Suspended particle and drug ingredient concentrations in hospital dispensaries and implications for pharmacists’ working environments

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Abstract

Objectives The aim of this study was to assess the present status of working environments for pharmacists, including the concentrations of suspended particles and suspended drug ingredients in dispensaries.

Methods We conducted a survey on the work processes and working environment in 15 hospital dispensaries, and measured the concentrations of suspended particles and suspended drug ingredients using digital dust counter and high-performance liquid chromatography tandem mass spectrometry (LC–MS/MS), respectively. Of 25 types of powdered drugs that were frequently handled in the 15 dispensaries surveyed, 11 could be quantitatively determined.

Results The amounts of suspended particles were relatively high, but below the reference value, in three dispensaries without dust collectors. The sedative-hypnotic drug zopiclone was detected in the suspended particles at one dispensary that was not equipped with dust collectors, and the antipyretic and analgesic drug acetaminophen was detected in two dispensaries equipped with dust collectors. There was no correlation between the daily number of prescriptions containing powdered drugs and the concentration of suspended particles in dispensaries.

Conclusion On the basis of the suspended particle concentrations measured, we concluded that dust collectors were effective in these dispensaries. However, suspended drug ingredients were detected also in dispensaries with dust collectors. These results suggest that the drug dust control systems of individual dispensaries should be properly installed and managed.

Keywords Drug compounding · Suspended particle · Drug ingredient · Hospital pharmacist · Occupational exposure

Introduction

Drug compounding and filling environments must be clean to avoid contaminating prescribed medicines with other drugs or pathogens, and also to avoid exposure of pharmacists to the compounded drugs by inhalation or adsorption [1]. Allergic and carcinogenic effects resulting from pharmacists compounding drugs have been previously reported [2–4]. Moreover, the results of a questionnaire showed that many pharmacists working in community pharmacies and in hospital dispensaries developed allergic or irritation symptoms of the eyes, nose, oral cavity, and throat [5]. We hypothesized that these symptoms might result from drug particles contaminating the dispensary and that this contamination should be measured.

As a countermeasure to the symptoms described by pharmacists, dust collectors are installed [6, 7] at locations such as medicine preparing tables. However, the effects of removal of these dust collectors have not been studied.

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precisely and periodically. No study has reported the concentrations of suspended conventional drug particles in a dispensary room. The precision with which environmental chemicals can be detected has improved recently [8], making measurement of suspended drugs in a dispensary a possibility. In this study, we investigate the work processes and work environment of pharmacists by inspection and measurement of concentrations of suspended particles and suspended drug ingredients.

Subjects and methods

This environmental survey was accepted by 15 among 37 hospitals that had responded to our previous survey on subjective symptoms reported by hospital pharmacists [5]. Of these, four were large-scale hospitals with 400 beds or more, three were medium-sized hospitals with 200–399 beds, four were small-sized hospitals with 99–199 beds, and four were mental hospitals. The survey was conducted once per hospital in March 2014, December 2014, or January 2015. The outdoor temperature and suspended particulate matter (SPM) values at the nearest official measuring points during the survey time ranged from 3.8 to 10.4 °C and from 0.003 to 0.028 mg/m³, respectively [9, 10].

Prior to measurements, we conducted a survey on the work environment and work process in the hospital dispensary, to include each of the following issues: arrangement of air conditioner and ventilating fan, dust collector setting, mean number of dispensary staff, mean number of prescriptions per day, mean number of prescriptions with powdered drugs, frequency of crushing tablets, procedures for crushing tablets, frequency of opening capsules, use of masks during drug compounding, and lists of powdered drugs dealt with frequently.

We measured the suspended particle concentrations in the dispensary of each hospital in accordance with the standards for working environment measurement [11] provided by the Ministry of Health, Labour and Welfare, Japan. Particle concentrations were measured using a digital dust indicator (model LD-3K2; Sibata Scientific Technology, Tokyo, Japan). Dust concentrations were measured at locations and times at which pharmacists’ exposure level was considered to be average (A-measurement) and maximal (B-measurement) [11]. A-measurement points were set at intervals of about 6 m, and B-measurement points were considered as those points where hospital pharmacists considered the scattering of drug dust to be the highest (Fig. 1). The number of A-measurement points varied between five and nine according to the area of the dispensaries. Measurements were taken at heights from 1.2 to 1.5 m above the floor to simulate the breathing zone of pharmacists for 10 min, respectively. In every hospital, the mass concentration conversion coefficient (K factor) was determined by performing the quantitative analysis described below. The K factor varied from 0.0008 to 0.0014 mg/m³/cpm.

Next, we measured the concentrations of suspended drug ingredients in each dispensary. Eleven drugs capable of quantitative determination were selected from 25 drugs reported to be compounded frequently in 15 hospitals. The drugs targeted in this analysis were the psychotropic drugs chlorpromazine, haloperidol, levomepromazine, olanzapine, and risperidone; the antiparkinson drug promethazine; the sedative-hypnotic drug zopiclone; the anti-peptic ulcer drugs famotidine and lansoprazole; the antipyretic and analgesic drug acetaminophen; and the antibiotic clarithromycin. The drugs that could not be detected or quantified were albumin tannate, amoxicillin, bethanechol chloride, bromhexine hydrochloride, carbocysteine, codeine phosphate, domperidone, furosemide, loperamide hydrochloride, pantethine, pranlukast, sodium valproate, teprenone and ursodeoxycholic acid.

Suspended particles were collected at representative A- and B-measurement points for each dispensary. Air samples were captured on a PTFE filter (PF-4) via vacuum filtration using a total flow volume of 155–911 l in 10 to 45 min using an air sampler (model ESH-501H; Okano Works Ltd., Osaka, Japan). The absorbed filter was immersed in 1:1 water:methanol (10 ml) and sonicated for 30 min in an ultrasound apparatus. The extracted samples were filtered using a 0.45 μm membrane filter.

Simultaneous multi-component quantitative analysis of 11 drugs was performed using high-performance liquid chromatography tandem mass spectrometry (LC–MS/MS)
LC–MS/MS was performed on a GL Sciences HPLC LC800 (GL Sciences Inc., Tokyo, Japan) coupled with an AB Sciex QTRAP 5500 mass spectrometer (AB Sciex, Foster City, CA, USA). As reference standards, haloperidol and acetyaminophen were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan) and the other nine tested drugs from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Methanol (analytic grade for residual pesticides) and formic acid (HPLC grade) were purchased from Wako Pure Chemical Industries, Ltd., and ammonium acetate (a special grade reagent) from Tokyo Chemical Industry Co., Ltd. Ultrapure water was provided by a Milli-Q system (Milli-Q Gradient A10; Merck KGaA, Darmstadt, Germany).

Separation was performed on a Shiseido Capcell Pak C18 column (75 × 1.0 mm, 3 μm) (Shiseido Co. Ltd., Tokyo, Japan) at 40 °C with an injection volume of 5 μl from filtered samples. Mobile phase solutions consisted of methanol (mobile phase A) and 10 mM ammonium acetate in 0.1 % aqueous formic acid (mobile phase B). The flow rate was maintained at 0.15 ml/min. The mixture ratio of mobile phase A and B changed from 5:95 to 100:0 over 6 min at a linear gradient, was held constant for 2 min, and then returned to 5:95 over 4 min.

The mass spectrometer was operated using an electro-spray atmospheric pressure ionization source in positive ion mode with multiple reaction monitoring. Detection of the ions performed by monitoring the transitions of m/z 320 to 86 for chlorpromazine, 377–123 for haloperidol, 329–100 for levomepromazine, 313–256 for olanzapine, 411–191 for risperidone, 285–86 for promethazine, 389–76 for zopiclone, 338–189 for famotidine, 370–252 for lan-soprazole, 152–110 for acetaminophen, and 748–158 for clarithromycin.

For each of the 15 studied hospitals, we also compared suspended particle concentrations in a dispensary with the number of staff in a dispensary, the number of prescriptions using powdered drugs, the frequency of crushing tablets, the frequency of opening capsules and dust collector setting.

Statistics

Statistical analysis was performed using Microsoft Office Excel 2007 SP3 (Microsoft, Seattle, WA, USA).

Ethics

The study protocol was approved by the Ethics Committee of Gifu University Graduate School of Medicine in advance. Each subject hospital was explained the objects and contents of the survey by letter and was allowed to refuse the survey when not desired.

Results

The relative humidity levels in the hospital dispensaries ranged from 20 to 51 % and were below 30 % in six dispensaries (Table 1). Ventilating fans were installed on the ceiling of four hospital dispensaries. Air supply and exhaust air conditioners were installed on the ceiling of five dispensaries. Four hospital dispensaries (26.7 %), comprising three small-sized hospitals and one mental hospital, were not equipped with dust collectors. The mean daily numbers of prescriptions with powdered drugs ranged from 4 to 98. Tablet drugs were crushed almost every day in 11 hospital dispensaries (73.3 %), several times a week in two dispensaries (13.3 %), and several times a month in two dispensaries (13.3 %). Frequency of opening capsules was almost daily in two hospitals (13.3 %), several times a week in four (26.7 %), several times a month in one (6.7 %), and almost never in eight (53.3 %). Masks were used during work in 12 dispensaries (80.0 %).

The mean suspended particle concentrations in 15 dispensaries at the A-measurement points ranged from 0.003 to 0.037 mg/m³ (individual values at A-measurement points of each dispensary ranged from 0.001 to 0.073 mg/m³) (Fig. 2). The suspended particle concentrations at the B-measurement point ranged from 0.004 to 0.059 mg/m³. The concentrations of suspended particles correlated well between A- and B-measurement points (r = 0.937, p < 0.001). In two hospitals, the suspended particle concentrations at B-measurement points were lower than those at A-measurement points. In three out of four dispensaries not equipped with dust collectors, suspended particle concentrations were high relative to other dispensaries. There was no correlation between the mean suspended particle concentrations at A-measurement points and the outdoor SPM values at the nearest official measuring points during the survey time (r = −0.028, p > 0.10).

No correlation was found between the number of prescriptions of powdered drugs per day and suspended particle concentrations at the A-measurement points among the 15 tested hospital dispensaries (Fig. 3). The dispensaries without dust collectors issued fewer prescriptions of pow-dered drugs than other dispensaries. There was no relationship between the mean number of dispensary staff and suspended particle concentrations (r = −0.436, p > 0.10).

Simultaneous multi-component quantitative analysis detected suspended drug ingredients in three dispensaries (Table 2). Zopiclone was detected at the A-measurement point of one hospital dispensary not equipped with a dust collector. Acetaminophen was detected at the A-measurement point and the B-measurement point of another hospital dispensary equipped with a dust collector, and at the B-measurement point of further hospital dispensary.
equipped with a dust collector. The other nine drug ingredients were not detected at any of the A- or B-measurement points of the 15 hospital dispensaries.

### Discussion

In three out of four dispensaries not equipped with dust collectors, suspended particle concentrations were high relative to other dispensaries, although all measurements were within the level (≤0.15 mg/m³) stipulated by the management standards of environmental sanitation for buildings in Japan [14]. By observing the work processes in each dispensary, it was found that suspended particles could be generated by handling powdered drugs and crushing tablets in all 15 hospital dispensaries. The lower concentrations at B-measurement points in two dispensaries with dust collectors may be attributable to the short handling time of powdered drugs (≤1 min) during the total measuring time (10 min), because of which drug dust concentrations were leveled. Neither the number of dispensary staff nor the number of prescriptions of powdered drugs correlated with suspended particle concentrations in this survey. In two dispensaries, the concentrations of suspended particles were <1/10th of the reference value, and no tested drug ingredients were detected, despite the

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**Table 1** Characteristics of work environments in 15 hospital dispensaries

| Work environment                                      | Values                      |
|-------------------------------------------------------|-----------------------------|
| Room temperature (°C)                                | 22.9 ± 2.3 (18–27)          |
| Relative humidity (%)                                 | 34.4 ± 9.2 (20–51)          |
| Floor area of dispensaries (m²)                       | 71.3 ± 57.1 (21–206)        |
| Number of A-measurement points⁴                       | 5.9 ± 1.4 (5–9)             |
| Number of staffs in a dispensary                      | 5.9 ± 4.7 (2–20)            |
| Installation of the dust collector                    | 11 (73.3 %)                 |
| Use of masks in a dispensary                          | 12 (80.0 %)                 |
| Mean number of prescriptions with powdered drugs      | 32.2 ± 26.8 (4–98)          |

The values are described as mean ± SD (range) or number (%)

⁴ The points at which pharmacists’ exposure level to suspended particles was considered to be average

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**Fig. 2** Relationship between suspended particle concentrations at A-measurement points and B-measurement points in 15 hospital dispensaries. *Square*: large-scale hospitals with 400 beds or more, *circle*: medium-sized hospitals with 200–399 beds, *diamond*: small-sized hospitals with 99–199 beds, *triangle*: mental hospitals. Open symbols and closed ones represent dispensaries with and without dust collectors, respectively

**Fig. 3** Relationship between the number of prescriptions of powdered drugs and suspended particle concentrations at A-measurement points in 15 hospital dispensaries. *Square*: large-scale hospitals with 400 beds or more, *circle*: medium-sized hospitals with 200–399 beds, *diamond*: small-sized hospitals with 99–199 beds, *triangle*: mental hospitals. Open symbols and closed ones represent hospital dispensaries with and without dust collectors, respectively
fact that the number of prescriptions of powdered drugs per day was 80 and over in each dispensary. The suspended particle concentrations in dispensary room did not correlate with those in atmospheric air. We conclude that atmospheric particles are unlikely to influence the concentrations of suspended particles in dispensaries. These results suggest that the favorable management of air flow, including the use of dust collectors in the dispensary [6, 7], is important to minimize drug contamination in hospital dispensaries.

Drug ingredients were detected from suspended particles in one dispensary not equipped with a dust collector and in two further dispensaries equipped with dust collectors. These results show that suspended particles of dispensed drugs are present in a dispensary, even if the suspended particle concentrations are below the reference value. For a pharmacist working in a dispensary with a drug concentration of 13 μg/m³ room air for 8 h, drug intake could reach 49.6–62.4 μg. The concentrations of suspended drug particles could be high in hospitals that did not accept this survey.

Our study has some limitations. This survey was conducted in only 15 hospitals; therefore, its results cannot be generalized. We did not measure all the powdered drugs dealt in each dispensary, because many drugs could not be quantified. The survey was conducted only for 1 h. The drugs chosen for testing would not be detected when those drugs are not dispensed or, if they were dispensed, the amounts dispensed during the survey would remain small. Therefore, we may have underestimated the concentrations of the measured drug ingredients. Despite these limitations, this study has shown that drug ingredients are suspended in dispensary air even in the presence of dust collectors. Of 25 kinds of powdered drugs that were frequently handled, amoxicillin, lansoprazole and chlorpromazine have been reported as causes of airborne contact dermatitis [4]. Amoxicillin has also been shown to cause occupational asthma [15]. The results also suggest that the suspended particles include various other excipients, which we did not measure.

The suspended particle concentrations tend to become higher as the daily number of prescriptions with powdered drugs increases in four dispensaries without dust collectors. Having evaluating each dispensary environment individually, we conclude that in three dispensaries not equipped with dust collectors and where the concentrations of suspended particles were relatively high, the installation of dust collectors is desirable. In one other hospital dispensary without a dust collector, we suggest that the remarkably small number of prescriptions with powdered drugs (only four per day) resulted in a relatively lower concentration of suspended particles. In two dispensaries in which dust collectors were installed and a drug ingredient was detected, we suggest that the suction force of the dust collector attached to the drug preparing table was small, and the ceiling ventilators or air conditioners disturbed the air flow of the dust collector from the pharmacists to the dust cleaner via the point of drug compounding work. Respreading of captured particles from a dust collector should be avoided by inspection and proper exchange of high-performance filters [7].

From the results of this study, we recommend that drug compounding spaces should be located giving consideration to the air flow in a dispensary room, and dust collector with sufficient suction force should be located so as not to be disturbed by the air flow from air conditioner or ventilator. Powder drug compounding generated drug dust in all the hospital dispensaries surveyed. The space where powdered drugs are compounded should not receive a direct flow from the air conditioner or ventilator. Furthermore, dust collectors should be installed such that they suck the air from the area opposite the pharmacists’ standing area.
Additionally, installation of a local exhaust ventilation system should be considered when airflow at the powder drug compounding spot cannot be controlled.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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