EXPOSURE CONTROL
monitoring and consultancy

MONITORING CONTAMINATION ON INNER WALLS OF SYRINGES USED FOR PREPARATION AND ADMINISTRATION OF HAZARDOUS DRUGS

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Aim of the study

To evaluate contamination on inner walls of barrel syringes used for preparation and administration of hazardous drugs by means of wipe sampling.

Background

When a syringe is filled with a hazardous drug, the inner surface of the syringe is directly exposed to the drug that may react and stick to the surface. After transferring the drug to its final container or after administration, the inner wall remains fully exposed to the environment and the process of hazardous drug evaporation to the working environment may take place. Furthermore, the syringe plunger may get contaminated either by contact with the inner wall of the syringe or the drug may infiltrate onto the plunger during manipulation of the syringe if the syringe is used for multiple manipulations. Such contamination could be transferred via gloves of the operators to other surfaces resulting in spread of contamination in the working environment. Obviously, this should be prevented as much as possible.

Study design

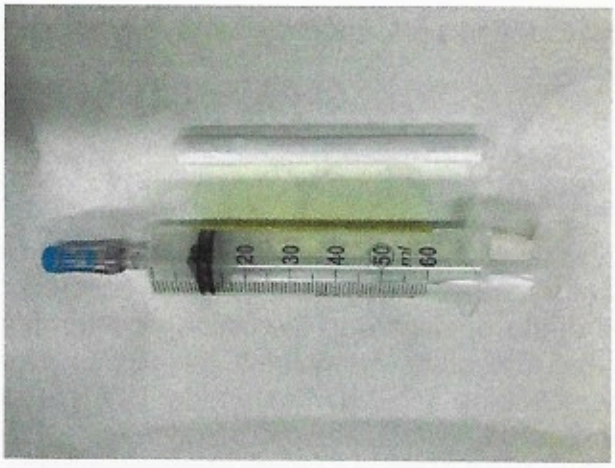
Between 4 and 7 October 2020, forty-three 50 ml BD Plastipak luer lock syringes (actually 60 ml) were collected by the hospital pharmacy of the University Hospital Leuven in Belgium.

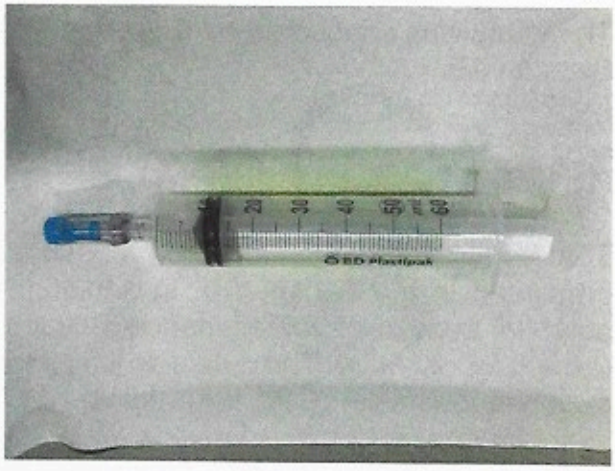
The syringes were collected after single use for the preparation of hazardous drugs. The drugs were transferred from the vials to the infusion bags using the ChemoClave and Spiros CSTD (ICU Medical). Drug volumes transferred varied from 36 to 60 ml. Fourteen pharmacists and technicians were involved in the preparation of the syringes (coded A – N).

The inner walls were wiped for each syringe using standard Cyto Wipe Kits for surface wipe sampling. Wiping with prewetted tissues (5 ml 0.1% formic acid solution and for cisplatin 5 ml 0.5 M HCl solution) and analysis were performed at the laboratory of Exposure Control in the Netherlands. The shape of the wipes was adapted to perform wiping on the inner walls of the syringes (Figure 1). The plunger was set at 10 ml to have sufficient access into the syringe barrel to perform the wipe sample. The wipe sample was taken by turning around the plunger to make sure the prewetted tissue contacted the total surface of the inner wall of the syringe.

Six hazardous drugs were tested because physical and chemical properties of drugs differ, and this could produce different results. Only 50 ml syringes were collected for testing to allow convenient access with the wipes. Considering the 50 ml requirement, the following drugs fitted into the study: 5-fluorouracil (50 mg/ml), cyclophosphamide (20 mg/ml), ifosfamide (40 mg/ml), methotrexate (100 mg/ml), doxorubicin (2 mg/ml), and cisplatin (1 mg/ml). Two till ten tests of each drug were performed depending on availability of the syringes during the collection period.

Figure 1: Tissue for wiping and syringe (left) and tissue inside syringe barrel (right)





Touching the plunger shafts was not allowed to avoid contamination on the inner walls of the syringes caused by the gloves of the operators during preparation. Only the external knob on the end of the plunger was used for holding. To ascertain this has not happened, the wipe samples were also analysed for nine other drugs in addition to the drug handled and transferred, except for cisplatin as the sample clean up procedure and the analysis was different compared to the other five drugs tested.

Materials and methods

The syringes were collected after single use and individually packed in a plastic mini bag. The syringes were still connected to the Spiros CSTD to avoid spills with the drugs. Each syringe was provided with a unique code and details are registered in the Tables 1-6. The syringes were stored at 2-8°C until sample preparation and analysis at the laboratory performed 14, 15 and 19 October 2020.

The wipe samples were taken with Cyto Wipe Kits from Exposure Control Sweden AB [1].

Before analysis, all wipe samples were extracted by adding 20 ml 0.1% formic acid solution. For cisplatin 20 ml 0.5 M HCl solution was used. Total extraction volume for the wipe samples was 25 ml.

LC-MS/MS was used for the analysis of cyclophosphamide, cytarabine, docetaxel, doxorubicin, etoposide, 5-fluorouracil, gemcitabine, ifosfamide, methotrexate and paclitaxel [2]. Platinum analysis of cisplatin was performed with stripping voltametry [3]. 0.5 ml of the extract was destructed using hydrogen peroxide, hydrochloric acid and UV-light resulting in the formation of platinum (PT) ions. Finally, the platinum ions were analysed instead of cisplatin. Samples were analysed in duplicate (including destruction). Mean values are reported.

Sponsorship

The study was sponsored by Equashield Medical Ltd. and performed by Exposure Control Sweden AB.

Results

The results of the contamination measured on the inner surface walls of the syringes are presented in the Tables 1-6. In addition, nine other drugs were measured to check for potential transfer of contamination by the gloves of the operators to the prepared syringes (except for cisplatin). The detection limit based on the extraction volume of 25 ml is 0.25 ng for cyclophosphamide (CP), cytarabine (CYT), gemcitabine (GEM), ifosfamide (IFO) and methotrexate (MTX), 5 ng for docetaxel (DOC), doxorubicin (DOX) and paclitaxel (PAC), 12.5 ng for etoposide (ETO) and 5-fluorouracil (5FU). Due to background levels of platinum (PT), the limit of quantification is set at 2.5 ng. This corresponds to 3.9 ng cisplatin.

Contamination was found for doxorubicin, methotrexate, cyclophosphamide and ifosfamide on the inner walls of all syringes (Tables 1-4). Contamination with 5-fluorouracil was detected on four out of ten syringes (Table 5). Contamination with platinum, representing cisplatin, was not detected on the four syringes tested (Table 6).
Mean levels of contamination differ between the drugs showing the highest contamination for ifosfamide (486 ng) and cyclophosphamide (298 ng), followed by 5-fluorouracil (52 ng) and doxorubicin (45 ng). The lowest level of contamination was found for methotrexate (6 ng), and cisplatin was not detected at all (< 3.9 ng). However, this does not correspond to the concentrations of the drugs prepared as the highest drug concentration was found for methotrexate (100 mg/ml), followed by 5-fluorouracil (50 mg/ml), ifosfamide (40 mg/ml), cyclophosphamide (20 mg/ml), and finally doxorubicin (2 mg/ml) and cisplatin (1 mg/ml).

It should be noticed that the results were not statistically evaluated for a potential effect of the concentrations of the drugs, the volumes transferred and the operators involved (worker´s effect). A potential effect of the volumes transferred is not expected as the means are about the same.

Contamination with the nine other drugs, to check for potential contamination by the gloves of the operators on the prepared syringes, was not found. This indicates that it is very unlikely that the measured contamination is caused by other (previous) activities than the handling itself.

Table 1: Contamination on the inner surface wall of seven doxorubicin syringes (2 mg/ml)

Sample	Date	Operator	Volume transferred (ml)	Doxorubicin (ng)
D4	2020-10-07	G	40	30
D5	2020-10-06	F	46	37
D6	2020-10-06	F	60	58
D7	2020-10-05	D	42.1	14
D8	2020-10-05	D	46.9	86
D9	2020-10-05	D	42.2	36
D10	2020-10-05	E	47.2	51
All 7	Mean		46.3	45

CP, CYT, DOC, ETO, 5FU, GEM, IFO, MTX, and PAC were not detected

Table 2: Contamination on the inner surface wall of two methotrexate syringes (100 mg/ml)

Sample	Date	Operator	Volume transferred (ml)	Methotrexate (ng)
M1	2020-10-06	D	48.6	5
M2	2020-10-06	D	48.6	6
All 2	Mean		48.6	6

CP, CYT, DOC, DOX, ETO, 5FU, GEM, IFO, and PAC were not detected

Table 3: Contamination on the inner surface wall of ten cyclophosphamide syringes (20 mg/ml)

Sample	Date	Operator	Volume transferred (ml)	Cyclophosphamide (ng)
C1	2020-10-06	F	46	230
C2	2020-10-05	D	53.9	415
C3	2020-10-05	M	45.3	124
C4	2020-10-05	M	51.4	503
C5	2020-10-05	E	50	345
C6	2020-10-05	D	40.5	289
C7	2020-10-05	H	52.5	11
C8	2020-10-05	H	48.5	78
C9	2020-10-05	E	55.9	323
C10	2020-10-05	E	50	658
All 10	Mean		45	298

CYT, DOC, DOX, ETO, 5FU, GEM, IFO, MTX, and PAC were not detected

Table 4: Contamination on the inner surface wall of ten ifosfamide syringes (40 mg/ml)

Sample	Date	Operator	Volume transferred (ml)	Ifosfamide (ng)
I1	2020-10-06	D	50	316
I2	2020-10-05	D	50	464
I3	2020-10-07	D	50	633
I4	2020-10-07	D	50	800
I5	2020-10-07	I	50	543
I6	2020-10-07	J	50	190
I7	2020-10-07	D	50	632
I8	2020-10-07	D	50	614
I9	2020-10-07	K	50	521
I10	2020-10-07	K	50	144
All 10	Mean		50	486

CP, CYT, DOC, DOX, ETO, 5FU, GEM, MTX, and PAC were not detected

Table 5: Contamination on the inner surface wall of ten 5-fluorouracil syringes (50 mg/ml)

Sample	Date	Operator	Volume transferred (ml)	5-Fluorouracil (ng)
F1	2020-10-07	K	50	ND
F2	2020-10-04	M	60	ND
F3	2020-10-06	K	48	ND
F4	2020-10-06	K	36	ND
F5	2020-10-06	D	60	58
F6	2020-10-06	L	51	ND
F7	2020-10-06	L	50	13
F8	2020-10-07	N	59.7	409
F9	2020-10-07	K	50	42
F10	2020-10-05	D	50	ND
All 10	Mean		51.5	52

CP, CYT, DOC, DOX, ETO, GEM, IFO, MTX, and PAC were not detected
ND: Not Detected (< 12.5 ng)

Table 6: Contamination on the inner surface wall of four cisplatin syringes (1 mg/ml)

Sample	Date	Operator	Volume transferred (ml)	Platinum (ng)
P6	2020-10-07	A	48.5	ND
P7	2020-10-06	B	50	ND
P8	2020-10-06	B	50	ND
P9	2020-10-06	C	40.2	ND
All 4	Mean		47.2	ND

ND: Not Detected (< 2.5 ng PT corresponding to < 3.9 ng cisplatin)

Discussion and Conclusion

Contamination was found for doxorubicin, methotrexate, cyclophosphamide and ifosfamide on the inner walls of all syringes. 5-fluorouracil was detected on a few syringes and cisplatin was not detected at all. In addition, differences in the levels of contamination were found between the drugs but it seems they are not correlated to the concentration of the drugs handled. This indicates that some drugs stick more to the inner walls of syringes than others especially doxorubicin followed by cyclophosphamide and ifosfamide. The sticking effect is about ten times lower for 5-fluorouracil, cisplatin and methotrexate. The differences can be explained by different product characteristics such as physical and chemical properties of the drugs.

Although the focus was to wipe the inner walls of the syringes, it cannot be excluded that the contamination measured also includes potential contamination on the plunger rods. Each syringe (except for cisplatin) was also checked for contamination with nine other drugs to measure contamination from the gloves of the operators that could be transferred to the plunger by handling the syringes. However, no other drugs were found except the ones tested indicating that the syringes were properly collected and the wipe testing at the laboratory was performed without contamination.

References

1 www.exposurecontrol.net
2 Exposure Control Sweden AB. LC-MSMS methods for the analysis of cytotoxic drugs in air, wipe and urine samples.
3 Metrohm Application Bulletin No. 220/1. Determination of ultra-trace levels of platinum by stripping voltametry.

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Bohus-Björkö, 2021-08-25

Appendix

Validation of wipe testing

As a separate study supplement, the remaining contamination on the inner walls of the syringes was measured after wiping to verify the effectiveness of the wiping procedure. Thereto, the syringes were placed upright with the plunger still at 10 ml, and 50 ml 0.1% formic acid solution was poured in the space between barrel and plunger. For the cisplatin syringes, 50 ml 0.5 M HCl solution was used. The liquid was removed after 60-90 min and analysed separately from the wipe samples.

The detection limit based on the extraction volume of 50 ml is 0.5 ng for cyclophosphamide (CP), cytarabine (CYT), gemcitabine (GEM), ifosfamide (IFO) and methotrexate (MTX), 10 ng for docetaxel (DOC), doxorubicin (DOX), and paclitaxel (PAC), 25 ng for etoposide (ETO) and 5-fluorouracil (5FU). Due to background levels of platinum (PT), the limit of quantification is set at 5 ng platinum corresponding to 7.8 ng cisplatin.

Remaining contamination was found for all doxorubicin, methotrexate, cyclophosphamide and ifosfamide syringes (Tables 7-10), for seven out of ten 5-fluorouracil syringes (Table 11), and for none of the cisplatin syringes (Table 12).
The results show higher amounts of drugs in the liquid than in the wipe samples, except for the cisplatin syringes where no contamination was found. This indicates that the wiping is less effective than the use of the liquid or the contamination was also present on other parts especially the plunger. If the plunger would have been contaminated, drug amounts can be higher in the liquid than in the wipe sample as the plunger was not wiped.

The liquids were also analysed for nine other drugs in addition to the drug handled and transferred, except for cisplatin as the sample clean up procedure and the analysis was different compared to the other five drugs tested. Contamination with the nine other drugs was not found.

Recovery

Two positive control samples for each drug (inner walls of syringes spiked with drug solutions) and two negative control samples (inner walls of syringes spiked with solutions not containing drugs) were also included in the study. These samples were obtained by dripping the solutions on the inner walls of the syringes. One hour after spiking, the samples were collected. The spiked amount was 1000 ng for doxorubicin, cyclophosphamide, ifosfamide, methotrexate and 5-fluorouracil, and 10 ng for cisplatin.

The recovery is based on the total contamination (tissue and liquid). However, the recovery is higher in the tissues than in the liquids for doxorubicin, 5-fluorouracil, methotrexate, and cisplatin and comparable for cyclophosphamide and ifosfamide (Tables 7-12). The results are contradictory compared to the results of the syringe samples and could be explained by a shorter time for the drugs to stick on the inner surface of the syringes after spiking compared to normal practice. In addition, the added liquid containing the drugs is easily absorbed by the

tissues before the liquid is added. Consequently, drug amount can be higher in the wipe samples.

The results show good recoveries for cyclophosphamide and ifosfamide, moderate recoveries for cisplatin, methotrexate and 5-fluorouracil, and a low recovery for doxorubicin indicating an underestimation of the measured contamination. The duplicates show little variation.

As expected, none of the ten drugs was detected in the negative control samples.

Table 7: Doxorubicin results seven syringes

Doxorubicine 2 mg/ml				DOX (ng)			Recovery (%)
Sample	Date	Operator	Volume transferred (ml)	Tissue	Liquid	Total	
D4	2020-10-07	G	40	30	812	842	
D5	2020-10-06	F	46	37	1978	2015	
D6	2020-10-06	F	60	58	2267	2325	
D7	2020-10-05	D	42.1	14	1975	1989	
D8	2020-10-05	D	46.9	86	1882	1968	
D9	2020-10-05	D	42.2	36	1925	1961	
D10	2020-10-05	E	47.2	51	2141	2192	
All 7	Mean		46.3	45	1854	1899	
Control 1				165	38	203	20
Control 2				179	4	183	18

CP, CYT, DOC, ETO, 5FU, GEM, IFO, MTX, and PAC were not detected

Table 8: Methotrexate results two syringes

Methotrexate 100 mg/ml				MTX (ng)			Recovery (%)
Sample	Date	Operator	Volume transferred (ml)	Tissue	Liquid	Total	
M1	2020-10-06	D	48.6	5	18	23	
M2	2020-10-06	D	48.6	6	24	30	
All 2	Mean		48.6	6	21	27	
Control 1				653	24	677	68
Control 2				610	75	685	69

CP, CYT, DOC, DOX, ETO, 5FU, GEM, IFO, and PAC were not detected

Table 9: Cyclophosphamide results ten syringes

Cyclophosphamide 20 mg/ml				CP (ng)			Recovery (%)
Sample	Date	Operator	Volume transferred (ml)	Tissue	Liquid	Total	
C1	2020-10-06	F	46	230	517	747	
C2	2020-10-05	D	53.9	415	945	1360	
C3	2020-10-05	M	45.3	124	332	456	
C4	2020-10-05	M	51.4	503	756	1259	
C5	2020-10-05	E	50	345	477	822	
C6	2020-10-05	D	40.5	289	761	1050	
C7	2020-10-05	H	52.5	11	883	894	
C8	2020-10-05	H	48.5	78	527	605	
C9	2020-10-05	E	55.9	323	695	1018	
C10	2020-10-05	E	50	658	827	1485	
All 10	Mean		45	298	672	970	
Control 1				480	443	923	92
Control 2				257	736	993	99

CYT, DOC, DOX, ETO, 5FU, GEM, IFO, MTX, and PAC were not detected

Table 10: Ifosfamide results ten syringes

Ifosfamide 40 mg/ml				IF (ng)			Recovery (%)
Sample	Date	Operator	Volume transferred (ml)	Tissue	Liquid	Total	
I1	2020-10-06	D	50	316	1213	1529	
I2	2020-10-05	D	50	464	895	1359	
I3	2020-10-07	D	50	633	1127	1760	
I4	2020-10-07	D	50	800	1254	2054	
I5	2020-10-07	I	50	543	424	967	
I6	2020-10-07	J	50	190	220	410	
I7	2020-10-07	D	50	632	1065	1697	
I8	2020-10-07	D	50	614	345	959	
I9	2020-10-07	K	50	521	527	1048	
I10	2020-10-07	K	50	144	810	954	
All 10	Mean		50	486	788	1274	
Control 1				466	459	925	93
Control 2				276	622	898	90

CP, CYT, DOC, DOX, ETO, 5FU, GEM, MTX, and PAC were not detected

Table 11: 5-Fluorouracil results ten syringes

5-Fluorouracil 50 mg/ml				5FU (ng)			Recovery (%)
Sample	Date	Operator	Volume transferred (ml)	Tissue	Liquid	Total	
F1	2020-10-07	K	50	ND	47	47	
F2	2020-10-04	M	60	ND	ND	ND	
F3	2020-10-06	K	48	ND	26	26	
F4	2020-10-06	K	36	ND	ND	ND	
F5	2020-10-06	D	60	58	118	176	
F6	2020-10-06	L	51	ND	86	86	
F7	2020-10-06	L	50	13	29	42	
F8	2020-10-07	N	59.7	409	1239	1648	
F9	2020-10-07	K	50	42	ND	42	
F10	2020-10-05	D	50	ND	69	69	
All 10	Mean		51.5	52	161	213	
Control 1				599	ND	599	60
Control 2				626	ND	626	63

CP, CYT, DOC, DOX, ETO, GEM, IFO, MTX, and PAC were not detected
ND: Not Detected

Table 12: Cisplatin results four syringes

Cisplatin 1 mg/ml				PT (ng)			Recovery (%)
Sample	Date	Operator	Volume transferred (ml)	Tissue	Liquid	Total	
P6	2020-10-07	A	48.5	ND	ND	ND	
P7	2020-10-06	B	50	ND	ND	ND	
P8	2020-10-06	B	50	ND	ND	ND	
P9	2020-10-06	C	40.2	ND	ND	ND	
All 4	Mean		47.2	ND	ND	ND	
Control 1				5	ND	5	77
Control 2				5	ND	5	77

ND: Not Detected