ORIGINAL ARTICLE

Occupational exposure to cytotoxic drugs in two UK oncology wards

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Aims: To investigate the potential exposure to cytotoxic drugs of staff on two oncology wards in a large district, UK hospital under normal working conditions.

Methods: Cytotoxic drug exposure was monitored in urine samples, surface wipes, and on disposable gloves by using a number of commonly used marker drugs, namely cyclophosphamide, ifosfamide, methotrexate, and the platino coordinated drugs. Questionnaire data on their work practices, potential exposure, use of protective personal equipment, and relevant training were collected from nursing, domestic, and clerical staff on two oncology wards.

Results: The majority of staff were female with a mean age of 31 years. Roughly half of the staff studied were specifically trained nurses with an average of 3.5 years experience of administering cytotoxic drugs. No cytotoxic drug preparation or reconstitution was carried out on the wards. Disposable gloves, plastic armlets and aprons, but not eye protection, were invariably worn where there was potential exposure to cytotoxics. No cytotoxic drug was detected in any of the staff's urine samples. Isolated disposable latex gloves from nurses administering drugs showed some contamination, as did some surfaces within the wards' sluice rooms, but not in the ward areas where the drugs were stored and checked prior to administration.

Conclusions: The risk management strategies in place, including use of personal protective equipment, staff training, and other organisational measures, have ensured that internal exposure is lower than the detection limits for the current biological monitoring methods. Levels of contamination appear significantly lower than earlier, non-UK published studies where different risk management strategies were in place and, in particular, ward staff may have been involved in some degree of cytotoxic drug reconstitution.

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There has been concern for many years about potential exposure and subsequent effects in healthcare workers who handle cytotoxic or antineoplastic drugs.^{1,2} Many of these drugs have mutagenic, teratogenic, or carcinogenic properties, where no effect threshold dose can be identified. Studies have been reported on the cancer risk and adverse effects on pregnancy outcome,^{3–5} and some indication of genotoxic damage in the peripheral lymphocytes of nurses has been found.^{6–8} However, the relevance of such findings in the context of current UK exposure is unclear. In the UK, occupational exposure to such chemicals is subject to the Control of Substances Hazardous to Health Regulations (COSHH, 1999). Guidance for the safe handling of cytotoxic drugs in the clinical setting has been issued over the years; recently in *The cytotoxics handbook*⁹ and a Royal College of Nursing technical report.¹⁰ The latter report noted the need for more information on current clinical practices and facilities in the UK as well as the need to confirm the efficacy of these practices. This study was set up to determine whether the exposure risk on wards where cytotoxic drugs were handled was appropriately controlled.

There have been a number of historical studies looking at cytotoxic drug exposure in hospital staff, including measurements of atmospheric levels, surface contamination, or the levels of drugs in the urine of staff involved in both the preparations of cytotoxic drugs and their administration to patients. This published work has largely been carried out in continental Europe and the USA.^{2,11–12–19} We can find no recent published data for clinical staff in the UK. Current good work practices in the UK have segregated the formulation of cytotoxic drugs ready for administration to patients to within special pharmacy units, with trained, largely nurse based teams administering the drugs to patients. Other nursing and

ancillary staff are also involved in patient care. In the earlier published studies some of the clinical staff could be involved in a degree of cytotoxic drug preparation as well as administering the drugs to patients.

Any drug absorption in hospital staff is generally assumed to be via the skin or mucus membranes, and to a lesser extent inhalation.^{15–17} Of concern is that ward staff may be exposed not only from spillages of the drugs, but also via contact with patients' body fluids, such as vomit, sweat, and urine. These are known to contain cytotoxic drugs,²⁰ but may be perceived to be of less risk. The need for research on the effectiveness of current control measures on oncology wards and the influence of the levels of training in health and safety measures has been highlighted.^{10,21}

This report details a small study in two oncology wards of a large district teaching hospital, where the handling of these drugs has been implemented under COSHH and good work practices are in use. Urine drug levels, and surface and disposable glove contamination were studied using the measurement of four marker cytotoxic drugs. The drugs investigated were cisplatin and carboplatin by platinum measurements, methotrexate, cyclophosphamide, and, for the latter part of the study, ifosfamide.

POPULATION AND METHODS

The subjects were volunteers who worked on one of two adult oncology wards (A and B). Both wards are in the same medical directorate within the hospital's management structure, and the responsibility for carrying out risk assessments and establishment of policy guidelines for appropriate control measures lies with the management of this directorate. Such

Table 1 Surface contamination in wards

	Position	Platinum	CP	Ifos	MTX
Ward B	Handle and door of storage fridge	9.5 ng as metal; (15 ng as cisplatin; 18 ng as carboplatin)	ND	10 ng	17 ng
Ward B	Bench in "prep" room (0.5 m × 0.5 m)	10 ng as metal	ND	5 ng	19 ng
Ward B	Top of pulper in sluice room (0.5 m × 0.5 m)	259 ng (1036 ng.m ⁻²)	ND	131 ng (524 ng.m ⁻²)	12 ng
Ward A	Handle and door of storage fridge	6 ng as metal; (9 ng as cisplatin; 11 ng as carboplatin)	ND	ND	17 ng
Ward A	Prep bench (0.5 m × 0.5 m)	<1 ng as metal	ND	ND	15 ng
Ward A	Top of pulper in sluice room (0.5 m × 0.5 m)	<1 ng as metal	312 ng (1248 ng.m ⁻²)	ND	15 ng
Ward A	Rim of sluice	2 ng as metal	843 ng	ND	11 ng
Blank floor wipes	Taken at HSL no exposure (0.7 m × 0.7 m)	1 ng as metal	ND	ND	12 ng

Results expressed as total amount or amount per square metre. Ward A used large doses of cyclophosphamide, ifosfamide, and methotrexate. Ward B used large doses of platinum containing drugs.
CP, cyclophosphamide; Ifos, ifosfamide; MTX, methotrexate; ND, non-detected.

Table 2 Glove contamination by platinum, cyclophosphamide (CP), ifosfamide (Ifos), and methotrexate (MTX)

Source of gloves	n	Platinum	CP	Ifos	MTX
Ward A: drug administration team	5	5.05 (3.4–6.8)	ND	ND	ND
Ward A: other ward duties	4	1.4 (0.4–2.4)	ND	ND	ND
Ward B: drug administration team	3	19.5 (5.8–36)	ND	673 (ND–1806)	34.7 (ND–49.3)
Ward B: other ward duties	4	3.1 (2.4–4)	2.8 (ND–11.2)	5.2 (ND–20.9)	11.8 (ND–27)
Blank disposable latex glove	2	<1	ND	ND	<20
Detection limits (ng/glove)		0.24	5	5	18

Gloves collected on an ad hoc basis from drug administration nursing staff, and those undertaking other ward duties where the wearing of disposable glove is usual.
Results are quoted as mean (range) in ng/glove.
Ward A used large doses of cyclophosphamide, ifosfamide, and methotrexate. Ward B used large doses of platinum containing drugs. ND, non-detected.

Cyclophosphamide was measured by adaptation of a method described by Sessink and colleagues.²² Briefly, urine is extracted twice with ethyl acetate and derivatised with trifluoroacetic anhydride. This derivative was then extracted using hexane and measured by gas chromatography-mass spectrometry. The detection limit was 1 nmol/l. Later analyses allowed measurement of levels of ifosfamide in the same chromatographic run. Urinary platinum was measured using electrothermal vaporisation coupled to inductively coupled plasma mass spectrometry, adapted from Shramel and colleagues.²³ Basically, urine samples and standards are matrix matched with a final nitric acid concentration of 0.66% (v/v). Internal standardisation using iridium was used to correct for matrix suppression. The detection limit was 9 pmol/l and the coefficient of variation was 12.4%. This method has adequate sensitivity to quantitate levels of urine platinum in a high percentage of control subjects who have only environmental exposure to platinum. This environmental exposure is probably caused by platinum released from vehicle catalytic converters.

Methotrexate was measured using an in-house developed enzyme linked immunoassay which has a lower detection limit of around 2 nmol/l. Calibration for urine analyses was performed using blank urine spiked with the drug.

The surface wipe samples and whole gloves were extracted by continuous mixing for three hours with 20 ml of ultra pure water and then subsequently analysed as urine samples. Recoveries of wipes spiked with respective drugs had been shown to be 91% (±13%) for platinum containing drugs, 67% (±18%) for cyclophosphamide, and 97% (±21%) for methotrexate. Recoveries of latex gloves spiked on the inside surface of the glove with drug and dried for three hours at room temperature were 67% (±15%) for platinum containing drugs,

120% (±23%) for cyclophosphamide, and 82% (±13%) for methotrexate.

RESULTS

Cyclophosphamide or methotrexate were below the analytical detection limit in all urine samples collected in both the cross sectional and longitudinal elements of this study. Urinary platinum levels were not significantly different to those found in the control group using the non-parametric ANOVA, Kruskal-Wallis test (fig 1). The surface wipe samples showed a similar pattern of contamination on both wards (table 1). The area where the drugs are stored and checked ready for administration showed little or no level of contamination. In contrast in the sluice room, the pulper unit and sluice showed a greater level of contamination. The contamination followed the relative usage of the different drugs on the two oncology wards.

No cyclophosphamide, ifosfamide, or methotrexate was detected on any glove collected from ward A (table 2). In contrast, two of the latex gloves collected from those administering cytotoxic drugs on ward B had significant contamination. One glove was contaminated with 1806 ng ifosfamide, 36 ng platinum, and 34 ng methotrexate; the other contaminated glove had 214 ng ifosfamide, 14 ng platinum, and 49 ng methotrexate. Much lower levels of glove contamination were noted on those gloves from ward B staff undertaking other nursing duties. Very low level platinum contamination was noted on most of the collected gloves.

The demographic data from the questionnaires (n = 29) suggested a largely female staff of reproductive age (86% female, with a mean age of 31 years, range 24–49 years). One of these staff reported having recently stopped being involved in administering cytotoxic drugs, in line with the hospital

policy, as she was pregnant. Nursing staff who administered cytotoxic drugs reported usually handling them on every shift and up to several times a shift, although the amounts of drugs handled varied considerably. On average, they had been administering cytotoxic drugs for 3.4 years. All staff reported wearing latex gloves, plastic armlets, and aprons when administering cytotoxic drugs. Eye protection tended not to be worn, even when administering the drugs (only 4/15 infusion team staff), and masks were not used at all. The use of gloves and plastic aprons were almost invariably used for contact with patient body fluids, but vinyl gloves as well as latex gloves may be used for these operations. Gloves were infrequently used when bathing or washing patients, or making beds; their use related to the infectious status of the patient rather than cytotoxic drug hazard. The questionnaires suggested that 10 reportable incidents concerning cytotoxic drugs had occurred in the past 10 months and all had been reported through the hospital's reporting scheme. No incidents occurred close to the period of this study. The majority had occurred on ward B and involved spillages, extravasation problems, leakage from taps, and connections to infusion bags.

DISCUSSION

This small study appears to be the only recent UK investigation of exposure of nursing staff on oncology wards to cytotoxic drugs. In contrast, many previous published, non-UK studies were of either pharmacy workers^{13 16 17} or nurses who undertook a significant amount of drug reconstitution or preparation as well as administering the drugs to the patient.^{6 24} Current good practice in the UK has been to reduce to an absolute minimum the amount of preparation of drug that the administration/infusion nurses undertake on the wards, with specialised pharmacy units undertaking the drug preparation, and the drugs being administered by specially trained nursing staff.

It is reassuring that no drug was detected in any urine sample. Studies, albeit using intravenous clinical doses, have suggested that most of any intact cyclophosphamide excreted, which is about 10% of the internal dose, is excreted within 24 hours of dosing. Likewise 80% of absorbed methotrexate, 30% of cisplatin, and 50% of carboplatin would be recovered as either parent compound or elemental metal within 24 hours of dosing.^{25–28} The data in these studies suggest that the apparent half lives of urinary excretion are roughly 5 hours for methotrexate, 12–24 hours for cyclophosphamide or ifosfamide, 72 hours for cisplatin, and 24 hours for carboplatin. Using the toxicokinetic model of Droz and Fiserova-Bergerova,²⁹ these half lives suggest that urine measurements for these chemicals may be largely influenced by exposure in the previous 24 hours. However, for those drugs where half lives are in the order of 24–72 hours, the urine measurement may more strongly reflect the extent of exposure over the previous week.

The use of urinary rather than blood measurements in occupational exposure assessment is common because of their wider acceptability to workforces and practicality of collection. These factors would allow wider scale studies of exposure to these cytotoxic drugs in other clinical and non-clinical settings.

The level of platinum in the urine of nurses and controls reflects the general level of elemental exposure to this metal, probably from vehicle catalytic converters. The urine platinum results shown in fig 1 were expressed corrected for creatinine as this has been confirmed as a useful way of expressing such data.³⁰ The lack of any detectable cyclophosphamide found in this study is in contrast to a recent Turkish study of nurses, where 40% of all urine sample were greater than our detection limit (1 nM).⁶ However, these nurses were using only rudimentary precautions as well as undertaking an element of drug reconstitution. Minoia and colleagues³¹ found

in a study of two Italian hospitals that around 30% of urine samples had cyclophosphamide levels greater than our detection limit for nurses administering cytotoxic drugs.

A limited amount of low dose cyclophosphamide data allows calculation of the urinary detection limits in terms of absorbed or external dose. A human volunteer study suggested that a dermal application of 1 mg of cyclophosphamide resulted in 1% of this applied dose being excreted in urine unchanged.²⁴ However, single dosing studies in rats suggested that 5% of a larger dermal, ingested, or intratracheal dose of 1 mg/kg cyclophosphamide was excreted unchanged within 24 hours. Therefore, the detection limit of our cyclophosphamide assay may approximate to a potential dermal exposure in the order of 40 µg in the previous 24 hours. It must be emphasised that a “non-detected” urine result does not signify no exposure or risk. Based on the cancer risk assessment by Sessink and colleagues,³² continuing uptake of cyclophosphamide commensurate with our current urine detection limit may represent an annual cancer risk of 3–20 per million.

Interestingly, Minoia and colleagues³¹ found levels of cyclophosphamide and ifosfamide of between 20 and 11 800 ng/glove on the inside of latex gloves used by the nurses administering drugs. We have reservations concerning the feasibility of removing disposable, clinical gloves without potentially introducing contamination onto the inner surfaces of the glove, which is why we preferred analysing contamination on the whole glove. In any case we suggest that the data of Minoia *et al* imply higher levels of potential dermal exposure than found in our study. McDevitt and colleagues¹⁵ did not undertake any biological monitoring in a study of an outpatient chemotherapy department operating to the 1986 OSHA guidelines, but reported considerable levels of cyclophosphamide surface contamination on countertops in the administration facility (up to 270 000 ng/m²). Such levels are much larger than those found in the most contaminated areas of our study, which were in the sluice room (1248 ng/m²) and outside the sluice room where we found little or no surface cytotoxic drug contamination.

It is noted that this is a limited study and we may need to be cautious about its representative nature of normal levels of exposure and contamination, and especially after a spillage. However, it highlights that monitoring the extent of occupational exposure to cytotoxic drugs in the clinical setting is feasible using environmental or biological monitoring techniques for some of the commonly encountered drugs. The study may also emphasise several other points. Firstly, undertaking appropriate risk assessments and implementing control measures may have significantly reduced the risk to oncology ward staff from that highlighted in earlier, non-UK published reports. These measures include the clear separation of the clinical roles of drug preparation and administration, emphasis on well trained, specialised teams administering the cytotoxic drugs, and the invariable use of disposable latex gloves to lessen skin-drug contact. There is the continuing potential for spillages during administration, as the rate of reportable incidents showed, as well as our finding of a contaminated latex glove from a member of an infusion team. Since there is some uncertainty on the rates of permeation through latex gloves by cytotoxic drugs, it is sensible to reinforce the continuing use of good quality gloves which are changed frequently. Consideration of using gloves made of nitrile rather than latex may be appropriate to lessen the risk of latex sensitisation. The relative under use of eye protection to protect against generated drug aerosols or accidental splashes in those administering the drugs diverges from recent guidance¹⁰ and opinion within the specialist health services sector of the Health & Safety Executive (personal communication). However, this under use of eye protection parallels recent data on Dutch oncology nurses where 91% of those administering cytotoxic drugs wore gloves, but only 3% used any form of eye

protection.³³ In contrast there has been a recent increased clinical use of eye protection to protect against virus containing blood aerosols. Eye protection which is unobtrusive and does not lead to heightened, undue concern in patients is now available, which is the argument often proposed against goggles and face visors as protective equipment.

Some concerns remain about cytotoxic contamination around ward sluice areas derived from handling patients' urine collections containing active drug and where less trained staff, perhaps not so conscious of potential hazards, may work. Overall the results suggest that appropriate implementation of recent guidance on ward handling of cytotoxic drugs has reduced the risk of drug exposure. It should be noted that cytotoxic drugs are also encountered in domiciliary oncology treatment, veterinary medicine, and hospital pharmacy departments. There appears to be no UK data on the nature and efficacy of current control measures in these situations.

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