Original

Investigation of the Levels of Ifosfamide Vaporized from Powder and Solution

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Abstract

Background: While antineoplastic agents have an important role in cancer therapy, they may be harmful for healthcare workers. Ifosfamide and cyclophosphamide are categorized as hazardous drugs. These drugs are volatile and may enter the body through inhalation. However, few reports have addressed the volatilization of ifosfamide.

Objectives: The aim of this study was to determine the levels of ifosfamide in air after volatilization from solution or powder.

Methods: Ifosfamide volatilized from solution and powder at near room temperature was determined in air by liquid chromatography-tandem mass spectrometry.

Results: The levels of ifosfamide in air from solution at 25 and 40℃ were 3.1 and 293 pg/L, respectively, indicating a 100-fold difference between the temperature studied. Similarly, the levels of ifosfamide volatilized from powder increased with temperature. At comparable temperatures, air levels of ifosfamide were one to two orders of magnitude lower after volatilization from powder compared to that in solution.

Conclusion: Our results revealed the risk of exposure to ifosfamide at high temperatures. Special attention should be paid to temperatures and drug states when ifosfamide formulations are prepared.

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—Key words—
ifosfamide, volatilization, exposure

Introduction

The antineoplastic drugs take an important role in cancer therapy. However, the antineoplastic drugs may become harmful for healthcare workers. The National Institute for Occupational Safety and Health (NIOSH) announced the alert about prevention of exposure to hazardous drug to healthcare workers[1)]. The NIOSH criteria includes: carcinogenicity, teratogenicity, reproductive toxicity, genotoxicity, organ toxicity at low doses, and drugs that mimic existing drugs in structure or toxicity.

The antineoplastic alkylating drugs such as ifosfamide and cyclophosphamide are categorized as hazardous drug according to the criteria of NIOSH. Ensslin et al. has reported that these ifosfamide and cyclophosphamide were detected in the urine of the healthcare worker who wore gloves and handled these drugs in safety cabinets[2)]. On the other hand, ifosfamide was detected in air samples taken during preparation of injection[3)] and cyclophosphamide was not effectively controlled by high efficiency particular (HEPA) filters[4)]. Connor et al. showed that vaporization of these two drugs at room temperature and their tendencies of volatile de-

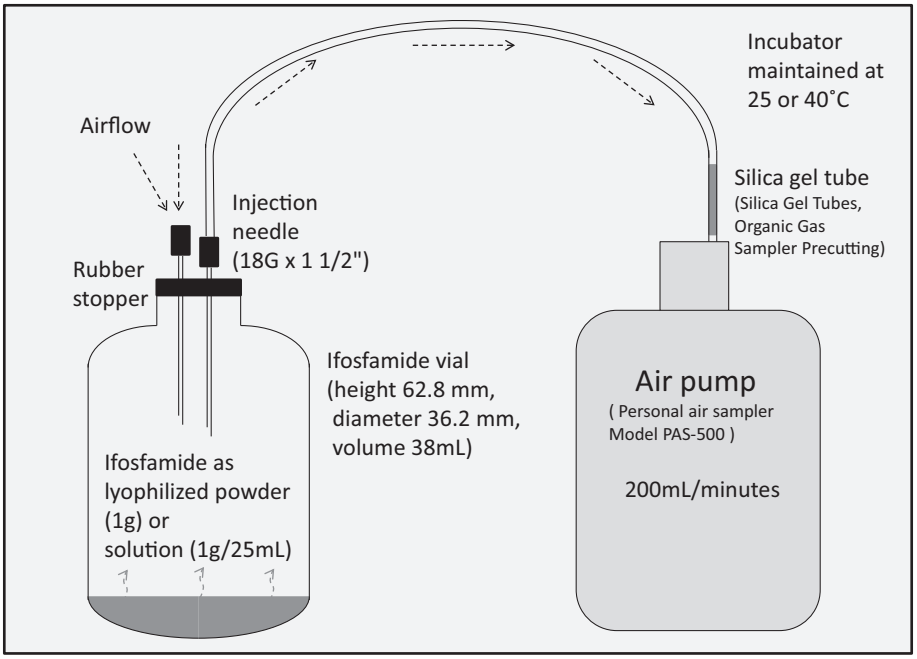

Fig. 1 Method for measurement of ifosfamide

pended on temperature using desiccator technique and bacterial assay[5]. These reports strongly suggested the volatilization of the two drugs. However, the levels of ifosfamide in air at each temperature remain obscure, while the levels of cyclophosphamide in air have been determined[6][7]. Therefore, we studied the levels of ifosfamide in the form of gas at different temperatures volatilized from solution and powder states of ifosfamide in the following sections.

Methods

Preparation of air samples

In order to determine the levels of ifosfamide in the form of gas, ifomide (Shionogi & Co., Ltd.) containing 1 g of ifosfamide in a vial was used as lyophilized powder or solution states. Twenty-five mL of saline was added to the vial for preparing the solution samples. The air samples of ifosfamide were obtained as illustrated in Fig. 1. Rubber stopper of the commercially available ifosmfamide vial of was punctured by two injection needles (18 G (1.20 mm) × 1 1/2" (38 mm), Terumo). Because of the two needles, the vial was kept under ordinary pressure. Air above the powder or solution was aspirated at 200 mL/minutes through the needle for 3 hours by air sampler (Personal air sampler Model PAS-500, Shibata Scientific Technology) and ifosfamide in the form of the gas was trapped on the silica gel tube (Silica Gel Tubes, Organic Gas Sampler Precutting, Shibata Scientific Technology). The vial and air sampler were kept at 25℃ or 40℃ in the incubator throughout the experiments.

Determination of ifosfamide by liquid chromatography-tandem mass spectrometry (LC/MS/MS)

Ifosfamide trapped on the silica gel tube was extracted with methanol for determination by LC/MS/MS. Ultra High Performance Liquid Chromatography (UHPLC) system (ACQUITY UPLC) and Triple Quadrupole Mass Spectrometer (ZEVO TQ MS) was used for LC/MS/MS with Electrospray ionization. ACQUITY UPLC HSS TS3 (50 mm × 2.1 mm, 7.8 μm) column was kept at 40℃ and mobile phase of water/acetonitrile gradient was at 0.6 mL/min. The temperature of ion source at 150℃ and capillary voltage of 3.30 kV were kept for multiple reaction monitoring in which precursor and product ions were m/Z 261.13 and 91.87, respectively. The detection limit of ifosfamide was 0.02 ng.

Results

The levels of ifosfamide in air volatilized from solution were shown in Table 1. The levels of ifosfamide from solution at 25℃ were 0.11 ng, which corresponded to 3.1 pg/L of ifosfamide in air, while the levels at 40℃

Table 1 Volatilization of ifosfamide from solution

	ifosfamide (ng)	
	25℃	40℃
	0.10	14.41
	0.09	8.94
	0.14	8.35
Mean	0.11	10.57
S.D.	0.03	3.34

Table 2 Volatilization of ifosfamide from powder

	ifosfamide (ng)	
	25℃	40℃
	ND	0.11
	ND	0.11
	ND	0.04
Mean	—	0.09
S.D.	—	0.04

ND, not detected

were 10.57 ng, which corresponded to 293 pg/L of ifosfamide in air. The difference of the data between the two temperatures was approximately 100-fold.

The levels of ifosfamide in air volatilized from powder were shown in Table 2. The levels of ifosfamide from powder at 25℃ were under detection limit, which were 0.02 ng and corresponded to 0.6 pg/L of ifosfamide in air. The levels of ifosfamide at 40℃ were 0.09 ng, which corresponded to 2.5 pg/L in air. The levels of ifosfamide in air from powder were decreased compared with the levels from solution at comparable temperatures in order of one to two magnitudes. On the other hand, the difference of the data volatilized from powder between the temperatures was higher than 4-fold.

Discussion

The difficulty in decreasing the risk of handling hazardous drugs for the healthcare workers is not only due to the strong toxicity of the drugs but variety of contamination routes (contact to skin and eyes, oral intake of the drug through the finger, inhalation of the drug etc). The risk of the healthcare worker is evaluated how long hazardous drugs are taken in the body through the routes. It is particularly difficult to protect from inhalation of the volatilized drugs, since such drugs in the form of gas can pass through HEPA filter and medical masks. Therefore, the attention to the volatilization of the drugs should be carefully paid.

The reports on their tendencies of vaporization of the anticancer drugs were limited. Connor et al. evaluated the ability of mutagenicity of the antineoplastic agents such as ifosfamide to vaporize at 23℃ and 37℃[5]. A bacterial mutagenicity assay was used to determine the mutagenicity of these agents in the vapor phase. Ifosfamide in air showed the mutagenicity at both 23 and 37℃, and the ability was higher at 37℃ compared with 23℃. In this study, we tested the levels of ifosfamide in at similar temperature such as 25 and 40℃ and revealed that temperature-dependent increase of the ifosfamide levels in air. These results are consistent with the previous study of Connor et al[5].

We showed here that the levels of volatilization of ifosfamide were 3.1 pg/L at 25℃, while it was 293 pg/L at 40℃ in a solution study. In the case of volatilization from powder, the levels of ifosfamide were lower than detection limit (<0.6 pg/L) at 25℃, while it was 2.5 pg/L at 40℃. The levels of cyclophosphamide volatilized from solution which were 0.32–0.93 ng/36 L determined by Nakanishi et al.[6] or 10–72 ng/5 L by Sato et al[7]. The levels of ifosfamide shown here were approximately corresponded to them in order of magnitude.

Our results revealed the inhalation toxicity of ifosfamide as gas in addition to ordinary toxicity such as oral and dermal toxicity. Ifsofamide can exert its toxicity without contact by healthcare workers, and its volatilization continues until it is cleaned off. Therefore, the contamination of the drug in medical environments should be strictly avoided, although the threshold inhalation dose of ifosfamide in toxicity for human is not determined. The results obtained here showed the levels of ifosfamide in air increased as the temperature is raised. Thus, ifosfamide solution should be prepared in cool places, since higher temperature markedly accelerates the volatilization of ifosfamide. Our results also showed that there was a difference between the volatilization from solution and powder. Ifosfamide was notably more volatilized from solution compared with powder, although the mechanisms of these resulting differences were not clear to date. When injections including ifosfamide are mixed, attentions should be paid to the state of the drug in respect of the volatility.

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Conflicts of interest

The authors have no competing interests to declare for this study.

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散薬および溶解液の状態から気化するイホスファミド量の調査

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—キーワード—
イホスファミド，揮発，曝露

背景：抗腫瘍薬にはがん治療において重要な役割がある一方，医療従事者に対しては有害である可能性がある．イホスファミドとシクロホスファミドは，危険性医薬品に分類される．これらの薬剤は揮発し，吸入することで体内に入る可能性がある．しかし，イホスファミドの揮発に関する報告がほとんどない．

目的：本研究の目的は，溶解液または散薬の状態から揮発した後，空気中のイホスファミドの濃度を調査することである．

方法：室温付近において，溶解液または散薬の状態から揮発したイホスファミドを LC-MS/MS によって，空気中の濃度を定量する．

結果：25℃ と 40℃ の溶液からの空気中のイホスファミドの濃度はそれぞれ 3.1pg/L と 293pg/L であった．この 2 つの温度の濃度には 100 倍の差がみられた．これと同様に，散薬からの揮発においてもイホスファミドの濃度は，増加した．対応する温度において，イホスファミドの空気中濃度は，溶液と比較すると散薬からの揮発において 1〜2 桁，低い値となった．

結論：我々の結果は，高温においてイホスファミドに曝露のリスクを明示した．イホスファミド製剤を調製するときには，温度と薬剤の状態について特別な注意を払う必要がある．

利益相反基準に該当無し

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