

Use of a closed-system drug transfer device reduces contamination with doxorubicin during bolus injection

Tom Marler-Hausen, Chris Holt, Christine Headley and Paul Sessink

It has been known for many years that cytotoxic drugs may cause adverse health effects in healthcare workers involved in the preparation and administration of these substances (National Institute for Occupational Safety and Health, 2004). Extensive safety precautions are therefore taken to prevent healthcare workers from being exposed to these substances (International Society of Oncology Pharmacy Practitioners Standards Committee, 2007; Mathias et al, 2019). They include administrative measures such as guidelines, protocols, education and training, and technical measures such as clean-room facilities, biological safety cabinets, isolators and closed-system drug transfer devices (CSTDs). In addition to these measures, personal protective equipment (PPE) is used to optimise workers' safety.

Despite all these precautions and measures, there is still a potential risk for staff to be exposed to cytotoxic drugs. Studies continue to show exposure of healthcare workers by analysis of cytotoxic drugs or their metabolites in urine (Connor et al, 2010; Ndaw et al, 2010; Sugiura et al, 2011a; Sugiura et al, 2011b; Ramphal et al, 2014; Hon et al, 2015; Kibby, 2017; Ndaw et al, 2018), and genetic damage is observed in peripheral blood lymphocytes (McDiarmid et al, 2010; Roussel et al, 2019). In addition, surface wipe sampling shows environmental contamination with cytotoxic drugs in many pharmacies, and inpatient and outpatient departments, where the drugs are prepared and administered to patients (Kibby, 2017).

Many countries around the world have developed guidelines for the safe handling of cytotoxic drugs (Mathias et al, 2019). In the UK, the NHS Pharmaceutical Quality Assurance (NHSPQA) committee recently published recommendations for safe handling of cytotoxic drugs in clinical areas (Santillo et al, 2018).

The process of administering an intravenous (IV) bolus with a cytotoxic drug involves actions that can lead to environmental contamination: removal of the cap, connection of the syringe to the IV line, and disconnection of the syringe after administration. Following the prescribed administration procedures, nurses frequently report small spills of cytotoxic drugs, especially with

ABSTRACT

Background: Administration of doxorubicin via bolus injection may result in environmental contamination and a risk of nurses becoming exposed. Small spills are frequently observed by nurses when syringes are connected to, and disconnected from, infusion lines. **Aims:** The effect of a closed-system drug transfer device (CSTD) on the release of doxorubicin was studied during administration via bolus injections. **Methods:** 10 administrations with the currently used technique and 10 administrations using the CSTD were compared by analysis of doxorubicin contamination on gauze pads, tissues and gloves. **Findings:** Using the current technique, contamination was found during nine administrations, which was mainly on the gauze pads and, to a lesser extent, on the tissues and gloves, indicating release of doxorubicin during administration. With use of the CSTD, contamination was found only on one pair of gloves. **Conclusion:** Use of a CSTD significantly decreased the number of spills and level of contamination compared with the currently used technique and, consequently, the use of such devices offers a safer working environment for nurses.

Key words: ■ Surface contamination ■ Bolus injection ■ Doxorubicin ■ Nurse administration ■ Closed-system drug transfer device

doxorubicin, which is easily observed by its red colour.

The NHSPQA took the view that short-term actions need to be taken to reduce the risks of exposure for healthcare workers, including the application of CSTDs to be added to IV syringes following removal of the caps (Santillo, 2018).

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Table 1. Doxorubicin on the outside surface of 10 outsourced and 10 in-house prepared syringes		
Syringe	Doxorubicin (ng)	
	Outsourced	In-house
1	9	93
2	15	6
3	<1	<1
4	<1	<1
5	<1	<1
6	<1	<1
7	<1	140
8	<1	15
9	<1	871
10	47	<1
Number of positive samples	3	5
P value	>0.05	
Min contamination	<1	<1
Max contamination	47	871
Median contamination	<1	3
P value	>0.05	
Positive controls*	200 000 242 000	
Positive controls [†]	567 000 557 000	
Negative control [‡]	<1	

* 2 tissues + 5 drops doxorubicin (about 0.2 mg) + 100 ml extraction liquid; [†] 2 tissues + 10 drops doxorubicin (about 0.4 mg) + 100 ml extraction liquid; [‡] 2 tissues + 100 ml extraction liquid

The use of CSTDs is controversial, with a Cochrane review concluding that there is currently no evidence to support or refute the routine use of closed systems (Gurusamy et al, 2018); however, this study was criticised for flaws in its methodological design, lack of homogeneity in the performance of the CSTDs (specifically, which type of device was included in the data synthesis), differences in the characteristics of study participants, whether pharmacists and technicians are likely have different safe handling procedures than nurses leading to differing results, and whether the outcome measures recorded differed, specifically, the health outcomes, which were outside the remit of most of the included studies (McDiarmid et al, 2018; Gurusamy et al, 2019; McDiarmid et al, 2019).

Administration of cytotoxic drugs using CSTDs is not routine practice in the UK (Lennan, 2017), whereas their use is now strongly supported in the USA, following publication of the USP 800 (US Pharmacopeia, 2019), and they are used in many other countries, such Germany and Israel (Mathias et al, 2019).

Following the key recommendation by the NHSPQA committee, to administer IV boluses with cytotoxic drugs using CSTDs to prevent potential exposure (Santillo, 2018), the present study sought to evaluate whether the use of the Tevadaptor CSTD could reduce environmental contamination with doxorubicin when administering IV boluses in a large chemotherapy unit. Doxorubicin was selected as an appropriate representative cytotoxic drug to measure because it accounts for 90% of the IV boluses administered in our hospital.

Methods

Study design and sample collection

The study was undertaken at three departments of the University College Hospital Macmillan Cancer Centre in London:

- The Pharmacy Aseptic Suite, where doxorubicin boluses are prepared
- Chemotherapy Day Care, where doxorubicin boluses are administered to patients
- The Teenage and Young Adult Service, where doxorubicin boluses are administered.

The study was focused primarily on contamination during the administration of doxorubicin in a bolus and whether the implementation of the CSTD led to a reduction in contamination. By conducting the study in a clinical area we also gained an insight into whether using the CSTD is practical in a busy clinical area. However, the outcome of the study could be biased by contamination from elsewhere and not linked to the administration itself. Two important issues were considered:

- Contamination with doxorubicin on the outside surface of prepared syringes, which can easily be transferred to other surfaces that are touched
- Contamination on surfaces in the working environment more specific in the three departments participating in the study.

To determine any impact of external contamination on prepared syringes, contamination on the outside surface of prepared doxorubicin syringes was measured by wipe sampling for 10 outsourced syringes and 10 syringes prepared in the Pharmacy Aseptic Suite of the hospital (Table 1). These 20 syringes were not used for administration to patients. Positive control samples were prepared by dripping doxorubicin on the outside surface of syringes, followed by wipe sampling to validate recovery, storage and analysis. Tissues not used for wipe sampling were also analysed for doxorubicin and were considered as negative control samples.

Background environmental contamination with doxorubicin was measured on several surfaces in the Pharmacy Aseptic Suite after cleaning at the end of shift, and in the Chemotherapy Day Care and Teenage and Young Adult Service during daily administration and patient care activities. An overview of the different surfaces, including surface area, is presented in Table 2.

Contamination following the administration of doxorubicin using current standard practice (without a CSTD) was compared with the use of a CSTD. The study was performed at the Chemotherapy Day Care unit during normal working hours and under normal clinical conditions, with chemotherapy-trained nurses administering treatment. Current PPE practices

Table 2. Surface contamination with doxorubicin in each department

Department	Description of surface	Surface area (cm ²)	Doxorubicin (ng/cm ²)
Chemotherapy Day Care	Working surface	4800	<0.0002
	Handle chemotherapy fridge	217	<0.005
	Four plastic trays	6016	0.03
	Four infusion poles	1508	<0.0007
Pharmacy Aseptic Suite	Table check between sluices	10200	<0.0001
	Sluice surfaces	8568	<0.0001
	Work surface isolator 1	5775	<0.0002
	Work surface isolator 2	5775	<0.0002
	Work surface isolator 3	5775	<0.0002
	Work surface isolator 4	7425	0.008
	Counter final check suite	6600	<0.0002
	Counter assembly suite	5400	<0.0002
Teenage and Young Adult Service	Transport bag	3000	<0.0003
	Lid chemo bin	1600	<0.0006
	Three infusion poles	942	<0.001
	Four plastic trays	5016	<0.0002

when administering any bolus chemotherapy drug did not change for either administration and adhered to current practice. PPE included a plastic apron, 1 pair of gloves and plastic armlets. When changing the syringe cap, the nurse wore gloves. Each nurse involved was briefed on the study and instructed on how to handle the CSTD before administering doxorubicin to patients. Each procedure was observed by the investigator (PS), who collected the samples to ensure that the procedure was carried out consistently.

When using the CSTD, the nurses removed the cap from the syringe and replaced it with the CSTD's syringe adaptor lock. This was performed in a separate room over a plastic tray that was cleaned with a detergent wipe prior to use and covered with a tissue, and while wearing gloves and a plastic apron. Potential leakage during removal of the cap and attachment of the CSTD was measured by analysing contamination on the tissues covering the plastic trays, and on the gloves of the nurses. Gloves were changed before administering doxorubicin to patients.

For all administrations (10 with and 10 without a CSTD) a plastic tray with a layer of tissue was placed under the side port where the bolus was infused. For administrations without an CSTD a MaxZero needleless connector was attached to the side port of the intravenous line prior to administration of the doxorubicin bolus. For the administration with an CSTD, the Leur lock adapter was attached to the side port of the intravenous line prior to connecting the syringe adaptor lock and administering the doxorubicin infusion. A piece of gauze was held around the connection port when connecting, infusing and disconnecting the syringe (Figure 1 and Figure 2). After administration, the tissue, gauze pads and gloves of the nurse were collected separately and analysed for contamination with doxorubicin.

Closed-system drug transfer device

The syringe adaptor lock and the Luer lock adaptor, parts of the Tevadaptor CSTD were used for this study. The syringe adapter lock attaches to the syringe; and the Leur lock adapter attaches to the side port in the IV line. The CSTD prohibits the release of the drug in vapour, aerosol or liquid form during preparation, administration and waste handling, and prevents the introduction of microbial and airborne contaminants into the drug or fluid path, allowing the system to minimise environmental contamination and exposure of healthcare personnel to hazardous drugs.

Sample preparation

The wipe samples (syringes and surfaces) were performed using Cyto Wipe Kits. The kits contain materials to take wipe samples from different types of surfaces. The wipe samples were taken by dripping 17 ml distilled water onto the surfaces. Next, one tissue was used to spread the liquid over the entire surface. The second tissue was then used to dry the surface. Both tissues were collected in a container.

The wipe samples were stored at room temperature after sampling and during transport until arrival at the laboratory. At the laboratory, the wipe samples were stored at 4°C until sample preparation and analysis.

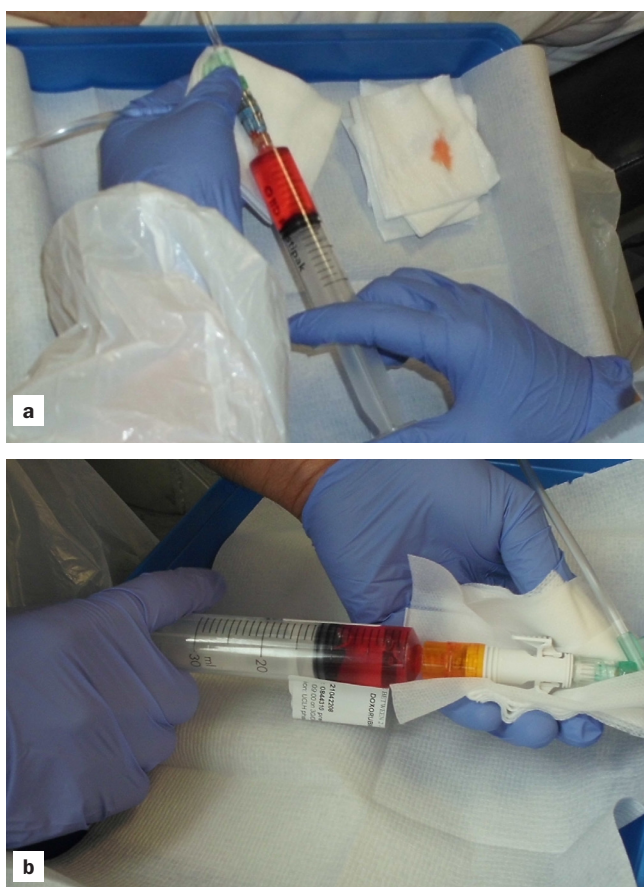


Figure 1. Doxorubicin administration. Collected samples: tissue on the plastic tray, gauze pads and gloves (a) without the use of a closed-system transfer device (CSTD) and (b) using an CSTD

Table 3. Doxorubicin on gauze pads, tissues and gloves during the attachment of the closed-system drug transfer device (CSTD), and during administration using the two injection systems (ng)

Activity	Attachment CSTD		Administration							
Sample type	Gloves	Tissues	Gloves		Gauze pads		Tissues		Total	
Injection system: syringe	CSTD	CSTD	Current	CSTD	Current	CSTD	Current	CSTD	Current	CSTD
1	<1	<1	<1	<1	165	<1	<1	<1	165	<1
2	<1	<1	<1	<1	4070	<1	<1	<1	4070	<1
3	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
4	<1	<1	<1	<1	108300	<1	124	<1	108424	<1
5	<1	<1	92	<1	6766	<1	<1	<1	6858	<1
6	<1	<1	<1	<1	4471	<1	8	<1	4479	<1
7	<1	<1	127	<1	28837	<1	40	<1	29004	<1
8	<1	<1	<1	<1	38	<1	148	<1	186	<1
9	<1	<1	15	<1	1938	<1	<1	<1	1953	<1
10	<1	<1	53	116	694	<1	<1	<1	747	116
Number of positive samples	0	0	4	1	9	0	4	0	9	1
<i>P</i> value									0.0005	
Min contamination	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Max contamination	<1	<1	127	116	108300	<1	148	<1	108424	116
Median contamination	<1	<1	<1	<1	3004	<1	<1	<1	3012	<1
<i>P</i> value			>0.05		0.0005		>0.05		0.0005	
Negative controls*			<1	<1	<1	<1	<1	<1		

* sample + extraction liquid 100 ml

The samples were prepared for analysis by adding distilled water up to a total volume of 100 ml. After extraction, a part of the extract was used for analysis.

Equipment and liquid chromatography with tandem mass spectrometry analysis

Analysis were performed with a Xevo TQ-S micro mass spectrometer combined with an Acquity UPLC H-class sample manager and quaternary solvent manager controlled by MassLynx software. An Acquity BEH C18, 1.7 μ m, 2.1x100 mm separation column operated at 40°C was used for gradient separation of doxorubicin with a flow of 0.3 mL/min. Elution started with a composition of 95% solvent A (100% MilliQ RO-water with 0.1% formic acid) and 5% solvent B (100% ACN), with a delay of 1 minute. Between 1 and 3 minutes, the composition changed to 100% B. Starting conditions were restored between 3.75 and 4 minutes. Total runtime was 5 minutes. The mass spectrometer was operated with a capillary voltage of +1.5 kV, a desolvation temperature of 600°C and a nitrogen flow of 1100 L/min. Cone gas flow was set at 50 L/min (nitrogen). Argon was used as collision gas. Retention time of doxorubicin is 3.5 minutes. The calibration curve is linear in a range up to 100 ng/ml with a limit of detection of 0.01 ng/ml based on 1 μ l injections.

Statistical analysis

Statistical analysis was performed using SPSSv25.

Contamination with doxorubicin on the in-house and the outsourced prepared syringes was compared using chi-square test (number of contaminated syringes) and Mann-Whitney U test (level of contamination).

Contamination with doxorubicin on the gauze pads, the tissues and the gloves used during administration was compared between the current system and with the use of an CSTD using chi-square test (number of positive samples) and Kruskal-Wallis test (level of contamination).

P values below 0.05 were considered as significantly different.

Ethical approval

The study was performed in compliance with institutional guidelines. The nurses participated voluntarily.

Results

Contamination on the outside surface of syringes

Contamination on the outside surface of prepared doxorubicin syringes was observed for 30% of the outsourced prepared syringes (median <1 ng) and for 50% of the in-house prepared syringes (median 3 ng) (Table 1). The number of positive samples and the level of contamination on the syringes did not

significantly differ between the in-house and the outsourced prepared syringes (chi-square test and Mann-Whitney) the positive control samples contained doxorubicin and the negative control sample did not.

Surface contamination in the three departments

Sixteen surface wipe samples were collected from the three departments (Table 2). Contamination with doxorubicin was detected on only two surfaces: the plastic trays in the Chemotherapy Day Care unit (0.03 ng/cm²) and the work surface of an isolator in the Pharmacy Aseptic Suite (0.008 ng/cm²).

Contamination on gauze pads, tissues and gloves during administration using the two injection systems

The current Luer lock syringe connection technique showed release of doxorubicin during nine out of 10 administrations (Table 3). During one administration, contamination was measured on gauze pads, gloves and tissue. The gauze pads were most frequently contaminated ($P=0.046$; chi-square test) and also showed the highest contamination (median 3004 ng; $P=0.001$; Kruskal-Wallis Test). Contamination on the gloves and the tissues was found less frequently and was substantially lower ($n=4$; median <1 ng). Pairwise comparisons showed significant differences in contamination between gloves and gauze pads, and also between tissues and gauze pads ($P=0.004$; adjusted by the Bonferroni correction for multiple tests), but not between gloves and tissues. The negative control samples did not contain doxorubicin.

With the use of the CSTD, there was contamination with doxorubicin during one out of 10 administrations; levels of contamination on the gloves were very low and would likely have come from the syringe/background levels (Table 3). Removal of the cap and attachment of the CSTD syringe adaptor lock did not result in contamination of gloves and tissues (Table 3). The negative control samples did not contain doxorubicin.

Contamination (gloves, gauze pads and tissues) was less frequently observed for the 10 administrations using the CSTD compared with the 10 administrations using the current technique ($P=0.0005$; chi-square test). Total contamination (gloves, gauze pads and tissues) for the 10 administrations with the CSTD was significantly lower than for the 10 administrations using the current technique ($P=0.0005$; Mann-Whitney U test). Comparison of the contamination per sample type showed a significant difference for the gauze pads, but not for the gloves and the tissues ($P=0.0005$).

Discussion

This study has demonstrated that in standard clinical practice the outside surface of cytotoxic syringes can be contaminated with the drug itself. Thirty percent of the outsourced prepared syringes and 50% of the syringes prepared in the Pharmacy Aseptic Suite were contaminated with doxorubicin. There was no significant difference in the number of contaminated syringes and the level of contamination between the in-house and the outsourced prepared syringes, indicating comparable contamination during drug preparation. Comparable contamination results have been found in another study (Call et al, 2017).

Contamination on the outside surface of syringes is caused during the preparation process, but it is always questionable whether the contamination is caused by drug vials potentially contaminated on the outside, by small spills during preparation or by a combination of both. Contamination on vials can easily be transferred via the gloves of the technicians to the syringes. It is important to stress the need to deliver syringes free of contamination with drugs on the outside surface when they are handed over to healthcare workers such as nurses administering the drugs. Because it cannot be 100% guaranteed that prepared syringes, or infusion bags containing cytotoxic drugs, are free of contamination on the outside surface, gloves must be worn by all healthcare workers who touch these products. This includes those touching them during transport, unpacking, double checking of labels, administration and discarding cytotoxic waste.

The surface wipe samples taken in the three departments show only contamination with doxorubicin on the plastic trays at Chemotherapy Day Care unit and on the work surface of an isolator in the Pharmacy Aseptic Suite. Levels of contamination are very low, indicating effective cleaning, and there is no need for additional measures. Levels of contamination are substantially lower compared with previous studies performed in the UK (Ziegler et al, 2002; Mason et al, 2005). However, these studies are more than 10 years old and were undertaken at a time when fewer protective measures are likely to have been taken, in addition to which the studies also monitored other cytotoxic drugs and included the monitoring of other surfaces.

Release of doxorubicin was found during nine out of 10 IV bolus administrations using the current technique. Contamination occurred most frequently and with the highest contamination easily visible on the gauze pads compared with tissues and gloves. This was not unexpected because it is common practice to use a gauze pad while administering cytotoxic boluses to collect potential spills when connecting and disconnecting the syringe. Contamination of gloves or tissues was always observed to occur with contamination on the gauze pads. It is clear that current practice, without the use of a CSTD, results in highly frequent release of doxorubicin during administration. While the gauze pads capture the largest amount of doxorubicin during connection and disconnection of a bolus syringe, the current practice does not prevent release of doxorubicin during administration, and healthcare workers are currently at risk of exposure for almost all IV bolus injections.

Doxorubicin was found during one out of 10 administrations when using the CSTD and was detected only on the gloves of the nurse during administration. This observation is in contradiction with the current technique results, where all contaminated samples were associated with gauze-pad contamination along with tissues and gloves. It is hard to ascertain how contamination on the gloves in this administration occurred, but it is most probably caused by doxorubicin being present on the outside surface of the syringe. If so, one might also have expected contamination on the gloves used during attachment of the CSTD, but for all attachments contamination on the gloves and tissues was below the detection limit. It was observed that some parts of the syringe were touched during attachment of the CSTD which were probably not contaminated, while the

whole syringe was touched during administration including the contaminated parts.

Attachment of the CSTD was performed without any contamination on the gloves and the tissues. However, it is not ideal to perform this procedure in the ward because there is always a risk of spillage, resulting in environmental contamination and exposure of the nurses. The ideal approach is to attach the CSTD during preparation inside an isolator in the aseptic suite.

Conclusion

The current technique of administering doxorubicin by bolus injection via a syringe results in environmental contamination, indicating a potential risk for nurses being exposed. In the study described in this article, the use of the Tevadaptor syringe adaptor lock and Luer lock adaptor CSTD resulted in a substantial and significant reduction of the contamination and showed that this was an effective way to prevent spills of the cytotoxic drug. **BJN**

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KEY POINTS

- Nurses are at risk when administering intravenous (IV) bolus injections to patients, because spills are reported frequently and were observed in the present study
- Prepared syringes are frequently contaminated with cytotoxic drugs on the outside surface
- Whenever syringes containing cytotoxic drugs are touched, gloves have to be worn to protect healthcare workers from exposure to the drugs
- Potential contamination during administration of IV boluses can be prevented by using closed-system drug transfer devices

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CPD reflective questions

- What are the risks of exposure to cytotoxic drugs for healthcare workers?
- How are nurses exposed to cytotoxic drugs?
- How can exposure to cytotoxic drugs be prevented?