Contamination from handling cytotoxic agents

Contamination of personnel who handle cytotoxics has been proven via traces in urine. Despite safety standards for handling cytotoxics, operators can still be exposed to them, mainly through skin contact. Identification of sources of contamination is recommended to improve working procedures.

Previous studies

Studies of contamination on vials, plungers of syringes, gloves, infusion bags, and work surfaces have been published.

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Vials

Some authors have measured the amount of cytotoxic drug present on the outer wall of vials containing these agents, on receipt from the pharmaceutical supplier. A significant number of vials had a quantifiable level of external contamination (up to 2.5 ng of 5FU per vial) [1-3].

Plungers of syringes

The contamination of the plungers of syringes used for handling cytotoxic drugs was measured [4]. The results showed that all the plungers were contaminated, amounts varying from 3.7 ng to 445.7 ng of cyclophosphamide.

Gloves

Gloves offer the first line of protection when handling cytotoxic drugs and are frequently in contact with these agents. A few studies showed that gloves used for biological safety cabinets (BSCs) were frequently (42–100%) contaminated during preparation of the drugs and cleaning of the hood [4, 5]. Favier et al. showed a contamination rate of 100% after only one dose was prepared. The amounts of cytotoxic agent detected were significant: Sessink et al. demonstrated up to 87 μg, and Favier et al. 180 μg [5, 6]. Because of the number of potential sources of contamination (drug preparation, vials, syringes, infusion bags, various surfaces), it is almost impossible to prevent contamination on the outside of gloves during normal work. Therefore changing gloves is recommended at least every 30 minutes. In addition, the quality of gloves must be carefully checked as shown by Wallemacq et al. [7].

Infusion bags

Infusion bags are an important source of contamination of gloves and environment. Studies carried out on the external surface of bags prepared in a pharmacy have shown that they became contaminated with cytotoxic agents, independent of the equipment used for their preparation (isolators or BSCs) [8, 9]. Favier et al. [8] found measurable amounts of 5FU on infusion bags varying from 70% to 100% for isolators, and 10% for BSCs.

Work surfaces

In several publications, surface contamination with different cytotoxic drugs (mainly cyclophosphamide, ifosfamide, 5FU and methotrexate) was estimated using a wipe sampling method [5, 8-10]. These studies were carried out on different surfaces, inside and outside the isolators and BSCs. The samples selected were potentially contaminated areas such as the work surface inside the isolator or the BSC, the floor in the preparation room, computers and furniture. Substantial levels of several antineoplastic agents were detected at various sites in drug preparation areas, whatever the equipment used. For example, Connor et al. indicated that 76% of the pharmacy samples were contaminated with measurable amounts of cytotoxic drugs.

Rhône Alpes studies

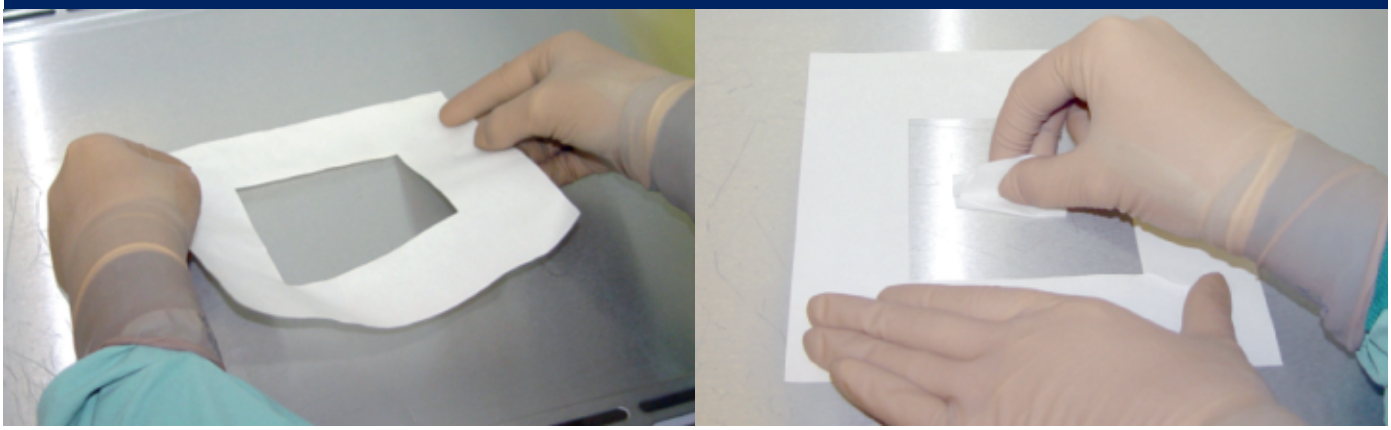
In 1999 we carried out a similar study in six French hospitals that perform between 3,500 and 26,500 preparations per year with the objective of determining the level of contamination with 5FU of different cytotoxic drug preparation units, three using BSCs and three using isolators [8]. The main results were:

- A higher rate of contamination inside and outside isolators compared with BSCs, with measurable amounts of 5FU detected in 79.2% (19/24) of the surface samples within isolators and 8.3% within BSCs (1/12). In the preparation rooms, 29.6% (8/27) of the surface samples outside isolators were found contaminated and no positive samples outside BSCs (0/29).
- 86.2% (25/29) of the samples collected on the outside of infusion bags prepared within isolators were contaminated but only 3.3% within BSCs (1/30).

In 2007, we carried out a larger study in 30 hospitals of the French Rhône Alpes region that are monitored by the ONCORA cytotoxics laboratory. The aims of this study were to measure the contamination with 5FU at various hospital sites (including the drug preparation and administration areas), to observe practices during the preparation of cytotoxic drugs and to make a comparison with the 1999 study.

The sampling locations were selected as potential areas of contamination on the basis of the results of previous studies. In each cytotoxic drug preparation unit, at least two samples were collected on the work surface within BSCs or isolators (one before cleaning and one after in order to evaluate the effectiveness of the decontamination procedures). Four more samples were also taken: two samples on the outer operator's gloves

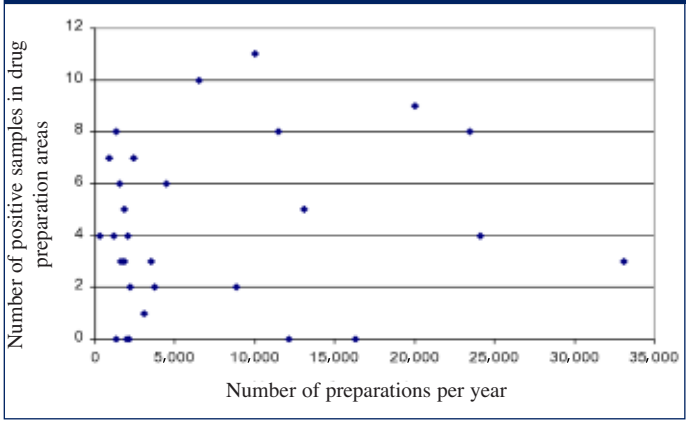
Figure 1: How we obtained standard samples from flat surfaces



and two on the outside of infusion bags. In addition, it was possible to get samples in some outpatient clinics. Samples from objects and surfaces were performed with moistened filters wiping calibrated surfaces when possible (for gloves and infusion bags, immersion in distilled water was used), see Figure 1. The preparation of cytotoxic drugs was centralised under the control of a pharmacist in 24 hospitals, 16 using BSCs and eight using isolators. It was under the responsibility of nurses in the last six hospitals, all equipped with BSCs. The number of doses prepared ranged from 325 to more than 33,000 per year. The preliminary results on the 555 collected samples were:

- Measurable amounts of 5FU were detected in 28% of the samples collected in preparation areas and 23% in the administration areas.
- A high rate of contamination of the outer preparation gloves (more than 60%) and a 20% rate of contamination of infusion bags were found. Some gloves were heavily contaminated.
- The level of contamination in the immediate preparation areas did not correlate significantly with the number of doses of chemotherapy prepared per year (see Figure 2). This confirms the importance of establishing strict working procedures under the control of a pharmacist.
- If we compare the results of the first two groups of hospitals performing preparation under the control of a pharmacist with BSCs or with isolators to those of the preliminary study, we still find a difference in terms of contamination between the two techniques, but with a smaller gap, suggesting that operating procedures have been improved.
- In the areas where the drugs are administered, many samples taken on nurses' gloves after they had connected or disconnected infusion bags were found to be contaminated. 5FU was detected in nearly half of the samples, but the number of samples collected was a little bit too low (only 18 samples collected): these preliminary results need to be confirmed by a larger study of contamination at the time of administration.

Figure 2: Contamination does not correlate with number of doses prepared



Conclusion

Contamination studies show that occupational exposure of workers handling cytotoxic agents can be controlled only if all the possible sources of contamination are identified and if suitable systems of protection are used. The validation of work procedures should include surface analysis of critical points such as gloves and various surfaces in pharmacies and wards. In addition, initial and continuing education of technicians, pharmacists and nurses is highly recommended to obtain as low a level as possible of cytotoxic contamination.

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Medical devices for safe handling of cytotoxic drugs

The main objectives of these devices are to protect patients against bacterial contamination and healthcare workers against chronic exposure to chemical contamination. Many manufacturers have developed medical devices for the safe reconstitution of cytotoxics.

For many years, the use of chemotherapy has been growing considerably. Because of the increase in this activity and the risk incurred by healthcare workers when handling cytotoxic drugs, safety devices have been developed to improve quality in the preparation of these drugs. Pharmacy technicians also require training.

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Selection criteria for medical devices

Limitation of contamination

The imperative to limit both microbial and chemical contamination has led to the adoption of closed systems. According to the American Society of Health-System Pharmacists (ASHP), closed-system drug-transfer devices mechanically prevent the transfer of environmental contaminants into the system and the escape of drug or vapour out of the system [1]. This echoes the definition adopted by the National Institute for Occupational Safety and Health (NIOSH) [2]. This definition, taking into account drug vapour, clearly indicates that air-venting devices, even those with a 0.20 μm filter membrane, are not strictly closed-system devices. The recommendations of the GERPAC-Europharmat workgroup (the French isolators users' group - *Les Journées Nationales d'Etudes sur les Dispositifs* Médicaux) based their definition on that of the ASHP, but specified that closed systems should protect the operator against the escape of vapour, liquids and solids [3].

Compliance with these recommendations cannot be considered a substitute for ventilated cabinets or isolators.

Avoidance of needle risks

Avoiding the use of needles achieves several goals. Needles increase the risk of operator exposure to cytotoxic drugs by contact or injection. Moreover, the absence of a needle is a good way to decrease contact with liquid aerosols. These are caused by drug droplets squirting out, when the needle is withdrawn from the vial, if overpressure has been caused during manipulation. For these reasons, ASHP, GERPAC and Europharmat recommend needleless systems if possible. Unfortunately, the use of air-venting systems is not always possible, e.g. if the vial opening is too small, or for soap solutions. Needles are necessary in such cases. A needle safety transfer device may protect operators against the risk of puncture, but does not decrease the risk of aerosol formation.

Container–contents interactions

It is important to take into account the possible physicochemical interactions between anticancer drugs and the device. In particular, devices containing plasticisers such as PVC should be avoided as much as possible [4-6]. It is then preferable to use devices made of polyolefins (polyethylene, polypropylene) or polyurethane. In addition, chemical contaminants from the surroundings cross the wall of a device (permeation). It can occur during sterilisation with peracetic acid [7] or hydrogen peroxide. Permeation through medical devices is a potential toxic risk to the patient and the loss of stability of the drug may be revealed by a pH change.