Contamination of Blister Packs by Pomalidomide after Use in Clinical Situation

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Abstract

Blister pack is commonly used as package of internal medicine in our country. In addition, emptied blister packs of some particular drugs are recovered by pharmacists to check appropriate use of them in our country. Pomalidomide (PML) is an orally active thalidomide analog and used for multiple myeloma. Because it has both high efficacy and risk of teratogenicity, the use of Pomalyst® capsules is strictly managed according to RevMate® procedure. In our country, pharmacists must recover emptied blister packs of Pomalyst® capsules from all patients according to guidance from Celgene corporation. However, the risk of exposure of PML via the used blister packs to pharmacists have not been assessed well.

To prevent pharmacists from unintended exposure to PML, the contamination level of PML on the surface of used blister packs in usual clinical situation was assessed in this study.

The used blister packs of Pomalyst® capsules, 7 tablets PTP sheets, were recovered from 5 patients. PML was extracted and its amount was analyzed by LC-MS/MS. Separation was performed on a ACQUITY UPLC® BEH C18 column (Waters, 1.7 µm, 2.1mm x 50 mm). The mobile phase consisted of a mixture of phase A (0.1% formic acid in water) and phase B (acetonitrile). Transition channel of the protonated molecular ions of 274.17/201.12 was used for detection of PML.

The amount of PML was 2.33 ± 4.60 µg per blister pack (0.1–10 µg per blister pack).

In this study, although most of used blister packs were contaminated by PML at a very low level, a sheet was contaminated at a high level of approximately 10 µg of pomalidemide. Because PML is known for high teratogenicity, our data suggested that standard protection procedure was recommended to prevent unintended exposure to the drug for pharmacists.

(Keywords: blister packs, comtamination, PML)

Introduction

Pomalidomide (PML) (Pomalyst®, Celgene) is a thalidomide analogue approved for use in patients with “recurrent and/or intractable myelodysplastic syndrome” .

Because of teratogenicity of PML, Pomalyst® is strictly managed according to the RevMate® procedure in Japan.

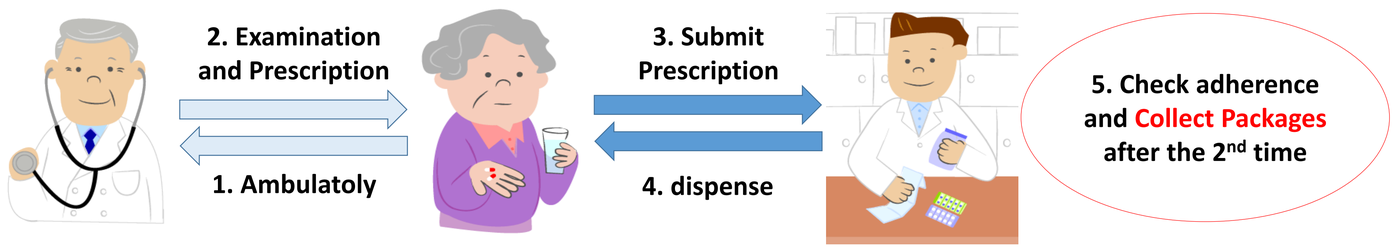

Fig. 1 The management of use of Pomalyst® capsules in accordance with RevMate® procedure

Pomalyst® is packaged in the blister packs (Push Through Package (PTP) sheet), which is used for most medicine in Japan.

According to the procedure for the use of Pomalyst®, pharmacists have to collect emptied blister packs of Pomalyst® capsules from all patients to confirm correct intake of Pomalyst®.

However, the risk of exposure to PML via used blister packs for pharmacists have not been assessed well.

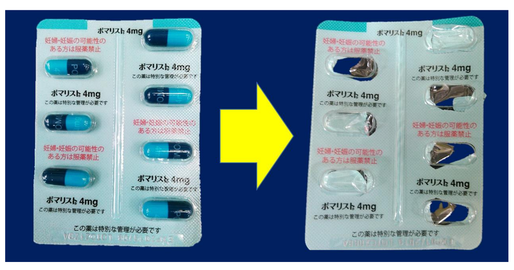

Fig. 2 Blister packs of Pomalyst® used in Japan

PURPOSE

To assess the risk of collection of used blister packs of Pomalyst®, we analyzed PML contamination level on the surface of used blister packs.

Materials and Methods

【Chemical profiles】

The empirical formula for PML is $C_{13}H_{11}N_3O_4$ and the gram molecular weight is 273.24.

A blister pack of Pomalyst® contains 7 capsules.

Voriconazole (m.w. 349.3) was used as an internal standard (I.S.) of LC-MS/MS.

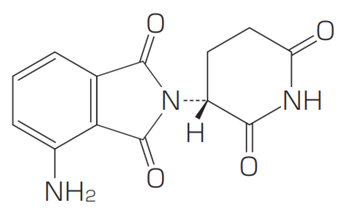

Fig. 3 Structure of PML

【Sample preparation】

Collected used blister packs were cut into small pieces (Fig. 4).

The pieces were shaken in 50mL methanol for 10 minutes to elute PML on used blister packs.

After addition of I.S., methanol was collected and evaporated using rotary vaporizing vessels.

The residue was dissolved in methanol and the concentration of PML was analyzed using LC-MS/MS.

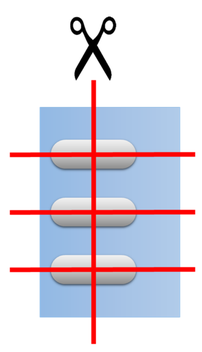

Fig. 4 Used blister packs were cut into pieces

【LC-MS/MS conditions】

LC:	ACQUITY UPLC system (Waters)
Column:	ACQUITY UPLC BEH C18 (Waters, 1.7 µm, 2.1 × 50 mm)
Injection volume:	5 µL
Column temp.:	40˚C
Mobile phase:	0.1% formic acid in milliQ water (A), and acetonitrile (B)
Flow rate:	0.5 mL/min
Gradient condition (A:B):	95:5 → 50:50 (1 min) → 50:50 (2 min) → 5:95 (2.1 min) → 5:95 (3 min) → 95:5 (3.5 min)
MS:	Xevo® TQ (Waters)
Capillary voltage:	1kV
Desolvation temp.:	500℃
Source temp.:	150℃
Cone gas flow:	50 L/hr
Desolvation gas flow:	1000 L/hr

Results

Contamination level of PML on used blister packs

PML was detected from all of 5 used blister packs (Table 1). The amount of PML per package was **2.33 ± 4.60 µg as mean** and **266.5 ng as median**, respectively.

In our study, PML was deteted up to 10 µg per package.

Table 1 The amounts of PML on 5 used blister packs of Pomalyst®

Sample No.	Amount of PML [ng/package]	C.V. %
1	124.9 ± 7.1	5.7
2	266.5 ± 7.1	2.7
3	10539.5 ± 91.0	0.9
4	97.5 ± 6.2	6.4
5	597.3 ± 27.8	4.7

Contamination level of lenalidomide on used blister packs

We previously assessed contamination and exposure risks of another thalidomide analogue, lenalidomide (Revlimid®, Celgene).

In that study, we analyzed the amount of lenalidomide on used blister packs collected from 5 patients .

Lenalidomide was detected from all packages while the amount was varied.

As results, lenalidomide was detected from all packages (392.3 ± 485.1 ng as mean and 137.2 ng as median per packages).

Table 2 The amounts of lenalidomide on used blister packs of Revlimid®

Sample No.	Amount of lenalidomide [ng/package]
1	1249.5
2	267.4
3	137.2
4	76.5
5	230.6

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Discussion

According to HIGHLIGHTS OF PRESCRIBING INFORMATION for Pomalyst® (USA)

Thalidomide is a human teratogen that is induces a high frequency of severe and life-threatening birth defects.

In some embryo fetal developmental studies, PML was reported to be teratogenic in both rats and rabbits, when administered during the period of organogenesis.

In case of Revlimid®

In our previous study, we revealed that lenalidomide was detected from used blister packs of Revlimid® capsules up to 1 µg per package.

According to our data, standard protection procedures, such as usage of gloves, are recommended for handling Revlimid® capsules or its used blister package.

In the present study

PML was detected from all used blister packs, and the highest contamination level was approximately 10 µg per package.

According to our data, although the exposure level of pharmacists to drugs was not assessed in our study, as is the case with Revlimid® capsule, standard protection procedures, such as usage of gloves, are recommended for handling Pomalyst® capsules or its used blister package.

What kind of precautions?

Caution for pharmacists

- ✓ Put on latex or nitrile groves dispensing
- ✓ Trash gloves and blister packs into a plastic bag with zipper

Education for patients

- ✓ Not to allow other people to touch the blister packs
- ✓ Not to leave blister packs scattered about
- ✓ Wash hands after taking drugs

CONCLUSION

Standard protection is recommended when touching Pomalyst® blister packs after use in order to prevent unintended exposure to PML.

Disclosure

We have nothing to disclose about present study.