External contamination of antineoplastic drug vials: an occupational risk to consider

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ABSTRACT

Risk management for workers involved in the handling and preparation of cytotoxic drugs is challenging. This study aims to investigate drug contamination of the exterior surfaces of cytotoxic drug vials. Two batches of commercially available cytotoxic drugs in unprotected vials (ifosfamide, etoposide phosphate and cyclophosphamide) and plastic shrink wrap vials (doxorubicin, cytarabine and busulfan) were tested without removing the flip-off cap or the plastic wrap, and without prewashing. The results showed significant trace amounts of cytotoxic drugs on the exterior surfaces in both unprotected (eg, cyclophosphamide, ifosfamide) and protected plastic shrink wrap vials (eg, cytarabine), indicating that the secondary packaging of protected vials does not systematically prevent exposure to the handlers. These results focus on the need for guidelines to prevent cytotoxic vial contamination and safety recommendations for staff in the handling and storage of these vials.

INTRODUCTION

Guidelines and procedures to reduce the risk of occupational exposure have been proposed by occupational and safety agencies for at least the preparation and administration steps.[1–3] Despite safe handling practice guidelines, several studies have reported exposure to cytotoxic agents by contamination of the workplace during the preparation and storage of hazardous drugs.[4–7] Evidence of cytotoxic drug contamination has been detected on floors and work surfaces, inside and outside biological safety cabinets and on gloves.[6–8] In addition to these sources of contamination, several studies have shown that the external surfaces of vials supplied by pharmaceutical companies contain cytotoxic drugs on the external parts of the vials.[9–16] As a result, despite safety-controlled conditions, handling cytotoxic drugs still runs the risk of genotoxic, adverse reproductive and cytotoxic effects for occupationally exposed professionals.[1 2 16] To limit such a risk, some pharmaceutical companies have set up additional cleaning steps in their process to limit contamination from the external surface.[9] In addition, some companies have also included a plastic shrink wrap or break-proof plastic container at the end of the filling process.[14] While there are no occupational exposure limits for cytotoxic agents in work environments, there are no legal guidelines concerning maximum acceptable contamination limits for external vials. Contamination of the outside of vials is a potential occupational hazard which needs to be considered. An example of measurable contamination would be cyclophosphamide levels >1.00 ng/cm², which were shown in some studies to result in intake of the drug by exposed workers.[2] The aim of this study was to assess in 2020 the real impact of the external decontamination process of vials by pharmaceutical companies.

MATERIALS AND METHODS

Cytotoxic production

The centralised unit for sterile preparations prepares treatments for both adult haematology and paediatric immunohaematology departments. Approved by the European office for haematopoietic stem cell transplantation accreditation, the main focus of the unit is the preparation of high-dose chemotherapy drugs for haematopoietic stem cell transplantation. In 2019 the total volume of sterile preparations was 18 149 units, approximatively 70 preparations each day. Operators need to handle cytotoxic agent vials when they prepare the materials to be put in the isolator. Despite the mandatory use of protective gloves, the risk of occupational exposure to cytotoxic drugs needs to be considered.

Study design

Contamination of the external surface of cytotoxic agent vials was investigated using the products routinely ordered and stored in our pharmacy in a dedicated and geographically separated area. The choice of these compounds was a balance between the medications most widely prescribed in our hospital and their toxicity, as well as the analytical aspects. All the drugs were provided from the French market. Cytotoxic drugs were unpacked from the cardboard packaging in which they were delivered and stored on the dedicated rack. Cyclophosphamide and ifosfamide (Endoxan 1 g powder for injection, Holoxan 2000 mg/50 mL powder for injection; Baxter, Guyancourt, France), protected cytarabine with shrink wrap (Cytarabine Accord 2000 mg/20 mL; Accord Healthcare, Lille, France), protected doxorubicin with shrink wrap (Doxorubicin Teva 50 mg/25 mL solution for injection; Teva Santé, La Defence, France), etoposide phosphate (Etopophos 100 mg powder for injection; Bristol-Myers Squibb, Rueil-Malmaison, France) and protected busulfan with shrink wrap (Busulfan Fresinius Kabi 6 mg/mL, Sèvres, France) were selected as available vials. Examples of unprotected and protected vials are shown in figure 1. Samples were collected from two different batches of each

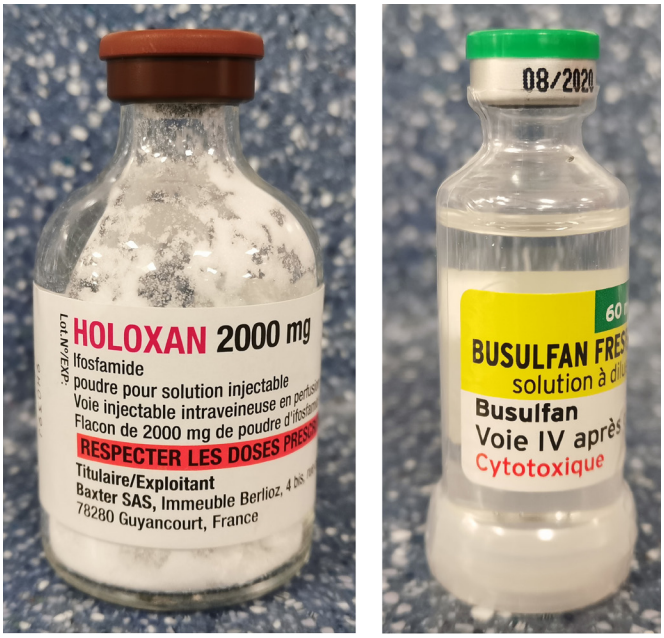

Figure 1 Examples of unprotected and protected vials. (Reproduced with permission of Baxter SA and Fresenius Kabi Laboratories).

drug (delivered on different days). Personal protective equipment was worn during sampling and gloves were changed after sampling of each vial.

Sampling with wipes and determination of cytotoxic agents

An ashless cellulose filter paper (Whatman no 42; Merck, Saint Quentin Fallavier, France) wetted with 300 µL of sterilised water was used for wiping 10 individual drug vials. One wipe was used for 10 vials. The technique consisted of sampling the external surfaces of each vial without removing the flip-off cap or wiping the external plastic cap cover. After wiping the surface of the vials, the filter paper was carefully wrapped, put into a glass tube and then stored at 2–8°C before extraction. A mixture of methanol/water (60/40, v/v) was then introduced into the glass tube. The tube was mixed for 10 min and 0.5 mL was introduced into another glass tube and evaporated under a nitrogen stream. The residue was reconstituted in 0.3 mL of mobile phase and transferred to a glass vial for analysis. Analysis of cytotoxic drugs was performed by liquid chromatography coupled with high resolution mass spectrometry using Q-Exactive Plus (ThermoScientific, Bremen, Germany). The separation of the compounds was carried out with a Hypersil Gold column (2.1 mm × 100 mm, 3 µm; ThermoFisher Scientific, Les Ulis, France) and thermostated at 30°C. The autosampler tray was maintained at 10°C. A volume of 10 µL was injected. A linear gradient programme with (a) water acetic acid 0.1% and (b) acetonitrile acetic acid 0.1% was performed. The retention times were 11.2 min, 10.8 min, 11.3 min, 10.8 min, 1.5 min and 1.8 min for cyclophosphamide, doxorubicin, etoposide phosphate, ifosfamide, cytarabine and busulfan, respectively. Each compound was identified according to its exact mass (mass resolution 70 000) in full scan mode and by its main ion fragments (mass resolution 17 500) in parallel reaction monitoring mode. Cyclophosphamide was detected with [M+H]+261.03 and with selection ion fragments 140.00, 106.04, 233.00. Doxorubicin was detected with [M+H]+544.18 and with selection ion fragments 361.07, 113.05, 130.08, 86.05. Etoposide phosphate was detected with [M+H]+669.15 and with selection ion fragments 589.19, 229.04, 185.05. Ifosfamide was detected with [M+H]+261.03 and with selection ion fragments 92.02, 78.01, 233.00. Cytarabine was detected with [M+H]+244.09 and with selection ion fragment 112.05. Busulfan was detected with [M+H]+264.10 and with selection fragment 151.10. For each drug, the corresponding labelled stable isotope was used as the internal standard. The following limits of quantification (quantity on cellulose filter paper) was determined for each compound: cyclophosphamide (1 ng), doxorubicin (10 ng), etoposide (2 ng), ifosfamide (1 ng), cytarabine (2.5 ng) and busulfan (5 ng). The method was validated according to guidance from the Food and Drug Administration.[17] For each cytotoxic drug tested, the within-run and between-run precision of the assays was less than 10% and the assay accuracy was in the range of 89.3–111.4%.

RESULTS

None of the vials inspected during the study showed any signs of breakage or damage. The 10 vials of each drug were from the same manufacturer. The results are summarised in table 1. In wipe samples, cyclophosphamide and ifosfamide were detected at low levels for 10 vials. The data from the cytarabine sample confirmed a high level of external vial contamination (>2000 ng by 250 ng) despite the plastic shrink wrap protection.

DISCUSSION

The external vial contamination of three of six different cytotoxic agents available on the French market suggests that there is a large variation in the cytotoxic contamination level. It is well known that a significant amount of drug contamination exists

Table 1 Total amount of cytotoxic agents found on the exterior of the vial from wiping 10 vials

Active drug	Active form in vial	Manufacturer involved	Amount of active ingredient in 10 vials (mg)	Amount of active ingredient on surfaces of 10 vials (ng)	
				Batch 1	Batch 2
Cyclophosphamide	Powder for injection	Endoxan 1 g (Baxter)	10 000	30 ng >5 and <50	12 ng >5 and <50
Cytarabine	Liquid	Cytarabine 2000 mg/20 mL with plastic overwrap (Accord Healthecare)	20 000	250 ng >200 and <2000	100 ng >25 and <250
Doxorubicin	Liquid	Doxorubicin 50 mg/25 mL with plastic overwrap (Teva Santé)	500	<10 ng	<10 ng
Etoposide phosphate	Powder for injection	Etopophos 100 mg (Bristol-Myers Squibb)	1000	<2 ng	<2 ng
Ifosfamide	Powder for injection	Holoxan 2000 mg/50 mL (Baxter)	20 000	5 ng >0.5 and <10	150 ng >50 and <200
Busulfan	Liquid	Busulfan 60 mg/10 mL with plastic overwrap (Fresenius)	600	<5 ng	<5 ng

under the flip-off caps, which is why we did not remove them in our study. In our unit, vials are unpacked from their cardboard boxes but the vial flip-off remains.[15] Regarding the formulation form, the highest contamination level was reported for the ready-to-use product cytarabine. However, external contamination of vials containing powder were also found. There are three factors of contamination levels (detailed in table 1): the form of the drug, the nature of the drug and the production process of the drug. External contamination of both unprotected and protected vials was seen. The plastic shrink wrap of protected vials does not guarantee an absence of contamination and it is therefore necessary to apply the same handling instructions as those used for unprotected vials. In the case of cytarabine, vial decontamination after the filling step in the production chain does not seem sufficient to guarantee that all vials are free of surface contamination. These results are opposite to those found in the study by Connor *et al* which evaluated the effect of the sleeves from unprotected and protected cisplatin vials. The levels of contamination were significantly lower for the vials with sleeve protection than for those without sleeve protection ($p<0.0001$).[9] Combining improved decontamination equipment and sleeve protection, the authors noted the possibility to substantially reduce the surface contamination of drug vials with cisplatin and decrease the potential exposure of hospital workers to the drug. The study by Schierl *et al* also found that contamination of unprotected vials is about 10 times higher than contamination of protected vials, but without the protection fully preventing the risk of cytotoxicity.[11] A recent study that investigated the contamination of the exterior of cytotoxic drug vials available in Canada confirmed our results, with a majority of samples positive to at least one cytotoxic drug.[18] Moreover, the authors reported cross-contamination with another type of cytotoxic drug and the lack of efficiency of protective film.

Our study highlights the need to ensure appropriate cleaning of commercial vials and to wearing appropriate gloves to prevent contamination when transporting vials to the production area. Cleaning the vials with soapy water and a towel wipe eliminated the presence of contamination on most of the vials.[10] One limitation of the study concerns the solvent used to sample the drugs on the exterior of the vials. The majority of drugs are soluble in water, except for busulfan which is soluble in dimethyl sulfoxide. Presumably, the recovery would be greater if a second wipe was used.

CONCLUSION

This study shows that contamination at nanogram to microgram levels of cytotoxic drugs still exists. Consequently, it is essential to protect all skin surfaces potentially in contact with cytotoxic drugs when unpacking the vials and to apply a validated procedure for their external decontamination. Moreover, pharmaceutical companies must revise their guidelines and double their efforts to establish decontamination protocols to ensure the supply of contamination-free vials.

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