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Research Article

Detecting Coadministered Drugs that Affect the Incidence of Long QT Syndrome Associated with Fluoroquinolone Antibiotics Using a Spontaneous Reporting System

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ABSTRACT

Background: Fluoroquinolone antibiotics (FQs) are known to induce long QT syndrome (LQTS). However, the combination of FQ and non-FQ drugs that elevate the incidence of LQTS has not been extensively studied. Here, we analyzed concomitant drugs that influence the risk of FQ-induced LQTS using a spontaneous reporting system.

Methods: We assessed adverse event reports in the Japanese Adverse Drug Event Report (JADER) database. The reporting odds ratio (ROR) and its 95% confidence interval (CI) were applied for signal detection. Furthermore, we evaluated the time-to-onset data for drug-related LQTS.

Results: The single use of garenoxacin, moxifloxacin, and ciprofloxacin was significantly associated with LQTS with RORs (95% CIs) of 3.16 (2.24 – 4.44), 7.65 (5.29 – 11.07), and 1.98 (1.06 – 3.70), respectively. The concomitant use of garenoxacin and disopyramide showed a much higher ROR of 884.18 (95% CI, 106.41 – 7346.92) than use of garenoxacin without disopyramide (ROR, 2.59; 95% CI, 1.78 – 3.78) and disopyramide without garenoxacin (ROR, 67.26; 95% CI, 54.18 – 83.49). The median time-to-onset for FQs alone (3.00 days) was significantly shorter than those for bepridil (49.00 days), disopyramide (26.50 days), clarithromycin (9.50 days), and famotidine (11.00 days) (all $p<0.001$). In contrast, the time-to-onset of LQTS was not significantly different between single administration of FQs and coadministration of FQs and these four non-FQ drugs (4.00 days) ($p=0.9363$).

Conclusion: We identified drugs that may increase the risk of FQ-associated LQTS when coadministered. Attention is required to concomitant use of disopyramide with FQs, such as garenoxacin.

Keywords: Long QT syndrome; Fluoroquinolone antibiotic; Drug-drug interaction; Disproportionality, Spontaneous reporting system; Signal detection

Abbreviations: RR: Reporting Ratio; GRNX: Garenoxacin; MFLX: Moxifloxacin; LVFXL Levofloxacin; CPFX: Ciprofloxacin; TFLX: Tosufloxacin; PZFX: Pazufloxacin; GFLX: Gatifloxacin

INTRODUCTION

Drug-induced long QT syndrome (LQTS) is a rare but serious side effect that leads to fatal ventricular arrhythmia called torsade de pointes (TdP) resulting in syncope and sudden cardiac death. Drugs suspected to cause LQTS include not only antiarrhythmic drugs but also non-cardiovascular drugs, such as antibiotics, antipsychotics, and antihistamines [1]. A previous retrospective study showed that 51% of hospitalized patients received at least one QT-prolonging drug [2]. Thus, patients are exposed to a large number of drugs suspected to cause LQTS.

Fluoroquinolone antibiotics (FQs) are widely used drugs with a broad antimicrobial spectrum and good tolerability. On the other hand, some FQs have been suggested to induce LQTS by blocking the human ether-a-go-go-related gene (hERG) channel that underlies the rapidly activating delayed rectifier potassium current (I_{Kr}) [3–5]. It has been shown that FQs alone increase the incidence

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of LQTS [6,7]. As FQs are frequently used for prophylaxis and treatment of infection, these antibiotics are predicted to often be prescribed together with other QT-prolonging drugs. It has been reported that co-administration of two or more QT-prolonging drugs is a risk factor for drug-induced LQTS [8,9]. There have been several case reports of LQTS or TdP associated with concomitant use of FQs and other drugs, e.g., levofloxacin (LVFX) and imipramine [10], ciprofloxacin (CPFX) and methadone [11], CPFX and sotalol [12], garenoxacin (GRNX) and disopyramide [13]. As some combinations with FQs are not described in the contraindications or precautions for co-administration in the package inserts of ethical drugs, attention should be paid to their concomitant use. However, it is unclear which combinations of FQs and other drugs actually increase the risk of LQTS.

Spontaneous reporting systems provide real-world data and are used to detect adverse events related to post-marketed drugs. In these systems, two or more suspected drugs for each event can be given. Therefore, these systems have also been used for the detection of adverse events associated with drug–drug interactions [14–16]. In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has released a spontaneous reporting system database called the Japanese Adverse Drug Event Report (JADER) database. While data mining approaches have been used to detect adverse events by disproportionality analysis, the detection of possible drug–drug interactions is based on the following concept: when a suspected adverse event is reported more frequently with the combination of two drugs compared to the situation where they are used alone, this association may indicate the existence of a drug–drug interaction [17]. This study was performed to identify co-administered drugs that affect the incidence of FQ-associated LQTS using the JADER database.

MATERIALS AND METHODS

Data sources

We evaluated adverse event reports in the JADER database from April 2004 to March 2016. In this study, we collected adverse events reported in the JADER database and evaluated signal detection using DRiFOs® (Luminary Medical K.K., Japan), an online system for licensed users to search the most updated adverse drug events reported to the PMDA using the JADER. The adverse events reported in the JADER database comply with the definitions provided by the Medical Dictionary for Regulatory Activities (MedDRA) ver. 19.0. For the detection of LQTS, preferred terms (PTs) were extracted from Standardized MedDRA Queries (SMQs), which have been released by the MedDRA Maintenance and Support Services Organization. The SMQs are groupings of PTs related to defined medical conditions or areas of interest [18]. Among the PTs that matched the SMQ for *torsade de pointes/QT prolongation* (SMQ code: 20000001), we used 6 PTs categorized in a narrow scope as follows: electrocardiogram QT interval abnormal (PT code: 10063748), electrocardiogram QT prolonged (PT code: 10014387), long QT syndrome (PT code: 10024803), long QT syndrome congenital (PT code: 10057926), torsade de pointes (PT code: 10044066), and ventricular tachycardia (PT code: 10047302). In the JADER database, each drug was assigned a code according to its association with adverse events; suspected drug, concomitant drug, or interacting drug. In this study, all drugs allocated with suspected drug or interacting drug were used for analysis. For signal detection of concomitant drug use, we focused on the combination of FQs and non-FQ drugs. Among these combinations, three or more reports were used for signal detection.

Signal detection

The reporting odds ratio (ROR) was calculated using two-by-two contingency tables of the presence or absence of a particular drug and a particular adverse event in the case reports [19]. Safety signals were considered significant when the lower limit of the 95% confidence interval (CI) of the ROR value exceeded 1 [19,20]. For detection of concomitant use risk, the combination of two suspected or interacting drugs was considered as a drug of interest. The RORs and 95% CIs of co-administration group and single drug use groups were calculated individually. The possibility of an adverse event occurring due to a suspected drug–drug interaction was expected to be elevated if the ROR of the concomitant use group was higher than those of single use groups and these 95% CIs were mutually exclusive [14–16].

Time-to-onset analysis

The JADER database contains information about start date of drug administration and onset date of adverse event of interest, which can be used for time-to-onset analysis. The median of the data, interquartile ranges (IQRs), and the Weibull shape parameter (WSP) were utilized for evaluation of the time-to-onset data for drug-induced LQTS. Time-to-onset from the JADER database was calculated from the start date of drug administration to the occurrence of LQTS. In the case of co-administration, we adopted the later start date of FQs or concomitant drug administration. Time-to-onset exceeding 90 days was considered as 90 days. The WSP test is used for statistical analysis of time-to-onset data and can describe the non-constant ratio of incidence of adverse events [20,21]. The shape parameter β of the Weibull distribution was used to indicate the hazard without a reference population. When β was equal to 1, the hazard was considered to be constant over time. If β and the lower limit of the corresponding 95% CI exceeded 1, the hazard was estimated to increase over time.

Statistical analysis

All statistical analyses were performed using JMP 13 (SAS Institute Inc., Cary, NC, USA). In all analyses, $p<0.05$ was taken to indicate statistical significance.

RESULTS

Number of reports and RORs of LQTS for each drug

A total of 404445 reports were included in this study and the number of LQTS reports was 2732. Table 1 shows the number of LQTS reports and RORs for FQs and other drugs with 20 or more case reports of LQTS. Among the FQs analyzed, the RORs (95% CIs) of GRNX, moxifloxacin (MFLX), LVFX, CPFX, tosufloxacin (TFLX), pazufloxacin (PZFX), and gatifloxacin (GFLX) were 3.16 (2.24 – 4.44), 7.65 (5.29 – 11.07), 1.16 (0.79 – 1.71), 1.98 (1.06 – 3.70), 1.38 (0.57 – 3.34), 1.51 (0.63 – 3.66), and 0.55 (0.08 – 3.95), respectively. As the lower limits of 95% CIs of GRNX, MFLX, and CPFX exceeded 1, the signals for association with LQTS were considered to be significant for these drugs. The lower limits of 95% CIs for all non-FQ drugs except imatinib exceeded 1.

Number of reports and RORs of LQTS associated with concomitant use of FQs and non-FQ drugs

We evaluated the reports of LQTS related to co-administration of FQs and other drugs shown in Table 1. The number of case reports was 45, in which GRNX and disopyramide, LVFX and bepridil,

Table 1: Number of reports and RORs of QT prolongation associated with FQs and other drugs.

	Drugs	Cases (n)	Non-cases (n)	Total (n)	RR (%)	ROR(95% CI)
FQs	GRNX	34	1,598	1,632	2.08	3.16(2.24 – 4.44)
	MFLX	30	582	612	4.9	7.65(5.29 – 11.07)
	LVFX	26	3,300	3,326	0.78	1.16(0.79 – 1.71)
	CPFX	10	743	753	1.33	1.98(1.06 – 3.70)
	TFLX	5	532	537	0.93	1.38(0.57 – 3.34)
	PZFX	5	486	491	1.02	1.51(0.63 – 3.66)
	GFLX	1	265	266	0.38	0.55(0.08 – 3.95)
Non-FQ drugs	Bepridil	330	314	644	51.24	175.63(149.71 – 206.02)
	Amiodarone	175	1,526	1,701	10.29	17.95(15.28 – 21.09)
	Pilsicainide	162	491	653	24.81	51.51(42.95 – 61.78)
	Disopyramide	128	280	408	31.37	70.47(56.97 – 87.17)
	Nilotinib	127	1,396	1,523	8.34	13.98(11.61 – 16.83)
	Clarithromycin	115	2,775	2,890	3.98	6.32(5.22 – 7.64)
	Arsenic trioxide	104	293	397	26.2	54.22(43.21 – 68.03)
	Cibenzoline	92	689	781	11.78	20.28(16.26 – 25.30)
	Donepezil	90	1,570	1,660	5.42	8.68(7.00 – 10.77)
	Famotidine	67	3,112	3,179	2.11	3.22(2.52 – 4.11)
	Sulpiride	62	1,308	1,370	4.53	7.11(5.49 – 9.20)
	Nifekalant	61	36	97	62.89	254.82(168.49 – 385.38)
	Cilostazol	42	1,853	1,895	2.22	3.37(2.48 – 4.59)
	Digoxin	42	430	472	8.9	14.57(10.59 – 20.05)
	Aprindine	41	238	279	14.7	25.7(18.41 – 35.88)
	Furosemide	40	2,125	2,165	1.85	2.79(2.04 – 3.83)
	Propofol	37	1,472	1,509	2.45	3.73(2.69 – 5.18)
	Fluvoxamine	37	972	1,009	3.67	5.66(4.07 – 7.88)
	Flecainide	37	90	127	29.13	61.27(41.70 – 90.00)
	Haloperidol	35	1,205	1,240	2.82	4.31(3.08 – 6.05)
	Olanzapine	34	1,732	1,766	1.93	2.91(2.07 – 4.09)
	Sevoflurane	34	754	788	4.31	6.7(4.74 – 9.47)
	Risperidone	33	2,591	2,624	1.26	1.88(1.33 – 2.66)
	Paroxetine	30	2,673	2,703	1.11	1.66(1.15 – 2.38)
	Azithromycin	29	1,221	1,250	2.32	3.52(2.43 – 5.10)
	Verapamil	28	357	385	7.27	11.64(7.91 – 17.13)
	Imatinib	27	3,971	3,998	0.68	1(0.68 – 1.46)
	Crizotinib	27	767	794	3.4	5.22(3.55 – 7.67)
	Pirmenol	27	21	48	56.25	190.93(107.81 – 338.13)
	Escitalopram	25	323	348	7.18	11.48(7.63 – 17.27)
	Quetiapine	24	1,891	1,915	1.25	1.87(1.25 – 2.81)
	Carvedilol	24	1,001	1,025	2.34	3.55(2.36 – 5.33)
	Sotalol	24	82	106	22.64	43.41(27.50 – 68.52)
	Voriconazole	23	956	979	2.35	3.56(2.35 – 5.39)
	Chlorpromazine	22	538	560	3.93	6.05(3.95 – 9.29)
	Trazodone	21	361	382	5.5	8.61(5.54 – 13.39)
	Aripiprazole	20	1,881	1,901	1.05	1.57(1.01 – 2.44)
	Solifenacin	20	656	676	2.96	4.51(2.88 – 7.05)
	Bisoprolol	20	450	470	4.26	6.58(4.20 – 10.31)

LVFX and disopyramide, LVFX and clarithromycin, and LVFX and famotidine had three or more cases (Table S1). Table 2 shows the RORs of LQTS associated with these combinations and single drug use without the other co-administered drug. The RORs (95% CIs) of the combinations of GRNX and disopyramide, LVFX and disopyramide, LVFX and clarithromycin, LVFX and famotidine were 884.18 (106.41 – 7346.92), 88.32 (21.10 – 369.76), 4.91 (1.55 – 15.51), and 6.05 (1.91 – 19.20), respectively. Of these, only the concomitant use of GRNX and disopyramide showed a much higher ROR value compared with their single use, and these 95%

CIs were mutually exclusive, indicating a possible association of this combination with the increased incidence of LQTS.

Time-to-onset analysis of LQTS associated with FQs, non-FQ drugs, and their combinations

We analyzed the time-to-onset of LQTS related to FQs, non-FQ drugs, and their combinations. FQs were regarded as a drug of interest due to the small number of case reports. Table 3 shows the medians of time-to-onset and Weibull parameters of LQTS associated with FQs, non-FQ drugs (bepridil, disopyramide, clarithromycin, and famotidine), and their combinations. The median values (IQRs) of time-to-onset for FQs, bepridil, disopyramide, clarithromycin, and famotidine alone were 3.00 (1.00 – 5.00), 49.00 (16.50 – 90.00), 26.50 (2.00 – 90.00), 9.50 (6.00 – 30.00), and 11.00 (3.00 – 90.00) days, respectively. In addition, the median value (IQR) for combination of GRNX or LVFX and these non-FQ drugs was 4.00 (2.00 – 6.00) days. The onset date of LQTS for FQs alone was significantly shorter than those for these four non-FQ drugs alone ($p<0.001$). On the other hand, there was no significant difference in the onset date of LQTS between single use of FQs and concomitant use of GRNX or LVFX with non-FQ drugs ($p=0.9363$). The WSP β and lower limit of the corresponding 95% CI for GRNX, LVFX, and bepridil alone were 2.19 (1.49 – 3.03), 2.65 (1.65 – 3.95), and 1.47 (1.30 – 1.66),

Table 2: RORs of QT prolongation associated with concomitant use of FQs and non-FQ drugs.

Drugs	Total (n)	Cases (n)	Non-cases (n)	RR (%)	ROR (95% CI)
GRNX no disopyramide	1,625	28	1,597	1.72	2.59(1.78 – 3.78)
Disopyramide no GRNX	401	122	279	30.42	67.26(54.18 – 83.49)
GRNX and disopyramide	7	6	1	85.71	884.18(106.41 – 7346.92)
LVFX no bepridil	3,322	22	3,300	0.66	0.98(0.64 – 1.49)
Bepridil no LVFX	640	326	314	50.94	173.21(147.59 – 203.28)
LVFX and bepridil	4	4	0	100	-
LVFX no disopyramide	3,318	23	3,295	0.69	1.03(0.68 – 1.55)
Disopyramide no LVFX	400	125	275	31.25	69.99(56.46 – 86.77)
LVFX and disopyramide	8	3	5	37.5	88.32(21.10 – 369.76)
LVFX no clarithromycin	3,233	23	3,210	0.71	1.05(0.70 – 1.59)
Clarithromycin no LVFX	2,797	112	2,685	4	6.35(5.24 – 7.70)
LVFX and clarithromycin	93	3	90	3.23	4.91(1.55 – 15.51)
LVFX no famotidine	3,250	23	3,227	0.71	1.05(0.69 – 1.58)
Famotidine no LVFX	3,103	64	3,039	2.06	3.15(2.45 – 4.04)
LVFX and famotidine	76	3	73	3.95	6.05(1.91 – 19.20)

Table 3: Time-to-onset and Weibull parameters of QT prolongation associated with FQs, non-FQ drugs, and their combinations.

	Drugs	n	Median (IQR) (day)	p-value (vs. FQs)	Scale parameter α (95% CI)	Shape parameter β (95% CI)
FQs	FQs a)	80	3(1.00 – 5.00)	-	4.72(3.73 – 5.95)	1.19(0.98 – 1.44)
	GRNX	24	4(2.00 – 5.00)	-	3.51(2.79 – 4.35)	2.19(1.49 – 3.03)
	MFLX	27	1(1.00 – 7.00)	-	7.54(4.15 – 13.15)	1.08(0.67 – 1.61)
	LVFX	17	4(2.00 – 5.00)	-	3.46(2.74 – 4.31)	2.65(1.65 – 3.95)
	CPFX	6	5(2.50 – 12.75)	-	8.75(3.28 – 22.25)	1.18(0.54 – 2.08)
	TFLX	2	4(4.00 – 4.00)	-	-	-
	PZFX	3	2(2.00 – 3.00)	-	-	-
	GFLX	1	6(6.00 – 6.00)	-	-	-
Non-FQ drugs	Bepridil	193	49(16.50 – 90.00)	<0.0001	56.94(51.3 – 63.04)	1.47(1.30 – 1.66)
	Disopyramide	32	26.5(2.00 – 90.00)	0.0004	40.98(23.12 – 70.26)	0.72(0.52 – 0.97)
	Clarithromycin	42	9.5(6.00 – 30.00)	<0.0001	24.19(16.14 – 35.58)	0.85(0.66 – 1.06)
	Famotidine	23	11(3.00 – 90.00)	0.0003	27.46(14.11 – 51.32)	0.74(0.51 – 1.01)
Combinations	GRNX or LVFX and non-FQ drugs b)	13	4(2.00 – 6.00)	0.9363	3.8(2.80 – 5.06)	2.36(1.34 – 3.76)
	GRNX and disopyramide	2	2.5(1.00 – 4.00)	-	-	-
	LVFX and bepridil	4	3.5(2.00 – 5.00)	-	-	-
	LVFX and disopyramide	3	6(3.00 – 6.00)	-	-	-
	LVFX and clarithromycin	3	6(3.00 – 6.00)	-	-	-
	LVFX and famotidine	1	1(1.00 – 1.00)	-	-	-

a) FQs included GRNX, MFLX, LVFX, CPFX, TFLX, PZFX, and GFLX. b) Non-FQ drugs included bepridil, disopyramide, clarithromycin, and famotidine. Statistical analysis was performed using the Steel test.

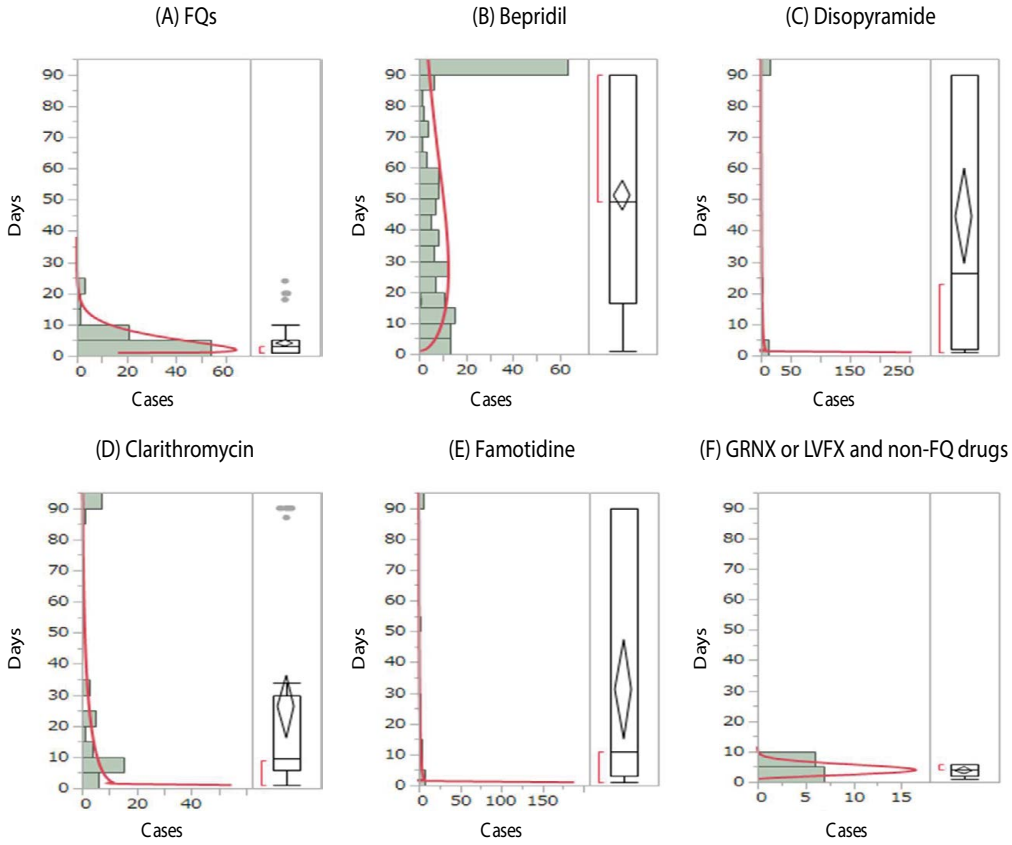

Figure 1: (A-F) Histogram and box plot of time-to-onset of QT prolongation associated with FQs, non-FQ drugs, and their combinations. FQs (A) included GRNX, MFLX, LVFX, CPFX, TFLX, PZFX, and GFLX. Non-FQ drugs (F) included bepridil, disopyramide, clarithromycin, and famotidine.

respectively (Table 3). Furthermore, the β and lower limit of the corresponding 95% CI for combination of GRNX or LVFX and non-FQ drugs (bepridil, disopyramide, clarithromycin, or famotidine) were 2.36 (1.34 – 3.76) (Table 3). Figure 1 shows the time-to-onset profiles for FQs, non-FQ drugs, and combinations of GRNX or LVFX and these non-FQ drugs. Nine of 13 case reports of LQTS related to concomitant use of GRNX or LVFX and non-FQ drugs (bepridil, disopyramide, clarithromycin, or famotidine) contained information about the start date of both FQs and non-FQ drugs (Table S2). In eight cases, LQTS occurred after the administration of GRNX or LVFX additionally started under conditions of treatment with bepridil, disopyramide, or clarithromycin; in one case, LQTS appeared after commencement of treatment with LVFX and famotidine on the same day.

DISCUSSION

Signal detection using spontaneous reporting systems is useful to evaluate the occurrence of rare side effects [22]. In this study, we performed signal detection analysis for FQ-induced LQTS using the JADER database. The significant associations of GRNX, MFLX, and CPFX with LQTS were detected. A previous *in vitro* study revealed that the rank order potencies of hERG inhibition were MFLX>LVFX>CPFX [3]. In a systematic review, the rank order of propensity to cause cardiac arrhythmias appeared to be MFLX>LVFX>CPFX [6]. Furthermore, MFLX has been used as a positive control to evaluate the potential of QT prolongation in a phase I study [23–25]. Based on these findings and our results, MFLX is considered to have a higher risk of LQTS among the post-marketed FQs. On the other hand, in addition to the aforementioned study [6], a previous large cohort study revealed that the risk of serious arrhythmia associated with CPFX was not significantly different from that with penicillin V with no proarrhythmic effect [26]. Moreover, Sasaoka et al. [20] reported no significant association of CPFX with LQTS in signal detection analysis using the JADER database. In contrast, our results showed a significant association of CPFX with LQTS. However, the lower limit of 95% CI of the ROR for CPFX was close to 1. These findings and our results suggest that CPFX may have a relatively low risk of LQTS among the post-marketed FQs. For GRNX, we found the potential risk of LQTS in this study. In contrast, it has been reported that no clinically significant effect on QT interval was seen in a phase I clinical trial [27] and that there was no incidence of LQTS in the post-marketing surveillance [28]. However, these previous studies had small sample sizes. Furthermore, there are limited data regarding the proarrhythmic effect of GRNX, because this drug has been marketed exclusively in Japan (as of September 2019). Therefore, our results provide important information about the safety of GRNX

The mechanisms of LQTS due to drug–drug interactions can be divided into two classes, i.e., pharmacokinetic interactions defined as alterations in the metabolism of drugs known to prolong the QT interval and pharmacodynamics interactions defined as additive effects of two drugs directly causing QT prolongation [8,29]. LQTS associated with concomitant use of FQs and other drugs corresponds to the latter. In this study, case reports of LQTS related to co-administration of FQs and non-FQ drugs were extracted to detect risk of concomitant use. There were only five combinations of two suspected or interacting drugs with three or more cases even when we used a spontaneous reporting system. There were very few reports of LQTS associated with co-administration of MFLX, the safety signal of which in single drug use was considered significant. This would be attributed to avoidance of concomitant use of MFLX with class IA or III antiarrhythmic drugs, because contraindications for their co-administration are noted on the package inserts of

these drugs in Japan. In this study, we found that the concomitant use of GRNX and disopyramide may be associated with a higher risk of LQTS compared with their single use. In addition, there were three reports of LQTS related to co-administration of LVFX and disopyramide, although no signal was detected in concomitant use. Disopyramide is a class IA antiarrhythmic drug, which may contribute to the incidence of LQTS by inhibiting the hERG channel that underlies the I_{Kr}. Similarly, FQs are considered to cause LQTS mediated through I_{Kr} inhibition [3 – 5]. These findings suggest that co-administration of FQs and disopyramide may increase the risk of LQTS by pharmacodynamics interaction. In contrast to cibenzoline, another class IA antiarrhythmic drug, disopyramide has a weak inhibitory effect on the slowly activating delayed rectifier potassium current (I_{Ks}) [30]. The cardiac delayed rectifier potassium current is composed of the I_{Kr} and I_{Ks}, the contributions of which to action potential repolarization are increased in bradycardia and tachycardia, respectively. Bradycardia itself is known as a risk factor for LQTS [31]. Thus, I_{Kr} blockers with no or weak inhibitory potential against I_{Ks} tend to raise the risk of TdP as the heart rate becomes slower. It has been reported that FQs inhibit I_{Kr} but not I_{Ks} [3]. Among the post-marketed FQs, only MFLX is contraindicated for co-administration with disopyramide in Japan. GRNX, LVFX, and CPFX are prescribed with caution when co-administered with disopyramide, although TFLX and PZFX are not restricted for concomitant use with disopyramide. However, the difference in risk for incidence of LQTS between MFLX and the other FQs remains to be clarified. Our results suggested that attention equivalent to contraindications for concomitant use of MFLX and disopyramide should be paid to other FQs, such as GRNX

In general, hERG inhibitors provoke electrophysiological changes immediately after administration, and hence LQTS is thought to occur within a few days following administration of these inhibitors except for specific lipophilic drugs [20]. In this study, LQTS occurred a few days after administration of FQs alone. Moreover, the observations that the β and lower limit of the corresponding 95% CI for GRNX and LVFX alone were >1 suggested that their hazards may increase over time

In this study, time-to-onset analysis of LQTS indicated that single use of FQs had significantly earlier onset of LQTS in comparison with bepridil, disopyramide, clarithromycin, and famotidine, but had early onset similar to concomitant use of FQs and these non-FQ drugs. In addition, LQTS occurred after commencement of FQ co-administration in almost all cases. These results reflect the clinical situation where patients receiving H_2 blockers and antiarrhythmic drugs are additionally prescribed antibiotics, such as FQs, for prophylaxis and treatment of infection. Therefore, special attention should be paid during the first few days after patients begin receiving FQs in addition to certain QT-prolonging drugs.

This study had several limitations. First, in the JADER database, a case from the same patient could be reported two or more times as different cases from different manufacturers or healthcare professionals, and therefore we could not exclude these duplicate cases. Therefore, this study may have overestimated the risk of LQTS related to FQs, non-FQ drugs, and their combinations. Second, we focused on the combination of two drugs for signal detection in this study. However, there have been reports of simultaneous use of three or more drugs that were suspected to cause LQTS. We cannot exclude the possibility that the third drug may act as a confounding factor on the association between concomitant drug use and risk of LQTS. Last, we did not analyze the risk of FQ-associated LQTS using the ROR adjusted for age, gender, etc., due to the small number of case reports. The signal detection method is used to build a hypothesis of adverse events. Further investigations using other approaches are needed to identify the associations between co-administration of FQs and risk of LQTS.

CONCLUSION

We identified concomitant drugs that may increase the risk of FQ-related LQTS using the JADER database. Consideration similar to contraindications for co-administration of MFLX and disopyramide may be needed for other FQs, such as GRNX. Furthermore, special attention should be paid during at least the first few days after patients begin taking FQs with concomitant prescription of QT-prolonging drug(s).

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest related to this research.

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