

Article

Ethyl loflazepate as a treatment for patients with idiopathic and psychogenic taste disorder

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Abstract: Ethyl loflazepate (EL) is a benzodiazepine derivative that has been reported to activate the gustatory cortex. Our department routinely uses EL as a first-line treatment for idiopathic and psychogenic taste disorders, although little has been reported in the literature with respect to patient outcomes, so we conducted a retrospective study examining its safety and efficacy. Between 2008 and 2020, 49 patients (14 males and 35 females; mean age, 62.1 years) were diagnosed with taste disorders and received EL as their only treatment for >14 days. Severity of taste disorder was evaluated using the paper disc method by Sakai et al [7], and treatment efficacy was evaluated using the Visual Analogue Scale, wherein patients gave subjective ratings for their symptoms (reductions by >50% after administration of EL for 4 weeks were defined as improvements). Results showed that the improvement rates for patients with idiopathic and psychogenic taste disorders were 55% and 70%, respectively. Additionally, the majority (78%) improved within 2 weeks, and side effects were mild (seven cases of sleepiness and one case of dizziness). We conclude that EL is an appropriate first-line medication for patients with idiopathic and psychogenic taste disorders.

Keywords: ethyl loflazepate, idiopathic taste disorder, psychogenic taste disorder

1. Introduction

Ethyl loflazepate (EL) is a benzodiazepine derivative that is safe for elderly individuals and is well documented to treat anxiety and dental psychosomatic disorders [1–3]. Note worthily within the last two decades, research has also reported that this drug activates the gustatory cortex [4]. Our department systematically diagnoses and treats taste disorders [5], and we frequently employ EL as a first-line therapy when they are suspected of arising spontaneously or having a psychological origin. At present, few investigations have evaluated outcomes following the administration of EL in patients with idiopathic or psychogenic taste disorders [6], so we conducted a retrospective study examining its safety and efficacy among cases presented to our team.

2. Materials and Methods

2.1. Participants

Between January 2008 and January 2019, patients complaining of gustatory dysfunction were admitted to the Department of Oral Medicine at Hokkaido University Hospital Dental Center and treated with EL. In total, the safety of EL was assessed in 55 patients, although 6 dropped out early because of side effects. This rendered a final number of 49 patients [14 males and 35 females; age, 62.1 years (range, 29×84 years); and average duration of the disease, 25 months] for efficacy analysis, given that they received the drug for >2 weeks (Figure 1 and Table 1).

With regard to efficacy analysis, EL was a first-line therapy for 42 patients and a second-line therapy for 7 patients who were previously treated for oral candida with the antifungal drug Flored gel®, yet they experienced no improvements in taste. Upon examination, 22 and 27 patients were diagnosed as having an idiopathic or psychogenic taste disorder, respectively, per the criteria listed in Figure 1. Of note, the former has no established etiology (Table1), whereas the latter is considered to have a psychological basis according to various tests (e.g., CMI, SDS, and PHQ-9). Subjective symptoms of taste disorders were judged according to the definition shown in Table2 [5].

This study was conducted with the approval of the Hokkaido University Hospital Independent Clinical Research Review Committee (Approval No. 018-0381: Clinical study in patients with taste disorders.). All eligible patients gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki.

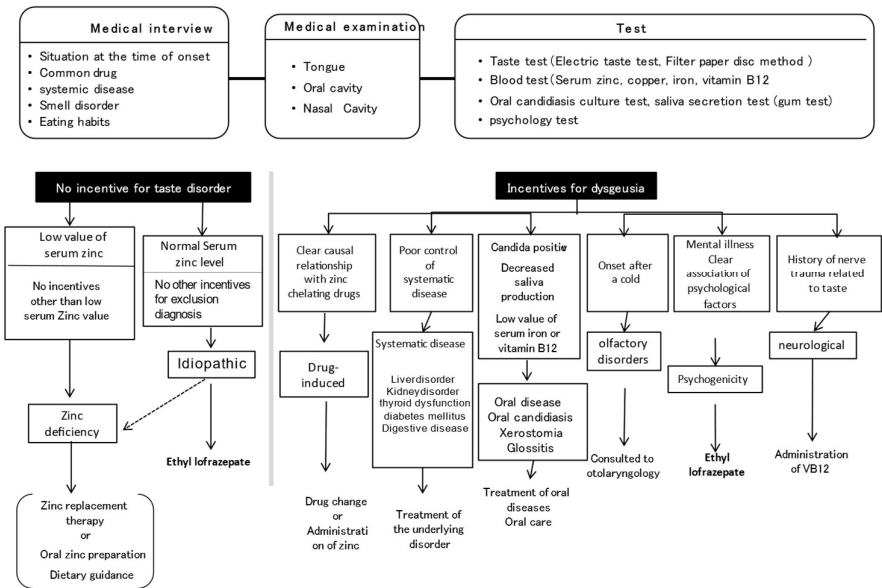


Figure1. Diagnosis and treatment of taste disorders

- **Zinc deficiency**: Serum zinc level is less than 70 $\mu\text{g} / \text{dl}$ and there are no other obvious causes.
- **Idiopathic**: There are no other obvious causes of taste disorder, excluding psychogenicity.
- **Oral disease**: Those with taste disorders closely related to oral diseases such as candidiasis, xerostomia, glossitis and tongue coating
- **Psychogenic**: Psychological factors clearly related to onset and progress of the symptoms.
- **Systematic disease**: Currently, the state of control of systemic disease is poor (Liver disorder, renal disorder, diabetes, gastrointestinal disorder).
- **Drug induced**: There is described in the side effects information, and it is clear causal relationship
- **Post common cold**: Aware of the taste disorders after the common cold
- **olfactory disorders**: Simultaneous disorder of taste disorder and olfactory disorder, and taste is normal, but it involves only olfaction disorder.
- **Latrogenic**: Those that developed after middle ear surgery or laryngeal microsurgery and palatine tonsil surgery

Table 1:Taste disorders are caused by several factors

Phantogeusia :It has a certain taste even though there is nothing in the mouth
Hypogeusia : The taste of food becomes lighter
Taste hypersensitivity : The taste of food becomes strong
Defferent taste : Feel the taste different from the original taste
Dissociable : You don't feel only a specific taste
Bad taste :It tastes bad no matter what you eat

Table 2 :Subjective symptoms of taste disorders

2.2. Clinical examination

Severity of taste disorder was evaluated using Taste Discs® (Sanwa Kagaku, Nagoya) and the method outlined by Sakai et al. [7]. Scores for perception of sweetness, saltiness, sourness, and bitterness in the tympanolar region that were <3.5, 3.5–4.5, 4.5–5.5, and >5.5 were recognized as normal taste function, mild taste disorder, moderate taste disorder, and severe taste disorder, respectively. Measurement of serum zinc levels was performed using an atomic fluorescence analyzer (AA240FS, Agilent, Santa Clara, CA, USA), with normal values ranging from 70 to 111 $\mu\text{g}/\text{dL}$ according to Harrison’s Principles of Internal Medicine [9].

2.3. Administration of EL

One tablet (1 mg) of EL was administered before going to bed at night. If a patient experienced daytime sleepiness or heart flutters, the dosage was reduced to 0.5 mg.

2.4.Evaluation of efficacy

Treatment efficacy of EL was evaluated using the Visual Analogue Scale (VAS) [10]. Patients who exhibited improvements after 4 weeks were defined as those with >50% decrease in subjective symptoms, and those regarded as unchanged had <50% decrease in subjective symptoms.

In two cases, no improvement in patients' conditions was detected after 2 weeks, so administration of EL was discontinued, and patients were given another agent for a duration of 2–4 weeks. Consequently, these individuals were only evaluated at the time when they decided to discontinue EL treatment.

2.5. Statistical analysis

Improvement rates according to age, gender, duration of the disease, subjective symptoms, cause of dysgeusia, period of EL administration, length of time to experience an effect from EL, serum zinc values, and severity of taste disorder were compared using Fisher's exact test, and $p < 0.05$ was considered significant. The type and incidence of adverse events were examined as a means to determine safety.

3. Results

Among the 55 patients assessed for treatment safety, 6 dropped out because of sleepiness and 1 dropped out because of urticaria. Shortly after discontinuing EL administration, these negative effects lessened or abated in the five cases (**Figure 2**).

Out of the 49 patients evaluated for treatment efficacy, phantogeusia was observed in 26 cases, hypogeusia in 10 cases, and complaints of different taste in 7 cases. In addition, 31 patients displayed an improvement in taste disorder (i.e., rate of 63%), 18 remained unchanged (i.e., rate of 37%), and no one experienced worsening of their condition. Moreover, no significant differences in improvement rates for the indices delineated above were observed (**Table 2**). Adverse events of drowsiness or dizziness were reported by seven patients and one patient, respectively, although all symptoms were minor, so administration of EL continued. For two patients, side effects from EL were slightly more intense, so the drug's dosage was reduced to 0.5 mg.

Across all patients who regained at least some taste function, they were able to cease treatment after maintaining a consistent dosage of EL over the course of 2–3 months.

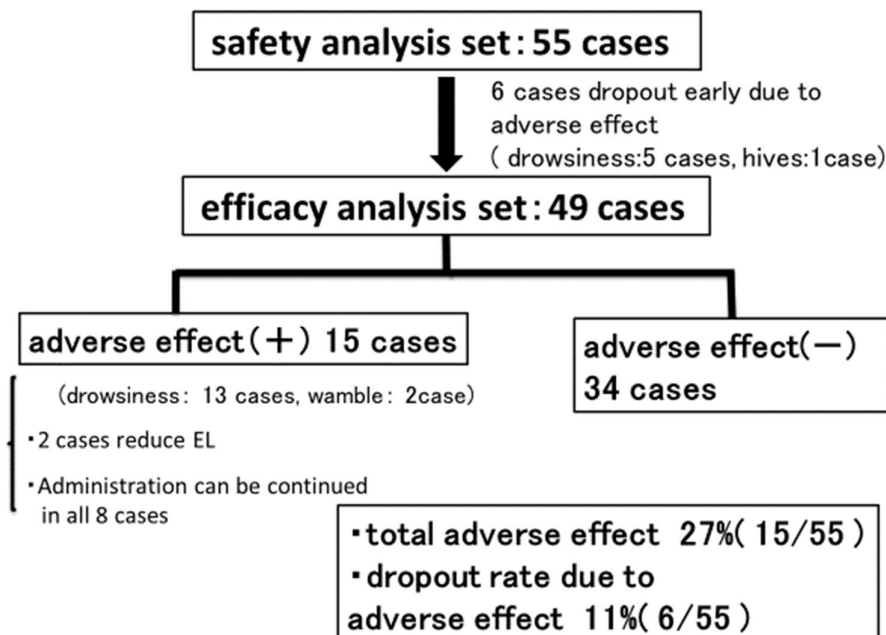


Figure2:Profile of this study

		Improve rate	
Age(median:65 years)	65 years of age or older Under 65	63% (17/27) 64% (14/22)	n.s.
Sex	Man Woman	71% (10/14) 60% (21/35)	n.s.
Desease period	Over 1 year Less than a year	58% (11/19) 67% (20/30)	n.s.
Subjective symptoms of taste	Self-motivated Hypogeusia Different taste	65% (17/26) 80% (8/10) 57% (4/7)	n.s.
Causes	Psychogenic Idiopathic	70% (19/27) 55% (12/22)	n.s.
Dosing time	First dose After administration of other drug	62% (26/42) 71% (5/7)	n.s.
Period until the effect appears ※19 effective cases out of 31 cases	~ 7 day 8~14 day 15~28 day	39% (12/31) 39% (12/31) 22% (7/31)	n.s.
Filter paper disc method	Normal Mild Moderate degree Severe	71% (12/17) 60% (6/10) 72% (8/11) 46% (5/11)	n.s.

Figure3:Results for effectiveness analysis

4. Discussion

Causes of taste disorders are multitudinous and can be attributed to the common cold, zinc deficiency, olfactory dysfunction, and systemic, oral, iatrogenic, idiopathic, and psychogenic diseases [8]. Treatment for the majority of these issues is well established, but effective options for managing the last two remain to be identified [5]. Within the realm of otolaryngology, zinc replacement therapy has traditionally been recommended for individuals with idiopathic and psychogenic dysgeusia [11–13], which is why our department has actively administered polaprezinc. Unfortunately, improvement rates have not exceeded 22%.

Against this background, one contemporary investigation by Takahashi et al[1]. reported that EL is successful at correcting or improving abnormal taste function emerging spontaneously, and another by Shimura et al[4]. found that EL specifically stimulates the gustatory cortex. Moreover, unlike benzodiazepine drugs and polabrezinc [16,17, 18, 19], EL is known to act in a short time (i.e., half-life is 122 h) and for ultra-long, prevents or treats anxiety, and appears to exert minimal side effects (e.g., memory loss and drowsiness) or to possess addictive qualities [14,15]. Thus, we believed that EL would be an ideal therapy for the cases presented to our hospital.

In this study, there was an overall improvement rate in taste disorders of 63%(31/49): 55%(12/22) for patients with idiopathic dysgeusia and 70%(19/27 for patients with psychogenic dysgeusia. In addition, 78%(12/31) of those for whom EL was effective experienced improvement within 2 weeks of administration. Surprisingly, no significant differences in improvement rates by age, gender, duration of the disease, subjective symptoms, cause of dysgeusia, period of EL administration, length of time to experience an effect from EL, serum zinc values, or severity of taste disorder were observed. Prior research, in particular, has demonstrated that upon treatment, the duration of a disease decreases significantly after ≥6 months and it takes a while for patients to experience improvements [11], yet for our cohort, there was no significant difference in improvement rates between patients with a course of >1 year vs. <1 year. This finding bears witness to the expediency of EL over other medications commonly employed in such instances.

Concerning lack of improvement or side effects, the incidence rate was 27%(15/49). Five patients chose to discontinue EL treatment in favor of different drugs because they experienced no alteration in their condition, and the rest predominantly had mild sleepiness. Written on the medical packaging for EL are the main side effects, including psychiatric disorders (e.g., drowsiness and reduced cognition and concentration) and central and peripheral nervous system disorders (e.g., stabilization and speech problems, and head sensations), and a minor side effect, that is, loss of taste. Importantly for the latter, the frequency of loss of taste is described as <0.1%, but we could not locate evidence of this phenomenon in the literature nor did anyone in our cohort complain of this. A mere amount of 1 mg of EL was administered to our patients because the drug's manufacturers state that the daily dosage for insomnia is 2 mg. Hence, this would likely induce strong sleepiness. Going forward, healthcare professionals should be diligent in informing their patients regarding the aforementioned side effects and monitoring them carefully after EL administration.

5. Conclusions

This study examined the safety and efficacy of EL in patients with idiopathic and psychogenic taste disorders between 2008 and 2020 and found that it resulted in an overall improvement rate of 63%(31/49). In particular, among the 24 patients for whom EL was effective, 78%(24/31) experienced improvements within 2 weeks and an improvement rate of 50% was observed when the disease had lasted a year or longer. In addition, adverse reactions occurred in 13 patients, with the most common being sleepiness. We conclude that EL monotherapy could be given as a first-line treatment for patients with idiopathic and psychogenic taste disorders.

6. Author Contributions: Ken-Ichiro,S. and Yutaka,Y. conceived of and designed the study. .Ken-Ichiro,S, Hiroyuki,Hato,Takashi Iori,Jun,Sato, Noritaka,Ohga and Haruhisa,Watanabe developed the theory, collected the data, and performed the computations.Hikaru,S and Ken-Ichiro,S verified the analytical methods. Yoshimasa,K encouraged Ken-Ichiro,S to investigate [a specific aspect] and supervised the findings of this work.

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