Stability of Polaprezinc-Containing Oral Rinse and Its Clinical Effectiveness against Radiotherapy-Induced Oral Mucositis

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Abstract
Objective: Oral mucositis is one of the serious and frequent acute side effects due to chemoradiotherapy (CRT) for head and neck cancer. In this study, we prepared an oral rinse as a hospital preparation for the treatment of oral mucositis, which was a suspension of polaprezinc (PZ), a zinc-containing therapeutic agent for gastric ulcer, in carboxyvinyl polymer (CP), a water-soluble large molecule.
Methods: We carried out stability tests of the PZ-CP oral rinse, and investigated its effects on the radiation-induced oral mucositis in patients who received CRT for head and neck cancer.
Results: In the stability test, the pH, viscosity, adhesion and PZ content in the preparations did not change throughout 28 days after preparation. In the clinical evaluation on the basis of the distribution of the Grade of oral mucositis, the Grade of oral mucositis in the PZ group was significantly lower than in the control group at 6 and 7 weeks (p = 0.016, p = 0.018). The incidence of severe oral mucositis of Grade 3 was 15.0% (3 cases) in the PZ group and 41.7% (10 cases) in the control group at 6 weeks, and was 15.0% (3 cases) in the PZ group and 33.3% (8 cases) in the control group at 7 weeks.
Conclusion: These results suggest that PZ-CP oral rinse inhibits the aggravation of oral mucositis induced by CRT or promotes its healing.

Key words: polaprezinc, radiotherapy, oral mucositis, oral rinse, carboxyvinyl polymer

Introduction
Radiotherapy plays an important role in the treatment of head and neck cancer, but it may cause oral mucositis, and severe pain due to radiotherapy-induced oral mucositis significantly reduces the QOL (quality of life) of patients4. Moreover, severe oral mucositis may prevent continuation of the radiotherapy5, and a report has shown that the five-year survival rate was significantly lowered by the cessation of radiotherapy due to oral mucositis6. Therefore, treatment of oral mucositis in head and neck cancer patients who receive radiotherapy is now considered important4.

For the treatment of oral mucositis, polaprezinc (PZ) suspended in sodium alginate solution has been used in many hospitals, and its stability5 and clinical effectiveness6 have already been reported. PZ, a zinc-containing therapeutic agent for gastric ulcer, has mucosal protective action8, free radical scavenging action9,10 and wound healing-promoting action11,12, showing a high affinity to the site of mucosal injury. Since excessive generation of free radicals is involved in the pathogenesis of radiation-induced oral mucositis13, PZ may serve as an effective therapeutic agent.

In Hyogo College of Medicine Hospital, to enhance the adhesion of PZ to the oral mucosa, we have suspended PZ in carboxyvinyl polymer (CP), a water-soluble high molecular weight compound employed as a base of oral spray14, and used the PZ-CP oral rinse for treatment of oral mucositis. However, there is no report on the stability of PZ in CP solution and clinical effectiveness of PZ-CP oral rinse.

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In this study, we examined the stability of the PZ-CP oral rinse, and then assessed the effectiveness of the PZ-CP oral rinse on oral mucositis after a chemoradiotherapy (CRT) regimen in patients with head and neck cancer.

Methods

1. Material

PZ (Promac® D Tablets 75, ZERIA Pharmaceutical Co., Ltd.) was used as an active ingredient, and CP (HIVISWA-KO® 105, Wako Pure Chemical Industries, Ltd.) was used as a base. Xylitol (special-grade reagent, Wako Pure Chemical Industries, Ltd.) was used as a sweetener and sodium hydrogen carbonate (Yoshida Pharmaceutical Co., Ltd.) was used as a pH-adjusting agent. The other reagents used were of special grade (Wako Pure Chemical Industries, Ltd.).

2. Preparation of PZ-CP Oral Rinse

PZ-CP oral rinse was prepared according to Table 1. Formulation of the PZ-CP oral rinse was designed, considering the results of the preliminary test. First, xylitol, methyl p-hydroxybenzoate and CP were dissolved in an appropriate amount of purified water. Next, Promac® D Tablets 75 were suspended in a small amount of purified water, and then purified water was added to the suspension, and the final volume was adjusted to 280 mL. Thereafter, the mixture was stirred sufficiently.


The PZ-CP oral rinse was stored under four distinct conditions: 5°C with or without light-shielding and 25°C with or without light-shielding, in sterile polyethylene containers. The oral rinse was visually observed to check the apparent changes from the outside of the container, and the pH, viscosity, adhesion and PZ content were measured on days 0, 1, 3, 7, 14 and 28 after preparation.

3-1. Measurement of pH and viscometry

The pH was measured using a pH meter (Yokogawa Electric Corporation). The viscosity was measured using a viscometer (RVDV-I, Brookfield Engineering Labs), and the measurement conditions were as follows: spindle, No. 3; sample temperature, 25°C; and the number of revolutions, 10 rpm.

3-2. Adhesion test

The procedure of the adhesion test was as follows: (i) 10 mL of PZ-CP oral rinse was accurately weighed in a metering glass (Miyahara Measuring Instruments Co., Ltd.) that had been weighed. (ii) The metering glass was held upside-down on a beaker, so that most of the oral rinse flowed down. (iii) The weight of the metering glass was measured again after 30 sec. The extent of adhesion of the oral rinse to the metering glass is presented as the percentage of the original weight of the preparation.

3-3. Measurement of PZ content

The PZ amount in the oral rinse was measured by chelometric titration. After 10 mL of oral rinse was accurately weighed, 50 mL of 10% hydrochloric acid was added, and the mixture was shaken sufficiently. The filtered solution of 5 mL was used as a sample. Chelometric titration was performed using 0.025 mol/L EDTA as a chelating agent. The amount of PZ is expressed as the percentage of the original amount on day 0.


The study included patients who received CRT for head and neck cancer at Hyogo College of Medicine Hospital. Twenty-four patients who received CRT from January 2009 to December 2009 were basically treated with mouthwash with azulene (control group), and 20 patients who underwent CRT from March 2010 to August 2011 were subjected to mouthwash with PZ-CP oral rinse in addition to azulene (PZ group).

As the content of treatment, the patients with oral cancer received a total irradiation dose of 60 Gy, and also received concurrent super-selective arterial infusion chemotherapy with cisplatin. Cisplatin (50 mg/body) was administered

| Table 1. Polaprezinc oral rinse prescription |
|--------------------------------------------|-----------------|
| Polaprezinc (Promac® D Tablets 75)         | 14,000 Tablets  |
| Carboxyvinyl Polymer (HIVISWA-KO® 105)     | 1.260 g         |
| Xylitol                                    | 12.600 g        |
| Sodium Hydrogen Carbonate                  | 1.260 g         |
| Methyl p-Hydroxybenzoate                   | 0.078 g         |
| Purified Water                             | ad. 280,000 mL  |
basically once a week, 3-4 times in total, during radiotherapy. The patients with laryngeal cancer and pharyngeal cancer had a total irradiation dose of 66 Gy, and also received concurrent intravenous chemotherapy with carboplatin or docetaxel. Carboplatin (100 mg/body) was administered basically twice a week in the first and second weeks and thereafter once a week, 6-8 times in a total, during radiotherapy. Docetaxel (20 mg/m²) was administered basically once every two weeks, 3 times in total, during radiotherapy. Radiotherapy was carried out using divided irradiations of 2 Gy with a Linear Accelerator.

An azulene oral rinse was prepared by dissolving 10 g of HACHIAZULE GARGLE ® in 500 mL water, and used for mouthwash that patients performed about 4 times a day. PZ-CP oral rinse at a volume of 10 mL was used 4 times a day. In mouthwash, the oral rinse reached the oropharynx and was retained for 1 min before being spat out. After mouthwash, eating was prohibited for 30 min. The treatment with PZ-CP oral rinse and azulene oral rinse was repeated for 7 weeks from the onset of radiotherapy. The inpatients’ adherence in the oral rinse treatment was managed by nurses, while, for the confirmation of the outpatients’ adherence, doctors checked the remaining amount of the preparations on the occasion of medical examination once a week.

Common Terminology Criteria for Adverse Events ver. 3.0 Mucositis/stomatitis (clinical exam) was used to evaluate the severity of oral mucositis, as the primary outcome measure. Oral mucositis was assessed weekly by a radiation oncologist. The survey items included age, sex, cancer site, stage, regimen, the expression status and incidence of oral mucositis, which were examined retrospectively from medical records.

In statistical analyses, the characteristics of the patients were compared by Mann-Whitney U test or Fisher’s exact test, and the distribution of Grade of oral mucositis was evaluated by Mann-Whitney U test. The p value of less than 0.05 was regarded as being statistically significant.

This study was approved by Hyogo College of Medicine Hospital ethics committee (approved No.791), and was conducted after informed consent was obtained from each patient.

Results

1. Stability Tests of PZ-CP Oral Rinse

PZ-CP oral rinse was a viscous clouded suspension immediately after preparation, and the appearance did not change throughout 28 days after preparation in each storage condition. In addition, no change in the pH, viscosity, adhesiveness and PZ content in preparations was observed throughout 28 days after preparation (Fig. 1).

2. Clinical Evaluation

Characteristics of the patients are shown in Table 2. The PZ group included 20 patients, consisting of 19 males and 1 female. Their median age was 66 (45-86) years old. The control group had 24 patients, consisting of 21 males and 3 females. Their median age was 67 (21-80) years old. There were no significant differences in the characteristics of the patients.

Oral mucositis occurred in all cases. Table 3 shows the incidence of oral mucositis. Comparison of the distribution of the Grade of oral mucositis showed that the Grade of oral mucositis in the PZ group was significantly lower than in the control group at 6 and 7 weeks (p = 0.016, p = 0.018). The incidence of severe oral mucositis of Grade 3 was 15.0% (3 cases) in the PZ group and 41.7% (10 cases) in the control group at 6 weeks, and was 15.0% (3 cases) in the PZ group and 33.3% (8 cases) in the control group at 7 weeks.

Discussion

Oral mucositis caused by administration of anti-cancer drugs and radiotherapy might involve inflammation induced by free radicals in the oral mucosa. It is also possible that the oral mucosa becomes vulnerable to infection because of a decrease in the leukocyte count, resulting in inflammation secondary to local infection8). In addition, radiation-induced impairment of salivation might reduce self-cleaning functions in the oral cavity, leading to local infection. In Japan, symptomatic treatment has mainly been carried out in patients with oral mucositis and no effective therapeutic method has been established.

In our hospital, for treatment of CRT-induced oral mucositis in the patients with head and neck cancer, mouthwashing with azulene had been used basically, but not sufficiently effective. Then, considering the report that PZ, a zinc-containing therapeutic agent for gastric ulcer, was effective against oral mucositis8), we started to use the PZ-CP oral rinse in addition to azulene for mouthwash. Our preliminary test indicated that PZ was highly dispersible and hard to precipitate in the CP solution, suggesting that the PZ-CP oral rinse preparations show less variation in the content of PZ, and do not require re-mixing before
Fig. 1. The stability of the PZ-CP oral rinse
(a) Time course of changes in pH. (b) Time course of changes in viscosity.
(c) Time course of changes in adhesion. (d) Time course of changes in PZ content.
Each point represents the mean ± S.D. of three experiments.

| Table 2. Characteristics of the patients |
|-----------------|-----------------|-----------------|
| Age             | PZ (n=20)       | control (n=24)  |
| Median (Range)  | 66 (45～86)      | 67 (21～80)      | 0.912\(^a\) |
| Male/Female     | 19/1            | 21/3            | 0.614\(^b\) |
| Sex             |                 |                 |
| Cancer site     | PZ              | control         |
| Oral Cavity     | 5               | 6               | 0.503\(^b\) |
| Nasopharynx     | 5               | 2               |
| Oropharynx      | 3               | 2               |
| Hypopharynx     | 4               | 8               |
| Larynx          | 3               | 6               |
| Stage           | PZ              | control         |
| I               | 4               | 2               | 0.609\(^b\) |
| II              | 4               | 5               |
| III             | 3               | 7               |
| IV              | 9               | 10              |
| Regimen         | PZ              | control         |
| Docetaxel + Radiation | 11         | 16              | 0.561\(^b\) |
| Carboplatin + Radiation | 4          | 2               |
| Cisplatin\(^c\) + Radiation | 5       | 6               |

\(^a\)Mann-Whitney U test. \(^b\)Fisher’s exact test. \(^c\)Super-selective arterial infusion.
each use. Thus, CP was considered appropriate as a base for the preparations.

In this study, we examined the stability and clinical effectiveness of the PZ oral rinse containing CP as a suspension base. Our data showed that the pH, viscosity, adhesiveness and PZ content did not change throughout 28 days in distinct storage conditions in terms of light and temperature. Currently, we employ a time period of 7 days after preparation until the expiration for PZ-CP oral rinse when stored in a dark and cold place. The present study supports that our set up of the expiration period and storage conditions in our hospital are reasonable and appropriate.

As expected, PZ-CP oral rinse effectively reduced the incidence of severe oral mucositis of Grade 3 in agreement with the pharmacological characteristics of PZ that PZ persistently adhers to the injured site of the gastric mucosa at a high affinity, leading to mucosal protection and wound healing. We therefore assume that similar persistent adhesion of PZ to the injured site of oral mucosa might result in clinical effects after the long-term use of PZ-CP oral rinse. In addition, carboxyvinyl polymer used as a base might enhance the adhesion of PZ to the mucosal surface, or itself exhibit mucosal protective activity.

It is noteworthy that the present chemoradiotherapy regimens employed in our hospital are different from a standard chemoradiotherapy using Cisplatin or Cetuximab for head and neck cancer. It has been reported that the incidence of mucositis of over Grade 3 was 43%\(^{[40]}\) and 56%\(^{[47]}\) in patients undergoing the standard chemoradiotherapy using Cisplatin and Cetuximab, respectively, being higher than that in the present study. In those reports, however, the total dose of radiation was higher than our study, and no significant difference in the incidence of mucositis was observed between patients undergoing radiotherapy alone and radiochemotherapy. Furthermore, there is also a report that 85-100% of head and neck cancer patients who received radiotherapy to the fields including the oral region, suffered from oral mucositis\(^{[49]}\). Together, chemoradiotherapy-induced oral mucositis in patients with head and neck cancer is mainly attributable to radiotherapy, rather than chemotherapy. Nonetheless, the possibility cannot be ruled out that different effectiveness of anticancer agents might affect our results, considering the small number of subjects and the variation of therapeutic contents in the present study.

The present regimens employed in our hospital, though a little different from a standard therapy, frequently cause
oral mucositis and reduces the QOL of patients. In addition, oral mucositis could be a cause for decreased therapeutic effects including cessation of treatment. In this study, we ascertained the stability and effectiveness of the PZ-CP oral rinse, in which no problem was detected. It was confirmed that the effectiveness of the PZ-CP oral rinse was greater than the control group. In addition to the retrospective survey in the present study, a prospective study should be performed in future, in order to ascertain the therapeutic usefulness of the PZ-CP oral rinse.

References


