Multicenter study of environmental contamination with cyclophosphamide, ifosfamide and methotrexate in 66 Canadian hospitals: 2016 follow-up study

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PS-013

Background

- Oncology workers are occupationally exposed to antineoplastic drugs.
- This exposure can induce adverse health effects.
- In order to reduce their exposure, contamination on surfaces should be kept as low as possible; no health-based safe exposure limit is known.
- Since 2004, the National Institute for Occupational Safety and Health periodically updates a list of drugs that should be considered hazardous, including antineoplastic drugs.
- Previous multicenter studies of environmental contamination were conducted in Quebec (2008-2010, 2012 and 2013) and in Canada (2014, 2015).

Purpose

- To monitor environmental contamination with cyclophosphamide, ifosfamide and methotrexate in oncology pharmacy and patient care areas in Canadian hospitals.
- To describe the impact of some factors that may limit contamination

Material and Methods

- Descriptive study.
- 202 directors of pharmacy departments in hospitals with at least 50 acute care beds across 10 Canadian provinces were contacted in January 2016.
- 12 standardized sites were sampled (surface of 600 cm^2) : 6 in the pharmacy and 6 in patient care areas.
- Samples were collected between February and June 2016 at the end of a working day or the next morning, before cleaning surfaces.
- Participants filled out a form describing their practice such as outer package removal, exterior vials cleaning, closed-system drug transfer devices use, location of priming IV tubing and antineoplastic drug consumption.
- Analysis were conducted by the Institut National de Santé Publique du Québec
- Samples were analyzed for the presence of cyclophosphamide, ifosfamide and methotrexate by ultra-performance liquid chromatography tandem mass spectrometry technology.
- Descriptive analyses were done to evaluate surface contamination.
- Sub analyses were performed according to working practices and cyclophosphamide contamination (Kolmogorov-Smirnov test for independent samples).

Table I. Limits of detection and limits of quantification

	Limits of detection	Limits of quantification
	pg/cm²	
Cyclophosphamide	0.36	1.21
Ifosfamide	0.95	3.17
Methotrexate	0.97	3.25

Results

- **Global profile:** 66/202 Canadian hospitals participated in the 2016 study (33%)
- **Cyclophosphamide**: 75th percentile value was 6.8 pg/cm². Highest concentration was 85 000 pg/cm² (exterior surface of an antineoplastic drug container)
- **Ifosfamide:** 75th percentile value was lower than the limit of detection. Highest concentration was 1500 pg/cm^2 (front grille of the hood)
- **Methotrexate:** 75th percentile value was lower than the limit of detection. Highest concentration was 4 800 pg/cm^2 (front grille of the hood)

Figure 1. Cyclophosphamide surface concentration in Canadian multicenter studies

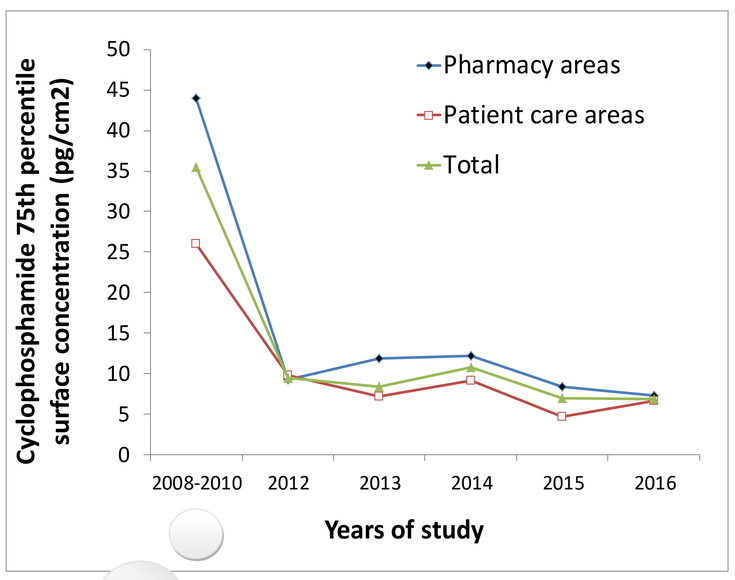

Figure 2. Proportion of positives samples in Canadian multicenter studies

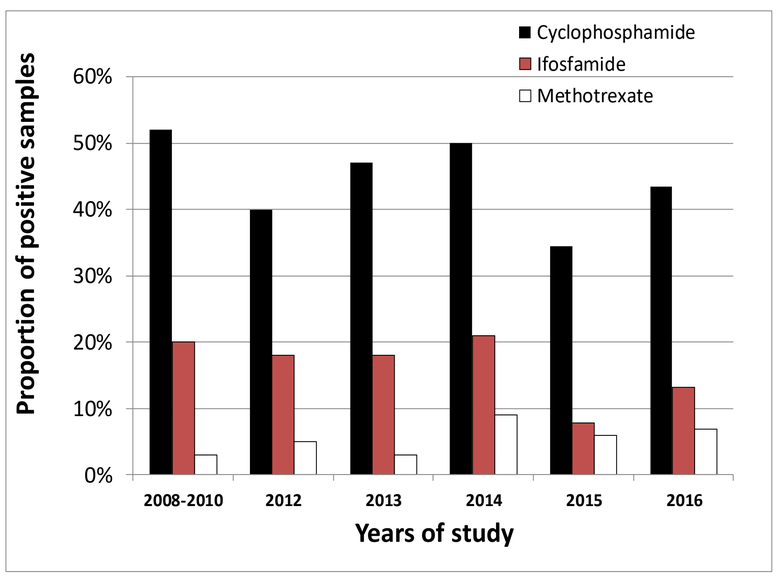

Table II. Cyclophosphamide, ifosfamide and methotrexate positive samples in pharmacy and patient care areas in the 2016 study (n=66 centers)

Sample sites (n samples)	Positive samples n (%) Cyclophosphamide	Ifosfamide	Méthotrexate
Pharmacy areas			
Shipment reception counter (65)	7 (10.8)	4 (6.2)	7 (10.8)
Storage shelf (64)	25 (39.1)	22 (34.4)	11 (17.2)
Front grille inside the hood (66)	45 (68.2)	18 (27.3)	18 (27.3)
Floor in front of the hood (63)	44 (69.8)	14 (22.2)	4 (6.3)
Service hatch or counter for post-preparation validation (66)	21 (31.8)	3 (4.5)	3 (4.5)
Trays used for drug delivery (66)	18 (27.3)	2 (3.0)	1 (1.5)
Total (390)	160 (41.0)	63 (16.2)	44 (11.3)
Patient care areas			
Storage shelf (62)	17 (27.4)	3 (4.8)	0 (0)
Counter used for priming or validation (65)	34 (52.3)	3 (4.6)	1 (1.6)
Arm rest (63)	56 (88.9)	19 (30.2)	2 (3.2)
Patient room counter (52)	25 (48.1)	6 (11.5)	1 (1.9)
Outpatient clinic counter (59)	16 (27.1)	4 (6.8)	2 (3.4)
Exterior surface of antineoplastic drug container (61)	18 (29.5)	1 (1.6)	2 (3.3)
Total (362)	166 (45.9)	36 (9.9)	8 (2.2)
Total (pharmacy & patient care areas) (752)	326 (43.4)	99 (13.2)	52 (6.9)

Sampling sites with more than 50% of positive samples are highlighted. A sample was considered positive if it was above the limit of detection

Cyclophosphamide surface concentration remained stable in the last years, in participating Canadian centers.

Over the years, we observed stabilization in surface contamination.

Use of CSDT devices is not associated with lower surface contamination

Significantly higher surface contamination was found in centers where : more antineoplastic drugs were prepared, higher cyclophosphamide usage was observed, IV tubing was primed by nurses in patient

Table III. Comparison of cyclophosphamide surface concentration

Comparisons (n samples)	75th percentile of cyclophosphamide concentration (pg/cm²)
Participation in multicenter studies	**p=0.044**
Participation in 6 studies (n=200)	12.0
Participation in 1-5 studies (n=552)	5.2
Use of closed-system drug transfer devices	**p=0.060**
Use (n=255)	9.0
No use (n=497)	5.7
Removal of outer packaging	**p=0.730**
Removal (n=578)	7.9
No Removal (n=174)	4.7
Cleaning of vials after receipt	**p=0.832**
Cleaning (n=483)	7.8
No cleaning (n=269)	5.4
Antineoplastic drugs usage	**p<0.0001**
< 5 000 preparations/year (n=316)	2.0
5000-15 000 preparations/year (n=194)	13.0
> 15 000 preparations/year (n=195)	15.0
Cyclophosphamide usage	**p<0.0001**
< 500 g/year (n=434)	3.1
500-1 000 g/year (n=171)	9.8
> 1 000 g/year (n=147)	21.0
Prime antineoplastic IV tubing	**p=0.004**
In healthcare unit by nurses (n=278)	9.7
In pharmacy (n=474)	4.7

*Kolmogorov-Smirnov for independent samples.
The limit of detection was of 0.36 pg/cm² (19.8 pg/mL) for cyclophosphamide.

Conclusion

- Environmental surveillance is one part of a comprehensive approach for minimizing hazardous exposures in healthcare.
- By repeating annually and systematically this multicenter study, it increases all stakeholders' awareness about the level of traces of hazardous drugs and the potential strategies that can minimize contamination. This study highlights a low level of contamination of three hazardous drugs amongst 66 Canadian hospitals.
- Regular environmental monitoring is a good practice to maintain contamination as low as reasonably achievable.

European Association of Hospital Pharmacists, Cannes, France, March 22-24th, 2017

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