Use of a Closed System Device to Reduce Occupational Contamination and Exposure to Antineoplastic Drugs in the Hospital Work Environment

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Objectives: The aim of the preset study was to evaluate the applicability of a closed system device to protect against occupational contamination and exposure to antineoplastic drugs in the work environment of a hospital.

Methods: We compared the contamination by and exposure to cyclophosphamide (CPA) between a conventional mixing method and a mixing method using a closed system device. Wipe samples in the preparation room, gloves samples and 24-h urine samples of pharmacists preparing antineoplastic drugs were collected. Working surfaces inside the biological safety cabinet (BSC), front side of the air grilles of the BSC, stainless steel trays, working table and floor were wiped. At first, sample collection was done on 5 days over an interval of 2 weeks using the conventional mixing method. After 2 weeks training for using the closed system device, sample collection was done 5 days over an interval of 2 weeks using the closed system device.

Results: When pharmacists prepared antineoplastic drugs by the conventional method, CPA was detected from all wipe samples, and the mean and median concentrations of CPA were 1.0 and 0.16 ng cm\(^{-2}\), respectively (range was from 0.0095 to 27 ng cm\(^{-2}\)). When pharmacists prepared antineoplastic drugs with a closed system device, CPA was detected from 75% of the wipe samples at mean and median concentrations of 0.18 and 0.0013 ng cm\(^{-2}\), respectively (the range was from lower than detection limit to 4.4 ng cm\(^{-2}\)). Using the closed system device significantly reduced the surface contamination of CPA for all wipe sampling points in the preparation room (Mann–Whitney’s U-test). The range of CPA of glove samples used in the conventional method and closed system device ranged from lower than detection limit to 3200 ng per glove-pair and from lower than detection limit to 740 ng per glove-pair, respectively. Using the closed system device significantly reduced the gloves contamination of CPA (Mann–Whitney’s U-test). The range of urinary CPA of six pharmacists preparing the antineoplastic drugs with the conventional method and closed system device ranged from lower than detection limit to 3200 ng per day and from lower than detection limit to 740 ng per day, respectively. Using the closed system device significantly reduced the amount of urinary CPA in pharmacists preparing the antineoplastic drugs (Wilcoxon’s signed ranks test).

Conclusions: We concluded that a closed system device can reduce occupational contamination and exposure to antineoplastic drugs in the hospital work environment.

Keywords: antineoplastic drugs; biological monitoring; closed system device; hospital work environment; surface contamination

INTRODUCTION

Antineoplastic drugs are clearly beneficial for patients but there is concern about the health risk to medical workers handling them (Connor and...
McDiarmid, 2006; Shirato, 1992). Usually, antineoplastic drugs are diluted with a diluting solution and then mixed into infusions by medical workers before administration to patients. In these processes, the air, working table, clothes and medical equipment used may be contaminated by these antineoplastic drugs (NIOSH, 2004). Increases in hair loss, skin rash, infertility, miscarriage, genotoxic damage and leukemia or other cancers have been observed among healthcare workers handling antineoplastic drugs (Falck et al., 1979; Thiringer et al., 1991; Undeger et al., 1999; Valanis et al., 1999; Jakab et al., 2001; Burgaz et al., 2002; Krstev et al., 2003; NIOSH, 2004). In Japan, there have been reports of nurses preparing antineoplastic drugs being exposed to these drugs with the cautionary note that lymphocyte DNA damage could be induced by such drugs (Yoshida et al., 2006; Sasaki et al., 2008).

The guidelines for safe handling of antineoplastic drugs in hospital issued by the Japan Pharmaceutical Association recommend preparing antineoplastic drugs using a biological safety cabinet (BSC) (Kitada et al., 2005). In 2006, BSCs were installed in 57% of the hospitals in Osaka prefecture, Japan (Yoshida et al., 2008). The use of BSCs reduced the exposure to antineoplastic drugs, but some reports showed that preparation rooms continue to show contamination by these drugs (Sessink et al., 1992a; Connor et al., 1999). This can occur due to spills of the aerosol generated when a drug solution is withdrawn from a vial. The inside of vial should be kept at negative pressure to reduce spills during the mixing operation, and 76% of the hospitals in Osaka prefecture use this technique (Yoshida et al., 2008). However, this technique alone is not sufficient to completely prevent spill generation.

As a possible countermeasure, a closed system device is available. In Japan, the only commercially available device is sold by PhaSeal® (Carmel Pharma Japan, Tokyo, Japan). Figure 1 shows the structure of PhaSeal®, which consists of a protector equipped with an expansion chamber, membrane and air cannula and an injector luer lock equipped with a membrane, safety latch, luer (female) and specially cut cannula (Carmel Pharma Japan, 2006). An outline of the method of extracting an antineoplastic drug solution from a vial using PhaSeal® is in the web page of Carmel Pharma USA (http://www.carmelpharmausa.com/econtent/94; accessed 5 Dec 2008). The connection of the protector and injector luer lock is covered with a membrane. When the protector is connected with the injector luer lock, the membrane of the protector adheres tightly to the membrane of the injector, so the specially cut cannula of the injector luer lock can be inserted into the vial without exposure to the outside air. When air is injected from the syringe into the vial, the expansion chamber equalizes the pressure of the vial by transferring the air from the vial to the chamber. When the drug solution is extracted from the vial to the syringe, the expansion chamber equalizes the pressure in the vial by transferring air from the chamber into the vial. Because PhaSeal® seals the cannula and equalizes the pressure of the vial, spill generation can be prevented. Reports have shown that such a closed system device can prevent contamination of work environments (Sessink and Ryden, 1999; Vandenbroucke and Robays, 2001; Connor et al., 2002; Nygren et al., 2002; Spivey and Connor, 2003; Harrison et al., 2006). However, the statistical evaluation of the exposure of healthcare workers who prepare antineoplastic drugs with such a closed

![Image](http://annhyg.oxfordjournals.org/)
system device has not been reported. In Japan, closed system devices are not known to most healthcare workers and their use has not been reported.

The aim of the present study was to evaluate the applicability of a closed system device in the Japanese medical environment. We compared the contamination levels of cyclophosphamide (CPA) in the preparation room and the exposure of pharmacists who prepared antineoplastic drugs when using a conventional mixing method (conventional method) and a mixing method employing a Closed System method (CS method).

METHODS

This study was approved by the ethical review board of the Osaka Prefectural Institute of Public Health.

Study design

The present study examined procedures conducted in an antineoplastic drug preparation room of a hospital in Osaka prefecture, Japan. Four BSCs of the same type (VH-1300BH-2A/B3-C, NKsystem, Osaka, Japan) were installed in the room (Fig. 2). These BSCs had a return air system and return air was filtered with an High Efficiency Particulate Air filter (HEPA filter) and a charcoal filter. Six pharmacists (pharmacist A, B, C, D, E and F) were engaged in preparing antineoplastic drugs in this hospital. One to four of the pharmacists prepared antineoplastic drugs from 9:00 to 17:00 from Monday to Friday. The pharmacists wore disposable polychloroprene gloves, a disposable polypropylene gown which had long sleeves and closed fronts, a disposable cap and a disposable surgical mask. All pharmacists used the technique in which the inside of vial was kept at negative pressure.

The procedure for preparing antineoplastic drugs was as follows. Antineoplastic drugs and infusion solutions were carried to the working table of the preparation room and put on a stainless steel tray. The tray was carried into the BSC, and the drugs and infusion solutions were mixed. The antineoplastic drug solutions on the tray were transferred to the working table and packed in plastic zipper bags and then transferred outside the preparation room.

The interior of the BSC was cleaned with 70% ethanol after the mixing operation, and the trays were washed with distilled water every second day. The floor of the room was mopped with chlorhexidine gluconate and benzalkonium chloride after the mixing operations on every Friday. There was no set schedule or routine for the frequency and procedure of cleaning the working table. These cleaning procedures were not changed during the present study.

In order to evaluate the contamination of CPA in the preparation room when the pharmacists used the conventional method, wipe samples and the gloves used were collected after the preparation of antineoplastic drugs at the end of the work shift on Thursday or Friday. Also collected were 24-h urine samples of the pharmacists who prepared the antineoplastic drugs. Sample collection was done on 5 days over an interval of 2 weeks. The urine samples of pharmacist A, B, C, D, E and F were collected on 3, 2, 2, 2, 2 and 2 days, respectively. Next, the pharmacists were given 2-week training on the handling of the closed system device. At 2 weeks after the training, wipe, glove and urine samples were collected.

**Fig. 2.** Ground plan of the preparation room and wipe sampling points.
collected on 5 days over an interval of 2 weeks in order to evaluate the contamination from CPA when the pharmacists had used the CS method. The urine samples of pharmacist A, B, C, D, E and F were collected on 4, 3, 1, 2, 3 and 1 days, respectively. The concentrations of CPA in the wipe and glove samples and the amount of CPA excreted in the urine were compared between the conventional and CS methods.

Wipe sampling

Wipe sampling points of the preparation room are described in Fig. 2. Before the mixing operation, working surfaces inside the BSC were wiped [Fig. 2(1)]. After the pharmacists finished preparing the drugs, wipe samples were obtained from the working surfaces and front side of the air grilles of the BSC [Fig. 2(2)], trays [Fig. 2(3)], working tables [Fig. 2(4)] and floors [Fig. 2(5)]. Each sampling location was marked with vinyl colored tape and measured with a tape measure to determine the sample area. We calculated the area of non-flat surface as the front side of the air grilles of the BSC by measuring vertically and horizontally with the tape measure. The wipe sampling procedure was done according to Sessink et al. (1992b). A 10-ml portion of the sampling solution of 0.03 M sodium hydroxide was dropped onto the surface, which was then wiped using two sheets of tissue paper (JK wiper 150-S, 225 × 215 mm, Nippon Paper Crecia, Japan). One tissue was used to wipe the surface wet with the sampling solution and then was stored in a storage tube. The second tissue was used to firmly wipe the same surface from top to bottom and from left to right until it was dry, and this was also stored in the same storage tube. Because the front side of the BSC air grille has a complex structure, one tissue was wetted with 5 ml of sampling solution and used to wipe the air grille, and the second tissue was wetted with 5 ml of sampling solution and used to wipe it again. To the wipe samples, 20 ml of 0.03 M sodium hydroxide was added and the samples were sonicated for 1 h in an ultrasonic bath (Trassonic T570, ELMA, Japan). A 5-ml portion of the supernatant was stored at −30°C until measurement.

Glove sampling

One pair of gloves which the pharmacist removed after preparing antineoplastic drugs was collected in the 250 ml polypropylene wide-mouth container (AS ONE, Osaka, Japan). To this container, 30 ml of 0.03 M sodium hydroxide was added, and the container was shaken vigorously for 2 h. A 5-ml portion of the extract solution was stored at −30°C until measurement.

Urine sampling

All urine samples of the pharmacists were collected separately in the 500 ml polypropylene wide-mouth container (AS ONE) from the beginning of the mixing operation to the next day. Each urine sample was stored at −30°C until measurement. The urine sample was analyzed separately, and a total amount of CPA in each urine sample was calculated.

Quantitative determination of CPA

The CPA in the wipe, glove and urine samples was measured according to the method of Sessink et al. (1993). Briefly, after addition of isophosphamide as the internal standard and 0.5 ml Tris–hydrochloric acid buffer (1 M, pH 8.0), the sample was extracted twice with 20 ml of diethyl ether. We confirmed that isophosphamide had never been handled in the preparation room. After evaporation, the diethyl ether extract was reacted with 0.1 ml ethyl acetate and 0.1 ml trifluoroacetic anhydride at 70°C for 30 min. The reacted mixture was dried under a nitrogen flow and reconstituted with toluene. The CPA of the wipe and glove samples was measured with a high-resolution gas chromatograph (HP-5890 SERIESE 2 Plus, Hewlett-Packard, Santa Clara, CA, USA)/quadrupole mass spectrometer (HP-5972, Hewlett-Packard) equipped with a capillary column of DB-5MS (0.25 mm internal diameter × 30 m, 0.25 μm film thickness, Agilent J&W, Santa Clara, CA, USA). Urinary CPA was measured with a high-resolution gas chromatograph (HP 6890, Hewlett-Packard)/high-resolution mass spectrometer (JMS 700D, JEOL, Tokyo, Japan) equipped with a capillary column of DB-5MS (0.25 mm internal diameter × 30 m, 0.25 μm film thickness, Agilent J&W). The high-resolution gas chromatograph conditions were as follows. The carrier gas was helium at 1 ml min⁻¹, the injection mode was splitless for 2 min, the injection volume was 2 μl and the injection temperature was 250°C. Oven temperature was set at 100°C for 2 min, then raised at 20°C min⁻¹ to 200°C and at 4°C min⁻¹ to 280°C and finally kept constant for 5 min. In quadrupole mass spectrometry conditions were as follows. The ion detection mode was selected ion monitoring, the ionizing mode was the electronic impact ionizing mode and the detector temperature was 280°C. The quantity and qualifier ions were 307 and 309, respectively. The high-resolution mass spectrometry conditions were as follows. Resolution was 10 000, the ion detection mode was selected ion monitoring and the ionizing mode was the electronic impact ionizing mode. The ionizing temperature was 280°C, ionizing energy 38 eV and ionizing current 600 μA. The quantity and qualifier ions were 307.0226 and 308.0289, respectively.

The mean recovery rates of 120 ng CPA from the surface of BSC and the gloves were 93.8 ± 2.3% (n = 8) and 52.8 ± 11.4% (n = 5), respectively. The mean recovery rate of 1.0 ng CPA from 5-ml urine sample

[Note: The rest of the text is not transcribed due to the image limitations.]

was 107.6 ± 4.6% (n = 5). The limits of measurement of CPA from the wipe, glove and urine samples were 6.0, 6.0 and 0.1 ng, respectively. In order to check the negative blank, we added 10 ml of 0.03 M sodium hydroxide to the unused tube with two sheets of tissue paper immediately after wipe sampling was finished. And the negative wipe blank samples were measured as same as other wipe samples. In the present study, CPA was not detected from any negative blank wipe samples.

Statistical analysis

Comparison of the CPA amount prepared per day in the preparation room between the conventional method and the CS method was conducted using the t-test. Zero was assigned as the undetectable amount. Comparison of CPA concentrations of wipe and glove samples between conventional method and CS method was conducted using Mann–Whitney’s U-test because there was no normal distribution. Spearman’s correlation was used to assess the relationships between CPA amount of urine samples and CPA concentration of corresponding wipe and glove samples. These calculations were conducted by using SPSS 12.0 J software (SPSS Japan, Japan).

RESULTS

Amount of CPA prepared in the preparation room

During the period of the present study, the mean amount of CPA prepared in the preparation room was 2.54 ± 1.49 g day⁻¹. The mean CPA amounts prepared during the period of the conventional method and the CS method were 2.76 ± 1.50 and 2.36 ± 1.46 g day⁻¹, respectively. Comparison of the two groups shows that the amount of CPA prepared was not significantly different.

Contamination of wipe samples

Table 1 shows the concentration of CPA in wipe samples in the preparation room. In the conventional method, CPA was detected from all wipe samples, with the mean and median CPA concentrations being 1.0 and 0.16 ng cm⁻² (range 0.0095–27 ng cm⁻²), respectively. The mean CPA concentration of working surfaces inside the BSC after preparation was 1.3 times as high as before preparation. The mean CPA concentrations of the trays were 1.3, 1.1, 1.3 and 9.4 times as high as those of the working surface inside the BSC, the BSC front side air grille, working table and floor, respectively. In the CS method, CPA was detected from 75% of the wipe samples, with the mean and median CPA concentrations being 0.18 and 0.013 ng cm⁻² [range not detected (ND)–4.4 ng cm⁻²], respectively. The mean CPA concentration of working surfaces inside the BSC before preparation was similar to that after preparation. Mean CPA concentrations of the BSC front side of air grille were 1.3, 2.6, 6.8 and 10 times as high as the working surface inside BSC, trays, working table and floor, respectively. The median CPA concentrations of all wiped surface points for the period of CS method were significantly lower than those of the conventional method (Mann–Whitney’s U-test).

The mean CPA concentrations of working surfaces inside the BSC before preparation, working surfaces inside the BSC after preparation, the BSC front side of air grille, tray, working table and floor for CS method were reduced by 27, 23, 24, 8.1 and 20% respectively, based on the mean values for the conventional method.

Contamination of glove samples

The outline of the amounts of CPA in glove samples is described in table 2. CPA was detected from

<table>
<thead>
<tr>
<th>Wipe sampling points</th>
<th>Sampling time</th>
<th>Conventional Method</th>
<th>Closed System Method</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SD</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Working surface inside BSC</td>
<td>Before&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>0.94 ± 0.03</td>
<td>0.082</td>
</tr>
<tr>
<td>Working surface inside BSC</td>
<td>After&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21</td>
<td>1.2 ± 0.06</td>
<td>0.093</td>
</tr>
<tr>
<td>BSC front side of air grille</td>
<td>After&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>1.4 ± 0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>Trays</td>
<td>After&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21</td>
<td>1.6 ± 0.08</td>
<td>0.11</td>
</tr>
<tr>
<td>Working table</td>
<td>After&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>1.2 ± 0.08</td>
<td>0.93</td>
</tr>
<tr>
<td>Floor</td>
<td>After&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25</td>
<td>0.17 ± 0.06</td>
<td>0.085</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>127</td>
<td>1.0 ± 0.16</td>
<td>0.16</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mann–Whitney’s U-test.

<sup>b</sup>Before = before preparation, After = after preparation.
15 of 22 glove samples from the conventional method, and the mean and median of CPA concentrations were 310 and 28 ng per glove pair (range ND–3200 ng per glove pair), respectively. For the CS method, CPA was detected from six of 27 glove samples, and the mean and median of CPA concentrations were 51 and ND ng per glove pair (ND–740 ng per glove pair), respectively. The median value for the CS method was significantly lower than that for conventional method \((P = 0.004, \text{Mann–Whitney’s } U\text{-test})\). The mean value for CS method was reduced to 16% of the mean value for the conventional method.

**CPA in urine samples**

Table 3 shows the total amount of CPA in urine samples of the pharmacists. The mean and median values among the six pharmacists during the conventional method were 39 and 12 ng day\(^{-1}\), respectively. The mean and median values during the CS method were 4.9 and 2.0 ng day\(^{-1}\), respectively. The median CPA amount of urine samples for the CS method was significantly lower than for the conventional method \((P = 0.046, \text{Wilcoxon’s signed ranks test})\). The mean CPA of urine samples for the CS method was reduced to 13% of the conventional method. We assessed the relationship between the CPA amount of 27 urine samples of six pharmacists collected during the period of the present study and CPA concentration of the corresponding wipe and glove samples. No significant correlation was found.

**DISCUSSION**

In the conventional method, CPA contamination at a relatively high level was found on the working surface inside BSCs before the preparation procedure. This result suggested that a contamination generated on previous days could not be cleared by the cleaning method of this hospital. Inside of BSCs was cleaned with 70% ethanol in this hospital, but the appropriate cleaning agent should be used in order to inactivate antineoplastic drugs. For example, Massoomi et al. reported that in order to inactivate antineoplastic drugs, 2% hypochlorite detergent and a thiosulfate benzyl alcohol were used (Massoomi et al., 2008).

CPA was detected in all wipe samples for the conventional method, which shows that the entire preparation room was contaminated with the drugs. There was a danger of pharmacists entering the room being exposed to CPA, even if they did not handle CPA. Similar studies have been conducted in Canada, US and Belgium. For the conventional method, the ranges of CPA concentrations of working surfaces inside the BSC, the BSC front side of the air grille, working table and floor were 0.01–12.19, 0.12–40.13, 0.0–0.67 and 0.01–2.36 ng cm\(^{-2}\), respectively, in Connor’s study (Connor et al., 1999) and 0.131–6.608, 0.240–5.909, 0.098–0.210 and 0.045–0.885 ng cm\(^{-2}\), respectively, in Vandenbroucke’s study (Vandenbroucke and Robays, 2001). The working table contamination of the present study (0.08–4.0 ng cm\(^{-2}\)) was much higher than that of the previous studies. After finishing the mixing operation, the pharmacists removed their personal protection equipment and placed it in a waste box inside the preparation room. At this time, the pharmacists seemed to be exposed to CPA by contacting with contaminated fixtures without personal protection equipment. The working table was

### Table 2. Amount of CPA in gloves samples (ng per glove pair)

<table>
<thead>
<tr>
<th></th>
<th>Conventional method</th>
<th></th>
<th>Closed system method</th>
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<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>Mean</td>
<td>Median</td>
<td>Range</td>
<td>Detection rate (%)</td>
<td>(n)</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>310</td>
<td>28</td>
<td>ND–3200</td>
<td>68</td>
<td>27</td>
</tr>
</tbody>
</table>

\(^a\)Mann–Whitney’s \(U\text{-test}\).

### Table 3. Total amount of CPA in urine samples (ng day\(^{-1}\)) from the pharmacists

<table>
<thead>
<tr>
<th>Pharmacist</th>
<th>Conventional method</th>
<th>Closed system method</th>
<th>(P) value (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sampling days (days)</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>A</td>
<td>3</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>170</td>
<td>170</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>D</td>
<td>2</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>E</td>
<td>2</td>
<td>8.5</td>
<td>8.5</td>
</tr>
<tr>
<td>F</td>
<td>2</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Mean and median among the six pharmacists

| Pharmacist | Sampling days (days)| Mean                 | Median               | Range             | Detection rate (%) |
| A          | 3                   | 39                  | 12                   | 4.9               | 2.0               | 0.046               |

\(^a\)Wilcoxon’s signed ranks test.
probably contaminated when a contaminated tray was placed on it. Another reason for the high contamination of the working table was that the pharmacists scarcely wiped it because no cleaning routine had been established. Thus, routine methods for cleaning all places in the preparation room need to be established. Before this study, we thought that the outside of the BSC would not be very contaminated compared to the inside. We did not collect the wipe samples of outside of the BSC before the work shift because we thought that CPA could not be detected from outside of the BSC during 1 day preparation. Our findings reinforced the importance of environmental monitoring in order to promote safety measures.

With the CS method, CPA was not detected in 52% of the working surfaces inside the BSC and 40% of the trays. The CPA contamination level of all wipe sampling points with the CS method was significantly lower than for the conventional method, though the amount of CPA prepared and cleaning procedure of the preparation room were not different between the two methods. The closed system device reduced the generation of spill which was an original source of contamination. Consequently, CPA contamination was reduced inside BSC both before and after work shift and whole interiors regardless of use of same cleaning procedure. To improve the cleaning procedure is seemed to make further decreasing the contamination level of CPA. Vandenbroucke and Robays reported that a closed system device reduced CPA contamination of working surfaces inside the BSC (range 0.131–6.608 to 0.051–0.654 ng cm$^{-2}$), the BSC front side of air grille (range 0.240–5.909 to 0.071–3.372 ng cm$^{-2}$), working table (range 0.098–0.210 to 0.008 ng cm$^{-2}$) and floor (range 0.045–0.885 to 0.025–0.110 ng cm$^{-2}$) (Vandenbroucke and Robays, 2001). Harrison et al. also reported that a closed system device significantly reduced the contamination of the BSC front side of air grille and working table (Harrison et al., 2006). The present study confirmed these findings. In the Vandenbroucke and Robays study (Vandenbroucke and Robays, 2001), the work environment was improved within 6 months after the introduction of the closed system device. In the present study and the Harrison et al. study (Harrison et al., 2006), the work environment was improved within 3 months from implementation of the closed system device. Thus, closed system devices can relatively rapidly reduce CPA contamination.

CPA contamination of gloves used during the CS method was significantly lower than that during the conventional method. This was probably due to the fact that CPA spills remained within the closed system device. The urinary CPA level was significantly reduced for the CS method. The present study showed the utility of a closed system device not only for significant reduction of CPA contamination of the occupational environment but also the amount of pharmacist exposure to CPA. Wick et al. (2003) reported a decrease in the urinary CPA level in pharmacists in addition to reductions in surface contamination. The present study confirmed this result. The mean CPA concentrations of all the wipe sampling points in the preparation room, gloves and urine samples for CS method were reduced by 18, 17 and 13%, respectively, based on the mean value for the conventional method. From this result, the closed system device seemed to reduce in similar rates of efficacy between the contamination level of the preparation room and the exposure level of CPA. Sessink et al. (1992b, 1995, 1997) reported that the mean CPA amounts in the urine of pharmacists and/or pharmacy technicians in 1992, 1995 and 1997 study were 50 (range 0–500), 180 (range 10–530) and 140 ng day$^{-1}$ (range 0–520 ng day$^{-1}$). Urinary CPA levels from use of the conventional method (mean 39 ng day$^{-1}$, range ND–300 ng day$^{-1}$) were the same as these previously reported levels, but the urinary CPA level for the CS method (mean 4.9 ng day$^{-1}$, range ND–43 ng day$^{-1}$) was much lower.

The purpose of using BSCs is to protect workers from inhaling the spills of antineoplastic drugs generated during mixing operations, while the purpose of using a closed system device is to prevent the generation of spills. The present study confirmed that CPA contamination was reduced by the closed system device probably due to reduction of spills generation. However, because we could not negate the possibility of leakage from the closed system device by accident, workers should not prepare antineoplastic drugs outside the BSC even if they use a closed system device. NIOSH recommends not using the closed system device as a substitute for BSC (NIOSH, 2004).

Up to 25% of CPA administered is excreted in the urine as an unchanged substance for 24 h and >50% of CPA is metabolized to 4-ketoCPA and carboxyphosphamid via 4-hydroxyCPA by cytochrome P450 and oxidase in the liver (Fujita, 1986). In the present study, though the urinary CPA level was reduced by the closed system device, the CPA amount of the urine samples did not show correlation with the CPA concentration of the corresponding wipe and glove samples. The difference of exposure routes to CPA is likely to affect the change in the metabolism and excretion of uptaken CPA. Although all interiors in the preparation room were contaminated by CPA, the pharmacists contacted them without personal protection equipment. The skin exposure as well as inhalation was considered to be one additional possible route of exposure. Urinary CPA level seemed to depend on not only the amount of CPA exposure but also the exposure route and individual metabolic and excretion capacity of the workers. Because all BSCs in the preparation room were a return air system, the
system may affect the exposure amount of CPA. Further studies are needed to clarify the exposure evaluation including the urinary metabolized CPA level.

**CONCLUSION**

The entire preparation room was confirmed to be contaminated with CPA. The closed system device tested was able to significantly reduce CPA contamination of surfaces in the preparation area and gloves which the pharmacists used during the mixing operation. Using the closed system device also reduced the amount of urinary CPA of the pharmacists. A closed system device should be able to help protect workers from contamination by antineoplastic drugs.

**REFERENCES**


