during the study stages [mean and standard deviation in brackets (\(n = 5\))]

<table>
<thead>
<tr>
<th></th>
<th>Preparation room</th>
<th>Outpatient clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP (BI)</td>
<td>Pt (BI)</td>
</tr>
<tr>
<td>BI</td>
<td>6.4 (3.0)</td>
<td>2.3 (0.2)</td>
</tr>
<tr>
<td>AI</td>
<td>7.1 (2.1)</td>
<td>4.0 (1.8)</td>
</tr>
</tbody>
</table>
concentrations showed that the measures in the outpatient clinic were effective, whereas the measures in the preparation room resulted in only minor improvement. Discussion of the efficacy of the measures implemented is presented below for each workplace separately.

**Preparation room.** Regarding the contamination level, CP concentrations ranged from several tens to several hundreds of pg cm\(^{-2}\) in the preparation room; for Pt, values of about one order of magnitude lower were observed. The difference between CP and Pt results can be explained by different levels of consumption (see Table 2) and also by different method recoveries (see Table 1). In comparison with data from literature, the contamination level of the preparation room investigated in the present study seems to be closely comparable with that found in other well-developed European countries, the USA, and Canada (Connor et al., 1999; Acampora et al., 2005; Mason et al., 2005; Martins et al., 2008).

Unfortunately, this level was not further reduced by the measures introduced. Most interestingly, no reduction was observed even at the post-preparation work table, where regular cleaning with prewetted towels every 2 h was applied. In our study, Meliseptol cleaning towels containing 50% 1-propanol were used, and the work table was wiped three times during the day before sample collection. Meliseptol towels were applied because they met the requirements of pharmacy managers (i.e. easy availability on the market and high microbial safety). Although Meliseptol towels are primarily designed for the disinfection of surfaces, they are also considered to be effective for mechanical decontamination as the solvent has a relatively high polarity and should easily dissolve a broad spectrum of compounds including CP and Pt-containing drugs. Nevertheless, the obtained results showed that the measure was not effective. In our opinion, this was most probably due to an insufficient cleaning frequency; cleaning of the working surface should preferably be performed after each handling activity. Besides implementing of a higher frequency of cleaning, the use of other cleaning agents could also be considered. Strong oxidising agents such as sodium hypochlorite (bleach) were shown to be effective in deactivating some ADs (Castegnaro et al., 1997; Hansel et al., 1997). Alternatively, cleaning with water and sodium hydroxide is recommended in the guidelines of the Japan Pharmaceutical Association (Yoshida et al., 2011).

Also the other two measures implemented in the preparation room (the manual decontamination of drug vials and the shifting of the cleaning of the isolators from the beginning of cleaning procedure to the end) were shown to be ineffective. Based on these findings, neither external vial contamination nor cross-contamination via cleaner gloves was confirmed to be an important source of contamination. Taking this into account, other contamination sources should probably be considered such as the possible release of ADs during admixture activities. Although preparation is carried out inside the enclosed isolator, the inner contamination generated during admixture activities can be spread to the outer working environment in the form of external contamination of the infusion bags and other material passing through the isolator. According to this, further contamination reduction could be achieved by the use of closed-system transfer devices. For example, the Phaseal system was shown to be fairly effective. Siderov et al. (2010) reported a 70% reduction in contamination after 12 months of using the Phaseal system. Significant reductions in contamination related to the use of the Phaseal system were also demonstrated by Harrison et al. (2006) and Yoshida et al. (2009).

**Outpatient clinic.** Relatively high contamination was determined in the outpatient clinic. Regarding the data collected BI, CP and Pt concentrations reached up to several thousands and hundreds of pg cm\(^{-2}\), respectively. These concentrations seem to be higher than all of those previously reported in the literature for drug administration areas (Connor et al., 1999; Maydl et al., 2005; Hedmer et al., 2008; Connor et al., 2010).

To our knowledge, this is the first study which reports on the efficacy of certain protective measures suggested to reduce the contamination of drug administration areas. Using the measures implemented, the concentrations decreased by almost one order of magnitude. This lower contamination level is comparable to most of the studies mentioned above (Connor et al., 1999; Hedmer et al., 2008; Connor et al., 2010).

Significant reductions in both CP and Pt levels were revealed on three out of the five sampling spots monitored (table, floor, and phone). The remaining two specific sampling spots did not show a significant reduction in either CP or Pt (Fig. 1b). Surprisingly, these were the infusion pump (CP) and the floor at lavatories (Pt), which were directly affected by the measures implemented. In both cases, non-significant results arose because of the occurrence of one outlier in the particular AI data set.
According to the authors, the outlier of the lavatory AI data set can be simply explained by patients’ reluctance to urinate in a sitting position, which cannot be fully prevented by the measures. Similarly, the outlier of the infusion pump AI data set can be explained by the violation of good working practice. It may be anticipated that under stress, nurses may avoid the relatively time-consuming flushing of the infusion set with neutral solution before its disconnection from the cannula, which may lead to accidental spillage of ADs and increase concentrations on surrounding surfaces.

Besides this, it is also possible that the external contamination of infusion bags, another potential source of contamination (Crauste-Manciet et al., 2005), which was not targeted by our study, affected the infusion pump contamination level. Since the traditional technique of AD preparation with needle and syringe cannot prevent the external contamination of infusion bags, the possibility of cross-contamination of the infusion pump via nurses’ hands cannot be excluded. Furthermore, we cannot rule out even the possibility that BI contamination affected levels measured AI, since the efficacy of traditional cleaning techniques to eliminate surface contamination with ADs was repeatedly shown to be limited (Vandenbroucke and Robays, 2001; Acampora et al., 2005; Roberts et al., 2006; Turci and Minoia, 2006; Hedmer et al., 2008). There is increasing evidence that some drug residue can persist for months on work surfaces and floors (Schierl, 2008; Connor, 2010).

Nevertheless, the measures introduced into the outpatient clinic seem to be generally effective in reducing AD contamination, including the places that were not directly related to the measures (phone receiver, top of the work table). This is believed to be the consequence of a decrease in cross-contamination in these places. Since these objects are often handled by unprotected workers’ hands, overall exposure may decrease, as direct uptake by skin is believed to be an important exposure route (McDevitt et al., 1993; Sessink et al., 1994a,b; Kromhout et al., 2000).

Effect of the amount of drug handled. The efficacy of the measures demonstrated in the present study can be potentially underestimated by the increased consumption of CP and Pt during the AI period. It could be anticipated that a higher number of handling events will lead to a greater amount of ADs being released into the working environment (inadvertently or by means of accidental spillages). An association between workload and contamination level was previously suggested by Hedmer et al. (2008) and Yoshida et al. (2011).

Nevertheless, we do not consider workload to be an important factor, as comparable concentration changes were determined for both CP and Pt despite different increases in their consumption (see Table 2). In agreement with the findings of other studies (Schmaus et al., 2002; Brouwers et al., 2007; Schierl et al., 2009), we suggest that working practices and personnel expertise affect contamination levels in a more extensive way than AD consumption.

CONCLUSIONS

Protective measures supporting the closed administration of drugs, the seated urination of oncology patients, and the regular cleaning of highly exposed surfaces effectively reduced AD contamination in the outpatient clinic, thus lowering the occupational exposures of nurses and other hospital workers. Due to the measures introduced, contamination in the outpatient clinic was reduced to the level found in the preparation room, where relatively strict measures are routinely applied according to valid international standards and national legislation. However, as many ADs are recognized as carcinogens, for which safe limits cannot be established, further efforts to limit exposure to these compounds should be explored and their efficiencies evaluated.

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