医薬品相互作用研究
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45（3）23-28（2021）

Evaluation of the Palatability of Isosorbide by Human Gustatory Sensation and Electric Taste Sensor

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（Received July 5, 2021; Accepted October 22, 2021）

Abstract

The present study examined the ability of common household drink products to mask the unpalatable taste of a commercial isosorbide liquid formulation（ISO-L）. ISO-L, marketed as ISOBIDE, was mixed with a number of common soft drinks, and healthy adult volunteers evaluated the resulting tastes. The electronic taste system α-ASTREE（E-tongue）was used in parallel to evaluate taste combinations. Several drinks satisfactorily masked the unpalatable taste of ISO-L. Although the taste of ISO-L was not fully masked by the mineral water dilution, it was masked well by orange juice. In addition, the electronic taste system not only differentiated tastes, but also ranked the extent of masking in the same order as that by human volunteers. ISO-L may conveniently be prepared as a more palatable formulation using common household drinks, particularly orange juice. The dilution of ISO-L with a beverage represents an effective strategy for increasing compliance by patients. The electric taste evaluation method described in the present study may be used in initial screening for palatability.

Keyword: palatability; isosorbide; household drink; electric taste sensor; human gustatory sensation

1. INTRODUCTION

The isosorbide liquid formulation（ISO-L）is primarily used to treat intracranial hypertension, ocular hypertension, and Meniere's disease[1, 2)] . One of its liquid formulations, marketed as ISOBIDE®, was approved for use in Japan in 1968. ISO-L increases plasma osmolarity, decreases brain, intraocular, and inner ear lymph pressure, and exerts diuretic effects[3)] . However, the taste of ISO-L is unpalatable because it is sweet, acidic, and bitter. Unpalatable medication may adversely influence the motivation of and compliance by medicated patients. Osmotic diuretics, such as ISO-L, have been used since the 1980s in Japan to control inner ear endolymphatic hydrops[4)] . However, the daily consumption of ISO-L has been shown to place a burden on patients with Meniere's disease, and a satisfactory therapeutic effect cannot be achieved when patients are not compliant. Therefore, the consumption of ISO-L following its dilution with the same volume of water is recommended to prevent non-adherence.

Previous studies investigated the effects of suppressing the unpalatability of medicines and its implications for clinical use[4-7)] . However, masking of the unpleasant taste of ISO-L has not been sufficiently examined. A taste analyzing system manufactured by Alpha MOS has recently become commercially available. The α-ASTREE™ Electronic Taste Sensor（E-tongue）is a liquid and taste analyzer that is already used in

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the food industry[8] and is gaining popularity in the pharmaceutical industry[9] . It comprises several different coated sensors based on chemFET technology, which transforms chemical information into electrical signals. A previous study using the E-tongue system suggested that the dilution of ISO-L with apple juice was useful for unpleasant taste suppression[10] . Masking the unpleasant taste of ISO-L may increase patient compliance and, thus, significantly contribute to treatment success. However, unpleasant taste suppression and improvements in the palatability of ISO-L have not yet been evaluated using a human panel.

Therefore, the aim of the present study was to conduct a systematic and quantitative evaluation of the effectiveness of beverages other than apple juice for the taste masking of ISO-L in Japan using human gustatory sensation tests and the E-tongue system. The results of palatability studies using gustatory sensation tests were compared to those obtained using the E-tongue system.

2. Materials and Methods

2.1. Chemicals and Matrices (Beverages)

The isosorbide liquid formulation, ISO-L（ISOBIDE®, Syrup 70%, Kowa Co., Ltd., Tokyo, Japan）was used in the present study. Mineral water, “Crystal Geyser”（CG）, was purchased from Otsuka Beverage Co., Ltd.（Tokushima）, oolong tea, “Oolong cha”（OT）, and green tea, ”IYEMON”（GT）, were obtained from Suntory（Osaka）, a lemon-tasting drink, “C1000 Lemon Water”（LTD）, from House Wellness Foods Corp.（Tokyo）, and a plum-tasting drink, “Seiryo-Kabai COOLER”（PTD）, from Itoen Inc.（Tokyo）. Apple juice（AJ）, orange juice（OJ）, grapefruit juice（GFJ）, and grape juice（GJ）as “Tropicana 100% Juice” were purchased from Kirin Beverage Co., Ltd.（Tokyo）. All other reagents were of special reagent grade.

2.2. Human Gustatory Sensation Test

Gustatory sensation tests were performed by 16 healthy adult volunteers using a previously described method[6] . Nine volunteers were males and seven were females. The protocol and experimental design for all gustatory sensation tests were approved by the Ethical Committee of the Department of Hospital Pharmacy, Kitasato Institute Hospital（approval number 08081）. They were also reviewed for approval by the Ethics Committee of Josai International University（approval number 15W20008）. Each volunteer was randomly assigned a specific sequence of preparations and received samples in that order. Informed consent was obtained from all subjects involved in the present study, which was conducted according to the guidelines of the Declaration of Helsinki.

Table 1 shows commercial beverages（matrix）for dilution. ISO-L was diluted to 50% with the respective beverage before tasting. Volunteers refrained from eating and drinking for 1 hr before the first tasting and between tastings and were asked to rinse their mouth with water.

Sample preparations were administered at approximately 5-min intervals to allow time for tasting and rating of the preparation and cleaning of the mouth. All samples were held in the mouth for 10 sec. After tasting, subjects were asked to score the preparation for palatability.

A scoring system on a scale of 1-5, with 1 indicating the highest score and 5 the lowest, was employed as follows: 1, highly palatable; 2, moderately palatable; 3, average palatable; 4, slightly palatable; 5, not palatable.

2.3. Electronic Taste Sensor Measurements and Data Analysis

The taste sensor system, the “ α -ASTREE™” Liquid and Taste Analyzer（Alpha M.O.S., Toulouse, France）, was used to measure the electronic potential of the ISO-L solution. The taste sensor consists of an array of electrodes or sensors, a 16-position auto sampler（LS-16）, and an associated electronic interface module. Seven taste sensors; ZZ, AB, BA, BB, CA, DA, and JE, are used. Each sensor consists of a silicon transistor with an organic coating that affects the sensitivity and selectivity of the sensor[11] . This system was found to offer good characterization and differentiation between the majority of food groups and pharmaceutical products. Therefore, integral signals for each sample comprised a vector with seven individual sensor determinations. We measured each sample four times after sensor conditioning and performed data analyses. The artificial taste sensor system and measurement method used in the present study are essentially the same as those described in a previous study[10] .

Euclidean distance is expressed by the square root of the squared sums of differences in each parameter. The Euclidean distance calculates the distance between

the center of gravity of a placebo sample（CG, water）and that of the drug sample（ISO-L + drink）. If the taste is similar, the distance is small. If the difference in the sensor output value between two samples is small, the taste resembles that of the placebo sample. In measurements of taste by α-ASTREE™, five samples were diluted and tested. Each sample volume was 80 mL with an analysis time of 180 sec and acquisition time of 120 sec. Data were analyzed with Alpha Soft（Alpha M.O.S., Toulouse, France）.

2.4. pH Measurements

The pH of beverages alone and physical mixtures of ISO-L and beverages were measured using a pH meter（HORIBA, Twin pH B-212, Kyoto, Japan）immediately after preparation.

2.5. Sugar Content Analysis

The sugar content in each beverage was assessed with an Atago, MATER-2M sugar refractometer（Endo Scientific Instruments Co., Ltd., Shizuoka, Japan）.

2.6. Analysis of Experimental Data

The average overall palatability score within each matrix group was calculated and compared using the Steel-Dwass test, a non-parametric method, and Tukey's test, a parametric method. Correlations between the overall palatability scores and taste intensities using the taste senor were analyzed for a simple linear regression（*R*: Pearson product-moment correlation coefficient）. The latest version of Microsoft Excel was used for statistical analyses.

3. Results

3.1. Palatability Studies by the Human Gustatory Sensation Test

Figure 1 shows the mean score of each resulting mixture for taste obtained by the gustatory sensation test. Ten of the samples used in Figure 1 were organoleptically graded according to the relative palatability of ISO-L diluted to 50% in CG, AJ, OJ, GFJ, GJ, OT, GT, PTD, and LTD. As expected, an undiluted solution of ISO-L（P）, as a negative control, received the highest score of 3.80. CG received a mean score of 3.29, while GT, OT, LTD, and PTD scores were worse than that of CG. In contrast, OJ had a palatability score of 2.67, indicating that it was more palatable than the other beverages. The palatability of OJ was significantly different from that of P, whereas no significant differences were noted between P and other dilutions. The ranking order of taste-masking efficacy was OJ > AJ > GFJ > GJ > CG > GT > OT > LTD > PTD > P.

3.2. Taste Sensor Measurement and Data Analysis

The Euclidean distance of P, undiluted ISO-L, was adjusted to 100%, and the taste-masking effects of commercially available soft drink dilutions were compared. As shown in Figure 2, the distance for ISO-L

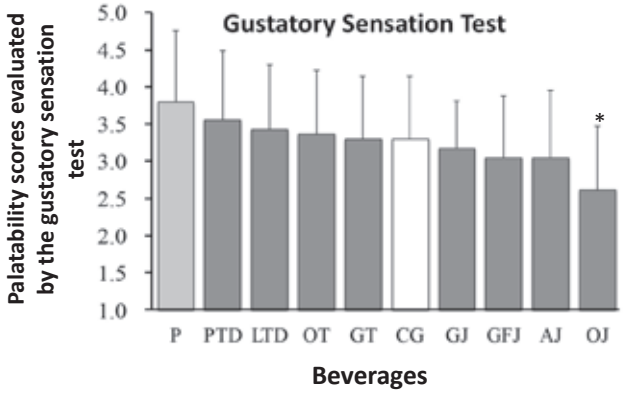

Figure 1. Palatability scores of ISO-L with commercial beverages by human gustatory sensation tests. Error bars represent the mean ± SD（n=16）. *$p<0.01$ significantly different from undiluted ISO-L（P）by the Steel-Dwass test.

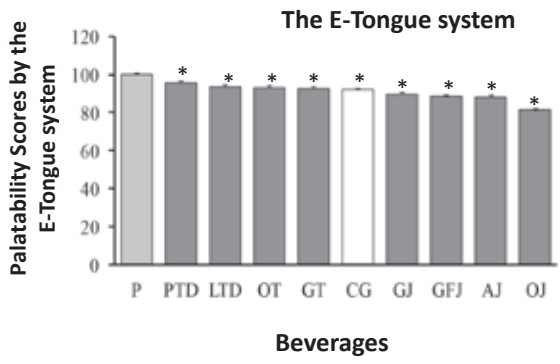

Figure 2. Suppression of the unpleasant taste of ISO-L with various commercial beverages as assessed by the E-tongue system. Error bars represents the mean ± SD（n=4）. *$p<0.01$ significantly different from undiluted ISO-L（P）by Tukey's test.

in the presence of a taste-masking excipient was lower than those for samples without any taste-masking excipients as assessed by the E-tongue system. The taste-masking effects of CG, the mineral water dilution, were slightly better than those of P.

Dilutions with fruit juices（OJ, AJ, GFJ, and GJ）successfully suppressed the unpleasant taste and improved palatability. The taste of ISO-L was not fully masked by CG, but was largely masked by OJ. PTD, LTD, OT, and GT did not mask the unpleasant taste of P.

3.3. Relationship between Sensor Values and the Human Gustatory Sensation Test

Figure 3 shows a plot of palatability values against scores from the gustatory sensation test, in which a higher score represents worse palatability. The results obtained showed a strong correlation between the sensor value and human gustatory sensations（*R=0.9998*）and demonstrated that the sensor value correctly evaluated the overall palatability of ISO-L formulations.

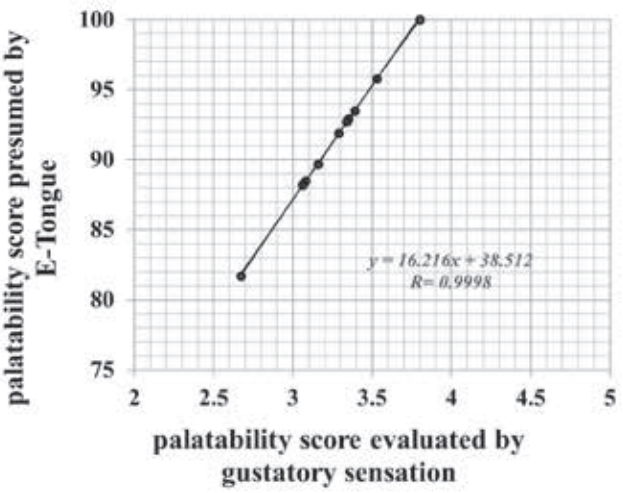

Figure 3. Correlation between average palatability scores obtained in gustatory sensation tests and those by the E-tongue system.

4．Discussion

Although ISO-L is a branded product of an isosorbide liquid formulation that is currently available on the market, the taste of this pharmaceutical preparation has not yet been fully optimized. The package insert for ISO-L instructs users to “dilute 2-fold with cold water if necessary”. Therefore, we examined masking effects on taste when each stock solution was diluted to 50% with CG[12] ; however, the unpleasant taste of ISO-L was not effectively masked. The addition of fruit juices, particularly OJ, masked the unpleasant taste of ISO-L, thereby improving palatability. This result was similar to a previous trial with the E-tongue system that used AJ in conjunction with ISO-L; however, other soft drinks in combination with ISO-L were not examined[10] . The addition of OJ appeared to be more effective than AJ for reducing the unpleasant taste of ISO-L, and, thus, may increase compliance with a prescribed regimen. These results demonstrate that suitable and readily-available beverages may be used to mask the unpalatable taste of isosorbide.

Improvements in the palatability of ISO-L by OJ may be achieved not only by the components’ sweetness, but also by their inherent sourness. PD and CD were less palatable than CG. ISO-L blends well with sour beverages, masking the unpleasant taste. Preparations offering high sweetness and moderate acidity through the addition of beverages may be preferable; however, the underlying mechanisms with sour beverages remain unclear. The balance of sweetness and sourness is important[13] . Tanaka et al. reported that food and beverages affect palatability differently depending on the combination of powder formulations[14] . The present results suggest that some beverages also improve the palatability of liquid formulations, thereby decreasing non-compliance by patients who are reluctant to take medication with an unpleasant taste.

Table 1. Commercially Available Soft Drinks used in the Present Study.

Drinks	Sugar contents Brix (%)	*pH* values	*pH* values after a 2-fold dilution
Apple juice (AJ)	12	3.8	2.9
Orange juice (OJ)	12	3.7	3.3
Grapefruit juice (GFJ)	10	3.2	3.1
Grape juice (GJ)	12	3.4	2.9
Oolong tea (OT)	0	5.9	2.7
Green tea (GT)	0	6.1	2.7
Plum-tasting drink (PTD)	4.5	2.7	2.5
Lemon-tasting drink (LTD)	6	2.8	2.5
Water (CG)	0	5.8	2.9

Table 1 shows the degrees Brix of the beverages and the pH of each resulting mixture. A good correlation was

noted between the observed palatability scores by the gustatory sensation test and the predicted scores（*Y*）calculated based on a multiple regression analysis using the Brix values of beverages and the pH of the resulting mixtures.

$$Y = 5.83 - 0.0104 \cdot Brix - 0.898 \cdot pH \quad (r^2 = 0.933,\ p<0.01)$$

Since the predictive performance of the equation described above has not yet been established, a more substantive trial is needed in the near future.

When the palatability of ISO-L diluted with commercial beverages was measured using the E-tongue taste sensor, it discriminated between the taste of each sample. The present study differed from the previous study in that the group distance between each active sample and water（placebo）was calculated in order to rank masking beverages. However, the correlation between E-tongue assessments and human rankings is encouraging. According to E-tongue assessments, the best masking beverage for ISO-L was OJ, followed by AJ and GFJ. The order of ranking was the same as that from human subject palatability tests. The method of taste evaluations using the E-tongue system excels in objectivity[9] , and is considered to be a good index that forecasts the taste of medication without the need for human sensory testing[15-17] . Moreover, the electronic taste sensor may predict tastes not experienced by individuals[18, 19] . Taste perception is one of the most important factors for increasing patient compliance. Masking the unpleasant taste of a drug may increase patient compliance, thereby improving treatment outcomes. The failure to mask taste from the first dose may have a negative impact on compliance, whereas increasing the palatability of a drug may enhance a patient's willingness to repeat the same preparation in the future.

In conclusion, the method described herein offers good predictability for the taste of generic liquid formulations. The results obtained demonstrate that taste improvements in generic formulations may be applied as a rational method to increase patient compliance.

Acknowledgments

The authors thank Dr. T. Yajima, Alpha M.O.S Japan for the analytical service.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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