Suppression of Bitterness and Improvement of Palatability of Commercial Prednisolone Powder

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The aim of the study was to suppress the bitterness and improve the palatability of pediatric prednisolone powder (PP) by the addition of simple sucrose syrup (SS) and various beverages and foods. Bitterness suppression was evaluated using the human gustatory sensory test. The suppression of the bitterness and improvement of palatability of PP by addition of SS solutions was investigated using standard taste substances: sucrose for sweetness, tartaric acid for sourness, and sodium chloride as saltiness. Dilution with SS solutions of up to 50% (w/w) was successful in bitterness-suppression and improvement of palatability, but at 80% (w/w) SS, the palatability of the diluted solution was reduced. The kinematic viscosities of SS solutions were therefore evaluated using the Uberorde viscosity meter, to see whether the high viscosity of the more concentrated solutions was responsible for the reduced palatability. The kinematic viscosity of the 80% SS was 16.60 mm^2/s. Judging from above information, the palatability might become worse when the kinematic viscosity of syrup exceeded 15 mm^2/s. Finally, the ability of various beverages and foods with low viscosity to suppress the bitterness and improve the palatability of PP were examined. The additions of orange juice or a carbonated lemon drink to simple syrup solution were most effective in suppressing bitterness and improving palatability of PP.

Key words prednisolone powder; bitterness; palatability; sweetness; sourness; kinematic viscosity

In the treatment of pediatric patients, palatability of medicines is the most critical factor determining compliance. Pediatric patients often do not understand the need to take medicines, and may refuse to take them if they have an unpleasant taste or smell. In particular, a bitter taste may give rise to a significant decrease of compliance.[1—4] Therefore, it has been proposed that the selection and/or administration of medicines for pediatric patients should take bitterness and palatability into consideration.[5,6]

Several studies have examined the suppression of the bitterness of clarithromycin dry syrup, and its implications for clinical use.[7—10] However, other bitter medicines, such as prednisolone powder (PP), have not been sufficiently studied.[11] PP is used in the treatment of respiratory and renal failure and nephritis,[12] and often has to be taken regularly for extended periods of time, so lack of compliance can be a problem.

The present study was performed to determine a method of reducing the bitterness and improving the palatability of commercial PP. The kinematic viscosities of simple syrup and commercial syrup solutions were also evaluated using an Uberorde viscosity meter, as highly viscous solutions sometimes reduce palatability.

Experimental

Materials Prednisolone Powder (Takeda)® 1% (Takeda Chemical Industries, Ltd., Osaka) was purchased for use in this experiment. Quinine hydrochloride was purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). As additives, sucrose sweeteners were obtained from Wako Pure Chemical Industries, Ltd. Osaka and simple sucrose syrup (SS) from EBISU Pharmaceutical Co., Ltd. (Osaka). Tartaric acid (sourness standard) and NaCl (saltiness standard) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka).

The acidic sports drink Pocarisweat® was purchased from Otsuka Pharmaceutical Co., Ltd. (Tokyo). Milk (Meg Milk®) and coffee milk (Snow Brand coffee milk®) were obtained from Nippon Milk Community Co., Ltd. (Kobe), carbonated Coca-Cola® and a carbonated beverage with a grape taste (Fanta Grape®) from Coca-Cola Japan Co., Ltd. (Tokyo), a carbonated lemon-tasting drink (CC lemon®) from Suntory (Osaka), and orange juice from Asahi Soft Drinks Co., Ltd. (Tokyo). Strawberry and chocolate jelly were purchased from Ryukakusan Co., Ltd. (Tokyo) and condensed milk from Snow Brand Milk Products Co., Ltd. (Hokkaido). All other reagents used were high grade.

Bitterness Suppression of PP by Simple Syrup or Acidic Sports Drink A 0.5 g sample of PP was suspended in 12.5 ml of water, acidic sports drink, or 5, 10, 25, 50, 80 or 100% simple sucrose syrup (SS). The suspensions were agitated with stirrer bar at 300 rev./min for 30 s. Samples of PP (0.5 g) were also evenly mixed in 10 g of strawberry jelly, chocolate jelly and condensed milk using a glass rod for 30 s.

The bitterness intensities of these suspensions were evaluated in human gustatory sensation tests. The intensities of sweetness, sourness and saltiness[13] were evaluated by comparison with standard solutions representing these basic tastes, as summarized in Table 1.

Bitterness Suppression of PP by Standard Solutions of Basic Taste Substances (Sweet, Sour, Salty and Mixtures) A 0.5 g sample of PP suspended in 12.5 ml of a 34% sucrose solution (sweetness intensity $\tau 4$) was denoted SW4; a mixed solution of SW4 and tartaric acid solution corresponding to sourness intensity $\tau 2$, was denoted SW4SO2; a mixed solution of SW4 and tartaric acid solution corresponding to sourness intensity $\tau 4$ was denoted SW4 SO4; a mixed solution of SW4 and NaCl solution corresponding to saltiness intensity $\tau 2$ was denoted SW4 SA2; a mixed solution of SW4 and NaCl solution corresponding to saltiness intensity $\tau 4$ was denoted SW4 SA4; a mixed solution of SW4 SA2 plus NaCl solution, corresponding to saltiness intensity $\tau 1$ was denoted SW4 SO2 SA1; and a mixed solution of SW4 SA2 and NaCl solution, corresponding to saltiness intensity $\tau 1$ was denoted SW4 SO4 SA1. The bitterness and palatability of each sample were evaluated in gustatory sensory tests in healthy volunteers.

The Effect of Kinematic Viscosity on Palatability The kinematic viscosities of 5, 10, 20, 50, 60, 70, 80, 90 and 100% SS were measured using an Uberorde kinematic meter (Shibatakagaku Ltd.) at 25 °C. The palatability

Table 1. Concentration of Standard Solutions Used

Score (τ)	Sweetness (mM)	Sourness (mM)	Saltiness (mM)
	Sucrose	Tartaric acid	Sodium chloride
0	29.24	0.17	20.53
1	87.72	0.60	51.34
2	187.72	1.73	130.05
3	409.36	4.66	273.79
4	994.15	11.99	616.02

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(ease of swallowing) of each sample was evaluated by gustatory sensory tests in healthy volunteers as described in the next section. In both experiments, water was used as control. When bitterness suppression and improvement of palatability by beverages and food were being examined, the kinematic viscosity of the beverages was measured simultaneously using the Uberorde kinematic meter.

Gustatory Sensation Tests (Bitterness and Palatability Evaluation) The protocol and experimental design for all gustatory sensation tests was given prior approval by the ethical committee of Mukogawa Women's University.

Gustatory sensation tests were done using the equivalent density examination method of Katsuragi *et al.*[14] 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 ($n=8$) 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.

The palatability score was evaluated by the S.D. method as described in a previous paper.[15] The subjects were asked to score the sample in comparison with water using symmetrical terms representing both extremities of difficulty/ease of drinking: −2, very difficult to drink; +1, difficult to drink; 0, neither; easy to drink; 1, very easy to drink 2.

Statistical analysis was carried out using the Mann–Whitney *U*-test.

Results and Discussion

Effect of Simple Syrup or Acidic Sports Drink on the Bitterness and Palatability of PP Firstly, the effect of suppression of the bitterness and/or palatability of PP by SS was examined. The relation between bitterness intensity (vertical axis) and palatability (horizontal axis) is shown in Fig. 1. The bitterness intensity of water (control) was $\tau 3.5$. The bitterness intensity decreased significantly as the concentration of sucrose in the syrup increased. The 100% SS suppressed the bitterness of PP the most effectively. The acidic sports drink used in the present study contains sweetener and its sweetness was estimated to be about 6% SS, *i.e.* almost the same as that of 5.0% SS ($\tau 2.0$). However, the bitterness-suppression effect obtained with the acidic sports drink was greater than the effect of 10% SS.

Secondly, the effect on the palatability of a PP solution was examined. The palatability improved as the concentration of sucrose in the syrup increased up to 50% SS. When 80% (w/w) SS was used, however, the palatability of the diluted solution was reduced due to the high viscosity of the mixture. The palatability of 100% (w/w) SS was almost same as 5% (w/w) SS, even though 100% SS is extremely sweet and shows high efficacy from the standpoint of bitterness suppression. These highly concentrated sucrose solutions remain in the mouth for longer due to their high viscosities.

The bitterness-suppressing effect and improvement of palatability of PP solution mixed with acidic sports drink, correspond to those of 25% SS. The bitterness-suppressing effect and improvement of palatability were thought to be due to the sourness and/or saltiness of the acidic beverage. Accordingly, the suppression of bitterness and improvement of palatability by sourness and saltiness were examined, as well as the effect of kinematic viscosity on palatability.

Suppression of the Bitterness and Improvement of Palatability by Sweetness, Sourness or Saltiness The bitterness-suppressing effect and improvement of palatability of a PP solution by the addition of sourness (sourness intensity: $\tau 1$, $\tau 2$, or $\tau 4$) or saltiness (saltiness intensity: $\tau 1$, $\tau 2$, or $\tau 4$) is shown in Fig. 2. The bitterness intensity decreased significantly as the sourness intensity ($\tau 2$ or $\tau 4$) or saltiness intensity ($\tau 2$ or $\tau 4$) increased, and the effect was increased as the sourness or saltiness intensities increased. However, the palatability of the solutions was dramatically decreased as the sourness or saltiness intensities ($\tau 2$ or $\tau 4$) increased. Palatability was only improved by the addition of solutions with a low intensity of sourness ($\tau 1$). Thus, adequate bitterness suppression and palatability improvement could not be achieved by the addition of only sourness or saltiness.

Figure 3 shows the result of an attempt to suppress bitterness and improve the palatability of a PP solution by the addition of a solution with sweetness intensity ($\tau 4$) plus slight sourness or saltiness. Solutions SW4 SA2 and SW4 SA4 did not improve palatability, but SW4 SO2 and SW4 SO4 were very effective in improving palatability; the maximum improvement was found when SW4 SO2 SA1 and SW4 SO4 SA1 were added.

These results show that the addition of slight sourness or saltiness, in addition to strong sweetness, is most effective in bitterness-suppression and improvement of palatability.

Mukai *et al.* reported that the addition of flavored powder into Aminoleban® EN was so useful in reducing the bitterness intensity of Aminoleban® EN as nutritional products.[15] Especially, sweet or acidic component in flavored product seems effectively to reduce the bitterness, even though the mechanism of the synergistic effect of acidic and sweetness

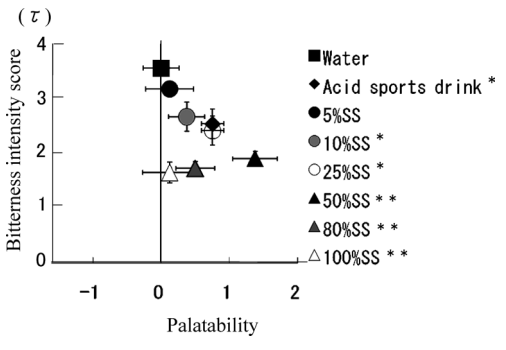

Fig. 1. Changes in Bitterness Intensity Scores and Palatability Caused by the Addition of Different Concentrations of Simple Syrup

$*p<0.05$, $**p<0.005$. Bitterness intensity compared with water suspension using Mann–Whitney *U*-test. Values are means±S.E. ($n=8$).

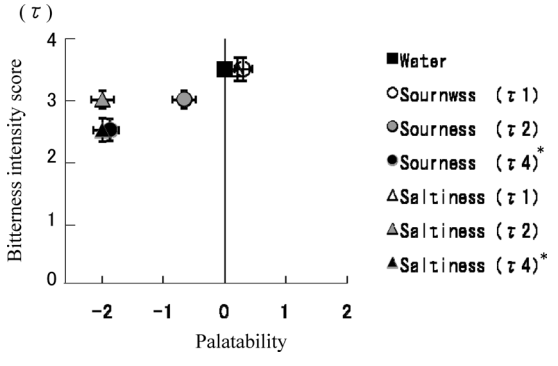

Fig. 2. Changes in Bitterness Intensity Scores and Palatability Caused by the Addition of Sourness or Saltiness Using Standard Basic Taste Solutions

$*p<0.05$. Bitterness intensity compared with water suspension using Mann–Whitney *U*-test. Values are means±S.E. ($n=8$).

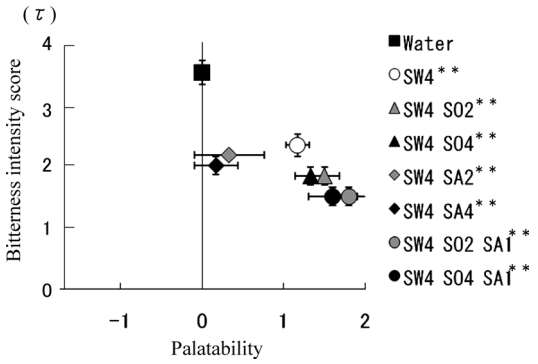

Fig. 3. Changes in Bitterness Intensity Scores and Palatability Caused by the Addition of Sweet, Sour, and Salty Solutions

SW4: sweetness (τ4); SW4SO2: sweetness (τ4) and sourness (τ2) mixed; SW4SO4: sweetness (τ4) and sourness (τ4); SW4SA4: sweetness (τ4) and saltiness (τ2) mixed; SW4SA2: sweetness (τ4) and saltiness (τ2) mixed; SW4SO2SA1: sweetness (τ4), sourness (τ2) and saltiness (τ1) mixed; SW4SO4SA1: sweetness (τ4), sourness (τ4) and saltiness (τ1) mixed. $**p<0.005$. Bitterness intensity compared with water suspension using Mann-Whitney *U*-test. Values are means±S.E. (n=8).

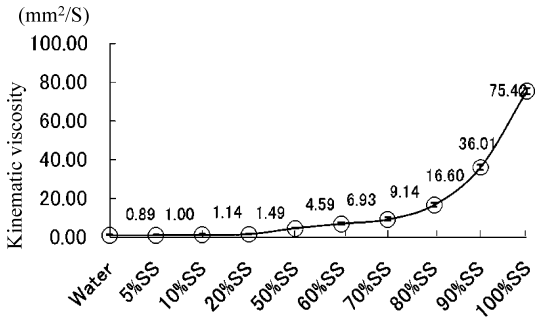

Fig. 4. The Relationship between Kinematic Viscosity and Concentration of Simple Syrup

Values are means±S.D. (n=3).

could not adequately dissolved. The effect was expected to be caused *via* multiple pathways (for example reaction through second messenger).

Effect of Kinematic Viscosity on Palatability The kinematic viscosity of 5, 10, 20, 50, 60, 70, 80, and 90 and 100% SS was measured and the data are shown in Fig. 4. The kinematic viscosity of water was 0.89 mm^2/s. The kinematic viscosity of SS increased as the density of the syrup increased. In particular, when the concentration of SS exceeded 70%, the kinematic viscosity increased dramatically. The kinematic viscosity of 80% SS was 16.6 mm^2/s.

The relation between kinematic viscosity and palatability which seems to be ease of swallowing is shown in Fig. 5. In general, solutions over 70% SS were regarded as less easy to swallow than water. The palatability of 80% SS became worse compared with 70% SS.

We sometimes experienced that the patients complained to high kinematic viscosity and bad palatability for several syrup formulations such as Polaramin® syrup, Asverin® syrup, Bisolvon® syrup, and Alimezine® syrup, those used for pediatric treatment.

Therefore, we evaluated the kinematic viscosity of commercial syrups, and results were shown in Table 2. Even in the case of Polaramin® syrup with lowest kinematic viscosity among above four syrups, the value was 18.11 mm^2/s, and the value was larger than that 80% SS (16.60 mm^2/s).

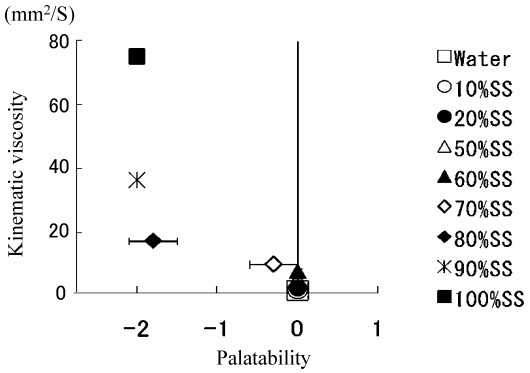

Fig. 5. The Relationship between Kinematic Viscosity and Palatability Scores for Different Concentrations of Simple Syrup

Values are means±S.E. (n=8).

Table 2. Kinematic Viscosity of Commercial Syrups

Product name	Kinematic viscosity (mm^2/s)
Meptin® syrup	2.79
Mucodyne® syrup	3.74
Periactine® syrup	4.95
Polaramin® syrup	18.11
Asverin® syrup	29.36
Bisolvon® syrup	50.90
Alimezine® syrup	92.79
Mixture syrup (Bisolvon® syrup +Meptin® syrup+Mucodyne® syrup)	8.53

The kinematic viscosity of Alimezine® syrup was 92.79 mm^2/s, and its high kinematic viscosity was so much complained by patients in our hospital.

Therefore, judging from above information, the palatability become worse when the kinematic viscosity of syrup exceeded 15 mm^2/s. The high kinematic viscosity of syrup was responsible for bad palatability and the syrup being difficult to handle. It should be remembered that the data in the present study were obtained from adults, and cannot be directly extrapolated to use in infants. Therefore, it is recommended that these formulations are diluted with water when their kinematic viscosity exceeds 15 mm^2/s, in order to improve patient compliance. It should also be kept in mind that kinematic viscosity may vary depending on temperature.

Suppression of Bitterness and Improvement of Palatability by Commercial Beverages and Foods When medicines are to be taken with beverages and foods, it may be necessary to examine the stability of the mixture and the interaction of the medicine with the food or beverage. In the present study, PP solution was made up just prior to use, as described in a previous report.[11] Bitterness suppression and palatability improvement were evaluated when PP was taken with various beverages and food. We have already determined that substances are relatively easy to swallow if their kinematic viscosity is below 15 mm^2/s. All the beverages and foods used in the study, except condensed milk and jelly, have kinematic viscosities below 15 mm^2/s and are easy to swallow. The effects of taking PP together with one of the tested beverages or foods is shown in Fig. 6. With all beverages (except milk) and foods tested, bitterness was suppressed, and palatability improved compared with water. The

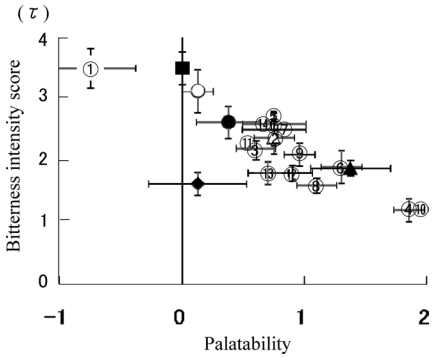

Fig. 6. Bitterness Intensity Scores and Palatability of Mixtures of PP with Commercial Beverages

■: water, ○: 5% SS, ●: 10% SS*, △: 25% SS*, ▲: 50% SS**, ◆: 100% SS**. 1: milk; 2: acidic sports drink*; 3: CC lemon*; 4: CC lemon and 100% SS (1 : 1)**; 5: carbonated cola drink*, 6: carbonated cola drink and 100% SS (1 : 1)**; 7: carbonated grape-tasting drink*; 8: carbonated grape-tasting drink and 100% SS (1 : 1)**; 9: orange juice**; 10: orange juice+100% SS (1 : 1)**; 11: coffee milk*; 12: coffee milk and 100% SS (1 : 1)**; 13: condensed milk**; 14: chocolate jelly*; 15: strawberry jelly*. $*p<0.05$, $**p<0.005$, Bitterness intensity compared with water suspension using Mann–Whitney *U*-test. Values are mean±S.E. ($n=8$).

improvement of palatability was particularly strong when the PP solution was mixed with the more sour beverages (CC lemon® or orange juice).

The effect of mixing with milk had a negligible effect on bitterness, but palatability deteriorated, probably because milk is neither sweet, sour, or salty. Mixing with condensed milk had a greater effect on bitterness than 50% SS, but less improvement of palatability. Overall, strong sweetness suppressed bitterness, and high kinematic viscosity reduced palatability. Suppression of bitterness and palatability by a sour beverage alone was less than by 50% SS. However, when 100% SS was mixed with a sour beverage, the bitterness suppression and improvement of palatability was greater than that caused by 50% SS. Mixtures of 100% SS plus orange juice or CC lemon were most effective in bitterness suppression and improvement of palatability.

Effect of bitterness suppression and improvement of palatability were clearly observed in the carbonated drink. This mechanism with the carbonic acid is not clarified yet. However, there have been articles which suggest interaction between the bitter substance and carbon dioxide and the interaction is useful in the standpoint of palatability.[16,17] In addition, the coolness and the sourness of the carbonic acid are expected to be effective in bitterness suppression and improvement of palatability.

Fructose and glucose at concentrations below 50% are commonly used to sweeten commercial beverages. The sweetness of fructose is dependent on temperature (being stronger at low temperatures, and weaker at high temperatures), while glucose has about 65—80% of the sweetness of sucrose. Therefore, it was thought that the sweetness intensity of commercial beverages, such as Coca Cola and Fanta, would be below that of 50% SS, and that suppression of bitterness and improvement of palatability of PP solutions by these beverages would be achieved not only by their sweetness (equivalent to that of 50% SS), but also by their inherent sourness and saltiness.

The bitterness of PP could not be reduced to under the threshold level by the addition of any of the beverages or foodstuffs used in this experiment. Viscosity seems to be a critical factor for palatability.

The previous article reported that the usefulness of the gel and/or the sherbet in infants in bitterness suppression.[18] Of course the gel and/or sherbet will prevent the formulation from spreading on the surface on the tongue, and thereby suppress the bitterness. However, usually in this case, the infants have to take the comparatively large amount or volume of matrix. When large amount of the solid comes in the mouth, the infants easily chew and the matrix of gel or sherbet containing the formulation might be destroyed so quickly. Therefore the usages of jelly or sherbet in infants rather have the risk to increase the bitterness of the formulation and decrease the compliance.

Bitterness suppression using SS demonstrated in the present study seems conventional, safety, and effective method for bitterness suppression in infants. It is recommended that powder or dry syrup with bitter taste such as PP, was suspended in 50—70% SS and used for the infant. Even though the suspendability of various formulations in SS might vary, the appropriate agitation might help the suspension stable.

Even though we did not examine the effect of artificial sweetener as bitterness suppression, it might be another choice for infant.

Conclusions

1. The bitterness-suppressing effect of beverages and foods on PP increased as their intensity of sweetness, sourness and saltiness increased. The maximum bitterness suppression was achieved by mixing sweetness, sourness and a little saltiness.

2. Agents that are exclusively sour or salty are unable to improve palatability; agents that are very sweet ($\tau 4$) and also contain some sourness and a little saltiness improved palatability the most.

3. Kinematic viscosity influences palatability; a kinematic viscosity exceeds 15 mm^2/s and has a negative effect on palatability.

4. The addition of sweetness to acidic beverages is most effective in suppressing the bitterness of PP solution and improving its palatability. This method of suppressing bitterness and improving palatability may provide useful information which will allow patient compliance to be improved.

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