A Double-Blind Study on Clonazepam in Patients With Burning Mouth Syndrome

Siegfried M. Heckmann, MD; Elena Kirchner, MD; Miriam Grushka, MD; Manfred G. Wichmann, MD; Thomas Hummel, MD

Objectives/Hypothesis: In the treatment of burning mouth syndrome (BMS), various approaches have been tried with equivocal results. The aim of the present randomized clinical trial was to determine the efficacy of clonazepam, a GABA agonist designed as an antiepileptic drug that exerts the typical effects of benzodiazepines.

Study Design: Randomized clinical trial.

Methods: Twenty patients with idiopathic BMS were carefully selected. Clonazepam (0.5 mg/day, n = 10) or placebo (lactose, n = 10) were randomly assigned to the patients.

Results: Patients on clonazepam significantly improved in pain ratings (P < .001). These changes were less pronounced in the placebo group (P < .11). No significant changes were observed in a mood scale (P = .56) or for depression scores (P = .56). Taste test and salivary flow increased over sessions, but were not different between groups (P = .83 and P = .06, respectively).

Conclusions: Clonazepam appears to have a positive effect on pain in BMS patients.

Key Words: Pain, taste, glossodynia, treatment, irritation, hypogeusia.

Level of Evidence: 1b

INTRODUCTION

Burning mouth syndrome (BMS) is a complex disorder characterized by painful and burning sensations of the oral cavity, often including perioral structures such as the lips.1,2 According to a Cochrane survey study, idiopathic BMS is a veritable Crux medicorum.3 Treatment is problematic. In the few existing studies the following treatments were used: antidepressants, analgesic mouth rinse, alpha-lipoic acid, and hormone therapy. No specific therapy for BMS has yet been found.

Dysesthesia in BMS patients can be tremendously painful, leading some sufferers to consider suicide, especially as a cure is elusive. BMS is frequently found in women at peri- and postmenopausal ages.4 Numerous precipitating factors have been reported, including nutritional deficiencies, local oral infections, denture lesions, xerostomia, peripheral neuropathies, and psychogenic factors.5–10 Other symptoms may include bitter or metallic taste. The pains often ease during the daytime, is ameliorated by eating and drinking, and is exacerbated by speaking.

The syndrome is often underdiagnosed, and when diagnosed it is often poorly managed.11,12 The patient’s disorder is described either as BMS of unknown origin or idiopathic BMS. In idiopathic BMS, abnormal blood circulation of the oral mucosa following dry ice stimulation was detected and has been interpreted as an abnormal neuromicrovascular regulation indicating neuropathological involvement at the level of cranial nerves.13

Treatment of BMS is very difficult and protracted, as no therapy has been proven to be substantially effective in treating this syndrome.14 The treatment plans studied include attempts at using gabapentin, which also proved to have no substantial effect.15 Clonazepam has been cited as effective in approximately 70% of BMS patients.16 Clonazepam is a GABA agonist and was designed as an antiepileptic drug. In addition, clonazepam exerts the typical effects of benzodiazepines. Despite the spectacular success rate, the therapeutic effectiveness of clonazepam has not yet been tried in an appropriate study. The aim of this clinical trial was to investigate the effect of clonazepam in a double-blinded, randomized, controlled study in BMS patients.

MATERIALS AND METHODS

Investigations were performed according to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects. Before commencement of the study, the protocol was approved by the ethics committee of the University of Erlangen Medical School. Twenty-three patients suffering from BMS were referred to the oral pain clinic of Erlangen University Dental
School. The patients were informed about the opportunity to take part in this therapy study. Inclusion was restricted to idiopathic cases. To reduce possible risks from the intake of clonazepam, the following exclusion criteria applied: general diseases such as diabetes mellitus, hepatitis, jaundice, inflammation and malfunction of the liver; human immunodeficiency virus infection; vitamin B-12 deficiency; asthma; narrow angle glaucoma; sleep apnea syndrome; reduction of the general state of health; present candida infection of the oral mucosa; allergies toward dental materials or dentures or drugs used in the present study (benzodiazepines); severe diseases of the central nervous system including epilepsy, Parkinson's disease, dementia; psychiatric diseases including anorexia/bulimia, risk of suicide, depressions, myasthenia gravis; radiation therapy; pregnancy and lactation; and alcoholism.

During the second session, the patients received a physical examination of their oral cavity including a test for possible pathological infections with candida. Blood parameters were screened for liver function, electrolytes, iron, kidney function, and immunological parameters. The Beck Depression Inventory (BDI), consisting of 21 questions, was used to screen for major changes in terms of depression. In addition, to investigate subtle changes in the patients’ mood the Zerssen Mood Scale was used. This scale uses 28 questions regarding the patients' mood, which are answered by selecting one of two opposite mood descriptors or neither of them. Positive characteristics are valued at zero points, whereas negative characteristics add two points and an answer of undecided adds one point. A sum of 27 points or higher resulted in exclusion from the study. The Mini-Mental State Examination scale, with a maximum cutoff of 30 points, served to detect dementia.

As a consequence of this initial examination, three patients could not participate in the study: one patient due to candida infection, one patient who did not reach 24 points on the Mini-Mental State Examination scale, and one patient suffering from diabetes.

Two weeks before the start of the medication several investigative parameters were applied. They were repeated after completion of medication at session 5, and 2 weeks later at session 6 (Fig. 1). Both the BDI and Zerssen Mood Scale were performed at these stages to investigate the possible influence of the medication on the psychological status of the patients.

**Parameters of Oral Investigation**

**Taste test.** For quantitative assessment of gustatory function, a standardized validated test based on filter papers impregnated with tastants was used. Strips with the basic tastes sweet, sour, salty, and bitter (in four concentrations each) were applied onto the extended tongue, which was then taken back into the closed mouth. Before application of each taste strip, patients rinsed their mouths with water. Following presentation of the strip, patients were asked to identify the taste from a list of four descriptors (sweet, sour, salty, and bitter). The sum of correct identifications was used for further statistical analysis.

**Smell test.** The odor identification part of the Sniffin'-Sticks test battery were used to screen for changes in olfactory function. Following presentation of a common odor, subjects were each asked to identify it from a list of descriptors. The sum of correct identifications was used for further analysis.

**Salivary flow rate.** The salivary flow rate was measured using a cotton swab. It was weighed and placed onto the patient’s tongue for 1 minute. After that, the cotton swab was weighed again and the resulting difference was used to calculate salivary flow rate.

**Pain ratings.** Patients rated the sensation of burning pain in the mouth on a scale ranging between 0 and 10, with 0 indicating no pain and 10 indicating maximum possible pain.

**Blinding and Randomization**

After initial examination, blinding and randomization were performed by an independent individual using a specialized software program (RANDLIST; DatInf, Tübingen, Germany). To this end, enrollment numbers were established, and the subjects to be investigated were randomized in such a way as to form five groups made up of four participants each (i.e., two were assigned clonazepam and two were assigned a placebo). One group was made up of four male and one of three male subjects and one female subject. The other groups consisted of four female participants each.

**Treatment**

Screw-top bottles were prepared containing either 63 capsules Rivotril (0.5 mg clonazepam) or 63 placebo capsules.
(lactose monohydrate). The bottles were sealed and labeled with the study code and the enrollment number. A low dose of clonazepam (0.5 mg/day\textsuperscript{16}) and placebo were given to the patients, whereby 10 subjects received clonazepam (five men and five women; mean age, 67.5 years; range, 49–89 years) and 10 subjects received placebo (two men and eight women; mean age, 65.4 years; range, 49–78 years). Patients were advised to take the drug as a whole on an empty stomach with approximately 200 mL of water. The subjects took one capsule containing 0.5 mg of clonazepam or placebo (lactose monohydrate). The bottles were sealed and labeled with the medication.23 This is supported by the present results with clonazepam compared to placebo (\textit{F} [4,72] = 3.11; \textit{P} = .011) (Table II).

The taste test score increased in both groups over time (\textit{F} [2,36] = 4.18; \textit{P} = .023); however, there was no difference in increase between the two groups (\textit{F} [2,36] = 0.19; \textit{P} = .83). Similar findings were made for salivary flow, which increased over sessions (\textit{F} [4,72] = 2.79; \textit{P} = .033) but was not different between groups (\textit{F} [4,72] = 2.40; \textit{P} = .06). Importantly, pain ratings changed significantly over sessions (\textit{F} [4,72] = 16.8; \textit{P} < .001); these changes were much more pronounced in patients receiving clonazepam compared to placebo (\textit{F} [4,72] = 3.11; \textit{P} = .011) (Table II).

DISCUSSION

The results of our study indicate that clonazepam is effective in the treatment of pain in patients with BMS. At the same time, clonazepam was well tolerated by all subjects. The medication had no significant effect on either Zerssen or BDI scores, indicating that clonazepam produced no major change in psychological states (Table II). clonazepam appeared to be dose related; instead, both were observed at the lower dose range.\textsuperscript{23} The role of taste in burning mouth syndrome is not straightforward, although recent studies demonstrate a decrease of taste function.\textsuperscript{16} This is supported by the present results with a slight (but nonsignificant) improvement of taste and smell function following treatment.

The effect of clonazepam may be explained through its agonistic action at the inhibitory GABA-A receptor, which is also found in taste pathways. If BMS results because taste damage produces a loss of the inhibition normally exerted on central structures mediating oral pain, then a GABA agonist might be expected to counter that loss of inhibition and thus relieve the oral pain phantom.\textsuperscript{24}

Apart from this, benzodiazepines are GABA-receptor agonists that bind to both peripheral and central receptor sites, promote brain stem serotonergic descending pain inhibition,\textsuperscript{25} and suppress the spontaneous central neuronal hyperactivity that occurs after deafferentation.\textsuperscript{26} Clonazepam is currently used as an anticonvulsant and differs from other benzodiazepines in that it possibly binds more to central than to peripheral benzodiazepine receptor sites, and it has a strong effect on the brain's serotonergic system. It also has a longer half-life than many of the other benzodiazepines, which may result in fewer withdrawal effects upon discontinuation of the medication.\textsuperscript{23}

### RESULTS

At the baseline session, the subjects receiving placebo (n = 10) or clonazepam (n = 10) were not significantly different in terms of age (\textit{t} = 0.44, \textit{P} = .67), gender distribution (\textit{y}^2 = 1.98, \textit{P} = .18), duration of disease (\textit{t} = 0.82, \textit{P} = .42), scores in olfactory (\textit{t} = 0.50, \textit{P} = .63) or gustatory tests (\textit{t} = 0.87, \textit{P} = .40), scores in the BDI (\textit{t} = 0.23, \textit{P} = .82) or the Zerssen Mood Scale (\textit{t} = 1.09, \textit{P} = .29), and ratings of oral pain (\textit{t} = 1.37, \textit{P} = .19) or salivary flow (\textit{t} = 1.33, \textit{P} = .20) (Table II).

The taste test score increased in both groups over time (\textit{F} [2,36] = 4.18; \textit{P} = .023); however, there was no difference in increase between the two groups (\textit{F} [2,36] = 0.19; \textit{P} = .83). Similar findings were made for salivary flow, which increased over sessions (\textit{F} [4,72] = 2.79; \textit{P} = .033) but was not different between groups (\textit{F} [4,72] = 2.40; \textit{P} = .06). Importantly, pain ratings changed significantly over sessions (\textit{F} [4,72] = 16.8; \textit{P} < .001); these changes were much more pronounced in patients receiving clonazepam compared to placebo (\textit{F} [4,72] = 3.11; \textit{P} = .011) (Table II).

#### TABLE I. Descriptive Statistics at Baseline Separately for Patients Receiving Placebo (n = 10) or Clonazepam (n = 10).

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>Placebo 62.9</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>Clonazepam 65.0</td>
<td>12.4</td>
</tr>
<tr>
<td>Duration of disease, yr</td>
<td>Placebo 3.6</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Clonazepam 2.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Zerssen Mood Scale, U</td>
<td>Placebo 7.2</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Clonazepam 8.6</td>
<td>2.5</td>
</tr>
<tr>
<td>BDI, U</td>
<td>Placebo 0.6</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Clonazepam 0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Pain ratings, U</td>
<td>Placebo 6.0</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Clonazepam 7.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Salivary flow, mL/min</td>
<td>Placebo 3.0</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Clonazepam 2.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Taste test score, correct items</td>
<td>Placebo 11.7</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>Clonazepam 10.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Odor test score, correct items</td>
<td>Placebo 12.5</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Clonazepam 13.2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

The groups did not differ significantly for the conditions/scores listed. BDI = Beck Depression Inventory.

Apart from this, benzodiazepines are GABA-receptor agonists that bind to both peripheral and central receptor sites, promote brain stem serotonergic descending pain inhibition,\textsuperscript{25} and suppress the spontaneous central neuronal hyperactivity that occurs after deafferentation.\textsuperscript{26} Clonazepam is currently used as an anticonvulsant and differs from other benzodiazepines in that it possibly binds more to central than to peripheral benzodiazepine receptor sites, and it has a strong effect on the brain's serotonergic system. It also has a longer half-life than many of the other benzodiazepines, which may result in fewer withdrawal effects upon discontinuation of the medication.\textsuperscript{23}
Clonazepam has been reported to be most effective in low doses in younger individuals and in patients who have had fewer years of burning sensations. When higher doses are required to reduce burning pain, they appear to be associated with problematic side effects, leading to discontinuation of medication usage. In contrast, higher doses of up to 4 mg have also been used with a positive treatment outcome.

It has to be mentioned that the current results do not justify the long-term use of benzodiazepines for the treatment of this disorder. In fact, nothing is known about whether there were any long-term benefits to these patients beyond week 9 of the present study. It also has to be mentioned that long-term use of benzodiazepines is especially problematic in an elderly population, which has been investigated in this study.

CONCLUSION

Clonazepam has a positive effect on pain in patients with burning mouth syndrome and does not cause major side effects that would severely restrict its application. Studies are currently planned to verify the options of long-term treatment to achieve a high degree of sustainability.

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