La combinación del sistema PhaSeal®

The objective of this study was to compare the environmental contamination generated during the preparation of cytostatic agents using three different methods through simulations using fluorescein, and the time required for preparation of each method.

Method: A comparative study of the processing of fluorescein mixtures using three types of closed systems was conducted at the centralized unit for hazardous drugs of the Pharmacy Department of a General Teaching Hospital.

Environmental contamination was detected in critical points of connection, and in splashes produced at any other points. The main variable was qualitative detection of contamination through ultraviolet light when three methods were compared (method A: ChemoClave®, method B: SmartSite® valve and Texium® connector, method C: PhaSeal™ with BD luer extension). A final number of 60 mixtures were prepared to detect differences of at least 5%.

Results: Qualitative contamination at the critical points during preparation, was seen in groups A and B for every mixture that was processed. No contamination at all in critical points was seen in any of the mixtures prepared using PhaSeal™. Statistically significant differences were found between arms A and C (p < 0.001) and arms B and C (p < 0.001); no differences were found between arms A and B.

Conclusions: The combination of PhaSeal™ system in conjunction with the BD luer extension for administering hazardous drugs from a tree modality system has been shown to be the system with the lowest level of contamination during processing without increasing the time required for preparation of the mixture.

KEYWORDS
Hazardous substances; Equipment and supplies; Antineoplastic agents; Drug compounding; Drug contamination.

A comparative study of contamination in three closed systems for the preparation of hazardous drugs through simulations with fluorescein

Estudio comparativo de contaminación de tres sistemas cerrados para la preparación de fármacos peligrosos mediante simulación con fluoresceína

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Originals

How to cite this article/Cómo citar este artículo:
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Recibido el 1 de abril de 2018; aceptado el 8 de agosto de 2018.

DOI: 10.7399/fh.11024

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Palabras clave
Sustancias peligrosas; Equipos y suministros; Agentes antineoplásicos; Preparación de fármacos; Contaminación de fármacos.
A comparative study of contamination in three closed systems for the preparation of hazardous drugs through simulations with fluorescein

Introduction

Occupational exposure to antineoplastic drugs that have carcinogenic, mutagenic, teratogenic and/or reprotoxic properties is a concern for all health care professionals involved in their preparation and administration on a continuing basis.

Although antineoplastic agents constitute the largest group of hazardous drugs (HDs), there are at present other very diverse categories of medications currently in use in our country that affect a wide range of health professions and clinical areas.

Several factors can play a role in the environmental contamination generated after the handling of HDs: installations, maintenance, staff training, personal protective equipment, decontamination, handling protocols and closed system drug-transfer devices (CSTDs).

In its standard on handling HDs (USP 800), the United States Pharmacopeia (USP) requires the use of CSTDs for administering HDs, and recommends the adoption of CSTDs during HDs compounding as long as the pharmaceutical forms allow for it. Studies have shown the effectiveness of closed transfer systems in minimizing environmental contamination.

The USP 800 guidelines recognize the importance of conducting studies for CSTDs and not simply considering them as interchangeable systems. In recognition of these differences, the National Institute for Occupational Safety and Health (NIOSH) is developing performance protocols that may be useful for this purpose, however, these protocols are not yet complete.

In Spain, as in the rest of Europe, there are no specific regulations regarding closed systems. They are usually considered as medical devices regulated under Royal Decree 1591/2009 and belonging to Class IIa devices. Several studies have shown the effectiveness of closed transfer systems in minimizing environmental contamination.

The sample size was calculated on the basis of the percentage of contamination in groups A and B will be around at least 50% and that in contamination in each group. Contamination is expected to be found only at the critical points. According to preliminary studies it is expected that contamination in groups A and B will be around at least 50% and that in group C it will reach a maximum of 10%.

Method C

- 20 mm PhaSeal® Protector™ 50 vial access
- PhaSeal injector™

Secondary objectives were the measurement of the degree of contamination and the time required for preparation of each method.

Methods

A comparative study of the processing of fluorescein mixtures using three types of closed systems was conducted at the centralized unit for hazardous drugs preparation of the Pharmacy Department (PD) of a General and Teaching Hospital.

Table 1: Components used in the reconstitution and dilution/transfer to the infusion

<table>
<thead>
<tr>
<th>Method</th>
<th>Reconstitution</th>
<th>Transfer to bag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method A</td>
<td>20 mm universal spike with vial access CLAVE® connector with a 0.22 µm vent filter</td>
<td>Bag spike with a 0.22 µm vent and a CLAVE® connector</td>
</tr>
<tr>
<td>Method B</td>
<td>20 mm anchoring spike with a SmartSite™ valve port with a 0.22 µm vent filter</td>
<td>BD luer extension set with a SmartSite™ valve</td>
</tr>
<tr>
<td>Method C</td>
<td>20 mm PhaSeal™ Connector</td>
<td>BD luer extension set with a SmartSite™ valve</td>
</tr>
</tbody>
</table>

The primary objective of this study was to qualitatively compare the environmental contamination generated during the preparation of cytostatic agents using three different methods through simulations using fluorescein:

1. Method A: valve administration system (ChemoClave® by ICU Medical).
2. Method B: administration system using the tree modality (SmartSite® valve and Tevadaptor® by BD).
3. Method C: administration system using the tree modality (PhaSeal™ by BD).

Secondary objectives were the measurement of the degree of contamination and the time required for preparation of each method.

Figure 1. Images of the three types of closed systems used in the study.
experience and an oncology pharmacist who usually work in the cytostatic drug preparation area participated in the simulation.

A total of 60 mixtures were processed using vials of fluorescein in a simulation of the preparation of HDs. Amber glass vials with 25 mg of fluorescein powder were prepared beforehand. To ensure there was no fluorescein contamination on the outside of the vials, they were scanned with UV light before bringing them into the BSC.

The fluorescein mixtures were processed in the BSC after scrubbing the cabinet with alkaline detergent and disinfecting it with alcohol. A sterile drape with an absorbent upper side and impermeable bottom was then placed. Each nurse then prepared 10 fluorescein mixtures of each of the three methods by performing the following procedures: inserting the spike into the vial of fluorescein, reconstituting the vials using 50 mL of saline solution (0.05% concentration), removing 40 mL of the solution using a 60 mL syringe with the proper connector, transferring the solution to an infusion bag with 250 mL 5% glucose solution using the CLAVE® valve of the bag’s access spike [Method A], the SmartSite® valve of the extension line [Method B] or the PhaSeal® connector [Method C].

A UV light lamp (UV light 365 nm, Cole-Parmer) was used to detect fluorescein. The light of the BSC was turned off after each preparation and any contamination was detected with the UV lamp. From a qualitative perspective, it was deemed that there was contamination at the critical points if it was visually present at any of the 3 points. In addition, secondarily, a further quantitative analysis was made by placing the critical points on filter paper and measuring them at their largest diameter. A cotton swab was inserted into the PhaSeal® connector to check for contamination. Figure 2 shows detection of fluorescence through UV light.

Another secondary variable was the measurement of the time required to prepare the mixture for each method. The pharmacist was responsible for supervising the processing of the mixtures and measuring the fluorescence generated by each preparation. To reduce variability in the interpretation of the results, the same person performed all of the assessments and photographs were taken to increase control over the process.

The statistical analysis was performed with IBM SPSS Statistics for Windows software, Version 21, Armonk, N.Y.: IBM Corp. Frequencies were used for categorical variables (presence or absence of contamination) and measures of central tendency and dispersion were used for the quantitative variables (size of the drops, local contamination and preparation time). Mean and standard deviation were calculated if they followed a normal distribution and if they did not, median and 25th and 75th percentiles were calculated. Results with p-value < 0.05 were considered to be statistically significant.

The statistical analysis of the main variable, the comparison of the qualitative contamination between the three groups, was performed using the chi square exact Fisher’s test. An alpha value of 5% (p ≤ 0.05) was applied to compare possible differences between variables.

The dimension of the contamination at the critical points of the three groups was compared with the Mann-Whitney U test, as they do not follow a normal distribution.

The preparation times for the three groups were analyzed using Student’s t test for independent samples.

### Results

Table 2 gives a qualitative description of the presence of contamination at the critical points during preparation and the time required for preparation of each of the three methods.

Table 3 examines the quantitative local contamination at the various critical points in greater depth.

With regard to qualitative contamination at the critical points during preparation, contamination was seen in groups A and B for every mixture that was processed. No contamination at all was seen in any of the mixtures on any of the critical points prepared using PhaSeal®. Statistically significant differences were found between arms A and C (p < 0.001) and arms B and C (p < 0.001). No differences were found between arms A and B.

However, when we analyzed the size of the contamination at the critical points during preparation, we found greater contamination in arm A than in arm B at the critical points of the connector and the vial spike and these differences were statistically significant (p = 0.001). The differences in the bag transfer device between groups A and B were not statistically significant (p = 0.100).

The increase in the average time required for the preparation of a mixture in arms B and C with regard to arm A was 5.25 and 2.05 seconds respectively, but these differences did not reach statistical significance (p = 0.058; p = 0.363). The differences between arms B and C were not statistically significant either (p = 0.219).

### Discussion

In order to adequately assess closed systems, criteria to determine that a closed system is effective should be established. Although it would be ideal for all contamination to be totally contained, it is quite unlikely that this is feasible and therefore a limit as low as is reasonably achievable should be set.

Since no standard exists for the assessment of closed systems with respect to reducing contamination, there are no recommendations on which one to use. In the absence of a standard, a number of methods have been proposed that have allowed the effectiveness of several devices marketed as closed systems to be assessed. Most of the studies that attempt to demonstrate that there is less environmental contamination when closed sys-

### Table 2. Contamination, and time of the different methods. Time of preparation in the three methods are indicated through mean and standard deviations in parentheses

<table>
<thead>
<tr>
<th>Contamination critical points</th>
<th>Method A</th>
<th>Method B</th>
<th>Method C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixture time (mean seconds)</td>
<td>83.3</td>
<td>88.6</td>
<td>85.4</td>
</tr>
</tbody>
</table>

### Table 3. Local contamination in critical points. Size of contamination points in the different methods are indicated through median and interquartile ranges 25-75 in parentheses

<table>
<thead>
<tr>
<th>Syringe connector (cm)</th>
<th>Method A</th>
<th>Method B</th>
<th>Method C</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.00-0.05)</td>
<td>(0.00-0.05)</td>
<td>(0.00-0.05)</td>
<td>(0.00-0.05)</td>
</tr>
<tr>
<td>Vial spike (cm)</td>
<td>0.10</td>
<td>0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>(0.00-0.05)</td>
<td>(0.00-0.05)</td>
<td>(0.00-0.05)</td>
<td>(0.00-0.05)</td>
</tr>
<tr>
<td>Bag spike/bag valve (cm)</td>
<td>0.08</td>
<td>0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>(0.00-0.05)</td>
<td>(0.00-0.05)</td>
<td>(0.00-0.05)</td>
<td>(0.00-0.05)</td>
</tr>
</tbody>
</table>
tems are used have assessed surface contamination, employing sampling techniques that allow an assessment of the residual contamination by cytostatic drugs. Other studies have used surrogate markers such as fluorescein, titanium tetrachloride and radioactive technetium.

Our study was performed with fluorescein, a marker which, although not considered to be overly sensitive, is useful for detecting contamination and the formation of droplets during handling and provides a simple and inexpensive method that can be used as a first step to easily identify which systems are not closed. In addition, fluorescein, unlike other markers, does not cause any harm to those handling it.

The use of drug administration systems with a tree modality, in which the different HDs are connected through safety valves to an administration tree, is very extended in our country. This is considered to be a closed system as the bags are not disconnected after the infusion has ended. The drugs are prepared in the BSC and added to the bag through a safety valve after the extension tube has been purged with clean saline solution. For a system to be considered as being entirely closed, its critical point through which the drug is added must be free of any contamination.

The other type of drug administration system that is used in our country is the ChemoClave® valve administration system. In this drug administration system the various mixtures that constitute the patient’s treatment are added on one by one, through a series of connections and disconnections. The already processed hazardous drug is sent by the PD in an infusion bag with a spike that does not require purging and which is connected in the nursing unit to an extension via a closed male luer connector (Spiros®) to the CLAVE® valve of the bag’s spike. The extension is then connected to the pump administration set available at the hospital, via its one-way connector to the infusion bag’s spike. In an earlier study we had already pointed out that such an administration system cannot be considered closed as the connection between the bag’s CLAVE® valve and the extension’s Spiros® connector is not dry.

The study of contamination at critical points has revealed that there is contamination at said points during preparation both with the ChemoClave® system and the system that uses Texium® and SmartSite®. No contamination was found with PhaSeal®, whose connections were found to be totally dry and is the only system that leaves the BSC without any visible contamination.

The quantitative analysis showed that the B system is less contaminated at the critical points of the connector and the spike than the A system. This is consistent with a previous study performed with fluorescein.

With regard to processing time, the system that took the least time was the A system, which does not require purging of the system. However, no statistically significant differences were found, probably because although methods B and C require purging, their extensions with a luer connector make the connection to the saline bag easier than a conventional spike. A previous study of handling staff preferences, we found that luer connections were preferred to conventional connections because they reduce the risk of mechanical injury and make handling easier. No differences were found in the time required for preparation of the mixture between arms B and C, probably because although the filtration system with Texium® and SmartSite® is simpler, it has a greater resistance to flow than the PhaSeal® system.

The use of filters to equalize pressure when transferring HDs is highly contested with regard to their ability for achieving truly effective filtering of the aerosol gas contained in the air that is passed out of the system. In our view, what is even more relevant is the fact that the connections of these filter systems are not dry and this therefore translates into environmental contamination inside the BSC and likely spreads outside of it.

Due to the importance of ensuring that the closed system selected is capable of containing the HDs from reconstitution to administration, it is of vital importance that systems with dry connections be used during processing, so that the infusion bags with the HD leave the BSC without any contamination and that administration be carried out with a system that is really closed.

In our study, the combination of PhaSeal™ system in conjunction with the BD luer extension for administering HDs from a tree modality system has been shown to be the system with the lowest level of contamination during processing without increasing the time required for preparation of the mixture.

Funding

No funding.

Conflict of interests

No conflict of interests.

Contribution to the scientific literature

The article offers a systematic comparison of different closed systems for handling of hazardous drugs. The main value of the research lies in the testing of compatible closed-system combinations which cover the whole chain of reconstitution, transfer and application of the pharmaceutical compounds.

The constant marketing of closed-system transfer devices for the safe handling of hazardous drugs makes necessary a continuous training of health professionals together with the evaluation of the features of the different systems. The evaluation of closed-systems in relation to contamination decrease has not yet been standardized and there are no recommendations about which closed-system to use.

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