

Consequences of Respidone and Olanzapine on salivary IgA and some electrolytes levels in psychotic patients

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Abstract

Background: Saliva is a complex secretion and plays an essential role in the maintenance of oral health. It's constituted by water, organic and inorganic components which have biological functions essential for homeostasis of the oral cavity. Saliva also contains a wide variety of unique proteins, such as secretory IgA. Variations in salivary flow can be affected, reversibly or irreversibly, by numerous physiological and pathological factors. Saliva is a promising option for diagnosing certain disorders and monitoring the evolution of certain pathologies or to measure medicines or drugs.

Aim: The aim of this study was to evaluate the effect of atypical antipsychotic drugs (Respidone and Olanzapine) on salivary IgA and electrolytes levels.

Patients and methods: The study sample consists of 20 diagnosed psychiatric patients (age range 20-40). They were divided into 2 groups of 10 patients (1st group were treated with Respidone and the 2nd group treated with Olanzapine), two samples were taken from each patient of both groups, one before starting treatment and the other after 2 months of subjecting them to selected treatment.

Results: The result of the current study showed significant reduction ($p < 0.05$) between salivary levels of immunoglobulin A and electrolytes (Na^+ , K^+ , Ca^{++}) in psychiatric patients before and after 2 months of Olanzapine and Respidone therapy. Olanzapine induced a greater percentage of IgA reduction than that of Respidone

Conclusion: Both Respidone and Olanzapine significantly reduced salivary IgA and electrolytes of Na^+ , K^+ and Ca^{++} level, and both drugs caused reduction of saliva secretion.

Key words: Respidone, Olanzapine, psychiatric patients, Saliva, immunoglobulin A

Introduction

Saliva is a glandular secretion that is essential for the maintenance of healthy orodental tissue. Saliva is a complex fluid and many of the functions of saliva have a protective role, acts as a lubricant and cleanses the teeth (1)

Saliva plays a very important role in oral health, it maintains the integrity of oral hard and soft tissues and protects against immunologic bacterial, fungal and viral infections. Saliva controls the equilibrium between demineralization and remineralization in a cariogenic environment, salivary buffers can reverse the low pH in plaque and allow for oral clearance thus preventing demineralization of enamel. The flow rate and viscosity of saliva may also influence the development of caries (2).

Saliva is comprised primarily of water along with electrolytes such as sodium, potassium, calcium, bicarbonate, magnesium and fluoride. Secretory proteins such as amylase, lipase, albumin, histatin, lysozyme and mucins, immunoglobulins, primarily IgA, IgG & IgM, salivary IgA is the predominant immunoglobulin in secretions of the mucosal immune system. It is found in the saliva, intestinal secretions, bronchoalveolar lavage fluid, urine, tears, and other mucosal fluids. The basic function of immunoglobulins is to help the body protect itself against potential pathogens; it inhibits attachment and replication of pathogenic microorganisms, preventing colonization by these pathogens; it is also capable of neutralizing toxins and viruses, immunoglobulins and has always been the subject of research in finding the relationship with psychotic disorders and few works with controversial results have been done in this respect. Also some of the typical antipsychotic drugs have been noticed to affect the serum concentration of immunoglobulins (3, 4).

Secretion of IgA in saliva is the first line of defense of the host against pathogens which invade mucosal surfaces, salivary IgA antibodies could help oral immunity by preventing microbial adherence, neutralizing enzymes, toxins and viruses; or by acting in synergy with other factors such as lysozyme and lactoferrin, some studies have also demonstrated a lower incidence of caries as a result of a high salivary IgA concentration. In addition, low levels of salivary IgA have been presented as a risk factor for upper respiratory infection and have also been associated with an increased risk for periodontal disease and caries (5).

Oral reactions to medications are common and affect patients' quality of life. Almost all classes of drugs, particularly those used continuously, such as antidepressants, antihypertensive, anxiolytics, hypnotics, diuretics, antipsychotics among others, including vitamins, minerals and phyto-pharmaceuticals, may cause oral alterations. If not suitably treated, these may aggravate the patient's general state of health and affect his/her oral health (6).

Olanzapine is one of the atypical antipsychotics; it is useful for the management of several symptoms commonly encountered in palliative care, such as delirium, delusion, hallucinations, apathy and lack of motivation (7).

Risperidone is also one of the atypical antipsychotics called serotonin-dopamine antagonists (SDA), which have high affinities for both the dopamine D2 receptor and the serotonin 5-HT2 receptor in the brain (8).

With noticeable neglect of oral health status in psychiatric patients, and the expected additional effect of the antipsychotic drugs on salivary component (such as electrolytes and Immunoglobulins), and to determine the difference of such effects between different drugs, and to help psychiatrists and dentists better control oral health either by prevention or intervention, such studies have been done.

This study was undertaken to evaluate the effects of Respidone and Olanzapine on the IgA and electrolytes (sodium, potassium, calcium) levels in saliva of diagnosed psychiatric patients.

Patients and Methods

Study Design and Sampling

A total of 20 patients (age range 20-40 years old) were selected from (Erbil psychiatric hospital psychiatric outpatient clinic) after they were diagnosed by psychiatrist for presence of psychosis. They were divided into 2 groups of 10 patients (1st group were treated with Olanzapine and the 2nd group treated with Respidone); two saliva samples were taken from each patient of both groups, one before starting treatment, and the other after 2 months of subjecting to selected treatment.

Inclusion Criteria

1. Age range between 20-40 years.
2. Person under antipsychotic medication (Olanzapine or Respidone).

Exclusion criteria

1. Patient not within the age range.
2. Patient with systemic disease.
3. Persons with smoking habit.
4. Fever and cold.
5. Pregnant and lactating women.
6. Alcohol taking.
7. Patient with medication.

Collection of Saliva Samples

Collection of whole saliva samples which was used in the current study were performed under resting conditions in a quiet room during the afternoon, between 9:00 am and 12:00 am, at least 1 hour after eating, by the spitting method or direct expectoration method: Subjects were asked to collect saliva in their mouths and to spit it into a sterile plastic dish with a diameter of 6 cm for 5 minutes.

Salivary IgA measurement by Enzyme Linked Immunosorbent Assay (ELISA)

For the quantitative determination of the SIgA in the saliva we employed the ELISA method with salivary secretory IgA Kit of (salivary secretory IgA Kit IBL-Germany) in accordance with the manufacturer's instructions. Salivary SIgA levels (mg/ml) in each sample were calculated using a standard curve obtained from calibrators in the kit.

Saliva electrolytes analysis

The fresh saliva specimen was kept in an ice bucket and sent to the laboratory for analysis within one hour. For the determination of salivary ions, saliva was diluted at either 1/100 or 1/1000 and K⁺, Na⁺ and Ca²⁺ concentrations were determined using flame emission spectrometry

Statistical analysis of data gained from Saliva sample
IgA level for each sample was estimated; the difference between IgA levels in pre-treatment and post-treatment values were calculated, and the mean of IgA difference calculated. Values of standard error, Standard deviation, P value and significance were determined. All data were analyzed using the Statistical Package for Social Sciences (version 21.0; SPSS Inc., Chicago, Illinois, USA).

Paired t-test was used to analyze differences between the pre and post saliva sample variable of the two group, and a t-test for independent variable to evaluate differences between the group; values of less than 0.05 were considered statistically significant. The same procedure was done for estimation of value salivary electrolytes (sodium, potassium, calcium).

Results

Effects of Olanzapine and Respidone on the salivary IgA levels in psychiatric patients

By comparison of salivary immunoglobulin levels (IgA) between psychiatric patients before and after 2 months of 4 mg/d Respidone therapy, significant differences were also noted as shown in Table 1.

Table 1: Effect of Respidone and Olanzapine on Salivary IgA levels of 20 psychiatric patients

IgA (mg/ml)	Before	After	P value
Respidone/mg	0.167±0.004	0.159±0.005	0.003
Olanzapine/ mg	0.174±0.005	0.159±0.004	0.022

By comparison of immunoglobulin levels (IgA) between psychiatric patients before and after 2 months of 4 mg/d Olanzapine therapy, significant differences were noted as shown in Table (1).

Effect of Olanzapine and Respidone on salivary electrolytes (Na⁺, K⁺, Ca⁺⁺) in psychiatric patients.

The levels of salivary electrolyte (Na) of psychiatric patient before and after 2 months of 4mg/day of Respidone therapy are significantly reduced as noted in Table 2.

Table 2: Effect of Respidone and Olanzapine on Salivary (Na) levels found in 20 psychiatric patients

Na (mm/l)	Before	After	P value
Respidone	7.78±0.39	4.12±0.33	0.001
Olanzapine	7.55±0.6	4.32±0.59	0.001

The levels of salivary electrolytes (Na) of psychiatric patient before and after 2 months of 4mg/day of Olanzapine therapy are significantly reduced (Table 2).

Comparing the effect of Respidone on salivary electrolytes (K) levels between psychiatric patient before and after 2 months of 4mg/day therapy of the drug, the levels were significantly reduced as noted in Table 3.

Table 3: Effects of Respidone and Olanzapine on salivary (K) levels that found in 20 psychiatric patients

K (mm/l)	Before	After	P value
Respidone (mg)	17.91±0.22	17.48±0.23	0.048
Olanzapine (mg)	17.58±0.22	17.43±0.18	0.045

Comparing the effect of Olanzapine on salivary electrolytes (K) levels between psychiatric patient before and after 2 months of 4mg/day therapy of named drugs the levels significantly reduced as also noted in Table 3.

The levels of salivary electrolytes (Ca) are significantly reduced in psychiatric patient before and after 2 months of 4 mg/day of Respidone therapy as noted Table 4.

Table 4: Effects of Respidone and Olanzapine on salivary (Ca) levels that were found in 20 psychiatric patients

Ca (mm/l)	Before	After	P value
Respidone(mg)	1.99±0.25	1.42±0.26	0.00
Olanzapine(mg)	1.52±0.15	1.44±0.14	0.00

Effects of Olanzapine on the salivary Ca levels

The levels of salivary electrolyte (Ca) are significantly reduced in psychiatric patient before and after 2 month of 4 mg/ day of Olanzapine therapy as aslo noted Table 4.

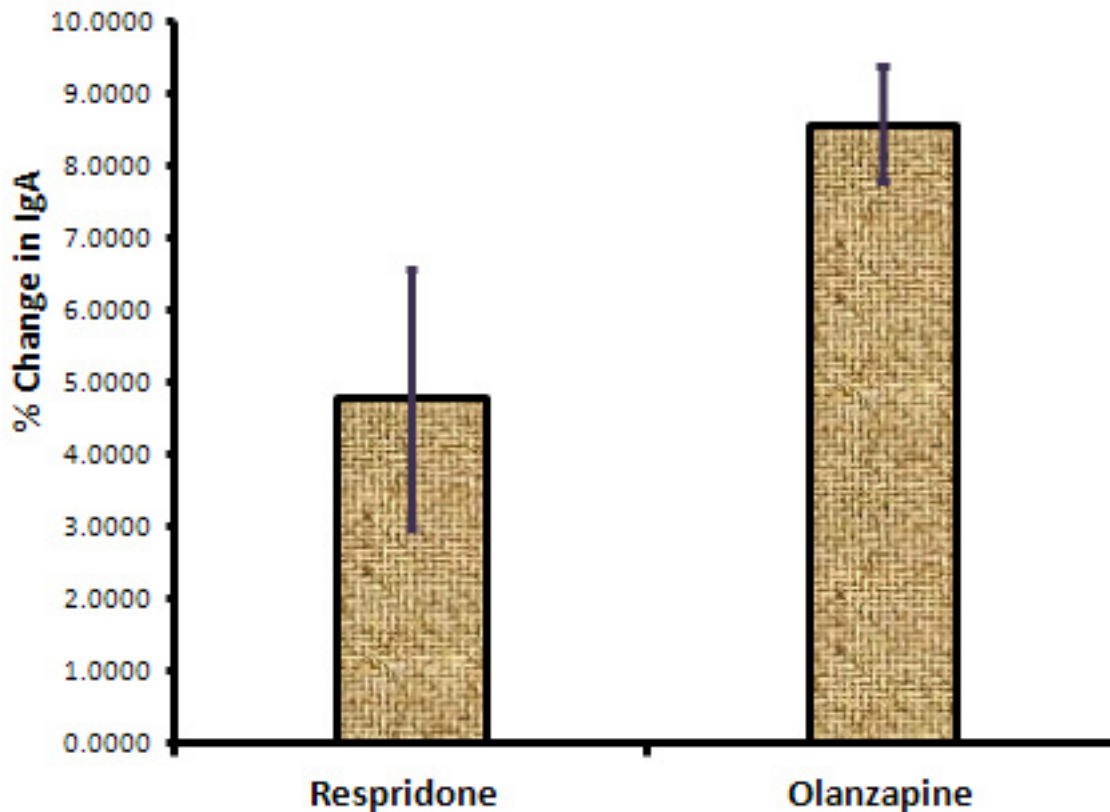
Comparing effect of Respidone & Olanzapine on Salivary IgA, Na, K, and Ca.

The result of this study showed that no significant differences were found in the effect of both drugs (Respidone and Olanzapine) on salivary IgA after two months of 4mg/day therapy. Also the result showed that both drugs have the same reduction effect on salivary electrolytes (Na, K,Ca) after tow month therapy. This mean that there were no significant differences of their effect on the salivary electrolytes as seen in table 5. However Olanzapine induced a greater percentage of changes in IgA in psychiatric patients than that of Respidone as shown in Figure 1.

Table 5: Salivary levels of IgA and salivary electrolytes (Na, K, Ca) in psychiatric patient treated with both Respidone and Olanzapine

	Respidone	Olanzapine	P value
IgA(mg/ml)	0.159±0.005	1.59±0.004	1
Na(mm/l)	4.12±0.33	4.32±0.59	0.74
K(mm/l)	17.48±0.23	17.43±0.18	0.86
Ca(mm/l)	1.42±0.26	1.44±0.14	0.94

Figure 1. Percentage of IgA changes in psychiatric patients treated with Respidone and Olanzapine



Discussion

Saliva is a complex biofluid that plays an essential role in the maintenance of oral health. It constitutes water, organic and inorganic components which have biological functions essential for homeostasis of the oral cavity. It contains a wide variety of unique proteins, including proline rich proteins (PRPs) and enzymes such as lysozyme, lactoferrin, peroxidases, and secretory IgAs. A major protective function results from the salivary role in stabilizing the ecological balance in the oral cavity via clearance, aggregation and reduced adherence by both immunological and non-immunological means as well as direct antimicrobial activity.

As salivary immunoglobulin levels (IgA) in psychiatric patients with the effect of Olanzapine and Respidone (Atypical Antipsychotic Therapy) at a daily dose of 4 mg, was one of the aims of the current study, a statistically significant reduction in the level of IgA is reported in psychiatric patient when they were treated with the Respidone or Olanzapine drugs.

Higher drooping was noticed when Olanzapine was used, although no significant difference reported between salivary levels of IgA in patients treated with both drugs but Olanzapin induced a greater percentage of reductions of salivary IgA than that of Respidone. Therefore physicians should be aware of oral infection or dental caries in psychiatric patients treated with both drugs especially with Olanzapine. No data is available about the influence of antipsychotic agents on salivary IgA. However Jafarzadeh

et al. (2008) found an increase in the salivary IgA levels with increase of patient age up to 60 years. The reduction of salivary IgA found by the current study does not support this statement, and can be explained by the curtailment effect of antipsychotic drugs on salivary volume production generally, and its constitutes specifically (5). In another study Hussein (2010) observed the effect of antipsychotic drugs on serum IgA levels (9), found insignificant difference in serum IgA levels before and after 2 months of treatment with antipsychotic drugs. This result did not agree with those found by the current study, and the difference is expected to be due to that, antipsychotic drugs need more time and/or there dose to show there effect systemically on blood, rather than salivary IgA which affected more rapidly. While Burns et al, (1982) suggested there were higher levels of IgA in serum rather than saliva (10), this again supports the current study explanation of need of higher dose and duration of therapy with antipsychotic drugs to reduce these higher levels of serum IgA.

The finding of current study showed that both Olanzapine and Respidone significantly reduced the salivary Na levels, at the same time they showed almost similarity in their effects on salivary Na level when they were compared together. The same reduction in salivary Na levels was reported by Godoy, et al (2012) who measured changes in salivary Na in patients who were under Clozapine administration, and they explained such droop in Na levels by its relation to decrease the salivary flow rate (11). Hence the same explanation can be used in the current study, as both Olanzapine and Respidone have the same xerostomia effect, a result and explanation supported also by Tayab et al, (2012) (12).

Few studies are available around this subject, going to results that atypical antipsychotic drugs (Olanzapine & Resperidone) can affect the amount of saliva secreted and may alter the composition of saliva via their receptor effects on the dual sympathetic and parasympathetic innervations of the salivary glands, as it is regarded as the main factor responsible for the decrease in the salivary flow rate, and the decrease in electrolyte levels (13).

Although most explanations for changes of salivary Na levels go with those blaming salivary flow rate, still many factors should not be neglected such as dietary Na intake differences

The finding of the present study showed that Resperidone significantly reduced the salivary K levels, while Olanzapine shows no significant effect on K levels. This result could be attributed to the fact that Resperidone occupied Dopamine D2 receptor more significantly than Olanzapine and as occupation of these receptors provide a valid predictor of anticholinergic effect, which might explain the greater reduction k levels associated with Resperidone (14).

The finding of the present study showed that Resperidone significantly reduced the salivary Ca levels, while Olanzapine showed no significant effect on Ca levels. Catalán, et al, (2014) concluded that changes in electrolyte concentrations and pH in saliva have an important role in the enamel demineralization of teeth (15). The results of this study, showed general reduction in the levels of all three investigated electrolytes (Na, K, Ca). That's to say there were changes in the levels of electrolytes, and its mostly seen that Resperidone showed greater effect, whilst Olanzapine showed less effect on the level of electrolytes. These findings are expected to have many explanations, one of them is how far the patient follow the regular dosage of the treatment , as it has been reported that swing in the levels of antipsychotic drugs may affect the levels of secretion of saliva and also the levels of electrolytes, Reynolds (2011) and Mos, (2015) stated that non constant levels of antipsychotic in serum as result of inconstant daily dosage of the drug intake causes xerostomia for the patients. This results from stimulation of sympathetic postsynaptic alpha-1 adrenergic receptors, and thus leads to an increase in water and electrolytes secretion, also increase in the stimulation of Beta-1 adrenergic receptors resulted in elevated secretion of enzymes and proteins in saliva (16, 17). Also it was noticed that activation of somato dendritic alpha-2 adrenergic receptors inhibited saliva secretion(17).

Another explanation for this fluctuation, is that the expected effect of the antipsychotic drugs on the glandular tissue of the salivary gland itself and the resultant effect on the reduction of salivary secretion. This effect was noticed by Vinayak et al (2013) when they studied the Salivary glands, and noticed a swelling in patients treated with clozapine which do not manifest hypersalivation (18). The effect of the antipsychotic drugs on glandular tissues themselves leads to thickening and stasis of saliva, claiming calcium

salts and its precipitation in the ducts, and this leads to calculus formation and obstruction, resulting in distension of the gland.

Conclusion

Based on this study's results the following conclusion can be made;

1. Both Olanzapine and Resperidone show significant reducing effect on salivary IgA levels in psychiatric patients. Nevertheless Olanzapine induced a greater percentage of IgA reduction than that of Resperidone
2. Both Olanzapine and Resperidone have significant reducing effect on salivary electrolytes (Na⁺, K⁺ and Ca⁺⁺) levels in psychiatric patients.
3. Both Olanzapine and Resperidone caused reduction of saliva secretion (Xerostomia).

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