

Quetiapine에 의한 QTc 간격의 변화

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ABSTRACT

Change in the QTc Interval after Quetiapine Administration

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Objective : Among causes of sudden death presumed to be related with use of atypical antipsychotics, all drugs which could induce torsade de pointes had been known to prolong QTc interval. Therefore, to monitor the changes of QTc interval on EKG seemed to be an important marker for the antipsychotic-induced cardiotoxicity, further to prevent sudden death due to fatal ventricular arrhythmia. There are several studies and case reports about cardiac toxicity in some patients who were administered newly developed atypical antipsychotics. The aims of this study were to know whether quetiapine causes changes in QTc interval, and to identify affecting factors. **Methods** : For the 31 inpatients (21 females, 10 males) with schizophrenia (N=25) or schizoaffective disorder (N=5), schizophreniform disorder (N=1) according to DSM-IV, the EKG monitoring was successively taken on baseline and the 2nd, 4th and 6th weeks after quetiapine administration, and serial changes of every EKG parameters including QTc interval was comparatively analyzed. Furthermore, variables such as cardiovascular risk factors (weight gain, hyperlipidemia, thyroid function, etc.), dose of drugs, drug combination, severity of psychotic symptoms, changes in the activity of autonomic nervous system despite of sex and age were also successively assessed on baseline and the 2, 4, and 6 weeks after quetiapine administration. **Results** : 1) Every EKG parameters (heart rate, PR interval, QRS and QT) including QTc interval and diastolic blood pressure were not changed significantly on the 2, 4, and 6 weeks after quetiapine administration as compared with baseline. The systolic pressure was significantly declined from the 2 weeks after quetiapine administration as compared with baseline ($p<0.05$). 2) Among variables affecting the EKG parameters including QTc interval, age, dose of drugs, hyperlipidemia and thyroid function were not correlated with. However, the body weight on the 6 weeks after quetiapine administration had significant negative correlation with QT ($r=-0.427$) and QTc interval ($r=-0.406$), and the drug combination on the 6 weeks after quetiapine treatment had significant positive correlation with QRS ($r=0.393$) and QT ($r=0.415$), while severity of psychotic symptoms on the 4th week had correlation with QT ($r=0.380$) ($p<0.05$, respectively). Otherwise, the QTc interval on the 6 weeks after was significantly prolonged in female patients ($p<0.05$). **Conclusion** :

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Even though the administration of quetiapine did not cause significant changes in the QTc interval in this study, we need to pay attention toward the possibly related factors. (Korean J Psychopharmacol 2004;15(3):296-304)

KEY WORDS : Quetiapine · Sudden death · Torsade de pointes · QTc interval · Body weight · Sex.

서론

갑작스러운 사망 (sudden death)은 항정신병약물 사용과 관련이 있는 것으로 알려져 있다. Phenothiazine 계열 약물 중 25%는 갑작스러운 사망을 유발할 수 있다.¹⁾ thioridazine, Mehtonen²⁾, phe-nothiazine, thioridazine, Hunt, Stern⁴⁾, Jackson⁵⁾ 등은 갑작스러운 사망을 유발할 수 있다. haloperidol, torsade de pointes, QTc, Sharma⁶⁾ QTc 500 ms, torsade de pointes, QTc 가가

가, sertindole,⁷⁻¹⁰⁾ ris-peridone,^{11,12)} clozapine,¹³⁻¹⁵⁾ olanzapine,¹⁶⁻¹⁸⁾ ami-sulpiride,¹⁹⁾ quetiapine,^{20,21)} ziprasidone^{22,23)}

torsade de pointes, QTc, potassium rectifier channel, 가²⁴⁾, QTc 450 msec, QTc 500 msec²⁵⁾, QTc

가¹⁷⁾

, 23% 가 di-clozapine, olanzapine, quetiapine 가 QTc

²¹⁾ benzothiazepine, quetiapine, olanzapine

²⁰⁾

대상 및 방법

1. 연구대상

2002 6 2003 5 DSM -²⁶⁾

quetiapine 31 (21 , 10)

quetiapine

quetiapine

quetiapine, quetiapine, 1

quetiapine, QTc

25 (80.7%), 5 (16.1%), 1 (3.2%), 32.4 ± 10.4, 6.0 ±

Quetiapine QTc

7.3 , 1.6 ± 0.1 m (1).

2. 연구방법

31 quetiapine ,
2 , 4 6
(heart rate), PR, QRS, QT, QTc
(가,
,), , ,
(Clinical Global Impression, CGI ;
Brief Psychiatric Rating Scale, BPRS),
(, , , ,
, , QTc

Table 1. Demographic data (N=31)

Age (years)	32.4 ± 10.4
Below 40	23 (74.2%)
40 - 49	5 (16.1%)
Over 50	3 (9.7%)
Sex	
Female	21 (67.7%)
Male	10 (32.3%)
Duration of illness (years)	6.0 ± 7.3
Height (m)	1.6 ± 0.1
Psychiatric diagnosis	
Schizophrenia	25 (80.7%)
Paranoid	17 (54.8%)
Undifferentiated	6 (19.4%)
Residual	2 (6.5%)
Schizophreniform disorder	1 (3.2%)
Schizoaffective disorder	5 (16.1%)

These data represent mean ± S.D.

Table 2. Sequential changes of EKG parameters (N=31)

	Baseline	Quetiapine treatment			p-value*
		2nd Week	4th Week	6th Week	
Heart rate/min	82.0 ± 18.4	80.4 ± 15.4	80.8 ± 14.9	79.6 ± 11.3	0.810
PR (msec)	152.0 ± 21.4	156.5 ± 20.8	157.9 ± 16.5	151.1 ± 22.5	0.328
QRS (msec)	89.4 ± 10.5	86.3 ± 8.1	91.4 ± 10.1	91.2 ± 9.4	0.076
QT (msec)	361.0 ± 33.0	371.4 ± 34.5	370.8 ± 25.5	372.9 ± 29.5	0.225
QTc (msec)	393.8 ± 19.3	404.0 ± 27.8	404.4 ± 19.3	404.6 ± 19.6	0.147

These data represent mean ± S.D., * : Comparison of average by repeated measure ANOVA

quetiapine 2 , 4 6
3. 통계분석
Windows SPSS(version
10.0)
(frequency analysis)
. Quetiapine , quetiapine 2 ,
4 6
(repeated measured ANOVA)
Tukey B
Scheffe
t
t
Pearson
p<0.05
결 과

1. Quetiapine 투여 전후의 심전도 지표 비교

QTc (,
PR , QRS, QT, QTc)
2 , 4 , 6
(2).

2. Quetiapine 투여 전후의 자율신경계활성도 지표 비교

quetiapine 2, 4, 6 (3).
quetiapine 2 (p<0.05)(3).

3. 심전도 지표에 영향미치는 요인

QTc
quetiapine 4.
quetiapine ,

Table 3. Sequential change of autonomic activity (N=31)

	Baseline	Quetiapine treatment			p-value*
		2nd Week	4th Week	6th Week	
Pulse rate/min	81.5 ± 7.3	82.4 ± 7.8	83.8 ± 6.1	82.9 ± 7.1	0.343
RR/min	20.1 ± 0.5	19.8 ± 0.9	20.1 ± 0.9	20.1 ± 0.9	0.236
Systolic BP (mmHg)	113.2 ± 12.5	107.1 ± 12.4	106.1 ± 10.2	107.1 ± 10.4	0.010
Diastolic BP (mmHg)	72.3 ± 8.4	70.0 ± 9.3	71.6 ± 7.3	68.7 ± 6.2	0.143

These data represent mean ± S.D.

* : Comparison of average by repeated measure ANOVA with Tukey B and Scheffe's tests

Table 4. Sequential changes of affecting variables (N=31)

	Baseline	Quetiapine treatment			p-value*
		2nd Week	4th Week	6th Week	
BPRS	96.6 ± 12.2	89.3 ± 15.2	79.0 ± 19.4	62.2 ± 24.9	0.000
CGI	5.4 ± 0.6	5.1 ± 0.9	4.3 ± 1.0	3.6 ± 1.1	0.000
FBS (mg/dl)	92.8 ± 13.4	(-)	90.6 ± 10.2	(-)	0.306
T ₃ (ng/dL)	7.7 ± 1.5	(-)	7.0 ± 2.2	(-)	0.102
Free T ₄ (ng/dL)	1.6 ± 1.9	(-)	1.7 ± 1.9	(-)	0.367
TSH (μIU/ml)	1.7 ± 1.5	(-)	2.2 ± 1.3	(-)	0.103
Cholesterol (mg/dl)	183.7 ± 19.8	(-)	192.2 ± 15.9	(-)	0.038
Triglyceride (mg/dl)	201.4 ± 104.5	(-)	194.9 ± 33.3	(-)	0.746
Body weight (kg)	62.0 ± 11.9	62.8 ± 11.8	62.8 ± 12.0	62.9 ± 12.1	0.286
BMI (kg/m ²)	23.9 ± 3.8	24.2 ± 3.9	24.2 ± 4.0	25.1 ± 6.1	0.229
Dosage (mg)	0.0 ± 0.0	308.1 ± 151.7	588.7 ± 187.4	656.5 ± 182.5	0.000
Drug combination	0.7 ± 0.9	0.7 ± 1.0	0.6 ± 1.1	0.6 ± 1.1	0.626

These data represent mean ± S.D.

* : Comparison of average by repeated measured ANOVA with Tukey B and Scheffe's tests, or paired t-test

Table 5. Correlation of EKG parameters with affecting variables

	QRS (4W)	QRS (6W)	QT (B)	QT (4W)	QT (6W)	QTc (6W)
Body weight (B)			- 0.509*			
Body weight (4W)	0.423*					
Body weight (6W)					- 0.427*	- 0.406*
Drug combination (6W)		0.393*			0.415*	
BPRS (4W)				0.380*		

These data represent correlation coefficients ().

(B) : baseline, (4W) : 4th wk after quetiapine treatment, (6W) : 6th week after quetiapine treatment. * : p<0.05

Quetiapine QTc

. , quetiapine 6 QT(= -0.427) QTc (= -0.406) 가 , quetiapine 6 QRS(= 0.393) QT(=0.415) , quetiapine 4 BPRS 가 QT(=0.380) 가 (p<0.05) (5). 가 (22.7%)가 가 , (12.9%), , (9.7%) , , 가

Table 6. Drug combination (N=31)

Quetiapine monopharmacy	13 (41.9%)
Quetiapine polypharmacy	18 (58.1%)
Antipsychotics=1 (3.2%)	
Antianxiety drugs=7 (22.7%)	
Antipsychotics+antianxiety drugs=4 (12.9%)	
Antidepressants+antianxiety drugs=3 (9.7%)	
Antianxiety drug+lithium=1 (3.2%)	
Antipsychotics+antianxiety drugs+benztropine=1 (3.2%)	
Antianxiety drug+benztropine+propranolol=1 (3.2%)	
Antipsychotics	
Chlorpromazine	1
Thioridazine	2
Risperidone	4
Antianxiety drugs	
Clonazepam	12
Lorazepam	4
Diazepam	1
Antidepressants	
Paroxetine	1
Citalopram	2
Trazodone	1
Zolofit	1
Other drugs	
Lithium	1
Propranolol	1
Benztropine	2

These data represent No (%)

3.2% (6). , PR, QRS, QT, quetiapine 2 , 4 , 6 가 (7). quetiapine 6 QTc (394.6 ± 13.3 msec) (409.4 ± 20.6 msec) (p<0.05)(7).

고 찰

QTc long QT syndrome, (hypokalemia) (hypomagnesemia), 가 (azole antifungals, macrolide antibactericidals, class - class - antiarrhythmic agents) .²⁷⁾ Liberatore Robinson²⁸⁾ thioridazine lithium syncope 1 (first degree AV block) (sinus bradycardia), QT , U wave , 가 torsade de pointes가 . Reilly ²⁹⁾ QTc 65 , , thioridazine droperidol . Warner ³⁰⁾ QTc chlorpromazine 2,000 mg , thioridazine (repolarization) Hartigan - Go ³¹⁾ . Metzger Friedman³²⁾ haloperidol torsade de pointes cardiomyopathy . ³³⁾ 가가 QTc , QT

Table 7. Comparison of EKG parameters according to sex

	Female (N=21)	Male (N=10)	p-value*
Heart rate/min			
Baseline	78.1 ± 18.9	90.2 ± 14.9	0.087
2nd Wks	78.6 ± 13.7	84.2 ± 18.7	0.353
4th Wks	78.4 ± 14.9	85.8 ± 14.5	0.204
6th Wks	79.4 ± 12.2	80.2 ± 9.8	0.854
PR (msec)			
Baseline	147.4 ± 23.5	161.6 ± 12.2	0.084
2nd Wks	154.4 ± 21.1	160.8 ± 20.5	0.430
4th Wks	158.0 ± 16.5	157.7 ± 17.3	0.963
6th Wks	149.3 ± 21.4	154.8 ± 25.5	0.537
QRS (msec)			
Baseline	88.6 ± 9.2	91.2 ± 13.0	0.522
2nd Wks	85.1 ± 7.8	88.8 ± 8.6	0.247
4th Wks	88.6 ± 9.1	97.2 ± 10.0	0.023
6th Wks	89.1 ± 9.6	95.6 ± 7.9	0.074
QT (msec)			
Baseline	368.0 ± 33.1	346.1 ± 28.7	0.083
2nd Wks	375.3 ± 36.5	363.2 ± 30.2	0.371
4th Wks	376.7 ± 24.8	358.4 ± 23.5	0.061
6th Wks	377.8 ± 29.7	362.5 ± 27.7	0.181
QTc (msec)			
Baseline	395.1 ± 18.4	391.2 ± 22.0	0.609
2nd Wks	406.1 ± 31.0	399.6 ± 20.4	0.549
4th Wks	406.9 ± 21.6	399.1 ± 12.6	0.302
6th Wks	409.4 ± 20.6	394.6 ± 13.3	0.048
Systolic BP (mmHg)			
Baseline	110.5 ± 12.8	119.0 ± 9.9	0.075
2nd Wks	103.3 ± 10.2	115.0 ± 13.5	0.012
4th Wks	103.8 ± 10.2	111.0 ± 8.8	0.066
6th Wks	104.8 ± 10.8	112.0 ± 7.9	0.069
Diastolic BP (mmHg)			
Baseline	71.4 ± 7.9	74.0 ± 9.7	0.438
2nd Wks	69.5 ± 8.0	71.0 ± 12.0	0.687
4th Wks	70.5 ± 7.4	74.0 ± 7.0	0.218
6th Wks	67.6 ± 6.2	71.0 ± 5.7	0.158

These data represent mean ± S.D., * : Two-tailed t-test

link¹⁹⁾ (ventricular fibrillation)
 ,
 QTc (posterior hypothalamus)
 . Age- (vagus)

Quetiapine QTc
 (myocardium) ⁴⁵⁾
 QT
 (heart rate variability) (autonomic neurocardiac function integrity) 가
 , GABA , QT
 , - , 34-36) , Fayek ²⁵⁾
 . Agelink ³⁷⁾ QT
 (cardiovascular autonomic reactivity) cy-
 tochrome P - 450 ,
 , clozapine ,
 (heart rate variance) 가 ,
 . Choy ³⁸⁾ 가, ⁴⁷⁾ 2 ,
 QT ,
 quetiapine .
 Drici ³⁹⁾ haloperidol, risperidone, sertindole, ⁴⁸⁾ QT
 clozapine, olanzapine QT
 (repolarization) . Drolet ,
⁴⁰⁾ thioridazine K+ 12 QT repolari-
 repolarization QT zation repolarization
 . Kobayashi ⁴¹⁾ Kobayashi
⁴²⁾ haloperidol, thioridazine, pimozide, clozapine ion channel , QTc
 (brain - type) (cardiac - type) 12
 G - protein - activated inwardly rectifying K+
 (GIRK) channel 가
 . Suesbrich ⁴³⁾ haloperidol ,
 HERG(human ether - a - go - go related gene) channel , quetiapine
 K+ channel 6 QTc
 , Rampe ⁴⁴⁾ sertindole QT
 potassium channel HERG QTc
 . HERG , quetiapine 12 ,
 channel potassium flux 가 1 quetiapine
 , torsade de pointes 가 .

중심 단어 : Quetiapine · Torsade de pointes · QTc

결론

참고문헌

torsade de pointes

QTc

QTc

가

가

(N=25), (N=

5) (N=1) 31 (

21, 10) quetiapine

QTc

1) QTc (

, PR, QRS QT)

2, 4, 6

2

(p<0.05).

2) QTc

6

QT(= -0.427) QTc (= -0.406)

가, 6

QRS(=0.393) QT(=0.415)

4 (BPRS) QT(=

0.380) 가 (p<0.05).

6 QTc

(p<0.05).

quetiapine QTc

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