

A study of the effects of saliva stimulation by nizatidine on dry mouth symptoms of primary biliary cirrhosis

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Received: June 29, 2012 Revised: August 15, 2012

Accepted: November 14, 2012

Published online: March 27, 2013

Abstract

AIM: To elucidate the effect of saliva stimulation by nizatidine on oral symptoms of primary biliary cirrhosis (PBC) by administering it to PBC cases.

METHODS: From among 73 cases that had been definitively diagnosed as PBC at our hospital by February 2010, we selected 27 cases of PBC, 4 males and 23 females, as subjects. We obtained subjects' consent after giving them a full explanation of the administration of nizatidine. Nizatidine 150 mg was administered internally twice daily, after morning and evening meals. To observe changes in the quantity of saliva secreted, chewing gum tests were carried out four times: before the initial dose, and after 6 mo, 12 mo and 24 mo of administration. For subjective dry mouth symptoms, a visual analog scale (VAS) method was used to assess their feelings of oral dryness and eating difficulty, five times: before the initial dose, and after 1, 6, 12 and 24 mo of administration in 8 cases. The nutritional condition and the hepatic functional reserve were compared between before and after the nizatidine treatment.

RESULTS: The result of a chewing gum test on the subjects before the administration of nizatidine showed that 50% produced less than 10 mL of saliva, *i.e.*, the standard under which cases are considered to have hyposalivation. The results of these tests showed that the quantity of saliva secreted was 10.5 ± 6.8 mL before administration of nizatidine, 10.9 ± 6.0 mL after 6 mo, 10.6 ± 4.9 mL after 12 mo, and 11.8 ± 6.8 mL after 24 mo administration. Thus, there was a slowly increasing trend in the quantity of saliva in the whole group. The percentage of subjects with saliva production above 10 mL was 45.8% after 6 mo administration of nizatidine, that is, only a slight change from before its administration, but it was 64.3% after 12 mo, that is, a significant increase. The saliva secretion by subject patients was examined before the beginning of administration of nizatidine, 12 mo later, and 24 mo later, and Fisher's combined probability test was used to examine the results for increases in saliva secretion. The analysis yielded *P* values of 0.51 and 0.53 for 12 mo later and 24 mo later, respectively. Thus, although there was no statistically significant increase, it was confirmed that saliva secretion tended to increase. A VAS method was employed to study the intensities of subjective symptoms of oral dryness and eating difficulty. Almost every case indicated some improvement of subjective oral dryness on the VAS early in the administration, *i.e.*, one month after. We also studied the effects of the administration of nizatidine on nutritional condition, hepatic functional reserve, and long-term prognosis of PBC. No significant improvements in cholinesterase (ChE) level, albumin (Alb) level, or Child-Pugh score were found during the period of observation from the beginning to the end of administration of nizatidine, nor in comparison with the non-administration group. A comparative analysis between before administration and 24 mo later yielded *P* values of 0.41 for Alb, 0.56 for ChE, and 0.59 for the Child-Pugh scores.

CONCLUSION: It was confirmed that administering

nizatidine to cases of PBC with dry mouth increased the secretion of saliva and improved the symptoms.

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Key words: Primary biliary cirrhosis; Nizatidine; Dry mouth; Sicca syndrome; Visual analog scale

Kikuchi T, Hirano K, Genda T, Tszura H, Sato S, Kanemitsu Y, Narita Y, Iijima K, Ichida T. A study of the effects of saliva stimulation by nizatidine on dry mouth symptoms of primary biliary cirrhosis. *World J Hepatol* 2013; 5(3): 90-96 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v5/i3/90.htm> DOI: <http://dx.doi.org/10.4254/wjh.v5.i3.90>

INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic progressive cholestatic hepatic disease, in the onset of which an auto-immune mechanism is involved. This disease is characterized serologically by anti-mitochondrial antibody positivity and high serum immunoglobulin M values, histologically by chronic non-suppurative destructive cholangitis of the hepatic lobules, and the presence of florid duct lesions that involve severe inflammation and biliary epithelial inflammation^[1,2]. The condition develops gradually from the asymptomatic phase when no subjective symptoms are observed into the symptomatic phase when itching, jaundice, and other symptoms appear. A group of cases with poor prognosis may finally develop from cirrhosis to hepatic failure to death. There are no radical cures for this disease other than liver transplantation. Thus, it is one of a group of intractable liver diseases for which there are no established treatments^[3].

PBC shows a high rate of complication by Hashimoto's disease or collagen diseases, such as Sjogren syndrome^[4,5]. Sjogren syndrome includes dry mouth and dry eyes; dry mouth and/or dry eye symptoms of PBC are called sicca syndrome, and are found in approximately 70%, of patients with PBC^[6-8]. However, only 20% to 30% of PBC cases with these symptoms meet the diagnostic criteria for Sjogren syndrome^[9] and many such patients are not well treated for these symptoms.

It has been reported that nizatidine, an H2 blocker, has a saliva stimulation effect, in addition to its effects of accelerating gastric juice release and increasing the pressure of the lower esophageal sphincter which suppress the onset of gastroesophageal reflux disease^[10].

We report here a study of whether administering nizatidine, which has a saliva stimulation effect, improves dry mouth as a subjective symptom of PBC.

MATERIALS AND METHODS

From among 73 cases that had been definitively diagnosed as PBC at our hospital by February 2010, we selected 27 cases of PBC as subjects, including 4 males and 23 females, giving them a full explanation of the administration

of nizatidine and thereafter obtaining their consent. Nizatidine 150 mg was administered internally twice daily, after morning and evening meals. In order to observe changes in the quantity of saliva secreted, chewing gum tests were carried out four times: before the initial dose, and after 6, 12 and 24 mo of administration. For subjective dry mouth symptoms, a visual analog scale (VAS) method was administered five times to assess patients' feelings of oral dryness and eating difficulty: before the initial dose, and after 1, 6, 12 and 24 mo of administration in 8 cases. The VAS scale ranged from 0 to 10 (0: no subjective symptoms; 1-3: mild; 4-6: moderate; 7-9: severe; 10: very severe).

In addition, nutritional condition and hepatic functional reserve of patients were checked in terms of albumin (Alb) levels, cholinesterase (ChE) levels, as well as Child-Pugh scores before and after the nizatidine treatment. Data were compared between the nizatidine administration group and the nizatidine non-administration group.

Statistical analysis

The obtained data were statistically analyzed using SPSS v.17 to perform Willcoxon signed-rank tests or paired *t* tests with a level of significance of $P < 0.05$.

RESULTS

The average age of the subjects was 66.7, and the female subjects accounted for 85% of the subject group. The aspartate aminotransaminase level was 63.7 IU/L and the alanine aminotransaminase (ALT) level was 69.2 IU/L, indicating that liver function was mildly impaired. In comparison, the alkaline phosphatase level was 679.1 IU/L and the γ -glutamyl transpeptidase level was 242 IU/L, thus indicating high biliary enzyme values. In the phase before administering nizatidine, any significance differences, in addition to ALT value, were identified between the administered and non-administered group (ALT: $P = 0.04$). The 12 cases on which liver biopsies were performed were histologically classified according to Scheuer's classification as 11 cases in stage 1 and 1 case in stage 2, with no case in which there was a high level of fibrosis. The M-2 antibody-positive rate was 67%. In 14 cases, 54% of the subjects, collagen disease complications were found, such as Sjogren syndrome, chronic thyroiditis, and/or rheumatoid arthritis (Table 1).

The changes in the quantity of saliva secreted that were observed in the chewing gum tests were 10.5 ± 6.8 mL (2.2-30 mL) before the start of administration of nizatidine, 10.9 ± 6.0 mL after 6 mo, 10.6 ± 4.9 mL after 12 mo, and 11.8 ± 6.8 mL after 24 mo of administration. Thus, they showed a slowly increasing trend (Figure 1A). In order to further analyze the changes in the quantity of saliva secreted, we divided the subject group into one sub-group with less than 10 mL before the start of administration of nizatidine and another with 10 mL or more before administration of the drug. The sub-group with initial secretion of large quantities of saliva, of 10 mL or more, did not show a significant increase after 6 mo of administration. On the other hand, the sub-group

Table 1 Characteristics of the patients at baseline

	All PBC cases	Cases with nizatidine	Cases without nizatidine	P value
No. of cases	73	27	46	
Age (mean \pm SD)	65.6 \pm 12.2	68.2 \pm 11.8	64.1 \pm 12.3	0.32
Sex (male/female)	9 (18%)/64 (88%)	4(%) /23(85%)	5 (18%)/41 (88%)	0.72
Histological classifications	24/8/3/2	11/1/0/0	13/7/3/2	0.12
Scheuer (1/2/3/4)	65%/22%/8%/5%	92%/8%/0%/0%	52%/26%/12%/8%	
Alb (g/dL)	4.0 \pm 0.3	4.1 \pm 0.3	4.0 \pm 0.4	0.50
ChE (IU/L)	288.3 \pm 66.4	302.2 \pm 68.5	277.9 \pm 64.0	0.24
AST (IU/L)	55.6 \pm 47.3	64.6 \pm 44.5	50.3 \pm 48.5	0.10
ALT (IU/L)	58.2 \pm 64.6	75.7 \pm 67.0	48.0 \pm 61.5	0.04
γ GTP (IU/L)	183.8 \pm 205.6	221.0 \pm 254.7	162.0 \pm 169.8	0.10
ALP (IU/L)	638.7 \pm 446.8	661.0 \pm 616.3	625.7 \pm 315.5	0.12
T-Bil (mg/dL)	0.69 \pm 0.37	0.71 \pm 0.33	0.67 \pm 0.39	0.33
Plt ($\times 10^3/\mu$ L)	21.7 \pm 8.8	23.2 \pm 10.9	20.7 \pm 7.3	0.74
M2 antibody (< 5/5)	17 (23%)/56 (77%)	9 (33%)/18 (67%)	8 (17%)/38 (83%)	0.15
ANA (< 40/40)	23 (32%)/50 (68%)	7 (26%)/20 (74%)	16 (35%)/30 (65%)	0.60
Collagen disease complication (presence/absence)	45 (62%)/28 (38%)	13 (48%)/14 (52%)	32 (70%)/14 (30%)	0.08

PBC: Primary biliary cirrhosis; Alb: Albumin; ChE: Cholinesterase; AST: Aspartate aminotransaminase; ALT: Alanine aminotransaminase; γ GTP: γ -glutamyltranspeptidase; ALP: Alkaline phosphatase; T-Bil: Total bilirubin; Plt: Platelet; ANA: Anti-nuclear antibody.

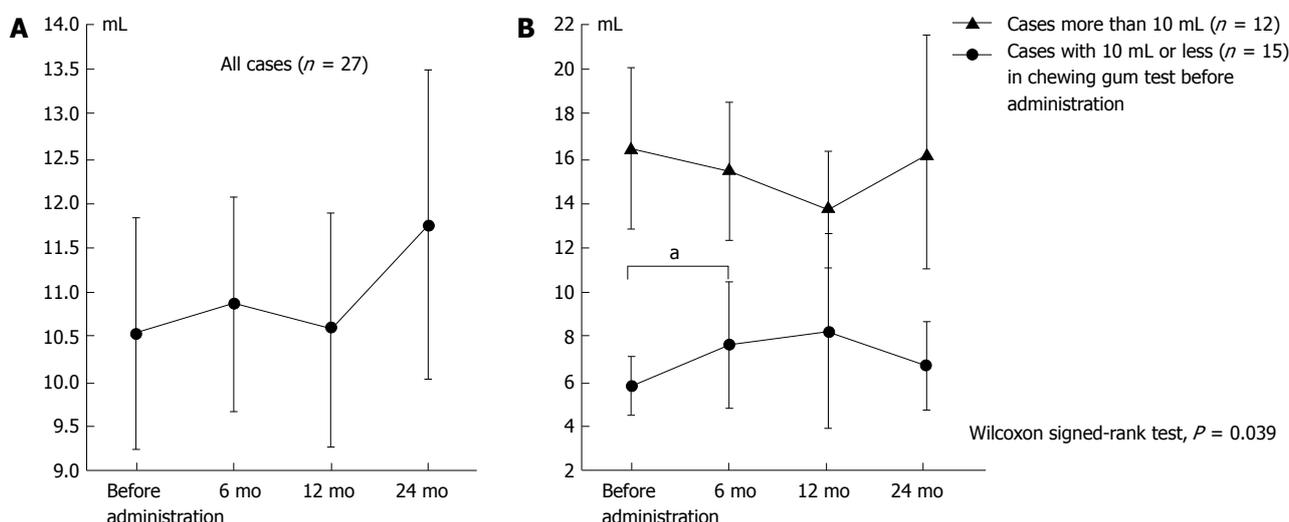


Figure 1 Course of saliva secretion before and after the administration of nizatidine in all cases (A) and in cases with 10 mL or less of saliva in chewing gum test before administration (B). ^a $P < 0.05$.

with initial secretion of small quantities of saliva, less than 10 mL, showed a statistically significant increase after six months of administration, with $P = 0.039$ in the Wilcoxon signed-rank test (Figure 1B). The percentage of all subject patients with saliva secretion of 10 mL or more was 48.1%, before the start of administration, and 45.8% after 6 mo of administration, thus indicating no large changes. However, this increased significantly to 64.2% after 12 mo of administration. The saliva secretion by patients was examined before the beginning of administration of nizatidine, 12 mo later, and 24 mo later, and Fisher's combined probability test was used to examine the results for increases in saliva secretion. The analysis yielded P values of 0.51 and 0.53 for 12 mo later and 24 mo later, respectively. Thus, although there was no statistically significant increase, it was confirmed that saliva secretion tended to increase (Figure 2).

A VAS method was employed to check the patients in terms of their subjective feelings of oral dryness and eating difficulty. In almost every case, feelings of oral dryness improved according of the VAS evaluation after 1 mo of administration of nizatidine (Figure 3A). In general, this showed a continuing modest increase after 12 and 24 mo of administration although, in some cases, it was seen to fall back to the level before the start of administration. Feelings of eating difficulty were also improved after one month of administration in some cases, according to the VAS evaluation. However, this parameter improved less and in a smaller number of cases than feelings of oral dryness. In addition, while the symptoms continued to improve in the long-term in some cases, no improvements were observed at all in other cases. Indeed, in some cases, even long-term administration of nizatidine not only failed to produce a significant positive

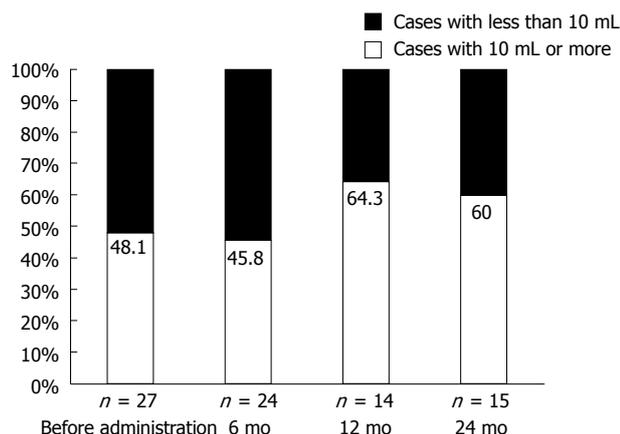


Figure 2 The percentage of all t patients with saliva secretion of 10 mL or more before and after the administration of nizatidine.

effect, but the symptoms actually worsened, back to the levels before the start of administration (Figure 3B). The VAS evaluation results showed that, over time, while both feelings of oral dryness and of eating difficulty improved with the administration of nizatidine by a statistically significant difference, feelings of oral dryness improved by a more significant amount.

The ChE and Alb values were compared between before and after the administration of nizatidine. ChE before administration was 302.2 IU/L, 297.5 IU/L after 1 mo of administration, 300.5 IU/L after 6 mo of administration, 304.0 IU/L after 12 mo of administration, and 314.0 IU/L after 24 mo of administration. No significant improvements in either ChE or Alb were found over the period of observation. A comparative analysis between values before administration and 24 mo later yielded *P* values of 0.41 for Alb, 0.56 for ChE, and 0.59 for the Child-Pugh scores. Thus, no significant improvements were found. These values were also compared between the nizatidine administration group and the nizatidine non-administration group of patients with PBC, yielding *P* values of 0.67 for Alb and 0.73 for ChE. Thus, no statistically significant differences were found (Table 2).

Furthermore, in order to study the effect of nizatidine on hepatic functional reserve, changes in Child-Pugh scores were checked and analyzed. Before the start of administration of nizatidine, one case in the subject group showed a Child-Pugh score of 6 points in class A, one case 7 points in class B, and the remaining 25 cases 5 points in class A. After an average of 58.5 mo (15-100 mo) of observation, the equivalent results were: one case with 7 points in class B; one case that developed into symptomatic PBC progressing to liver failure to death during the observation period; and the remaining 25 cases with 5 points in class A. In the 46 cases of PBC in the nizatidine non-administration group, 42 were checked in terms of Child-Pugh scores when their illness was diagnosed as PBC: 41 of them showed 5 points in class A, and one showed 6 points in class A. The Child-Pugh scores after an average of 46.3 mo (10-98 mo) of observation of this group were: one case with 6 points in class A; one

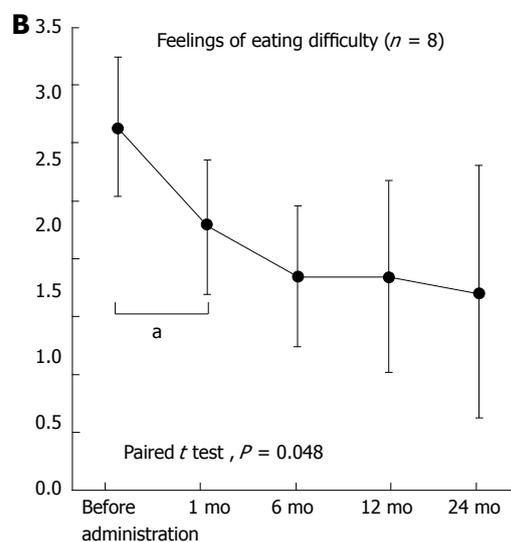
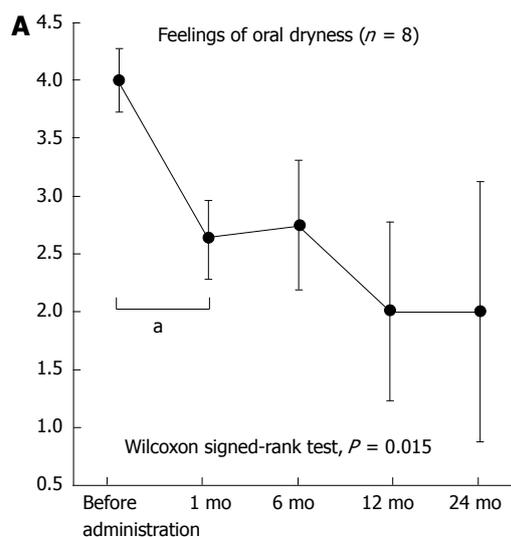


Figure 3 Visual analog scale method employed to check the subjects in terms of their feelings of oral dryness (A), and eating difficulty (B). ^a*P* < 0.05.

case of death; and the remaining 40 cases with 5 points in class A. A comparative analysis between the nizatidine administration group and the nizatidine non-administration group indicated no significant differences (Table 2).

DISCUSSION

Dry mouth and dry eye symptoms are frequently found in cases of PBC. It is assumed that these common symptoms are associated with a high rate of autoimmune disease complications with PBC. The likelihood that PBC has at least one autoimmune disease complication is 84%, and is 41% for the presence of at least two complications^[11-13]. Sjogren syndrome, rheumatoid arthritis, and scleroderma are the most frequent complications of PBC, with cross-sectional study on more than 5000 Japanese cases of PBC indicating that they were found in 13.5%, 7.3% and 2.0% of PBC cases, respectively^[14-16]. Another report showed and an even higher frequency of Sjogren syndrome as a complication of PBC, at 26% to 72%^[15,17-19]. PBC is char-

Table 2 The effects of the administration of nizatidine on the nutritional condition, the hepatic functional reserve, and the long-term prognosis of primary biliary cirrhosis

	Nizatidine administration group (<i>n</i> = 27)			Nizatidine non-administration group (<i>n</i> = 46)		
	Before administration	24 mo	<i>P</i> value	Before treatment	24 mo	<i>P</i> value
Alb	4.1 ± 0.3	4.2 ± 0.3	0.41	4.0 ± 0.4	4.1 ± 0.3	0.67
ChE	302.2 ± 68.5	314.0 ± 62.3	0.56	277.9 ± 64.0	286.5 ± 71.1	0.73
Child-Pugh score	5.1 ± 0.4	5.1 ± 0.4	0.59	5.0 ± 0.2	5.0 ± 0.2	0.99

Alb: Albumin; ChE: Cholinesterase.

acterized by high rates of complications of other autoimmune diseases and by slow progression of the disease in many cases^[20,21]. In many cases of PBC, patients are in the asymptomatic phase, without subjective symptoms, even after onset, and complications in these cases are found only during detailed examinations after a definitive diagnosis of PBC is made, or after patients enter the symptomatic phase. The way in which PBC develops has yet to be well elucidated. Some reports indicate that PBC is associated with medical history of the patient and their family as well as their lifestyle. Various environmental factors such as infections including urinary tract infection as well as cigarette smoking, and a history of administration of estrogen, can cause immune tolerance failures, which lead to the onset of PBC^[22-25]. It is well conceivable that immune tolerance failures due to such environmental factors may lead to the onset of not only PBC but also other autoimmune diseases. In this study, Sjogren syndrome was found as a complication in 25% of the cases, rheumatoid arthritis in 14.8%, and CREST syndrome in 7.4%. Thus, the frequency of Sjogren syndrome as a complication appeared to be relatively low. This may be partially because this study was based on chewing gum tests, which could not detect cases with dry eye symptoms but without oral symptoms, and partially because a definitive diagnosis of the syndrome might not have been made in some cases. In many cases, salivary secretion disorder due to secondary Sjogren syndrome as a PBC complication is milder than primary Sjogren syndrome as a clinical symptom, and there were many asymptomatic PBC cases in the subject group with a mild complaint of dryness. Another report indicated that hepatic dysfunctions were found in 38.2% of cases of collagen diseases, and that 15.9% of cases with such disorders were found to have PBC on diagnosis^[26]. It is therefore necessary for various medical departments to cooperate closely to detect such complications of PBC early and exactly, in order to begin the most appropriate treatment.

Saliva has an essential role in functions such as cleaning the oral cavity, inhibiting the proliferation of bacteria and fungi in the mouth, protecting oral mucosa, and helping swallow food^[27]. In PCB patients aged 60 or more, an age group with a predilection for PBC, subjective symptoms of oral dryness are found in 60%-70% of cases, and more than 20% of these cases have oral candidiasis, which is likely to damage their quality of life^[28]. Sicca syndrome with PBC has been treated with immunomodulators, with-

out substantial clinical effects. Our study demonstrated that administering nizatidine to cases of PBC with subjective symptoms of oral dryness and eating difficulty increased the quantity of saliva secreted, leading to improvements in the subjective symptoms.

Actions of both sympathetic and parasympathetic nerves are involved in the secretion of saliva^[29,30]. Nizatidine simulates parasympathetic cholinergic nerves, to accelerate the gastrointestinal motility by inhibiting acetylcholine esterase. In addition, it increases the quantity of acetylcholine secreted by inhibiting acetylcholine esterase at the endings of cholinergic nerves, stimulating muscarinic receptors in the salivary glands to increase saliva secretion^[30-32]. Other H2-receptor antagonists such as ranitidine and cimetidine cause increases in acetylcholine concentration at cholinergic nerve endings, but do not increase saliva secretion as a result. Cevimeline, an anticholinergic agent, was found to be effective for dry mouth symptoms in Sjogren syndrome but produced side effects and its administration is now limited^[10,33-35]. In view of the foregoing, other H2-receptor antagonists are not expected to produce similar effects to those of nizatidine. In this study, nizatidine exhibited a stronger effect in accelerating saliva secretion in cases where saliva secretion in the chewing gum test was under 10 mL before the start of internal administration. The subjects were an average of 66.7 years old, and older people generally have reduced salivary gland secretion and more frequent occurrence of dry mouth symptom. However, the internal administration of nizatidine was thought to stimulate muscarinic receptors in the salivary glands and revitalize salivary gland cells, leading to increased saliva secretion.

Measured with the VAS method, both feelings of oral dryness and feelings of eating difficulty improved after only one month of internal administration of nizatidine. This may have been partially because the patients were sensitive to changes in the oral cavity and easily sensed such changes. The VAS results for both symptoms improved in almost every case after one month of administration, although in some cases they returned after 6 to 12 mo of admto where they were before the start of administration inistration. It is assumed that the cases involving worsening of symptoms may initially have felt subjective improvements in the symptoms because of psychological factors in addition to increased saliva secretion, but grew accustomed to the ongoing symptoms

over time. Another possibility is that nizatidine's salivary gland stimulation effect on the salivary secretion ability of older patients where salivary secretion had previously become poor may be only transient, finally resulting in the reduction in saliva secretion and the worsening of symptoms in some cases.

In this study, the H₂-receptor antagonism of nizatidine stimulated appetite and increased saliva secretion, making the oral mucosa moister thus making it easier to masticate food. We studied how these effects of nizatidine improved the intake of food, and the effect on nutritional condition, hepatic functional reserve, and the long-term prognosis of PBC. The ChE and Alb values did not significantly improve after the administration of nizatidine, and the values in the nizatidine administration group, before or after administration, were not significantly different from the nizatidine non-administration group. The increased saliva secretion and improved dry mouth symptoms did not directly lead to improvements in nutritional condition in this short observation period. We also studied whether increased saliva secretion affects hepatic functional reserve by checking the Child-Pugh scores before and after the administration of nizatidine. The results showed no significant improvements in hepatic functions between before and after administration of the drug. Furthermore, no significant differences in hepatic functions were found between the nizatidine administration group and the nizatidine non-administration group. These results are partially because the cases of PBC in the control group were all in the asymptomatic phase, and partially because the general prognosis of PBC is relative good. PBC has a 5-year survival rate of 91% for men and 92% for women, and a ten-year survival rate of 81% for men and 85% for women, while the disease itself has an extremely long asymptomatic phase^[36]. It is therefore possible that while this study found no significant difference made by nizatidine with respect to hepatic functional reserve, a longer observation period might reveal changes in hepatic functional reserve due to the administration of nizatidine. To determine whether increased saliva secretion caused by the administration of nizatidine may affect the long-term prognosis of PBC, it will be necessary to administer the drug for a longer time to a greater number of cases of PBC in both the symptomatic phase and in the asymptomatic phase, and to observe various changes in these cases.

In this study, we actually started to administer nizatidine to more than 27 of the 73 cases that had been definitively diagnosed as PBC at our hospital. Some of the patients, however, could not continue to come to the hospital for regular examinations. Only the 27 cases continued to undergo regular chewing gum tests and VAS interviews every six months for two years. In selecting patients for the nizatidine administration group and for the non-administration group, we did not take any particular action to avoid bias, but we determined that there was no bias between the two groups because there was no statistically significant difference between the groups in terms

of their hepatic functions (without ALT: $P = 0.04$).

Strictly speaking, as the control group, a placebo should have been administered to the nizatidine non-administration group. One reason this was not done was that many cases dropped out and could not continue to take nizatidine, or undergo VAS interviews or chewing gum tests. This aspect will be improved in any future study.

In this study, we confirmed that administering nizatidine to cases of PBC with dry mouth increased saliva secretion and improved dry mouth symptoms. However, we were unable to show that this improvement led to improvement in the nutritional condition and long-term prognosis of the patients. The prognosis of PBC is generally good. However, it can be inferred that there is a group of PBC cases with poor prognoses, and a further extensive study is needed to establish effective treatments for such a group.

COMMENTS

Background

Dry mouth and/or dry eye symptoms of primary biliary cirrhosis (PBC) are called sicca syndrome, and are found in approximately 70% of patients with PBC. The authors have investigated whether administering nizatidine, which has a saliva stimulation effect, improves dry mouth as a subjective symptom of PBC.

Research frontiers

It was confirmed that administering medicines for gastric ulcers to patients with hepatic problems improves their symptoms. Further, readily available medicines such as H₂ Blockers were found to have a significant value in treatment if they are internally used.

Innovations and breakthroughs

It was noted that administering nizatidine not only increased the saliva secretion but also improved xerostomia, a subjective symptom.

Applications

When nizatidine are administered to PBC patients with PBC who have dietary intake difficulties, increase of saliva secretion and improvement of subjective symptoms are expected. However, the influence of dietary intake on the improvements of their liver function and their prognosis should be closely monitored.

Terminology

Sicca syndrome: Dry mouth and dry eye symptoms of PBC are called sicca syndrome, and are found in a high percentage of patients with PBC. Commonly, it is not diagnosed precisely and left without any effective medical treatment.

Peer review

The paper investigated the effects of saliva stimulation by nizatidine on dry mouth symptoms of PBC. It's well designed and written.

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P-Reviewer Liu Q S-Editor Zhang DN L-Editor Hughes D
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