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Cytotoxic Drug Contamination on the Outside of Vials Delivered to a Hospital Pharmacy

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We recently carried out a study of two UK hospital pharmacy units preparing cytotoxic drugs using isolators that showed low level contamination on floor surfaces and disposable gloves worn by staff. It has been suggested that this level of contamination may be related to some level of contamination on the drug vials as delivered from manufacturers rather than leakage from the isolators. We have investigated the level of cytotoxic drug contamination on the external surfaces of the drug vials as delivered to a hospital pharmacy stores. We monitored 30, randomly chosen vials for the drugs cisplatin, carboplatin, cyclophosphamide, ifosfamide and methotrexate using well-established methods. A 0.5 m^2 floor area directly in front of the shelves used for storing the cytotoxic drugs was also wipe sampled and the disposable gloves worn while wiping the vials for each drug were also analysed. A significant number of vials had a quantifiable level of external contamination. Levels of contamination up to 344 ng/vial were found. Levels of glove and floor contamination for some drugs were found to be comparable with values found in our study of the clean rooms where the isolators were situated and the pharmacy staff prepared the cytotoxic drugs.

Keywords: anti-neoplastics; environmental monitoring; cisplatin; carboplatin; cyclophosphamide; ifosfamide; methotrexate

INTRODUCTION

Concerns have been raised about the occupational exposure of hospital staff to cytotoxic drugs (Sessink *et al.*, 1992b; McDevitt *et al.*, 1993; Sorsa and Anderson, 1996). Many cytotoxic drugs are themselves carcinogenic or possibly reproductive toxicants (Skov *et al.*, 1992; Hansen and Olsen, 1994; Valanis *et al.*, 1999). Studies have largely centred on exposure to those clinical staff administering the drugs and the pharmacy staff who prepare the prescriptions for administration to the patients (Evelo *et al.*, 1986; Ensslin *et al.*, 1994, 1997; Sessink *et al.*, 1992a, 1994a; Sorsa and Anderson, 1996; Burgaz *et al.*, 1999). Limited studies have also been published on cytotoxic exposure in pharmaceutical manufacturing plants (Pyy *et al.*, 1988; Sessink *et al.*, 1994b)

Two recent UK studies of cytotoxic drug exposure in pharmacies and oncology wards have been reported, where many elements of good, current occupational practice were apparent (Mason *et al.*, 2001, 2004; Ziegler *et al.*, 2002). In the ward study, drug administration was carried out by trained and experienced, nurse-led teams who used appropriate personal protective equipment. The two UK pharmacies studied were both using isolators to contain the cytotoxic drug during preparation by trained technicians and were also using appropriate management and personal protective equipment to control any potential exposure. Data from the UK pharmacies, using very sensitive environmental and biological monitoring techniques, still suggested contamination on surfaces external to the isolators, on the discarded disposable gloves worn by staff and even some evidence of low level absorption of cytotoxic drugs (Mason *et al.*, 2001). However, the level of external drug contamination in this UK study appeared considerably less than had been reported in earlier, non-UK studies, where laminar flow or microbiological safety cabinets rather than isolators were largely used to contain the drugs (Sessink *et al.*, 1992b; Ensslin *et al.*, 1997; Minoia *et al.*, 1998). Potential sources for cytotoxic drug contamination external to enclosures in the recent UK study have been considered; these include the possible contam-

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ination of the drug vials as supplied from the manufacturer. This source of contamination appears to have only been investigated in a limited fashion in only a few studies (Sessink *et al.*, 1992b; Delporte *et al.*, 1999; Nygren *et al.*, 2002). We considered it necessary to explore the possibility of external contamination of vials in the light of our recent pharmacy study (Mason *et al.*, 2001, 2004), which still suggested some level of contamination within pharmacy units where isolators were used as the primary containment measure.

This paper presents data from an initial investigation of the contamination on the outside of vials containing cisplatin, carboplatin, cyclophosphamide, ifosfamide and methotrexate as supplied to hospital pharmacies. Well-characterized assays of high sensitivity are available for these cytotoxic drugs. The vials monitored were those supplied to a single UK pharmacy stores from six different manufacturers.

MATERIALS AND METHODS

Description of cytotoxic stores

Cytotoxic drugs were stored in the pharmacy in a small area separate from other pharmaceutical products. Essentially, two columns of simple dexion-framed shelving facing each other were used to store the drugs. The shelving units were ~1 m wide by 2 m high with shelves from knee to head height. The distance between the two facing shelving units was only ~0.6 m. Drugs were unpacked from the transport/delivery packaging and stored on the appropriate shelf either in the primary packaging box for an individual drug vial or in shrink-wrapped multiples. While carrying out the wiping exercise a number of stores portering staff removed various amounts of cytotoxic drugs from the shelving.

Wipes sampling

Thirty individual drug vials of each drug (cisplatin, carboplatin, cyclophosphamide, ifosfamide and methotrexate) were wiped. Drugs were taken randomly from the shelving of this hospital pharmacy store. Individual drug vials were removed from external packaging and wiped using a folded two-ply Kim-Wipe (Kimberley-Clark) wetted with 1 ml of an appropriate solvent. The solvents used were milli-Q purified water for cisplatin and carboplatin, 50% methanol:water for cyclophosphamide and ifosfamide, and 30 mM sodium hydroxide for methotrexate. These solvents were selected on the basis of the good solubility of the individual drugs in the respective solvents (Allwood *et al.*, 2002). Each vial and the cap were carefully and extensively wiped with the damp, folded tissue, which was then placed in a 25 ml Sterilin screw-capped bottle. Appropriate blank tissues were also collected.

A floor area of 0.5 m^2 directly in front of the shelving storing the cytotoxic drugs in the pharmacy was wiped, extracted and analysed using a previously reported method (Mason *et al.*, 2001; Ziegler *et al.*, 2002), allowing comparison with surface contamination data we have collected from oncology wards and pharmacy areas where compounding of cytotoxic drugs is carried out. Floor wiping was carried out immediately prior to vial wiping and after completion of the vial wiping exercise. Using a similar method, two areas of floor in our laboratory with no possible cytotoxic exposure were also wiped.

Disposable gloves were worn whilst locating vials on shelving, removing the appropriate vials from packaging and wiping each set of 30 vials for each drug. These gloves were also collected in screw-cap vials for later analysis. Two pairs of unused, blank gloves from the same batch were also kept for analysis for each cytotoxic drug. Extraction of drugs from wipes and vials was carried out as soon as possible after collection.

Wipes taken for individual drugs on vials were extracted with constant shaking for at least 2 h with, respectively, 20 ml of methanol for cyclosphosphamide and ifosfamide or 20 ml of milli-Q water for cisplatin, carboplatin and methotrexate. The floor wipes were extracted with 20 ml of milli-Q water as previously reported (Mason *et al.*, 2001, 2004; Ziegler *et al.*, 2002). Disposable gloves were manually shredded and then extracted as a pair with 50 ml of methanol for cyclophosphamide and ifosfamide, 50 ml of milli-Q water for cisplatin and carboplatin and 50 ml of 10 mM sodium hydroxide for methotrexate. Where analysis of extracts was not immediately possible, they were stored at –20°C until analysis.

All wipe and glove samples were allocated unique laboratory identifiers and logged into the database according to our standard UKAS accredited procedures to ensure intregrity of the sample–result chain.

As a separate exercise, duplicate blank wipes and pairs of disposable gloves were spiked with a known amount of the respective cytotoxic drugs and extracted according to the methods above.

Analytical procedures

Methotrexate, cyclophosphamide and ifosfamide were measured in extracts of the collected wipes and gloves using previously published methods (Mason *et al.*, 2001; Ziegler *et al.*, 2002). Essentially, 5 ml of the methanol extract was air dried derivitized using trifluoroacetic anhydride. Cyclophosphamide and ifosfamide were measured by the same analytical procedure using gas chromatography–mass spectrometry (GC-MS) in chemical ionization mode (Sessink *et al.*, 1993; Ziegler *et al.*, 2002). The analytical detection limit in primary samples or extracts for these two drugs is ~1 nM (~5 ng/vial). Methotrexate was measured in a neutralized aliquot

Table 1. The nature of the drug in the vials wiped for each active ingredient and the total amount of active drug found external to the vial from wiping 30 vials

Specific drug	Active form in vial	No. of manufacturers involved	Total active ingredient in 30 vials (mg)	Total active ingredient on surfaces of 30 vials (ng)	Range of active ingredient on vials (ng)	Vials contaminated above assay detection limit (%)
Carboplatin	Liquid	2	6350	1352	7–251	100
Cisplatin	Liquid	1	300	14	ND–9	13
Cyclophoshamide	Solid	2	22000	78	ND–39	10[a]
Ifosfamide	Solid	1	50000	558	ND–344	3
Methotrexate	Liquid	2	14100	149	ND–18	40

The percentage of vials with detectable contamination and the ranges of external contamination found on the vials for each drug are also shown.
[a]On two wipe samples from vials of cyclophosphamide there was detectable ifosfamide.

Table 2. The extent of contamination found on floor wipes taken immediately in front of the stores shelving for cytotoxic drugs and on the disposable gloves worn during wiping the vials for specific cytotoxics

Vials of specific drug	Floor level (ng/m^2)			Disposable gloves (ng/pair)	
	Pharmacy stores		Non-exposed area		
	Pre-vial wiping	Post-vial wiping		During vial wiping	Blank unused sample
Carboplatin	6348[a]	3928[a]	<1[a]	38[a]	<1[a]
Cisplatin				28[a]	
Cyclophoshamide	1048	574	ND	ND	ND
Ifosfamide	ND	ND	ND	ND (1632[b])	ND
Methotrexate	41	18	ND	13	ND

Results for floor wipes taken from an area with no potential cytotoxic exposure and blank disposable gloves are also shown.
[a]Platinum results are shown as elemental concentrations rather than converted to platino-coordinated active ingredients.
[b]The contamination found was 1632 ng of cyclophosphamide, not ifosfamide.

of the extract using an in-house immunoassay (Ziegler *et al.*, 2002); the detection limit is ~0.2 nmol/l (2 ng/vial) in such extracts.

Cisplatin and carboplatin were measured as elemental platinum in aqueous extracts using direct nebulization, inductively coupled plasma mass spectrometry (Elan 6100; Perkin Elmer). Aqueous standards in 1% (v/v) HCl covered the range 0–100 μg/l; 10 μg/l iridium was spiked into standards and samples as internal standard. Both isotopes of platinum (^{194}Pt and ^{195}Pt) were analysed along with the internal standard (^{193}Ir) The analytical detection limit for this assay is ~0.05 μg/l (~1 ng/vial).

The within-run analytical precision of the methotrexate, cyclophosphamide/ifosfamide and platinum methods are 9, 10 and 3%, respectively.

RESULTS

None of the vials or its packaging inspected during this study showed any signs of breakage or damage.

The 30 sample vials of carboplatin came from two manufacturers and were in liquid form: 10 vials containing 50 mg of drug were from one manufacturer; the remaining 20 sampled vials were from another manufacturer and contained either 150 or 450 mg of drug. The 30 vials of liquid cisplatin were all from one manufacturer and contained 10 mg of active drug. The 30 sampled vials of lyophilized cyclophosphamide were from two manufacturers and contained either 200 or 1000 mg of drug. All the ifosfamide vials were from one source and contained either 1000 or 2000 mg drug, also in powder form. The methotrexate came from two manufacturers in liquid form. The vials contained largely either 50 or 500 mg of drug, although one vial containing 5000 mg was also sampled.

The results from this study are summarized in Tables 1 and 2. The percentages of the vials sampled for each drug which had some measureable level of cytotoxic drug contamination were between 3 and 100%. The highest percentage was associated with the most sensitive measure of contamination (platinum measurements). There was no apparent relationship between the vial drug size and the apparent level of external vial contamination for any of the drugs. Except for the apparent low level external contamination on all the vials of carboplatin from two different manufacturers, the data from this study suggests a variable incidence of vials with some level of low

level external contamination with the active ingredient. There were a few anomalous results for cyclophosphamide and ifosfamide. Two wipes from 1 g vials of cyclophosphamide from the same batch of a manufacturer were confirmed to be contaminated with similar levels of ifosafamide and a pair of disposable gloves worn whilst wiping a number ifosfamide vials had confirmed cyclophosphamide contamination when later analysed by GC-MS.

Recovery of drugs from spiked wipes used for vials and gloves was found to be >80% for all drugs. Mean recoveries for the floor wiping protocol has been reported as 91% for platino-coordinated drugs, 67% for cyclophosphamide and 97% for methotrexate (Ziegler *et al.*, 2002).

DISCUSSION

The finding of some cytotoxic drug on a number of vials, the floor area in front of the shelving used to store cytotoxic drugs and the disposable gloves worn while wiping the vials suggest that there is low level contamination on the external surfaces of some vials. This contamination does not appear related to broken vials or poor packaging as supplied to the hospital pharmacies. Using platinum measurements as the most sensitive marker of contamination, on the sampled carboplatin vials the average level of external contamination on each vial was 0.000027% of the amount of the drug within the vial. Therefore, there is very low level contamination associated with vials of cytotoxic drugs supplied by manufacturers. Although the platino-coordinated drug levels were highest on the floor and vials, there does not seem to be a good relationship between the drugs found on the floor and the total amount of each drug found on the 30 vials sampled.

The number of studies which have studied contamination of the external surfaces of cytotoxic drug vials as delivered to hospital pharmacies is small. The recent paper of Nygren *et al.* (2002) is of only six vials of cisplatin from three manufacturers. The range of results in Nygren's small study were between 2 and 102 ng on each vial, which appear comparable with the data we found. Sessink *et al.* (1992b) checked for cyclophosphamide contamination on nine vials, for fluorouracil on 20 vials and for methotrexate contamination on 15 vials. He reported one vial to be contaminated with 60 ng of cyclophosphamide and one vial of methotrexate had 15000 ng active ingredient on the outside. Delporte *et al.* (1999) investigated fluorouracil contamination on 90 vials (three batches from three manufacturers). Three vials from the same manufacturer had external contamination of between 5000 and 18000 ng/vial. Another 27 vials had levels of detectable contamination but lower than the limit of quantitation for their method.

The levels of platinum on the floor of the pharmacy store appear high according to the floor contamination measurements we have made within the clean room areas of two UK pharmacy units formulating cytotoxic drugs. In the study of areas where drug prescriptions were compounded, maximum platinum values of ~130 ng/m^2 were found on the floor in front of the isolators, whereas we have found an initial value of >6000 ng/m^2 in the pharmacy stores area where the cytotoxics were shelved. It should be pointed out that the pharmacies investigated earlier (Mason *et al.*, 2001) were not the same pharmacies as those stores studied here. Also, care has to be taken in assuming that measured platinum in such samples equates to active platino-coordinated cytotoxic drug.

The levels of cyclophosphamide found on the store floors (1048 and 574 ng/m^2) also seemed comparable with the levels found earlier in floor areas of pharmacy units where cytotoxic prescriptions were compounded within isolators (median 290, range 22–1596 ng/m^2) (Mason *et al.*, 2001, 2004). Currently, we have no data to suggest whether our floor wiping technique is inadequate in removing all cyclophosphamide or platino-coordinated cytotoxics from the floor or that the post-vial-wiping floor sample represents freshly deposited drug that we disturbed from shelves, vials and packaging. However, we note that no ifosfamide was detectable on the floor either pre- or post-vial sampling, whereas significantly more ifosfamide was found on the vials sampled than cyclophosphamide.

The level of platinum contamination found on the disposable gloves used for wiping the 30 vials of carboplatin or cisplatin are comparable with the levels on gloves taken from UK pharmacy technicians undertaking cytotoxic drug formulation and from oncology ward cytotoxic administration nurses (Mason *et al.*, 2001; Ziegler *et al.*, 2002). In all studies the level of platinum on blank, unused gloves has consistently been <1 ng/pair.

It was interesting that a relatively high level of cyclophosphamide contamination was found on a pair of gloves used as personal protective equipment (PPE) during sampling of vials containing ifosafamide and that two wipes from cyclophosphamide vials showed ifosfamide contamination. These anomalous results were rechecked analytically and an audit trail of sampling handing procedures did not suggest any sample mishandling within the laboratory. This may suggest some possible general cyclophosphamide or ifosfamide contamination on the shelving within the pharmacy stores or possible cross-contamination between vials as supplied by the drug manufacturers.

There are 45 chemotherapeutic drugs listed in the *Cytotoxics Handbook* as being used routinely in clinical practice (Allwood *et al.*, 2002). Our monitoring strategy covers only six of these drugs (cisplatin, carboplatin, oxaliplatin, cyclophosphamide, ifosfamide

and methotrexate). For several of them (cyclophosphamide, ifosfamide and platino-coordinated drugs) their assay necessarily uses sophisticated analytical technology. While our monitoring strategy covers commonly used cytotoxic drugs in clinical oncology, we cannot assume that their use in monitoring will necessarily be appropriate to identify exposure to cytotoxics in all hospital situations. There is a need for readily available, inexpensive assays which can cover a wider range of cytotoxics or development of some generic measurement method. Such assays could be used to ensure the efficacy of control measures and risk reduction strategies.

This study suggests that some of the cytotoxic contamination discovered external to isolators in the preparation rooms (Mason *et al.*, 2001, 2004) may be related to this source of low level drug found on the material as supplied by the manufacturer rather than leakage from the isolator. The level of external cytotoxic contamination on the vial or packaging supplied by the manufacturer may be very low. However, this study highlights the need to ensure that the appropriate control measures are applied in handling the supplied cytotoxic drugs prior to reconstitution or compounding for prescriptions within enclosures. We point out that appropriate control measures must also protect stores staff and other non-technical pharmacy or hospital staff who are potentially exposed by this route. We have only undertaken a limited survey based on 30 vials per active ingredient; the possibility of isolated cases of greater contamination on some vials or of the vial packaging cannot be ruled out. We have not currently investigated possible contamination of primary packaging and delivery packaging, which may better reflect potential exposure of hospital pharmacy stores staff.

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