Original Article

Assessment of changes in QT interval induced by atypical antipsychotic medications used by patients hospitalized in the psychiatric ward

Masoumeh Nazarinasab[1], Hamzeh Rostami[1], Habib Haybar[2], Amir Mohmmad Eghbalnejad Mofrad[3*]

[1] Department of Psychiatry, Golestan hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. [2] Atherosclerosis research center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz. Iran. [3] Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Correspondence: Amir Mohammad Eghbalnejad Mofrad. Medicine department, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. E-mail:amir_gforce69@yahoo.com

ABSTRACT

Background: Prolonged QT interval is one the side effects of atypical antipsychotic medications the aim of this study is assessment of changes in QT interval induced by atypical antipsychotic medications used by patients hospitalized in the psychiatric ward of golestan hospital in 2016. methods: this Retrospective cohort study was conducted on patients admitted to the psychiatric ward of Ahvaz Golestan Hospital in 2016 for 14 months. 105 patients were divided into three 35-member groups receiving Olanzapine, respiridone, and quetiapine. The patients were subjected to ECG assessment at the time of admission and one month after the onset of the treatment. The Qt Prolongation was measured based on Qt interval and the existing relevant criteria. Finally, the Data were analyzed using SPSS software version 22. Results: patients' age was 26.74 ±3.56 in the olanzapine group, 27.43 ±4.62 for the Resperidone group and 26.4 and 1.5 for the Quetiapine group, which was not statistically significant (p-value: 0.434). The mean of the medications dosages administered to the patients during the first month of treatment were 25.55 ±0.94 for the Olanzapine group, 5.28±0.23 for the Resperidone group and 396.57 ±78.78 for the Quetiapine group respectively. The mean of QT interval variations were 448.80 and 6.82 In the Olanzapine group, 452.77 and 18.36, In the Resperidone group, and 447.31 and 10.86 in the Quetiapine group respectively which showed statistically significant differences between the groups (p <0.001). Conclusion: compared with the Olanzapine and quetiapine, Resperidone proved have a more significant impact on QT interval variations.

Keywords: QT interval, atypical antipsychotic medications, psychiatric disorders

Introduction

Today Antipsychotic medications are not only used for treatment of psychosis and schizophrenia, but are being increasingly used for treatment of non-psychotic patients. The second generation of these medications is widely used in clinics and is the world's most common choice among patients' treatment regimens. Considering the increased use of these medications and their undeniable side effects, many researchers have focused their studies on the side effects of these medications. the studies on the most frequently used second generation of these medications show that extrapyramidal side effects usually appear after taking Resperidone, hyperglycemia and dyslipidemia usually appear after taking Olanzapine and Clozapine, hyperprolactinemia usually occurs after taking Sertindole and Zipracidone, prolonged QT interval usually appears after taking Amisulpride and Resperidone and finally weight gain usually appears after taking Olanzapine and Clozapne. Prolonged QT interval is caused by all atypical medications, but except for Ziprasidone and Sertiandole, which can significantly prolong the QT interval, other medications can lead to minor complications of this kind if the patient doesn't

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Masoumeh Nazarinasab, Hamzeh Rostami, Habib Haybar, Amir Mohmmad Eghbalnejad Mofrad. Assessment of changes in QT interval induced by atypical antipsychotic medications used by patients hospitalized in the psychiatric ward . J Adv Pharm Edu Res 2019;9(S2):140-145.
Source of Support: Nil, Conflict of Interest: None declared.

have any risk factors and doesn't suffer from any underlying heart condition [1]. Cardiovascular complications are among the important complications caused by such medications. The factors that usually lead to such complications include glucose metabolism disorders and lipid changes [2, 3]. Qt prolongation is one of the important complications associated with cardiovascular side effects. Qt prolongation leads to the active phase (premature contraction) in the final phase of cardiac depolarization, increasesing the risk of ventricular arrhythmias and fatal ventricular fibrillation [4]. The risk of qt prolongation is higher in women and elderly people with high systolic blood pressure [5]. Cardiovascular complications however, are not commonly seen in children and adolescents, and they seem to be immune to such complications [6, 7]. QT prolongation that is diagnosed by Electrocardiogram (ECG) is usually known as torsade de points which can lead to ventricular fibrillation [8] torsade de pointes is of great importance because this abnormal heart rhythm can lead to sudden death and exhibit that characteristics of Polymorphic Ventricular Tachycardia in ECG [9]. The risk factors that can be used to development of Qtc prolongation to Tdp include: 1-Bradycardia, 2- congenital Qtc syndrome, 3-female gender, 4-old age, 5- Renal problems. Studies however, show that an overdose of these medications can't have a significant contribution to cardiac toxicity, resulting in Tdp and sudden death [1, 5] studies also show that cardiac toxicity and cardiac death are most commonly seen in schizophrenic patients [10], according to other studies. These medications can prolong Qt intervals and potentially increase the mortality rate of patients [8, 9]. Hock Heng et al. (2008) conducted a systematic study on atypical medication-induced cardiac complications in 200 patients receiving these medications, the findings showed that only three patients suffered from ventricular tachycardia and three others died of cardiac complications. Studies show that overdose on such medications could not significantly contribute to cardiac toxicity resulting in Tdp and sudden death [1] considering the importance of QT prolongation, and the lack of research in this field in Iran, in the present study attempts are made to assess the QT interval changes induced by atypical antipsychotic medications in patients hospitalized in the psychiatric ward of golestan hospital in 2016.

Material and Methods

After obtaining the permission and approval of the Ethics Committee of Ahwaz University of Medical Sciences, a retrospective cohort study was conducted on patients admitted to the psychiatric ward of Ahvaz Golestan Hospital in 2016 for 14 months. The inclusion criteria included age of 18 -65 years, lack of cardiovascular disease approved by a cardiologist, psychotic problems such as schizophrenia, Bipolar psychosis, schizophrenia , Delusional disorders, acute psychosis, and NOS psychosis disorder approved by a psychiatrist, as well as non-use of atypical antipsychotics for 2 weeks before the treatment. Also, the exclusion criteria included: history of seizure, active suicidal ideations, abnormal ECG at the beginning of examination, pregnancy, severe medical condition (blood pressure and diabetes), allergic reaction to antipsychotics, and use of medications that cause Qt prolongation (e.g. Antiarrhythmia: Quinidine, Procainamide, Disopyramide, Ajmaline. Calcium channel blockers: Prenylamine, Bepridil, Terodiline, and Psychiatric medications: Thioridazine, Chlorpromazine, Haloperidol, Droperidol, Amitriptyline, Nortriptyline. Antihistamines and anti-malaria medications: Erythromycin, Clarithromycin, Ketoconazole, Pentamidine, Quinine, Chloroquine, Halofantrine. Antagonists and serotonin agonists: Ketanserin, Cisapride as well as specific diseases during lactation). Thus, 105 patients were divided into three 35-member groups receiving Olanzapine, respiridone, and quetiapine. The patients were subjected to ECG assessment at the time of admission and one month after the onset of the treatment. The Qt Prolongation was measured based on Qt interval and the existing relevant criteria. Finally, the Data were analyzed using SPSS software version 22.

Results

In the Olanzapine group, 19 members (54.3%) were male and 16 (45.7%) were female. In the Resperidone group, 16 members (45.7%) were male and 19 members (54.3%) were female, and in the Quetiapine group 16 members (45.7%) were male and 19 memebrs (54.7%) were female. There was no significant difference between the two groups in terms of the number of male and female patients (p value: 0.710).

The mean of the medications dosages administered to the patients during the first month of treatment were 25.55 ±0.94 for the Olanzapine group, 5.28±0.23 for the Resperidone group and 396.57 ±78.78 for the Quetiapine group respectively.

The mean of the patients' age was 26.74 ±3.56 in the olanzapine group, 27.43 ±4.62 for the Resperidone group and 26.4 and 1.5 for the Quetiapine group, which was not statistically significant (p-value: 0.434).

The mean and standard deviation of the QT interval in the ECG of the patients before the onset of drug therapy was 440.2 and 7.29 in the olanzapine group, 440.57 and 4.84 in the Resperidone group and 440.46 and 5.45, in the Quetiapine group, which proved to be statistically significant (P value: 0.805).

Univariate analysis of QT interval variations

The mean of QT interval variations were 448.80 and 6.82 In the Olanzapine group, 452.77 and 18.36, In the Resperidone group, and 447.31 and 10.86 in the Quetiapine group respectively which showed statistically significant differences between the groups ($p < 0.001$). QT interval variation and prolongation in the Resperidone group turned out to be significantly higher than that in the Quetiapine and Olanzapine groups (p-value: * 0.005, ** <0.001).

Multivariate analysis of QT interval variations

After taking other variables under control, gender turned out to have no statistically significant effect on QT interval variations (p-value: 0.247). age also turned out to have no statistically significant effect on QT interval variations (p-value: 0.528) .after controlling other variables, the comparison of olanzapine and respridone groups in terms of QT interval variations showed statistically significant difference between the two groups (p-value: 0.01). Comparison of QT interval variations in the Respridone and Quetiapine groups, however, showed no significantly different between the two groups (p-value = 0.067). The Comparison of QT interval variations in the Quetiapine and Olanzapine groups showed no significant difference between the two groups either (p-value = 0 .488).

Discussion and Conclusion

Univariate analysis of QT interval variations obtained from the three groups (i.e. the users of Resperidone, Quetiapine and Olanzapine) showed significant differences between the three groups. In this comparison, QT interval variation and prolongation in the Resperidone group were significantly higher than those in the Quetiapine and Olanzapine treatment groups (p <0.001). Also, the multivariate analysis of QT interval variations, with variables affecting QT variations being under control, showed statistically significant differences between the olanzapine and Respridone treatment groups (p-value: 0.01). No significant difference was observed between the Respridone and Quetiapine groups in this regard, the difference between the two groups, however, turned out to be marginal (p-value = 0.067). The Quetiapine and Olanzapine treatment groups didn't show any significant difference in this regard (p-value = 0.448).

In addition, with other variables being under control, gender turned out to have no significant effect on QT interval variations (p-value: 0.247), the effect of age on QT interval variations also turned out to be statistically insignificant (p-value: 0.528).

Comparison of results with other studies and potential mechanisms.

Generally, antipsychotics are divided into typical and atypical groups. The Typical medications are Dopamine D2 Receptor Antagonists, while atypical medications are serotonin-dopamine antagonists [11]. It is also necessary to classify typical antipsychotics in terms of potency. Medications such as Chlorpromazine are classified as low-potency medications while haloperidol and TFP are classified as high-potency medications. Among antipsychotics, low-potency typical medications mostly lead to "Torsade de pointes." [12] The findings of a number of challenging studies on the effects of typical and atypical medications on Torsade de pointes and sudden cardiac arrest have already been published. Liperoti et al. figured out that Use of conventional antipsychotics was associated with a nearly 2-fold increase in risk of hospitalization for ventricular arrhythmias or cardiac arrest, while there was no increased risk associated with the use of atypical antipsychotics [13]. Contrary to this finding, a study on two types of antipsychotics showed that the use of risperidone, as compared to haloperidol, was associated with a greater risk of arrhythmias and sudden death due to cardiac disorders [14]. The difference between these studies confirms the need for conduction of the present study. On the other hand, HeneSSy et al. conducted a Study on schizophrenia patients and found that cardiac arrhythmias were higher in these patients, as compared to the control group, but this study could not determine whether the arrhythmias is caused by the disease itself or is actually induced by the treatment medication. These findings were consistent with the study of Ray et al. Suggesting a higher incidences of cardiac arrests among the consumers of antipsychotics [15]. In fact, the reason for increased prevalence and frequent use of atypical medications could be associated with their previous side effects. The frequent and serious incidence of motor disorders in patients taking typical medications led to limited use of such medications by these patients [16]. Since the atypical antipsychotics exhibited less complications, these medications were considered as a safe alternative treatment, and were widely used instead of previous medications. The use of these medications was increased by about two-fold over the four years since they were introduced into the market. Although typical anticoagulants turned out to be associated with arrhythmias and cardiac arrest due to QT prolongation [17]. It was still believed that the atypical medications are better choice in this regard [18]. However, the limited published information has already indicated that this class of medications share similar electrophysiological effects with typical medications [19]. Numerous case report studies have already indicated the incidence of this arrhythmia in some atypical medication users [20, 21] Lin et al. found that age and female sex, from among the effective factors, have a significant relationship with antipsychotic-induced QT interval prolongation [22]. While, in our study, no significant relationship was observed between age and sex and QT interval variation. In an attempt to justify the differences between the findings, we can argue that the QT interval variations are mainly associated with a specific class of anti- Psychotics and could be dosage-dependent and occur at high treatment doses. These findings are not consistent with previous findings and the lower dosage of the medications administered in our study could serve as the most likely justification for this difference. In the study conducted by Pandurangi et al. The mean QT interval was higher in the patients taking olanzapine, speridone and haloperidol medications, but this didn't hold true for other Antipsychotic medications [23]. However, no significant difference was observed between these medications in terms of QT interval, while lack of a significant difference between these medications, especially between atypical ones, such as olanzapine and risperidone was quite unexpected. In our study, the number of male patients was approximately the same as female patients, while the number of female patients was higher in the above

study. This difference between the two studies could be attributed to the sampling and case selection methods. Harrigan et al. investigated the changes in the ECG of 160 patients with psychiatric disorders, in this study the mean QT interval increased, but did not reach 500 MS in any of the cases. The medications tested in this study included haloperidol, Thioridazine, ziprasidone, Quetiapine, olanzapine, and Risperidone [19]. This change in ECG is to a limited extent confirmed by our study. Also finaly its very importanat to mentation that the first step to developing psychiatric researches is to present limitations and low quality steps of study that we presented them several times [24-28] and even here in this article.

The limitations of this study include small sample size, the limited number of atypical antipsychotic medications and the lack of patients follow up on different time intervals for the QT interval. Moreover, the present study was a retrospective study and for accurate observation of the medication's effect on QT interval variations, it is better to conduct a prospective cohort study with a longer investigation term and with inclusion of older age patients with a longer history of medication use. Although we took advantage of the previous studies and their findings in our study, we are not sure, in some cases, whether these findings are accurately and reliably recorded in the literature. QT interval variation alone, can't account for the risk factors associated with heart diseases, and it is necessary to take PR interval, heart beat arte and QRS interval into account as well.

Conclusion

The results of the study on the QT interval variations in all three groups of Atypical Anti-psychotic users showed that none of the three atypical antipsychotics have led to a pathological QT interval prolongation associated with cardiac complications. But compared with the other two medications, Resperidone proved have a more significant impact on QT interval variations.

Acknowledgements

The present research article has been extracted from the "Thesis" conducted as a research project funded by Research Deputy of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

References

1. Tan HH, Hoppe J, Heard K. A systematic review of cardiovascular effects after atypical antipsychotic medication overdose. Am J Emerg Med [Internet]. 2009;27(5):607–16. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2759317&tool=pmcentrez&rendertype=abstract
2. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol [Internet]. 2012;8(2):114–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22009159
3. Jalali T, Eghbalnejad AM. Serum lipid profile and insulin resistance in women with polycystic ovary syndrome (PCOS). 2018;5(3):107–11.
4. Panoulas VF, Toms TE, Douglas KMJ, Sandoo A, Metsios GS, Stavropoulos-Kalinoglou A, et al. Prolonged QTc interval predicts all-cause mortality in patients with rheumatoid arthritis: An association driven by high inflammatory burden. Rheumatol (United Kingdom). 2014;53(1):131–7.
5. Rossing P, Breum L, Major-Pedersen a, Sato a, Winding H, Pietersen a, et al. Prolonged QTc interval predicts mortality in patients with Type 1 diabetes mellitus. Diabet Med. 2001;18(3):199–205.
6. Almandil NB, Liu Y, Murray ML, Besag FMC, Aitchison KJ, Wong ICK. Weight gain and other metabolic adverse effects associated with atypical antipsychotic treatment of children and adolescents: a systematic review and meta-analysis. Paediatr Drugs [Internet]. 2013;15(2):139–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23519708
7. Alipour-Parsa S, Haybar H, Namazi MH, Safi M, Khaheshi I, Memaryan M, et al. Evaluation of pentraxin-3 level and its related factors in patients undergoing primary percutaneous coronary intervention. ARYA Atheroscler . 2017;13(2):73–8.
8. Van Noord C, Eijgelsheim M, Stricker BHC. Drug- and non-drug-associated QT interval prolongation. Vol. 70, British Journal of Clinical Pharmacology. 2010. p. 16–23.
9. Chohan PS, Mittal R, Javed A. Antipsychotic medication and QT prolongation. Pakistan J Med Sci. 2015;31(5):1269–71.
10. Leung JYT, Pang CCY, Procyshyn RM, Barr AM. Cardiovascular effects of acute treatment with the antipsychotic drug olanzapine in rats. Vascul Pharmacol [Internet]. 2014 Sep [cited 2018 Mar 4];62(3):143–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24969105.
11. Arnt J, Skarsfeldt T. Do Novel Antipsychotics Have Similar Pharmacological Characteristics? A Review of the Evidence. Neuropsychopharmacology [Internet]. 1998 Feb [cited 2018 Apr 2];18(2):63–101. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9430133
12. Goodnick PJ, Parra F, Jerry J. Psychotropic drugs and the ECG: focus on the QTc interval. Expert Opin Pharmacother [Internet]. 2002 May 25 [cited 2018 Apr 2];3(5):479–98. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11996627

13. Liperoti R, Gambassi G, Lapane KL, Chiang C, Pedone C, Mor V, et al. Conventional and Atypical Antipsychotics and the Risk of Hospitalization for Ventricular Arrhythmias or Cardiac Arrest. Arch Intern Med [Internet]. 2005 Mar 28 [cited 2018 Apr 2];165(6):696. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15795349
14. Hennessy S, Bilker WB, Knauss JS, Margolis DJ, Kimmel SE, Reynolds RF, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. BMJ [Internet]. 2002 Nov 9 [cited 2018 Apr 2];325(7372):1070. Available from: ttp://www.ncbi.nlm.nih.gov/pubmed/12424166
15. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death. N Engl J Med [Internet]. Massachusetts Medical Society ; 2009 Jan 15 [cited 2018 Apr 2];360(3):225–35. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa0806994
16. Technology I of M (US) C on HC, Goodman C. American Medical Association Drug Evaluations. National Academies Press (US); 1988 [cited 2018 Apr 2]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK218423/
17. Roden DM. Drug-Induced Prolongation of the QT Interval. Wood AJJ, editor. N Engl J Med [Internet]. 2004 Mar 4 [cited 2018 Apr 2];350(10):1013–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14999113
18. Glassman AH. Schizophrenia, antipsychotic drugs, and cardiovascular disease. J Clin Psychiatry [Internet]. 2005 [cited 2018 Apr 2];66 Suppl 6:5–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16107178
19. Harrigan EP, Miceli JJ, Anziano R, Watsky E, Reeves KR, Cutler NR, et al. A Randomized Evaluation of the Effects of Six Antipsychotic Agents on QTc, In the Absence and Presence of Metabolic Inhibition. J Clin Psychopharmacol [Internet]. 2004 Feb [cited 2018 Apr 2];24(1):62–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14709949
20. Hasnain M, Vieweg WVR, Howland RH, Kogut C, Breden Crouse EL, Koneru JN, et al. Quetiapine, QTc interval prolongation, and *torsade de pointes* : a review of case reports. Ther Adv Psychopharmacol [Internet]. 2014 Jun 5 [cited 2018 Apr 2];4(3):130–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25057346
21. Heinrich TW, Biblo LA, Schneider J. Torsades de Pointes Associated With Ziprasidone. Psychosomatics [Internet]. 2006 May [cited 2018 Apr 2];47(3):264–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16684946
22. Lin C-H, Chen M-C, Wang S-Y, Lin C-Y. Predictive factors for QTc prolongation in schizophrenic patients taking antipsychotics. J Formos Med Assoc [Internet]. 2004 Jun [cited 2018 Apr 2];103(6):437–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15278188
23. Pandurangi A, Bhogale G, Patil N, Nayak R, Chate S. A short term prospective study of the effects of the commonly used antipsychotic drugs on ECG parameters. J Sci Soc [Internet]. Medknow Publications and Media Pvt. Ltd.; 2015 [cited 2018 Apr 2];42(3):185. Available from: http://www.jscisociety.com/text.asp?2015/42/3/185/165573
24. Pakseresht S, Nazarinasab M, Ghanavati F. Comparison of serum zinc level in patients with major depression with a healthy control group. Minerva Psichiatrica. 2017;58(1):10-6.
25. Nazarinasab M, Motamedfar A, Moqadam AE. Investigating mental health in patients with osteoarthritis and its relationship with some clinical and demographic factors. Reumatologia. 2017;55(4):183.
26. Nazarinasab M, Motamedfar A, Najafian M, Tabibi H. Investigating the effects of relaxation therapy on decreasing anxiety in patients with elective caesarean section in Imam Khomeini Hospital, Ahvaz, Iran during 2016. Medical Studies/Studia Medyczne. 2018 Jan 1;34(2):107-11.
27. Nazarinasab M, Motatamedfar A, Nea Matatpour S, Javadi S. Assessment of depression after stroke and its relation to brain lesion. Minerva Psichiatrica. 2018;59(1):39-44.
28. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.

Table 1. Patient characterizations in three groups

Variable		Olanzapine	Resperidone	Quetiapine	p-value
Age (Mean SD)		26.74±3.56	27.43±4.62	26.4±1.5	0.434
Gender	Male	19(54.3%)	16(45.7%)	16(45.7%)	0.710
	Female	16(45.7%)	19(54.3%)	19(54.3%)	0.710
QT interval		440.20±7.29	440.57±4.84	440.46±5.45	0.805

Table 2. Single-variable analysis of differences between three groups

Single-variable analysis	d-QT interval	p-value
Olanzapine**	444.80±6.82	
Quetiapine*	447.31±10.86	<0.001
Respridone	452.77±18.36	

(* →p-value: 0.005 **→p-value :< 0.001)

Table 3. Multivariate Analysis of Differences between three groups

Multivariate Analysis of Differences	B	SE	Beta	p-value
Sex(female to male)	2.737	2.350	0.104	0.247
Age	0.216	0.341	0.057	0.528
QT1	0.995	0.191	0.443	<0.001
(O to R)	-7.219	2.756	-0.258	0.010
(Q to R)	-5.121	2.765	-0.183	0.067
(Q to O)	2.098	2.755	0.075	0.448