Effects of Fluoxetine and Venlafaxine and Pilocarpine on Rat Parotid Glands

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Abstract: This study assessed the effect of the antidepressants, Fluoxetine and Venlafaxine, on the size (GS), mass (M), cellular volume (CV), of rat parotid salivary glands and salivary flow rate (SFR), as well as the secretagogue action of pilocarpine on this flow. Ninety animals were divided into 9 treatment groups with the antidepressants, antidepressants associated with the application of pilocarpine, antidepressants and physiologic serum, physiologic serum (control) and pilocarpine (positive control). Thirty hours after the end of treatment, saliva collection began, to determine the SFR. Next, the salivary glands were removed, GS and M measured, and the specimens processes for histomorphometric analysis and CV determination. The variable GS presented statistically significant increase among the groups that were treated for 30 days with Fluoxetine (p=0.0002) and Venlafaxine (p=0.0112) when compared with the group treated with physiologic serum (control). The group treated with Fluoxetine for 30 days revealed increase in M (p=0.0190) and diminished SFR (p=0.0031), statistically significant, when compared with the control group. CV revealed increase in acinic cells between the Fluoxetine (30 days) (p=0.0005) and Venlafaxine (30 days) (p=0.0004) groups as well, when compared with the control group. The group treated with Venlafaxine for 60 days in association with pilocarpine presented SFR similar to the control group treated for 60 days. Both Fluoxetine and Venlafaxine reduced the SFR and caused increase in CV, resulting in hypertrophy of the glands, with Fluoxetine having a more pronounced anticholinergic action. The pilocarpine increased the SFR in the group that received Venlafaxina.

Keywords: Antidepressants, xerostomia, hyposalivation.

INTRODUCTION

Normal salivation is an essential demand for oral health, due to its important contributions to the oral defense mechanisms. Diminished salivary secretion could lead to caries disease and deterioration of the mucosa [1-3].

Salivary secretion is neurologically controlled by stimulation of reflex action. The salivary glands are enervated by the sympathetic and parasympathetic autonomic nervous system (ANS). Sympathetic enervation is linked by means of the type $\alpha 2$ and $\beta 2$ adrenergic receptors[4], while parasympathetic enervation is linked to the muscarinic receptor M3. The primary acinar content is modified as it passes through the system of salivary gland ducts. This process occurs be cause the cells of the duct receive stimulus from the sympathetic and parasympathetic pathways [5].

Depression is the commonest form of affective disorders, and may range from discrete to severe. Various studies have worked with the hypothesis that depression arises from the deficiency of monoamines (noradrenaline, serotonin and dopamine), the most adequate treatment being to raise the supply of these neurotransmitters in the central nervous system (CNS). Statistical data have shown that depression has increased as a result of the longer life expectancy, and is common among the elderly population [6].

The treatment of psychiatric disorders and affective disturbances mainly involves antidepressant, antipsychotic and anxiolytic drugs. Studies revealed that patients with psychiatric alterations that make use of these drugs complain of dry mouth [7]. Depressive alterations accompanied by the symptom of dry mouth are 20% more frequent in women than in

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men [8]. The most affected age group ranges from 30 years to 59 years [5].

Antidepressants have an affinity for the adrenergic and cholinergic receptors present in the salivary glands, and present an anticholinergic effect. The action of antidepressant drugs may be related to this affinity, and the reduction of the cholinergic and sympathetic influx to the CNS. The main side effect of these drugs is inhibition of the secretagogue effect caused by cholinergic stimulation, thus causing hyposalivation [9]. Other side effects include: nausea, dizziness, somnolence, sweating and tremors [10].

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) and considered to be better than of the class, is the result of research to find medications as effective as the tricyclic medications, but with few tolerability and safety problems. This drug does not inhibit the reuptake of other neurotransmitters, having no affinity for the adrenergic, muscarinic, cholinergic, H1-histaminic or dopaminic receptors [11]. Although they are considered safe drugs and present easily attainable therapeutic doses, the SSRIs present significant side effects, such as: nausea, diarrhea, headaches, insomnia and xerostomia [12].

Venlafaxine is an antidepressant drug with a completely different chemical structure from that of other antidepressant agents. Its action mechanism resembles that of other known antidepressant, such as: fluoxetine, sertraline and paroxetine, since it is directly associated with potentiating neurotransmitter activity in the CNS [13, 14].

This drug is presented as a selective serotonin and noradrenalin reuptake inhibitor, and presents weak activity as dopamine reuptake inhibitor, clinically significant only at high doses [11]. It does not show affinity for adrenergic receptors $\alpha 1$, and muscarinic or histaminic receptors [11,15]. Consequently, it is less likely to produce side effects related to these pharmacological properties [16].

Various treatments are proposed for enhanced salivary secretion, among them, the use of a salivary flow stimulating drug pilocarpine chloride which acts by stimulating the parasympathetic ANS. [17]. This drug has been used because it stimulates the cholinergic receptors, among them the muscarinic M3 receptor present in the salivary glands, resulting in the expulsion of the stored salivary contents [18], thus an increase in saliva production and release was observed with the use of pilocarpine [19].

The aim of the present study is to verify the action of these two antidepressant drugs Fluoxetine and Venlafaxine on the salivary flow rate, as well as to make a histomorphometric analysis of the rat parotid glands submitted to chronic treatment with such drugs, and to assess the secretagogue action of Pilocarpine on this flow. The aim of the present study is to verify the action of these two antidepressant drugs Fluoxetine and Venlafaxine on the

MATERIAL AND METHODS

This study was approved by the Research Ethics Committee of Tuiuti University of Paraná, under the registration number CEP-UTP 55/2003.

The animal model enrolled in this investigation consisted of male rats (*Rattus norvegicus albinus, Wistar* strain) obtained from the Central Animal Facility of the Pontifical Catholic University of Paraná. The animals were, weighed approximately 250g, and were maintained in cages with water and food *ad libidum,* on a light/dark cycle of 12 hours.

Ninety animals were divided into nine groups had been used, each group consisting of 10 animals (Table **1**). The administration route and doses were according to Manual of Drugs Veterinary [20] and the treatment period was observed by method Grégio *et al*. (2006) [9]. The experimental groups had received two antidepressants drugs, injectable solution of Fluoxetine (**F**) (20mg/Kg - intraperitoneal) (lot 20040625,

Table 1. Controls and Experimental Groups in Accordance the Drug, Treatment, Time, Dose and Administration

Group Drug	Treatment	Dose	Administration	Time
1 Positive control	Pilocarpine	1-60 days	0.05 mL	Topic (P60)
2 Experimental (FS)	Fluoxetine Physiological Serum	1-30 days 31-60 days	20mg/kg 0.1 mL	Intraperitoneal Intraperitoneal
3 Experimental (VS)	Venlafaxine Physiological Serum	1-30 days 31-60 days	40mg/kg 0.1 mL	Intraperitoneal Intraperitoneal
4 -Experimental (F30)	Fluoxetine	1-30 days	20 mg/kg	Intraperitoneal
5 -Experimental (V30)	Venlafaxine	1-30 days	40mg/kg	Intraperitoneal
6 Experimental (VP)	Venlafaxine Pilocarpine	1-60 days 31-60 days	40mg/kg 0.05 mL	Intraperitoneal Topic
7 Experimental (FP)	Fluoxetine Pilocarpine	1-60 days 31-60 days	20mg/kg 0.05 mL	Intraperitoneal Topic
8 Control (S60)	Physiological Serum	1-60 days	0.1 mL	Intraperitoneal
9 Control (S30)	Physiological Serum	1-30 days	0.1 mL	Intraperitoneal

SOURCE: Data of research.

Galena Química e Farmacêutica Ltda., Campinas, Brazil) and Venlafaxine (**V**) (40 mg/Kg - intraperitoneal) (lot D/VN/002/02, Galena Química e Farmacêutica Ltda., Campinas, Brazil). Controlled Groups S30 and S60 had received solution injectable from physiological serum (**S**) (0.1mL - intraperitoneal) and the P60 group received gel base prepared with 1% from Pilocarpine hydrochloride (**P**) (0,05mL – topic) (Gerbras Química e Farmacêutica Ltda., São Paulo, Brazil).

SIALOMETRY

According to described methodology for Onofre *et al.* [21], saliva samples were collected 30 hours after the end of treatment. The animals had received two drops of 4% pilocarpine hydrochloride eye drops (Allergan pilocarpina® 4%, Allergan Produtos Farmacêuticos Ltda., Guarulhos, Brazil), to stimulate the salivation. After one minute, saliva were collected in a collecting pot that was weighed in scale of high precision - Belmark® U210A (Bel Engenharia, Piracicaba, Brazil), getting in such a way the salivary flow rate (SFR).

The values of amount of saliva had been gotten in accordance with the described formula below [22,23].

Parotidean Gland Exsiccation and Size Measurement

Glands were obtained from each group right after the saliva collection. Rats were weighted and anaesthetised by intraperitoneal administration of 100 mg/kg sodium thiopental (Thionembutal®, Abbott Laboratórios do Brazil Ltda.) and killed.

The right and left parotid glands were dissected and were carefully removed. Fresh gland masses were determined with a BelMark® U210A precision scale. After this, the millimetric longitudinal dimensions were achieved using a high-precision digital calliper Mitutoyo 500 Mical® (Mitutoyo Co., Tokyo, Japan). The average of the glands size and the glands mass was carried through, for attainment of variable so size (GS) and mass (M) for each rat. After the measurement of the part, gland tissue had been fixed in 10% neutral formalin solution and embedded in paraffin. Four μm sections were obtained and submitted for routine hematoxylin-eosin (in accordance with the routine of the Laboratory of Experimental Pathology of the PUCPR).

On microscope examination were used microscopy Olympus® BX50 (Olympus Corporation, Ishikawa, Japan), using objective of 40X and 100X (oil immersion). The images had been captured with digital camera Sony® CCD-IRIS DXC-107A (Sony Eletronics Incorporation, Tokyo, Japan) connected to the microscope and a microcomputer. With a program for analysis of images (Image-Pro® Plus, Cybernetics, Silverspring, U.S.A.), the histological analysis front to the use of antidepressants and the pilocarpine was evaluated.

Histomorphometry of Parotid Glands

To establish the comparisons among the groups, with regard to the cellular volume (CV), the variable presented had been used in the study of Onofre *et al.* (1997).

Processed gland volume (vp) was calculated for each animal using the following equation $Vp=m/d\times rf$, where m is fresh mass, d is density and rf is the shrinkage caused by histological processing. For these calculations, we used d=1.089 g/cm3 and rf=0.7 by the method of Onofre *et al.* (1997).

For the stereological evaluation of acinar volume density (Vvi) and total volume (Vti) it was used an objective of 40X connected to the program Image-Pro® Plus, where if it got a vertical grating with ten horizontal lines and ten lines, determining one hundred points of which forty had been chosen to perhaps. In these forty chosen points had been counted how many points coincided with acini (Pi). The Vvi by means of the formula was calculated then: Vvi=Pi/Pt, where Pt mentions the number to it of selected points (40).

Having obtained the Vvi and processed gland volume (Vp) values, we calculated the total acinar volume (Vti) by the formula Vti = Vvi×Vp. Nuclear volume was determined from the measurement of the orthogonal diameters of 50 nuclei per gland using a microscopy technique as stated before. We calculated the mean radius of the geometric mean diameter by r2 = d1×d2 and the nuclear volume by the formula for the volume of a sphere: $V=4/3\times\pi\times r3$.

The cytoplasmic volume was calculated as of the nucleus densities and the cytoplasm of acinar cells [24]. In this respect, it was counted the points over nuclei (Pn) and over the cytoplasm (Pcyti) in 40 histological fields of the cells under study. The corrected nuclear volume density ($p$ncorr) was calculated by the equation $p$ncorr = (Pn/Pn+Pcyti)/Ko, where Ko is the correction factor and it is calculated by the formula $Ko = 1+3t/2d$, where d is the mean nuclear diameter and t is section thickness.

The corrected cytoplasm volume density is $p$cyticorr = 1-$p$ncorr. By divinding $p$cyticorr by $p$ncorr it was obtained the cytoplasm/nucleus ratio (RC/N) of the acinar cells. On the basis of nuclear volume (Vni) and the C/N ratio, it was calculated the cytoplasmic volume (Vcyti) by the equation Vcyti = Vni×RC/N. This then permitted to calculate the cell volume by Vc= Vni + Vcyti.

Statistical Analysis

To rest the presupposition of normality of the variables for each group, the Komolgorov-Smirnov test was used. The Levene test verified the homogeneity of the variances among the groups.

When the analysis of variance Anova found differences among the means of the groups and treatments, the Tukey HSD multiple comparisons test was used for the variables that presented homogeneity of variances among the groups. For the variables that did not present homogeneity of variances among the groups, the Games-Howell test was used.

For all the tests the level of significance of 5% ($p<0.05$) was applied.

RESULTS

All the groups presented normality of distribution of the data for the variables GS, M, SFR and CV of the studied glands ($p>0.05$), with exception of the variable SFR in the group S60, the variable GS in groups FS and S30, and the variable M in the group F30.

Table 2. Values of Studied Variables in Accordance with Groups Treated with Physiological Serum (1-30 days), Fluoxetine (1-30 Days) and Venlafaxine (1-30 Days)

Groups Variables	9(Saline 30)		4(Fluoxetine 30)		5(Venlafaxine 30)	
	Mean	Sem	Mean	Sem	Mean	Sem
Gland size (mm)	7.036	±0.506	9.501	±1.404	8.696	±1.409
Mass (mg) Salivary flow	0.075	±0.010	0.103	±0.032	0.064	±0.018
rate (mL/min)	0.051	±0.025	0.013	±0.006	0.026	±0.022
Volume of cells (mm^3)	6965.683	±3792.959	10384.305	±4869.539	11945.905	±7891.179

SOURCE: Data of research.

The variables GS and M showed homogeneity of variance ($p>0.05$) and the variables SFR and CV did not present homogeneity of variance ($p<0.05$).

Groups treated for 30 days

Table **2** shows the means and standard deviations of the studied variables in accordance with the groups treated for 30 days.

There was statistically significant difference between the means of the variable GS among the following groups: F30 ($p=0.0002$), V30 ($p=0.0112$), when compared with group S30 (control).

For the variable M, there was statistically significant difference for the following groups: F30 and V30 ($p=0.0011$), F30 and S30 ($p=0.0190$), the highest mean being found for the group F30 and the lowest mean for the group V30.

The variable SFR (Fig.**1**), presented statistically significant difference between groups: F30 and S30 ($p=0.0031$).

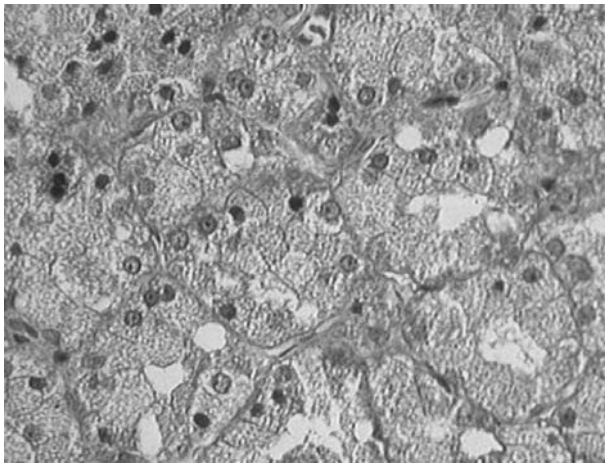

Fig. (1). Histological aspect of the salivary gland of the Fluoxetine 30 group being show disorganized glandular parenchyma.There was a loss of borders to the serous cells, which were also increased in size, with a consequent reduction or disappearance of the central lumen (H.E.; original magnification: 400X).

There was statistically significant difference for the variable CV between the following groups: F30 (Fig. **2**) and S30 ($p=0.0005$), V30 and S30($p=0.0004$).

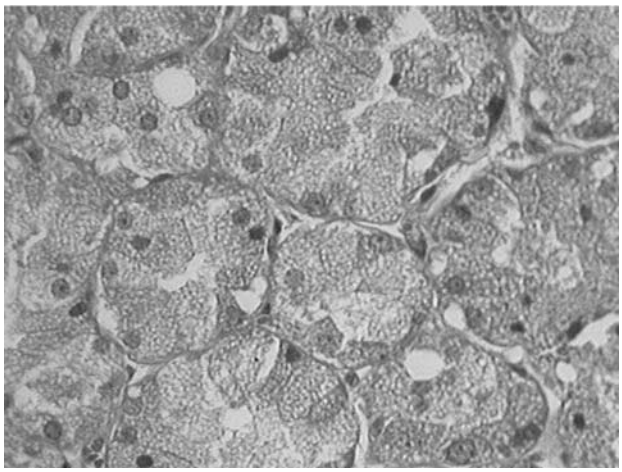

Fig. (2). Histological aspect of the salivary gland of the Venlafaxine 30 group. There was a loss of borders to the serous cells, which were also increased in size, with a consequent reduction or disappearance of the central lumen (H.E.; original magnification: 400X).

Figs. **3** and **4** show rat parotid glands from groups V30 and S30, respectively.

Groups Treated for 60 Days

Tables **3** and **4** show the means and standard deviations of the studied variables in accordance with the groups treated for 60 days.

The variable GS did not show statistically significant differences among the groups. Group P60 presented the highest mean and group FP the lowest mean among the groups.

There were statistically significant differences for the variable M between groups P60 and FP ($p=0.0351$), FS and FP ($p=0.0161$), VS and FP ($p=0.0015$), VS and S60 ($p=0.0132$).

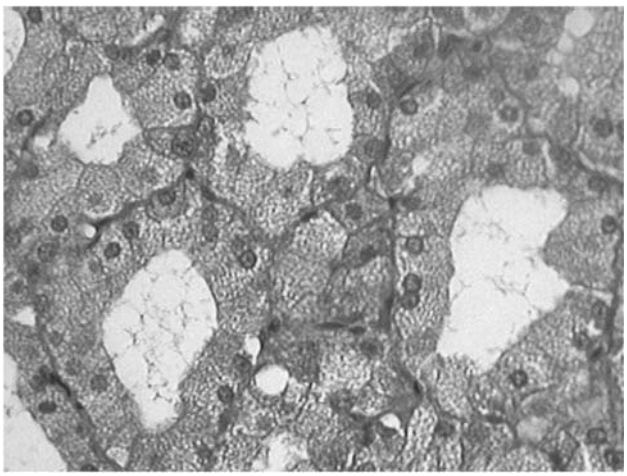

Fig. (3). Well-structured glandular parenchyma divided into lobules. Inside the lobules, intercalary ducts were covered by cuboidal cells while striated ducts were found covered by columnar cells. group Saline 30 (H.E.; original magnification: 400X).

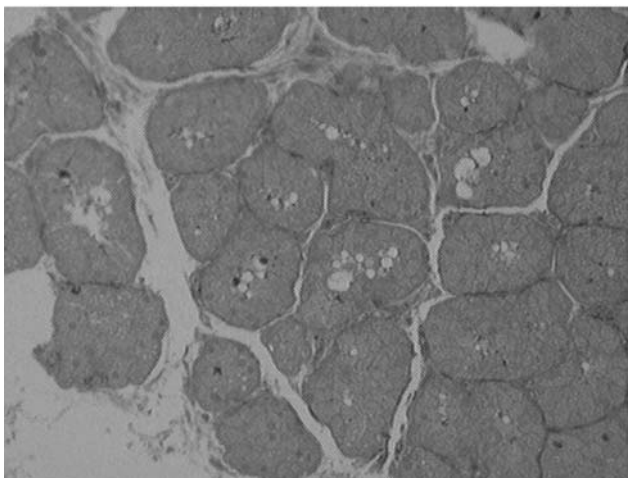

Fig. (4). Organization of glandular parenchyma divided into lobules by the connective tissue septa. The acini returned to exhibit a central lumen and the edges of the serous cells could be seen again - group Fluoxetine +Pilocarpine 30, (H.E.; original magnification: 200X).

For SFR, there were statistically significant differences between the following groups: P60 and VS (p=0.0047), P60 and FP (p=0.0451), VS and VP (p=0.0214).

The variable CV showed statistically significant differences between groups P60 and VS (p=0.0231), P60 and VP (p=0.000003), FS and VP (p=0.0005); VS and VP (p=0.0111), VP and FP (p=0.0327), VP and S60 (p=0.0001). Group P60 obtained the lowest mean and group VP the highest mean.

DISCUSSION

The anticholinergic effects of drugs that act on the CNS have not yet been completely explained. The majority of authors opt for defining the autonomic capacity of these drugs in linking to the adrenergic and cholinergic receptors, altering the quality and quantity of salivary flow. But several other factors must be considered, because in addition to interaction with and affinity to the sympathetic and parasympathetic CNS and ANS, other neurotransmitters, proteins and amino acids are capable of resulting in alteration of activity in the salivary glands [5].

This study observed that Fluoxetine (F30) produced increase in GS and M of the rat parotid salivary glands, in addition to increasing CV in comparison with the control group S30. This effect probably occurred because the drugs with central action promote an action of salivary gland hypertrophy [9]. This result corroborates those of Madrigal and Micheau [25], who characterized hypertrophy of the glands by widening of the acini and accumulation of secretion granules, cause by drugs with central action.

The anticholinergic action of psychotropic drugs [5, 25] was proved once again, because in the group treated with Fluoxetine for 30 days (F30), the animals' SFR was lower in comparison with the control group (S30), thus justifying the increase in GS and M, as there was retention of saliva in the acini lume and little of it being released.

The antidepressants SRIs when compared to the tricyclic drugs have not presented significant effect in the flow rate, probably due to lack of anticholinergic activity [26,27]. The flow reduction could occur through the serotonin receptor action presented at the peripheric microcirculation [28]. According to Schubert and Izutsu [29], the salivary flow can be effected by drugs through alteration at the blood flow of the salivary glands. For Grubb and Karas [30], the seratonin has important phisiology participation at the autonomic regulation, since, one time CNS controls the sympathetic, the parasympathetic and the serotonin mechanisms, probably one decrease or activation of the release of serotonin at the CNS would result of the alteration of both sympathetic and parasympathetic. These hypotesis contribute with our finds regarding the reduction of the SFR caused by Fluoxetine.

The uncertainty as regards the exact biochemical action mode of antidepressants frequently causes the development of new drugs to be empirical. This lead to the introduction of a heterogeneous group of compounds (to which Venlafaxine belongs), the atypical antidepressants. In practice, the most recent drugs may definitively be superior to the tricyclic drugs in terms of side effects and acute toxicity, but they have not been shown to have a faster action or be more effective [11,27,28].

With regard to the results obtained by Venlafaxine (V30) both GS and CV had higher values in comparison with the control group, and in addition there was diminished SFR when compared with the control (S30), once again demonstrating the anticholinergic action of psychotropic drugs and the effect of acinar cell hypertrophy [9,25].

Venlafaxine has fewer anticholinergic and adrenergic α-blocker effects than the other antidepressant [16]. This would cause a reduction in the adverse effects, because at low doses, this drug predominantly blocks serotonin and noradrenalin reuptake, and at high doses also inhibits dopamine reuptake. This hypothesis reinforces the great expectation in the use of Venlafaxine in comparison with Fluoxet-

Table 3. Values of Studied Variables in Accordance with Groups Treated with Pilocarpine (60 Days), Physiological Serum (60 Days), Fluoxetine (30 Days) + Physiological Serum (31-60 Days), Fluoxetine (1-60 Days) + Pilocarpine (31-60 Days)

Groups	1(Pilocarpine 60)		8(Saline 60)		2(Fluoxetine S)		7(Fluoxetine+Pilocarpine)	
Variables	**Mean**	**Sem**	**Mean**	**Sem**	**Mean**	**Sem**	**Mean**	**Sem**
Gland size (mm)	8.492	±1.026	7.885	±0.628	8.350	±0.077	7.496	±1.103
Mass (mg)	0.092	±0.013	0.074	±0.021	0.095	±0.014	0.068	±0.020
Salivary flow rate (mL/min)	0.066	±0.027	0.052	±0.028	0.036	±0.016	0.033	±0.013
Volume of cells (mm^3)	5825.418	±1968.070	6505.564	±3343.475	6809.347	±3189.246	7519.797	±4272.808

SOURCE: Data of research.

ine, and is in agreement with the present study findings, since the value of SFR for Venlafaxine (V30) was higher when compared with the SFR value for Fluoxetine (F30). Furthermore, fluoxetine has metabolite of prolonged action and pharmacologically active [11].

The acinar cells present adrenergic α and β receptors, vasoactive intestinal peptide receptors (VIP), acetylcholine and P substance. The receptors for β adrenergic and for VIP, activate the cyclic AMP cascade, activating the G protein, which activates the adenylate cyclase enzyme. Whereas the α adrenergic receptors and the receptors for acetylcholine and P substance activate the inositol 1, 4, 5 triphosphate cascade (IP3) and of diacylglycerol. These biochemical reaction and interaction sequences influence both salivary secretion and composition [31].

Because Venlafaxine is a weak serotonin and noradrenalin reuptake inhibitor, it has fewer side effects than Fluoxetine [28]. Another hypothese for justifying, besides the others mentioned before, this is that the majority of types of serotoninergic receptors are coupled to the G proteins, affecting adenylate cyclase activity [32]. This enzyme, in turn, converts ATP into the second messenger, cyclic AMP [33] which, as central effect, presents activation of the protein kinase A (PKA), an enzyme that regulates ionic channels, which are responsible for the entry and exit of water and electrolytes from cells [34].

On the other hand, the CV of rat parotid glands in the group treated with Venlafaxine (V30) was greater than in the group treated with Fluoxetine (F30). This is probably owing to the fact that Venlafaxine, because it also inhibits noradrenalin reuptake, and this being the mediator of the sympathetic ANS, which in turn tends to modulate the composition of saliva, inducing the protein secretion mechanism [31,35], which may be accumulating inside the salivary gland, resulting in cellular hypertrophy.

In the present study, the secretagogue role of pilocarpine was observed, since the group of animals that received pilocarpine for 60 days showed the highest mean SFR value, when compared with group S60, that is, pilocarpine activates the muscarinic M3 receptors present in the salivary gland, which promote increased release of salivary secretion [36].

For Fluoxetine, the group treated for 30 days and then treated for a further 30 days with association of pilocarpine (FP) had a lower SFR than that of group S60. The group treated with Venlafaxine for 30 days and then treated for a

Table 4. Values of Studied Variables in Accordance with Groups Treated with Pilocarpine (60 Days), Physiological Serum (60 Days), Venlafaxine (30 Days) + Physiological Serum (31-60 Days), Venlafaxine (1-60 Days) + Pilocarpine (31-60 Days)

Groups Variables	1(Pilocarpine 60)		8(Saline 60)		3(Venlafaxine S)		6(Venlafaxine P)	
	Mean	**Sem**	**Mean**	**Sem**	**Mean**	**Sem**	**Mean**	**Sem**
Gland size (mm)	8.492	±1.026	7.885	±0.628	8.040	±0.949	8.060	±0.761
Mass (mg)	0.092	±0.013	0.074	±0.021	0.101	±0.016	0.089	±0.015
Salivary flow rate (mL/min)	0.066	±0.027	0.052	±0.028	0.020	±0.003	0.054	±0.026
Volume of cells (mm^3)	5825.418	±1968.070	6505.564	±3343.475	6809.347	±3189.246	7519.797	±4272.808

SOURCE: Data of research.

further 30 days with association of pilocarpine (VP) had a similar SFR to that of group S60. In this case, pilocarpine was able to restore the SFR to levels of control, corroborating the secretagogic action of pilocarpine in the treatment of hyposalivation caused by Venlafaxine.

The groups FS and VS presented lower SFR values than the group S60, proving that after suspension of the drug, withdrawal symptoms may occur, which appear within one to ten days and persist for up to three or four weeks. The most frequent symptoms are dizziness, vertigo, ataxia, gastrointestinal disorders, flu symptoms, sensorial disturbances, sleep alterations, psychic alterations and anticholinergic effects. As happens with other psychoactive substances, these symptoms may be the result of adaptive alterations, which most frequently involve the adjustment of the receptors to compensate the pharmacological activity of the drug, described as a rebound effect [11].

The advance of research in the psychopharmacology of antidepressants has offered patients drugs with very different pharmacokinetic profiles among them. In spite of this, the action mechanisms proposed for each of them remain linked to monoaminergic theories of increased offer of neurotransmitters in the synaptic gap and the subsensitization of presynaptic receptors [37].

There is a large variation of the effects of the antidepressant drugs on the salivary flow and its composition in clinical and pre-clinical studies. Some of the factors that could explain these variations are: pharmacokinetic, pharmacodynamic, doses and treatment time. The total protein concentration and α-amylase activity in the saliva stimulated by pilocarpine, after chronic treatment with fluoxetine, were not affected in studies of Kopittke [38]. It is possible that pilocarpine action could have increased the volume of water in the saliva, since it is a sialogogue, and subtle effects of the drugs on the salivary content may not be so evident. However this study, the doses and period treatment was different our study.

In terms of the number of drugs available, there has been a considerable enlargement of the therapeutic arsenal, both with expansion in the number of compounds of the same pharmacological group, and in the appearance of drugs with different action profiles from those of the original ones. The more recent compounds are more selective, leading to greater tolerability and adherence to treatment [11].

One verifies an effort in the sense of increasingly improving the action in receptor sites determinant of clinical efficacy, avoiding those responsible for side effects [26]. However, new inquiries become necessary due the complexity of the involved events in the salivar secretion mechanism.

CONCLUSIONS

It could be concluded that both Fluoxetine and Venlafaxine reduced the SFR and caused hypertrophy of the rat parotid gland, with Fluoxetine having a more pronounced anticholinergic action. Pilocarpine contributed to increasing SFR, mainly in the groups that received Venlafaxine, suggesting the use of pilocarpine for the treatment of hyposalivation caused by this drug.

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