Fluorouracil의 환경감시 및 제거약제에 관한 연구

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A Study on Environmental Monitoring of Fluorouracil and Decontamination Reagents

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Abstract : This study has been to examine the occupational exposure levels of Fluorouracil (5-FU) in a hospital and to investigate the most effective cleaning reagent for control. Fluorouracil is one of the cytotoxic drugs which are therapeutic agents used to treat cancer. The health practitioners working in the cytotoxic work room and oncology ward areas are exposed to adverse health risks like cytogenetic and DNA damage from cytotoxic drugs exposure by frequent skin contact from contaminated surfaces. Four kinds of cleaning reagents has been examined to degrade the 5-FU. It was found that 5-FU was only degraded soon after the reaction in 0.5%(w/v) NaClO solution. Therefore, 0.5%(w/v) NaClO solution has been chosen to decompose any residues on the contamination surfaces. A substantial level of contamination was found on the surfaces of cytotoxic work room and oncology ward areas. The contamination ranges of the surfaces in cytotoxic work room and oncology ward areas were from 2.0 to 13.8μg/m^2 and 5.39 to 11.53μg/m^2, respectively. Consequently, regulation of the occupational exposure limit, procedure of special cleaning, and the use of personal protective equipment are recommended during the manipulation and administration of the drugs to avoid skin contamination from cytotoxic drugs like 5-FU.

초 록 : 이 연구는 Fluorouracil(5-FU)가 병원에서 암치료제로 쓰이는 세포독성약제의 한 종류이기 때문에 병원내부에 5-FU의 폭로 정도와 그 관리를 위한 가장 효율적인 세척약제를 조사하기 위한 것이다. 이러한 세포독성 약제실이나 종약학 병동에서 근무하는 실무자들은 세포독성약제로 오염된 표면에 빈번하게 접촉하게 되면 세포유전성이나 DNA손상에 대한 위험이 높게 된다. 따라서 이러한 약제의 세척제실험을 위하여 4가지 약제로서 시행한 분해시험에서 0.5%(w/v) NaClO 용액만이 5-FU를 즉시 분해시켰으므로 이 용액은 오염표면의 잔유물을 분해시키는데 사용될 수 있다. 세포독성 약제실의 오염표면에서 확인된 농도범위는 2.0에서 13.8μg/m^{2}까지이고, 종약학 병동의 오염표면에서 측정한 농도범위는 5.39에서 11.53μg/m^{2}이었다. 5-FU와 같은 세포독성약제로부터 피부오염을 피하기 위하여 작업장의 노출허용기준과 같은 법적인 조치, 완벽한 표면세척제 및 보호구사용과 같은 엄격한 관리기준이 마련되어야 할 것이다.
Key Words : Fluorouracil, cytotoxic drugs, degradation, health practitioners, contamination surfaces

1. Introduction

Cytotoxic drugs are therapeutic agents used to treat cancer. Exposure to cytotoxic drugs will increase adverse health risks including genotoxic effects and genetic damage by frequent or potent skin contact from a variety of contaminated surfaces such as inhalation, ingestion or injection[1]. Skin contact is to be a major route of contamination from potential contaminated surfaces, because skin contamination may well occur from incidents such as spillage, splash, dripping or cross contamination. This contamination can be happened from inadequate personal hygiene, improper use of personal protective equipment(PPE), permeation of cyto-

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toxic drugs through glove materials and cleaning techniques[2,3].

It was found that hospital personnel compounding and administering cytotoxic chemotherapy are at risk of inadvertent occupational exposure to cytotoxic residues from potential surface contamination. In addition, both the surfaces of drug vials delivered from manufacturers, the external surface of antineoplastic drug vials and their primary packaging can also be sources of skin contamination as well as inside the isolator[4,5].

Health practitioners, for examples, nurses, technicians, pharmacists and physicians handling cytotoxic drugs have increasing risks of adverse health effects like carcinogenicity, genotoxicity, reproductive and organ toxicity from potential skin contact with a variety of contaminated surfaces and inhalational exposure[1]. These occupational exposures will mostly occur in the administration area, preparation area, oncology wards, and disposal area in hospitals.

Both skin contamination and inhalational exposure will be caused by surface contamination, vaporization/aerosolization of cytotoxic drugs, inadequate personal hygiene, improper use of PPE, inappropriate use of cytotoxic drug safety cabinets(CDSC) and most importantly, improper cleaning techniques during drug preparation, drug administration, patient care activities, spill management and waste disposal. It is well known that hospital personnel compounding and administering cytotoxic chemotherapy are at risk of inadvertent occupational exposure to cytotoxic residues[6-10]. To minimize or avoid skin and inhalable exposure to cytotoxic drugs, there are several guidelines[11-13] provided to reduce workplace risk. However, no occupational exposure limit for cytotoxic drugs is currently available.

5-FU is one of the most common cytotoxic drugs used in many hospitals. However, there is lack of occupational exposure data from surfaces contaminated with 5-FU. In addition, there is also insufficient information on the most effective cleaning reagent for the decontamination of 5-FU, even if there is a great concern about an appropriate cleaning procedure[11,14,15].

Therefore, the main objectives of this study were to examine the extent of occupational exposure levels of 5-FU in a hospital and to determine the most effective cleaning reagent for control.

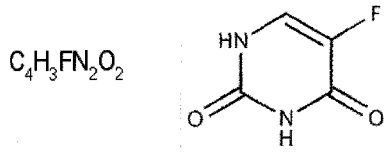

Fig. 1. The chemical formula and structure 5-FU.

2. Materials and Methods

2.1. Study Materials

The cytotoxic drugs investigated in this study were 5-fluorouracil which was manufactured in Mayne Pharma Pty Ltd(Mulgrave, Victoria). It has a white solid powder form, but it was diluted as 2500mg/100mL solution(DLB Brand). The CAS Registry number is 51-21-8 and the chemical structure is shown in Fig. 1.

Four cleaning reagent selected for the degradation test of 5-FU were 70% analytical grade ethanol, 0.5%(w/v) NaClO(Pharmaceutical grades & Sterile contamination control products), 0.03M NaOH solution and laboratory grade distilled water.

2.2. Sampling of Contaminated Surfaces

Polyvinyl alcohol Ghost™ Wipes(Les Orr. Environmental Express(USA) were wet with 1mL of 0.03M NaOH solution prior to undertaking surface sampling in the pharmacy.

Surface samples were taken from the pharmacy cytotoxic compounding section in work room and cytotoxic clean room, and the oncology wards like reception area, dispensing room, storage-cabinet/compactus and administration area. Outer packaging and drug vials(2,500mg/100mL and 325mg/15mL) of 5-FU in the pharmacy store were also wiped for the surface contamination test. Tweezers were used to transfer the Ghost™Wipes into a separate small glass vial with a Teflon cap. The samples were stored in a ice bag, then transferred to the laboratory. All the samples were stored in the freezer at $\leq$ -20℃ prior to laboratory analysis with the HPLC. During the sampling, the collectors were worn disposable nitrile gloves and disposable coveralls.

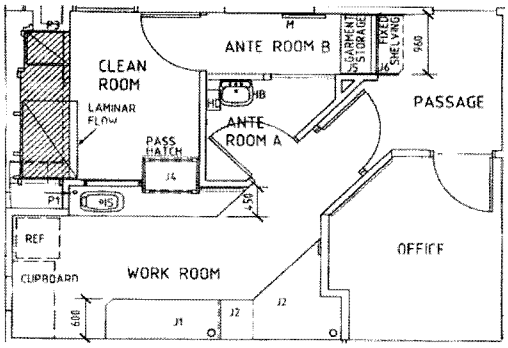

Fig. 2. Cytotoxic compounding area.

2.3. Airborne Sampling Materials

Prior to airborne monitoring in the pharmacy setting, the recovery of 5-FU from an airborne sampling filter manufactured by vinyl/acrylic copolymer (0.8μm, 25mm) was higher than 95%.

Positional airborne sampling was carried out inside the clean room, ante room, store room and work area as described in Fig. 2. Each sampling filter was loaded in an open-faced IOM (Institute of Occupational Medicine) sampler (Scotland, U.S. Patent No. 4,675,034, SKC Inc). The filter was positioned at about 1.5m above the floor. A calibrated battery-powered air sampling pump was connected to an airborne inhalable dust sampling head. The flow rate of the pump was 3L/min for around 3hours according to the length of cytotoxic preparation schedule. All the airborne samples were stored in a sterile container and then delivered to the laboratory. These samples were stored at ≤ 4℃ until analyzed using HPLC. To extract 5-FU from the filters, 0.5mL of the dissolving solution was added to each filter.

2.4. Degradation Test Method

One milliliter of 5-FU(1.25mg/mL) was diluted with each cleaning reagent, and made up to 10mL as total volume. This experiment was carried out under the ambient temperature at 22±1℃ in the laboratory. Twenty microlitre of each sample solution was taken by a syringe in different time intervals from 0, 15, 30, 60 and up to 80min, and injected into the HPLC with a UV detector. This experiment was undertaken twice and all data were aggregated on a graph. During the process, disposable nitrile gloves(30cm length) were worn to avoid skin contamination. Statistical analysis was performed by using MS EXCEL program on a personal computer.

2.5. Analytical Conditions and Instrument

5-FU was extracted from the Ghost™wipes using 2ml of 0.03M NaOH solution as dissolving agent prior to analysis with the HPLC with a UV detector. The recovery of 5-FU from the GhostTM wipes was 99%. The mobile phase for 5-FU was consisted of 0.05M sodium acetate which was adjusted as pH 4.0 using acetic acid. After making up the mobile phase, an ultrasonic bath was used for degassing about 15 minutes. Helium gas was bubbled through the mobile phase during the analysis. The conditions of HPLC (High Performance Liquid Chromatography) operation were 260nm(UV detector), 1.0mL/min(pump rate) and 2.7minute(retention time). The coefficient of linear regression from HPLC is R^2=0.9967 and lower limit of detection is 1.0μg/mL. The specific details of the HPLC are described as below;

- Perkin-Elmer Series 200 with UV/VIS Detector connected to a GBC, LC 1120,
- HPLC Pump and a SUPELCO, Supelcosil™,
- Reverse phase LC-18, 5-8985 column in a TC 1900 HPLC Temp. Controller
- A software program(ICI DP800 Chromatography DATA Station, Ver 2.50).

3. Results

3.1. Surface Contamination Monitoring

The sampling of this study was conducted at a hospital. Out of over 8000 cytotoxic drug compounds supplied in every year, more than 80 items of 5-FU are prepared. All stock solutions were stored in the pharmacy store, and then delivered to the pharmacy cytotoxic compounding section. Operators like pharmacists and senior pharmacy technicians prepared cytotoxic drug compounds in the cytotoxic compounding area. The compounding area comprises of an office, work room, cytotoxic ante and clean room housing where a class II vertical laminar flow cytotoxic cabinet is operated as described in Fig. 2. The cytotoxic ante and clean rooms are supplied with HEPA(high efficiency particulate air) filtered air to specified current standards.

Operators in the cytotoxic clean room wore surgical face masks, sterile coverall-gowns, shoe covers, safety goggles and double latex surgical gloves. After compounding and labelling injection solutions, only selected surfaces in the cytotoxic work and clean rooms were wiped down with 70% sterile ethanol.

On two oncology wards for inpatient and outpatient, nurses stored all compounded chemotherapy items in infusion bags of refrigerators and compactus. Nurses wore disposable surgical latex gloves during the administration to patients in wards.

Table 1 shows the results from surfaces tested for contamination with 5-FU. Samples were taken from the surfaces of the pharmacy compounding section, oncology wards and pharmacy store. It is well known that most surfaces of such areas may be contaminated by 5-FU residues. It was also found that the outer box stored in a container in the pharmacy compounding section was contaminated. From these results, it was found that there were cumulative contamination of most work surfaces in the cytotoxic work room in the pharmacy compounding section and the oncology wards, not the pharmacy store. The detection ranges of those areas were from <LOD(2 $\mu g/m^2$) to 13.8$\mu g/m^2$ in the pharmacy compounding section and from 5.39 to 11.53$\mu g/m^2$ in the oncology ward areas. These results could indicate background contamination causing significant skin contamination. Similar results were also discussed in a recent study[16].

Table 1. Analytical results from surfaces tested for contamination with 5-FU

Locations		No. of Samples	Results (μg) (GM ± STDV)
Pharmacy Compounding Section	Work Room	12	6.79 ± 0.70
	Ante Room	3	8.24 ± 4.30
	Outer Box*	1	6.0
	Drug Vial* Surface	1	< LOD
Oncology Wards	Reception Area	18	6.79 ± 1.06
	Dispensing Area	2	8.89 ± 3.31
	Storage Area	2	8.60 ± 3.76
	Administration Area	10	6.59 ± 0.40
Pharmacy Store	Outer Boxes*	3	< LOD
	Drug Vial* Surfaces	3	< LOD

GM: Geometric mean, STDV: Standard deviation, LOD: < 2μg as a limit of detection
*All outer boxes and drug vials had not been used.

Positive surface contamination was detected from samples taken in the pharmacy compounding section. This is probably caused to accidental cross contamination or inappropriate decontamination process, as discussed by previous studies[17-20]. Contamination was found on the surfaces of gloves during compounding and administration of cytotoxic drugs[21,22]. As potential source of skin contamination, the contamination of glove should be investigated. No contamination was detected from the products delivered directly from the distributor and in the main pharmacy store.

Wiped samples in work room were taken from computer keyboards and mouses, door handles, telephone, fridges, waste bin, bench top. The samples in ante room were taken from a door handle, water tap and floor, also, samples in reception area were taken from bench top, fridges, telephone, door handles, computer keyboards and mousse. The samples in dispensing room were taken from a table and chair. The other samples in storage area were taken from a cabinet and compactus, also samples in the administration area were taken from trolleys, injection pumps and patient chairs.

It was discussed that if there is continuous skin contamination from surfaces contaminated with 5-FU caused to inappropriate surface cleaning process, the health practitioners working in the two areas may have increased risk of adverse health effects like cytogenetic and DNA damage from chronic exposure to cytotoxic drugs[10].

3.2. Airborne Contamination in the Cytotoxic Drug Compounding Area

Airborne sampling were carried out in the cytotoxic compounding section and work area. Airborne monitoring was only carried out for 3 hours corresponding to the cytotoxic compounding session of the day which only five 5-FU infusions were prepared. No contamination were detected from the airborne samples from the clean room, store room, ante room and general cytotoxic office area, probably caused to the installation of an appropriate BSCs(exhaust biological safety cabinets) with HEPA filters in the clean room as shown in Table 2. All results were checked to be under the limit of detection(0.93 $\mu g/m^3$).

Table 2. Airborne sampling results

Locations		Sampling time (min)	Results
Positional airborne sampling	Next a Biological Safety Cabinet (BSC) in the Clean Room	180	<0.93μg/m^3
	Store Room	180	<0.93μg/m^3
	Inside Ante Room	180	<0.93μg/m^3
	General working area	180	<0.93μg/m^3

These results indicate that BSCs in this study were effectively used for stopping aerosols entering from the atmosphere. Regarding this, we may recall that if there is a failure of the HEPA filters, airborne contamination may occur in environmental areas outside of the clean room[7], and from routine activities and inappropriate cleaning after spillage in BSCs[6].

3.3. Comparision of Degradation Reagents

From the 5-FU degradation trials with the four cleaning reagents, no significant degradation of 5-FU with 0.03M NaOH, 70% analytical grade ethanol and laboratory grade distilled water were observed as described in Fig. 3. However, most 5-FU was degraded soon after the reaction in the solution of 0.5%(w/v) NaClO. Therefore, 0.5%(w/v) NaClO solution was chosen to decompose any residues on the contamination surfaces even if 70% sterile alcohol was recommended by both OSHA[23] and SHPA[13] to clean any surfaces contaminated with cytotoxic drugs.

Regular environmental airborne and surface monitoring should be carried out to ensure appropriate control of contamination. In order to eliminate/prevent possible health risks resulting from skin contact with surfaces contaminated with 5-FU, an appropriate cleaning procedure with 0.5% w/v NaClO should be adapted to decompose any residues on surfaces like bench top, reception area, store, telephone, keyboard and mouse, fridge, door handle, waste bin, trolley, pump, chair, floor, and so on. Spraying 0.5%(w/v) NaClO solution on surfaces after daily work will be suitable for the decontamination of Fluouracil. It is also recommended for the health practitioners to get good work practices and to wear PPE including gloves in accordance with the guidelines[11-13].

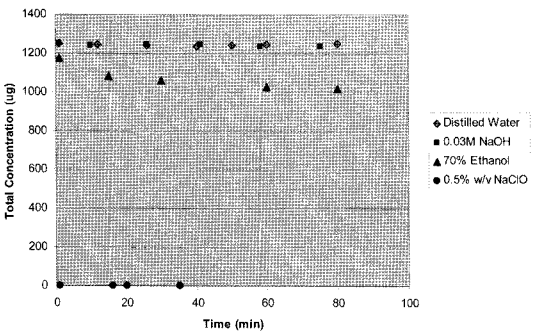

Fig. 3. Degradation of 5-FU with four cleaning reagents.

4. Conclusion

Surface wipe sampling and airborne sampling were carried out in this study. In order to degrade 5-FU, 4 kinds of cleaning reagents were also tested. The results are as belows:

1) Cumulative contaminations were detected in most work surfaces in the cytotoxic work room in compounding section. The detection ranges of this area and in oncology ward areas are from <LOD to 13.8μg/m^2, and from 5.39 to 11.53μg/m^2, respectively.

2) The results from the 5-FU degradation tests with distilled water, 0.03M NaOH, 70% ethanol and 0.5% w/v NaClO, have been obtained that 0.5% w/v NaClO was the most effective reagent for decomposing 5-FU.

3) Regulation of the occupational exposure limit, specific cleaning procedure of 5-FU and the usage of personal protective equipment should be recommended during the manipulation and administration of the drugs to minimize or avoid skin contamination and inhalable exposure of cytotoxic drugs.

References

1) NIOSH, "Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Healthcare Settings", National Institute for Occupational Safety and Health: U.S. Department of Health and Human Services, Public Health Service, Centres for Disease Control and Prevention, 2004-165, 2004.

2) W. Fransman, R. Vermeulen and H, Kromhout, "Occupationnal dermal exposure to cyclophosphamide in dutch hospital: a pilot study", Ann Occup Hyg., Vol. 48, pp. 237~244, 2004.

3) W. Fransman, R. Vermeulen and H. Kromhout, "Dermal exposure to cyclophosphamide in hospitals dur-

ing preparation, nursing and cleaning activities", Int Arch Occup Environ Health, Vol. 78, pp. 403~412, 2005.

4) M. Hedmer, A. Georgiadi, R. Bremberg, BAG. Jönsson and S. Eksborg, "Surface contamination of cyclophosphamide packaging and surface contamination with antineoplastic drugs in a hospital pharmacy in Sweden", Ann Occup Hyg, Vol. 49, pp. 629~637, 2005.
5) P. Gilbar, "External contamination of antineoplastic agent vials(editorial)", J Pharm PractRes, Vol. 35, pp. 264~265, 2005.
6) MG. Jakab, J. Major, A. Tompa, "Follow-up genotoxicological monitoring of nurses handling antineoplastic drugs", J Toxicol Environ Health A, Vol. 62, pp. 307~318, 2001.
7) TH. Connor, PJ. Sessink, BR. Harrison, JR. Pretty, BG. Peters, RM. Alfaro, et al. "Surface contamination of chemotheraphy drug vials and evaluation of new vial-cleaning techniques: results of three studies", Am J Syst Pharm, Vol. 62, pp. 475~484, 2005.
8) TH. Connor, MA. McDiarmid, "Preventing occupational exposures to antineoplastic drugs in health care settings, CA Cancer", J Clin, Vol. 56, pp. 354~365, 2006.
9) CA. Jackson, DA. Wilson, "World at work: Hospital pharmacy clean-rooms", Occup Environ Med, Vol. 63, pp. 68~70, 2006.
10) CL. Ursini, D. Cavallo, A. Colombi, M. Giglio, A. Marinaccio, S. Iavicoli, "Evaluation of early DNA damage in healthcare workers handling antineoplastic drugs", Int Arch Occup Environ Health, Vol. 80, pp. 134~140, 2006.
11) WorkSafe Victoria, "Handling Cytotoxic Drugs in the Workplace; Managing Health & Safety Risks Associated with Handling Cytotoxic Drugs in the Healthcare Industry", WorkCover Advisory Service. Worksafe Victoria : Division of the Victorian WorkCover Authority; 2003.
12) Queensland Workplace Health and Safety Strategy, "Guide for handling Cytotoxic Drugs and Related Waste", Department of Industrial Relations, Workplace Health and safety Queensland. Queensland Government; 2005.
13) SHPA Committee of Specialty Practice in Oncology, "SHPA standards of practice for the safe handling of cytotoxic drugs in pharmacy departments", J Pharm Pract Res, Vol. 35, pp. 44~52, 2005.
14) A. Acapora, L. Castigia, N. Miraglia, M.Pieri, C. Soave, F. Liotti, et al, "A case study: Surface contamination of cyclophosphamide due to working practices and cleaning procedures in two Italian hospitals", Ann Occup Hyg. Vol 49, pp. 611~618, 2005.
15) K. Touzin, JF. Bussières, E. Langlois, M. Lefebvre, C. Gallant, "Cyclophosphamide contamination observed on the external surfaces of drug vials and the efficiency of cleaning on vial contamination", Ann. Occup. Hyg,. Vol. 52, No. 8, pp. 765~771, 2008.
16) J. Siderov, "Is the death knell for cytotoxic manufacturing in hospitals ringing?", J Pharm Prac Res, Vol. 36, p. 78, 2006.
17) K. Labuhn, B. Valanis, R. Schoeny, K. Loveday, WM. Vollmer, "Nurses' and pharmacists' exposure to antineoplastic drugs: findings from industrial hygiene and urine mutagenicity tests", Cancer Bursing, Vol. 21, pp. 79~89, 1998.
18) PJ. Sessink, BC. Wittenhorst, RB. Anzion, RP. Bos, "Exposure to pharmacy to antineoplastic agents: reevaluation after additional protective measures", Arch Environ Health, Vol. 52, pp. 240~244, 1997.
19) E. Ziegler, HJ. Mason, PJ. Baxter, "Occupational exposure to cytotoxic drugs in the two UKoncology wards", Occup Environ Med, Vol. 59, pp. 608~612, 2002.
20) S. Crauste-Manciet, PJM. Sessink, S. Ferrari, JY. Jomier, D. Brossard, "Environmental contamination with cytotoxic drugs in healthcare using positive air pressure isolators", Ann Occup Hyg, Vol. 49, pp. 619~628, 2005.
21) G. Dranitsaris, M. Johnston, S. Poirier, T. Schueller, D. Milliken, E. Green, B. Zanke, "Are health care providers who work with cancer drugs at an increased risk for toxic events? A systematic review and meta-analysis of the literature", J Oncol Pharm Prac, Vol. 11, pp. 69~78, 2005.
22) HJ. Mason, S. Blair, C. Sams, K. Jones, SJ. Garfitt, MJ. Cuschieri, et al. "Exposure to antineoplastic drugs in two UK hospital pharmacy units", Ann Occup Hyg, Vol. 49, pp. 603~610, 2005.
23) OSHA, "Controlling Occupational Exposure to Hazardous Drugs. OSHA Technical Manual(TED 01-00-015). Section VI: Chapter 2", U.S Department of Labor, Occupational Safety & Health Administration. Washington, DC. URL : http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html. 1999.