2007

Safe handling of cytotoxics

Sewell, GJ

Hospital Pharmacy Europe

Safe handling of cytotoxics

Despite the adoption of standard protective measures, healthcare workers are still exposed to cytotoxic drugs. The risks to the operator and the environment may be reduced by considering effective decontamination and intervention methods

Sarah Roberts
BSc

PhD Student

Department of Pharmacy and Pharmacology
University of Bath
Bath
UK

Graham Sewell
PhD

Professor

Department of Pharmacy
Kingston University
Kingston-upon-Thames
UK

E: s.roberts@kingston.ac.uk

To protect the worker when handling cytotoxic drugs, more is needed than careful use of personal protective equipment and techniques. Despite the implementation of collective protective measures, many international studies have demonstrated levels of cytotoxic contamination in the surrounding environment and in the urine of operators.[1–6] The risk posed by cytotoxic drugs to the operator and the environment may be reduced, if not eliminated, by considering additional approaches: firstly, the application of effective decontamination methods, and secondly, the use of intervention (ie, a closed-system drug transfer device).

Routes of exposure

Cytotoxic contamination in the workplace and subsequent worker exposure may arise from several sources, even in the absence of manipulation errors. Figure 1 shows leakage onto the base of the isolator chamber which occurred when quinine sulphate was used as a fluorescent marker simulating cytotoxic manipulation in an isolator. The event occurred when withdrawing a syringe needle after addition to an infusion bag. Such surface contamination could be transferred to any surface coming into direct contact with it (eg, contact with gloves could later result in dermal exposure through glove penetration, or in transfer of contamination to further surfaces).[7] Successive use of the same syringe has also been implicated as a source of glove contamination by cyclophosphamide and of potential dermal contact with cyclophosphamide.[8]

If such surface contamination were not immediately removed, it could dry out, become airborne and contribute towards inhalation. It has been suggested that dried drug particles on surfaces or on the high-efficiency particulate air (HEPA) filter of the isolator or biological safety cabinet (BSC) may act as a reservoir, providing a source area from which molecules could slowly vaporise.[9] Some drugs, such as cyclophosphamide, can vaporise at room temperature or higher – and certainly, temperatures higher than room temperature may be reached under normal conditions in which cytotoxic drugs are manipulated, with factors such as continual running of isolators and BSCs, and ongoing use of ancillary equipment such as lighting and pump motors.[10]

Production of aerosols has also been demonstrated as a source of contamination when applying techniques used to reconstitute and dilute cytotoxic drugs.[11,12] Oral ingestion or accidental dermal exposure from needlestick injuries, spillages or breakages could also occur.[13] These events happen relatively less often, but can contribute to airborne and long-term workplace contamination.

Precontaminated sources taken into the environment before any manipulations are carried out will contaminate gloves and any surfaces subsequently touched. It has been demonstrated that the external surfaces of drug vials may be contaminated with the drug contained, which could also contaminate packaging. Levels found varied according to origin, indicating that precautionary measures taken are not standardised.[14–17] Contamination on vials' external surfaces may occur due to splashing, foaming or dusting during the filling process. This may be reduced by vial washing and subsequent application of protective sleeves.[14]

In the UK and France, current practice in hospital pharmacies is to use negative-pressure isolators.[18] Isolators offer containment, but there is no evidence for their superiority over BSCs. Isolators have their limitations and there is the potential for contamination to pass through hatches from the main chamber to the environment. Cytotoxic contamination has been reported on interior surfaces and on surfaces of the finished product in isolators and BSCs.[19]

If vaporisation were a common occurrence, the HEPA filters of both isolators and BSCs would not be effective in retaining molecules of cytotoxic vapour smaller than the filter's pore size. As a result, any cytotoxic aerosols generated would pass through the filter and be released into the environment. Therefore, whichever source is used, it is paramount to operator protection that the air be exhausted externally, away from the working environment.[13]

Guidelines

Recommendations on good practice have been produced by the Occupational Health and Safety

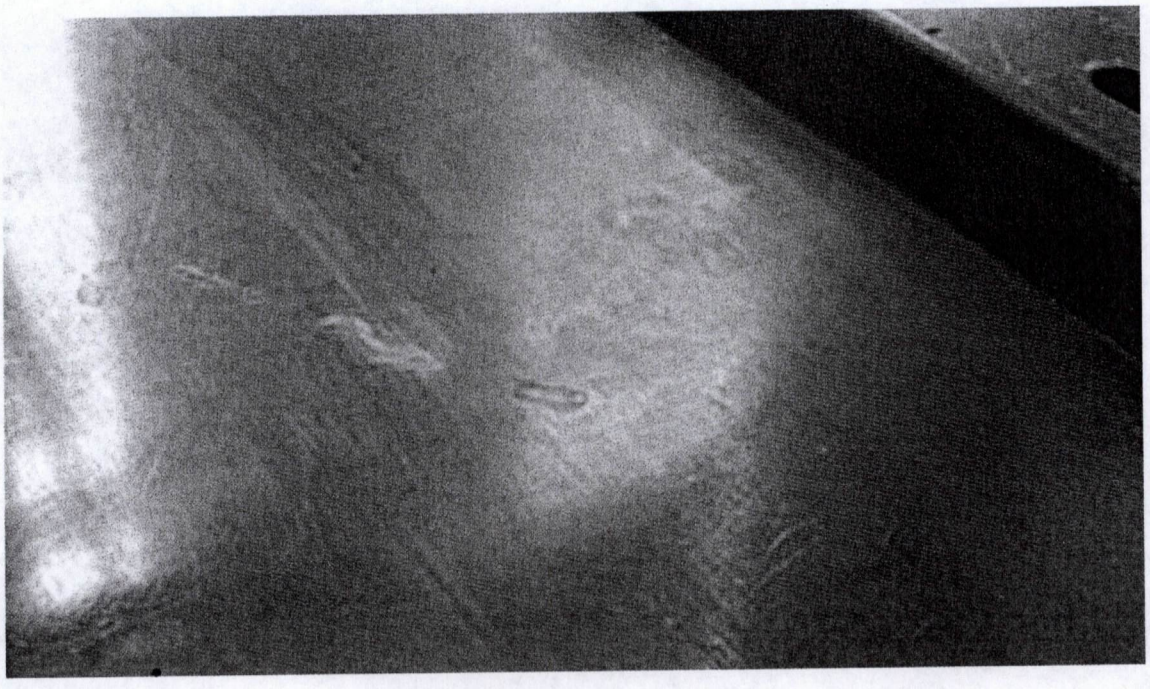

Figure 1. Contamination from a solution of quinine sulphate produced when withdrawing a syringe after addition to an infusion bag

Administration and the American Society of Health-System Pharmacists in the USA; by the International Society of Oncology Pharmacy Practitioners; by the Health and Safety Executive and the Royal College of Nursing, and the Management and Awareness of the Risks of Cytotoxic Handling group in the UK.[20–24]

Decontamination methods

EPA

Agents chosen for decontamination in areas where cytotoxic drugs are compounded are mainly intended for biological decontamination. Decontamination protocols should be carefully designed and validated to confirm a biological "kill", and likewise to confirm the removal or chemical degradation of cytotoxic drugs. Different biological agents have varying modes of action and efficacies against different micro-organisms; the same applies to cytotoxic drugs, which represent a diverse range of chemical structures.

It is recommended that all surfaces be cleaned according to a protocol, which includes an appropriate deactivation agent to facilitate the removal and/or breakdown of biological and chemical contamination.[13] Water-soluble cytotoxic drugs should be removed using wipes impregnated with an aqueous-based agent which binds the target drug, and the wipe should be disposed of afterwards.[25] The drug would be more likely to be picked up by applying a detergent formulated at a pH at which the target drug is ionised. One should consider the possibility that surface contamination may take the form of multidrug chemical contamination, since cytotoxic drugs are frequently handled simultaneously; here, a combination of agents may be required. The chemistry of any breakdown products (which may retain cytotoxic activity) should also be considered alongside removal of the target drug. Wiping with industrial methylated spirit is common practice, but may also play a part in the removal of less water-soluble drugs and degradation products.[25]

Intervention with closed-system containment device

The US National Institute for Occupational Safety and Health recommends the use of a closed-system drug transfer device to prepare cytotoxic drugs, and this has been acknowledged by the relevant European directive and by international guidelines.[13,23,26–28]

Studies carried out at research centres worldwide, using the PhaSeal® closed-system drug transfer device have all demonstrated a significant reduction of contamination.[29-33]

Preventing contamination at source is more effective than trying to remove the contamination once it has occurred. Eliminating the primary contamination event will also prevent secondary contamination of areas outside the immediate drug environment.[30]

However, while closed-system devices may have a role in minimising staff exposure, one cannot recommend that they replace trained pharmacy staff using personal protective equipment and a pharmaceutical isolator.[34] Containment by the device

Resources

US Occupational Health and Safety Administration
W: www.osha.gov

American Society of Health-System Pharmacists
W: www.ashp.org

International Society of Oncology Pharmacy Practitioners
W: www.isopp.org

UK Health and Safety Executive
W: www hse.gov.uk

UK Royal College of Nursing
W: www.rcn.org.uk

Management and Awareness of the Risks of Cytotoxic Handling (MARCH)
W: www.marchguidelines.com

can only be achieved in the area in which the device is used – there would be no influence over pre-contaminated sources brought into the pharmacy.

Conclusions

Despite the adoption of standard protective measures, healthcare workers continue to be exposed to cytotoxic drugs. Targeting decontamination to the chemistry of the drugs used should be considered, as should the implementation of a closed-system device. Manufacturers should also be encouraged to improve their decontamination procedures and to guarantee the supply of vials free of cytotoxic contamination. ■

References

1. Favier B, Gilles L, Desage M, Latour JF. Urinary cyclophosphamide excretion of pharmacy technicians handling antineoplastic drugs. *Bull Cancer* 2003;90:905-9.

2. Mason HJ, et al. Exposure to antineoplastic drugs in two UK hospital pharmacy units. *Ann Occup Hyg* 2006;49:603-10.

3. Pethran A, et al. Uptake of antineoplastic agents in pharmacy and hospital personnel. *Int Arch Occup Environ Health* 2003:76:5-10.

4. Sessink PJM, Anzion RBM, Petra HH, Bos RP. Detection of contamination with antineoplastic agents in a hospital pharmacy department. *Pharmaceutisch Weekblad* 1992;14:16-22.

5. Sessink PJM, et al. Occupational exposure to antineoplastic agents at several departments in a hospital. *Int Arch Occup Environ Health* 1992:64:105-12.

6. Sessink PJM, et al. Environmental contamination and assessment of exposure to antineoplastic agents by determination of cyclophosphamide in urine of exposed pharmacy technicians: is skin absorption an important exposure route? *Arch Environ Health* 1994;49:165-9.

7. Connor TH. Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs. *Am J Health-Syst Pharm* 1999;56:2450-53.

8. Favier B. Contamination of syringe plungers during the sampling of cyclophosphamide solutions. *J Oncol Pharm* 2005;11:1-5.

9. Kiffmeyer TK, et al. Vapour pressures, evaporation behaviour and airborne concentrations of hazardous drugs. *Pharm J* 2002;268:331-7.

10. Connor TH, Shults M, Fraser MP. Determination of the vaporization of solutions of mutagenic antineoplastic agents at 23 and 37°C using a desiccator technique. *Mutat Res* 2000;470:85-92.

11. Hoy RH, Stump MS. Effect of an air-venting filter device on aerosol production from vials. *Am J Hosp Pharm* 1984;41:324-6.

12. Spivey S, Connor TH. Determining sources of workplace contamination with antineoplastic drugs and comparing conventional IV drug preparation with a closed system. *Hosp Pharm* 2003;38:135-9.

13. US National Institute for Occupational Health and Safety. Preventing occupational exposure to antineoplastic drugs in healthcare settings.Washington DC: CDC; 2004. Available at: www.cdc.gov/niosh/docs/2004-165

14. Connor TH, et al. Surface contamination of chemotherapy drug vials and evaluation of new-vial cleaning techniques: results of three studies. *Am J Health-Syst Pharm* 2005;62:475-84.

15. Delporte JP, Chenoix P, Hubert PH. Chemical contamination of the primary packaging of 5-fluorouracil RTU solutions commercially available on the Belgian market. *Eur Hosp Pharm* 1999;5:119-21.

16. Favier B, Gilles L, Ardiet C, Latour JF. External contamination of vials containing cytotoxic agents supplied by pharmaceutical manufacturers. *J Oncol Pharm Prac* 2003;9:15-20.

17. Nygren O, Gustavsson B, Ström L, Friberg A. Cisplatin contamination observed on the outside of drug vials. *Ann Occup Hyg* 2002;46:555-7.

18. Allwood M, Stanley A, Wright P. The cytotoxics handbook. Oxford/New York: Radcliffe Medical Press; 2001.

19. Favier B, et al. Evaluation de la contamination de l'environnement matériel et humain par le 5-fluoro-uracile lors de la manipulation en unités de reconstitution des chimiothérapies. *J Clin Pharm* 2001;20:157-62.

20. US Occupational Safety and Health Administration. OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. *Am J Hosp Pharm* 1986;43:1193-1203.

21. US Occupational Safety and Health Administration. Controlling occupational exposure to hazardous drugs. *Am J Health-Syst Pharm* 1995;53:1669-85.

22. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic drugs in hospitals. *Am J Hosp Pharm* 1985;42:131-7.

23. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990;47:1033-49.

24. Sewell GJ. Cancer treatment and safety. *J Guild Healthcare Pharmacists* 2001;2(4):20-22.

25. Roberts S, Khammo N, McDonnell G, Sewell GJ. Studies on the decontamination of surfaces exposed to cytotoxic drugs in chemotherapy workstations. *J Oncol Pharm Prac* 2006;12:95-104.

26. Vandenbroucke J. Cytotoxic handling and the importance of appropriate gloving. *Hospital Pharmacy Europe* 2007;31:19-21.

27. MARCH. Management and Awareness of the Risks of Cytotoxic Handling. Leeds; Teva UK: 2007. Available at: www.marchguidelines.com

28. International Society of Oncology Pharmacy Practitioners. Standards of practice: safe handling of cytotoxics. Hamburg; ISOPP: 2007. Available at: www.isopp.org

29. Connor TH, Anderson RW, Sessink PJM, Spivey PJ. Effectiveness of a closed-system device in containing surface contamination with cyclophosphamide and ifosfamide in an i.v. admixture system. *Am J Health-Syst Pharm* 2002;59:68-72.

30. Sessink PJM, Rolf ME, Rydén NS. Evaluation of the PhaSeal hazardous drug containment system. *Hosp Pharm* 1999;34:1311-17.

31. Spivey PJ, Connor TH. Determining sources of workplace contamination with antineoplastic drugs and comparing conventional IV drug preparation with a closed system. *Hosp Pharm* 2003;38:135-9.

32. Tans B, Willems L. Comparative contamination study with cyclophosphamide, fluorouracil and ifosfamide. *J Oncol Pharm Prac* 2004;10:217-23.

33. Vandenbroucke J. Cytotoxic agents and contamination in hospitals. *J Oncol Pharm Prac* 2001:6;146-52.

34. MARC. Management and Awareness of the Risks of Cytotoxics. 2004.