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ORIGINAL ARTICLE

Salivary flow rate and decayed, missing, and filled teeth (DMFT) in female patients with schizophrenia on chlorpromazine therapy

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Abstract *Background/purpose:* The purpose of the study was to investigate relationship between saliva flow rates, estrogen levels, and caries prevalence in female psychiatric patients under antipsychotic therapy.
Materials and methods: Sixty-one institutionalized psychiatric females (31 patients treated with chlorpromazine only and 30 patients treated with chlorpromazine and biperiden) were compared with 36 unmedicated healthy females. The unstimulated whole saliva (UWS) flow rate and serum estrogen were measured. Caries prevalence was recorded in terms of decayed, missing, and filled teeth (DMFT).
Results: The UWS flow rate in the control group was 0.35 ± 0.18 mL/min and the DMFT 18.8 ± 5.7. In comparison, UWS flow rates were 0.25 ± 0.15 mL/min ($P = 0.003$) and 0.07 ± 0.05 mL/min ($P = 0.000$) in patients on chlorpromazine and patients on chlorpromazine as well as biperiden, respectively, and DMFT values were 22.7 ± 4.6 ($P = 0.003$) and 26.5 ± 5.3 ($P = 0.000$), respectively. Patients on chlorpromazine with amenorrhea had reduced UWS flow rate and estrogen levels with respect to controls ($P = 0.036$; $P = 0.000$, respectively). Correlation analysis revealed significant correlations between UWS flow rate and DT, DMFT, number of used drugs and estrogen level.
Conclusion: It seems that chlorpromazine-induced hyposalivation included (apart from its antimuscarinic effect) a neuroendocrine effect which affected the estrogen levels.

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Introduction

Saliva plays a crucial role in preserving and maintaining oral health and comfort. Reduced salivary flow predisposes individuals to oral disease and can seriously damage the quality of life. Xerostomia is subjective feeling of dry mouth and is primarily caused by decreased salivary secretion,[1,2] but it is not necessarily related to decreased salivary flow, since subjective feelings of oral dryness have been reported by individuals with normal flow rates.[3,4] Dehydration, Sjögren's syndrome, therapeutic radiation to the head and neck region, and xerogenic medications are some known causes of reduced salivary secretion. More than 500 medications have been reported to induce xerostomia and salivary gland hypofunction as potential side effects.[5]

Chlorpromazine remains one of the most commonly used and inexpensive treatments for people with schizophrenia,[6] despite well-documented adverse effects and the advent of a new generation of antipsychotic drugs. The frequent side effects of chlorpromazine are extrapyramidal syndrome, vegetative, such as xerostomia, and neuroendocrine side effects, such as menstrual disturbances.[7,8] By contrast, a common observation among people with psychiatric illness was poor oral health.[9] In the treatment of schizophrenia, some patients on chlorpromazine take antiparkinsonian drugs for correction of the extrapyramidal side effects, such as biperiden, which is also a known xerogenic drug.[10]

Xerostomia is rarely a solitary symptom. When present for an extended period of time, it induces a wide variety of other oral symptoms, such as oral burning, difficulties with speech, mastication and swallowing, altered taste perception and candidiasis.[11] Also, it has been shown that patients suffering from impaired salivary function due to an intake of medication exhibit an increased caries experience.[12,13] According to current knowledge salivary flow is without doubt the most important single saliva factor controlling the development of dental caries.[14]

We hypothesized that relationships exist between reduced salivary flow rate, induced by a typical antipsychotic drug, chlorpromazine, and caries prevalence as well as between salivary flow rate and estrogen status. In order to test these hypotheses we compared: (1) salivary flow rate and caries prevalence in long-term institutionalized psychiatric female patients on antipsychotic therapy which include chlorpromazine or combination of chlorpromazine + bipe-riden with respect to a control group of patients without any therapy; and (2) salivary flow rate and estrogen status in the same psychiatric patients with respect to a control group of patients.

Materials and methods

Patients

This cross-sectional study involved psychiatric female patients with schizophrenia (DSM-IV), who were residents of the Institution for Female Children and Adults, Višegrad, Bosnia and Herzegovina. According to the type and number of drugs used daily, 61 patients (aged 20–45 years, mean age 36.7 ± 6.8) were randomly selected and divided in two groups. The first group included 31 patients treated with an antipsychotic drug, chlorpromazine (25–175 mg per day) only; the second group included 30 patients who were treated with chlorpromazine with the same dose range and with an antiparkinsonian drug, biperiden (2–4 mg per day). All these patients received these medications for at least 1 year. Psychiatric patients with medical problems (i.e. diabetes mellitus, rheumatoid arthritis, Sjogren's syndrome) that might affect the oral condition were excluded.

The control group of patients included 36 dentate, healthy females, age 20–45 years, (mean age 33.4 ± 6.5) randomly selected from patients referred to the Department of Restorative Dentistry, Faculty of Medicine Foča, University of East Sarajevo, for conservative dental treatment. The criteria for being included in the control group in this study were: regular menstrual cycle, not using oral contraceptives, no history of treatment for cancer, no history of salivary disease, no drugs treatment in the past 6 months and no use of over-the-counter medications. Concerning the aim of the study to investigate the effects of drugs and estrogen status on salivation, such a control group seems appropriate.

Collection of saliva samples and examinations of dental status in psychiatric patients were done in 2010, in the Institution for Female Children and Adults by one investigator, whereas for the control patients in the Department of Restorative Dentistry, Faculty of Medicine, they were collected by another investigator. Therefore it could be reasonably assumed that potential bias during the investigation was avoided. The kappa statistic was used to evaluate inter- and intra-examiner reliability. The inter-examiner agreement for the caries experience (DMFT) and saliva collection ($\kappa=0.73$ and $\kappa=0.78$, respectively) and intra-examiner ($\kappa=0.84$ and $\kappa=0.87$ for the first investigator, and $\kappa=0.96$ and $\kappa=0.91$ for second investigators, respectively) indicated "good agreement" to "very good agreement". The study was conducted according to World medical Association Declaration of Helsinki (version 2004). After receiving Institutional Ethical Committee approval (Faculty of Medicine, Foča) the study was undertaken with the understanding and written consent of each person in the control group and for psychiatric patients from the chief doctor of the psychiatric unit as the legally authorized representative.

Saliva samples

Unstimulated whole saliva (UWS) was collected from all patients, controls, and psychiatric patients, between 7.00 AM and 9.00 AM by cotton swab (Salivette, Sarsted, Nümbresht, Germany), since the psychiatric patients have limited ability to participate in the collection of saliva by the drooling method. The patients were requested to

refrain from eating, drinking, tooth brushing and using tobacco 1 hour before the appointments. The average time of the saliva collection in medicated patients was 1 hour after the oral intake of drugs. Each subject was asked to swallow in order to empty the mouth before a saliva sample was collected. The saliva sample was collected by the subject placing the cotton swab (diameter 1 cm, length 2.5 cm) under the tongue for exactly 5 minutes. The cotton swab was replaced in the inner snap seal container and back into the Salivette outer centrifuge tube. All saliva samples were collected while the participant was sitting quietly and relaxed, leaning slightly forward. Saliva volume was estimated by weighing the Salivette tube immediately after collection and saliva density was assumed to be 1.00 g/mL. From this, the saliva flow rate was determined by dividing the volume of saliva by the collection time and is represented as mL/min.

Menstrual status and estrogen level

In the chlorpromazine group, each subject's current menstrual status was classified as regular (cycle length of 22–41 days), irregular (cycle length of 42–180 days), or amenorrheic (absent menses for >180 days), based on information provided from medical records. None of the participants in the medicated or control groups was menopausal.

From the patients on chlorpromazine therapy and controls, a non-fasting, morning venous blood sample (4 mL) was obtained for the determination of the 17β-estradiol level. The concentration of the hormone in the serum was measured immediately by chemiluminescent enzyme immunoassay (IMMULIATE Estradiol PPC) and expressed as pg/mL.

Caries detection

In each subject, caries experience was recorded in the WHO oral health assessment form[15] in terms of the decayed, missing, and filled teeth (DMFT) and its components. The dental examinations were performed with the use of artificial light, a plane mirror, and a sharp explorer. Caries was diagnosed at the cavitation level. Areas of teeth that showed visual evidence of undermined enamel or tactile evidence of soft tooth structure at the base of pits and fissures were recorded as carious.

Statistical analysis

Statistical analyses of the results were performed using the SPSS 11.5 for Windows program (SSPS Inc., Chicago IL, USA). The means and standard deviations were calculated, and one-way analysis of variance (ANOVA) was used to analyze differences between the groups. Correlations between salivary flow and DT, DMFT, and estrogen were subjected to Pearson's correlation coefficient testing. Correlations between salivary flow and daily total medication intake were subjected to Spearman's rank correlation. Statistical tests that yielded $P < 0.05$ were considered significant.

Results

Salivary flow rate

UWS in patients on chlorpromazine (25–175 mg) and chlorpromazine (25–175 mg per day) + biperiden (2–4 mg per day) were significantly reduced with respect to control group of patients ($P = 0.003$, $P = 0.000$, respectively), and significantly reduced in patients on chlorpromazine (25–175 mg) + biperiden (2–4 mg per day) with respect to patients on chlorpromazine (25–175 mg per day) ($P = 0.000$) (Table 1).

In patients on chlorpromazine therapy (50–100 mg and 100–175 mg), UWS were significantly reduced by 34.28% and 51.42%, respectively, with respect to the control group. When UWS were analyzed in three subgroups on chlorpromazine therapy, the only significant reduction was observed in patients on chlorpromazine therapy 100–175 mg compared with patients on chlorpromazine 25–50 mg (50%, $P = 0.011$).

The mean UWS flow rates and mean serum concentrations of estrogen for the patients on chlorpromazine and controls with respect to estrogen status are shown in Table 2. A significant difference was found between patients with amenorrhea and the control group regarding salivary flow rate ($P = 0.036$). The estrogen concentration was significantly lower in psychiatric patients with an irregular cycle, as well

Table 1 Unstimulated whole saliva (UWS) flow rates in control and psychiatric patients.

	N	UWS (mL/min) X ± SD	P*
1. Control group	36	0.35 ± 0.18	
2. Patients on chlorpromazine (25–175 mg/d):	31	0.25 ± 0.15	2:1 0.003
3. 25–50 mg chlorpromazine	10	0.34 ± 0.17	
4. 50–100 mg chlorpromazine	11	0.23 ± 0.14	4:1 0.013
5. 100–175 mg chlorpromazine	10	0.17 ± 0.12	5:1 0.001 5:3 0.011
6. Patients on chlorpromazine (25–175 mg/d) + biperiden (2–4 mg/d)	30	0.07 ± 0.05	6:1; 6:2; 6:3 0.000 6:4 0.002 6:5 0.045

*Only significant P values are given.
N = number of patients.

as in patients with amenorrhea than in the control females ($P = 0.049$, $P = 0.000$, respectively).

There was no significant difference in age between the investigated groups (data not shown).

Caries prevalence—DMFT

Table 3 shows the mean DMFT score for the control group and medicated patients. In the control group of patients the DMFT score was 18.81 ± 5.70. In comparison, DMFT scores were 22.71 ± 4.65 ($P = 0.003$) and 26.57 ± 5.38 ($P = 0.000$) in patients on chlorpromazine and patients on chlorpromazine + biperiden, respectively. Also, the DMFT score was significantly higher in patients on chlorpromazine + biperiden than in group of patients on chlorpromazine only ($P = 0.005$).

In the control group of patients, component DT accounted for 7.55% of the total DMFT score, the MT component for 28.81% and the FT component for 63.63%. Corresponding values for the patients in the chlorpromazine group were 27.25, 70.89, and 0.57%, and for the patients on chlorpromazine + biperiden were 26.34, 73.12, and 0.49%.

Correlation

Data on the bivariate correlations between the UWS flow rate, and the DT, DMFT, and total number of drugs used daily in medicated patients (patients on chlorpromazine and chlorpromazine + biperiden) are presented in Table 4. UWS flow rate significantly correlated with DT, DMFT, and total number of drugs used daily.

Analyzing relationship between UWS flow rate and estrogen levels, significant correlation was observed in the whole investigated population ($r = 0.267$; $P = 0.029$).

Discussion

The present study concerns the relationships between chlorpromazine-induced hyposalivation, menstrual disturbances, and DMFT in institutionalized female psychiatric patients. In this study only unstimulated saliva was collected because it is present in the mouth for about 14—16 hours of the day and is important for maintenance of oral health. Furthermore, the unstimulated whole saliva flow rate has been proposed as test of choice for detecting reduced salivary flow, since it may be reduced even when the stimulated whole saliva is unaffected.[16] The obtained results showed that UWS flow rates in psychiatric patients on combined therapy with chlorpromazine + biperiden was significantly lower with respect to flow rates in the control group as well as in the group of patients on chlorpromazine alone. Concerning the fact that two well-trained investigators collected saliva samples from the controls and psychiatric patients separately, it is unlikely that observed differences in UWS flow rates could be related to differences in collection of saliva by these two investigators. There are data indicating that mental illness could affect salivary flow due to the apathetic nature of psychiatric patients and their impaired eating and sleeping patterns.[17] It is interesting to note that the drug-induced hyposalivation had been analyzed for very few substances in randomized controlled trials (RCT),[18] like the biperiden study by Guthrie et al.[19] For chlorpromazine there seems to be no RCT, concerning hyposalivation, but there is a recent Cochrane systematic review concerning the effect of chlorpromazine on the subjective feeling of dry mouth-xerostomia.[7] In accordance with previous studies, the present study has shown that the number of drugs used daily was significantly negatively correlated with UWS flow rates. de Almeida et al[20] evaluated the effect of psychotropic drugs on stimulated salivary flow rate and demonstrated that a combination of antidepressive agents (fluoxetin) with benzodiazepines (clonazepam) caused the lowest stimulated secretion flow rate values with respect to a single antidepressive drug. Similarly, Bardow et al[21] showed that both the total number of daily used different medications, as well as the number of xerogenic drugs, were significantly positively correlated with a feeling of dry mouth and negatively with unstimulated salivary flow rate.

Another relevant factor for the association of salivary flow and drugs taken is the duration of exposure to drugs which received little attention in the literature. It is noteworthy to mention that the patients in our study had been taking chlorpromazine or chlorpromazine + biperiden for at least 1 year. This corresponds well with the finding of Navazesh et al[17] who noted that ambulatory dental patients who had been taking medication for a longer time had significantly lower unstimulated and stimulated salivary flow rates than those who taken medications for 1 or 2 years. Also, the study of Handelman et al[22] on elderly, long-term care patients demonstrated that the stimulated flow rate decrease as number of xerogenic medication and the time that they were taken increased. The recent longitudinal study of Thomson et al[23] concerning the medication exposure and xerostomia among older people showed that medication exposure (11 years) was strongly associated with both the prevalence and incidence of xerostomia.

The underlining mechanism of observed reduced salivation is very likely a combination of antimuscarinic effects of both drugs used in our psychiatric patients. Namely, chlorpromazine is a potent inhibitor not only of central dopamine D2 receptors, responsible for its antipsychotic effect, but also muscarinic cholinoceptors, while the main pharmacological effect of biperiden is blockade of central muscarinic cholinoceptors responsible for the control of extrapyramidal side effects of chlorpromazine.[24,25] It is interesting to note that within the group of patients taking chlorpromazine in doses from 25 to 175 mg, we observed a dose-dependent reduction of unstimulated salivary flow rate. This quantitative relationship could be related directly to the antagonistic effect on muscarinic chlolinoreceptors.[24]

It is known that elevated prolactine levels induced by typical antipsychotic drugs are associated with a high risk of menstrual disturbances and reduced estrogen levels among female patients.[8,26] It is established that salivary gland tissue contains estrogen receptors,[27] and scientific evidence of the association between the dry mouth and female sex hormone changes is based on studies of oral contraceptives, pregnancy, and menopause.[28—31] The fact that our results showed that a clear correlation exists between UWS and estrogen level in the whole investigated

Table 2 Unstimulated whole saliva (UWS) flow rates in control and psychiatric patients on chlorpromazine therapy with respect to estrogen status.

	N	UWS (mL/min) X ± SD	Estrogen (pg/mL) X ± SD
1. Control group	36	0.35 ± 0.18	115.61 ± 36.22
2. Chlorpromazine group	31	0.25 ± 0.15	88.03 ± 33.25
3. Normal cycle	16	0.27 ± 0.15	108.12 ± 16.98
4. Irregular cycle	8	0.24 ± 0.19	92.62 ± 22.57
5. Amenorrhea	7	0.20 ± 0.12	36.85 ± 7.4
P*		2:1 0.003 5:1 0.036	2:1 0.002 5:1; 5:3; 5:4 0.000 4:1 0.049

*Only significant P values are given.
N = number of patients.

population is in accordance with concept that changes in estrogen levels affect salivary flow rate. To our knowledge this is the first study demonstrating the relationship between UWS and reduced estrogen level in chlorpromazine-treated psychiatric female patients. By contrast, among psychiatric patients, significant reductions in UWS and estrogen were observed in patients with amenorrhea. Therefore it could be proposed that hyposalivation in psychiatric females could be a result of the antimuscarinic properties of chlorpromazine as well as its effect on estrogen levels.

It is well known that salivary flow rates[14] as well as mental illness[32,33] are significant etiological factors influencing the prevalence of caries. The mean DMFT in psychiatric patients in present study was 24.17. Our findings also show that there was a significant negative correlation between the UWS flow and the DMFT index. Although a relationship between drug-induced hyposalivation and DMFT has been found in some cross-sectional studies,[34] it is noteworthy to mention that such a study design for this type of correlation might not be too accurate. Therefore, further prospective studies will be needed to clarify the association between risk factors such as hyposalivation and caries incidence. Taking into account that the patients were treated with the psychotropic drugs for at least 1 year and that the DMFT is a life-time cumulative index of dental experience, the high DMFT values in our study could be related to other factors, in addition to the salivary flow, that are considered to have an impact on the oral health of psychiatric patients placed in an institution. Having in mind that our investigated groups were of a similar age distribution, none of them were menopausal, and had similar systemic health conditions (except for psychiatric status), a limitation of our study is the fact that we did not take into account factors such as differences in personal oral hygiene motivation and practice, or daily intake of drinks and cariogenic foods between the groups. It is interesting to note that similar DMFT scores in institutionalized psychiatric patients on long-term psychiatric medications were reported by Ramon et al[35] (26.74) and Vigild et al[36] (23.1), although the mean age of the study populations was different (54 years and 34–54 years, respectively) with respect to our patients (20–45 years). These high values of DMFT, in the present and mentioned studies, indicate that psychiatric patients had poorer dental health when compared with healthy controls. Possible explanation could be that patients in long-term care are dependent on the assistant helping them with their daily and oral hygiene activities. Moreover, they are less motivated, less efficient, or too disabled to perform oral hygiene and they rarely had regular dental visits. In our case, although we did not evaluate oral hygiene status, we generally observed poor oral hygiene levels in psychiatric patients in contrast to the control group.

Although the DMFT index and its components provide powerful data on dental caries some limitations exist. Namely, DMFT values do not provide any indication as to the number of teeth at risk or data that is useful in determination of dental needs. The index gives equal weight to

Table 3 DMFT index in control and psychiatric patients (mean ± SD).

	DMFT ± SD	DT ± SD	MT ± SD	FT ± SD
1. Control group	18.81 ± 5.70	1.42 ± 1.36	5.42 ± 3.73	11.97 ± 4.74
2. Patients on chlorpromazine (25–175 mg/d):	22.71 ± 4.65	6.19 ± 3.80	16.10 ± 5.43	0.13 ± 0.56
3. 25–50 mg chlorpromazine	22.40 ± 5.40	4.60 ± 4.24	17.80 ± 6.44	0.00 ± 0.00
4. 50–100 mg chlorpromazine	22.55 ± 5.55	5.45 ± 3.61	15.91 ± 6.22	0.36 ± 0.92
5. 100–175 mg chlorpromazine	23.20 ± 2.86	8.60 ± 2.36	14.60 ± 2.87	0.00 ± 0.00
6. Patients on chlorpromazine (25–175 mg/d) + biperiden (2–4 mg/d)	26.57 ± 5.38	7.00 ± 4.60	19.43 ± 7.17	0.13 ± 0.50
P*	2:1 0.003 4:1 0.045 5:1 0.024 6:1 0.000 6:2 0.005 6:3 0.035 6:4 0.035	2:1 0.000 3:1 0.009 4:1 0.001 5:1 0.000 6:1 0.000 5:3 0.009	2:1 0.000 3:1 0.000 4:1 0.000 5:1 0.000 6:1 0.000 6:2 0.02 6:5 0.019	2:1 0.000 3:1 <0.000 4:1 <0.000 5:1 <0.000 6:1 0.000

*Only significant P values are given.
DMFT = decayed, missing, and filled teeth; DT = decayed teeth; MT = missing teeth.

Table 4 Correlation between UWS and DT, DMFT, and number of drugs in medicated patients.

UWS	DT	DMFT	Number of drugs
P	r = −0.359 (0.005)	r = −0.314 (0.014)	σ = −0.612 (0.000)

σ = Spearman correlation coefficient; DMFT = decayed, missing, and filled teeth; DT = decayed teeth; P = level of significance; r = Pearson's correlation coefficient; UWS = unstimulated whole saliva.

missing, untreated decayed, and well-restored teeth. Our analysis of the components of the DMFT in psychiatric patients demonstrates that the mean number of missing teeth was the predominant part of the index, and that, the fewer teeth were restored. Such low numbers of filled and high numbers of missing teeth were also shown in studies of Ramon et al[35] and Vigild et al[36] indicating that extractions are often preferred to more conservative treatment in psychiatric patients. Furthermore, the use of a dental service can influence DMFT. Namely, better access to dental care increases the FT, as well as MT scores. An extremely low F component and much higher D and M components in the schizophrenic groups indicate a limited utilization of preventive and restorative dental service and that the past dental history largely consisted of emergency dental care with tooth extraction.

It can be concluded that the relationship between reduced saliva secretion induced by drugs, such as chlorpromazine and biperiden, and caries prevalence exists. The results of the present study also indicate that hyposalivatory effect of typical antipsychotic drugs could include the influence of their neuroendocrine effect, affecting estrogen level, besides the well-established influence of their antimuscarinic properties.

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