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What is This?

Evaluation of a closed-system cytotoxic transfer device in a pharmaceutical isolator

N Vyas[1,2], A Turner[2], JM Clark[1] and GJ Sewell[3]

Abstract

Purpose: The occupational risk associated with handling of cytotoxic anticancer drugs is well documented and, in many countries, pharmaceutical isolators are used to contain cytotoxic residues during preparation of cytotoxic infusions. Isolators are difficult to clean leading to concerns that cytotoxic contamination from the work area could be transferred to surfaces of products leaving the isolator. This study investigated the surface contamination arising from the preparation of five anticancer drug infusions (Epirubicin, Fluorouracil, Cisplatin, Oxaliplatin and Carboplatin) in a pharmaceutical isolator and compared use of a conventional syringe and needle technique with a closed-system drug transfer device (CSDTD).

Methods: Wipe samples were taken over 1 week from pre-defined areas in the isolator, gloves, preparation mats, and also from the surfaces of prepared cytotoxic infusion bags and pre-filled syringes to obtain *baseline* surface contamination data. Following operator familiarisation, the CSDTD was then introduced and sampling repeated for a further week (*intervention period*). The samples obtained were analysed using validated HPLC-UV, HPLC-FL and ICP-MS techniques, as appropriate.

Results: All surfaces sampled during baseline, including external surfaces of infusions and syringes, were contaminated with each marker drug. During the intervention phase, isolator surfaces were free from detectable contamination and the contamination measured on gloves, preparation mats and surface of infusions was markedly reduced. The frequency of contamination on syringe and infusion surfaces was also lower.

Conclusion: Surface contamination from cytotoxic infusion preparation in a pharmaceutical isolator was significant and could transmit cytotoxic residues to patient and public areas via infusion surfaces. The frequency and amount of contamination were reduced by the CSDTD.

Introduction

Chemotherapy is widely used in the treatment of most forms of malignant disease and is frequently combined with surgical and radiotherapy modalities. It is now recognised that many cytotoxic drugs present a risk to occupational health,[1–3] and exhibit mutagenic, teratogenic and carcinogenic properties.[4] Health care professionals, particularly nurses and pharmacy staff, may be exposed to cytotoxic drugs during reconstitution of drug vials, preparation and administration of infusions, handling contaminated body fluids and transporting or disposing of contaminated personnel protective equipment such as gloves and chemotherapy preparation mats.[5]

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Early concerns about health effects of anticancer drugs on health care staff were raised in 1970s[6] and these have been supported in subsequent reports.[7] The presence of cytotoxic drug residues in the work environment have been demonstrated by the biological monitoring of staff[8,9] and environmental monitoring of work surfaces.[10,11] These reports, together with more recent studies,[12,13] have generated a body of evidence to show both acute and long-term effects associated with occupational exposure to cytotoxic drugs. Acute symptoms include nausea, vomiting, headaches, hair loss and dizziness. Long-term health effects include increased mutagenic activity among nurses working on oncology wards, risk to reproductive health of female staff with increased risk of infertility, spontaneous abortions, isolated cases of haematuria and increased risk of leukaemia.[5,14,15]

These reports have prompted the publication of various guidelines on the safe-handling of cytotoxic drugs.[5,16,17] These have resulted in the centralised preparation of anticancer drug infusions in specialist pharmacy units throughout Europe and North America. In most countries, cytotoxic infusions are prepared in biological safety cabinets (BSC) whereas pharmaceutical isolators[18,19] are widely used in the UK and France and are increasingly being deployed in North America.

Despite improved practice, studies have shown the presence of cytotoxic drugs on various work surfaces in both BSCs and pharmaceutical isolators.[20–24] This contamination may be due to surface contamination on the vials[25–27] and the current use of 'open systems' using needles and syringes for the reconstitution and transfer of cytotoxic solutions. This practice also increases the risk of needle-stick injuries to the staff which along with dermal exposure to pharmacy staff while cleaning isolators or BSCs[28] is major cause of occupational exposure. These concerns have prompted the introduction of 'closed-system' drug transfer devices (CSDTD), a term widely used to describe a range of devices despite there being some debate over which devices are genuinely 'closed systems' and which are not.[17] Recent studies[29–33] have evaluated CSDTDs such as PhaSeal® and Tevadaptor®, and have shown them capable of reducing surface contamination when cytotoxic drugs are manipulated in BSC. However, the effectiveness of closed-system devices in pharmaceutical isolators has not previously been evaluated.

This study evaluated the effectiveness of a CSDTD, in this case the Tevadaptor® device, in reducing surface contamination in an isolator under standard working conditions at a specialist UK hospital pharmacy unit. Tevadaptor® is a 'closed-system device' used for reconstitution of hazardous drugs as well as for drug administration, and uses a carbon filter for external venting. As such, it would not meet some of the more stringent definitions of a 'closed-system' device.[17] The device consists of several components: The vial adaptor is used to dock with the drug vial septum to allow drug transfer and comes in 20 mm and 28 mm size, which fits most of vials available in the UK, and a 13 mm convertor ring for smaller sized vials. The syringe adaptor is used to fit on standard luer lock syringes which can then dock with the vial adaptor, connecting set or other components of Tevadaptor® to convert it into a closed system. These adaptors, when attached together, also prevent overpressure in vials and eliminate formation of aerosols. The Tevadaptor® device also includes a luer lock adaptor to attach to the patient's IV line, spike port adaptor and connecting set to administer IV infusion bags. This is also a needle-free system which removes the risk of needle stick injuries to pharmacy and nursing staff.

Methotrexate, epirubicin (EPI), 5-fluorouracil (5-FU), carboplatin, cisplatin and oxaliplatin were selected as marker drugs for this study on the basis of their frequency of usage in the pharmacy reconstitution unit. The marker drugs also represented different classes of cytotoxic drugs such as platinum (Pt) alkylating agents (cisplatin, carboplatin and oxaliplatin), antimetabolites (methotrexate and 5-FU) and antitumour antibiotics (epirubicin). Subsequent analytical development and validation studies revealed that the detection limits for the quantification of methotrexate were not sufficiently sensitive and therefore methotrexate was deleted from this study.

To ensure the safety of patients receiving infusions prepared with the CSDTD, preliminary studies (currently unpublished) were undertaken on the compatibility of the Tevadaptor® device with 11 anticancer infusions, including the marker drugs selected for this study. In each case, the device was chemically and physically compatible with all infusions for the duration of the normally assigned shelf-life.

Throughout the study, the standard isolator cleaning procedure was followed. At the start of each week interior surfaces of the isolator were sprayed with Klercide B® and left for 5 min. Surfaces were then wiped with low lint wipe and then sprayed with sterilised 70% denatured ethanol. After every second work-session (1.5 h) the isolator was cleaned with sterile neutral detergent, wiped with low lint wipe and then sprayed with sterilised 70% denatured ethanol. During the study, two sessions of work was carried out each day.

The study was conducted by taking wipe samples from pre-defined areas in the isolator and from the outer surface of prepared IV infusions. Samples were taken over a 1 week 'baseline period' using conventional needles and venting-pins, and then repeated over a further week 'intervention period' using the Tevadaptor® device. The drugs were than eluted from

wipes and analysed using validated methods. Data for baseline and intervention periods were compared to evaluate the effectiveness of CSDTD device in reducing contamination caused by anticancer drugs.

Methods

Study setting

Derriford hospital is a university hospital serving 450,000 people in Southwest UK, and includes a major cancer centre. The hospital pharmacy provides dispensary, clinical and aseptic manufacturing service to the hospital with a purpose-built aseptic suite and five pharmaceutical isolators dedicated to chemotherapy preparation.

Isolator design

A two-glove rigid negative pressure isolator (Envair CDC-'E' 2GD) was used for this study. The downflow HEPA filter provides full laminar air flow over the work zone, which is maintained at EU GMP Grade A and the aseptic suite provides a background environment classed as EU GMP Grade C. The air leaving the work zone is returned to the downflow fan system via main HEPA filters located underneath the work tray and residual air is exhausted externally via an additional HEPA filter. The products are introduced or removed from the isolator through air-flushed interlocking transfer chambers on each side of the isolator. During the study period, only this isolator was used for the preparation of infusions of marker drugs.

Sampling method and schedule

The sampling method and schedule was defined and validated prior to the commencement of the study. The areas to be sampled were the insides of both hatch doors, left, centre and right areas from isolator floor and both left and right sleeve (Figure 1). Each location was marked with sterile ink marker and numbered 1 to 7 starting from right hatch door to left hatch door in the order of sampling. The area wiped from each location was 400 cm^2. Each set of samples was taken just before the isolator was cleaned at the end of work session in the defined order using a fresh wipe for each surface. Wipe samples were also taken from the surface of prepared IV bags and syringes using one fresh wipe for each IV bag and one wipe to sample from each group of four syringes in each sample cohort.

The areas were wiped using a sterile dry wipe (Kler wipe®, Shield Medicare, UK, 18×20.5 cm^2) saturated with 10 mL water for injection. The wipe samples were taken in accordance with validated protocols[34] giving detailed instructions on the wiping technique and indicating when wipes should be turned to expose a fresh
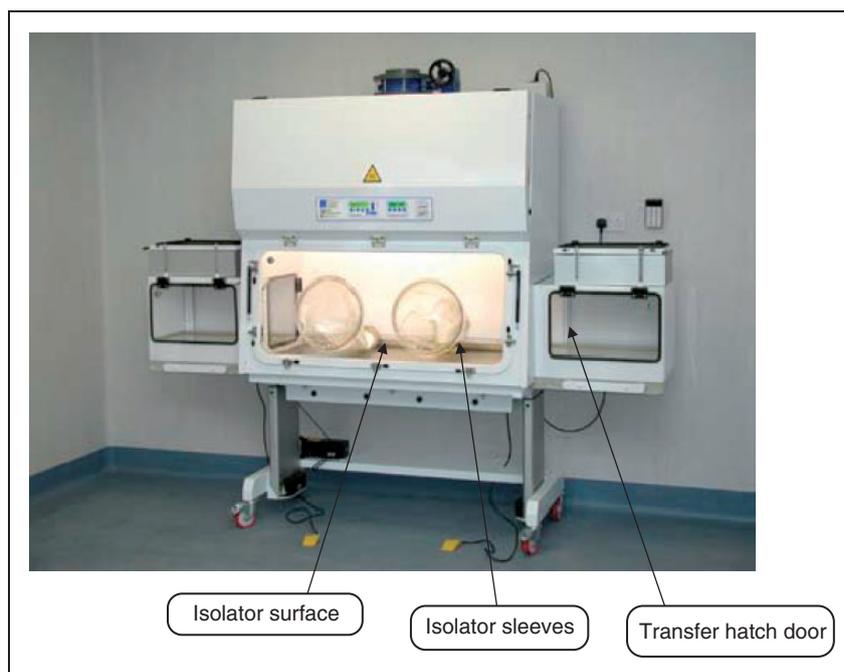
Figure 1. Schematic of isolator showing areas sampled.

surface. The isolator surfaces and IV bags were wiped from top to bottom and then back to the top once, in a sweeping motion, whereas syringes were wiped in a spiral motion.

A qualified pharmacy technician with >5 years' experience of cytotoxic manipulation in pharmaceutical isolators was selected for this study. Training by a technician from the manufacturer of the Tevadaptor® was arranged for this technician, who achieved observed competency in using the device before the study commenced. At the same time, training was also arranged for the nursing staff who would receive cytotoxic infusions in clinics with the Tevadaptor® infusion administration device fitted by pharmacy. The technician was also trained and competency-assessed in taking wipe samples from the designated areas and recording any spillages during the study. This part of the training and assessment was undertaken by an external quality control laboratory to ensure consistency and reproducibility of sampling, and all sampling validation data were obtained from the same technician used in the study.

Collection of samples

The study was performed in 1 week blocks. In week 1, the marker drug infusions were prepared with conventional practice of using needles and syringes and wipe samples were taken from work surfaces as well as prepared syringes and bags (baseline samples). In week 2, the infusions were prepared using Tevadaptor® device but no samples were taken (familiarisation week). In the third and final week, preparation was again undertaken with the Tevadaptor® device, but samples were taken and surface contamination of marker drugs was measured (intervention samples).

During preparation of EPI and 5-FU, a total of 14 wipe samples were taken from isolator surfaces during both baseline and intervention periods. For the Pt drugs, a total of 28 wipe samples from isolator surfaces were taken during each period. Additionally, two pairs of gloves and two preparation mats were sampled after preparation of EPI and 5-FU, and four pairs of gloves and four preparation mats were sampled after preparation of the Pt drugs during each study phase.

Wipe samples of the external surfaces of syringes and infusion bags were taken as described above. For both the baseline and intervention phases of the study, two batches each of EPI and 5-FU syringes were prepared, totalling 74 EPI and 70 5-FU syringes in the baseline week and 80 EPI and 106 5-FU syringes during the intervention period. At least 20% of the syringes prepared, taken randomly from both batches and not selected by the technician, were subjected to wipe sampling. During the baseline phase 28 syringes of both EPI and 5-FU were sampled from the pooling of the two batches of each drug. During the intervention phase 32 syringes were sampled for each marker drug. In the case of Pt-based drugs, 15 and 13 individual infusion bags were prepared during baseline and intervention phases, respectively, and all bags were subjected to surface sampling. After sampling, wipes were placed in 50 mL polypropylene sample tubes. The gloves and chemotherapy preparation mats used for each session were also collected. Samples were stored for up to 84 days at $-22°C$ prior to analysis. In-house studies confirmed no drug degradation occurred during the storage period.

Materials

Drugs and materials used for the study were: Epirubicin (batch: DT34B, Pharmacia UK Ltd), 5-Fluorouracil (batch: W022675AB) and oxaliplatin (batch; U015359AAX) both Hospira UK. Cisplatin (batch: 07M10NA) and carboplatin (batch 10C050C) both Teva U.K. Ltd. Oxaliplatin (batch: D9C665, Sanofi Aventis UK). All drugs and devices were used within their expiry date. All chemicals and reagents used were of analytical or high-performance liquid chromatography (HPLC) grade, as appropriate, and were obtained from Fisher Scientific UK Ltd. Klercide-CR® sterile filtered biocide B and Klerwipe® sterile low- particulate dry wipes (18×20.5 cm^2) were purchased from Shield Medicare, UK. Spiriclens sterile spray (denatured ethanol 70% in water for injection) was from Adams Healthcare, UK. Luer-lock Plastipak® syringes and BD Microlance 3® syringe needles were from BD Franklin Lakes, USA. Cytostatic protection gowns and cytostatic preparation mats were from Berner International, Germany. Nitrile gloves were from Ansell Ltd, UK and, Alcowipes® were from Seton Healthcare, UK. Polypropylene sample tubes (50 mL) were obtained from Sterilin Ltd, UK. Tevadaptor® CSDTD devices, vial adaptor (batch M0606H9), syringe adaptor (batch M0609H9), luer lock adaptor (batch M0375H9), and spike port adaptor (batch M0560G9) were provided gratis by Teva Medical Ltd, UK.

The HPLC system used for analysis of EPI and 5-FU consisted of HPLC 360 autosampler (Kontran Intruments), LDC analytical isocratic Constametric 3200 pump, Jasco 875-UV UV-visible detector, Jasco 821-FP spectrofluorometer and Chromjet integrator (Thermoseparation). The induction-coupled plasma spectroscopy linked to mass-specroscopy (ICP-MS) system used for total Pt assay was XSERIES 2 ICP-MS supplied by Thermo Scientific, UK. It consisted of 'Protective Ion Extraction and Infinity II ion optics', based upon a hexapole design with chicane ion deflector and a peltier-cooled chamber. Samples were

introduced via a split flow turbo pump and high performance glass concentric nebuliser. The instrument was controlled by Plasma Lab software, version 2.5.22.321.

Sample preparation

The wipe samples were transferred to 50 mL polypropylene centrifuge tubes and eluted with 30 mL 1%v/v HCl solution. These tubes were then centrifuged (500 g for 30 min) and sonicated (20°C) for further 30 min. Glove and chemotherapy preparation mat samples were transferred to high-density polyethylene (HDPE) bottles (1000 mL) and eluted into 100 mL 1% v/v HCl. In each case, the supernatant was taken for analysis (see below).

Drug analysis

The assays for the marker drugs were based on published methods and were then validated in-house. Briefly, the assay for EPI[35,36] used a Luna CN 5 µm, 250×4.6 mm^2 column, mobile phase of 0.05 M phosphate buffer, pH 4.0 (65%) and acetonitrile (35%) at 1 mL/min with fluorescence detection (λ_{ex} 480 nm, λ_{em} 560 nm) and the assay for 5-FU[37,38] used a Luna C_{18} 5 µm, 250×4.6 mm^2 column, mobile phase of 2% methanol in water and UV detection at 266 nm. Each HPLC sample was injected twice (100 µL) and bracketed with external standard injections.

The Pt-based drugs, cisplatin, carboplatin and oxaliplatin, were analysed (as total Pt) using ICP-MS as described by Brouwers et al.[39] The samples were eluted as described above and were then subjected to centrifugation at 500 g and sonication for 30 min. To supernatant (5 mL) from each sample was added 0.1 mL of 50 ppb/mL iridium (internal standard) before analysis in triplicate by ICP-MS. Standard solutions of 0.1, 0.2, 0.4 and 1 ng/mL were used as quality control samples. Blank samples were also prepared and analysed to show absence of contamination from external sources of Pt.

Method validation

To validate the assays, the test surfaces (gloves, syringe and IV bag surfaces, isolator surfaces) were spiked with known quantities of each drug individually and also as a part of a mixture. The contaminated surfaces were then left to dry and were then wiped using the described technique. Following elution (see above) the supernatant was subjected to assay and then validation for limit of detection (LOD), limit of quantification (LOQ), precision and recovery of each drug from the various surfaces. The above validation parameters are comparable with those described for method validation by Minoia and Turci[40] and were considered to be appropriate for this study.

Analytical validation data and recovery data for each of the marker drugs from the test surfaces are shown in Table 1. Although the amounts of EPI recovered were low, particularly from the isolator surface, the recovery was reproducible and considered acceptable for this comparative study, with relative standard deviation (RSD) values ranging from 5.3% to 16.6%.

Table 1. Validation data for analytical methods and recovery of marker drugs from wipe samples.

		EPI	5-FU	Cisplatin	Carboplatin	Oxaliplatin
Limit of detection (LOD, ng/cm^2)		0.0075	0.15	0.00075	0.00075	0.00075
Limit of quantification (LOQ, ng/cm^2)		0.0225	0.375	0.0075	0.0075	0.0075
Mean recovery (%)	Wipe tissue	34.6	94.3	83.5	95.6	80.6
	IV Bag	37.2	90.4	68.3	77.4	90.8
	Syringe	40.4	91.8	106.1	93.8	102.4
	Isolator surface	19.4	90.2	103.3	92.7	86.4
Precision of recovery (RSD%)	Wipe tissue	5.3	1.6	6.1	11.6	2.9
	IV Bag	5.5	4.1	3.6	4.6	15.9
	Syringe	7.3	2.2	1.6	2.1	4.7
	Isolator surface	16.6	1.7	3.4	8.5	14.8
Precision of analysis (RSD%)	Inter day	2.22	2.79	3.6	3.6	3.6
	Intraday	1.62	1.85	1.8	1.8	1.8

LOD and LOQ values for cisplatin, carboplatin and oxaliplatin are expressed as platinum (Pt) metal.
Precision of EPI was measured at 20 ng/mL, 5-FU at 80 ng/mL and Pt at 0.5 ng/mL.

Results

Surface contamination with marker drugs

The levels of the marker drugs EPI and 5-FU recovered from wipe samples during baseline and intervention (CSDTD) phases are shown in Table 2. Similar data for the Pt-based drugs, cisplatin, carboplatin and oxaliplatin, are presented in Table 3, where the residues recovered from each surface are expressed in terms of Pt metal (ng/cm^2).

During the baseline period, 71.4% and 78.5% of samples taken from isolator surfaces exhibited contamination (>LOD) with EPI and 5-FU, respectively. However, during the intervention period, all wipe samples taken from isolator surfaces were free of contamination (<LOD) for both EPI and 5-FU (Table 2).

Data for EPI and 5-FU residues on gloves and chemotherapy preparation mats used by the operator for each session are also shown in Table 2. Under normal working practice, operators are protected by thin nitrile inner gloves and then thicker outer gloves which are attached to the isolator sleeves. The outer gloves are most likely to be contaminated as they come in direct contact with drug vials, the surfaces of which have been shown to be contaminated with cytotoxic residues.[25–27] The chemotherapy preparation mats which are spread on the surface of pharmaceutical isolators may capture aerosols, droplets and spillages during the manipulation of anticancer drugs, and are also likely to come into contact with the contaminated surfaces of drug vials. Table 2 shows the total amount of EPI and 5-FU recovered from gloves and chemotherapy preparation mats was significantly reduced by the CSDTD. The total amount of 5-FU recovered from baseline samples of gloves over two batches was 14.62 ug whereas both samples collected during the intervention phase were free of measurable contamination (Table 2). For EPI the total amount recovered from gloves was reduced from 10.41 ug to 2.12 ug by the Tevadaptor® device.

Surface samples were also taken from prepared syringes and IV infusion bags. Both EPI and 5-FU are presented as solutions for injections in glass vials. This solution is then drawn up aseptically and pre-filled syringes are sent to the clinic ready for administration to patients. The syringes used were BD Plastipak® syringes and both drugs have been shown to be compatible with the syringe material.[19] A minimum of 12 syringes or 20% of the batch were sampled in each case. The surface contamination on the syringes was expected to be lower than on the isolator surfaces and so a single wipe was used to sample the surfaces of four syringes. During the baseline period, a total of 74 and 70 syringes of EPI and 5-FU, respectively, were prepared. In each case, a total of 7 wipes were used to sample the surface of prefilled syringes, equating to 28 syringes sampled for each drug infusion. Of these, 5 wipe samples (71.4%) of 5-FU and 4 wipe samples

Table 2. EPI and 5-FU on isolator surfaces (ng/cm^2) and syringes/gloves/mats (μg) at Baseline and with CSDTD intervention.

Location	Baseline				Intervention (CSDTD)			
	EPI		5-FU		EPI		5-FU	
	Batch1	Batch 2	Batch1	Batch 2	Batch1	Batch 2	Batch1	Batch2
Right door (ng/cm^2)	ND	0.05	0.74	2.74	ND	ND	ND	ND
Right floor (ng/cm^2)	ND	0.04	ND	1.27	ND	ND	ND	ND
Right sleeve (ng/cm^2)	0.9	0.09	2.1	3.58	ND	ND	ND	ND
Centre floor (ng/cm^2)	ND	0.04	0.59	1.17	ND	ND	ND	ND
Left sleeve (ng/cm^2)	0.03	0.05	0.39	2.93	ND	ND	ND	ND
Left floor (ng/cm^2)	0.02	0.34	ND	0.77	ND	ND	ND	ND
Left door (ng/cm^2)	ND	0.04	ND	0.70	ND	ND	ND	ND
Gloves/pair[a] (μg)	3.16	7.25	0.85	13.77	1.15	0.97	ND	ND
Preparation mat[a] (μg)	44.65	38.03	769.90	772.98	5.05	4.67	0.51	ND
Syringe surface:								
% contaminated[b] (N)	57.1 (28)		71.4 (28)		0 (32)		3.1 (32)	
Total contamination[c] (mean)	0.11 (0.004)		0.74 (3.59)		ND (0)		0.62 (0.019)	

ND: not detected.

[a]The values for gloves and preparation mats are total amounts of drug recovered (μg) from entire item.

[b]Percentage of syringes sampled with contamination >LOD (number of syringes in sample).

[c]Total contamination (μg) recovered from samples pooled from both batches (mean contamination per syringe sampled, μg).

Table 3. Platinum levels recovered from surfaces (ng/cm^2) and gloves/infusion bags/mats (ng) at baseline and with CSDTD intervention.

| Location | Platinum (Pt) | | | | | | | |
| | Baseline | | | | Intervention (CSDTD) | | | |
	Batch 1	Batch 2	Batch 3	Batch 4	Batch 1	Batch 2	Batch 3	Batch 4
Right door (ng/cm^2)	0.86	0.18	0.36	0.11	0.09	0.01	0.01	0.01
Right floor (ng/cm^2)	0.23	0.26	0.25	0.92	0.05	0.01	0.01	0.01
Right sleeve (ng/cm^2)	0.50	0.26	0.27	0.70	0.06	0.01	0.01	0.01
Centre floor (ng/cm^2)	0.16	0.09	0.08	0.09	0.04	0.01	0.01	0.00
Left sleeve (ng/cm^2)	0.25	0.47	0.17	0.09	0.08	0.01	0.01	0.01
Left floor (ng/cm^2)	0.07	0.54	0.05	0.20	0.03	0.01	0.01	0.01
Left door (ng/cm^2)	0.05	0.14	0.06	0.23	0.02	0.01	0.00	0.01
Glove/pair (ng)	9.63	5.18	3.25	12.84	0.21	0.28	1.8	0.54
Preparation mat (ng)	82.21	5.36	2291.30	265.12	0.35	0.67	2.63	5.01
IV bag surface:								
Total for 4 batches (ng)	11,013				1015.5			
Mean per bag (range)	734.2				78.1			
	(27–2904)				(3–747)			

The values for gloves, preparation mats and IV bag surface recovery are total amount of Pt in nanograms recovered from entire item.

(57.1%) of EPI were found to be contaminated. During the intervention phase, 80 and 106 syringes were prepared for EPI and 5-FU, respectively, and 8 wipe samples equating to 32 syringes, were taken for each drug. There was no detectable contamination for EPI but one 5-FU sample was positive, although at very low level compared to the baseline data (Table 2).

The analytical method employed to detect the presence of platinum was highly sensitive which in turn results in a higher frequency of surface contamination (>LOD) measured for the Pt-based drugs. The limit of quantification (LOQ) was established as 0.0075 ng/cm^2 and the sensitive assay explains, at least in part, why 100% of baseline samples and 64% of intervention phase samples taken from isolator surfaces showed measurable levels of platinum (Table 3). However, the total amount of platinum recovered from isolator surfaces, chemotherapy preparation mats and infusion bag surfaces all showed significant reduction with the CSDTD. One preparation mat used in batch 3 of baseline showed extensive contamination. This could possibly be attributed to an unrecorded spillage or a leak from the syringe that was unseen by the operator. The external surfaces of IV bags were sampled using one wipe per bag. This permitted the calculation of mean contamination/bag and the range of contamination for baseline and intervention arms, in addition to total contamination on bags for each study arm (Table 3). Both the total amount of platinum contamination on external surfaces of infusion bags and the mean contamination on each bag exhibited approximately 10-fold reductions during the intervention (CSDTD) phase.

Discussion

This is the first study in the UK on the effect of CSDTD in pharmaceutical isolators under actual practice conditions. As in previous studies[28,34] contamination levels on the inside of the isolator under baseline conditions (conventional syringe and needle transfer) were found to be significant (Tables 2 and 3). This was not surprising because essentially the isolator acts as a containment device.

The Tevadaptor® device significantly reduced the cytotoxic drug contamination on isolator surfaces and on the external surfaces of syringes and infusion bags leaving the isolator. The presence of some residual contamination of chemotherapy preparation mats and isolator gloves is inevitable in view of the well-documented surface contamination on drug vials.[25–27] This also explains why a CSDTD is unlikely to completely eliminate contamination on isolator gloves and preparation mats since contamination from drug vial surfaces will occur irrespective of the transfer system employed. However, these data show the Tevadaptor® device significantly reduced the cytotoxic drug contamination on the external surfaces of syringes and infusion bags, with the potential to reduce the occupational exposure risk to clinic staff.

Previous wipe sample studies in cytotoxic preparation areas have reported contamination levels similar to those found in the baseline phase of this study. Briefly, Sessink et al.[41] and Connor et al.[42] reported

5-FU in wipe and glove samples collected from pharmacy aseptic units in the range of 0.72–208.6 ng/cm^2 and 21–620 μg/pair, respectively. These data originate from pharmacy units using BSCs. More recent studies[23,43] on pharmaceutical isolators have reported contamination by Pt and 5-FU on isolator surfaces of 0.0005–0.013 ng/cm^2 and 9.73–87.6 ng/cm^2, respectively. Analytical methods used in these previous studies report comparable LOD and LOQ levels to those obtained in this study for quantification of contamination by marker drugs. The importance of sensitive analytical techniques can be clearly seen in this study. As stated earlier, the LOQ for methotrexate was highest among the marker drugs used in this study therefore it was not included in this study. On the other hand Pt was detected in all samples even though the total amount detected was lower than EPI and 5-FU. This can be explained by the lower LOQ for Pt. Clearly, any comparison of measures of contamination frequency between different studies must be treated with caution given the high dependency of positive results on the LOD and LOQ of the analytical method used.

This study also shows that external surfaces of significant numbers of pre-filled syringes and IV infusion bags sent to wards or clinics could be contaminated with measurable levels of cytotoxic drugs. This may have serious implications for health care staff involved in administration of cytotoxic drugs particularly if gloves are not always worn. The current UK practice does not, in theory, allow any staff to administer anticancer drugs without gloves therefore the risk of dermal exposure should be minimal. Studies[44,45] on cytotoxic permeability of glove material have concluded that modern versions of neoprene, natural rubber latex and some nitrile gloves are resistant to permeation of cytotoxic drugs in normal practice. However, staff should be vigilant and regularly check gloves for any holes which could allow cytotoxic drugs to enter. It is recommended that pharmacy operators preparing cytotoxic infusions should change gloves at least every 30 min.[28]

Various factors may affect the amount of contamination arising from each individual drug, for example the tendency of the formulation to produce aerosols and the seal of the vial septum around the needle used for fluid transfer. The amount of each drug prepared in the work area each session is another important consideration, and while direct correlations would seem unlikely it is reasonable to expect that the frequency and amount of contamination recovered would increase as the amount of drug manipulated in the isolator increases. With this in mind, the amount of contamination recovered was normalised for the amount of each drug prepared (Table 4). This also provides a more realistic comparison between the baseline and intervention (CSDTD) arms of the study by reducing bias related to the quantity of infusions prepared. Normalised values, expressed as microgram drug recovered per gram of drug prepared, also show significant reductions in the contamination of all swabbed surfaces combined, ranging from 8 to 18,000 fold, when the CSDTD was used.

Other closed-system devices such as Phaseal® and Codan CYTO® are also available. A comparison study[46] of the effectiveness of these devices was conducted using titanium tetrachloride and fluorescein which showed Phaseal® was the only air tight and leak proof device. We question the relevance of such studies and instead favour a challenge under 'real life' operating conditions as in this report. Recent studies have evaluated the Phaseal® device in BSCs and have reported a reduction in surface contamination with cytotoxic drugs such as Cyclophosphamide, Ifosfamide and 5-FU when the device was used over

Table 4. Total amounts of marker drugs used (mg) in test preparations, amount recovered from each surface sampled (μg) during baseline and intervention (CSDTD) periods, and amount of each drug recovered (μg) per gram drug used.

	EPI		5-FU		Platinum (as total Pt)	
	Baseline	Intervention	Baseline	Intervention	Baseline	Intervention
Amount used (mg)	4000	2200	11,400	32,400	2202.5	1279.8
Amount from isolator (μg)	660.0	ND	6780.0	ND	3.05	0.21
Syringe (μg)	0.11	ND	100.74	0.62	NA	NA
Bag (μg)	NA	NA	NA	NA	11.01	1.02
Gloves + Mats (μg)	93.09	11.83	1557.54	0.50	2.67	0.01
Drug recovered[a] (μg/g)	188.3	5.4	740.2	0.04	7.60	0.97

ND: not detected; NA: not applicable.

[a]Denotes total drug recovered (μg) from all surfaces per gram of drug used (or per gram Pt for Pt-based drugs) in both baseline and intervention phases of study.

periods of 6 months,[47] 2 weeks,[48] 24 weeks[31] or 36 weeks.[39] As mentioned earlier, there is debate as to what constitutes a genuine 'closed-system' device. The Tevadaptor® device used in this study utilises a carbon venting filter and would not be considered a 'closed system' under ISOPP guidelines[17]. It is therefore possible that a fully closed-system device (e.g. PhaSeal®) could result in further reduction of isolator contamination.

This study is the first to evaluate a CSDTD in a pharmaceutical isolator and the results showed a marked reduction in surface contamination within 2 weeks of using this device. Although isolators were cleaned at the end of each session, previous studies[34] have shown that complete removal of cytotoxic drug residues is very difficult and, therefore, the contamination in isolators persists and can accumulate. A CSDTD used in conjunction with a pharmaceutical isolator can significantly reduce contamination of the isolator workstation and also reduce the problem of contaminated infusions leaving the isolator. The other advantages of closed-system transfer device include elimination of needle stick injuries, elimination of the risk of exposure to staff involved in administration of IV chemotherapy associated with spiking and priming the IV infusions. CSDTDs may add extra cost to the health care system and, in the experience of the authors, could potentially double consumable expenditure in cytotoxic preparation services. However, there may also be savings to be made because isolator gloves and preparation mats could be used over longer periods as a result of lower contamination in isolators. In the absence of conclusive evidence on safe levels of cytotoxic exposure, this study suggests these devices should be incorporated into routine practice.

Conclusion

This study has shown that using isolators for cytotoxic preparation results in cytotoxic contamination of isolator gloves and work surfaces, as well as external surfaces of prepared IV infusion bags and syringes. This challenges the view that isolators are a sole solution to controlling or reducing cytotoxic contamination. The use of a CSDTD in conjunction with good working practices significantly reduced such contamination, often to below the limit of detection of the assay methods used in this study. This study makes a strong case for use of CSDTD's for the preparation of cytotoxic infusions in pharmaceutical isolators.

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