The Suppression of Enhanced Bitterness Intensity of Macrolide Dry Syrup Mixed with an Acidic Powder

Toshihiko ISHIZAKA,[a,b] Sachie OKADA,[a] Eri TAKEMOTO,[a] Emi TOKUYAMA,[a] Eriko TSUJI,[a] Junji MUKAI,[a,b] and Takahiro UCHIDA*,[a]

[a] *School of Pharmaceutical Sciences, Mukogawa Women's University; 11–68 Koshien 9-Bancho, Nishinomiya, Hyogo 663–8179, Japan: and* [b] *Department of Pharmacy, Izumi Municipal Hospital; 4–10–10 Fucyu-cho, Izumi, Osaka 594–0071, Japan.* Received April 26, 2007; accepted August 10, 2007; published online August 14, 2007

The aim of the present study was to identify a medicine which strongly enhanced the bitterness of clarithromycin dry syrup (CAMD) when administered concomitantly and to develop a method to suppress this enhanced bitterness. The bitterness enhancement was evaluated not only by gustatory sensation tests but also using pH and taste sensor measurements of the mixed sample. A remarkable bitterness enhancement was found when CAMD was mixed with the acidic powder L-carbocysteine. The acidic pH (pH 3.40) of the suspension made from these two preparations, seemed to be due to enhanced release of clarithromycin caused by the dissolution of the alkaline polymer film-coating. Several methods for preventing this bitterness enhancement were investigated. Neither increasing the volume of water taken with the mixture, nor changing the ratio of CAMD : L-carbocysteine in the mixture, were effective in reducing the bitterness intensity of the CAMD/L-carbocysteine mixture. The best way to achieve taste masking was to first administer CAMD mixed with chocolate jelly, which has a neutral pH, followed by the L-carbocysteine suspension. Similar results were obtained for the bitterness suppression of azithromycin fine granules with L-carbocysteine. The chocolate jelly will be useful for taste masking of bitter macrolide drug formulations, when they need to be administered together with acidic drug formulations.

Key words macrolide; acidic medicine; chocolate jelly; infant; bitterness; taste sensor

Medication refusal in children is generally due to its 'bad taste', to the quantity which has to be taken, or to an unpleasant odour, with taste being regarded as the major factor.[1—5] The antibiotic clarithromycin (CAM) is effective against *Staphylococcus aureus*, *Haemophilus influenzae*, *Mycoplasma*, *Chlamydia*, *Campylobacter* and other infective agents, and is an essential therapeutic in pediatric infectious diseases. As CAM is very bitter, a formulation has been developed for use in children, Clarithromycin Dry Syrup (CAMD) in which this bitterness is masked. However, when CAMD is given with an acidic beverage, there is a remarkable increase in bitterness due to the dissolution of the dry syrup coating film and consequent increase in the solubility of CAM. This can cause medication refusal in children.[6]

CAMD is often prescribed to children together with an antitussive, expectorant or antihistamine. If an acidic medicine is prescribed concurrently, the simultaneous administration of both medicines in water may causes a shift in pH towards the acidic range, thus increasing the solubility of CAM and increasing the bitterness of the CAMD solution.[7—9]

The present study was performed to assess the bitterness associated with the combined use of CAMD and other medicines, in order to find a drug which particularly enhances the bitterness intensity of CAMD. In the second phase, the optimal method for reducing this enhanced bitterness was investigated, and the applicability of the proposed method was tested for another strongly bitter medicine, azithromycin fine granules (AZMD).

Experimental

Materials Two macrolide dry syrups and five different medicines (for use with the macrolide dry syrup) were used in this study. The macrolide dry syrups were: clarithromycin, Clarith® dry syrup for pediatric use (CAMD), purchased from Taisho Toyama Co., Ltd., Tokyo, Japan; and azithromycin, Zithromac® Fine Granules for pediatric use (AZMD), purchased from Pfizer Pharmaceutical Co., Ltd., Tokyo, Japan. The five medicines were: bromhexine hydrochloride, Bisolvon® Fine Granules (B), purchased from Nippon Boehringer Ingelheim Co., Ltd., Tokyo, Japan; L-carbocysteine, Mucodyne® Fine Granules (L), purchased from Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan; ambroxol hydrochloride, Ambron® Fine Granules (A), purchased from Nippon Universal Pharmaceutical Co., Ltd., Tokyo, Japan; procaterol hydrochloride, Meptin® granules (P) purchased from Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan; and D-chlorpheniramine maleate, Polaramine® powder (M), purchased from Schering-Plough Co., Ltd., Tokyo, Japan. Okusurinomoune Chocolate jelly was obtained from Ryukakusan Co., Ltd., Tokyo, Japan.

Refined water, which has the same pH as saliva and the acidic sports drink, Pocarisweat® (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) was used as diluents. Quinine hydrochloride was purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.), dissolved, and diluted to 0.1 mM with KCl.

Methods. Evaluation of Medicines which Enhance the Bitterness of CAMD When Mixed Together The bitterness intensity of suspension filtrates of CAMD alone and together with each of the five powdered medicines (A, B, L, M, P) was investigated using pH measurements, human gustatory sensation tests ($n=9$), and taste sensor data (see below). Each sample was prepared on the basis of a single dose for a 15-kg child (3-year-old), suspended in 12.5 ml of water (pH 6.6), stirred for 5 min using an agitator, and filtered. This 5 min seemed sufficient for release of the active ingredients of each formulation.

Suppression of the Enhanced Bitterness of CAMD and Carbocysteine Mixtures Four methods were examined to achieve suppression of the bitterness of mixtures of Carbocysteine and CAMD.

Alteration of the Volume of Water Taken: A mixture of 0.5 g of CAMD and 0.25 g of Carbocysteine was suspended in 12.5, 25, 50, 75 or 100 ml of water, and agitated with a stirrer at 300 rev./min for 5 min. The resultant suspension was filtered using suction filtration, and the filtrate was used as a sample.

Alteration of the Ratio of the Mixture Components: A mixture of 0.5 g of CAMD and 0.25, 0.2, 0.15, 0.1 or 0.05 g of Carbocysteine was suspended in 12.5 ml of water, and agitated with a stirrer at 300 rev./min for 5 min. The resultant suspension was filtered using suction filtration, and the filtrate was used as a sample.

Alterations in the Method of Sample Preparation: Samples containing 0.5 g of CAMD and 0.25 or 0.05 g of Carbocysteine were prepared by three different methods as follows:

(a) CAMD and Carbocysteine were mixed together, the mixture suspended in 12.5 ml of water, and agitated with a stirrer at 300 rev./min for 5 min. The resultant suspension was filtered using suction filtration, and the

* To whom correspondence should be addressed. e-mail: takahiro@mukogawa-u.ac.jp

filtrate was used as a sample (sample A or A′).

(b) CAMD was suspended in 12.5 ml of water and agitated for 30 s. This suspension was mixed with Carbocysteine, and agitated with a stirrer at 300 rev./min for 5 min. The resultant suspension was filtered using suction filtration, and the filtrate was used as a sample (sample B or B′).

(c) Carbocysteine was suspended in 12.5 ml of water, and agitated for 30 s. This suspension was mixed with CAMD, and agitated with a stirrer at 300 rev./min for 5 min. The resultant suspension was filtered using suction filtration, and the filtrate was used as a sample (sample C or C′).

Bitterness Suppression by Chocolate Jelly: The samples were prepared as follows: 0.5 g of CAMD was mixed with 25 ml of chocolate jelly (C-mix); 0.5 g of CAMD wrapped in 25 ml of chocolate jelly (C-wrap); 0.25 g of Carbocysteine mixed with 15 ml of chocolate jelly (L-mix); 0.5 g of CAMD and 0.25 g of Carbocysteine mixed with 40 ml of chocolate jelly (C/L-mix); and 0.25 g of Carbocysteine suspended in 12.5 ml of water (L-SUS). The analytical samples were then prepared as mentioned below.

AZMD samples were also prepared using 1 g of AZMD and 50 ml of chocolate jelly under similar conditions to CAMD; AZ-mix, AZ-wrap and AZ/L-mix corresponded to C-mix, C-wrap and C/L-mix, respectively.

1. C-wrap (AZ-wrap) was placed into a beaker, mixed with L-suspension, agitated for 5 min, and filtered using suction filtration. The filtrate was used as a sample (C-wrap (AZ-wrap) L-SUS).
2. C-mix (AZ-mix) was placed into a beaker, mixed with L-suspension, agitated for 5 min, and filtered using suction filtration. The filtrate was used as a sample (C-mix (AZ-mix) L-SUS).
3. C-mix (AZ-mix) and L-mix were placed into a beaker, mixed with 12.5 ml of water, agitated for 5 min, and filtered using suction filtration. The filtrate was used as a sample (C-mix (AZ-mix) L-mix).
4. C (AZ)/L-mix was placed into a beaker, mixed with 12.5 ml of water, agitated for 5 min, and filtered using suction filtration. The filtrate was used as a sample (C (AZ)/L-mix).

Determination of Drug Concentration in Extracts from Mixtures of Dry Syrup and Jelly The determination of the concentration of drug in solutions extracted from mixtures of dry syrup and jelly was performed as follows. After mixing 0.5 g of the dry syrup and 25 ml of jelly for 30 s, the suspension was kept at room temperature for 0, 10, and 30 min. Then 2 ml water was added to the suspension and the solution was mixed for a further 30 s. The mixture was centrifuged at 2000 rev./min for 10 min, and the supernatant was diluted with buffer pH 11. A 1.5-ml sample of this solution was prepared by ultrafiltration, and the concentrations of CAM or AZM in the filtered solution were determined using HPLC. For the HPLC, 100 μl was injected onto a chromatograph (Shimadzu LC-10AT, Kyoto, Japan) equipped with a UV detector (Shimadzu SPD-10A, Kyoto, Japan), an integrator (Shimadzu C-R7Ae plus, Kyoto, Japan) and a reverse-phase column (Asahipak-ODP-50 4E, 4.6 mm i.d.×250 mm, Showa Denko, Tokyo, Japan). The column temperature was set at 40 °C. The following mobile phase system was used: 40 mmol/l K_2HPO_4 solution (with 10% (w/v) KOH solution, pH 11) : acetonitrile=2 : 3. The flow rate was 1.0 ml/min. The wavelength was set at 215 nm.

Measurements of pH In suspension samples of CAMD alone and mixtures of CAMD with each powdered medicine, pH was directly measured using a pH meter (HORIBA, F-21, Kyoto, Japan). In mixed suspension samples of CAMD and Carbocysteine, the pH was measured immediately and 10 s, 20 s, 30 s, 40 s, 50 s, 1 min, 2 min, 3 min, 4 min and finally 5 min after mixing. In samples including chocolate jelly to suppress the bitterness, the pH was measured immediately and 30 s, 1 min, 5 min, 10 min, 1 h, 2 h, 4 h, and 8 h after mixing.

Gustatory Sensation Tests Gustatory sensation tests were done using the equivalent density examination method of Katsuragi *et al.*[10] The standard quinine hydrochloride concentrations used were 0.01, 0.03, 0.10, 0.30, and 1.00 mM and the corresponding bitterness scores were defined as 0, 1, 2, 3, and 4, respectively. Before testing, the volunteers (n=9) were asked to keep the above standard quinine solutions in their mouths, and were told the concentrations and bitterness scores of each solution. After tasting 2 ml of a test formulation suspended in water, they were asked to give the sample a bitterness score. All samples were kept in the mouth for 15 s. After testing the sample, the volunteers rinsed their mouths well and waited for at least 20 min before tasting the next sample.

In gustatory sensation tests of the mixtures of dry syrup and chocolate jelly, the subjects were asked to give the sample a bitterness score immediately after tasting and after rinsing. In advance, the protocol or experimental design for all gustatory sensataion tests were approved by ethical committee of Mukogawa Women's University.

Sensor Measurement and Data Analysis The taste sensor system and the lipid components of the sensor used in the present study were essentially the same as those described in a previous paper.[11,12] The taste sensor system, SA402B of Intelligent Sensor Technology Co., Ltd., Atsugi, Japan, was used to measure the electric potential of the medicine suspensions and of the mixtures of dry syrup and chocolate jelly. In this sensor, the electrode set was attached to a mechanically controlled robot arm. The detecting sensor part of the equipment consists of eight electrodes composed of lipid/polymer membranes. Each lipid was mixed in a test tube containing poly(vinylchloride) and dioctylphenylphosphonate as a plasticizer, dissolved in tetrahydrofuran, and dried on a glass plate at 30 °C to form a transparent thin film, almost 200 μm thick. The electrodes consist of an Ag wire whose surface was plated with Ag/AgCl, with an internal cavity filled with 3 M KCl solution. The difference between the electric potential of the working electrode and the reference electrode was measured by means of a high-input impedance amplifier connected to a computer.

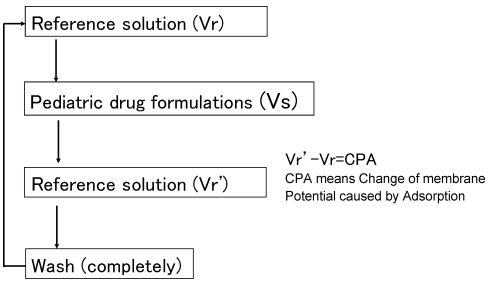

Chart 1. Measuring Procedure in This Study

Samples of the pediatric formulations, suspended in water or acidic sports drink for 1 h, were evaluated in the following manner. Fresh 30 mM KCl solution containing 0.3 mM tartaric acid (corresponding to saliva) was used as the reference sample (Vr) and also to rinse the electrodes after every measurement. The method used to measure the sensitivity and the selectivity of adsorption of the samples is summarized in Chart 1. The electrode was first dipped into the reference solution (Vr) and then into the sample solution or suspension (Vs). When the electrode is dipped into the reference solution again, the new potential of the reference solution is defined as Vr′. The difference (Vr′–Vr) between the potentials of the reference solution before and after sample measurement is defined as CPA (Change of membrane Potential caused by Adsorption) and corresponds to aftertaste. Each measuring time was set at 30 s, and the electrodes were rinsed after each measurement. In the present study, CPA values were used to predict the bitterness of the mixtures of CAMD and pediatric formulations, and of the mixtures of dry syrup and chocolate jelly. S-PLUS 2000J (Mathematical Systems, Inc., Tokyo, Japan) was used for regression analysis.

Results and Discussion

Evaluation of Medicines Which Enhance the Bitterness of CAMD When Mixed Together The bitterness intensity of suspension filtrates of CAMD alone and mixed with each powdered medicine was assessed on the basis of pH values, human gustatory sensation tests (n=9) and measured taste sensor data.

As shown in Table 1, suspension filtrates of single medicines and Pocarisweat showed acidity while CAMD suspensions were alkaline. Combinations of CAMD suspensions and suspensions of each of the other medicines were all alkaline except for mixtures of CAMD and Pocarisweat suspension filtrates and mixtures containing Carbocysteine, which showed acidity.

The bitterness of these samples was evaluated in human gustatory sensation tests and using a taste sensor. The bitternesses of suspension filtrates of all the single medicines were below the bitterness threshold[13] (τ1) (corresponding to the bitterness of a 0.03 mM quinine hydrochloride solution) in human gustatory sensation tests (shown in Fig. 1). In mixtures of CAMD and powdered medicine containing Carbo-

Table 1. pH Value of Each Sample

Number		Sample name	pH value
0		POCARISWEAT® (POCARI)	3.52
1	①	Clarithromycin (CAMD)	10.35
2	②	Bromhexine hydrochloride (B)	6.57
3	③	Procaterol hydrochloride (P)	4.84
4	④	Ambroxol hydrochloride (A)	6.42
5	⑤	L-Carbocysteine (L)	2.96
6	⑥	D-Chlorpheniramine maleate (M)	6.12
7	⑦	CAMD+B	10.37
8	⑧	CAMD+P	10.36
9	⑨	CAMD+A	10.22
10	⑩	CAMD+L	3.40
11	⑪	CAMD+M	10.35
12	⑫	CAMD+B+P	10.05
13	⑬	CAMD+B+P+A	9.86
14	⑭	CAMD+B+P+L	3.93
15	⑮	CAMD+B+P+M+A	10.13
16	⑯	CAMD+B+P+M+L	4.09
17	⑰	CAMD+L+A	4.06
18	⑱	CAMD+POCARI	3.70

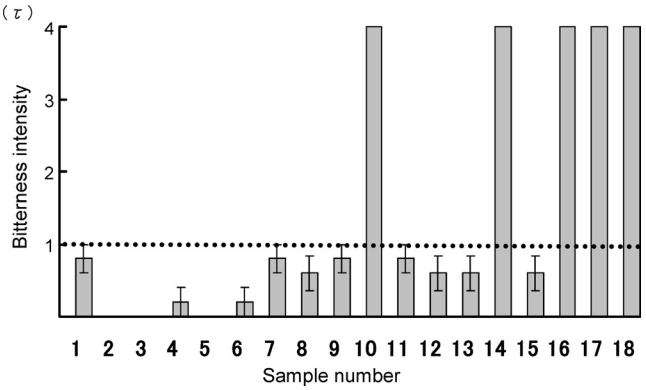

Fig. 1. Bitterness Intensity Scores as Evaluated by Gustatory Sensation Test

Values are mean±S.D. (n=9). A bitterness intensity score of τ1 is the bitterness threshold.[7]

cysteine, the bitterness was increased up to its saturation zone[13] (τ4) (corresponding to the bitterness of a 1.00 mM quinine hydrochloride solution), while the bitternesses of the other mixtures were below the bitterness threshold.

When the taste sensor was used to investigate masking of the bitterness, the CPA values for channel 3 were employed. The vertical axis of Fig. 2 shows the sensor output, and the membrane used is negatively charged. Thus a positive sensor output means an increase in the bitterness intensity. In the sensor outputs for the suspension filtrate of mixtures of CAMD with the powdered medicines, mixed suspension filtrates (nos. 10, 14, 16, 17), which have a pH under 5, showed a positive sensor output, while the others, which have alkaline pHs, showed no rise in sensor output.

These results demonstrate that the bitterness of mixed suspension filtrates reached its saturated zone (τ4) in both human gustatory sensation tests and taste sensor measurements under acidic conditions (below pH 5). It can thus be predicted that, when the pH of mixtures of CAMD and other agents drop to pH 5 or below, the mixtures will be perceived as bitter. A previous report[14] revealed the dissolution of the alkaline polymer film of CAMD under conditions below pH

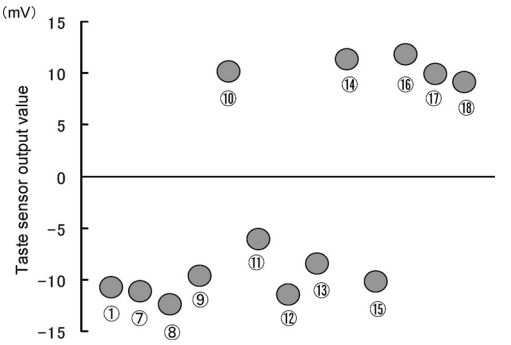

Fig. 2. Change of Taste Sensor Output (Channel 3 CPA Value) for Each Sample

6.5.

Mixing CAMD with a powdered medicine containing Carbocysteine seems to result in an increase of bitterness which is likely to lead to decreased medication compliance. An appropriate measure is therefore required to suppress this bitterness.

Suppression of the Bitterness of Mixtures of CAMD and Carbocysteine The results of the four methods used to suppress the bitterness of mixtures of CAMD and medicines containing Carbocysteine are given below.

(a) Alteration of the Volume of Water Taken The relation of the bitterness to the volume of water (12.5, 25, 50, 75 or 100 ml) taken with one dose (0.5 g of CAMD plus 0.25 g of Carbocysteine) was examined by measuring the pH (in triplicate) and in human gustatory sensation tests (n=9). With increasing volumes of water, pH values (mean±S.D.) became more acidic to 3.87±0.01, 3.55±0.02, 3.49±0.03, 3.40±0.01 and 3.24±0.03, respectively. In human gustatory sensation tests, the levels of bitterness intensity (τ) were 4, 4, 3, 2 and 2, respectively, showing a bitterness-suppression effect with 50 ml or more water. Even though we explained acidic condition increase solubility of CAM and thereby enhance the bitterness intensity of released CAM, the dilution effect by increasing water volume (12.5 to 100 ml) might compensate for pH decrease effect (pH 3.87 to 3.24) in the standpoint of bitterness intensity since the CAM concentration was decreased as increased water volume.

The bitterness intensity, however, did not fall below the bitterness threshold (τ1) at any dilution. Thus, although increasing the dilution may reduce the bitterness intensity, it remained above the bitterness threshold in the volume of water generally given to 3-year-old children. Suppression of bitterness will not therefore be accomplished by using an increased volume of diluents.

(b) Alteration of the Ratio of the Mixture Components The effect of the ratio of CAMD to Carbocysteine (within an limited range) on bitterness suppression was examined using pH measurements (in triplicate) and in human gustatory sensation tests (n=9). The quantities of Carbocysteine added to 0.5 g of CAMD were 0.25 g (CAMD : Carbocysteine=2 : 1), 0.2 g (5 : 2), 0.15 g (10 : 3), 0.1 g (5 : 1) or 0.05 g (10 : 1). These mixtures of the two medicines were suspended in 12.5 ml of water, and the bitterness of the suspension filtrate assessed. When measured after 5 min agitation, the pH values (mean±S.D.) were 3.87±0.01, 3.92±0.01, 4.00±0.01, 4.30±0.02 and 8.06±0.01, at ratios of 2 : 1, 5 : 2, 10 : 3, 5 : 1

and 10 : 1 CAMD to Carbocysteine, respectively. In other words, pH values increased with a decrease in the proportion of Carbocysteine, becoming alkaline at a mixing ratio (10 : 1) of CAMD to Carbocysteine. The bitterness intensity assessed in human gustatory sensation tests reached the saturated zone (τ4) in the acidic pH region. The level decreased to τ2 at an alkaline-shifted mixing ratio (10 : 1), showing a tendency towards bitterness suppression.

Based on findings from a previous report[14] that the bitterness of CAMD alone appears below pH 6.5, the bitterness intensity should be below the bitterness threshold (τ1) in the alkaline pH region, *i.e.,* at pH 8.06, which was the pH of the 10 : 1 CAMD : Carbocysteine mixture. The fact that the bitterness was greater than this in the present experiment may be related to a time-dependent change from immediately to 5 min after mixing.

(c) Alterations in the Method of Sample Preparation To clarify further the cause of the phenomenon described in (b) above, the dependence of bitterness on the way the samples were prepared was examined by time-dependent pH measurements (in triplicate) and human gustatory sensation tests (n=9). Different mixing orders were evaluated at two different CAMD : Carbocysteine ratios, that of a normal dose (2 : 1) and that of the threshold concentration (10 : 1). The three samples at 2 : 1 (a suspension of a CAMD and Carbocysteine mixture (A), a CAMD suspension mixed with Carbocysteine after 30 s (B), and a Carbocysteine suspension mixed with CAMD after 30 s (C)), showed different time-dependent pH changes in water from immediately to 20 s after mixing, but almost the same time-dependent change at about pH 3.8 after 20 s (Fig. 3). Thus, all filtrate samples were in the bitterness saturated zone (τ4) in human gustatory sensation tests due to the dissolution of CAM. The three samples (A′, B′, C′) at a threshold concentration ratio (10 : 1) were treated similarly. The pH of sample A′ decreased from about 6 to 4.50, but increased to 8.06 by the end of a run. That of sample B′ decreased from about 10 to 7.38, but increased finally to 8.65. That of sample C′ gradually increased from about 3 to 8.44 at the end of a run. All samples (A′, B′, C′) showed final pH values over pH 8, but had different levels of bitterness intensity (2, 0, 3, respectively). This may be presumed to arise from a unique pH transition pattern over each time course. Samples A′ and C′ had pH values below 6.5 for at least 2 min, at which point the dissolution of the alkaline polymer film of CAMD occurs. Further, sample C′ had a pH of 4 or below for more than 30 s, at which point the alkaline polymer film of CAMD dissolved rapidly. Sample B′ never showed a pH below 6.5. Based on these findings, it has been suggested that the bitterness of CAMD depends on time-dependent pH changes (time and minimum pH value) but not the final pH. It is therefore advisable for CAMD to be administered prior to Carbocysteine.

(d) Bitterness Suppression by Chocolate Jelly The effect of mixing with chocolate jelly on suppression of the bitterness of CAMD was also examined. The pH values of samples (initial preparations), such as C-wrap, C-mix and C/L-mix, were 7.92, 7.72 and 4.47, respectively. The analytical samples (C-wrapL-SUS, C-mixL-SUS, C-mixL-mix and C/L-mix) were prepared using these initial preparations, and the bitterness was assessed *via* time-dependent pH measurements (in triplicate), human gustatory sensation tests, and

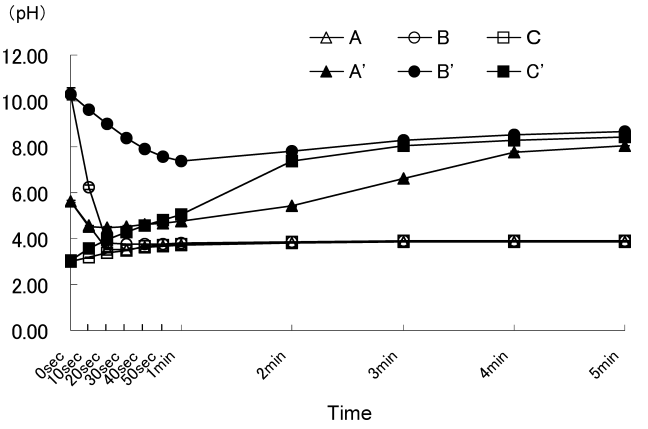

Fig. 3. Effect of the Order of Administration of CAMD and Carbocysteine on pH Measurements

Values are mean±S.D. (n=3). A: 0.5 g of CAMD and 0.25 g of Carbocysteine were mixed. This mixture was suspended in 12.5 ml of water. B: 0.5 g of CAMD was suspended in 12.5 ml of water and agitated for 30 s. This suspension was mixed with 0.25 g of Carbocysteine. C: 0.25 g of Carbocysteine was suspended in 12.5 ml of water and agitated for 30 s. This suspension was mixed with 0.5 g of CAMD. A′: 0.5 g of CAMD and 0.05 g of Carbocysteine were mixed. This mixture was suspended in 12.5 ml of water. B′: 0.5 g of CAMD was suspended in 12.5 ml of water and agitated for 30 s. This suspension was mixed with 0.05 g of Carbocysteine. C′: 0.25 g of Carbocysteine was suspended in 12.5 ml of water and agitated for 30 s. This suspension was mixed with 0.5 g of CAMD.

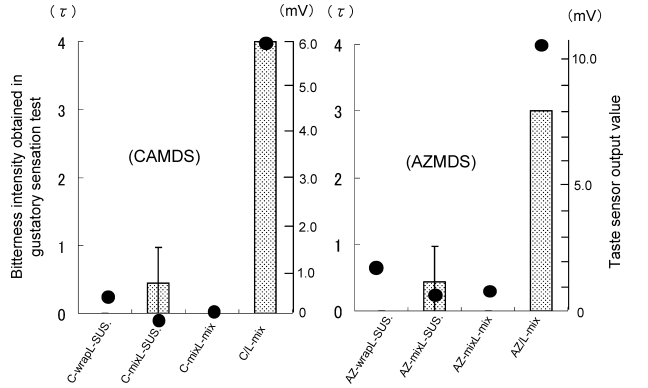

Fig. 4. Bitterness Suppression Associated with Mixing CAMD (AZMD) and Carbocysteine Using Chocolate Jelly (Assessment by Human Gustatory Sensation Tests and Taste Sensor)

Values are mean±S.D. (n=9). Bar chart shows bitterness intensity obtained in gustatory sensation test. ●: Taste sensor output value. For explanation see text.

taste sensor analyses. In human gustatory sensation tests, C-wrapL-SUS, C-mixL-SUS, C-mixL-mix and C/L-mix showed bitterness intensity levels (τ) of 0, 0, 0 and 4, respectively, immediately after administration, and 0, 0.44, 0 and 4 after rinsing. In our pilot study using gustatory sensation test, the levels of the bitterness intensity of C-mixL-mix and C/L-mix was equal to that of C-mix or filtrate sample (detail data not shown). In taste sensor analyses, the sensor outputs of C-mixL-SUS, C-wrapL-SUS and C-mixL-mix did not change, but that of C/L-mix increased by 5.99 mV (Fig. 4). Consequently, it has been demonstrated that, for concomitant administration of CAMD and Carbocysteine, the bitterness of CAM can be suppressed by mixing CAMD alone with chocolate jelly.

The suppression of the bitterness of AZMD was examined in the same way as CAMD. In human gustatory sensation tests, AZ-wrapL-SUS, AZ-mixL-SUS, AZ-mixL-mix and

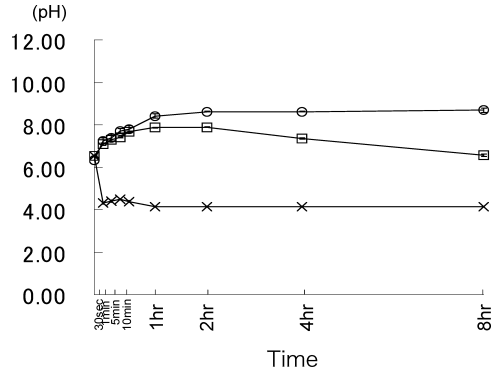

Fig. 5. Time-Dependent pH Measurement Data for Each Sample
Values are mean±S.D. (n=3). ○, C-mix; □, C-mixL-SUS.; ×, C/L-mix.

AL/L-mix showed levels of the bitterness intensity (τ) of 0, 0, 0 and 3, respectively, immediately after administration, and 0, 0.44, 0 and 3 after rinsing. In addition, the sensor output of AZ/L-mix only increased by 10.76 mV (Fig. 4). This shows that the taste sensor can replicate the results of human gustatory sensation tests, even in CAMD and AZMD studies using neutral jelly.

Secondly, to examine the duration of bitterness suppression by chocolate jelly, after blending C-mix with L-suspension (C-mixL-SUS), the pH of this mixture was measured over a period of 8 h. C-mix alone and C/L-mix were treated in the same way. The pH changes of each sample over time are shown in Fig. 5. The pH of C-mix alone gradually increased from 6.55 (the pH of jelly alone) to 8.6 at 2 h after mixing, and thereafter remained unchanged until 8 h. At this point, C-mix showed bitterness intensity (τ) of 0. The pH of C/L-mix decreased from 6.55 to 4 at 30 s after mixing, due to the direct influence of Carbocysteine suspension, and did not fluctuate significantly thereafter until 8 h. The bitterness intensity reached the saturated zone (τ4). The pH of C-mixL-SUS increased from 6.55 to 7.8 at 2 h and 4 h after blending, and decreased to 6.5 at 8 h. However, the pH fluctuation was too small to affect the bitterness, and C-mixL-SUS had bitterness intensity (τ) of 0. These results demonstrate firstly that chocolate jelly has no effect on the alkaline polymer film of CAMD unless the CAMD is mixed with another medicine, and secondly that the continued suppression of bitterness by chocolate jelly is obtained in an acidic suspension within 4 h after blending, irrespective of the surrounding pH. If mixing with an acidic suspension is avoided, blending CAMD with chocolate jelly resulted in continued suppression of bitterness for 8 h. This would allow the preparation to be kept in a refrigerator for several hours.

In the present study, CAMD wrapped in chocolate jelly seemed to be less bitter than CAMD mixed homogeneously with it. However, an infant does not always swallow a medicine in one gulp without chewing. If CAMD wrapped in chocolate jelly is administered, it is feared that bitterness might still be detected due to outflow of medicine from the jelly caused by chewing.

Alternatively, the following two administration methods were also found to reduce the bitterness below its threshold: 1) Both medicines are separately and homogeneously blended with chocolate jelly, and separately administered, and 2) CAMD is homogeneously mixed with chocolate jelly, and administered prior to the Carbocysteine suspension. Use of either of these methods can reduce the bitterness to the same level as the CAMD-wrapping method. Further, it has been confirmed for all methods that the bitterness suppression is maintained for up to 8 h after blending. It is also possible that multiple other medications may need to be administered concomitantly with CAMD. If each is separately mixed with chocolate jelly, the resultant dosing volume may become too large. As the smallest dosing volume possible should be used for administration to children, method 2) above is probably the optimal administration method.

Table 2. Drug Concentration in Solutions Extracted from Mixtures of Dry Syrup and Jelly

		Concentration (μg/ml)
CAMD	Water	19.2±0.4
	30 s	12.8±0.5*
	10 min	13.3±0.7*
	30 min	14.5±1.3*
AZMD	Water	40.6±1.5
	30 s	88.8±13.8*
	10 min	99.7±16.7*
	30 min	105.5±18.3*

*$p<0.01$ compared with water suspension using Student's t-test. The values are means±S.D. (n=3).

(e) Determination of Drug Concentration in Solutions Extracted from Mixtures of Dry Syrup and Jelly Table 2 shows the concentration of the drug in solutions extracted from mixtures of CAMD or AZMD and chocolate jelly. The concentration of CAM in water suspensions of CAMD (as control) was 19.2 μg/ml, while concentrations of CAM in solutions extracted from mixtures of CAMD with chocolate jelly 0.5, 10, 30 min after mixing were 12.8, 13.3, and 14.5 μg/ml, respectively. These values were almost the same or lower concentrations than control values. This shows that CAM was not released into the chocolate jelly matrix and that the jelly has as an efficient barrier function.

In the case of AZMD, the concentration of AZM in water suspensions of AZMD (as control) was 40.6 μg/ml, while concentrations of AZM in solutions extracted from mixtures of AZMD and chocolate jelly 0.5, 10, 30 min after mixing were 88.8, 99.7, and 105.5 μg/ml, respectively. The concentration of AZM in the extracted solution (88.8 μg/ml) was almost twice as high as the control (40.6 μg/ml). Nevertheless, when explored in gustatory sensation tests, the bitterness of AZMD in jelly was lower than that in AZMD water suspensions. This may be due to the sweetener or the cocoa element in the jelly.

Conclusion

In the present study of the causes of the increased bitterness intensity associated with the concomitant administration of CAMD and acidic Carbocysteine, and investigation of methods to reduce it, the following conclusions were reached:

(1) The most effective method of bitterness suppression is to mix CAMD and Carbocysteine separately with neutral jelly at a ratio of (0.2 g medicine/10 ml jelly), and to administer the jelly/CAMD mixture first, followed by jelly/Carbocysteine.

(2) For the concomitant administration of CAMD and Carbocysteine to children, the most suitable method to reduce the bitterness of CAMD is to mix the CAMD with neutral jelly in a ratio of (0.2 g CAMD/10 ml jelly) and to administer this mixture first, followed by Carbocysteine suspension.

(3) The increase in the bitterness intensity associated with the concomitant use of Azithromycin hydrate granules and Carbocysteine can also significantly be suppressed by this method.

(4) In evaluating the bitterness suppression of these macrolides, it is difficult to predict the bitter taste using only pH measurements, but it may be possible to replace the current human gustatory sensory assessment by using two non-sensory tests, pH measurements and the taste sensor.

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