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Effects of psychotropic medications on electrocardiography

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SOUHRN

Kontext a cíl: V posledních letech se počty psychiatrických pacientů trvale zvyšují a psychotropní látky se stávají nejčastěji užívanými léčivy. Tato léčiva mohou působit na kardiovaskulární systém; jejich nežádoucí účinky můžeme pozorovat při elektrokardiografickém (EKG) vyšetření. Cílem této studie bylo zkoumat nežádoucí účinky psychofarmak na EKG záznam.
Pacienti a metody: Do studie bylo zařazeno 85 pacientů s psychiatrickou diagnózou užívajících psychoaktivní látky. Z uvedeného počtu pacientů bylo 45 mužů a 40 žen ve věku od 23 do 94 let. U všech pacientů byl pořízen EKG záznam pro stanovení délky intervalu PR, délky intervalu QRS a délky korigovaného intervalu QT a následně se zkoumala případná spojitost mezi uvedenými parametry a 22 léky a léčivými látkami (Akineton, Haldol, Zyprexa, Prolixin, Dogmatil, Risperdal, Diazem [diazepam], Artane [trihexyfenidyl], Tegretol, Sulpirid, Cipram, Seroquel, Depakine, Stelazin, Anafranil, Rivotril, Clopixol, Largactil, Melleril, Epanutin, Nurodol a Desyrel).
Výsledky: Všechny statistické analýzy byly provedeny s použitím softwaru IBM SPSS software (verze 24.0, IBM, Armong, NY, USA) s 95% intervalem spolehlivosti a s hladinou významnosti $p < 0,05$. Kvantitativní proměnné byly hodnoceny Friedmanovou analýzou pro závislé výběry a Mannovým–Whitneyho U testem pro nezávislé skupiny. V této studii s univariační analýzou jsme zjistili, že přípravky Haldol, Epanutin a Nurodol mohou prodlužovat interval PR, zatímco Risperdal, Seroquel, Clopixol a Nurodol mohou prodlužovat komplex QRS a Depakine, Stelazin, Melleril a Nurodol mohou vyvolávat syndrom dlouhého intervalu QT. Na druhé straně byl v multivariační analýze přípravek Tegretol spojen s délkou komplexu QRS na hladině statistické významnosti 0,05 ($p = 0,044$), Diazem účinně prodlužoval interval PR na hladině významnosti 0,05 ($p = 0,037$) a Desyrel účinně prodlužoval korigovaný QT interval na hladině významnosti 0,05 ($p = 0,023$).
Závěr: V této studii jsme prokázali, že z psychoaktivních medikací Nurodol nejvíce ovlivňuje záznam EKG a může vyvolat dlouhý interval PR, dlouhý interval QRS a syndrom dlouhého intervalu QT. Proto je třeba, aby při podávání a užívání psychofarmak měli lékaři, zdravotní sestry i rodiny pacientů na paměti nežádoucí účinky uvedených léčiv na kardiovaskulární systém a dbali na pravidelnou kontrolu EKG záznamu.

Keywords:
ECG
Long QT
PR distance
Psychiatric drugs
QRS distance

ABSTRACT

Background and aim: In recent years number of psychiatric patients has increased and psychotropic medications are becoming mostly used drugs. These drugs may affect cardiovascular system and we can check side effects with electrocardiography (ECG). In this study we aimed to analyse psychiatric medications' side effects on ECG.
Objective and methods: Eighty-five patients included in this study have psychiatric diagnosis and have used psychoactive medications. Forty-five of these patients are male and 40 of them are female. Age varies from 23 to 94 years. ECG has been taken from the patients and PR duration, QRS duration, and corrected QT measured from each ECG. Twenty-two kinds of drugs (Akineton, Haldol, Zyprexia, Prolixin, Dogmatil, Risperdal,

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Diazem, Artane, Tegretol, Sulpirid, Cipram, Seroquel, Depaqin, Stelazin, Anafranil, Rivotril, Clopiksol, Largactil, Melleril, Epanutin, Nurodol, Desyrel) were analyzed statistically and PR duration, QRS duration, and cQT checked if there is an association with these drugs.

Results: All statistical analysis was performed with the IBM SPSS software package (version 24.0, IBM, Armong, NY, USA) at the 95% confidence interval level and $p < 0.05$ level of significance. Quantitative variables were analyzed by Friedman analysis for dependent group. Moreover the independent groups were compared with Mann–Whitney U test. In this study with univariate analyses we found that Haldol, Epanutin and Nurodol may cause long PR, risperdal, Seroquel, clopiksol, and Nurodol may cause long QRS duration, depakin, stelazin, Melleril, Nurodol may cause long QT. On the other hand with multivariate analyses Tegretol is associated with QRS duration at a level of significance of 0.05 ($p = 0.044$). Diazem is effective for increasing the PR duration at a level of significance of 0.05 ($p = 0.037$) and Desyrel is effective for increasing the QTC time at a significance level of 0.05 ($p = 0.023$).

Conclusion: In this study we showed that among psychoactive medications, Nurodol is the most related drug that affects ECG and may cause long PR, long QRS duration and long QT. So while using psychiatric tablets physicians, nurses, families should be aware of cardiovascular side effects and regular ECG controls should be checked.

Introduction

Life threatening arrhythmias may be caused by long QT, long PR and long QRS. Ventricular tachycardia may be caused by long QT and may cause sudden death.[1] Sudden death is an important issue for psychiatrists and cardiologists and most of the patients use psychoactive medications which may have cardiovascular side effects.[1]

Studies have shown that the use of antipsychotic drugs can increase the risk of sudden cardiac death.[2–5] Prolonged PR intervals, although often considered benign, have been associated with elevated left ventricular end-diastolic pressure, diastolic mitral regurgitation, and reduced left ventricular function.[6] Patients with heart failure and prolonged PR intervals are at a higher risk of atrial fibrillation, advanced AV block, and death.[6] A large study involving 25,512 patients demonstrated that prolonged PR is associated with an increased risk of atrial fibrillation, heart failure, and mortality.[7]

The prevalence of PR prolongation varies with age, ranging from 1% to 5% in individuals younger than 50 years and increasing significantly in older patients and those with organic heart disease.[8] Young athletes and patients with maternal anti-Ro/SSA antibodies may also present with prolonged PR intervals.[9] As a marker of cardiovascular aging, prolonged PR may indicate myocardial fibrosis and vascular inflammation.[10] Chronic PR prolongation can lead to neurohormonal activation and systemic vascular dysfunction, increasing the risk of adverse vascular events.[10] Given these considerations, the use of antipsychotic drugs in patients with heart failure, older adults, and certain high-risk groups should be carefully monitored with regular ECG assessments.

Antipsychotic drugs may also prolong QRS. Bogh et al. showed in their study that among 37473 patients who were admitted to emergency department patients who had longer QRS durations died earlier within 1 year.[11] Another study showed that in CABG patients with a narrow QRS complex, preoperative intermediate prolonged QRS is an independent predictor of all-cause mortality in the follow-up.[12] Antidepressants, antipsychotics have exerted an influence on the QRS duration.[13] So especially patients suffering from ischemia and coronary artery disease during antipsychotic treatment routine ECG should be checked and QRS durations should be measured in order to avoid side effects and deaths.

Several types of long QT syndrome are very important and may cause ventricular fibrillation and death. Antipsychotic and antidepressant drugs are known to cause significant long QT. Psychiatric patients constitute a population at a notable risk of drug-induced QT-prolongation.[14] On the other hand old patients who use psychiatric drugs should be carefully observed as concerns polypharmacy and prolonged QT.[15] Drug-drug interaction prevalence and prolonged QT in elderly and psychiatric patients have increased.[16] In a 5-year follow-up study it has been proven that escitalopram appears to prolong the QT interval, haloperidol carries a risk for QT prolongation, ziprasidone is associated with the greatest QT prolongation.[17] Elderly female patients with additional risk factors such as personal or family history of pre-syncope or syncope, electrolyte disturbances or cardiovascular diseases treated with antipsychotic and antidepressant drugs that may prolong the QTc interval, cause torsade de pointes and death should be monitored with ECG and checked for long QT.[18,19] In the past some drugs were withdrawn due to cause of prolongation of QT.[20] Among antipsychotics, sertindole was suspended, droperidol was withdrawn, thioridazine and pimozide restricted in United Kingdom.[20] Thioridazine and ziprasidone are associated with the greatest QTc prolongation.[20] In experimental studies it has been proven that haloperidol, thioridazine, sertindole, pimozide, risperidone, ziprasidone, quetiapine, olanzapine and antidepressants such as amitriptyline, imipramine, doxepin, trazadone, fluoxetine depress the delayed rectifier potassium current in dose dependent manner and it is reported that nearly 8% of psychiatric patients have prolonged QTc.[21]

In Cyprus there is no study for psychotrophic drugs and their cardiac side effects. So in this study we aimed to check side effects with electrocardiography (ECG) in a single center which is a psychiatric hospital named Baris hospital in North Cyprus. Also this is the first study to analyze Turkish Cypriot Psychiatry patients' ECGs and make investigation between psychiatric drugs and prolongation of PR, QRS and QTc among Turkish psychiatric patients.

Objective and methods

This study included 85 psychiatric patients receiving psychoactive medications from Baris Hospital, the only psychiatry hospital in North Cyprus. The study population comprised 45 male and 40 female patients aged from 23 to 94 years. ECG recordings were obtained from all participants, and PR interval, QRS duration, and corrected QT interval (QTc) were measured.

A total of 22 medications (Akineton, Haldol, Zyprexa, Prolixin, Dogmatil, Risperdal, Diazem, Artane, Tegretol, Sulpirid, Cipram, Seroquel, Depakine, Stelazine, Anafranil, Rivotril, Clopixol, Largactil, Melleril, Epanutin, Nurodol, and Desyrel) were analyzed for their associations with PR, QRS, and QTc intervals.

All statistical analyses were performed using IBM SPSS software (version 24.0, IBM, Armonk, NY, USA) at a 95% confidence interval and a significance level of p <0.05.

Results

Eighty-five patients were included in this study who have psychiatric diagnosis and use psychoactive medications. Forty-five of these patients are male and 40 of them are female. Age varies from 23 to 94 years. ECG has been taken from the patients and PR duration, QRS duration and corrected QT measured from each ECG. Twenty--two kinds of drugs (Akineton, Haldol, Zyprexia, Prolixin, Dogmatil, Risperdal, Diazem, Artane, Tegretol, Sulpirid, Cipram, Seroquel, Depaqin, Stelazin, Anafranil, Rivotril, Clopiksol, Largactil, Melleril, Apanutin, Nurodol, Desyrel) were analyzed statistically and PR duration, QRS duration, and cQT checked if there is association with these drugs.

All statistical analysis was performed with the IBM SPSS software package (version 24.0, IBM, Armong, NY,USA) at the 95% confidence interval level and p <0.05 level of significance. Quantitative variables were analyzed by Friedman analysis for dependent group. Moreover the independent groups were compared with Mann–Whitney U test. **Table 1** shows relationship with psychiatric drugs and their relationship with PR, QRS, and QTc from very weak to very strong (* very weak , **weak, ***strong, ****very strong). In this study with univariate analysis we found that Haldol, Epanutin, and Nurodol have strong relation with long PR. On the other hand risperdal, Seroquel, clopiksol, and Nurodol have strong relationship with long QRS duration. Also we found that depakin, stelazin, Melleril, Nurodol have strong relationship with long QTc. Prolonged PR, QRS, and QTc is strongly associated with Nurodol. So in psychiatric patients during Nurodol therapy regular ECGs should be taken and we should be careful about prolonged PR, QRS, and QTc.

Table 1 shows association between drugs (Akineton, Haldol, Zyprexia, Prolixin, Dogmatil Risperdal, Diazem, Artane, Tegretol, Sulpirid, Cipram, Seroquel, Depakin, Stelazin Anafranil, Rivotril, Clopiksol, Largactil, Melleril, Epanutin, Nurodol, Desyrel) and ECG changes like prolonged PR, prolonged QRS or prolonged QT. In this **table** * shows very weak association, ** shows weak association, *** shows medium association, **** shows strong association.

Table 1 – Psychoactive medications and ECG

	1	2	3	4	5	6	7	8	9	10	11
	Akineton	Haldol	Zyprexia	Prolixin	Dogmatil	Risperdal	Diazem	Artane	Tegretol	Sulfirid	Cipram
PR	***	****	**	***	**	**	*	***	***	**	**
QRS	*	**	***	*	***	****	*	***	**	***	***
QTC	***	**	***	***	***	**	**	***	**	***	***

	12	13	14	15	16	17	18	19	20	21	22
	Seroquel	Depaqin	Stelazin	Anafranil	Rivotril	Clopiksol	Lagactil	Melleril	Epanutin	Norodol	Deseryl
PR	***	*	**	**	***	**	*	*	****	****	**
QRS	****	**	**	***	**	****	***	*	*	****	***
QTC	***	****	****	***	*	**	*	****	**	****	***

* Very weak
** Weak
*** Medium
**** Strong

Table 2 – Univariate statistical analysis of drugs with QRS

Drugs	Coefficient	SE	t-value	*p*-value
Akineton	–0.003	0.003	–0.720	0.474
Haldol	–0.001	0.004	–0.202	0.840
Zyprexia	0.000	0.003	–0.080	0.936
Prolixin	–0.002	0.004	–0.487	0.628
Dogmatil	–0.005	0.005	–1.121	0.267
Risperdal	0.005	0.005	0.893	0.376
Diazem	–0.003	0.005	–0.557	0.580
Artane	–0.001	0.004	–0.336	0.738
Tegretol	–0.017	0.008	–2.057	**0.044**
Cipram	0.016	0.015	1.049	0.299
Seroquel	–0.004	0.006	–0.717	0.476
Depaqin	–0.005	0.006	–0.724	0.472
Stelazin	–0.004	0.006	–0.007	0.995
Anafranil	0.002	0.014	0.127	0.899
Rivotril	0.002	0.006	0.271	0.787
Clopiksol	–0.001	0.006	–0.105	0.917
Lagactil	–0.006	0.006	–0.978	0.333
Melleril	0.003	0.006	0.613	0.542
Epanutin	0.014	0.010	1.370	0.176
Desyrel	0.004	0.013	0.298	0.767

Table 3 – Univariate statistical analysis of drugs with PR

Drugs	Coefficient	SE	t-value	*p*-value
Akineton	–0.011	0.007	–1.486	0.143
Haldol	0.008	0.007	1.134	0.262
Zyprexia	0.005	0.007	0.679	0.500
Prolixin	0.000	0.007	–0.037	0.971
Dogmatil	0.002	0.009	0.236	0.814
Risperdal	0.021	0.010	1.996	0.051
Diazem	0.020	0.010	2.137	**0.037**
Artane	0.003	0.007	0.427	0.671
Tegretol	–0.026	0.016	–1.576	0.121
Cipram	–0.016	0.031	–0.527	0.600
Seroquel	0.020	0.012	1.609	0.113
Depaqin	–0.024	0.013	–1.839	0.071
Stelazin	–0.005	0.013	–0.418	0.678
Anafranil	0.018	0.028	0.647	0.520
Rivotril	0.008	0.012	0.646	0.521
Clopiksol	–0.022	0.013	–1.751	0.085
Lagactil	–0.015	0.013	–1.199	0.235
Melleril	0.015	0.011	1.343	0.185
Epanutin	0.007	0.021	0.347	0.730
Desyrel	–0.035	0.026	–1.316	0.194

Table 4 – Univariate statistical analysis of drugs with QTC

Drugs	Coefficient	SE	t-value	*p*-value
Akineton	0.018	0.022	0.796	0.430
Haldol	–0.038	0.023	–1.641	0.106
Zyprexıa	–0.014	0.022	–0.656	0.514
Prolixin	0.014	0.023	0.640	0.525
Dogmatil	0.046	0.029	1.605	0.114
Risperdal	–0.018	0.033	–0.539	0.592
Diazem	0.027	0.030	0.884	0.380
Artane	0.017	0.023	0.756	0.453
Tegretol	0.015	0.052	0.292	0.772
Cipram	–0.042	0.097	–0.438	0.663
Seroquel	–0.009	0.039	–0.221	0.826
Depaqin	0.031	0.041	0.759	0.451
Stelazin	0.012	0.040	0.289	0.774
Anafranil	–0.018	0.089	–0.203	0.840
Rivotril	–0.036	0.038	–0.938	0.352
Clopiksol	–0.035	0.040	–0.878	0.384
Lagactil	0.051	0.040	1.280	0.206
Melleril	0.033	0.035	0.928	0.357
Epanutin	–0.030	0.065	–0.453	0.652
Desyrel	0.194	0.083	2.336	**0.023**

In this study, we found that statistically Haldol, Epanutin, and Nurodol show strong association with prolonged PR, Risperdal, Seroquel, Clopiksol, and Nurodol show strong association with prolonged QRS duration, Depakin, Stelazin, Melleril, Nurodol show strong association with prolonged QT.

With univariate analysis it has been proven statistically that Tegretol is associated with prolonged QRS time at a significance level of 0.05 ($p = 0.044$) (**Table 2**).

With univariate analyses it has been proven statistically that Diazem is effective for increasing the PR time at a significance level of 0.05 ($p = 0.037$) (**Table 3**). It seems that there is a direct relationship between PR and Diazem.

With univariate analyses it has been proven statistically that Desyrel is effective for increasing the QTC time at a significance level of 0.05 ($p = 0.023$) (**Table 4**).

Discussion

In recent years usage of psychiatric drugs and sudden death of these patients have increased. Reasons of sudden deaths of chronic psychiatric patients may be multifactorial and in a recent study 52% of these patients' death remained unexplained.[22] Most of chronic psychiatric patients' deaths are considered as criminal cases. In a recent article causes of sudden deaths in psychiatric patients are multifactorial.[23]

In our study with univariate analysis we found that Haldol, Epanutin and Nurodol may cause long PR, Risperdal, Seroquel, Clopiksol and Nurodol may cause long QRS duration , Depakin, Stelazin, Melleril, Nurodol may cause long QT. On the other hand with multivariate analysis Tegretol is associated with QRS duration at a significance level of 0.05 ($p = 0.044$), Diazem is effective for increasing the PR time at a significance level of 0.05 ($p = 0.037$) and Desyrel is effective for increasing the QTC time at a significance level of 0.05 ($p = 0.023$).

This study is also the first study in north part of Cyprus to investigate the association between psychiatry and cardiology. Cardiologists and psychiatrist should study together to avoid side effects and death.

Conclusion

Despite being considered benign in some cases, prolonged PR intervals should be carefully monitored in patients with heart failure, young athletes, elderly individuals, and those with maternal anti-Ro/SSA antibodies.

Our multivariate analysis confirmed significant associations between specific psychiatric medications and prolonged PR, QRS, and QTc intervals. Tegretol was significantly associated with prolonged QRS ($p = 0.044$), Diazem was linked to increased PR ($p = 0.037$), and Desyrel was associated with prolonged QTc ($p = 0.023$).

Particular caution should be exercised with Nurodol, as it may prolong PR, QRS, and QTc intervals, increasing the risk of torsades de pointes and sudden death.

Given the multifactorial nature of sudden deaths in psychiatric patients, close monitoring through ECG as-

sessments is essential. Collaboration between psychiatrists, cardiologists, nurses, and caregivers is necessary to prevent adverse cardiovascular events and ensure patient safety.

Conflict of interest
None.

Funding
None.

Ethical statement
The study was conducted in accordance with the Declaration of Helsinki.

Informed consent
All subjects provided written informed consent for inclusion before they participated in the study.

Authors' contribution
Substantial contributions to the conception and design of the study: CC, AA, EB, DMO, BO, MU, AU, EH.
Acquisition of data: CC, AA, EB, AU, EH.
Drafting the article: CC, AA, EB.
Final approval of the version of the article: CC, AA, EB, DMO, BO, MU, AU, EH.

Data availability
Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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