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.

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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to-toxins handbook and a Royal College of Nursing technical report. 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. We can find no recent published data for clinical staff in the UK. Current good practice 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. 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, 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.

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
risk assessments and establishing control measures were performed in consultation with the hospital’s risk manager, occupational health department, and senior pharmacy staff. Policies on work practices and control measures in both wards are similar.

All staff on these two wards were given the opportunity to participate after explanation of the study by the hospital trust’s occupational health registrar. Volunteers were divided into three work-activity groups based on their potential for exposure to cytotoxic drugs.

One group consisted of those staff who administered cytotoxic drugs by intravenous injection or infusion system—“infusion team staff”. This is a nurse led activity, where all staff administering cytotoxic drugs as part of an infusion team have undergone a formal three month in-house training scheme, which covers clinical aspects of drug administration and health and safety issues associated with their use. The second group consisted of those nursing staff who did not administer cytotoxic drugs, but who were involved in patient care on the ward prior to, during, and after treatment with cytotoxic drugs. The third group consisted of staff who worked on the ward but were not involved in patient care. This included clerical, auxiliary, and domestic staff. None of these three groups were involved in drug formulation or preparation of the drugs for each patient are delivered from the pharmacy ready for use. However, infusion team staff have to undertake some manipulation of infusion bags, giving sets, lines, and syringes in order to ensure appropriate delivery of drugs to the patient.

The aggressive nature of many of these cytotoxic drugs treatments can lead to patients vomiting and contaminating bed linen with body fluids. Contaminated bed linen is taken to the sluice room, where it is double bagged and labelled “cytotoxic contaminated”. All urine from patients under cytotoxic treatment is collected and the urine volumes measured to check the hydration status of patients. The volume measurement of urine is carried out in the sluice room and the subsequent disposal of urine is via the sluice. A pulper or masher unit in the sluice rooms of one of these wards was used to pulp the disposable urine containers ready for incineration. Because of limited working space in the sluice rooms, the tops of pulper units in both wards were used as work surfaces for voluming the patients’ urine.

A questionnaire on working practices was sent to the staff prior to the study. General information on the subjects’ demographic characteristics, their experience of chemotherapy work, and level of current activity was sought. Questions on the use of personal protective equipment and the level of accidents with any cytotoxic drugs over the past year were also collected. A control group for urine measurements consisted of volunteers from the hospital’s occupational health department.

Ward A has 14 beds in single rooms and a small day treatment room. This ward is involved with haematological oncology where there is regular use of cyclophosphamide and methotrexate. Ward B is a 16 bedded, largely open plan oncology ward where there is frequent and high dose use of platinum containing drugs such as cisplatin and carboplatin. Sampling was arranged to be carried out during the normal treatment workload for cancer patients on both wards, but also to ensure it coincided with a high dose treatment using at least one of the marker drugs administered by one of the infusion teams. The urine collections on ward A were made following high dose infusions of 5.5 g cyclophosphamide and 2.9 g methotrexate to two different patients. Thirty end of shift urine samples were collected, 12 from those who administer the drugs, 12 samples from staff who do not administer the drugs but are involved in patient care, and eight samples from other staff who work on the ward. Urine collections on ward B were during a five day platinum infusion therapy (350 mg in total administered to this patient) among other ongoing treatment regimes on the ward; end of shift samples were collected from relevant ward staff. Nine samples were obtained from staff administering drugs, five samples from those involved in patient care, and nine samples from those who work on the wards but are not involved in patient care.

During a high dose cyclophosphamide treatment regime (8.6 g administered over two days), three nursing staff on ward A were studied longitudinally. Urine samples were collected at the end of each daily shift by these staff over a working week from the beginning of the dosing regime. Twenty urine samples were collected in this longitudinal study. There were no reported drug spillages or accidents during any period of the urine sampling. All urine samples were collected in 25 ml Sterilin bottles from staff and immediately stored in a −20°C transportable freezer which was located on the ward. Samples were kept frozen until analysis.

Surface wipe samples were taken from the bench in ward B, where drugs were checked ready for administration to the patient, the handle and door of the refrigerator where the drugs were stored, and the top of the pulper unit used for disposing of urine containers in the sluice room. In ward A, wipe samples were taken from the handle and door of the refrigerator used to store the drugs, the small preparation bench where drugs were checked, and the top of the pulper unit in the sluice room and the rim of the sluice itself. The samples were collected using a method from previous studies investigating surface contamination by methotrexate and cyclophosphamide. It was carried out by wiping thoroughly the surface with four Kleenex professional wipes (20 cm × 21 cm, Kimberly Clark) which had been wetted with 10 ml of 30 mM sodium hydroxide. Where possible defined surface areas were wiped; for background levels, 0.5 square metre areas of floor surface in non-contaminated areas were tested. All the wipes samples were collected into sealed plastic bags and kept at −20°C until analysis.

Disposable gloves were collected on an ad hoc basis from staff working on wards. Several staff who had worn the gloves as part of their usual personal protective equipment for specific work activities retained the gloves rather than discard them. The gloves were collected into sealed plastic bags and kept at −20°C until analysis. Nine gloves were collected from ward A and seven gloves from B. The gloves could be identified as belonging to a member of the cytotoxic drug administration team or nursing staff carrying out other ward duties.

Figure 1  Urinary platinum results expressed as mmol/mol creatinine.
Cyclophosphamide was measured by adaptation of a method described by Sessink and colleagues. 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 0.24 ng/glove. 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 spectometry, adapted from Shramel and colleagues. 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 convertors.

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 performed using blank urine spiked with the drug. 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.

Table 1  Surface contamination in wards

<table>
<thead>
<tr>
<th>Position</th>
<th>Platinum (ng as metal)</th>
<th>CP (ng)</th>
<th>Ifos (ng)</th>
<th>MTX (ng)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ward A: Handle and door of storage fridge</td>
<td>9.5 ± 1.5</td>
<td>ND</td>
<td>10 ± 2</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>Ward B: Bench in &quot;prep&quot; room (0.5 m × 0.5 m)</td>
<td>10.0 ± 1.5</td>
<td>ND</td>
<td>5 ± 1</td>
<td>19 ± 3</td>
</tr>
<tr>
<td>Ward A: Top of pulper in sluice room (0.5 m × 0.5 m)</td>
<td>259 ± 12</td>
<td>ND</td>
<td>131 ± 5</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>Ward A: Prep bench (0.5 m × 0.5 m)</td>
<td>6.0 ± 1.5</td>
<td>ND</td>
<td>17 ± 3</td>
<td></td>
</tr>
<tr>
<td>Ward A: Top of pulper in sluice room (0.5 m × 0.5 m)</td>
<td>&lt;1 ± 0.2</td>
<td>ND</td>
<td>15 ± 3</td>
<td></td>
</tr>
<tr>
<td>Ward A: Rim of sluice</td>
<td>2.0 ± 0.5</td>
<td>ND</td>
<td>11 ± 3</td>
<td></td>
</tr>
<tr>
<td>Blank floor wipes Taken at HSL no exposure</td>
<td>1 ng as metal</td>
<td>ND</td>
<td>12 ng</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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.
expressing such data. Creatinine as this has been confirmed as a useful way of reflecting the general level of elemental exposure to this metal, settings.

These cytotoxic drugs in other clinical and non-clinical studies. These factors would allow wider scale studies of exposure to occupational exposure assessment is common because of their toxicokinetic model of Droz and Fiserova-Bergerova, allowing 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. 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, 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 colleagues 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 colleagues 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 even in 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 the continuing uptake of 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 guidance 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

**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 or nurses who undertook a significant amount of drug reconstitution or preparation as well as administering the drugs to the patient. 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. 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, 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. 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). However, these nurses were using only rudimentary precautions as well as undertaking an element of drug reconstitution. Minoia and colleagues 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.

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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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