QT interval prolongation and decreased heart rates after intravenous bolus oxytocin injection in male and female conscious rabbits

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Abstract. The aim of this study was to evaluate changes in heart rate (HR), QT and RR intervals and corrected QT (QTc) values in conscious male and female New Zealand rabbits which intravenously received oxytocin (OXT) at different dosages. Animals were divided into 6 equal groups: group I (n = 6 male, received 0.75 U OXT *per* animal); group II (n = 6 male, received 1.5 U OXT *per* animal); group III (n = 6 male, received 3 U OXT *per* animal); group IV (n = 6 female, received 0.75 U OXT *per* animal); group V (n = 6 female, received 1.5 U OXT *per* animal); group VI (n = 6 female, received 3 U OXT *per* animal). ECG recording were taken from all animals before injection and then at 2, 4, 6, 8, 10, 15 and 20 min of OXT administration. QT and RR intervals obtained at 2 min of OXT administration were significantly prolonged in all groups ($p < 0.05$) with one exception that is the 1.5 U OXT injected female group where only QT interval did not change. The prolongation of QT and RR intervals persisted for 20 min in 1.5 U OXT injected male group while only QT interval prolongation was obvious for 20 min in 3 U OXT injected female group as for the other groups the prolonged interval were observed for 8–10 min and then returned to baseline values. Generally, a significant prolongation of QTc was noticed in both male and female rabbits at the 2 and 4 min in all groups and bradycardia was noticed at 2 min of OXT administration in all groups. Heart beats returned to normal values in all groups after 8 min of OXT administration. The change of HR, RR, QT and QTc was gender- but not dose-dependent ($p < 0.001$). The male rabbits were more sensitive to OXT effect then female rabbits. In conclusion, OXT used in therapeutic dosages decreased heart rate and prolonged QT and QTc intervals. Although cardiovascular effect of OXT are of short duration, its use in patient with risk factors for malignant arrhythmias requires more attention.

Key words: Oxytocin — QT interval — Female and male rabbits

Introduction

Oxytocin (OXT) is a nonapeptide hormon synthesised in supraoptic and paraventricular nuclei of the hypothalamus and then passes down the axons of hypothalamic nuclei to be stored in the posterior pituitary where it is released into the blood.

Although OXT is commonly known as a female hormone, equivalent concentrations of OXT is found in male hypophysis, and stimuli of OXT release is similar for both sexes (Gutkowska et al. 1997). OXT is recognised as having endocrine and paracrine roles also in male reproduction (Thackare et al. 2006). Beside reproductive properties, recent studies indicate that OXT may also influence cardiovascular system. Heart is shown to synthesise and release OXT (Jankowski et al. 1998) but the information on the effect of peripheral or central administration of OXT on cardiovascular system is controvertial. Administration of OXT resulted in either increased heart rate (HR; Petty et al. 1985; Pinder et al. 2002) or in contrast had negative inotropic and chronotropic effects on heart (Mukaddam-Daher et al. 2001). On the other hand, Roseag et al. (1998) documented that pure

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OXT did not have any direct negative inotropic properties in human atrial tissue.

Although controvertial information about central and peripheral administration of OXT effects on heart exists, there is a scarcity of data on its effect on QT interval and corrected QT (QTc) values (Charbit et al. 2004). As certain drugs effects QT and QTc intervals, clinician should know these drugs and their unpleasant effects in advance. Of these effects, the most striking is the potentially life-threatening form of polymorphic ventricular tachycardia termed torsades de pointes (TDP) resulting from the prolongation of QT and QTc intervals (Heist and Ruskin 2005). Intravenous OXT is widely used during caesarean section and curettage to decrease blood lose, to prevent or control postpartum bleeding following parturition, and to initiate uterine contraction during parturition (Kayaalp 1997; Kaya 2002). Although OXT is commonly used, its adverse effect on heart was not appreciated until the report of Royal London College of Obstetricians and Gynaecologists in 2001 where two women died of hypotention and tachycardia following OXT administration (URL: http://www.cemach.org.uk). To the best of our knowledge there is only one study evaluating the effect of OXT on QT and QTc in patients under anesthesia (Charbit et al. 2004). It was not clear whether this effect resulted from OXT or anaesthetics used as anaesthetic drugs are also known to prolong QT and QTc intervals (Booker et al. 2003). Many factors such as hydratation status, mental stage, haemorrhages along with anaesthetics are known to affect heart.

Studies evaluating OXT effects on heart were conducted in either only females, diseased subjects or in patients under anaesthesia. The present study was therefore designed to evaluate the effect of OXT on HR, RR, QT, and QTc values in both conscious male and female healthy rabbits.

Materials and Methods

Animals

The study involved 18 male and 18 female conscious New Zealand rabbits, 6–8 months old, weighing between 2.5–3 kg. Rabbits were fed *ad libitum* in individual cages and brought to the laboratory around an hour before the begining of experiment. Animals that were extremely excited and not suitable for electrocardiographic recording were substituted. Area where clips would be attached were clipped 3 days before the experiment commenced. The Laboratory Animal Care and Use Committee of Faculty Veterinary Medicine, University of Kafkas approved the experimental protocols.

Injection procedure

Both male ($n = 18$) and female ($n = 18$) rabbits were divided into 3 equal groups of 6 in each. OXT (5 U/ml; Vetaş, Istanbul, Turkey) was administrated as an intravenous bolus *via* auricular vein as quickly as possible (approximately 1–3 s). The gender and injected doses of the groups were as follow ($n = 6$ for each group): I. male, 0.75 U OXT; II. male, 1.5 U OXT; III. male, 3 U OXT; IV. female, 0.75 U OXT; V. female, 1.5 U OXT; VI. female, 3 U OXT.

Electrocardiographic recording (ECG)

Alligator clips were attached to limbs. The ECG values of baseline (before the injection) and at 2, 4, 6, 8, 10, 15 and 20 min of the OXT administration were recorded by direct writing ECG (Logos 8821, Logos Medical Co. Ltd., Tokyo, Japan). ECG was standardised at 1 mV = 20 mm, with chart speed of 50 mm/s with filter off. Leads I, II, III, aVR, aVL and aVF were determined. QT interval was manually calculated from the beggining of Q wave to the end of T wave. The same leads (II and aVR) were selected for all QT interval measurements. Animals were not given any sedatives or anaesthetics before and during ECG.

The QT interval was corrected for heart rate with the use of Carlsson formula (Carlsson et al. 1993) as below:

$$QTcC = QT - 0.175\ (RR\text{-}300)$$

Statistical analysis

Within group comparisons of HR, RR, QT, and QTcC were made at baseline and 2, 4, 6, 8, 10, 15 and 20 min of injection using one-way ANOVA (Turkey's multiple *t*-test) on MINITAB statistical package (version 11.2, 1996). The factors effecting (gender and dose) the measurements (HR, RR, QT, QTcC) were analysed using the multiple ANOVA methods. Data are represented as mean ± SEM (standard error of the mean).

Results

Different doses of OXT administration on HR, RR, QT and QTc values in rabbits of different genders were evaluated at a predefined time interval in this study.

QT and RR intervals obtained at 2 min of OXT administration were significantly prolonged in all groups ($p < 0.05$ or $p < 0.001$) with the exception of 1.5 U OXT injected female group where QT interval did not change. The prolongation of QT and RR interval persisted for 20 min in 1.5 U OXT injected male group while only QT prolongation was obvious for 20 min in 3 U OXT injected female group, for other groups the prolonged intervals lasted for 8–10 min and

Table 1. Time course of HR and RR, QT, and QTcC intervals changes in conscious male rabbits injected 0.75, 1.5 and 3 U OXT

Dose of OXT	Values (ms)	Baseline (before injection)	Time after OXT injection (min)						
			2	4	6	8	10	15	20
0.75 U Group I	RR	274 ± 2.9	292 ± 2.5***	298 ± 2.7***	282 ± 3.2	280 ± 3.7	278 ± 3	269 ± 1.8	275 ± 2.7
	QT	150 ± 2.0	163 ± 2.5***	163 ± 2.3***	161 ± 2.1***	158 ± 2.1	156 ± 2.1	155 ± 1.5	157 ± 1.8
	HR	220 ± 2.5	205 ± 1.9***	201 ± 1.6***	213 ± 2.4	214 ± 2.8	216 ± 2.4	222 ± 1.5	218 ± 2.1
	QTcC	151 ± 2.0	164 ± 2.5***	164 ± 2.3***	162 ± 2.1***	159 ± 2.1	157 ± 2.1	156 ± 1.5	158 ± 1.8
1.5 U Group II	RR	273 ± 2.8	308 ± 4.1 ***	312 ± 5.4***	303 ± 5.1***	305 ± 3.6***	301 ± 4.8***	297 ± 4.9***	298 ± 3.7***
	QT	152 ± 1.8***	169 ± 2.1***	171 ± 2.3***	165 ± 2.1***	166 ± 1.4***	167 ± 1.6***	167 ± 1.8***	164 ± 1.3***
	HR	220 ± 2.1	196 ± 2.5***	194 ± 3.2***	199 ± 3.3***	197 ± 2.3***	200 ± 3.2***	203 ± 3.1***	202 ± 2.5***
	QTcC	152 ± 1.8	169 ± 2.1***	172 ± 2.3***	165 ± 2.1***	167 ± 1.4***	168 ± 1.6***	168 ± 1.8***	164 ± 1.3***
3 U Group III	RR	268 ± 3.6	308 ± 15***	328 ± 9.9***	310 ± 7***	299 ± 4.3	297 ± 6.8	296 ± 7.0	291 ± 6.3
	QT	147 ± 1.8	170 ± 3.2***	167 ± 3.2***	161 ± 2.5***	161 ± 2.6***	164 ± 3.0***	159 ± 2.9	159 ± 2.6
	HR	225 ± 2.9	180 ± 5.6***	187 ± 5.4***	196 ± 4.4***	203 ± 4.7***	205 ± 4.5	205 ± 4.5	208 ± 4.1
	QTcC	148 ± 1.8	171 ± 3.2***	168 ± 3.2***	162 ± 2.5***	162 ± 2.6***	165 ± 3.0***	160 ± 2.9	162 ± 2.6

Data are the mean ± SEM of six animals in each group. Values are different basal levels with different superscript in the same line * $p \leq 0.01$, ** $p \leq 0.05$, *** $p \leq 0.001$. OXT, oxytocin; U, international unit; HR, heart rate. QTcC, QTc values estimated with Carlsson formula.

Table 2. Time course of HR and RR, QT, and QTcC intervals changes in conscious female rabbits injected 0.75, 1.5 and 3 U OXT

Dose of OXT	Values (ms)	Baseline (before injection)	Time after OXT injection (min)						
			2	4	6	8	10	15	20
0.75 U Group IV	RR	256 ± 3.6	283 ± 6.5***	285 ± 5.9***	282 ± 4.2***	274 ± 4.9	272 ± 6.5	263 ± 3.4	259 ± 4.0
	QT	152 ± 1.6	163 ± 1.8***	166 ± 1.4***	168 ± 1.6***	160 ± 1.4***	157 ± 1.8	155 ± 1.5	153 ± 1.6
	HR	236 ± 3.5	215 ± 5.4***	213 ± 5.3***	214 ± 3.1***	221 ± 3.9	224 ± 5.2	229 ± 3.2	233 ± 4.0
	QTcC	153 ± 1.6	164 ± 1.8***	167 ± 1.4***	168 ± 1.6***	160 ± 1.4***	158 ± 1.8	156 ± 1.5	154 ± 1.6
1.5 U Group V	RR	250 ± 4.2	274 ± 7.3**	261 ± 5.6	262 ± 4.5	258 ± 4.3	259 ± 5.3	258 ± 4.1	243 ± 3.9
	QT	147 ± 2.4	158 ± 2.5	159 ± 3.2*	159 ± 2.4*	161 ± 2.9*	156 ± 3.0	155 ± 2.7	152 ± 2.2
	HR	242 ± 4.0	223 ± 5.6*	233 ±5.1	230 ± 3.9	234 ± 3.9	234 ± 4.7	234 ± 3.7	248 ± 4.0
	QTcC	148 ± 2.4	159 ± 2.5	160 ± 3.2**	160 ± 2.4**	162 ± 2.9**	157 ± 3.0	155 ± 2.7	152 ± 2.2
3 U Group VI	RR	237 ± 5.0	292 ± 11***	277 ± 5.6***	266 ± 4.5***	299 ± 7.1***	247 ± 4.9	245 ± 4.6	248 ± 3.9
	QT	142 ± 2.2	162 ± 4.0***	162 ± 2.6***	160 ± 2.7***	161 ± 2.6***	156 ± 2.2***	154 ± 2.6***	154 ± 2.3***
	HR	256 ± 5.7	213 ± 7.1***	219 ± 4.7***	227 ± 4.0***	231 ± 3.9***	245 ± 5.3	247 ± 4.7	244 ± 3.9
	QTcC	142 ± 2.2	163 ± 4.0***	163 ± 2.6***	161 ± 2.7***	157 ± 2.6***	156 ± 2.2***	155 ± 2.6***	154 ± 2.5***

Data are the mean ± SEM of six animals in each group. Values are different basal levels with different superscript in the same line * $p \leq 0.01$, ** $p \leq 0.05$, *** $p \leq 0.001$. OXT, oxytocin; U, international unit; HR, heart rate. QTcC, QTc values estimated with Carlsson formula.

then returned to baseline values (Tables 1 and 2). As for QTc values, a significant prolongation was noticed in both male and female rabbits at the 2 and 4 min in all groups (Tables 1 and 2).

Heart beat rates were between 220 and 256 beats/min before the OXT injection. A bradycardia was recorded at 2 min of OXT administration in all groups. Bradycardia differed within the male and female groups. The most striking finding was in rabbits of 1.5 U OXT injected male group where bradycardia lasted for 20 min whereas HR returned to normal values in all other groups after 8 min of OXT administration (Tables 1 and 2).

The MANOVA statistics showed a significant effect of gender on HR, RR, QT and QTcC ($p < 0.001$). Mean HR (beats/min), RR (ms), QT (ms) and QTcC (ms) values were determined as 205, 291, 161 and 162 for male, and 231, 261, 157 and 157 for female, respectively. On the other hand, regardless of gender the effect of three different doses of OXT

(0.75, 1.5 and 3 U) on HR, RR, QT and QTcC values did not significantly differed ($p > 0.05$). Mean HR (beats/min), RR (ms), QT (ms) and QTcC (ms) values were 218, 279, 159 and 159 for 0.75 U OXT, 218, 278, 160 and 161 for 1.5 U OXT and 218, 279, 159 and 159 for 3 U OXT, respectively. The male rabbits were more sensitive to OXT effects then female rabbits as male rabbits had lower HR, higher RR, and more prolonged QT and QTcC intervals when compaired to female.

Discussion

This was the first study where OXT effects on QT and QTc were evaluated in concious healthy male and female subjects. The results revealed that QT and QTc intervals were prolonged and short time bradycardia was induced in male and female conscious rabbits by administration of OXT. These changes were more evident in male then female rabbits. These findings indicate that OXT administration might have had an adverse effect on cardiac repolarisation.

Effects of OXT on cardiovascular system have been disclosed by both *in vivo* and *in vitro* studies previously. Mukaddam-Daher et al. (2001) showed a negative inotropic and chronotropic effects of OXT on heart of dogs. These effects were attributed to decreased HR and force, initiated by release of acetylcholine (ACh) through specific receptors on intrinsic cholinergic neurons in which nitric oxide is involved. On the other hand, OXT is reported to induce release of atrial natriuretic peptide (ANP) through activation of atrial cardiomyocyte receptors. Released ANP then increases cyclic guanosine monophosphate (cGMP) production which results in decreased heart force and contraction causing bradycardia (Gutkowska et al. 1997). It is also known that increased cGMP activity initiates negative inotropic and chronotropic effects through decreased intracellular calcium concentration (Doyle et al. 1997). Remarkable bradycardia in both male and female rabbits given OXT was obtained at 2 min of the injection in the present study (Tables 1 and 2). In human, undergoing Caesarean operation under both general (Charbit et al. 2004) and spinal anesthesia (Pinder et al. 2002), OXT increased heart beats approximately in 2 min after the injection. These findings contradict to our results. However, comparison of conscious subjects with subjects undergoing anaesthesia and/or surgery may be misleading as anaesthesia, preoperative hydration, mental stage and haemorrhage may also alter cardiovascular system before and during the surgery.

Prolongation of QT interval of ECG predisposes towards the development of life-threatening cardiac arrhythmias known as TDP. QT intervals are affected by electrolytes status (Meenagh et al. 2004), gender (London 2001) and noncardiac drugs (Akita et al. 2004). OXT may also have an effect on heart as reported by Charbit et al. (2004) where OXT prolonged QTc interval in women under anaesthesia. In our study, QTc prolongation was also observed at 2 or 4 min and approximately returned to baseline values at 8 and 10 min except for 1.5 U OXT injected male and 3 U OXT injected female group. This short time effect may be related to the short half life of OXT, reported to be 3.6 min (Fuchs and Dawood 1980), and may not be considered as life threating. However, patients with risk factors identified for TDP such as female gender, heart disease, hypokalemia, drugs and Long QT syndrom interacting with QT interval (Viskin et al. 2003), should carefully be monitored during OXT administration. As anaesthetic drugs such as halothane, enflurane, isoflurane, sevuflurane, thiopental and propofol also prolong QT or QTc interval through blockade of K^+-channel during the anaesthesia (Booker et al. 2003), additional OXT use in such patients may increase the risk of TDP. Prolongation of QT interval in our study may also be related to the K^+-channel, however, no clear data exist to indicate the direct effect of OXT on cardiac repolarisation. However, Mukaddam-Daher et al. (2001) clearly shown that OXT may primarly act on OXT receptors present on parasymphatetic postganglionic fibers to stimulate the release of ACh acting on muscarinic receptors in heart. Furushima et al. (1999) also found out that the muscarinic receptor involved in ACh-induced QT prolongation and TDP in patients with Long QT syndrome. ACh activated K^+-channel are found in sinoatrial pacemaker, atrial and ventricular cells and regulate heart rate (Tamargo et al. 2004). These may also be the case in our study where OXT might have played role in the blockadge of the K^+-channel resulting in QT interval prolongation.

OXT is a well known female hormone and therefore commonly used in female. However, studies also show that OXT is also released from male hypothalamo-pituitary magnocellular system as much as female (Ivell et al. 1997). Male reproductive system has OXT receptor and OXT is used as a therapeutic agent due to its effect in male reproductive tract and prostate (Thackare et al. 2006). This therefore led us to include male rabbits in this study. The results obtained clearly show that OXT had similar effect on heart in both sexes, however, the male rabbits were more sensitive to OXT then female rabbits as male rabbits had lower HR, higher RR, and more prolonged QT and QTcC intervals when compaired to female. This may be extrapolated as both sexes have the same OXT receptors in heart.

In conclusion, OXT has a marked and short-period effect when used as an intravenous bolus in therapeutic dosages as it decreased heart rate and prolonged QT and QTc intervals especially in male rabbits. This may result in induction of TDP especially in patients with the risk of malignant arrhythmias. The results obtained may suggest that caution should be exercised when using OXT as a bolus and may

require further detailed studies to clarify mechanism of its effect on heart.

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