Side-by-Side Comparison of Methods for Environmental Monitoring for Hazardous Drug Contamination

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ABSTRACT

Background: Exposure to hazardous drugs is known to have deleterious effects on health care workers. To assess risk, environmental monitoring is conducted to ascertain drug contamination on surfaces, as dermal contact is the main route of exposure. Conventional monitoring employs wipe sampling whereby the wipe must be sent to a laboratory for analysis. This means that quantitative results are not available for some time, during which the risk remains unknown. A new device, the HD Check system, developed by BD, which uses lateral-flow immunoassay technology, allows for near real-time qualitative assessment of contamination (positive or negative); however, its sensitivity relative to the traditional method is unknown.

Objective: To evaluate the ability of this novel device to detect drug contamination relative to the conventional method.

Methods: Five sets of different known drug concentrations were compared between the conventional wipe sampling method and the HD Check systems for methotrexate (MTX) and cyclophosphamide (CP). Stainless steel surfaces were tested, and the drug concentrations ranged from 0 ng/cm^2 to twice the limit of detection (LOD) of each HD Check system.

Results: For MTX, positive results were obtained in every test trial at all drug concentrations examined with the HD Check system (LOD = 0.93 ng/cm^2). For CP, test results with the HD Check system (LOD = 4.65 ng/cm^2) were all positive at the LOD and twice the LOD; however, at 50% and 75% of the LOD, the result was positive in only 90% (9/10) of the trials. The conventional method was able to quantify the test drug concentrations with a high level of accuracy and reproducibility.

Conclusions: These results suggest the potential utility of the novel device as a screening tool for higher levels of drug contamination with MTX and CP, but additional research is needed to determine its suitability for lower concentrations, especially of CP.

Keywords: hazardous drugs, wipe sampling, surface contamination, HD Check system, risk assessment

RÉSUMÉ

Contexte : L'exposition à des médicaments dangereux est connue pour avoir des effets délétères sur les travailleurs de la santé. Pour évaluer les risques, une surveillance environnementale est menée pour vérifier la contamination des surfaces par les médicaments, car le contact cutané est la principale voie d'exposition. La surveillance conventionnelle utilise un échantillonnage par frottis, lequel doit être envoyé à un laboratoire pour analyse. Cela signifie que les résultats quantitatifs ne sont pas disponibles pendant un certain temps – temps pendant lequel le risque reste inconnu. Un nouvel appareil, le système HD Check de BD, qui utilise la technologie d'immunodosage à flux latéral, permet une évaluation qualitative en temps quasi réel de la contamination (positive ou négative); cependant, sa sensibilité par rapport à la méthode traditionnelle est inconnue.

Objectif : Évaluer la capacité de ce nouveau dispositif pour détecter la contamination médicamenteuse par rapport à la méthode conventionnelle.

Méthodes : Cinq ensembles de différentes concentrations connues de médicaments ont été utilisés pour comparer la méthode conventionnelle d'échantillonnage par frottis et les systèmes HD Check pour la méthotrexate (MTX) et la cyclophosphamide (CP). Des surfaces en acier inoxydable ont été testées et les concentrations de médicament variaient de 0 ng/cm^2 à deux fois la limite de détection (LD) de chaque système HD Check.

Résultats : Pour la MTX, des résultats positifs ont été obtenus dans chaque essai à toutes les concentrations de médicament examinées avec le système HD Check (LD = 0,93 ng/cm^2). Pour la CP, les résultats des tests avec le système HD Check (LD = 4,65 ng/cm^2) étaient tous positifs à la LD et au double de la LD; cependant, à 50 % et 75 % de la LD, le résultat n'était positif que dans 90 % (9/10) des essais. La méthode conventionnelle a été en mesure de quantifier les concentrations de médicament à l'essai avec un niveau élevé de précision et de reproductibilité.

Conclusions : Ces résultats suggèrent l'utilité potentielle du nouveau dispositif comme outil de dépistage pour des niveaux plus élevés de contamination médicamenteuse par la MTX et la CP, mais des recherches supplémentaires sont nécessaires pour déterminer son adéquation à des concentrations plus faibles, en particulier de CP.

Mots-clés : médicaments dangereux, prélèvement par frottis, contamination de surface, système BD HD Check, évaluation

INTRODUCTION

The risk of occupational exposure to hazardous drugs, also known as cytotoxic or antineoplastic drugs, has been documented since the 1970s.[1,2] The adverse health effects associated with occupational exposure to hazardous drugs include reproductive toxicities and genotoxic effects, as well as a higher risk for certain cancers.[3-5] According to CAREX Canada (a multi-institution team of experts providing knowledge about exposure to carcinogens), approximately 75 000 Canadians are exposed to hazardous drugs in the course of their work.[6] One of the most common means to assess the risk of health care workers' exposure to hazardous drugs is environmental monitoring or surface wipe sampling.[7] This is because the route of exposure to hazardous drugs for health care workers is believed to be dermal uptake or skin contact.[8,9] Essentially, workers can be exposed if they touch a drug-contaminated surface. As such, environmental monitoring is recommended in many best practice documents, including the US Pharmacopeial Convention's General Chapter <800>,[10] the International Society of Oncology Pharmacy Practitioners' standards of practice for the safe handling of cytotoxics,[11] and the National Association of Pharmacy Regulatory Authorities' *Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations*.[12]

At present, environmental monitoring typically involves using a moistened wipe material to wipe a surface in a predetermined pattern. The surface area that is commonly sampled is 10 cm × 10 cm (or 100 cm^2).[13] After sample collection, the wipe material is placed into a container such as a vial, which is then sealed, labelled, and sent to a laboratory for analysis. The gold standard laboratory analytical method is liquid chromatography with tandem mass spectrometry (LC-MS/MS) and the results are usually reported in units of nanograms per square centimetre (ng/cm^2).[13] Because the wipes must be sent to a laboratory, the results are typically not available until days or weeks after the sample collection date. Surface contamination levels may change during this lag period, and, in turn, the level of risk may also evolve.[14]

Recently, monitors based on lateral flow immunoassay (LFIA) have been developed to allow for near real-time detection of hazardous drugs on surfaces.[15,16] These monitors consist of a test line and a control line. The colour of the test line changes in intensity based on the concentration of the drug, while the control line serves to indicate that the monitor is working properly (i.e., a form of quality control). The user then inserts the monitor into a digital reader, which indicates whether drug is present (i.e., the result is either positive or negative). The advantage of this novel technology is that analysis in a laboratory is not required, and therefore the results indicate the presence of drug contamination within a few minutes after sampling. However, to the author's knowledge, this novel technology has never been evaluated in terms of its ability to detect surface contamination relative to the conventional wipe method described above.

This study aimed to compare the novel LFIA technology with an established surface wipe sampling and analysis method to assess the suitability of LFIA monitors to screen for hazardous drug contamination on work surfaces in health care settings. In other words, the goal was to ascertain whether the sensitivity of an LFIA monitor is suitable for employment of such devices as a substitute for conventional wipe sampling, to allow for near real-time detection of hazardous drugs on work surfaces. If deemed adequate, LFIA monitors could be considered for routine use in Canada and other jurisdictions for the purposes of environmental monitoring, assessment of exposure risk, and training, to name a few applications that would aid in reducing hazardous drug exposure among health care workers.

METHODS

In this controlled laboratory study, 2 methods—LFIA monitoring and conventional wipe sampling and analysis—were tested side by side with various known concentrations of hazardous drugs on stainless steel surfaces. This method of comparison has been used previously in the occupational hygiene domain for assessing direct-reading instruments relative to an established sampling method for chemical hazards.[17-22] The LFIA monitors evaluated were from the HD Check system line of products, which are manufactured by BD and are currently the only lateral flow devices commercially available.[23] Specifically, the HD Check assays for methotrexate (MTX) and cyclophosphamide (CP) were evaluated. The conventional wipe sampling method employed was developed by members of the author's team and is suitable for analyzing both MTX and CP.[24]

Test Surface

Stainless steel plates were chosen as the test surface, because stainless steel is the material used for biological safety cabinets, the typical location of drug preparation within health care facilities. Because 100 cm^2 is the typical surface area for wipe samples,[16] each stainless steel plate had dimensions of 10 cm × 10 cm.

Drug Concentrations

For both MTX and CP, the following 5 concentrations were assessed: 0 ng/cm^2 (control/blank), 50% of the limit of detection (LOD) of the corresponding HD Check system, 75% of the LOD of the HD Check system, the LOD of the HD Check system, and twice (200%) the LOD of the HD Check system. The manufacturer's LOD was 0.93 ng/cm^2 for the MTX HD Check system and 4.65 ng/cm^2 for the CP HD Check system.

Replicate Samples

For each drug (MTX and CP), 10 replicate samples of each of the aforementioned concentrations were evaluated by the 2 methods. This resulted in 20 samples (10 for the HD Check system and 10 for the conventional method) for each of the 5 drug concentrations tested. Overall, 100 test plates were examined for each drug, 50 for the HD Check system and 50 for the conventional wipe method. The total number of pairs of samples is consistent with other side-by-side tests[17,18,20] and allows for an understanding of the variability within each method.

Sample Collection

Two sets of plates were set up for each sampling round per test drug concentration (20 altogether). One set of samples (n = 10) was collected using conventional wipe sampling for laboratory analysis, and the other set of samples (n = 10) was collected using the HD Check system. A small volume (50 µl) of known drug concentration (as detailed above) was placed on each test of the plates. After the surface was allowed to dry naturally (for about 15 min), the residual drug was wiped by a single individual (C.Y.H.) using the conventional method.[24] Briefly, this method involved use of a Whatman filter moistened with a solution of water/methyl alcohol 20:80 with 0.1% formic acid. Subsequently, the wipe samples were analyzed by high-performance liquid chromatography tandem mass spectroscopy (HPLC-MS/MS), as described by Colombo and others,[24] at the Occupational and Environmental Hygiene laboratory, University of British Columbia, Vancouver, British Columbia.

After the first 10 plates were wiped via conventional testing, the same individual (C.Y.H.) sampled the remaining 10 plates with the HD Check system (to minimize the likelihood of inter-individual variability). Subsequently, the HD Check results were read using the system's digital reader, according to the manufacturer's instructions, and the findings, either positive or negative, were documented.

The wiping pattern for both conventional wipe sampling and HD Check sampling involved a back-and-forth motion in the vertical direction, followed by a back-and-forth motion in the horizontal direction. For the conventional wipe method, the wipe material was folded over to reveal a "fresh" side before wiping in the horizontal direction.

The sample collection procedure was repeated for every test drug concentration for each of the 2 HD Check assays (for MTX and CP). Between test drug concentrations, each set of plates was cleaned as described by Jeronimo and others.[25]

RESULTS

With the HD Check assay for MTX, positive results were obtained in every test trial at all drug concentrations examined. In other words, the assay was able to detect positive contamination at concentrations less than its LOD (specifically, 50% and 75% of 0.93 ng/cm^2). The corresponding average MTX concentrations detected by conventional wipe sampling and analysis were as follows: 0.457 ng/cm^2 at 50% of the LOD, 0.690 ng/cm^2 at 75% of the LOD, 0.919 ng/cm^2 at 100% of the LOD, and 1.854 ng/cm^2 at 200% of the LOD (Table 1).

With the HD Check assay for CP, test results were all positive at 100% and 200% of the assay LOD (where LOD = 4.65 ng/cm^2). The corresponding average CP concentrations determined by conventional wipe sampling were 4.542 ng/cm^2 at 100% of the LOD and 9.224 ng/cm^2 at 200% of the LOD. However, at 50% and 75% of the LOD, the HD Check results were positive in only 9 of the 10 test trials. At these 2 concentrations, the corresponding average CP concentrations detected by the conventional wipe sampling method were 2.235 ng/cm^2 and 3.374 ng/cm^2, respectively (Table 2).

DISCUSSION

The objective of this study was to ascertain whether a novel direct-reading device based on LFIA technology, the HD Check system, can detect hazardous drug contamination levels to the same extent as the conventional wipe sampling method. By conducting side-by-side comparisons of the 2 methods, the investigator found that the MTX assay was capable of detecting drug contamination from stainless steel surfaces at all (100%) concentrations tested, including at 50% of the LOD of 0.93 ng/cm^2. However, the CP assay was able to detect the presence of drug concentration in all instances only for contamination with solutions at 100% and 200% of the LOD of 4.65 ng/cm^2; at 50% and 75% of the LOD, the assay detected the drug on the surface in only 90% of the test trials.

Relatively speaking, the LODs of the HD Check assays are higher than average or median concentrations found in previous surface contamination studies conducted in Canada. Hon and others[26] evaluated surface contamination levels on more than 400 surfaces and objects found throughout the hospital medical system in health care facilities in British Columbia and reported an average CP concentration of 0.201 ng/cm^2. In their study of Quebec hospitals, Bussières and others[27] reported median concentrations of 0.0035 ng/cm^2 for CP and less than 0.0060 ng/cm^2 for MTX. In a more recent Canadian study involving 83 centres,[28] the same author group found that the 75th percentile concentration for CP was 0.004 ng/cm^2, whereas the 75th percentile concentration for MTX was less than 0.0020 ng/cm^2. Moreover, surface contamination levels in Canadian facilities are showing a downward trend over time.[29]

Of note, the US Pharmacopeial Convention's General Chapter <800>,[10] a best practice document that is widely referenced for use by hospital pharmacies in North America, has indicated a maximum threshold level of 1 ng/cm^2 for CP to reduce the risk of uptake among exposed individuals. Therefore, the promising results offered by the HD

TABLE 1. Side-by-Side Comparison of Results for Methotrexate

Concentration[a]	Sample ID	Wipe Sampling Result (ng/cm^2)[b]	HD Check Result
50% of device LOD	BD-T-M-50-1	0.472	Positive
	BD-T-M-50-2	0.460	Positive
	BD-T-M-50-3	0.594	Positive
	BD-T-M-50-4	0.495	Positive
	BD-T-M-50-5	0.360	Positive
	BD-T-M-50-6	0.414	Positive
	BD-T-M-50-7	0.422	Positive
	BD-T-M-50-8	0.483	Positive
	BD-T-M-50-9	0.402	Positive
	BD-T-M-50-10	0.468	Positive
	Overall[c]	0.457 (0.064)	100%
75% of device LOD	BD-T-M-75-1	0.517	Positive
	BD-T-M-75-2	0.888	Positive
	BD-T-M-75-3	1.014	Positive
	BD-T-M-75-4	0.085	Positive
	BD-T-M-75-5	0.626	Positive
	BD-T-M-75-6	0.701	Positive
	BD-T-M-75-7	0.978	Positive
	BD-T-M-75-8	0.575	Positive
	BD-T-M-75-9	0.784	Positive
	BD-T-M-75-10	0.733	Positive
	Overall[c]	0.690 (0.269)	100%
100% of device LOD	BD-T-M-100-1	1.152	Positive
	BD-T-M-100-2	0.399	Positive
	BD-T-M-100-3	0.072	Positive
	BD-T-M-100-4	0.658	Positive
	BD-T-M-100-5	0.478	Positive
	BD-T-M-100-6	0.889	Positive
	BD-T-M-100-7	0.896	Positive
	BD-T-M-100-8	1.615	Positive
	BD-T-M-100-9	1.133	Positive
	BD-T-M-100-10	1.899	Positive
	Overall[c]	0.919 (0.558)	100%
200% of device LOD	BD-T-M-200-1	1.609	Positive
	BD-T-M-200-2	1.275	Positive
	BD-T-M-200-3	2.135	Positive
	BD-T-M-200-4	1.919	Positive
	BD-T-M-200-5	2.009	Positive
	BD-T-M-200-6	1.983	Positive
	BD-T-M-200-7	1.978	Positive
	BD-T-M-200-8	1.902	Positive
	BD-T-M-200-9	1.540	Positive
	BD-T-M-200-10	2.188	Positive
	Overall[c]	1.854 (0.288)	100%

[a]LOD = limit of detection of the BD HD Check system. For methotrexate, LOD = 0.93 ng/cm^2.
[b]All wipe sampling results have been corrected for the blank.
[c]Overall results presented as average (standard deviation) for conventional wipe sampling and as percent positive for HD Check system.

TABLE 2. Side-by-Side Comparison of Results for Cyclophosphamide

Concentration[a]	Sample ID	Wipe Sampling Result (ng/cm^2)[b]	HD Check Result
50% of device LOD	BD-T-C-50-1	2.181	Positive
	BD-T-C-50-2	2.434	Positive
	BD-T-C-50-3	1.405	Positive
	BD-T-C-50-4	2.587	Positive
	BD-T-C-50-5	2.416	Positive
	BD-T-C-50-6	2.512	Positive
	BD-T-C-50-7	2.208	Negative
	BD-T-C-50-8	2.341	Positive
	BD-T-C-50-9	2.134	Positive
	BD-T-C-50-10	2.131	Positive
	Overall[c]	2.235 (0.333)	90%
75% of device LOD	BD-T-C-75-1	3.814	Positive
	BD-T-C-75-2	2.778	Positive
	BD-T-C-75-3	3.187	Negative
	BD-T-C-75-4	4.114	Positive
	BD-T-C-75-5	3.519	Positive
	BD-T-C-75-6	3.263	Positive
	BD-T-C-75-7	3.153	Positive
	BD-T-C-75-8	3.402	Positive
	BD-T-C-75-9	2.889	Positive
	BD-T-C-75-10	3.625	Positive
	Overall[c]	3.374 (0.410)	90%
100% of device LOD	BD-T-C-100-1	4.217	Positive
	BD-T-C-100-2	3.949	Positive
	BD-T-C-100-3	4.541	Positive
	BD-T-C-100-4	4.625	Positive
	BD-T-C-100-5	4.757	Positive
	BD-T-C-100-6	5.096	Positive
	BD-T-C-100-7	3.954	Positive
	BD-T-C-100-8	4.535	Positive
	BD-T-C-100-9	5.284	Positive
	BD-T-C-100-10	4.463	Positive
	Overall[c]	4.542 (0.437)	100%
200% of device LOD	BD-T-C-200-1	9.381	Positive
	BD-T-C-200-2	9.266	Positive
	BD-T-C-200-3	9.439	Positive
	BD-T-C-200-4	7.394	Positive
	BD-T-C-200-5	10.407	Positive
	BD-T-C-200-6	10.199	Positive
	BD-T-C-200-7	9.837	Positive
	BD-T-C-200-8	8.250	Positive
	BD-T-C-200-9	8.313	Positive
	BD-T-C-200-10	9.752	Positive
	Overall[c]	9.224 (0.955)	100%

[a]LOD = limit of detection of the BD HD Check system. For cyclophosphamide, LOD = 4.65 ng/cm^2.
[b]All wipe sampling results have been corrected for the blank.
[c]Overall results presented as average (standard deviation) for convention wipe sampling and as percent positive for HD Check system.

Check system must be tempered by the recognition that even though the device yielded positive findings at 50% of the LOD, that value is still higher than the drug concentrations typically found on hospital surfaces.

That being said, all of the maximum values reported in the aforementioned surface contamination studies were greater than 0.93 ng/cm^2 and 4.65 ng/cm^2, the LODs of the MTX and CP HD Check assays, respectively. As such, HD Check systems could be of value to screen for those surfaces likely to be highly contaminated, such as biological safety cabinets after drug preparation or after a spill or leak of drugs. If the HD Check system yields a positive result, then cleaning of the surfaces would be needed, or it might be necessary to sample the surface with a conventional wipe method to quantify the amount of contamination. In fact, this scheme was proposed following the 2020 Safe to Touch Conference, composed of experts with experience in hazardous drug handling, monitoring, and research. The consensus statement issued by conference attendees included the recommendation to "employ both qualitative and quantitative tests for ongoing surface contamination monitoring".[30]

Some limitations of this study should be noted. The results are applicable only to the 2 assay systems evaluated (for MTX and CP). Other assays that are commercially available were not evaluated, and their results may differ from those reported here. The LODs listed in product materials of the HD Check systems are actually 0.1 ng/cm^2 for MTX and 0.5 ng/cm^2 for CP; however, these values are based on a sampling area of 1 ft^2 or 930 cm^2 (Product Manager, BD, written personal communication, July 27, 2021). Had this larger wipe sampling area been tested, rather than the typical 100 cm^2 employed in the current study, the findings might have been different. Finally, only stainless steel surfaces were examined, and the results might differ for other types of surfaces found in health care facilities (e.g., laminate, metal, plastic).

CONCLUSION

Despite its limitations, this study showed that the HD Check system was able to positively identify hazardous drug contamination at concentrations below the listed LODs with a fair degree of repeatability, relative to a conventional wipe sampling method. To confirm these findings, it is suggested that future studies examine the HD Check system to detect drug contamination at lower gradients of the LOD (i.e., less than 50% of the LOD). It would also be important to test the ability to detect drug contamination on other types of surfaces, as well as uneven surfaces such as keyboards and calculators, which have been found to have drug contamination in prior studies.[14] If the HD Check system is able to reliably detect positive drug contamination at lower concentrations (i.e., closer to the average reported in surface contamination studies), as well as from different types of surface materials, it could be considered an extremely useful tool for health care facilities to qualitatively assess drug contamination through environmental monitoring and, in turn, minimize the risk (though actual quantification of exposure levels will still not be possible with this device).

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