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The Journal of Medical Research 2019; 5(5): 180-184

Research Article

JMR 2019; 5(5): 180-184
September- October
ISSN: 2395-7565
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www.medicinearticle.com
Received: 24-09-2019
Accepted: 18-10-2019

Gingival overgrowth caused by Olmesartan Medoxomil: Observational study

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Abstract

Objective: Olmesartan Medoxomil is a type 1 receptor antagonist an antagonist of type 1 receptor (AT1) of angiotensin II (A-II) that inhibits numerous actions of A-II in the renin-angiotensin-aldosterone system (RAAS). A-II is a significant and multifunctional peptide involved in the pathophysiology of blood hypertension and for this reason it represents the main target in several classes of drugs used to treat and control arterial hypertension, such as angiotensin converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARB) and renin direct inhibitors. The aim of the study is to evaluate whether the two drugs that have as an active principle Olmesartan Medoxomil, with and without the diuretic hydrochlorothiazide, are able to determine gingival overgrowth. **Study Design:** 108 subjects were examined and divided into three groups: G1, subjects treated with Olmesartan Medoxomil and hydrochlorothiazide (n=60); G2, subjects received only Olmesartan Medoxomil (n=24); G3, control group without pharmacological therapies (n=24). The plaque index (IP) and the gingival overgrowth index (OI) were recorded, considering the vertical and horizontal components. **Results:** Vertical overgrowth averaged between 0.17 ± 0.15 (G3) and 0.34 ± 0.26 (G2) showing statistically significant differences ($p < 0.05$) compared to the other groups. Horizontal overgrowth ranged from 0.18 ± 0.26 (G3) to 0.49 ± 0.35 (G2) showing statistically significant differences ($p < 0.05$). **Conclusions:** antihypertensive agents as Olmesartan Medoxomil may result in mild gingival overgrowth in the upper and lower frontal dental elements not related to other etiological factors.

Keywords: Gingival overgrowth, hypertension, angiotensin II, antihypertensive agents.

INTRODUCTION

The term gingival overgrowth means excessive growth of the gingival tissue due to an increase in the size of the individual cells that compose it [1].

Gingival overgrowth appears in both the free and the attached gingiva. It mainly affects the interdental papillae in the anterior mandibular portion, affecting the buccal surface and, in lesser extent, palatal and lingual surfaces [2].

Gingival overgrowth is classified according to the etiology: inflammatory (plaque and calculus deposits), gingival fibromatosis (familiar and idiopathic forms), hormones (gingivitis and pregnant epulis), neoplastic and, at the end, drug-induced (related to intake of anticonvulsants, calcium antagonists and cyclosporins).

It is a widely held view that more than 20 drugs prescribed regularly can act as etiological factors in this clinical case [3]. Mainly three groups of drugs have been associated with iatrogenic gingival overgrowth. Anticonvulsants, particularly diphenyldantoin (phenytoin or dantoin); calcium channel blockers, such as nifedipine, a substance used in various cardiovascular pathologies [4, 5]. immunosuppressors such as cyclosporine A (CsA), a drug used in the transplanted organ patient for prevention of graft rejection [6].

Despite the pharmacological diversity, all three types of drugs, in relation to their mechanism of action, act in a similar way at cellular level. In fact, they are able to inhibit the ionic flow of intracellular calcium [7, 8]. Circumstance that would cause, as a common side effect, overgrowth of the gingival connective tissue.

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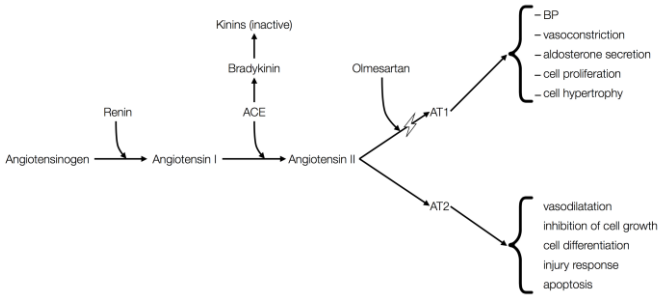

Figire 1: The antihypertensive mechanism of angiotensin receptor blocking. The diagram describes the renin-angiotensin-aldosterone system (RAAS) in which renal renin release catalyzes the conversion of angiotensinogen into A-I and subsequently into A-II from circulating and pulmonary angiotensin converting enzymes (ACEs). A-II produces a multitude of physiological effects including vasoconstriction, release of aldosterone from the adrenal cortex, and release of catecholamines by activation of angiotensin receptors (AT1) at the level of smooth muscle tissue vessels. Olmesartan and analogs, blocking the effect of A-II on AT1, produce anti-hypertensive effect (BP: blood pressure) [9].

The renin-angiotensin-aldosterone system (RAAS) plays a key role in regulating blood pressure and the pathogenesis of hypertension. It consists in an enzymatic cascade: angiotensinogen, produced by liver, is converted to angiotensin I (A-I) by renin, secreted by juxtaglomerular cells by kidneys. The angiotensin-converting enzyme (ACE) converts A-I into A-II (Fig. 1). ACE inhibitor drugs block the formation of A-II, also preventing the degradation of bradykinin. The consequent accumulation of bradykinin, as well as the substance P and related active peptides, can contribute to the development of side effects such as cough and angioedema [9]. In addition, ACE inhibitors may block the RAAS completely. In vitro studies have shown that angiotensinogen can be converted into A-II by dependent non-renin enzymes, such as tissue plasminogen activator, cathepsin G, elastase and chymostatin [9].

The primary receptors for A-II are AT1 and AT2; the blockage of the AT1 receptors consequently triggers an increase in circulating angiotensin II levels, with possible overstimulation of the AT2 receptors. These effects include vasodilation, sodium and water retention, cell proliferation and overgrowth [9].

- At cellular level, A-II modulates cell growth, differentiation and apoptosis; the over stimulation of this receptor may favor the production of inflammatory cytokines (eg IL-6), the expression of adhesion molecules and the consequent recall of inflammatory cells, chemotaxis, activation of macrophages, fibroblasts growth and the synthesis of extracellular matrix proteins by activating the tissue remodeling process [10].
- At renal level, A-II modulates the growth and synthesis of extracellular matrix, determining fibrogenesis and overgrowth of renal tubular cells [11]. One of the main targets of A-II in renal fibrosis is TGF-β, a pro-fibrotic cytokine; it in fact stimulates its synthesis and transcription, and induces specific receptors for TGF-β, enhancing fibrogenesis, accumulation of extra-cellular matrix, inflammation and apoptosis.[11] All this leads to long-term instability of renal failure.
- The selective blockade of AT1 and the over-stimulation of AT2 caused by the angiotensin receptor blockers (ARBs) may result positive to have a beneficial effect on mediating vasodilatation and controlling hypertension. However, it would appear that in the long term, AT2 stimulation could also exert hypertrophic and anti-angiogenic influence on cardiovascular tissues. Thus, the long-term consequences of ARBs therapy may be less advantageous than what was supposed and could even be harmful in some circumstances. The potential consequences of such effects could include cardiac overgrowth, vascular fibrosis and a decrease in vascularization in hypoxic tissues such as myocardium [12].

In 1996, Yanagisawa and his colleagues studied normotensive rats whose AT2 receptor was pharmacologically blocked. This did not have any effect on blood pressure, instead rats showed overgrowth and fibrosis; this suggests that the effects of A-II can be partly mediated by the AT2 receptor. The chronic blockade of AT1 with Losartan lowered blood pressure, inducing overgrowth of muscle cells and hyperplasia. This study, and many others, suggest both pro-hypertrophic and anti-hypertrophic effects of AT2 [13].

Despite a low content of AT1 and AT2 receptors in the heart, A-II has been shown to increase the risk of overgrowth in rat cardiac myocytes; this action is then blocked by specific AT1 receptor antagonists [14].

In vivo studies on animal pointed out A-II as a hypertrophic heart agent, despite the emodinamic loading effects. A-II growth stimulation's on myocytes can be primary or secondary to a greater synthesis and release of other growth factors by myocytes and non-myocyte cells.

The evidence that A-II acts on myocytes to stimulate their growth, either directly or through mediation of other factors, was first reported in the embryonic mycocytes of chicks [15]. If the AT1 receptor can block or reduce the proliferation and cellular overgrowth caused by A-II, the intake of Olmesartan Medoxomil could trigger the overgrowth of other body areas, including gums. This happens because Olmesartan Medoxomil blocks the AT1 receptor.

The aim of the study is to evaluate whether the two drugs with Olmesartan Medoxomil as the active principle both with and without diuretic hydrochlorothiazide, are able to determine gingival overgrowth.

MATERIALS AND METHODS

The study design was prospective observational. Groups were not influenced in any way during the process. Their exposure was spontaneous and not conditioned by the researcher. For this reason the participation of the ethics committee was not necessary. The research followed the U.E. guidelines of good clinical practice, in accordance to the Helsinki declaration. The experimental purpose of the clinical data was disclosed to each patient.

108 subjects (62 males, 46 females) from the Cardiology Department, suffering from hypertension and treated with these drugs were divided into three groups: G1 = 60 subjects treated with Olmesartan Medoxomil and hydrochlorothiazide (average dosage 20.5 ± 1.51 mg / day) (mean age 66 ± 11); G2 = 24 subjects treated with Olmesartan Medoxomil (average dosage 21.2 ± 2.2 mg / day) (mean age 63 ± 7); G3 = 24 healthy subjects not on medication (60± 15).

Patients in the study were examined at the Odontostomatological Clinic at the University Hospital of Trieste from June 2014 to January 2016.

Subjects with total edentulism were excluded from the study, as those who were taking other drugs that could potentially interfere with periodontal tissues such as cyclosporine, nifedipine, calcium channel blockers and diphenylantoin. The participation of those who underwent hormonal therapy and periodontal surgery in the upper (1.3 to 2.3) and lower (3.3 to 4.3) frontal region was also prevented. One of the main inclusion criteria was that patients had to have at least the elements from 1.3 to 2.3 and 3.3 to 4.3. The teeth notation used is the ISO system by WHO.

The individual periodontal signs of the II (1.3 to 2.3) and V (4.3 to 3.3) region were recorded, including the presence of restorations; the

plaque index (IP), the presence of plaque on the four surfaces (vestibular, mesial, distal, and lingual or palatal) were detected through the passage of a PCP12 probe (Hu-Friedy) and the percentage of surfaces covered by plaque were evaluated. The gingival overgrowth index (OI) was examined considering the vertical [16] and horizontal [17] analysis of the gingival increase (Table 1). Applying Seymour's method, the horizontal component of the overgrowth have been assessed. This method consists in dividing the upper and lower anterior segments into five gingival units, both buccally and lingually and measuring the area between two teeth. Furthermore, both vertical and horizontal components (expressed in millimeters) have been evaluated.

Table 1: It's a representation of the detection method with different levels of overgrowth, both horizontal and vertical.

	Vertical overgrowth	**Horizontal overgrowth**
Grade 0	Abscence of overgrowth	Abscence of overgrowth
Grade 1	Rounding of marginal gingiva	Gingival thickness <2 mm
Grade 2	Gingival margin covers less than the half of the dental crown	Gingival thickness ≥2 mm
Grade 3	Gingival margin covers more than the half of the dental crown	

All data were recorded by a professional dental hygenist from the Odontostomatologic Clinic of the University of Trieste. The gingival overgrowth's percentage per patient has been calculated as if follows: adding the overgrowth grades of different sites (six sites for the vertical overgrowth and ten sites for the horizontal overgrowth), afterwards, the result was divided by the total number of sites and it was multiplied by 100. The exceeding 30% outcome, suggests the presence of gingival overgrowth [18]. (Fig. 2 and Fig. 3). Due to the fact that it does not exist a unified method to combine vertical and horizontal overgrowth, we decided to use the 30% as cutoff value.

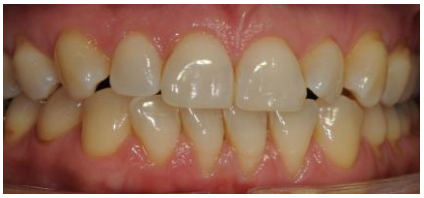

Figure 2: Subject with no sign of total gingival overgrowth (OI<30%) (horizontal overgrowth 0; vertical overgrowth 0) who was taking Olmesartan Medoxomil and hydrochlorothiazyde for 52 months.

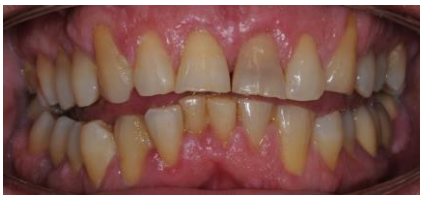

Figure 3: Subject with signs of total gingival overgrowth (OI>30%) (total mean horizontal overgrowth 0,6; total mean vertical overgrowth 0,15) who was taking Olmesartan Medoxomil and hydrochlorothiazyde for 18 months.

Statistic analysis

Continuous variables were described with mean and standard deviation while nominal variables were described with frequency. Parametric tests were chosen after testing the normality with the Shapiro-Wilk test and the variance with the Levene test. Univariate ANOVA was used to evaluate differences for IP, horizontal and vertical overgrowth, number of restorations and teeth. The non-parametric distribution of the OI% data allowed us to use the Kruskall-Wallis test. A p-value lower than 0.05 was accepted as statistically significant.

All the variables taken into consideration were statistically analyzed with the SpSS 18.0, statistical software for Mac OS X.

RESULTS

Statistically, there were no significant changes with regard to sex, age and duration of drug therapy among the groups examined (Table 2).

Table 2: Summary data of the three study groups.

	Group 1 (G1=Olmesartan Medoxomil + idroclorotiazide) (n=60)	**Group 2 (G2=Olmesartan Medoxomil) (n=24)**	**Group 3 (G3= control) (n=24)**	**Significance**
Male ; Female	34;26	17;7	11;13	NS*
Age (SD years)	66.32 (11.37)	63.38 (7.73)	60.54 (15.49)	NS*
Duration of therapy (SD months)	42.45 (30.87)	78.50(41.75)		NS*
Restoration (SD mean)	3.07 (2.81)	2.54 (2.13)	2.29 (2.85)	NS°
IP (SD mean %)	39.13 (24.17)	32.50 (29.16)	32.33 (30.45)	NS°
Number of teeth (SD mean)	11.23 (11.85)	11.29 (1.76)	11.04 (2.20)	NS°
Vertical overgrowth (SD mean expressed in mm)	0.17 (0.30) #	0.34 (0.26) #	0.17 (0.15) #	p=0.019
Horizontal overgrowth (SD mean expressed in mm)	0.33 (0.35) #	0.49 (0.35) #	0.18 (0.26) #	p=0.0089

NS *: not significant (Kruskal-Wallis test p <0.05). NS°: not significant (Unova univaria test). # Test Bonferroni p <0.05.

The frequency of conservative or prosthetic restorations ranged from 2.29 (G3) to 3.07 (G1) with no statistically significant differences. Additionally, the number of teeth and the plaque index did not show statistically significant differences (p> 0.05). However, the plaque index ranged from 32.33% (G3) to 39.13% (G1) and exceeded the stability criteria of periodontal disease.

Vertical overgrowth averaged between 0.17 ± 0.15 (G3) and 0.34 ± 0.26 (G2) showing statistically significant differences (p <0.05) compared with the other groups.

Horizontal overgrowth ranged from 0.18 ± 0.26 (G3) to 0.49 ± 0.35 (G2) showing statistically significant differences (p <0.05). Comparing the

three groups, it was found that both mean horizontal overgrowth and vertical overgrowth showed statistically significant differences <0.05 (Fig. 4 and 5).

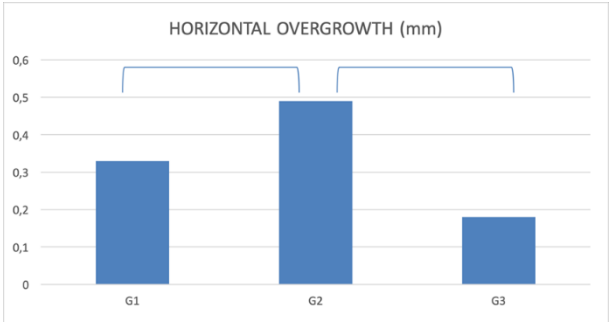

Figure 4: Horizontal overgrowth mean of the three groups (Test Bonferroni p<0,05).

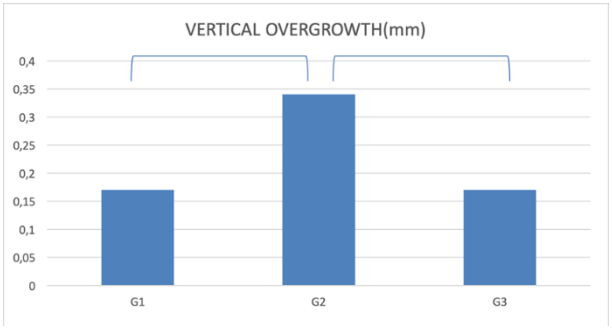

Figure 5: Vertical overgrowth mean of the three group (Test Bonferroni p<0,05).

The subjects affected by gingival overgrowth (OI>30% as cut-off value) in G1 were 25 of the 60 overall enlisted patients (41%), those in G2 were 18 over the 24 enlisted patients (75%) and those in the G3 were 6 over the 24 total patients (25%). From the statistical analysis, significative differences between G1 and G2 as compared to G3 may be recorded. (Fig. 6.)

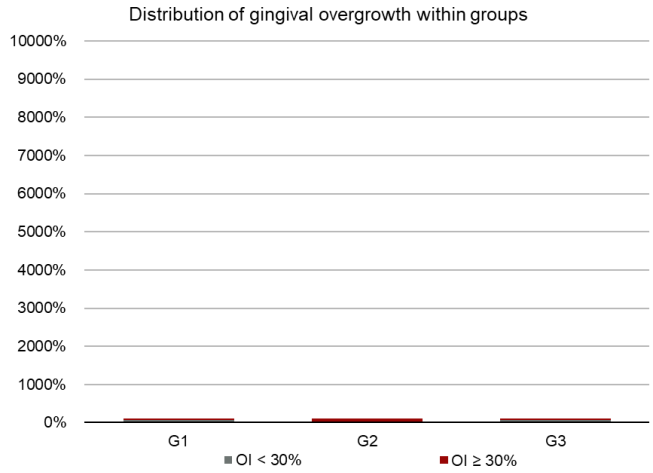

Figure 6: Distribution of gingival overgrowth within groups.

DISCUSSION

Currently the AT1 receptor antagonist drugs are widely used to control blood hypertension, the most frequent cardiovascular disease. They have few side effects such as cough, gastrointestinal disorders, headache and dizziness.

The aim of our study is to evaluate whether two drugs with active agents based on Olmesartan Medoxomil, one of which with diuretic hydrochlorothiazide, could cause gingival overgrowth among its side effects.

The Mire study conducted in 2005 showed that the binding of A-II with the AT1 receptor can cause vasoconstriction, water and sodium retention, cell proliferation and overgrowth. The latter co uld therefore also occur at the gingival level.

Unlike other drugs, with CsA, which have shown gingival overgrowth influenced by age, in both gender and for dose and duration of therapy [19, 20], no statistically significant difference from the demographic point of view, has emerged from our study.

Furthermore, in this study the presence of local irritative factors such as conservative or prosthetic restorations and bacterial plaque are not determinative of significant changes in the degree of gingival overgrowth. Even in subjects using CsA it has been shown that optimal plaque control and removal of local irritants do not prevent gingival increase but may reduce the severity of lesions.[18,20]

The antihypertensive action of Olmesartan is increased by the addition of hydrochlorothiazide. It was observed that the combination of Olmesartan with diuretic agent leads to a greater antihypertensive efficacy and an increase in the percentage of those with optimal blood pressure control. Furthermore, compared to single medication therapy, it reduces the frequency and severity of adverse circumstances and increases the patients' compliance. We observed that the use of Olmesartan alone showed greater vertical and horizontal overgrowth than subjects taking Olmesartan associated with hydrochlorothiazide, indicating that this side effect is also significantly reduced. Probably, the ability of hydrochlorothiazide to eliminate sodium and water has an anti-hypertrophic effect even at the peripheral cellular level.

Gingival overgrowth seems to be a collateral effect that accompanies these medications. All subjects presenting gingival overgrowth (OI> 30%) were reported at the Pharmacovigilance Committee of the University Hospital of Trieste.

The gingival overgrowth grading system had some limitations considering that there is no available grading system that considers both the vertical and the horizontal components in a univocal way. Nonetheless, the venture made between those two systems seemed to work.

Considering the practical results the study has achieved, it would be interesting to expand the study and deepen the issue, involving other medical centers also outside of our country

The clinical implication that our experience suggests is to establish a connection with the patient physician so to evaluate possible alternatives to the drugs prescribed, in order to reduce or better avoid the the possbile side effects described in our study.

This study suggests that examined subjects who used Olmesartan Medoxomil show a mild gingival overgrowth in the upper and lower frontal teeth; this condition is unrelated to plaque index and the presence of local irritative factors.

Gingival overgrowth is a risk factor for plaque accumulation and periodontal pocket formation and for the subsequent progression of periodontal disease. To prevent this, in patiens taking these medications, regular check-ups would be useful.

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