DETERMINATION OF CYCLOPHOSPHAMIDE BY GC-MS IN SPANISH HOSPITALS AND VIALS SURFACES

Hennef, 30 April 2008

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CENTRO NACIONAL DE CONDICIONES DE TRABAJO. BARCELONA

POSTERS

- **Determination of cyclophosphamide by GC-MS in work and vials surfaces of hospital pharmacies**
  Torrado S., Rosell M.G., Guardino X.

  Proceedings of the International Symposium of the International Association of the Social Security (AISS)
  Athens, 4-6 june 2007

- **Determination of cyclophosphamide by GC-MS in vials surfaces of hospital pharmacies. Application to compare cleaning procedures**
  Torrado, S.; Rosell, M.G.; Guardino, X.

  VII Meeting of the Spanish Society of Chromatography and Related Techniques
  (SECyTA)
  Granada, 17-19 october 2007

OUTLINE

- Introduction
- Experimental
  - Sampling and analytical method
  - Validation and chromatograms
  - Sampling strategy
- Results
  - Hospital surfaces
  - Outside of the vials
- Cleaning of vials surfaces
- Conclusions

INTRODUCTION

- Preparation of the drug from the vial provided by the manufacturer to a suitable way to be applied to the patients is made in hospital pharmacies, where a specific room is designated for this task equipped with vertical laminar airflow safety hoods and where operating procedures are established.
- Although this substances should not be present on work surfaces due to the safety measures mentioned, previous studies have reported their detection.
- Origin: concern of the head of hospital pharmacy of Oncology Catalan Institute (Dra Clopés).
- Cyclophosphamide was measured as a model compound as it is one of the most commonly used antineoplastic drugs and is very toxic (group 1 IARC).
- Two different methodologies for the detection of cyclophosphamide described in the literature have been adapted to develop and validate a method to determine it on surfaces.

OBJECTIVES

- Determine the presence of cyclophosphamide on the work surfaces of the room where it is prepared and also where it is applied.
- Determine the potential contamination on the outside of the vials delivered to hospital pharmacies.
- Find a suitable cleaning protocol that removes all the cyclophosphamide present on the exterior surface of the vials.

EXPERIMENTAL

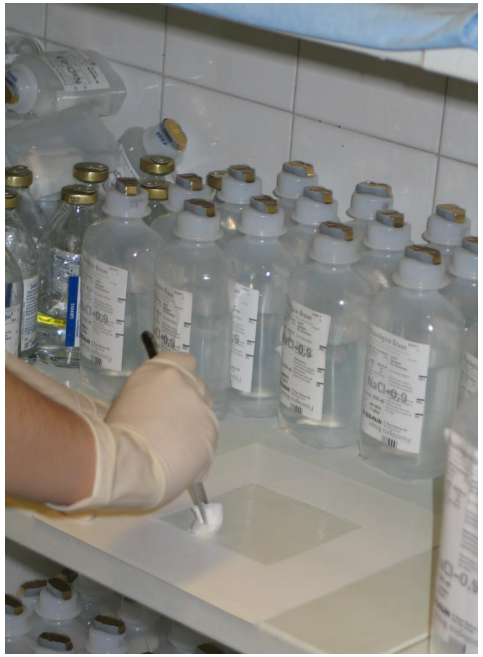
Sampling method

Work surfaces sampling

A wipe sampling method to collect cyclophosphamide on surfaces was used. A tissue was moistened with 1 ml of sodium hydroxide 0.03 M and a surface area of 10x10 cm was wiped twice.

Vials sampling

Wipe sampling was made twice on the vial surface and on the cover surface under the rubber protection.



EXPERIMENTAL

Analytical method (I)

Sample preparation

1- Addition of cyclophosphamide-d_6 as internal standard.

2- Extraction with 20mL of ethyl acetate.

3- Derivatization with 50 µl of trifluoroacetic anhidride (30min, 70ºC).

4- Evaporate until dryness and reconstitute with 100 µl of toluene.

5- Detection of cyclophosphamide by GC/MS.

EXPERIMENTAL

Analytical method (II)

Analysis

- ***Column:*** Methyl-5%phenylpolysiloxane 30m x 0.25mm, film 0.25µm.
- ***Temperatures***:

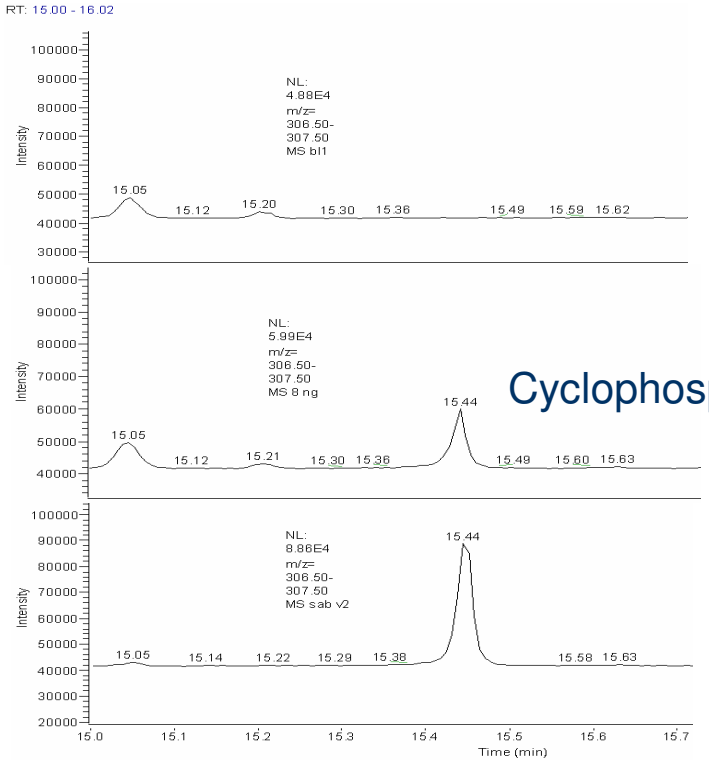
  - Column: 100ºC 1m, 20ºC/m to 160ºC, 4ºC/m to 200ºC, 20ºC/m to 280ºC 5m.

  - Injector: 250ºC.

  - Detector: 280ºC
- ***Carrier Gas:*** He at 1ml/m.
- ***Injection mode:*** splitless.
- ***Acquisition mode***: SIM (ions 307, 309 for CP and 313, 315 for CP-d_6)

EXPERIMENTAL

Chromatograms



Cyclophosphamide

Chromatograms of a blank sample (top), calibration sample (middle) and vial sample (bottom).

EXPERIMENTAL

Validation

Limit of detection and recovery.

LOD (ng/cm^2)	Recovery	
	Sampling	Extraction
0.002	89±9%	96±13%

Precision and accuracy.

	Precision (%RSD)	Accuracy (%relativ error)
3 ng	8.9	14.1
10 ng	10.2	7.2

EXPERIMENTAL

Sampling strategy

- **Number of institutions: 8**

•Hospital Universitari de Bellvitge
•Hospital de Barcelona
•Hospital Clinic de Barcelona
•Hospital Vall d'Hebron
•Institut Català d'Oncologia
•Hospital de la Santa Creu i Sant Pau
•Corporació Sanitària Parc Taulí (Sabadell)
•Hospital General de Vic

- **Work surface samples: 66**

  40 in pharmacies (inside and outside the cytostatics preparation room)
  26 in outpatient clinics

- **Vials sampled: 16** (2 from each hospital)

RESULTS

Cyclophosphamide in pharmacy spots (ng/cm²)

		H1	H2	H3	H4	H5	H6	H7	H8
INSIDE	cabinet	0,069	0,292	0,040	ND	0,498	0,132	ND	0,692
	cleaned vial		0,027						
	floor	ND	0,038	ND	0,194	ND	ND	0,097	0,225
	table	ND		0,021	0,021			0,094	0,002
	mixer						30,623		
	telephone						ND		
	knob						ND		
	SASS						0,002		
	table				0,194				
	wall				ND				
OUTSIDE	store table	ND	0,050		ND				
	staff room	ND							
	trolley					ND	ND		
	table			ND					
	cabinet						ND		
	store box						0,046		0,435
	tray				0,103				
	floor				0,040				

ND: not detected

RESULTS

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	mixer						30,623		
	telephone						ND		
	knob						ND		
	SASS						0,002		
	table				0,194				
	wall				ND				
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	staff room	ND							
	trolley					ND	ND		
	table			ND					
	cabinet						ND		
	store box						0,046		0,435
	tray				0,103				
	floor				0,040				

RESULTS

Cyclophosphamide in pharmacy work surfaces (%)

Zone	Total samples	Contaminated samples	Percentage	Range (ng/cm^2)
Inside	28	18	64 %	0.002-30.62
Outside	12	5	42 %	0.002-0.103

RESULTS

Cyclophosphamide in outpatient clinics spots (ng/cm^2)

	H1	H2	H3	H4	H5	H6	H7	H8
table		ND						0,160
floor		0,035	0,018	0,350		2,484		0,036
tray		ND						
transport box		0,128	0,018	0,714		ND		0,434
armchair		ND	0,037	0,087				0,041
trolley			0,013			0,012		
waste floor			0,037					
waste cover			0,023	ND				
patient table		ND		ND		ND		
reception				0,091				

ND: not detected

RESULTS

Cyclophosphamide in outpatient clinics work surfaces (%)

Zone	Total samples	Contaminated samples	Percentage	Range (ng/cm^2)
Transport	5	4	80 %	0.004-0.714
Room	21	14	67 %	0.002-2.484

RESULTS

Outside of vials

The exterior surface of all the vials sampled were contaminated with CP, that was also detected on the cover of 5 vials

Vial part	ng/cm^2
Surface	0.002-0.306
Cover	0.054-0.330

Hospital	Vial	Cyclophosphamide (ng)
H1	1	4.42
	2	10.8
H2	3	1.17
	4	0.42
H3	5	3.50
	6	29.47
H4	7	4.58
	8	0.29
H5	9	35.13
	10	1.39
H6	11	0.87
	12	2.84
H7	13	1.44
	14	5.42
H8	15	4.82
	16	5.41

CONSEQUENCES

Cleaning of vials surfaces

- **Controlled contamination**

  The outside of the vial was contaminated with 25 ng of CP.

  A set of 6 vials for each kind of cleaning was prepared.

- **Cleaning procedure**

  The following cleaning substances were compared:

  - Ethanol
  - Isopropanol
  - Water
  - pH 2 soap
  - pH 5.5 soap
  - NaClO
  - NaOH 0.03 M

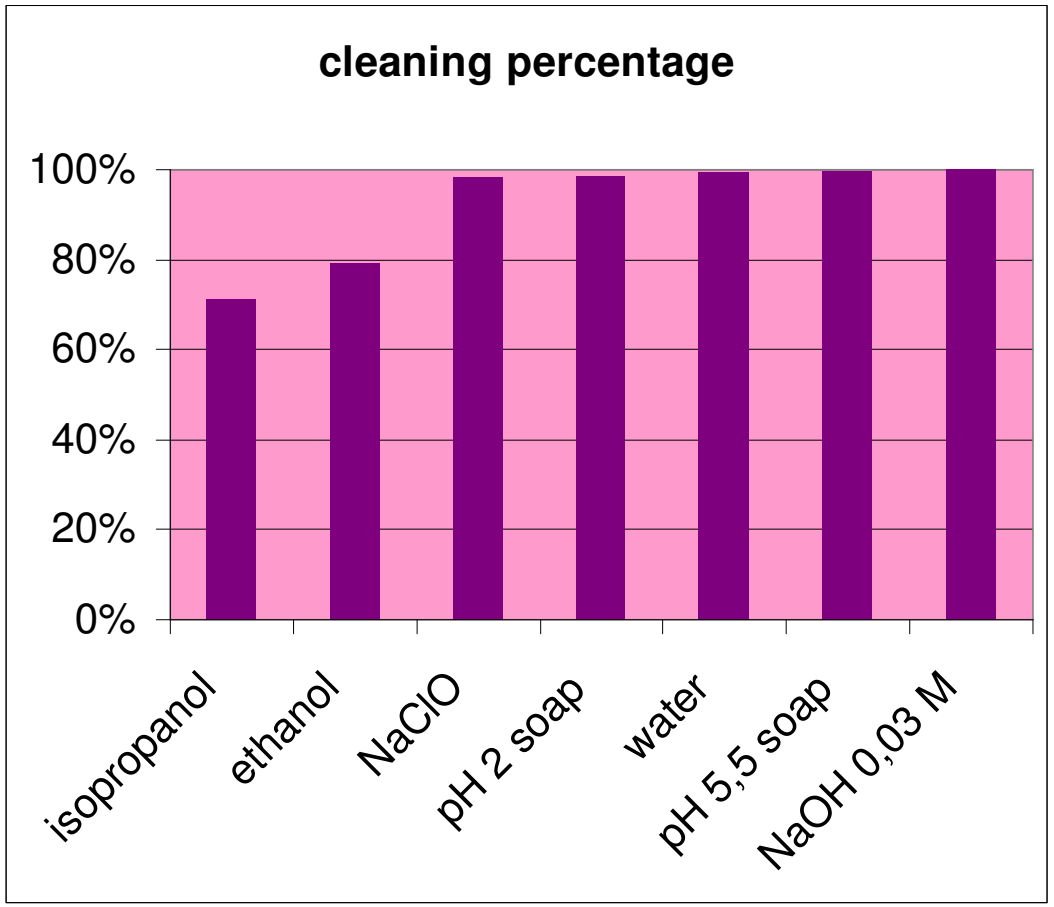
  One set of vials were not cleaned to keep as reference.

- **Vials sampling**

  A wipe sampling was applied twice to collect the remaining cyclophosphamide on the vial surface.

CONSEQUENCES

Cleaning comparison



CONSEQUENCES

Contact with manufacturer

- Meetings:
  - Improved cleaning procedure with Seidenader DAR 350, although they cannot ensure no contamination
  - Internal monitoring correct
- Visit to the plant…

CONCLUSION

- A method for determination of cyclophosphamide on surfaces has been developed and validated.
- Contamination of work surfaces with cyclophosphamide has been confirmed, both in hospital pharmacies and outpatient clinics.
- Cyclophosphamide has also been detected on the surface of vials supplied by the manufacturers.
- Due to protocols established for the preparation of citotoxic drugs, outside contamination of the vials can be considered an important source of the contamination detected. Therefore, manufacturers should provide clean vials in order to avoid occupational exposure along the whole circuit where vials are handled.
- Meanwhile, it has been checked that aqueous solutions are the best choice to clean the vials. Alcoholic solutions, commonly used in hospitals for desinfection, do not remove the cyclophosphamide completely.