医薬品相互作用研究
ノート掲載
34 (2) 35-40 (2010)

Preparation and Evaluation of Stability and Drug Release of Lidocaine containing Metronidazole Ointments Prepared in a Hospital for Cancerous Malodor

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(Received June 25, 2010 ; Accepted September 3, 2010)

We have so far provided evidence for the pharmaceutical and clinical evaluation of metronidazole (MTZ) ointments, which are widely used to reduce the malodor emanating from cancerous skin ulcers. Since cancerous skin ulcers emanate malodor due to infection and are associated with inflammation and hemorrhage, MTZ ointments containing lidocaine, an analgesic agent, (Lid-MTZ preparations) are prepared in many hospitals. To validate the quality of Lid-MTZ preparations, we performed a pharmaceutical evaluation of 2 drug preparations—MTZ-Hydrophilic ointment containing lidocaine (Lid-MTZ-Oint) and MTZ-Sangelose gel containing lidocaine (Lid-MTZ-SW-Gel)—by assessing the stability of their ingredients and their drug release properties.

The results of the drug-stability testing showed negligible changes in the concentrations of MTZ and lidocaine of the Lid-MTZ-Oint and Lid-MTZ-SW-Gel during the 60 days of preservation at 28° C or 40° C. The results of the drug-release analysis showed that the drug-release rates (%) of MTZ and lidocaine from Lid-MTZ-Oint at 8 h after the drug preparation were 73.2% and 93.5%, respectively, while those from Lid-MTZ-SW-Gel were 99.8% and 83.4%, respectively.

These results provide evidence of the stability and drug-release properties of Lid-MTZ preparations.

Key Words: hospital preparation, metronidazole, lidocaine, cancerous malodor, breast cancer

Introduction

Cancerous skin ulcers, which are often observed during advanced and recurrent breast cancer, emanate a strong malodor and decrease the quality of life (QOL) of patients remarkably by causing serious mental stress. The family members caring for these patients are also burdened with mental stress.

The malodor emanating from cancerous skin ulcers is considered to be originating mainly from rotten and dead tissues of focuses infected by anaerobic bacteria such as Bacteroides sp. and Peptostreptococcus sp. [1-5]. This malodor can be successfully controlled by treating the cancerous skin ulcers with topical metronidazole (MTZ) preparations[6,7].

The World Health Organization (WHO) also recommends the topical application of MTZ ointments on skin ulcers for controlling the malodor[8]; however, MTZ preparations are not yet available commercially in Japan. Therefore, many hospitals develop their own MTZ preparations[3-5,9-11] by using the formula given in

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the 6th edition of BYOIN YAKKYOKU SEIZAI [12].

For effective and safe use by the patients of MTZ ointments prepared in a hospital, the hospital needs to provide an assurance of the quality and the safety of the drug preparations and provide evidence of the clinical evaluation of these drugs. To achieve this objective, we had earlier performed a pharmaceutical evaluation of the stability and physical properties of MTZ preparations such as MTZ-Hydrophilic ointment (MTZ-Oint) with hydrophilic ointment base, MTZ-Carbopol Gel (MTZ-Gel) with Carbopol® 934-P as the base, and MTZ-Sangelose Gel with hydroxypropylmethylcellulose stearoxyether (Sangelose®) as the base[13,14](MTZ-SW-Gel). Moreover, we had provided evidences of the clinical evaluation of these drug preparations [15-17].

Cancerous skin ulcers are often accompanied by malodor as well as pain with bleeding and inflammation. For treating the bleeding and inflammation, MTZ preparations and lidocaine jelly, surface anesthesia, are simultaneously applied sometimes to the skin lesions of the patients. In some cases, MTZ preparations containing lidocaine (Lid-MTZ preparations) are used for topical application[11]. The methods to prepare Lid-MTZ preparations are published in the 6th edition of BYOIN YAKKYOKU SEIZAI[12]. In this study, we prepared MTZ-Hydrophilic ointment containing lidocaine (Lid-MTZ-Oint) and MTZ-sangelose gel containing lidocaine (Lid-MTZ-SW-Gel) in our hospital. To validate the quality of these Lid-MTZ preparations, we performed the pharmaceutical evaluation by examining the stability of the ingredients and the drug-release properties of these preparations.

MATERIALS AND METHODS

1. Reagents

The ingredients of the ointments were 2-methyl-5-nitroimidazole-1-ethanol (MTZ) (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan); hydrophilic ointment base (Merck Pharmaceutical Co., Ltd., Tokyo, Japan); hydroxypropylmethylcellulose stearoxyether (Sangelose®) (Daido Chemical Co., Ltd., Osaka, Japan); propylene glycol (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan); 4% lidocaine solution (4% Xylocaine® solution) (Astra Zeneca Co., Ltd., Osaka, Japan); and water for injection (stated in the Japanese Pharmacopoeia).

The reagents for HPLC were acetonitrile (Wako Pure Chemicals Co., Ltd., Tokyo, Japan) and ranitidine (internal standard) (Sigma-Aldrich Co., MO).

All other regents were commercially available as "analytical grade" products.

2. Preparation of Lid-MTZ-Oint and Lid-MTZ-SW-Gel

Lid-MTZ-Oint and Lid-MTZ-SW-Gel were prepared according to the methods described in previous studies[12,15-17](Table 1).

Table 1. Formula of the MTZ preparation containing lidocaine

Rp.	**Lidocaine containing MTZ-Oint (Lid-MTZ-Oint)**	
	2-Methyl-5-nitroimidazole-1-ethanol	1 g
	Propylene glycol (JP)	3 mL
	4% Lidocaine	5 mL
	Hydrophilic Ointment	91 g
Rp.	**Lidocaine containing MTZ-SW-Gel (Lid-MTZ-SW-Gel)**	
	2-Methyl-5-nitroimidazole-1-ethanol	0.8 g
	Propylene glycol (JP)	10 mL
	Sangelose®60L	0.25 g
	Sangelose®90L	0.75 g
	4% Lidocaine	5 mL
	Water for injection	83 mL

Lid-MTZ-Oint was prepared as follows: In a mortar, 1 g of MTZ crystals was mixed thoroughly with 3 mL of propylene glycol, after which 91 g of hydrophilic ointment was added and mixed. Finally, 5 mL of 4% lidocaine solution was added to this mixture and mixed uniformly.

Lid-MTZ-SW-Gel was prepared as follows: In a mortar, 0.8 g of MTZ crystals was mixed thoroughly with 10 mL of propylene glycol. Subsequently, 0.25 g of Sangelose ® 60L and 0.75 g of Sangelose ® 90L were slowly added individually to 83 mL of water maintained at 70℃ and mixed uniformly. This solution was cooled to 40℃ and mixed thoroughly with the MTZ crystals in propylene glycol. Finally, to this mixture, 5 mL of 4% lidocaine solution was added and mixed thoroughly again.

3. Stability

Thirty grams each of prepared Lid-MTZ-Oint and Lid-MTZ-SW-Gel were preserved in airtight plastic opaque containers for 60 days at 28℃ and 40℃, respectively. The stability of the drug preparation was assessed by analyzing the changes in the appearance and the concentration of MTZ in these drug preparations [17-19]. The drugs Lid-MTZ-Oint and Lid-MTZ-SW-Gel were

carefully observed immediately after preparation (day 0), and the concentration of MTZ was determined using HPLC. The changes in the appearance and the concentrations of MTZ and lidocaine of Lid-MTZ preparations preserved at 28℃ and 40℃ were again measured on days 0, 14, 30, and 60 by using HPLC.

HPLC instrumentation and chromatographic conditions: The HPLC system consisted of a LC-10ADvp pump (Shimadzu Co., Kyoto, Japan); an SPD-10Avp UV detector (Shimadzu Co., Kyoto, Japan) set at 324 nm for MTZ and 254 nm for lidocaine; a TSK-GEL ODS-80TM column (250 mm × 4.6 mm i.d., particle size of 5 μm, TOSOH Co., Tokyo, Japan) maintained at 30℃; and a CTO-10Avp column oven (Shimadzu Co., Kyoto, Japan). The mobile phase consisted of 0.02M KH2PO4 buffer (pH = 3) and acetonitrile (5:6), and its flow rate was adjusted to 1.2 mL/min.

Preparation of samples for measurement: Lid-MTZ-Oint or Lid-MTZ-SW·Gel (38 mg) was added to ranitidine (internal standard) and a mixture of 0.001 mol/L HCl (30 mL) and 1 mol/L HCl (0.5 mL) solutions to make a 50-mL solution of 0.001 mol/L HCl. This solution was sonicated for 5 min (final concentration of ranitidine, 200 μg/50 mL). The processed solution was filtered using DISMIC ®-3JP (φ, 0.5 μm), and 20 μL of this solution was injected into the HPLC column. The concentration of MTZ was calculated from the peak area ratio with an internal standard.

4. Release of MTZ and lidocaine from Lid-MTZ preparations

The rate of MTZ and lidocaine release from Lid-MTZ-Oint and Lid-MTZ-SW·Gel was measured using the Franz cell (static diffusion) method [17,20]. A cellulose membrane (seamless cellulose tubing, Sanko Junyaku Co.; size, 30/32) was mounted in a Franz diffusion cell (Trademark, LG-1084-MPC, Laboratory Glass Apparatus Co., Ltd.), and the donor cell was filled completely with 0.31 g of freshly prepared MTZ-Oint or MTZ-Gel. The receptor cell was filled with Ringer's solution, and the rates of release of MTZ and lidocaine from the donor cell to the receptor cell at 37℃ were measured using HPLC. The samples were extracted after 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h.

The mean dissolution time (MDT) was calculated from the dissolution time curves obtained for MTZ and lidocaine from the results of the drug-release analysis that was performed at 0 to 8 h by using moment analysis described by Tanigawara et al[21].

RESULTS AND DISCUSSION

1. Stability

The appearance of Lid-MTZ-Oint and Lid-MTZ-SW·Gel did not change during the 60 days of preservation. The concentrations of MTZ and lidocaine in Lid-MTZ-Oint were measured using HPLC and their time-dependent changes were analyzed. The results of the stability of these preparations are shown in Fig. 1. The concentrations of MTZ and lidocaine in Lid-MTZ-Oint showed negligible changes during preservation at 28℃ and 40℃ for 60 days after the Lid-MTZ-Oint preparation (Fig 1).

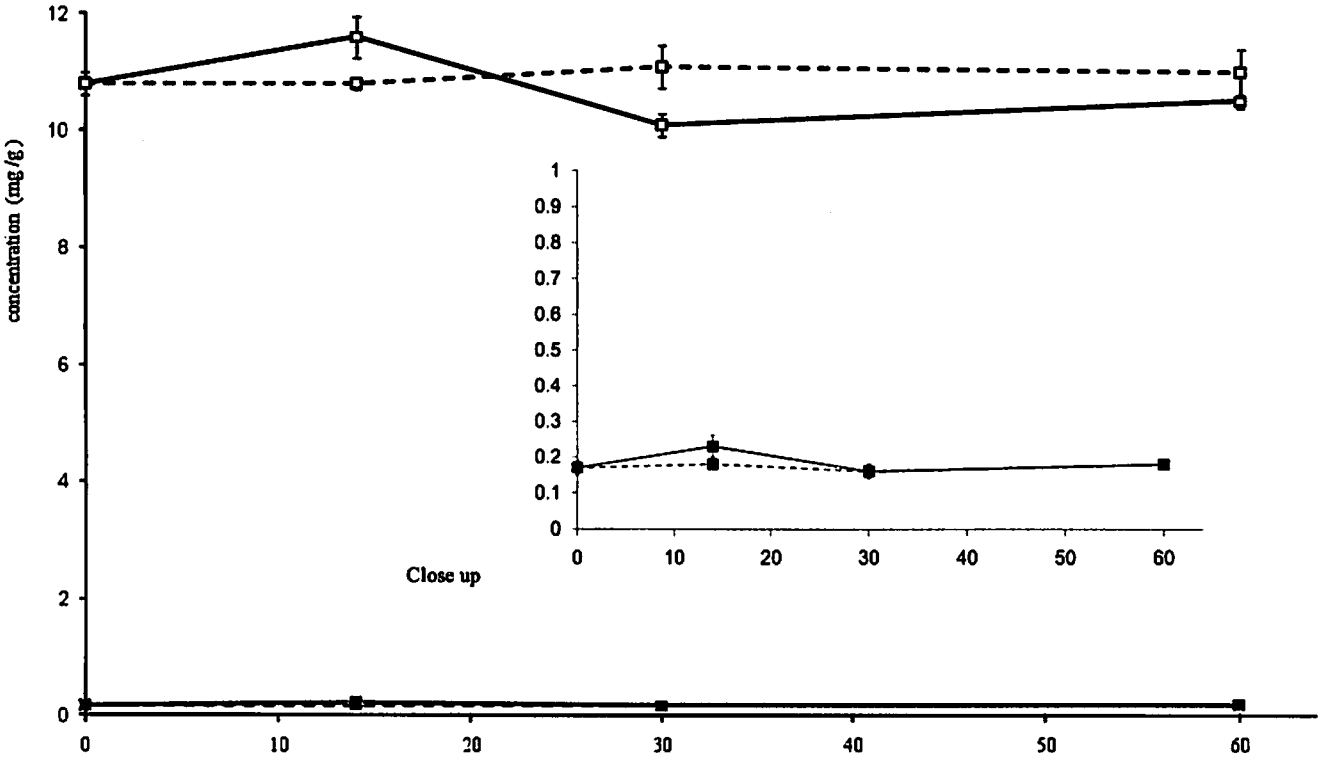
The concentrations of MTZ and lidocaine in Lid-MTZ-SW·Gel were also measured using HPLC, and their time-dependent changes are shown in Fig. 2. The concentrations of MTZ and lidocaine in the Lid-MTZ-SW·Gel showed negligible changes during preservation at 28℃ and 40℃ for 60 days after their preparation (Fig. 2).

Our findings show that the Lid-MTZ-Oint and Lid-MTZ-SW·Gel were stable at room temperature for 60 days after their preparations, thereby suggesting that the quality of the 2 preparations can be assured. Thus, for practical clinical applications, MTZ preparations and lidocaine jelly, surface anesthesia, neither need to be prescribed separately, nor to be applied simultaneously on the skin lesions and instead, MTZ ointments containing lidocaine can be prepared in a hospital and applied on the skin lesions of the patients. The MTZ preparations are often prescribed for patients with cancerous skin ulcers who mainly receive home care. Our findings indicate that MTZ preparations containing lidocaine are useful as preparations prescribed in the hospitals and for outpatients requiring long-term therapy.

2. Drug Release of MTZ and Lidocaine by using static Franz-type diffusion cells

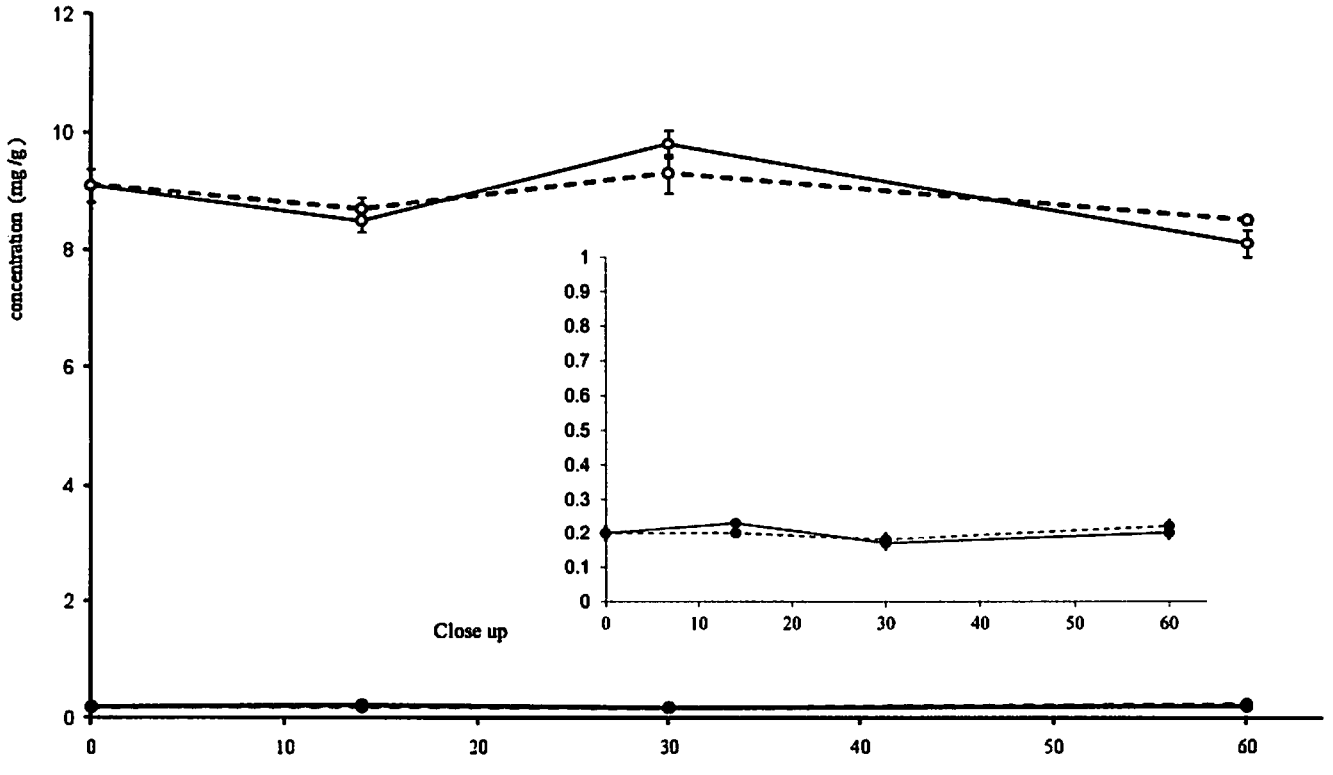
Fig. 3 shows the rates of MTZ and lidocaine release from Lid-MTZ-Oint, and the rates were calculated by considering the concentrations of MTZ and lidocaine as 100% immediately after Lid-MTZ-Oint preparation. The rate of MTZ release increased to 13.0%, 22.3%, 30.0%, 37.0%, 49.0%, 57.0%, 67.2%, and 73.2% after 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h, respectively, while that of lidocaine

Fig. 1. Stabilities of MTZ and lidocaine in Lid-MTZ-Oint stored at 28°C and 40°C



Each point represents the mean. (n = 5)
□—□ MTZ in Lid-MTZ-Oint at 28℃ □---□ MTZ in Lid-MTZ-Oint at 40℃
■—■ Lidocaine in Lid-MTZ-Oint at 28℃, ■---■ Lidocaine in Lid-MTZ-Oint at 40℃

Fig. 2. Stabilities of MTZ and lidocaine in the Lid-MTZ-SW-Gel stored at 28°C and 40°C



Each point represents the mean. (n = 5)
□—□ MTZ in Lid-MTZ-SW-Gel at 28℃, □---□ MTZ in Lid-MTZ-SW-Gel at 40℃
■—■ Lidocaine in Lid-MTZ-SW-Gel at 28℃, ■---■ Lidocaine in Lid-MTZ-SW-Gel at 40℃

release increased to 25.1%, 37.0%, 48.0%, 57.0%, 69.0%, 77.0%, 87.4%, and 93.5%, respectively (Fig. 3).

The MDT (mean±S.D.) for MTZ and that for lidocaine in Lid-MTZ-Oint were 2.53±0.16 h and 2.22±0.22 h, respectively.

Fig. 4 shows the rates of MTZ and lidocaine release from Lid-MTZ-SW·Gel, and the rates were calculated by considering the concentrations of MTZ and lidocaine as 100% immediately after Lid-MTZ-SW·Gel preparation. The rate of MTZ release increased to 28.7%, 49.0%, 63.0%, 76.0%, 90.0%, 95.0%, 98.0%, and 99.8% after 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h, respectively, whereas that of lidocaine release increased to 18.5%, 33.0%, 45.0%, 55.0%, 69.0%, 76.0%, 80.5%, and 83.4%, respectively (Fig. 4).

The MDT (mean±S.D.) for MTZ and that for lidocaine in Lid-MTZ-SW Gel were 1.59 ±0.15 h and 1.88±0.13 h, respectively.

The drug release analysis using the Franz cell method (static diffusion) revealed that the rate of MTZ release from the Lid-MTZ-SW·Gel base was higher than that from the Lid-MTZ-Oint base. On the other hand, the rate of lidocaine release from the Lid-MTZ-Oint base was higher than that from Lid-MTZ- SW·Gel base. These findings indicated that the drug-release profiles of MTZ and lidocaine from Lid-MTZ-Oint and Lid-MTZ-SW·Gel were significantly different, and this difference may be attributed to the differences in the solubility of MTZ and lidocaine in hydrophilic ointment base and Sangelose®. To date, we have used the same dosage regimen for both the MTZ preparations when applying them to the patients in spite of different bases. However it is imperative that the drug-release properties of both Lid-MTZ-Oint and Lid-MTZ-Gel·SW be carefully considered for deciding an optimal dosage regimen.

In conclusion, the findings of our study provide evidence for the stability and the drug release of Lid-MTZ preparations. In future, the clinical evaluation of these preparations will be performed to assess the efficacy and safety of MTZ-preparations as well as their usefulness including the QOL of the patients.

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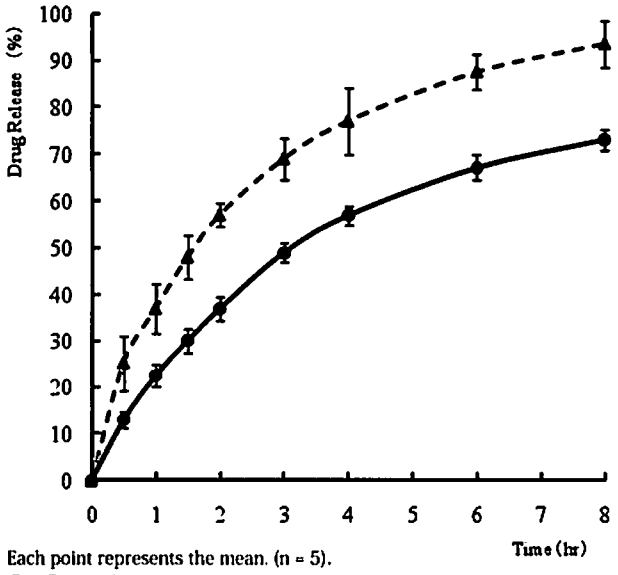
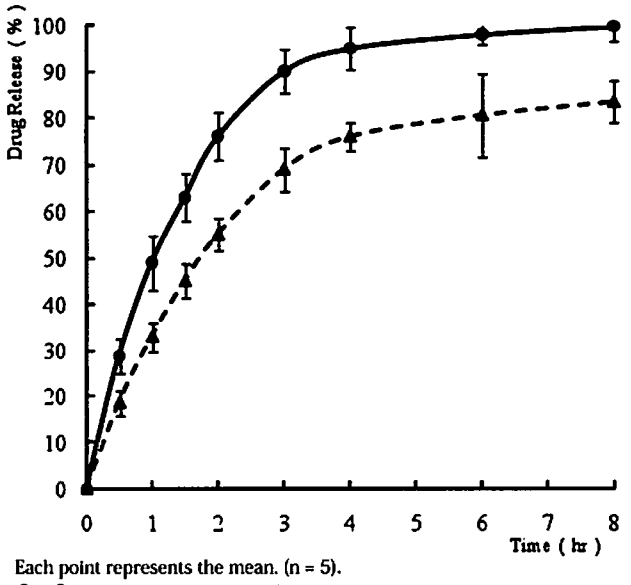
Fig. 3. Results of the drug release of MTZ and lidocaine from Lid-MTZ-Oint by using the static Franz-type diffusion cell for 0 day.



Each point represents the mean. (n = 5).
●—● MTZ from Lid-MTZ-Oint
▲···▲ Lidocaine from Lid-MTZ-Oint

Fig. 4. Results of the drug release of MTZ and lidocaine from Lid-MTZ-SW-Gel by using static Franz-type diffusion cell for 0 day.



Each point represents the mean. (n = 5).
●—● MTZ from Lid-MTZ-SW-Gel
▲···▲ Lidocaine from Lid-MTZ-SW-Gel

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