

# Effects of therapeutic doses of Pregabalin on QTc interval in conscious rabbits

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**Abstract.** – Pregabalin (PRG) is a new antiepileptic drug that has been used as supportive therapy for partial seizures in patients. Although many neuro-psychiatric and non-cardiac drugs are known to prolong ventricular repolarization as manifested by QTc prolongation on ECG of which provokes torsades de pointes, there is limited data available regarding the characteristics of QT interval in conscious laboratory animals after PRG administration. For that purpose, effects of different therapeutic doses of oral PRG administration on Heart Rate (HR), QT and QTc values in rabbits were evaluated at a predefined time interval in this research.

The study involved 28 New Zealand rabbits of both sexes, aged between 8 and 12 months. Animals were divided into four equal groups. Rabbits in control group (CG) received saline 0.5 ml/per animal orally. Group I, II and III were orally given single dose of PRG at 1.25 mg/kg, 2.5 mg/kg and 5 mg/kg, respectively. ECG records were taken before experiment (baseline) and at 1<sup>st</sup>, 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> hour (h) of experiment by direct writing electrocardiograph. HR, QT and QTc values were determined from ECG records.

Heart rates increased in all groups when compared to baseline values. The increases were evident at 4<sup>th</sup> h in group II ( $p < 0.001$ ), at 2<sup>nd</sup> h ( $p < 0.05$ ) and 4<sup>th</sup> h ( $p < 0.001$ ) in group III compared with CG. After application of PRG, QTc began to prolong at 1<sup>st</sup> h through the 4<sup>th</sup> of experiment and then turned to baseline values at 6<sup>th</sup> h of the experiment. The QTc values obtained at 2<sup>nd</sup> h in Group II and III ( $p < 0.05$ ) and 4<sup>th</sup> h ( $p < 0.001$ ) of application in group III were significantly different from CG. Changes obtained in HR, QT and QTc values in PRG treated rabbits were time and dose dependent ( $p < 0.001$ ).

Increase in HR and QTc prolongation determined in PRG given rabbits may implied that clinicians should take care of these changes when using this drug and further studies are required to fully understand the mechanism involved.

*Key Words:*

Pregabalin, ECG, QT.

## Introduction

Pregabalin (PRG) is a new antiepileptic drug (AED) used as adjunctive therapy for partial seizures and neuropathic pain in patients above 18 years old<sup>1</sup>. Its use significantly reduced the frequency of partial seizures in several double-blind randomized clinical trials. PRG is structurally related to the antiepileptic drug gabapentin and the site of action of both drugs is the  $\alpha_2\text{-}\delta$  Type 1 protein, an auxiliary subunit of voltage-gated calcium channels (L-type)<sup>2</sup>.

Literature exists on the cardiovascular side effect associated with many neuropsychiatry drugs for a long time. However, there are limited numbers of reports regarding to PRG cardiac side effects in recent years. PRG was first reported to be used cautiously in patients with cardiac disorders by European Medicines Agency<sup>3</sup>. Meanwhile, Murphy et al reported enhancement of heart failure in three patients prescribed PRG for the treatment of neuropathic pain<sup>4</sup>. Similarly, Laville et al reported sinus tachycardia following by atrial fibrillation and congestive heart failure in a patient given PRG<sup>5</sup>.

One of the adverse effect of non-cardiac drugs is QT interval prolongation. Many antiarrhythmic and non-cardiac drugs are known to prolong ventricular repolarisation and provoking *torsades de pointes* (TDP) resulting in inhomogeneous lengthening of action potential, T wave abnormality, and QT interval prolongation<sup>6</sup>. This tachycardia is characterized by wide complexes that change their axis from an upright to an inverted shape. This causes syncope and sudden death. PRG exerts its effects through  $\alpha_2\text{-}\delta$  Ca channels existing in many organs including heart<sup>7</sup>. These channels

have already been associated with QT prolongation<sup>8</sup>. To the best of our knowledge there are no available data showing PRG effect on QT changes. Therefore this study was designed to determine effect of PRG use on QT interval in conscious rabbits.

## Materials and Methods

### Animals and Groups

The study involved 28 New Zealand rabbits of both sexes, aged between 8 and 12 months. Rabbits were fed special pelleted rabbit diet (Bayramoglu Yem AS, Erzurum, Turkey) *ad libitum* in cages (four rabbits per cage; 70 cm deep × 70 cm wide × 50 cm high). Animals were kept at room temperature (22°-25°C) with 12h light: 12h dark cycle.

The mean body weight of control group (CG; n = 7), group I (n = 8), group II (n = 8) and group III (n = 7) were 2.57 ± 0.2, 2.65 ± 0.1, .59 ± 0,1 and 2.5 ± 0.1 kg, respectively. The Laboratory Animal Care and Use Committee of Faculty of Veterinary Medicine approved the whole experimental protocol.

### Drug Administer

Control group was orally given isotonic saline solution at dose of 0.5 cc/per rabbit. PRG was dissolved in isotonic saline solution and orally administered at therapeutic dose of 1.25 mg/kg (group I), 2.5 mg/kg (group II) and 5 mg/kg (group III).

### Electrocardiography Recording

Electrocardiographic procedure was performed as reported by Uzun et al<sup>9</sup>. Alligator clips were attached to four limbs. ECG records were taken before experiment (baseline) and 1, 2., 4. and 6 hour of experiment by direct writing electrocardiograph (Poly-Spectrum 12 channel ECG-System, Poly-Spectrum-8, Neurosoft, 5, Voronin str., Ivanovo, Russia). ECG recordings were loaded onto computer and analysed manually. ECG was standardised at 1 mV = 20 mm, with chart speed of 50 mm/sec with filter on (35 Hz) and Leads I, II, III, aVR, aVL; and aVF were recorded. QT interval was manually calculated from the beginning of Q wave to the end of T wave. Animals were not given any sedatives or anaesthetics before and during ECG recording.

The QT interval was corrected for heart rate with the formula used by Kijawornrat et al as below<sup>10</sup>.

$$QTc = QT/(RR)^{0.72}$$

### Statistical Analysis

Mean HR, RR, QT, and QTcC were compared within and between the groups at baseline (0. min), 1., 2., 4., and 6. hours by one-way ANOVA (Turkey's *t*-test) using MINITAB statistical package (Version 11.2, 1996). The factors effecting (time and dose) measurements (HR, RR, QT, QTcC) were analysed using the multiple ANOVA methods. Data were represented as mean ± SEM.

## Results

Different doses of oral PRG administration on HR, RR, QT and QTc values in rabbits were evaluated at a predefined time interval in this study. No clinically observable signs were detected in study animals. High quality electrocardiograms were obtained from all of the rabbits.

HR increased in all groups when compared to baseline values. The increase was also significant at the 4<sup>th</sup> of administration in group II ( $p < 0.001$ ), and 2<sup>nd</sup> ( $p < 0.05$ ) and 4<sup>th</sup> hours of administration group III ( $p < 0.001$ ) when compared to CG. HR in group II rised from 192 beats/min at baseline to 225 beats/min at 4<sup>th</sup> hour of PRG administration. Similarly, HR increased from 176 beats/min to 228 beats/min at 2<sup>nd</sup> hour and 232 beats/min at 4<sup>th</sup> hour of PRG administration in group III (Table I). Changes in percentage of RR and HR values are given in the Figure 1. The highest changes in these parameters were noted at 4<sup>th</sup> hour in the group administrated the highest dose of PRG. Statistical analyses revealed that these changes were dose and time dependent ( $p < 0.001$ ).

QTc values of CG remained similar throughout the study but QTc time prolonged in all PRG groups as an increase was noted at 1<sup>st</sup> hour through 4<sup>th</sup> hour of PRG administration and then returned to baseline values at 6<sup>th</sup> of the study. QTc values significantly prolonged in group II at 2<sup>nd</sup> hour of the study ( $p < 0.05$ ), and in group III at 2<sup>nd</sup> ( $p < 0.05$ ) and 4<sup>th</sup> hours ( $p < 0.001$ ) of the study when compared to CG. Similarly QT and QTc changes were time and dose dependent ( $p < 0.001$ ).

**Table I.** Time dependent HR and RR changes in conscious rabbits orally given different doses of pregabalin.

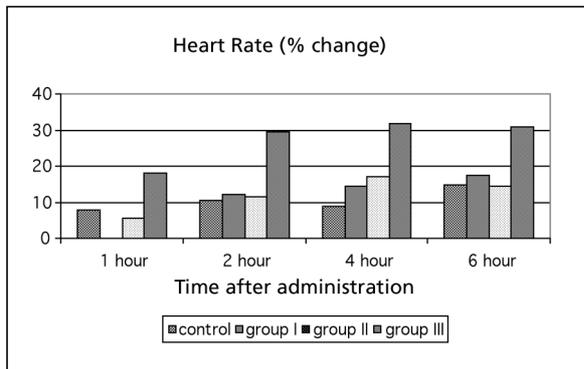
Groups	Before experiment (baseline values)		AFTER PRG ADMINISTRATION															
			1 hour				2 hour				4 hour				6 hour			
	RR (msec)	HR (beats/min)	RR (msec)	HR (beats/min)	RR (msec)	HR (beats/min)	RR (msec)	HR (beats/min)	RR (msec)	HR (beats/min)	RR (msec)	HR (beats/min)	RR (msec)	HR (beats/min)	RR (msec)	HR (beats/min)		
Control (n = 7)	326 ± 12	189 ± 7	301 ± 11	204 ± 7	292 ± 8	209 ± 6	296 ± 7	206 ± 5	279 ± 5	217 ± 4	279 ± 5	209 ± 6	206 ± 5	279 ± 5	217 ± 4	279 ± 5	217 ± 4	
Group I (n = 8)	321 ± 7	189 ± 4	323 ± 9	189 ± 5	289 ± 8	212 ± 6	280 ± 5	216 ± 4	273 ± 6	222 ± 5	273 ± 6	212 ± 6	216 ± 4	273 ± 6	222 ± 5	273 ± 6	222 ± 5	
Group II (n = 8)	323 ± 12	192 ± 7	298 ± 4	203 ± 3	283 ± 5	214 ± 4	267 ± 2***	225 ± 2***	275 ± 4	220 ± 4	275 ± 4	214 ± 4	225 ± 2***	275 ± 4	220 ± 4	275 ± 4	220 ± 4	
Group III (n = 7)	343 ± 6	176 ± 3	291 ± 6	208 ± 4	265 ± 5*	228 ± 4*	261 ± 6***	232 ± 5***	263 ± 6	230 ± 5	263 ± 6	228 ± 4*	232 ± 5***	263 ± 6	230 ± 5	263 ± 6	230 ± 5	

Values are different in the control group with different superscript in the same column \*  $p < 0.05$ ; \*\*\*  $p \leq 0.001$

**Table II.** The control and experimental groups QT and QTc changes in conscious rabbits orally given different doses of pregabalin

Groups	Before experiment (baseline values)		AFTER PRG ADMINISTRATION							
			1 hour		2 hour		4 hour		6 hour	
	QT (msec)	QTc (msec)	QT (msec)	QTc (msec)	QT (msec)	QTc (msec)	QT (msec)	QTc (msec)	QT (msec)	QTc (msec)
Control (n = 7)	166 ± 2	378 ± 10	156 ± 3	372 ± 7	154 ± 3	376 ± 8	156 ± 3	376 ± 8	150 ± 2	378 ± 7
Group I (n = 8)	166 ± 2	379 ± 5	171 ± 2***	391 ± 9	161 ± 1**	397 ± 8	164 ± 2	411 ± 5***	152 ± 3	389 ± 7
Group II (n = 8)	162 ± 3	370 ± 8	159 ± 2	382 ± 5	160 ± 2	399 ± 5*	153 ± 2	397 ± 6	143 ± 2	365 ± 5
Group III (n = 7)	171 ± 2	370 ± 5	160 ± 3	390 ± 5	153 ± 2	399 ± 4*	155 ± 2	410 ± 7***	150 ± 2	392 ± 6

Values are different the control group with different superscript in the same column \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .



**Figure 1.** The percentage changes in 1., 2., 4. and 6. hours after PRG administration of HR from baseline in control and experimental groups.

## Discussion

To the best of our knowledge, this was the first study to demonstrate the changes in HR and QTc values in conscious rabbits given different therapeutic doses of PRG.

In this study, HR increased in both control and treated groups as compared to baseline values but between group comparisons revealed a significant increase in groups II and III. This rise was time and dose dependent. QTc prolongation was evident at both 2<sup>nd</sup> and 4<sup>th</sup> hours of the study in the group receiving the highest dose of PRG. This may be related to the metabolism of PRG in rabbits.

Studies in human subjects showed that hepatic metabolism of PRG is negligible and 98% of it is discarded through kidneys without changes. Its elimination half life is about 6 hours<sup>11</sup>.

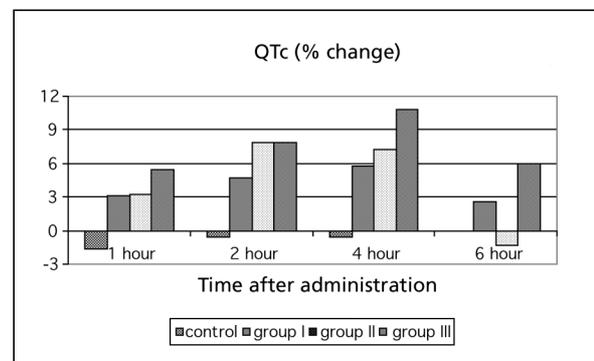
A previous study reported its fast absorption from the intestine of rabbits<sup>12</sup>.  $T_{max}$  value of PRG is reported to be 1 hour but this can prolong about 3 hours<sup>1</sup>. These data may suggest that effects of PRG are expected to occur at about 2<sup>nd</sup> and/or 4<sup>th</sup> hour of administration in rabbits.

PRG is a relatively new drug and thus its side effects are not widely known, especially those related to the heart. PRG was first reported to be cautiously considered in cardiac diseases<sup>3</sup>. In the present study, PRG was shown to exert its effect on the heart by increasing HR and prolonging QTc in rabbits. As no previous study reported such effect this findings are worth considering seriously. PRG has been reported to exert its effect through  $\alpha_2$ - $\delta$  Ca channels, known as voltage-gated L-type  $Ca^{2+}$  channels<sup>2</sup>. Because this type of Ca channels is present in rabbits, we carry out

our study in these animals<sup>13</sup>. Voltage-gated L-type  $Ca^{2+}$  channels play a key role in the excitation-contraction coupling of cardiac myocytes and in cardiac electrophysiological properties. Yada et al. reported that disorders of L-type  $Ca^{2+}$  channels can cause severe cardiac arrhythmias<sup>8</sup>. L-type  $Ca^{2+}$  channels are the key gateway for  $Ca^{2+}$  entry into cardiac myocytes. These ion channels open in response to cell membrane depolarisations induce  $I_{Ca}$  flows during the action potential plateau, increase cellular  $Ca^{2+}$  and trigger myocardial contraction.  $I_{Ca}$  may be associated with the genesis of cardiac arrhythmias under conditions such as heart failure and cardiac hypertrophy, in which the action potential plateau and QT intervals are prolonged<sup>14</sup>. Murphy et al reported decompensation of chronic heart failure in three patients at different age receiving PRG and hypothesised that PRG might have attached to  $\alpha_2$ - $\delta$  type Ca channels and thus resulted in potassium-evoked attenuation of  $Ca^{2+}$  influx<sup>4</sup>. These findings suggest that PRG effect on QTc time prolongation might be due to stimulation of cardiac L-type  $Ca^{2+}$  channels.

In this study, QTc prolongation was most evident in the highest therapeutic dose PRG group. As certain drugs effects QT and QTc intervals, clinicians are required to be aware of these drugs and their adverse effects in advance such as potentially life-threatening form of polymorphic ventricular tachycardia termed *torsades de point* (TDP) resulting from the prolongation of QT and QTc intervals<sup>15</sup>.

In conclusion, clinicians using PRG must be advised to take these findings into account when prescribing. Further detailed studies are needed to disclose the mechanism involved.



**Figure 2.** The percentage changes in 1., 2., 4. and 6. hours after PRG administration of QTc from baseline in control and experimental groups.

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