International Journal of Advances in Medicine
Amin OSM. Int J Adv Med. 2019 Oct;6(5):1599-1604
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20194226

Original Research Article

Pregabalin and PR interval prolongation: any association?

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Received: 05 July 2019
Revised: 02 August 2019
Accepted: 05 September 2019

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ABSTRACT

Background: Pregabalin is a well-tolerated medication that is commonly used in the treatment of chronic pain, epilepsy, fibromyalgia, and generalized anxiety disorders. A variety of pregabalin-related cardiac side effects have been described in the literature and first-degree AV block is a well-known consequence. We aimed to investigate whether pregabalin prolongs the PR interval or not.
Methods: This cross-sectional observational study was conducted at the Shorsh Military General Teaching Hospital, Iraq. A total of 80 patients, who had a multitude of cervical and lumbosacral radiculopathies were enrolled consecutively, from November 1, 2017, to January 31, 2019. Forty patients who were receiving pregabalin (the treatment group) were age-matched and gender-matched with another group of 40 patients who hadn't been prescribed pregabalin (the control group). A single 12-lead ECG was done in all patients and the PR interval was calculated; a value of >0.20 second is considered a prolongation in the PR interval and defines first-degree AV block.
Results: Thirteen patients (32%; 7 males and 6 females) demonstrated a prolongation in the PR interval in the pregabalin arm while the PR interval was prolonged in 5 patients only in the control group (12%; 2 males and 3 females). There was no statistical difference between the maximum PR prolongation in both groups (p-value=0.13; 95% CI, -0.0121 to 0.0317).
Conclusions: This study hasn't found a statistically significant prolongation in the PR interval among patients taking oral pregabalin monotherapy. Whether this observation is clinically significant or not, it needs further analytic studies to uncover its importance.

Keywords: Conduction defects, Heart block, Pregabalin, PR interval

INTRODUCTION

Pregabalin is a lipophilic synthetic analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). The medication binds alpha-2 δ-subunit of the voltage-gated calcium channels at the presynaptic membranes. These channels are also found in the heart.[1] The medication is well-tolerated and it has no significant drug-drug interactions; however, it may exert a multitude of cardiac side effects; tachycardia is the commonest one. PR interval prolongation has been observed by some researchers and documented through case reports, usually in patients with pre-existent heart disease and/or renal failure.[2] The cardiac conduction defects of pregabalin monotherapy have also been observed in patients with structurally normal heart and in the presence of normal kidney function.[3] The current medical literature provides sparse information about the cardiac side effects of pregabalin, in particular, heart blocks and conduction defects. Over the past 15 years, pregabalin has been used successfully in the management of a variety of diseases (with favorable responses) and in many countries in the World. However, the lack of large clinical trials about the ECG-related changes of pregabalin remains one of the most important targets for researchers to explore.

METHODS

This cross-sectional observational study was conducted at the outpatients' department of the Shorsh Military General Teaching Hospital, Sulaymaniyah, Iraq. From November 1, 2017, to January 31, 2019, a total of 80 patients were enrolled.

Initial work-up and inclusion criteria

Patients who had had acute or chronic radiculopathy pain in the upper limbs (cervical)and/or lower limbs (lumbosacral) were included consecutively. This radiculopathy was diagnosed clinically by a neurologist and confirmed by neurophysiological tests in the form of nerve conduction studies; all patients (n=80) underwent nerve conduction studies assessment by a single neurophysiologist. At the time of enrollment, 40 patients were already taking oral pregabalin, 300 mg/day in 2 divided doses for a variable period of time, ranging from 1 to 6 months. This "treatment group" was age-matched and gender-matched with another group of 40 patients who had cervical and/or lumbosacral radiculopathies, but those patients were on no medical treatment for this radiculopathy and no prior ingestion of pregabalin was noted (the control group).

All patients (n=80) underwent an extensive battery of investigations (on a single occasion): complete blood counts, erythrocyte sedimentation rate, urea and electrolytes (serum sodium, potassium, chloride, bicarbonate, calcium, phosphate, and magnesium), liver function tests, fasting lipid profile, fasting blood sugar, total serum protein and serum albumin, thyroid function, and general urine examination. Chest X-ray and transthoracic echocardiography were performed in all patients (which was done by a single cardiologist).

A 12-lead resting ECG was done on a single occasion by a technician using an automated ECG machine. The calculation and analysis of the PR interval were confirmed by a physician. The PR interval was measured from the onset of the P-wave to the onset of the R-wave; no single lead was always chosen for the interpretation and the PR interval was measured across many leads. A PR interval of 0.12 to 0.20 seconds is the normal range and is not gender-related; values greater than 0.20 second imply a prolonged PR interval.[2,3] Serum levels of pregabalin were not measured. A 24-hour Holter monitoring was done in one patient only; she gave a history of recurrent pre-syncope; this investigation turned out to be unremarkable.

Exclusion criteria

Patients were excluded from the study if they had pre-existent structural heart disease (e.g., cardiomyopathy, ventricular hypertrophy, ischemic heart disease), cardiac dysrhythmias and conduction defects (e.g., frequent atrial and/or ventricular ectopics; history of tachyarrhythmia; first, second, or 3rd degree AV block), renal impairment (of any degree, regardless of the etiology), electrolytes and acid/base disturbances (e.g., hyperkalemia, hypokalemia, hypocalcemia, or metabolic acidosis), and if they were receiving medications which could affect the cardiac conduction system (e.g., beta blockers, calcium channel blockers, or amiodarone).

Statistical analysis

The collected data were organized, tabulated, and statistically analyzed using IBM SPSS Statistics, version 25.0. The PR interval findings in patients taking pregabalin and those who were not taking this medication were compared. The comparison between these two groups (numeric scale variables) was done using the Chi-square (X2) test and the Student's t-test. We calculated the t-value, p-value, and 95% confidence interval (95% CI). A p-value of <0.05 was considered statistically significant.

RESULTS

This cross-sectional and observational study enrolled 80 patients consecutively. Forty patients were taking oral pregabalin for a variable period of time and in a daily dose of 300 mg, while 40 patients (the control group) were not taking this medication.

Males outnumbered females in both groups with a male: female ratio of 1.5 (treatment group) and 1.2 (control group). The mean ages of the patients were 54.2 and 53.8 years in the treatment and control groups, respectively. Eleven patients smoked cigarettes (treatment group) while 14 patients in the control group were smokers. None of the patients in both groups drank alcohol. Although some patients in both groups were hypertensive, diabetic, and/or hyperlipidemia, none of them ingested a medication which could affect the PR interval. The majority of patients were residents of the Sulaymaniyah Governorate. All patients (n=80) were of Kurdish ethnicity (Table 1).

The PR interval values of both groups are highlighted in Figure 1. The maximum, minimum, and mean PR interval of both groups are illustrated in figure 2. The average PR interval was 0.182 (±SD 0.038) second in the treatment group while the control group had an average PR interval of 0.169 (±SD 0.029) second; therefore, both average values were within their normal reference range. However, the maximum PR interval prolongation did not exceed 0.249 seconds in both groups. None of the patients had a more than 25% prolongation in the PR interval. In addition, no single patient had demonstrated a PR interval of less than 0.12 second.

Table 2 shows that the PR interval was prolonged in 13 patients (32%; 7 males and 6 females) out of the 40 ones who were receiving pregabalin (the treatment group). However, out of the 40 patients in the control group, only

5 patients (12%; 2 males and 3 females) demonstrated a prolonged PR interval. The minimum, maximum, and mean PR intervals of both groups were compared; no statistically significant difference between patients who have received pregabalin and patients who have not received pregabalin was found (Table 3).

Table 1: Patients' characteristics and their PR interval prolongation. A total of 80 patients were enrolled and were divided into 2 groups.

Patients characteristics		Patients taking pregabalin (n=40)*	Patients on no pregabalin (control group; n=40)
Gender	Male	24	22
	Female	16	18
Age (years)	Mean	54.2	53.8
	Median	56	54
Residence**	Sulaymaniyah	34	37
	Hawler	3	2
	Duhok	3	1
Occupation	Employee	13	10
	Retired	6	4
	Student	3	4
	Unemployed	18	22
Marital status	Single	7	5
	Married	33	35
Smoking	Non-smoker	29	26
	Smoker	11	14
Drinking alcohol and illicit drug ingestion		None	None
Diabetes mellitus		7	5
Hypertension		11	15
Hyperlipidemia		9	6
PR interval prolongation***	Males	7	2
	Females	6	3

*All patients were receiving oral pregabalin, 300 mg/d in 2 divided doses, for a variable period of time.
** All patients were residents of Iraqi Kurdistan and all them were of Kurdish ethnicity.
***Normal PR interval is 0.12 to 0.20 seconds; a value >0.20 second is considered a prolongation.
- None of the patients (n=80) was receiving a medication that could affect the cardiac conduction and the PR interval.

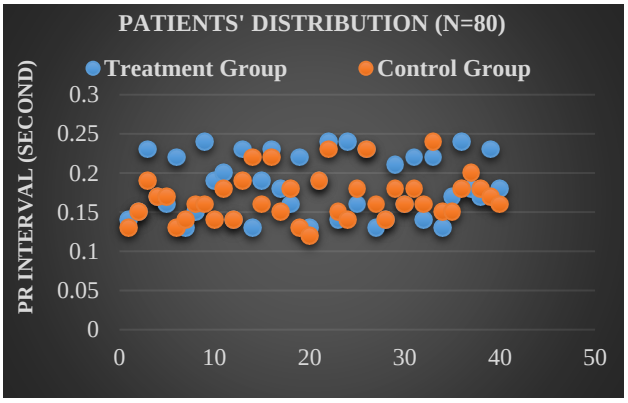

Figure 1: PR interval values among patients receiving pregabalin (n=40; treatment group) and patients receiving no pregabalin (n=40; control group). The normal PR interval is 0.12 to 0.20 seconds. Each dot (blue or orange) represents one patient's PR interval.

Table 2: Distribution of the prolonged and normal PR intervals among patients who were treated with pregabalin (n=40) and patients who were receiving no pregabalin (control group; n=40).

	Prolonged PR§	Normal PR	Total
Number of patients taking pregabalin*	13	27	40
Number of patients on no medical treatment	5	35	40
Total	18	62	80

*All patients were receiving pregabalin, 300 mg/d in 2 divided doses for a variable period of time.
§Normal PR interval is 0.12 to 0.20 seconds; a value >0.20 second is considered a prolongation.

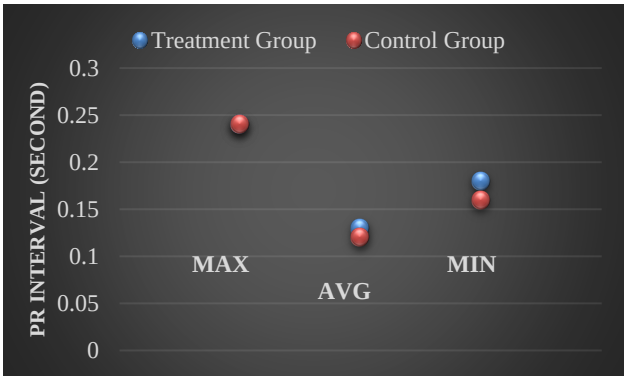

Figure 2: Maximum (MAX), minimum (MIN), and average (AVG; mean) PR interval values among patients receiving pregabalin (n=40; treatment group) and patients receiving no pregabalin (n=40; control group). The normal PR interval is 0.12 to 0.20 seconds. Each dot (blue or orange) represents one patient's PR interval. The maximum PR interval value in both groups is 0.24 second; therefore, their values (dots) overlap with each other and appear as a single orange dot.

Table 3: Association of different variables in both groups.

Variable	t-value	p-value*	95% CI	
			Lowest	Highest
Minimum PR**	1.3	0.36	0.0093	0.0273
Maximum PR**	2.4	0.13	0.0121	0.0317
Mean PR**	1.7	0.07	0.0016	0.0291

*P-value<0.05 is statistically significant.
** The association and statistical comparisons were analyzed for each variable in both groups, i.e., who were treated with pregabalin (n=40) and patients who were receiving no medical treatment (control group; n=40).
-CI, confidence interval; PR, PR interval.

DISCUSSION

Pregabalin is a synthetic analog of γ-aminobutyric acid (GABA) and is similar to gabapentin. However, it does not bind to GABA receptors or convert itself to GABA. Instead, it binds the alpha-2 δ-subunit of the voltage-gated calcium channels at the presynaptic membranes resulting in an inhibitory action on the release of several neurotransmitters (e.g., glutamate and noradrenaline).[4] It can be used in the treatment of epilepsy (add-on therapy), chronic neuropathic pain, fibromyalgia, and generalized anxiety disorders.[5] Pregabalin is not protein-bound and is excreted principally in urine, largely unchanged. It has a half-life of around 6 hours and its rate of kidney excretion is approximately 73 mL/hour.[6]

The presence of voltage-gated calcium channels in the heart cells renders these channels a target for pregabalin; the cardiac myocytes and the conduction system in the AV node are thought to be the main target. In addition, the inhibitory effect on the autonomic nerve terminals in the heart may result in the modulation of the neuronal excitability.[2]

The PR interval encompasses both the atrial contraction (P-wave) and the time needed for the electrical impulse to descend downwards through the AV node and the His-Purkinje fiber system to reach and activate the ventricles. An interval of 0.12 to 0.20 seconds is required normally in individuals with a resting heart rate of 60 to 100 beats/minute. Therefore, any medication which interferes with and delays the atrial activation and/or delays the conduction velocity in the conduction system may result in a PR interval prolongation.[7]

The term "first-degree AV block" is classically used to describe slowing in the conduction velocity through the AV node; this is translated as prolongation in the ECG's PR interval of more than 0.20 second. Hence, it is not a block per se. The clinical consequences of this low-grade delay (together with "type I second-degree AV block") are somewhat unclear when compared to type II second-degree AV block and complete heart block (i.e., high-grade AV blocks). First-degree AV block, sometimes seen intermittently, may be encountered as a physiological phenomenon in otherwise normal hearts and per se does not necessarily imply a sinister outcome. However, prolongation in the PR interval upon receiving medications may uncover an underlying sub-clinical structural heart disease and should be taken more seriously.[8] However, Cheng and coworkers found that PR-interval prolongation and first-degree AV block have been associated with future development of atrial fibrillation, need for permanent pacemaker use, and all-cause mortality.[9] On the other hand, Crisel and colleagues concluded that PR interval prolongations in elderly patients with chronic stable ischemic heart disease are more liable to progress to complications when using medications which affect the AV conduction.[10]

Our study has not revealed any statistically significant prolongation in the PR interval among patients using pregabalin, 300 mg/d, who have normal renal function and no structural heart disease/ cardiac conduction abnormalities. The prolongation in the PR interval, which was noted in those 13 patients, was marginal and ranged from 0.21 to 0.24 seconds (and that would be less 25% of the PR interval duration). The notion of pregabalin-associated PR interval prolongation and heart blocks in the literature mostly came from case reports/anecdotes.[2]

Aksakal and co-workers reported on a case of complete AV block (the ventricular rate was 39 beats/minute) in a patient with uremia and pregabalin overdose; in fact, this was the first reported pregabalin-related heart block outside the clinical trials of the medication before its release and approval for medical use.[11] Their patient was taking oral pregabalin at a dose of 300 mg/d over the preceding 8 months. She had a serum creatinine of 1.8

mg/dl and creatinine clearance of 50 mL/min (this would define stage 3 chronic kidney disease). Aksakal and co-workers stopped pregabalin therapy; after 96 hours, her complete AV block regressed to type II second degree AV block. Afterward, the heart rate returned to its sinus rhythm with a right bundle branch block morphology. Pregabalin action on the heart's L-type calcium channels was the presumed etiology.

Scarano and colleagues found an incomplete AV conduction block in a patient with neuropathic pain who was prescribed pregabalin; the PR prolongation was minimal and the patient had ischemic heart disease and stroke.[12]

Schiavo and colleagues reported on a case of extra-pulmonary (lower spine and sternum) tuberculosis who was prescribed pregabalin, 150 mg/d, to alleviate severe neuropathic pain in the lower back and legs (2). He demonstrated normal kidney function and normal ECG (and cardiac function) before the start of pregabalin therapy. The ventricular rate dropped down to 35 beats/minute, 21 days after receiving daily pregabalin. The ECG showed a first-degree AV block; the PR interval was 0.48 second. No etiology other than pregabalin administration was suspected and pregabalin therapy was halted. Twenty-four hours later, the ECG demonstrated normalization of the PR interval.

Şengüldür and colleagues managed a patient with a failed suicide attempt; the patient ingested 16 capsules of 150 mg pregabalin.[3] Initially, in the Emergency Department, the patient demonstrated normal vital signs and blood tests (apart from elevated creatinine kinase); the heart rate was 75 beats/minute and regular. However, the ECG showed a first-degree AV block with a PR interval of 0.35 second. He was treated with symptomatic and supportive plan. The PR interval regressed in the second day and was within its normal range in the 3rd day. This reversible first-degree AV block was ascribed to an overdose of pregabalin.

PR interval prolongation is considered an uncommon adverse drug reaction and the medication is relatively contraindicated in patients with atrial dysrhythmias associated with PR interval prolongation.[13] The use of pregabalin monotherapy in painful cervical and lumbosacral radiculopathies was found to result in substantial pain alleviation and associated symptoms improvement (e.g., sleep).[14] The medication appears to be safe when used in patients with normal renal and cardiac function.

Pregabalin was approved by the U.S. Food and Drug Administration in 2004 for medical use.[15,16] Since then, a number of generic formulations have been available in several countries but not in the United States.[17] Pregabalin has been found by a pharmaceutical company (by analyzing their clinical trials' ECG findings) to induce PR interval prolongation by an average of 3-6 msec and at daily doses ≥300 mg/day. Therefore, the PR interval prolongation appears to be ≤25% of the entire duration and did not appear to progress to higher degrees of heart blocks. In addition, patients with pre-existent PR interval prolongation or those who concomitantly ingest a medication which prolongs the cardiac conduction velocity had not developed further PR interval prolongation when prescribed pregabalin (15,16). On the other hand, pregabalin was found to induce ST-segment depression and ventricular fibrillation as "rare" adverse drug reactions encountered during the medication's clinical trials (15). The information in the pertinent medical literature is very scarce with respect to pregabalin-induced PR interval prolongation; to the best of our knowledge, this is the first study which directly addresses first-degree AV block that may result from the use of pregabalin. We hope that this small study will open the door to other researchers to dig out more deeply into cardiac conduction defects related to pregabalin monotherapy.

In summary, although some patients who had received pregabalin in our study demonstrated a marginal PR interval prolongation, this prolongation was not statistically significant. It is unclear whether this first-degree AV block is clinically significant or not. Further analytic studies are required to link the use of pregabalin with PR interval prolongation in patients with normal kidneys and heart.

Limitations of the study includes some points. The number of cases was relatively small; only 80 patients in total were selected over a period of 1 year and 3 months. Therefore, the results might have well been different if the number of cases was larger. The study is a cross-sectional and observational one, not an analytical or an interventional study. In addition, our patients were not randomized blindly to receive pregabalin therapy or placebo. The patients were enrolled consecutively according to whether they are on pregabalin or not. All patients were of Kurdish ethnicity. Arabs, who constitute the largest ethnic race in Iraq, were not included in the study. It is not known whether genetic factors are operative in the action and cardiac effects of pregabalin or not. This is a single institutional study that does not reflect the practice of therapeutics in the whole of Iraq.

CONCLUSION

This study hasn't found a statistically significant prolongation in the PR interval among patients taking oral pregabalin monotherapy. Whether this observation is clinically significant or not, it needs further analytic studies to uncover its importance.

ACKNOWLEDGEMENTS

Special gratitude goes to our patients and their families; without their kind and great help, our study would not have been accomplished and that this paper would not have been published.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Amin OSM. Pregabalin and PR interval prolongation: any association? Int J Adv Med 2019;6:1599-604.