

**Regular Article**

**Ability of Food/Drink to Reduce the Bitterness Intensity of Topiramate as Determined by Taste Sensor Analysis**

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The purpose of this study was to determine which foods and/or drinks are capable of reducing the bitterness of topiramate when consumed together with the medicine. The inhibitory effects of foods/drinks (yoghurt and nine other foods/drinks) on the bitterness of topiramate (5 mg/mL) were evaluated with a taste sensor using a bitterness-responsive membrane (C00). The effect of topiramate on the taste characteristics of the foods/drinks themselves was also evaluated by taste sensor outputs. The viscosities of the foods/drinks and the influence of the lactic acid and orotic acid components of yoghurt, the most successful of the tested substances in taste masking, on the bitterness of topiramate were also measured. Yoghurt was predicted to be the most effective of the foods/drinks tested in reducing the acidic bitterness-responsive sensor output of topiramate. The outputs of the astringency sensor, sourness sensor, and saltiness sensor to yoghurt were not reduced by the addition of topiramate. The viscosity and lactic acid and orotic acid components of yoghurt seemed to be the keys in reducing the bitterness of topiramate. Yoghurt is predicted to be the food/drink most capable of reducing the bitterness of topiramate without losing the taste of the food/drink itself.

Key words topiramate; taste interaction; food and drink; taste sensor

Topiramate is an anti-epileptic drug which appears to have various pharmacological effects on ion channels, stimulating or restricting excitation on nerve conduction. The drug was originally developed, approved and marketed in U.K., but since then it has been widely used in many countries for both adult and pediatric patients with various types of epilepsy, including symptomatic generalized epilepsy such as general tonic–clonic seizures, myoclonia, West syndrome, Lennox–Gastaut syndrome, and idiopathic generalized epilepsy such as juvenile myoclonic epilepsy.

A particular problem encountered in administering medicines to children is taste. Most pediatricians report that a drug’s taste and palatability can form the greatest barrier to successful completion of treatment. For the pediatric use of topiramate in Japan, broken or crushed tablets, or fine granules are used to ensure that the correct weight of active ingredient is given for the child’s bodyweight. However, as described in previous articles, crushing tablets containing bitter active ingredients risks enhancing their bitterness, which will thereby reduce compliance. The use of fine granules also risks enhancement of bitterness as they immediately disintegrate or dissolve in the mouth.

Several methods for improving the palatability of crushed tablets or fine granules have been tested using various foods and drinks. In some cases these have been useful but in other cases, combinations of foods or drinks and medicine make the palatability of the medicine worse than the original taste of the drug. For example, acidic sports drinks and orange juice enhance the bitterness intensity of macrolide-drug-loaded dry syrup formulations for children. This is because macrolide drugs, such as clarithromycin or azithromycin, are basic drugs, the solubility of which increases in acidic solvents such as acidic sports drinks and orange juice.

In the present study, therefore, we aimed to screen foods and drinks which might reduce the bitterness of topiramate when taken together with the medicine, using taste sensor analysis.

Firstly, we selected a taste sensor showing a good response to the acidic drug topiramate from various types of lipid-based taste-sensor membranes. The inhibitory effects of various foods and drinks on the bitterness of topiramate were then evaluated using this bitterness-responsive sensor. The standard concentration of topiramate used in this study was 5 mg/mL; this concentration was selected on the basis of the normal oral dosage regimen for a child of 1–4 years old, weighing 10–16 kg, which is 5–8 mg/kg/d. The effect of topiramate on the taste characteristics of the foods and drinks themselves was also evaluated, to avoid the prospect of children growing to hate the taste of the foods and drinks concerned. Finally, we investigated the bitterness-suppressing mechanism of yoghurt, the most effective of the foods/drinks tested in suppressing the bitterness of topiramate in the present study.

**Experimental**

**Materials** The samples used were topiramate (Kyowa Hakko Kirin Co., Ltd., Japan) solutions (1.25, 2.5, 5 mg/mL) and 10 mg/mL topiramate suspensions. Quinine hydrochloride (Sigma Chemical Co., Japan) solutions (0.01, 0.03, 0.10, 0.30 mg/mL) were used as a bitterness standards.

The foods and drinks tested with topiramate solution were: yoghurt (Meiji Bulgarian Plain Yoghurt; Meiji Co., Ltd., Japan), pudding (Puccin-pudding; Glico Co., Ltd., Japan), vanilla and chocolate-flavoured ice cream (Lady Borden vanilla and chocolate; Lotte Co., Ltd., Japan), Japanese tea (Kirin nama-cha; Kirin Co., Ltd., Japan), orange juice (Tropicana fruit × fruit orange; Kirin Beverage Co., Ltd., Japan), lactic

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drink (Calpis water: Calpis Co., Ltd., Japan), milk (Meiji Oishii Gyu-nyu; Meiji Co., Ltd., Japan), acidic sports drink (Pocari Sweat; Otsuka Pharmaceutical Co., Ltd., Japan) and cocoa (Van Houten Cocoa; Meiji Co., Ltd., Japan). These foods and drinks including semisolid foods like yoghurt, pudding, chocolate ice cream and vanilla ice cream were processed to a paste with stirred for 30 min at normal temperature (25°C) and their samples (0.4, 0.8, 8.0, 20 g) were diluted to 1, 2, 20 and 50% (w/w) with 39.6, 39.2, 32.0, 20.0 g of water respectively and the final volume of each sample was fixed at 40 g. The concentration of topiramate in each sample was fixed at 5 mg/mL. These samples without filtration were then used for taste sensor measurement.

Lactic acid (Kanto Chemical Co., Japan) and orotic acid (MP Biochemicals, Inc., Japan), both found in yoghurt, were used as organic acids.

The Taste Sensor Measurement The taste sensor SA402B (Intelligent Sensor Technology Inc., Atsugi, Japan) was used as same as our previous experiments. The electrode set was attached to a mechanically controlled robot arm. The detecting sensor part of the equipment consists of a reference electrode and taste sensor which acts as the working electrode and is composed of lipid/polymer membranes. In the first step, a reference solution (corresponding to saliva) is measured and the electric potential obtained (mV) is defined as $V_r_0$. Then a 40 g of sample was measured at normal temperature (25°C) and the electric potential obtained is defined as $V_s$. The sensor output is represented as the difference between the potentials of the sample and the reference solution $(V_s-V_r_0)$ and corresponds to the ‘taste immediately after putting in the mouth.’ The electrodes are then rinsed with a fresh reference solution for 6s. When the electrode is dipped into the reference solution again, the new potential of the reference solution is defined as $V_r_1$. The difference between the potentials of the reference solution before and after sample measurement $(V_r_1-V_r_0)$ is the change in membrane potential caused by adsorption (CPA) and corresponds to the so-called ‘after taste.’ Each sample was measured four times and the mean value of the last three measurements used in the data analysis.

Choice of Taste Sensor to Respond to the Bitterness of Topiramate Topiramate solutions (1.25, 2.5, 5 mg/mL), topiramate suspension (10 mg/mL), and quinine hydrochloride solutions (0.01, 0.03, 0.10, 0.30 mg/mL) were all evaluated using taste sensor membranes AC0, AN0 and C00. AC0 and AN0 are known to respond to basic bitterness, while C00 responds to acidic bitterness.

Influence of Foods and Drinks on the Bitterness of Topiramate The various foods and drinks were diluted with water and mixed with topiramate to final concentrations of 5 mg/mL topiramate and 1, 2, 20 and 50% (w/w) foods or drinks.

Influence of Topiramate on the Taste of Foods and Drinks Mixed samples, prepared as described under above subsection “Influence of Foods and Drinks on the Bitterness of Topiramate,” were also measured in the taste sensor using taste sensors AE1 (astringency sensor), AAE (umami sensor), CT0 (saltiness sensor) and CA0 (sourness sensor).

Measurement of Viscosity of Foods and Drinks The Viscotester (VT-03F, VT04F, Rion Co., Japan) was used to measure the viscosity of samples of each food/drink diluted with water to concentrations of 1, 2, 20 and 50% (w/w).

Influence of Organic Acids on the Taste Sensor Output of Topiramate Mixed samples of topiramate (5 mg/mL) and lactic acid (0.0025, 0.025, 0.25 mg/mL) or orotic acid (0.0025, 0.025, 0.25 mg/mL) were measured using the taste sensor.
membrane C00 (acidic bitterness sensor).

**Statistical Analysis** Results are expressed as the mean±standard deviation (S.D.). In Figs. 2 and 5, the Dunnet test, one-way ANOVA was used in the evaluation. In Fig. 4, the type of food/drinks and the concentration in viscosity were analyzed by two-way ANOVA. Type, concentration, type×concentration interaction were considered independent variables. p<0.05 was considered to represent statistical significance.

**Results**

**Choice of Taste Sensor to Detect the Bitterness of Topiramate** Sensors AC0 and AN0, which usually respond to the bitterness of basic medicines, did not respond to topiramate. However, sensor C00, which usually responds to bitterness derived from acidic drugs, did respond to topiramate (Fig. 1) in a dose-dependent manner. Therefore, taste sensor C00 was selected for the evaluation of bitterness suppression of topiramate.

**Influence of the Foods and Drinks on Bitterness of Topiramate** As shown in Fig. 2, yoghurt, orange juice, vanilla and chocolate ice cream, lactic drink and pudding all reduced the C00 sensor output of topiramate in a dose-dependent manner. Low concentrations of milk or cocoa did not reduce the C00 sensor output. As the concentration of the foods and drinks increased, however, all of the foods and drinks were capable of reducing the sensor output of topiramate to some extent. Acidic sports drink and Japanese tea successfully reduced the sensor output of topiramate at low concentrations, but the sensor output did not reduce further with increasing concentrations. Thus, for milk, cocoa, acidic sports drink and Japanese tea, a concentration-dependent reduction in bitterness could not be demonstrated (Fig. 2).

When topiramate solution was mixed with 50% foods and drinks, significant inhibitory effects were observed on the sensor output, compared with that of topiramate 5 mg/mL alone (−16.36±0.71 mV), for all 10 samples. The most effective of the foods and drinks at reducing the sensor output was yoghurt (−3.58±0.58 mV). After yoghurt, the rank of effectiveness according to sensor output was as follows: chocolate ice cream (−4.82±1.33 mV)>pudding (−5.59±0.18 mV)>lactic drink (−5.92±1.99 mV)>cocoa (−6.42±0.25 mV)>vanilla ice cream (−6.46±2.42 mV)>milk (−7.01±0.66 mV)>orange juice (−8.93±0.61 mV)>Japanese tea (−9.68±0.52 mV)>acidic sports drink (−12.36±0.65 mV).

When topiramate solution was mixed with 1% foods and drinks, significant inhibitory effects on sensor output were only found with chocolate ice cream (−3.58±0.58 mV), Japanese tea (−11.93±0.24 mV), yoghurt (−12.20±0.66 mV) and pudding (−12.93±0.62 mV).

**Influence of the Topiramate on the Taste of Foods and Drinks** In order to examine the effect of topiramate on the taste of foods and drinks, the AE1 sensor responding to astringency, AAE sensor responding to umami, CT0 sensor responding to saltiness, and CA0 sensor responding to sourness, were used in the taste sensor. The sensor output of foods and drinks with and without 5 mg/mL topiramate were then compared. Sensors AE1 and CA0 responded to 1% yoghurt diluted with water while AE1, CA0 and CT0 responded to 50% yoghurt diluted with water. No differences in sensor output were observed between yoghurt alone and yoghurt containing 5 mg/mL topiramate. Sensors AE1, AAE and CT0 responded to chocolate ice cream, pudding and Japanese tea, and no differ-

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Fig. 2. Effect of Different Foods and Drinks on C00 (Bitterness Sensor) Output in Response to Topiramate Solution (5 mg/mL)

* p<0.05, ** p<0.01, *** p<0.001 vs. control (1) (Dunnet test, one-way ANOVA). n=3, mean±S.D.
ences in sensor output were observed for these three samples containing 5 mg/mL topiramate (Fig. 3).

**Measurement of Viscosity of Foods and Drinks** The viscosity of water is 1.5 mPa·s. At a concentration of 1% or 2% all foods and drinks had nearly the same viscosity as water. At a 20% concentration of cocoa, milk, orange juice, acidic sports drink and lactic drink, viscosity was around 2.0 mPa·s, while at the same concentration of yoghurt, pudding, vanilla ice cream and chocolate ice cream, viscosity was 3–5 mPa·s. At a concentration of 50%, the viscosity of...
cocoa, milk, orange juice, acidic sports drink, lactic drink and green tea was 1.8–3.5 mPa·s, while at the same concentration, yoghurt, pudding, vanilla ice cream and chocolate ice cream had viscosities of 40–150 mPa·s (Fig. 4(a)). Four type of food/drinks (yoghurt, pudding, vanilla ice cream and chocolate ice cream) had significantly high viscosity compared with water. The influence of the viscosity of the foods/drinks on the taste sensor output of topiramate is expressed in Fig. 4(b). The x- and y-axes in Fig. 4(b) represent the logarithm of the viscosity of the food/drink, and the taste sensor output of topiramate with each food/drink, respectively.

**Influence of Organic Acids on the Bitterness of Topiramate** The C00 (acidic bitterness) sensor output of topiramate 5 mg/mL was suppressed by the addition of both lactic acid and orotic acid in a dose-dependent manner (Fig. 5).

**Discussion**

In the present study, we investigated whether the taste sensor could predict which foods and drinks could mask the bitter taste of topiramate 5 mg/mL. The dilution of each foods/drinks with water was needed for application to taste sensor measurement. Between each foods/drinks sample with and without dilution by water, relative concentration ratio of the target drug accompanied with bitterness and substance could inhibit the bitterness seems same. Therefore we expected that taste sensor could predict bitterness and/or its inhibition not only in the original sample but also in diluted samples. In fact we reported such case in our previous papers. They indicated well correlation between taste sensor output and human sense.

In general, diffusion coefficient of drug become smaller in high-viscosity solution like polymeric gel and the adsorption to taste sensor membrane also will become lower. The similar effect might be observed in the saliva juice around taste buds in human oral cavity. The 100% concentrations of yoghurt, pudding, vanilla and chocolate ice cream had higher viscosities than 50% concentrations of those (data not shown in text). These foods were expected to have great effect of taste masking with above mentioned mechanism. Also taste masking effect of jelly which has high viscosity was reported in our previous studies. They indicated well correlation between taste sensor output and human sense.

The viscosity was thought to be one of the reasons to suppress the bitterness of topiramate however, in case of yoghurt, diluted sample with low-viscosity also successfully suppressed the bitterness of topiramate. Not only the viscosity but also the component of foods/drinks would be important to suppress the bitterness.

Sourness is a characteristic taste of yoghurt. Keast and Breslin reported that sourness can suppress bitterness, if both their intensities are medium. We also found in a previous report that sourness in flavoured powders was effective in
reducing the bitterness of Aminoleban® EN. Yoghurt contains organic acids such as lactic acid (780 mg/100 g) and orotic acid (160 mg/100 g). According to the report by Omae et al., 1% concentration of yoghurt corresponds almost 0.078 mg/mL of lactic acid and 0.016 mg/mL of orotic acid. From the result of our study (Fig. 5), it was thought that these concentrations of organic acids could also suppress the taste sensor output of topiramate. It is thought possible that these organic acids in yoghurt may influence the bitterness suppression of topiramate. The acidic bitterness sensor C00 used in this study has a positively charged membrane and the mechanism of the taste sensor response is a change in membrane potential caused by changing the charge density. A change in the membrane potential caused by a sour substance (lactic acid or orotic acid) would elicit inhibition of the taste sensor output due to topiramate.

There have been several reports on taste mixture interactions. According to a study of taste mixture interactions in human sensation testing reported by Green et al., the sourness of citric acid was not suppressed by quinine sulfate (bitterness standard). Overall, these sources suggest that sour substances may be good bitterness suppressors without losing their own sour tastes. In this study, the sensor output of CA0 (sourness sensor) in response to yoghurt was almost unchanged by the addition of topiramate. From this result, it could be predicted that the taste of yoghurt would not itself be impaired by the addition of topiramate.

At some concentration, green tea, pudding and chocolate ice cream also suppressed the bitterness taste sensor output of topiramate. Even low concentrates of chocolate ice cream and pudding elicited a response from AAE (the umami sensor), while Japanese tea elicited a response from both AE1 (the astringency sensor) and AAE. Some reports have shed light on umami and the potential caused by changing the charge density. A change in the membrane potential caused by a sour substance (lactic acid or orotic acid) would elicit inhibition of the taste sensor output of topiramate. It is thought possible that these organic acids could also suppress the taste sensor output of topiramate. The acidic bitterness sensor C00 used in this study has a positively charged membrane and the mechanism of the taste sensor response is a change in membrane potential caused by changing the charge density.

In conclusion, from taste sensor measurements using taste sensor membrane C00, yoghurt is predicted to be the most useful food with which to limit the bitterness of topiramate without losing the taste of the food itself. It is hoped that these findings may help children to take topiramate without experiencing its bitter taste. In general, the ability to take medicines with appropriate bitterness-masking foods or drinks will contribute to improvements in patient compliance for many pediatric drugs.

**Conflict of Interest** This study was funded by Kyowa Hakko Kirin Co., Ltd. Masaki Nakashima, Hotaka Sanda, Takema Hase and Yutaka Tomoda are employees of Kyowa Hakko Kirin Co., Ltd. The authors have no further conflict of interest to declare.

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