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Development of a New Cleaning Method for Anticancer Drug Preparation Areas: Verification of the Substance Removal Effect of Cyclophosphamide by Electrolyzed Water

Hisanori Shimizu,[a,*] Hiromu Tanigawa,[a] Yuma Nonomiya,[a,b] Yume Otsuka,[a] Yuka Taniguchi,[a] Kazuo Kobayashi,[a] Yusuke Iwasaki,[c] and Masakazu Yamaguchi[a]

[a]*Department of Pharmacy, Japanese Foundation for Cancer Research, Cancer Institute Hospital, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan;* [b]*Division of Pharmaceutical Care Sciences, Center for Social Pharmaceutical Care Sciences, Keio University Faculty of Pharmacy, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan;* [c]*Department of Analytical Chemistry, School of Pharmacy and Pharmaceutical Sciences, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan*

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In Japan, wiping with distilled water and disinfectant ethanol is the most common method of cleaning biological safety cabinets (BSCs). In 2020, an electrolyzed water generator WOX-30WA-M2 was approved for hand disinfection. This medical device generates hypochlorite water (0.0035% hypochlorous acid and 0.015% hydrochloric acid: HClO water) and alkaline electrolyzed water (0.03% sodium hydroxide: AEW) from salt water. We investigated whether a new cleaning method for BSCs using HClO water and AEW is superior to the conventional cleaning method in removing anticancer drug residues. A model using stainless steel plates contaminated with cyclophosphamide (CPA) was prepared, and the level of CPA residue remaining after wiping was compared with the conventional method. The new cleaning method was more effective than the conventional method with respect to the level of CPA residue remaining. High-performance liquid chromatography was employed to confirm the effect of various solvents on CPA removal. The peak area of CPA decreased with increasing chlorine concentration, accompanied by the appearance of 3-chloro-CPA.Although the sum of CPA and 3-chloro-CPA areas could provide a more comprehensive evaluation of total compound recovery, accurate quantification was not feasible in this study because 3-chloro-CPA is unstable and no certified standard was available. As an alternative, we confirmed the qualitative restoration of CPA after solid-phase extraction (SPE) treatment, suggesting that the apparent loss was mainly due to reversible formation of chlorinated derivatives rather than irreversible degradation. Use of an electrolyzed water for cleaning BSCs should reduce inhalation exposure due to evaporation of residual anticancer agents and also reduce alcohol use. Sequential wipe-off of HClO water and AEW is non-corrosive to stainless steel and maintains the effectiveness of sanitization and antifouling, suggesting this is a safe method for cleaning BSCs.

Key words cyclophosphamide, hypochlorous acid, electrolyzed water, cleaning method, anticancer drug exposure

INTRODUCTION

Anticancer drugs are known to be carcinogenic to humans, underscoring the importance of preventing occupational exposure to these agents.[1)] As the use of biological safety cabinets (BSCs) is strongly recommended for the preparation of anticancer drugs, protecting workers from exposure and ensuring drug sterility are critical considerations.[2)]

In Japan, BSC cleaning has traditionally involved sequential wiping of cabinet surfaces with distilled water followed by disinfectant ethanol using disposable cloths. However, the Japanese guidelines do not strongly recommend regular environmental monitoring of surface contamination by hazardous drugs (HDs). In contrast, because highly volatile drugs such as cyclophosphamide and ifosfamide cannot be completely removed by wiping with distilled water,[3)] preventive strategies should include consideration of possible airborne exposure during ethanol-based decontamination procedures. Innovative methods for daily routine BSC cleaning that effectively remove substances while avoiding volatilization of HDs are therefore needed.

The *Guidelines for Occupational Exposure Control in Cancer Drug Therapy, 2019 Edition*, only weakly recommend sodium hypochlorite (NaClO), sodium thiosulfate, and sodium hydroxide for inactivating anticancer drugs.[2)] Therefore, several studies have examined the use of NaClO or ozone to

*To whom correspondence should be addressed. e-mail: hisanori.shimizu@jfcr.or.jp

clean surfaces contaminated with anticancer drugs.[4-6] However, there are no reports describing the details of changes in materials or the biological safety of decontamination or inactivation using chlorine-based agents. In addition, as chlorine-based agents can corrode equipment made of stainless steel and other metals, there is a critical need for more effective cleaning methods suitable for daily use.

In May of 2020, a strong acidic electrolyzed water generator was approved as a designated medical device for hand disinfection. According to the Ministry of Health, Labour and Welfare's *Document on the Similarity of Hypochlorous Acid Water and Sodium Hypochlorite*, hypochlorous acid water (hypochlorous acid: HClO) exhibits powerful disinfecting properties and is thus a promising cleaning agent for pharmacists performing clean operations.[7]

HClO and NaClO have been reported to react with cyclophosphamide (CPA), leading to the formation of chlorinated derivatives such as 3-chloro-CPA.[8,9] This reaction has been demonstrated under laboratory conditions, suggesting that chlorine-based oxidants can alter the chemical structure of CPA. However, most previous studies have focused on chemical or analytical aspects, and the actual removal efficiency of CPA under routine wipe-cleaning conditions has not been sufficiently verified.

Therefore, this study aimed to evaluate the practical decontamination performance of an electrolyzed-water–based cleaning method combining hypochlorous acid water (HClO water) and alkaline electrolyzed water (AEW), compared with the conventional cleaning method using distilled water and disinfectant ethanol. We designed experiments simulating daily wipe-cleaning procedures in BSCs to clarify the effectiveness, safety, and feasibility of this approach in real-world settings.

MATERIALS AND METHODS

Electrolyzed Water Generator Electrolyzed water was generated using a WOX-30WA-M2 electrolyzed-water generator (certification number: 302AGBZX00059000; Hoshizaki Sales Co., Ltd., Nagoya, Japan), hereinafter referred to as WOX. The components and concentrations of acidic electrolyzed water were as follows: 0.1% sodium chloride, 0.0035% hypochlorous acid, 0.015% hydrochloric acid, and water (>99.8%). The electrolyzed water was acidic, with a pH of 2.7.

The alkaline electrolyzed water (AEW) were as follows: 0.1% sodium chloride, 0.03% sodium hydroxide, water (>99.8%). AEW is an alkaline solution (pH <12). The production of electrolyzed water via electrolysis is illustrated in Fig. 1.[10] Electrolysis of concentrated salt water produces HClO water at the positive electrode and AEW at the negative electrode.

The WOX can generate large amounts of HClO water at a rate of 2 L/min. Because the efficacy may decrease due to the generation of chlorine gas after production, each experiment was conducted immediately after water sampling, and airtight containers were used for transport and storage.

Analysis of CPA Removal by Wiping Using an Anticancer Drug Contamination Model Stainless steel (SUS304: 30 × 30 cm) was used. CPA (Fujifilm Wako Co., Ltd., 030-12953, lot no. LEG4021) was dissolved in Otsuka Distilled Water® to generate a contamination model at various levels (spot contamination/900 cm^2: n = 3 per group). Subsequently, CPA was applied to the stainless steel at various levels, allowed to dry, and then fixed to prepare the contamination model (Fig. 2). The following CPA contamination levels were examined: (a) 1 μg, trace accumulation of contamination in the work environment; (b) 100 μg, spot contamination representative of practical work or environmental contamination caused by contact with gloves used for preparation; and (c) 10 mg, mimicking a spill of solution during preparation of anticancer drugs.

As a new cleaning method, cotton cloths were soaked with HClO water or AEW and used to wipe the stainless steel surface sequentially. Furthermore, Otsuka Distilled Water® and Saraya Ethanol Cross 80® were examined as controls, with wiping also performed sequentially. The cleaning procedure involved sweeping the entire surface with disposable gauze, at a single pass, followed by natural drying and at least 12 h of standing time. Subsequently, the wiping test was used to evaluate residual levels of CPA. All procedures were performed at 24°C in a Class II Type B biological safety cabinet (YS-B-A 953 II B3, Yuyama Manufacturing Co., Ltd.) under non-contaminated conditions. Gloves were replaced between plates to avoid cross-contamination. Samples were labeled with identification codes and subjected to single-blind testing, and the

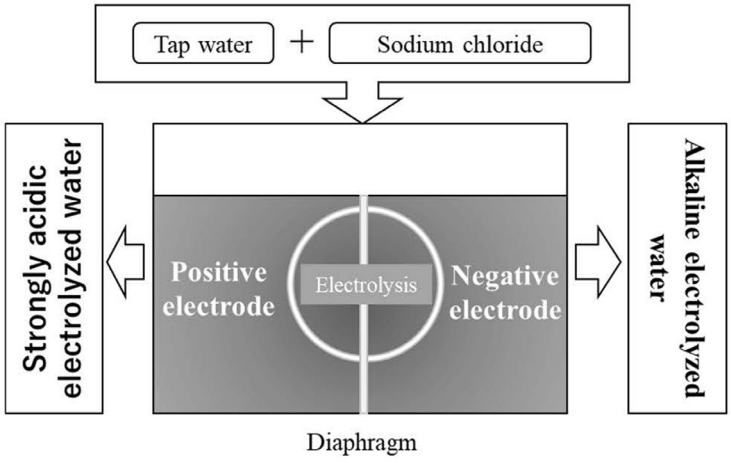


Fig. 1. Electrolysis of Sodium Chloride Solution

Electrolysis of concentrated salt water produces hypochlorous acid water at the positive electrode and alkaline electrolyzed water at the negative electrode. As the device is effective for hand disinfection, hypochlorous acid water (effective chlorine concentration 35 mg/kg) is diluted with tap water.

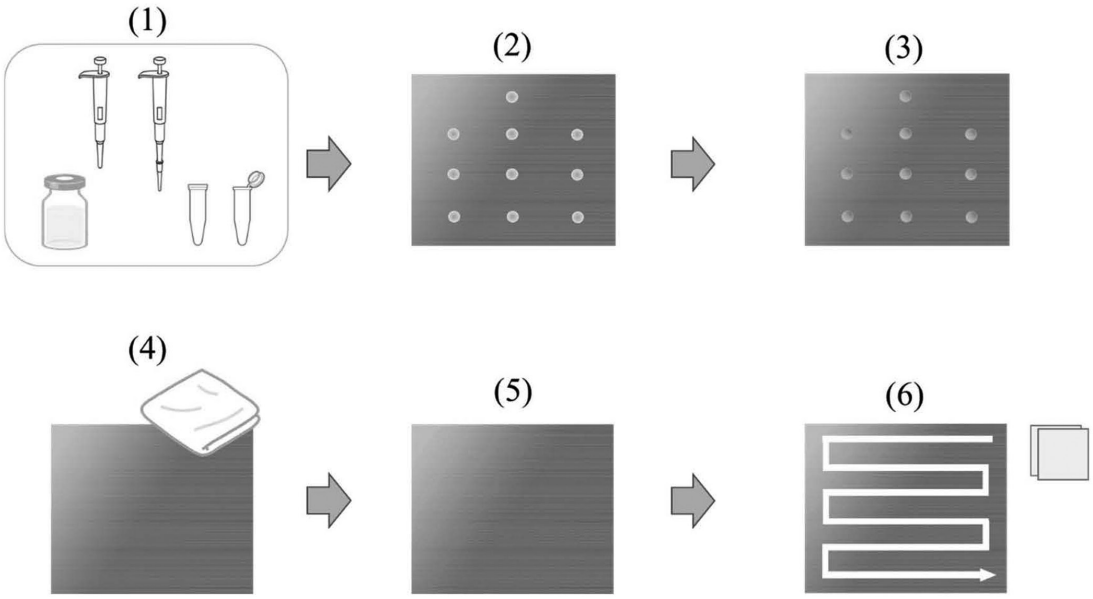


Fig. 2. Preparation of CPA Contamination Model and Wipe Cleaning Method

Analyses were performed at 24°C in a Class II Type B biological safety cabinet (YS-B-A 953 II B3, Yuyama Manufacturing Co., Ltd.) that was free from hazardous drug contamination. Gloves were changed between plates to prevent cross-contamination.

Workflow of contamination modeling and wipe-cleaning procedure:

(1) Preparation of CPA at various concentrations.

(2) Spot contamination on stainless-steel plates.

(3) Drying (fixing) of CPA on the surface.

(4) Wiping once with a cleaning solution (distilled water, disinfectant ethanol, or electrolyzed water).

(5) Natural drying for 12 h.

(6) Wipe test and quantitative analysis of residual CPA.

level of anticancer drug residue was determined by an external contractor.

In the practical application of this new cleaning method, electrolyzed water (HClO water → AEW) was used for sequential wiping. When necessary, a final wiping step with disinfectant ethanol was added to remove lipid-soluble contaminants and to prevent rust formation on stainless steel plates. This combination procedure is consistent with institutional safety protocols for daily cleaning of biological safety cabinets.

Statistical Analysis The level of CPA residue is expressed in nanograms (ng), and the Mann-Whitney *U* test was used to compare differences between groups. The significance level was set at $p \leq 0.05$.

Investigation of the Effects of Various Solvents and Confirmation of the Reversibility of the Products CPA solution was analyzed using LC-PDA and MS (LC: Shimadzu 20 series, MS: LCMS-8045 [Shimadzu]) to investigate changes in chromatographic retention time and spectra after adding various solvents. Measurement conditions were as follows: column, Sunshell C18 (2.1 × 100 mm, 2.6 μm); mobile phase, 0.1% formic acid (water):0.1% formic acid (acetonitrile) = 70:30; flow rate, 0.4 mL/min; sample injection volume, 5 μL; UV detection wavelength, 200 nm.

Chromatography was performed as follows: (a) CPA solution (1 mg/mL in ethanol) was prepared at a concentration of 0.1 mg/mL by adding 900 μL of solvent to 100 μL of CPA solution. The solvents were distilled water (control), HClO water, 0.015% HCl, AEW, 0.003% NaClO (same level of chlorine as HClO water), and 0.03% NaClO. (b) After reacting CPA solution with an adequate level of sodium hypochlorite, the solvent was removed by solid-phase extraction, and the reversibility of the product was verified. In addition, the structural formula of the product was determined by mass spectrometry.

RESULTS

CPA Residue Level after Wiping The CPA residue level (ng ± SD) was determined for the conventional method and new cleaning method as follows: 1-μg contamination model (conventional method, 16.1 ± 3.28; new cleaning method, 7.69 ± 2.54, $p = 0.0025$); 100-μg contamination model (conventional method, 642.7 ± 305.0; new cleaning method, 145.9 ± 55.2, $p = 0.05$), and 10-mg contamination model (conventional method, 21,100 ± 9,665.9; new cleaning method, 10,096.7 ± 4,368.3, $p = 0.147$) (Fig. 3).

The new cleaning method (HClO water → AEW) significantly reduced the residue level in the 1-μg contamination model compared with the conventional method (distilled water → disinfectant ethanol) ($p = 0.0025$).

Evaluation of the Effect of Various Solvents Using High-Performance Liquid Chromatography (HPLC)

Chromatographic Changes Due to Solvent Addition

In HPLC analysis, CPA showed a peak at a retention time of 1.46 min. No changes were observed in retention time after addition of solvent prepared with 0.015% HCl, a by-product of acidic electrolyzed water, or after the addition of AEW. The

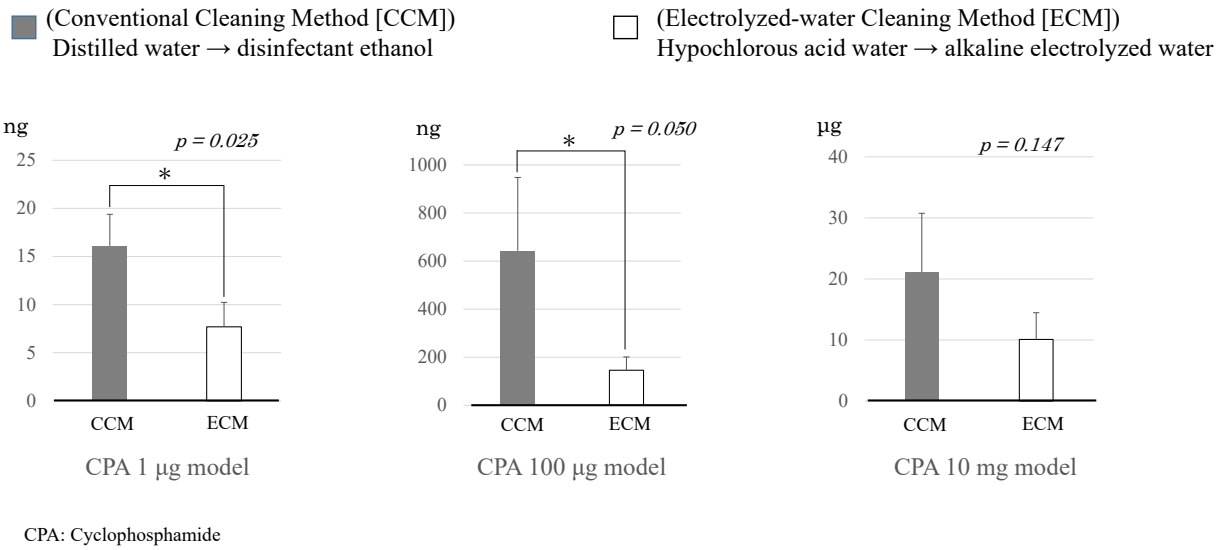


Fig. 3. Residual Level of CPA after Wipe Cleaning

Comparison of residual cyclophosphamide (CPA) levels after wipe cleaning using the Conventional Cleaning Method (CCM: distilled water → disinfectant ethanol) and the Electrolyzed-water Cleaning Method (ECM: HClO water → AEW). Data are shown as mean ± SD (n = 3 per group). Statistical analysis was performed using the Mann-Whitney U test. *$p \leq 0.05$ was considered statistically significant. The ECM showed significantly lower residual CPA levels than the CCM at 1-μg and 100-μg contamination models (p = 0.0025 and p = 0.05, respectively).

appearance of an unknown peak at a retention time of approximately 4.65 min and a decrease in the intensity of the CPA peak were observed after the addition of HClO water, 0.003% NaClO, and 0.03% NaClO. A similar decrease in the intensity of the CPA peak and appearance of an unknown peak were observed following addition of 0.003% NaClO, which contained the same level of chlorine as HClO water. Furthermore, following the addition of 0.03% NaClO, the CPA peak was below the detection limit, but the unknown peak was observed (Fig. 4).

Investigation of Reversibility and Identification of CPA Reaction Substances A solid-phase extraction method was used to investigate the reversibility of the unknown HPLC peak appearing after the addition of HClO water or NaClO to CPA. After addition of NaClO with a high chlorine content to CPA and confirmation that the CPA peak was below the HPLC detection limit, the peak reappeared at the correct retention time after removal of NaClO using solid-phase extraction (data not shown). According to a previous study, 3-chloro-CPA has been identified as a chlorinated derivative of CPA.[8] In the present study, we confirmed the presence of 3-chloro-CPA by LC–MS analysis, showing a molecular ion at *m/z* 295 ($[M + H]^+$) and a characteristic chlorine isotopic pattern (Supplementary Fig. S1).

DISCUSSION

The results of this study suggest that a new cleaning method using WOX (two-step electrolysis water cleaning [HClO water → AEW]) is more effective than the conventional cleaning method (purified water → disinfectant ethanol) for removing CPA from stainless steel surfaces.

The ECM significantly reduced the residual amount of CPA compared with the CCM; however, its effectiveness varied slightly depending on the CPA concentration (Fig. 3). The HClO water used in this study (approximately 0.0035%) was much less concentrated than the NaClO solutions (0.02–2%) evaluated by Adé A *et al.*,[11] but showed similarly high decontamination efficacy. Although the cleaning procedures differed and direct comparison is difficult, these findings suggest that the electrolyzed-water cleaning method is an effective approach for surface decontamination.

Hypochlorous acid exhibits approximately 80 times greater bactericidal activity than HClO ions and demonstrates stronger bactericidal activity than NaClO.[7] HClO water is designated as a food additive (disinfectant) and used for washing vegetables in food processing plants, exhibiting extremely low toxicity to humans (chlorine concentration: 10-100 ppm). The chlorine concentration of the electrolytic HClO water generated by the WOX system is 35 ppm (0.0035% HClO), leading to approval of the WOX system for hand disinfection, as it is safe for human use. Furthermore, we reported favorable results comparable to conventional cleaning methods through basic research on the sterilization and anti-fouling properties of electrolyzed water (Supplementary: Taniguchi *et al.*, 53rd Academic Conference of the Kanto Block, 2023; and Nonomiya *et al.*, 33rd Annual Meeting of the Japanese Society of Pharmaceutical Sciences, 2023). Therefore, we consider that the new cleaning method is a safe and effective approach for disinfection and stain prevention.

In this study, new stainless steel was used to eliminate the possibility of bias due to cumulative environmental contamination.[12] In addition, the stainless steel used in this study was SUS304, which is the same material used in BSCs. SUS304 steel is highly resistant to corrosion resulting from acetic acid and alkali substances, but it exhibits weak resistance to corrosion from hydrochloric acid, necessitating precautions against hydrochloric acid–induced corrosion.[13,14] Therefore, the use of AEW as a sequential cleaning agent for acidic electrolyzed water (containing hydrochloric acid) is reasonable as a corrosion-prevention countermeasure.

The use of disinfectant ethanol in conventional methods

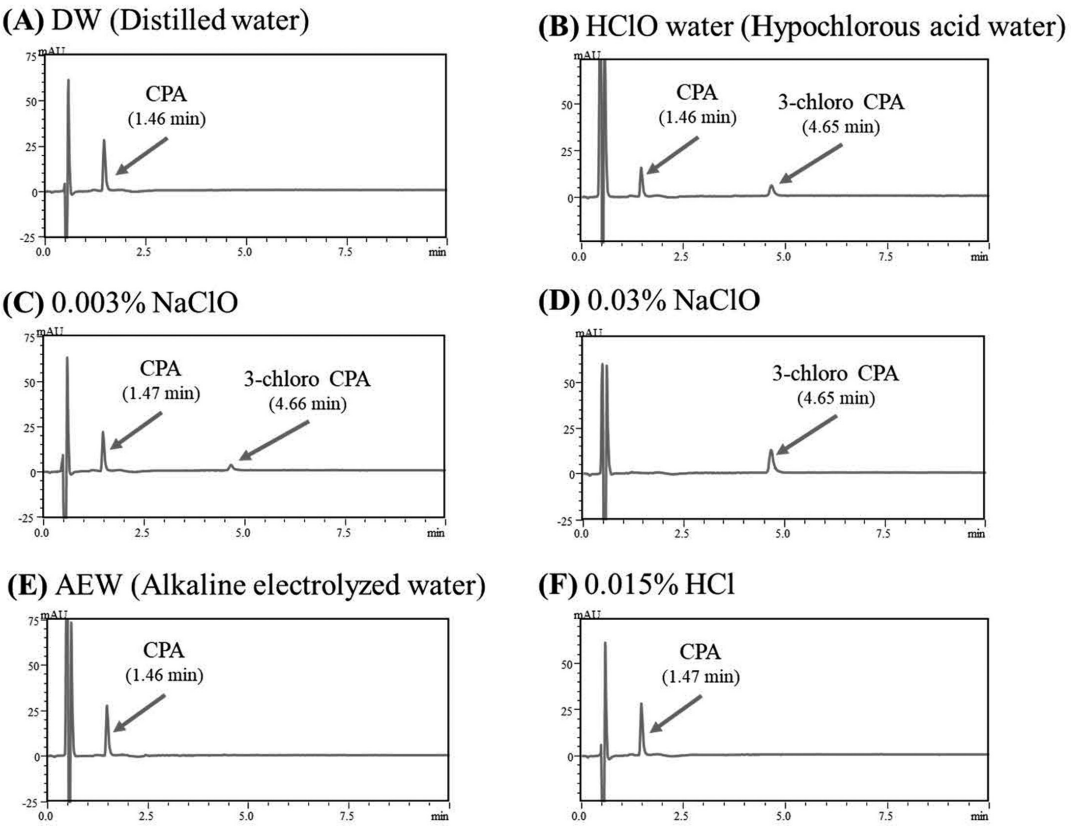


Fig. 4. HPLC Chromatograms of Cyclophosphamide (CPA) after Addition of Various Solvents

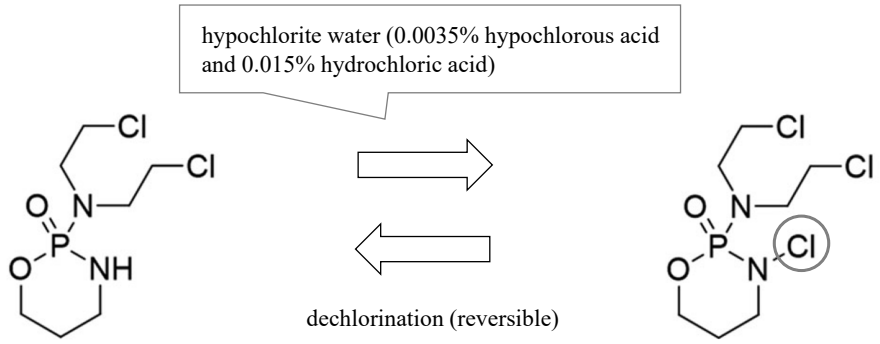
(A) Distilled water (DW); (B) Hypochlorous acid water (HClO water); (C) 0.003% sodium hypochlorite (NaClO); (D) 0.03% NaClO; (E) Alkaline electrolyzed water (AEW); (F) 0.015% hydrochloric acid (HCl). The peak area of CPA (retention time: 1.46 min) decreased with increasing chlorine concentration, accompanied by the appearance of 3-chloro-CPA at approximately 4.65 min. All chromatograms were recorded under identical LC–MS conditions.[8)]

poses a risk of environmental contamination of anticancer drugs due to volatilization. Therefore, the use of electrolyzed water can reduce the risk not only of bacterial contamination and soiling but also of environmental contamination on BSC surfaces. We believe that this method has the potential to enhance patient safety by guaranteeing the sterility of compounded drugs and to minimize risks to healthcare workers by helping prevent exposure.

HPLC experiments examining the effect of adding various solvents to CPA solution showed that a substance was produced from CPA depending on the level of chlorine present in HClO or NaClO. The unknown HPLC peak showed no change under acidic or alkaline conditions; however, its peak area increased with increasing chlorine concentration, indicating that the compound was formed via a chlorination reaction. In future studies, it will be necessary to verify the correlation between contact time and substance removal efficiency from the perspective of chlorine bleaching.

In this study, we adopted a single-pass, one-direction sequential wiping procedure (distilled water → disinfectant ethanol or HClO water → AEW), which is consistent with current hospital cleaning protocols and occupational safety guidelines (e.g., Japanese Society of Pharmaceutical Oncology, USP <800>, NIOSH, ISOPP Standards).[2,15-17)] This procedure was selected for its practicality, including reasonable working time, minimal material use, and ease of standardization across facilities. In daily oncology pharmacy operations, repeated wiping with distilled water alone often fails to completely remove residual cytotoxic agents, particularly those adsorbed to stainless-steel or glass surfaces. Therefore, we focused on chemically reactive cleaning media such as HClO water and AEW, which can degrade or neutralize contaminants rather than merely dilute them. Future studies may compare multiple-pass wiping protocols under controlled conditions to further evaluate the marginal benefits of repeated distilled water wiping. And then, even if the removal effect is slight, it is valuable to apply research that reliably returns high-level methods for sterilization, antifouling, and HDs removal to the anticancer drug preparation areas. It was believed that this process is related to "Improvement of the quality of Level 3B (personnel management/organizational response) through safe handling."[16)]

Iwasaki *et al.* reported that the retention time of CPA was restored after removal of NaClO using solid-phase extraction.[8)] In other words, generation of the unknown product is reversible in terms of the physical properties of CPA, and the reaction therefore would not be expected to irreversibly transform CPA into a harmful activated substance (e.g., phosphoramid mustard) *in vivo*. Furthermore, the unknown peak generated by reaction between CPA and sodium hypochlorite or HClO was identified by mass spectrometry and confirmed as 3-chloro-CPA (Fig. 5 and Supplementary Fig. S1), which has also been reported in previous study.[8)] The detection level of 3-chloro-CPA was dependent on the chlorine concentration in the sodi-



Cyclophosphamide (CPA)
Chemical formula: $C_7H_{15}Cl_2N_2O_2P$
Exact Mass: 260.02
Molecular weight: 261.08

3-Chlorocyclophosphamide (3-chloro CPA)
Chemical formula: $C_7H_{14}Cl_3N_2O_2P$
Exact mass: 293.99
Molecular weight: 295.52

Fig. 5. Chemical Structures of CPA and 3-Chloro CPA (Prodrug of CPA)

um hypochlorite and HClO solutions. Other studies identified 3-chloro-CPA as a prodrug of CPA,[9] and the substance detected using the new cleaning method was found to exhibit extremely low direct toxicity to humans. In that study, a chlorinated derivative of CPA was newly synthesized with the aim of developing a prodrug, and its biological activity was evaluated. The results demonstrated that chlorination of CPA led to a decrease in activity at the cellular level. Therefore, in the present study, we consider that the 3-chloro-CPA formed by reaction with HClO would exhibit lower biological activity compared to CPA itself. In addition, the reversibility of the reaction between CPA and HClO ions was clarified by solid-phase extraction. The results indicated that the reaction does not involve "decomposition" resulting from mixing of the two types of HClO water commercially available.[18-20] In the future, we will evaluate the effectiveness of new cleaning methods for other cytotoxic anticancer drugs.

Kobayashi *et al.* reported detecting trace levels of CPA in the work environment.[21] Furthermore, when contamination was detected on the surface of CPA vials, they were able to successfully remove it by soaking the vials in electrolyzed water.[20] Therefore, cleaning methods using an electrolyzed water generator approved for hand disinfection are considered suitable for daily cleaning to reduce occupational exposure of healthcare workers, as such methods exhibit a greater substance removal effect than the conventional cleaning method using distilled water and disinfectant ethanol. In practical use, electrolyzed water wiping was followed by disinfectant ethanol when necessary to remove lipid-soluble residues and prevent rust formation. AEW itself provides sufficient cleaning and mild bactericidal activity,[22,23] but ethanol wiping was added as a precautionary final step in routine operation.

The results of the present study indicate that cleaning methods using electrolyzed water are effective for the removal of accumulated CPA contamination on BSC surfaces, and they are also useful for sterilizing and preventing contamination of clean operating areas. The ability to produce large amounts of electrolyzed water at low cost indicates the approach is cost-effective. We plan to continue to verify the reactivity between electrolyzed water and various HDs as well as the method's substance removal effectiveness.

Limitations This study has several limitations. First, quantitative comparison of the total amount of CPA and its chlorinated derivative (3-chloro-CPA) could not be performed because a stable and commercially available standard for 3-chloro-CPA was not available. Therefore, evaluation was based on relative peak areas and qualitative confirmation of CPA recovery after solid-phase extraction (SPE) treatment. In future studies, the use of a stable isotope–labeled internal standard may enable accurate quantification of both CPA and 3-chloro-CPA and clarify the reaction kinetics more precisely.

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Conflict of interest The authors declare no conflict of interest.

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