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Changes in the viscosity of metronidazole gel mixed with other agents to treat malodorous ulcerated skin cancers

Iori HIROSAWA [1)], Kaname HASHIZAKI [2)], Kentaro MATSUMURA [1)], Makiko FUJII [2)], Kazuhiro WATANABE [1,*)]

[1)]Laboratory of Pharmacy Practice, Center for Education and Research on Clinical Pharmacy, Showa Pharmaceutical University
[2)]Laboratory of Physical Chemistry, School of Pharmacy, Nihon University

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Ulcerated skin cancers cause severe pain, bleeding, and the formation of exudate. When treating these symptoms with topical mixtures of metronidazole (MTZ) gel and other drugs in clinical settings, it has been observed that the gel does not always adhere well to the affected areas. In this study, the viscosity of MTZ gels mixed with other substances were measured with a viscometer, and the cause of the reduced viscosity was analyzed. Lidocaine jelly and sodium alginate, common additives for suppressing pain and bleeding, were added to the MTZ gel, and changes in the viscosity and pH of the different MTZ gel mixtures were measured. Viscosities were also measured after some sodium solutions were added to the MTZ gel. The results showed that the viscosities of MTZ gels mixed with lidocaine jelly and sodium alginate were decreased to one-tenth or less of MTZ gel without additives. There was no change in pH after addition of lidocaine jelly and sodium alginate to the MTZ gel. Addition of aqueous solutions of sodium chloride also reduced the viscosity of the MTZ gel. These data show that the viscosity of the MTZ gel decreased with the addition of other agents, presumably due to the effects of a cationic component.

Key Words: Topical metronidazole, Malodorous fungating tumors, Viscosity, Carboxyvinyl polymer

Background

Malodor associated with ulcerating tumors is caused by invasion into the skin or metastases. Cancers that are likely to develop skin ulcers include breast cancer, head and neck cancer, and squamous cell carcinoma of the skin. In particular, the rate of ulcers in breast cancer is high, with an incidence of approximately 4%. Such skin ulcers are accompanied by severe pain, bleeding, and formation of large amounts of exudate. The discharged fluid is infected with anaerobic bacteria such as Trichomonas species, fungi, and decomposition compounds such as putrescine and cadaverine, which are produced from bacteria and cause a strong odor [1–3)]. The malodor causes distress in patients and also affects those around them, such as family members and healthcare workers. Not only does this make it difficult for patients to maintain personal relationships, but it also lowers their self-esteem and reduces their quality of life. The quality of medical care can also be adversely affected. Thus, ulcerating tumors place a heavy burden on all concerned, making it important to simultaneously reduce both the pain and malodor [4)].

Metronidazole (MTZ) is a well-known and effective antibiotic that can reduce the malodor of ulcerating skin cancers [5,6)]. Thus, the World Health Organization and American Society of Clinical Oncology have recommended its topical application [4,7)]. However, until recently it was not approved in Japan, and formulations were individually prepared by each hospital [6,8,9)]. In 2015, a topical medicine containing MTZ, 0.75% MTZ (Rozex®) gel, was approved for use in Japan

[1)] Laboratory of Pharmacy Practice, Center for Education and Research on Clinical Pharmacy, Showa Pharmaceutical University, 3-3165 Higashi-Tamagawagakuen, Machida-shi, Tokyo 194-8543, Japan
[2)] Laboratory of Physical Chemistry, School of Pharmacy, Nihon University, 7-7-1 Narashinodai, Funabashi, Chiba 274-8555, Japan
* Corresponding author: Kazuhiro Watanabe
Tel: +81-42-721-1440; Fax: +81-42-721-1440; E-mail: kazunabe@ac.shoyaku.ac.jp

as a bactericide and for the reduction of odor at skin ulcer sites in cancer. MTZ gel acts against Gram-positive and Gram-negative anaerobic bacteria, which produce malodorous substances such as putrescine and cadaverine at the sites of ulcerating skin tumors in patients with advanced cancer. A clinical trial showed that MTZ gel reduced the intensity of malodors in 95.2% of breast cancer patients [10].

Patients with ulcerated skin cancer who develop either severe pain or bleeding are typically administered topical MTZ gel mixed with 2% lidocaine jelly or sodium alginate, respectively. However, the viscosity of these mixed MTZ gels decreases and they do not adhere well to the affected areas. Moreover, patients with ulcerated skin may find a topical agent painful to apply if the base material is too thick; however, the medicine will not adhere if the material lacks sufficient viscosity. Hence, the correct viscosity, expansibility of the base, and usability are essential for topical application. Carboxyvinyl polymer (CVP), which is used in MTZ gels, has moderate viscosity and good release characteristics, and as such, is used as a matrix for various pharmaceutical products. Its viscosity changes depending upon the pH and cationic components of the product. However, there have been no reports of its incompatibility with MTZ gel.

In this study, we examined the changes in viscosity and pH of MTZ gel mixed with other agents and analyzed the mechanisms leading to the observed changes, with the goal of elucidating the factors that affect its viscosity.

Methods

Materials

Rozex® gel 0.75% (containing 0.75% MTZ; MTZ gel), Xylocaine® Jelly 2% (containing 2% lidocaine) and Alto® (sodium alginate powder) were purchased from Galderma Co., Ltd. (Tokyo, Japan), Aspen Japan Co., Ltd. (Tokyo, Japan), and Kaigen Pharma Co., Ltd. (Osaka, Japan), respectively. Water was purchased from Otsuka Pharmaceutical Factory, Inc. (Tokushima, Japan). Sodium chloride was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan).

Viscosity measurements

Viscosity measurements were performed using a stress-controlled rheometer (HAAKE RS600; Thermo Fisher Scientific, Waltham, MA, USA) equipped with a Peltier-based temperature control device. All measurements were performed at 25 ° C. The viscosities of individual substances were measured by cone-plate geometry (35 mm diameter, 1 ° cone angle), and the viscosities of the mixed gels were measured with an evaporation assist plate (50 mm diameter, 0.5 mm gap). The viscosity of each sample was measured three times, and the results are presented as the mean ± standard deviation (SD). The viscosities of the MTZ gel and lidocaine jelly were measured at a shear rate of 10 s^{-1}; subsequently, the viscosities of lidocaine jelly or sodium alginate mixed with MTZ gel were measured. MTZ gel (0.22 g) was set in the apparatus and the viscosity measurement was started at a shear rate of 10 s^{-1}. After 2 min, lidocaine jelly, sodium alginate, or an aqueous solution of sodium chloride (0.9%, 0.09%, 0.009%; 0.05 mL) was added, and the viscosity was measured for 4 min. MTZ gel and lidocaine jelly were mixed at a weight ratio of 4:1, and MTZ gel and sodium alginate powder were mixed at a weight ratio of 20:1; those are the ratios used in actual clinical practice at St. Luke's International Hospital in Tokyo. Sodium alginate aqueous solution was prepared with the same amount of sodium alginate powder used in the previous test experiment in 0.05 mL water.

pH measurements

The pH values of the samples were measured using a pH meter (pHTestr 10 BNC, Oakton, Vernon Hills, IL, USA). The temperature of each sample was adjusted to 25 ° C, and after mixing for 3 min, the pH meter was directly placed into the prepared sample and the pH was measured. The pH of each sample was measured 3 times, and the measurement results were presented as the mean and standard deviation. The samples were prepared at the same ratios as those used in the viscosity tests.

Results

Viscosity measurements

The viscosity of the MTZ gel was 10.2±0.3 Pa·s at 25 ° C, and the shear rate was 10 s^{-1} (Fig. 1A). The viscosity of the lidocaine jelly was 2.6 Pa·s. The viscosities of the MTZ gels abruptly decreased upon addition of lidocaine jelly to 1.08±0.11 Pa·s (Fig. 1B). After sodium alginate powder was added, the viscosity decreased but fluctuated, possibly due to the powder; thus sodium alginate dissolved in aqueous solution was added to the MTZ gel. After 4 min, the viscosity abruptly decreased to 0.83±0.09Pa·s that after addition of the powder (Fig. 1D). Thus, the sodium alginate lowered the viscosity of the MTZ gel, and it was thought that the influence on viscosity after water was added was negligible.

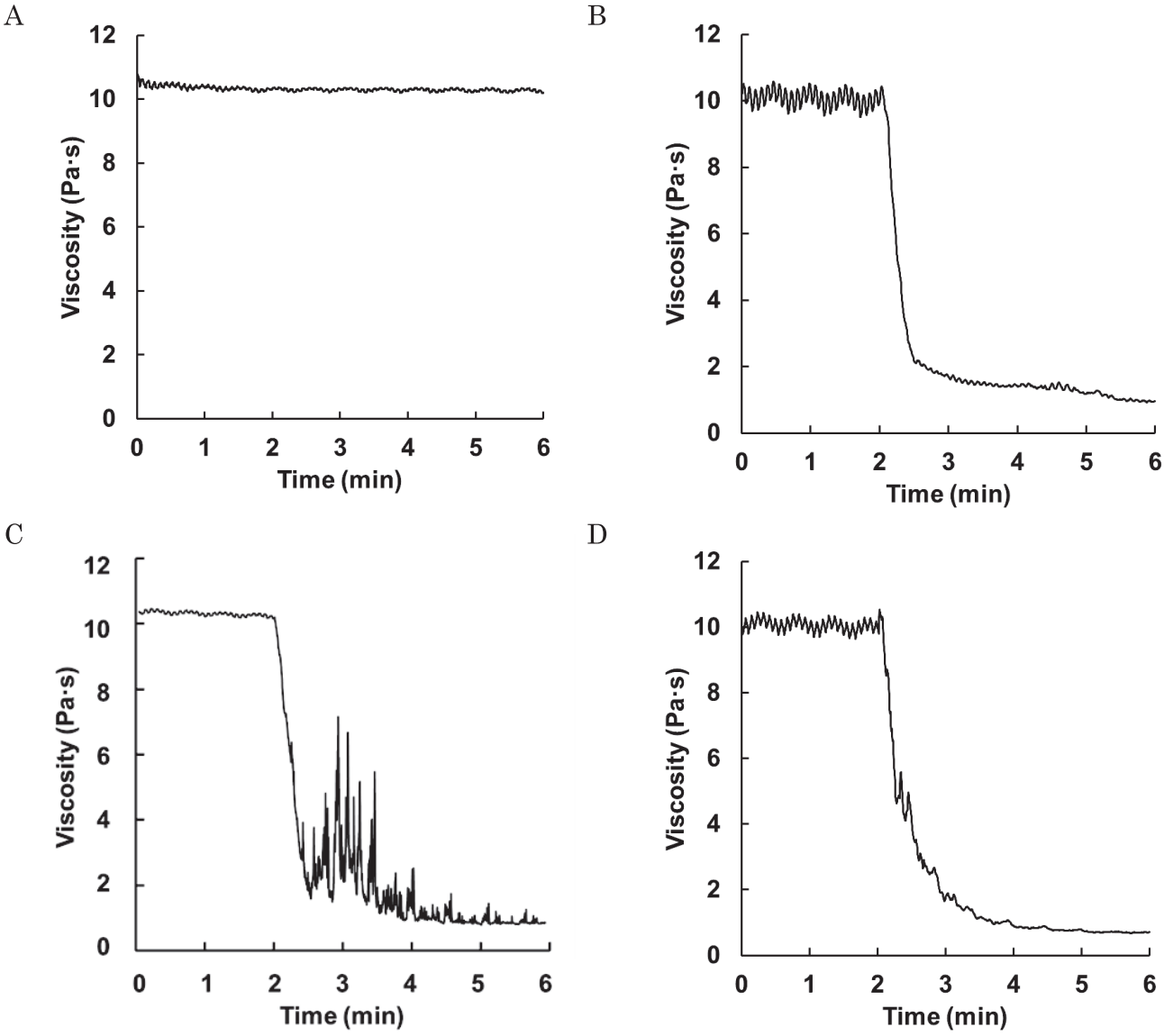

Figure 1. Changes in viscosity of the MTZ gel after the addition of other agents.

Lidocaine jelly, sodium alginate power, or sodium alginate solution was added 2 min after viscosity measurement of the original MTZ gel at 25°C. A, MTZ gel; B, MTZ gel + lidocaine jelly; C, MTZ gel + sodium alginate powder; D, MTZ gel + sodium alginate solution.

pH measurements

The MTZ gel had a pH of 4.87±0.02 and was a weak acid. The pH levels were 4.84±0.03 and 4.79±0.03 after lidocaine jelly and sodium alginate aqueous solution were added to the MTZ gel, respectively, which were similar to the pH of the original gel (Table 1).

Table 1. The pH of MTZ gel, lidocaine jelly, and MTZ gel mixtures (n=3)

Single and mixed reagents	pH (mean±SD)
MTZ gel	4.87±.87
Lidocaine jelly	6.27±.27
MTZ gel + lidocaine jelly (4:1)	4.84±.84
MTZ gel + sodium alginate solution (20:1)	4.79±.79

Changes in viscosity of MTZ gel after addition of sodium chloride

The viscosities of MTZ gels upon addition of sodium chloride aqueous solutions (three concentrations) were measured. All of the samples showed decreases in viscosity (Fig. 2). For low concentrations of sodium chloride, gradual restitution of the viscosity occurred, but for high concentrations (0.9%), it decreased to less than 1 Pa·s and remained in a state of low viscosity.

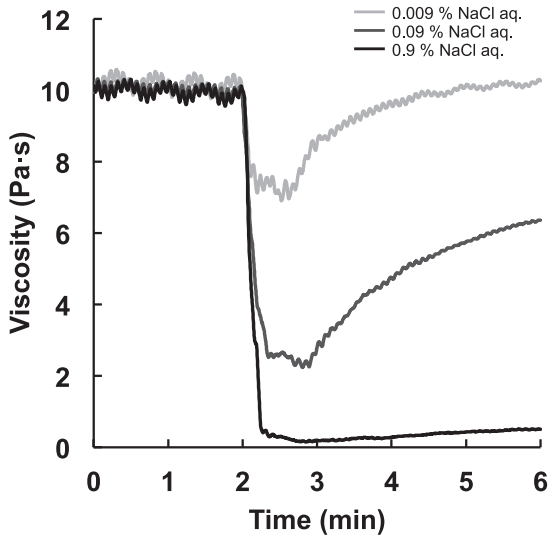

Figure 2. Changes in viscosity of the MTZ gel after addition of sodium chloride aqueous solutions.

Sodium chloride aqueous solutions at 0.009, 0.09, and 0.9 w/v% were added 2 min after viscosity measurement of the original MTZ gel at 25°C.

Discussion

In this study, the viscosity of the MTZ gel rapidly decreased when mixed with other agents. In clinical practice, MTZ gel is applied in two ways. In one, the gel is directly applied to the ulcer and the treated area is covered with a dressing. In the other, the gel is spread onto a dressing that is then placed over the ulcer. Thus, it is essential that the MTZ gel has adequate viscosity. The viscosity of the MTZ gel without

additional agents was approximately 10 Pa·s in this study. In contrast, the viscosity of the MTZ gel mixed with lidocaine jelly or sodium alginate decreased to 1 Pa·s, which was one-tenth that of the original gel. These findings showed that the decreases in viscosity in this study resulted in viscosities that were even lower than the typical viscosity of glycerin (1.5 Pa·s).

MTZ gel contains the gelling agent, CVP. CVP forms a transparent gel with good rheological characteristics, so it is widely used in both pharmaceutical products and cosmetics. MTZ gel also contains sodium edetate hydrate, propylene glycol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, and sodium hydroxide as additives, and adequate viscosity is maintained in the presence of these ingredients. This lower viscosity of the MTZ gel was thought to result from changes in the components of the gelling agent, namely CVP. CVP gel is prepared by dispersing CVP in water at a concentration of 1% or less, and then neutralizing it with a basic solution to a pH of 6–8. When dispersed in water, CVP has a pH of approximately 4, and the viscosity gradually increases with as the pH increases towards alkaline levels. The viscosity is highest at pH 6–8 and decreases as the preparation becomes more alkaline [12]. The pH of MTZ gel is approximately 5, which is relatively low, and there were no significant changes in pH after it was mixed with other agents, showing that the changes in viscosity of MTZ gel mixed with multiple agents were not due to changes in pH.

The viscosities of CVP gels are also affected by salt and buffers [11]; thus, we suspected that the change in viscosity of the MTZ gel was due to the presence of salt. To this end, we added aqueous solutions of sodium chloride to the MTZ gel, which resulted in a sharp decrease in viscosity, similar to that observed upon addition of lidocaine jelly or sodium alginate aqueous solution. Because the amount of sodium chloride solution was fixed at 0.05 mL, the decrease in viscosity was dependent on the concentration of sodium chloride and not on the addition of water. This was also supported by the fact that the change in viscosity was not strongly affected by the water of dissolved sodium alginate. Because CVP is anionic, neutralization of the charge occurs due to incorporation of the cationic components, resulting in the abrupt reduction of viscosity, aggregation, and turbidity. The addition of sodium chloride caused a sharp decrease in viscosity.

Sodium alginate powder contains 0.116 g Na/g. In this viscosity study, approximately 10 mg sodium alginate powder was added to 0.22 g MTZ gel, so a greater amount of sodium was added to the MTZ gel with addition of the powder than with addition of 0.05 mL of the 0.9% sodium chloride solution. Thus, sodium ions likely explain the effects of sodium alginate on MTZ gel.

Lidocaine jelly contains additives such as methyl paraben, propyl paraben, carmellose sodium, and a pH regulator. Carmellose sodium contains 6.5–8.5 Na/g; however, the causative substance in lidocaine jelly is unknown. Because it produced a sharp decrease in MTZ gel viscosity similar to that of sodium alginate and sodium chloride aqueous solution, a cationic component of the additive may be the cause. Realdon *et al.* [13] showed that the viscosities of hydrogels were reduced by procaine hydrochloride in a concentration-dependent manner. Because lidocaine has a similar cationic structure to procaine, cations may play a role in reducing the viscosity of the hydrogel.

Conclusions

The results of this study showed that the viscosity of MTZ gel was reduced by mixing it with other drugs such as lidocaine jelly and sodium alginate, possibly due to the effects of their cationic components.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

IH collected the data and wrote the manuscript. KH designed the study and collected the data. KM collected the data. MF and KW designed and supervised the study. All authors read and approved the final manuscript.

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