

## Investigation of oral selegiline and rasagiline administration on QT interval in conscious rabbits

M. UZUN\*, R. ALP\*\*, E. UZLU\*\*\*, S. ALP\*\*\*\*, M. CITIL\*\*\*, B. TOPCU\*\*\*\*\*, H.M. ERDOGAN\*\*\*

\*School of Health Science, Canakkale Onsekiz Mart University, Canakkale (Turkey); \*\*Department of Neurology, School of Medicine; \*\*\*Internal Medicine, School of Veterinary Medicine; \*\*\*\*Neurology Clinics, Kars State Hospital, Kars; \*\*\*\*\*Kars Vocational College, University of Kafkas, Kafkas (Turkey)

**Abstract.** – Rasagiline (RSG) and selegiline (SEL) are potent selective monoamine oxidase-B inhibitors and used in the treatment of Parkinson's disease. Selegiline is metabolized *in vivo* to l-methamphetamine and l-amphetamine which effect cardiovascular system. Therefore, the aim of this study was to evaluate and to compare the effects of long-term use of these drugs on QT interval in conscious rabbits.

The study involved 17 New Zealand rabbits of both sexes, aged between 7 and 14 months. Control group (CG, n=6) was orally given isotonic saline solution at dose of 0.5 cc/per rabbit. The SEL group (SG, n=6) received 5 mg/per rabbit SEL orally twice daily (09:00 am and 09:00 pm) for 14 days. The RSG group (RG, n=5) was orally given of RSG at 1 mg/per rabbit daily for 14 days. Electrocardiographic records were taken before the experiment (baseline) and at 1st, 7th, and 14th days of experiment by direct writing electrocardiograph for two groups.

Heart rate (HR), QT and QTc values were determined from ECG records. HR did not significantly differ in both treatment groups through the experimental period when compared to baseline values. The significant prolongation of QT and QTc values were observed at 7th, and 14th day ( $p < 0.01$ ) in SG and 1st day of experiment in RG ( $p < 0.05$ ) as compared to baseline values.

In conclusion, the results obtained suggest a statistically significant effect of SEL on QTc prolongation when compared to RAS. QTc prolongations should be taken into account in Parkinson's disease where autonomic system is involved.

### Key Words:

Rasagilin, Selegiline, ECG, QT, Rabbit.

### Introduction

Rasagiline (RAS) and selegiline (SEL) are potent selective monoamine oxidase-B inhibitors and used in the treatment of Parkinson's disease (PD). SEL, the first selective MAO-B inhibitor, has been commercially available in the United States since 1989<sup>1</sup>. SEL is metabolised to methamphetamine and amphetamine<sup>2</sup>. These metabolites increase synaptic release of catecholamines. Amphetamine is metabolised to the neurotransmitter *p*-hydroxyephedrine which takes part in depletion of nerve terminals of norepinephrine<sup>3,4</sup>. Methamphetamine and catecholamines modulate heart rate and blood pressure with cardiotoxic effects. Increased high catecholamine levels can also cause vasoconstriction, vasospasm, tachycardia and hypertension<sup>5</sup>. Kaye et al<sup>6</sup> already underlined that methamphetamine use can cause cardiac arrhythmias and that sudden cardiac death is often associated with high methamphetamine doses.

Rasagiline mesylate, a new selective MAO-B inhibitor, has been approved by European drug-regulatory authorities since 2005. RAS has been developed to produce a selective MAO-B inhibitor that, presumably, is not metabolised to toxic metabolites, amphetamine and methamphetamine, as it happens by products of SEL metabolism<sup>1</sup>.

One of the side-effects of several non-cardiac drugs is QT interval prolongation. In fact, many antiarrhythmic and non-cardiac drugs are known to prolong ventricular repolarisation with the appearance of the *torsades de pointes* (TDP) resulting in an inhomogeneous lengthening of action potential, T wave abnormality, and QT interval prolongation<sup>7</sup>.

Side-effects of SEL and RAS on cardiovascular system have already been discovered in few studies. However, it is lacking an experimental study evaluating the effect of SEL alone on corrected QT interval (QTc) prolongation. It has been observed that RAS has less side-effects in comparison to SEL. However, there is no report stating the effect of RAS on QTc. Therefore, the aim of this study was to evaluate and to compare effects of long-term use of RAS and SEL on QT interval in conscious rabbits.

## Materials and Methods

### Animals and Groups

The study involved 17 New Zealand rabbits of both sexes, aged between 7 and 14 months. Rabbits were fed special pelleted rabbit diet *ad libitum* in cages. Animals were kept at room temperature (22-25°C) with 12h light:12h dark cycle. The Laboratory Animal Care and Use Committee of University of Kafkas approved the experimental protocol.

### Drug Administration

Control group (CG, n=6) was orally given isotonic saline solution at dose of 0.5 cc/per rabbit. The SEL group (SG, n=6) received 5 mg/per rabbit SEL orally twice daily (09:00 am and 09:00 pm) for 14 days. The RAS group (RG, n=5) was orally given of RAS at 1 mg/per rabbit daily for 14 days.

### Electrocardiography (ECG) Recording

Electrocardiographic procedure was performed as reported by Uzun et al<sup>8</sup>. ECG records were taken for all rabbits before the experiment (baseline) and 1<sup>st</sup>, 7<sup>th</sup> and 14<sup>th</sup> day 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. 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 Fridericia et al<sup>9</sup>.

### Statistical Analysis

Mean HR, QT, and QTc were compared within and between the groups at baseline (before the experiment), 1<sup>st</sup>, 7<sup>th</sup>, and 14<sup>th</sup> days by one-way

ANOVA (Turkey's *t*-test) using MINITAB statistical package (Version 11.2, 1996). The factors affecting the HR, QT, QTc values were analysed using the multiple ANOVA methods. Data were represented as mean  $\pm$  SEM. Significant level was set at  $p < 0.05$ .

## Results

Heart rate (HR), QT and QTc values were determined from ECG records. HR did not significantly differ in both treatment groups throughout the experimental period when compared to CG and baseline values. The significant prolongation of QT and QTc values were observed at 7<sup>th</sup> and 14<sup>th</sup> day ( $p < 0.01$ ) in SG and 1<sup>st</sup> day of experiment in RG ( $p < 0.05$ ) as compared to baseline values. All data are given in Table I. Statistical analyses revealed that these changes were time dependent ( $p < 0.001$ ).

Changes in percentage of HR, QT and QTc values are given in the Figure 1A-C.

## Discussion

This study referred a significant changes in QT/QTc in rabbits receiving RAS and SEL in comparison to baseline and with control values.

Comparison of treated groups with CG revealed non-significant changes in HR. However, a 6.7% significant decrease against baseline HR was detected in RAS group respect to SEL group, during 14 days period. If this changes were not considered, one observer would conclude that there was no effect of RAS and SEL on HR in conscious rabbits.

Abbasi et al.<sup>10</sup> reported unchanged HR values after oral application of RAS and SEL for 5-21 days in anesthetized rabbits. Conversely, Finberg et al.<sup>11</sup> reported a sympathomimetic effect and increased HR after an intravenous injection of SEL at dose rates of 1-5 mg/kg. However, 1 mg/kg of SEL and RAS didn't exhibit sympathomimetic effect through sufficiently inhibited MAO-A and MAO-B. Our data agree with Abbasi et al. results but differ from that of Finberg et al. where SEL dependent HR increase was reported. This difference may be explained by dose of drug and route of application since Finberg et al. used an intravenous route and a dose 3 times higher than ours.

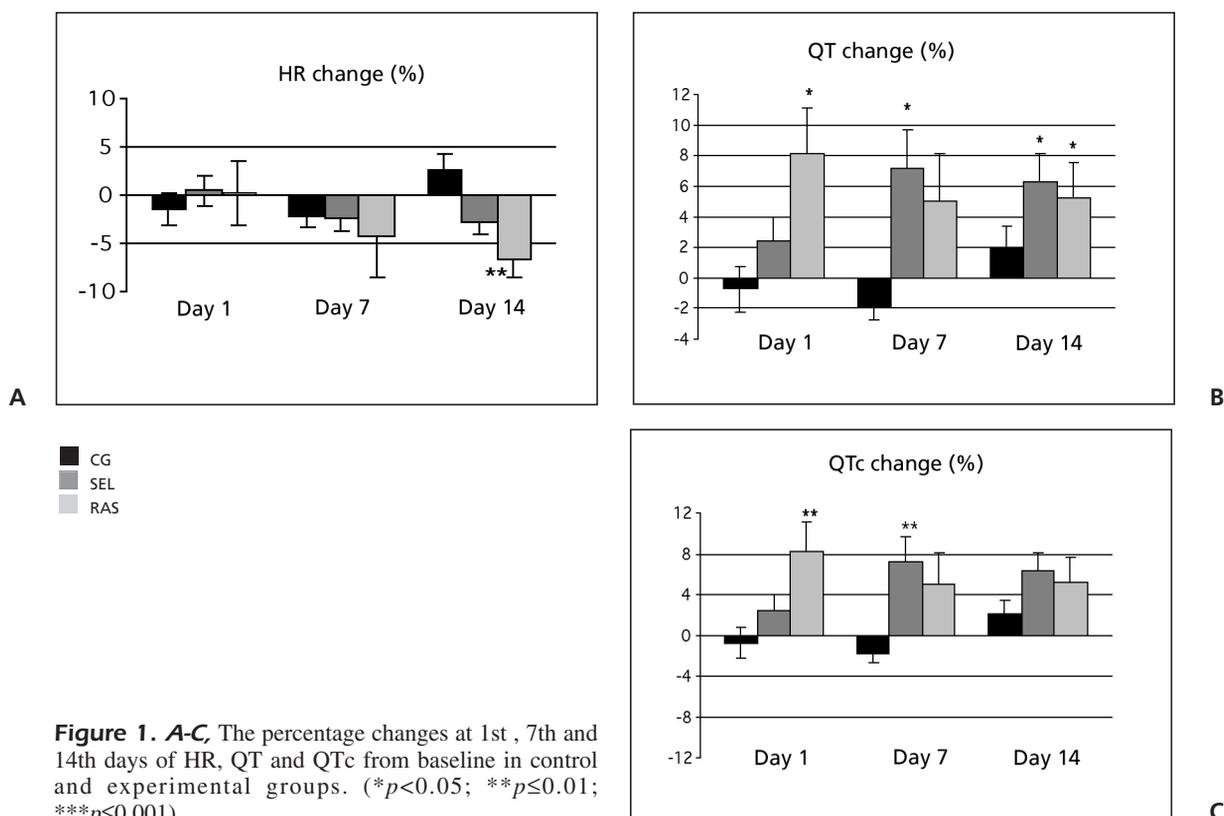
Investigation of oral selegiline and rasagiline administration on QT interval in conscious rabbits

**Table I.** Comparison of HR, QT and QTc changes in Control group (6 rabbits treated with saline: 1 ml per rabbit) and after oral administration of Selegiline (6 rabbits: 10 mg/per rabbit/per day) and of Rasagiline (5 rabbits: 1 mg/per rabbit/per day). Drugs were administrated for 14 days. The Heart Rate (HR), QT and Corrected QT values (QTc) were measured in conscious rabbits from ECG records before (baseline) and at 1, 7, and 14 days of experiment. Values are different in the same row ( $p < 0.05$ ,  $**p < 0.01$ ) and in the same column ( $^ap < 0.05$ ,  $^bp < 0.01$ ) compared to baseline and Control group, respectively.

Groups/ application	Values (ms)	Baseline	Time after application		
			Day 1	Day 7	Day 14
Control group (1 ml/per rabbit, n=6)	HR	240 ± 3	236 ± 3	234 ± 4	245 ± 4
	QT	147 ± 2	146 ± 2	145 ± 2	148 ± 2
	QTc	233 ± 4	230 ± 3	228 ± 3	237 ± 4
Selegiline group	HR	248 ± 3	248 ± 3	242 ± 4	240 ± 3
	QT	142 ± 2	144 ± 2	153 ± 4**	152 ± 2**
	QTc	227 ± 2	232 ± 3	243 ± 5** <sup>a</sup>	240 ± 3**
Rasagiline group	HR	242 ± 8	242 ± 8	228 ± 8	225 ± 7
	QT	138 ± 3 <sup>a</sup>	149 ± 4*	147 ± 3	148 ± 3
	QTc	219 ± 4 <sup>a</sup>	236 ± 5*	228 ± 4	229 ± 4 <sup>b</sup>

Use of SEL with L-Dopa caused sudden cardiac death in several cases of Parkinson's disease (PD); these deaths have been attributed to cardiotoxic effects of SEL<sup>12</sup>. In fact, methamphetamine, a metabolite of SEL, has been reported to prolong QTc suggesting that this prolonged QTc

might have played a role in the cardiac death<sup>13</sup>. SEL and RAS are non-cardiac drugs but many antiarrhythmic and non-cardiac drugs are known to prolong ventricular repolarisation and provoke *torsades de pointes* (TDP) resulting in an inhomogeneous lengthening of action potential, T



wave abnormality, and QT interval prolongation<sup>7</sup>. There has not been an experimental study evaluating the effect of SEL alone on QTc prolongation. RAS has less side-effects in comparison to SEL but there are also no reports stating the effect of RAS on QTc. Our data revealed a QTc prolongation at the end of 14<sup>th</sup> day when compared to baseline, and a prolongation at 7<sup>th</sup> day when compared to CG. Percent changes in HR, QT and QTc values compared to baseline values suggested a marked effect of SEL especially on QT/QTc time.

To the best of our knowledge, this is the first experimental study reporting SEL effect on QT/QTc. QTc time prolongation has already been reported in PD patients<sup>14</sup>. Therefore, the use of SEL may increase risk in PD patients whose QTc time is already prolonged.

Non cardiac drugs are already known to give rise to resulting in prolonged ventricular repolarisation and provoking *TDP*. These drugs share the same ability to block the rapid component of the delayed rectifier potassium channel (IKr), resulting in an inhomogeneous lengthening of action potential, T wave abnormality, and QT interval prolongation<sup>7</sup>. However, SEL and RAS seem not provoke the cardiac effect through the same mechanism. Prolonged QT/QTc time due to SEL and RAS may be attribute to the metamphetamine since QTc prolongation has already been reported in metamphetamine abuses<sup>13</sup>, because SEL is metabolised to methamphetamine and amphetamine<sup>2</sup>, the increased synaptic release of the catecholamines may influence the ventricular electrical activity by modifying the ventricular repolarisation time<sup>15</sup>. Amphetamine is also metabolised to the neurotransmitter *p*-hydroxyephedrine which depletes nerve terminals of norepinephrine<sup>3,4</sup>. Therefore SEL dependent QTc prolongation was attributed to the metamphetamine and catecholamines release.

The results obtained in this study may suggest a statistically significant effect of SEL on QTc prolongation when compared to RAS. QTc prolongations should be taken into account in PD patients where the autonomic system is involved.

### References

- 1) GUAY, DR. Rasagiline (TVP-1012): A new selective monoamine oxidase Inhibitor for Parkinson's disease. *Am J Geriatr Pharmacother* 2006; 4: 330-346.
- 2) REYNOLDS GP, ELSWORTH JD, BLAU K, SANDLER M, LEES AJ, STERN GM. Deprenyl is metabolized to methamphetamine and amphetamine in man. *Br J Clin Pharmacol* 1978; 6: 542-544.
- 3) GILL JR, MASON DT, BARTTER F. Effects of hydroxyamphetamine on the function of sympathetic nervous system in normotensive subject. *J Pharmacol Exp Ther* 1967; 155: 288-295.
- 4) CAVANAUGH JH, GRIFFITH JD, OATES JA. Effect of amphetamine on the pressor response to tyramine: formation of *p*-hydroxynorephedrine from amphetamine in man. *Clin Pharmacol Ther* 1970; 11: 656-664.
- 5) YASAR S, GOLDBERG JP, GOLDBERG SR. Are metabolites of l-deprenyl (selegiline) useful or harmful? Indications from preclinical research. *J Neural Transm Suppl* 1996; 48: 61-73.
- 6) KAYE S, MCKETIN R, DUFLOU J, DARKE S. Metamphetamine and cardiovascular pathology: a review of the evidence. *Addiction* 2007; 102: 1204-1211.
- 7) YAP YG, CAMM J. Risk of torsades de pointes with non-cardiac drugs. Doctors need to be aware that many drugs can cause qt prolongation. *Br Med J* 2000; 320: 1158-1159.
- 8) UZUN M, YAPAR K, UZLU E, CITIL M, ERDOGAN HM. QT interval prolongation and decreased heart rates after intravenous bolus oxytocin injection in male and female conscious rabbits. *Gen Physiol Biophys* 2007; 26: 168-172.
- 9) FRIDERICIA LS. Die systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. *Acta Med Scand* 1920; 53, 489.
- 10) ABASSI ZA, BINAH O, YAUDIM MB. Cardiovascular activity of rasagiline, a selective and potent inhibitor of mitochondrial monoamine oxidase B: comparison with selegiline. *Brit J Pharmacol* 2004; 143: 371-378.
- 11) FINBERG JPM, GROSS A, BAR-AM O, FRIEDMAN R, LOBODA Y, YAUDIM MBH. Cardiovascular responses to combined treatment with selective monoamine oxidase type B inhibitors and L-DOPA in the rat. *Brit J Pharmacol* 2006; 149: 647-656.
- 12) CHURCHYARD A, MATHIAS CJ, BOONKONGCHUEN P, LEES AJ. Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; 63: 228-234.
- 13) HANING W, GOEBERT D. Electrocardiographic abnormalities in methamphetamine abusers. *Addiction* 2007; 102 (Suppl 1): 70-75
- 14) OKA H, MOCHIO S, SATO H, KATAYAMA K. Prolongation of QTc interval in patients with Parkinson's disease. *Eur Neurol* 1997; 37: 186-189.
- 15) YEE KM, LIM PO, OGSTON SA, STRUTHERS AD. Effect of phenylephrine with and without atropine on QT dispersion in healthy normotensive men. *Am J Cardiol* 2000; 85: 69-74.