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Original Article

Assessment of drug-induced proarrhythmias due to pilsicainide in patients with atrial tachyarrhythmias

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ABSTRACT

Background: Pilsicainide, a pure Na^+ channel blocker, is a popular antiarrhythmic drug for the management of atrial tachyarrhythmias (AT), in Japan. However, serious drug-induced proarrhythmias (DIPs) may unexpectedly occur. We assessed the clinical background of AT patients presenting with DIPs caused by pilsicainide.

Methods: This study retrospectively enrolled 874 consecutive patients (543 men, 63.6 ± 15.3 years old, and 57.9 ± 16.5 kg of body weight), who were orally administered pilsicainide for AT management. We evaluated the relationship between DIPs and serum pilsicainide concentration, renal dysfunction (estimate glomerular filtration rate, eGFR), and electrocardiogram (ECG) parameters.

Results: Among the patients, 154 (17.6%) had renal dysfunction (eGFR < 50 mL/min), including 12 (1.4%) on hemodialysis. DIPs were present in 10 patients (1.1%): all had renal dysfunction, and one was on hemodialysis. The eGFR in DIP patients was significantly lower than that in the non-DIP patients (32.2 ± 15.1 *vs.* 68.4 ± 22.1 mL/min, $p < 0.001$). Among the clinical factors measured, only renal dysfunction (eGFR < 50 mL/min) was significantly associated with DIPs (OR 44.6; 95% CI 5.61–335.0, $p < 0.001$). Interestingly, among the ECG parameters, the corrected QT (QTc) intervals in DIP patients were longer than those in non-DIP patients (555.8 ± 37.6 *vs.* 430.7 ± 32.6 ms, $p < 0.001$). As pilsicainide concentration increased, both QRS and QTc intervals prolonged. The latter were improved by discontinuing pilsicainide administration, and additional treatments.

Conclusions: DIPs caused by pilsicainide administration were strongly associated with renal dysfunction. Hence, confirmation of renal function would be necessary prior to and/or during the pilsicainide administration.

1. Introduction

Pilsicainide has a pure Na^+ channel blocking action with slow recovery pharmacokinetics and, according to the Vaughan Williams classification, is considered an IC antiarrhythmic drug. In Japan, pilsicainide is a popular antiarrhythmic drug for the management of atrial tachyarrhythmias (AT), and in particular atrial fibrillation (AF) [1,2]. Pilsicainide is recognized as safe and easy-to-use. However, serious drug-induced proarrhythmias (DIPs) may unexpectedly occur [3,4]. There are only a few well-organized reports describing the association between DIPs and pilsicainide administration [3,4].

We assessed the complication rate of DIPs caused by pilsicainide, and the relationship between DIPs and the drug serum concentration, renal dysfunction, including the estimated glomerular filtration rate (eGFR), and 12-lead electrocardiogram (ECG) parameters, such as the QRS and corrected QT (QTc) intervals after pilsicainide administration.

2. Materials and methods

2.1. Study population

This is a retrospective study. Initially, 905 consecutive patients were enrolled who were orally administered pilsicainide for the management of ATs such as AF, supraventricular tachycardia (SVT), and frequent atrial premature contractions (APCs), between

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Table 1
Patients' characteristics.

Male (%)	543 (62.1)
Age (years)	63.6 ± 15.3
Height (cm)	157.7 ± 27.2
Weight (kg)	57.9 ± 16.5
BMI (kg/m^2)	22.7 ± 3.8
Pilsicainide toxicity (%)	10 (1.1)
Serum Cr (mg/dL)	0.95 ± 0.86 (0.83)
eGFR (mL/min)	68.0 ± 22.3
eGFR < 50 (%)	154 (17.6)
Hemodialysis (%)	12 (1.4)
HT (%)	393 (45.0)
DM (%)	132 (15.1)
DL (%)	196 (22.4)
IHD (%)	112 (12.8)
Stroke (%)	73 (8.4)
CHF (%)	165 (18.9)
Pilsicainide mean dose (mg/day)	89.4 ± 44.7
Pill in the pocket (%)	310 (35.5)
Concomitant drugs	
β-blocker (%)	170 (19.5)
CCB (%)	171 (19.6)
ARB (%)	275 (31.5)
ACE-I (%)	46 (5.3)
Diuretics (%)	124 (14.2)
Other AADs (%)	113 (12.9)

BMI, body mass index; DM, diabetes mellitus; Cr, creatinine; CKD, chronic kidney disease; CHF, chronic heart failure; IHD, ischemic heart disease, HT, hypertension; DL, dyslipidemia lipidemia; CCB, calcium channel blocker; ARBs, angiotensin receptor blockers; ACE-I, angiotensin-converting enzyme inhibitor; AAD, antiarrhythmic drug. Data are expressed as the mean ± SD, median, or numbers (%).

January 2005 and December 2014, at our institute. Thirty-one (3.4%) patients whose eGFR was not assessed were excluded; thus, 874 patients were finally enrolled into the study. Their characteristics are outlined in Table 1.

2.2. Ethical considerations and Institutional Review Board approval

The study protocol was approved by the Institutional Review Board (IRB) of the Toho University Medical Center Omori Hospital (approval number: 27-13), on May 13, 2015. All patients signed an informed consent form for the study protocol.

2.3. Administration of pilsicainide

Pilsicainide was used continuously or temporarily for the management of tachyarrhythmias. The administration of pilsicainide commonly started at 75–150 mg/day, and the dosage was determined by the age, weight, or clinical characteristics of the patients. In patients who used pilsicainide temporarily, the dosage begun at 25–100 mg/day. The patients underwent follow-up reviews every 1–3 months, and the presence of symptoms, physical examinations, 12-lead ECGs, and blood tests were assessed. However, patients who received pilsicainide temporarily did not undergo follow-up reviews, and were examined only once, or a few times, after the drug administration.

2.4. Definition of DIP

According to the definition of DIP due to pilsicainide, the patients had to meet the following criteria: (1) proarrhythmias, such as life-threatening arrhythmias (bradycardia or ventricular tachycardia/fibrillation), were caused by the drug; (2) ECG abnormalities were not caused by other etiologies; and (3) discontinuing the drug and having treatment improved ECG abnormalities. Regarding pilsicainide levels, although the effective concentration is known, the precise toxic threshold is generally unclear. The serum concentration of pilsicainide was determined using high performance liquid chromatography (HPLC).

2.5. Assessment of ECG parameters

The 12-lead ECGs were recorded by electrocardiography (Nihon Kohden, Tokyo, Japan). The QRS, JT, and QT interval (from the onset of the QRS complex to the end of the T wave) were measured automatically. However, we visually assessed whether the parameters measured were correct. The QTc interval adjusted the QT interval correctly by using the Bazett's formula: $QTc = QT/(RR)^{1/2}$, where QTc is the corrected QT interval, QT is the measured QT interval, and RR is the measured RR interval.

2.6. Statistical analysis

All continuous data were expressed as mean ± standard deviation, medians (quartile: 25–75%), or numbers (expressed as percentage, %). Comparisons between groups were analyzed using univariate (unpaired Student's *t*-test and Fisher's exact test) and multivariate analyses using a logistic regression model. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using the R commander software, version 1.24 [5].

3. Results

3.1. Baseline characteristics

The patients' mean age was 63.6 ± 15.3 years, 543 (62.1%) were male, and the body mass index (BMI) was 22.7 ± 3.8 kg/m^2. AF occurred in 677 patients (77.5%), SVT in 87 (10.0%), frequent APCs in 56 (6.4%), undetermined arrhythmias with palpitations in 10 (1.1%), and other forms of arrhythmia in the remaining 44 patients. The mean pilsicainide dose administered was 89.4 ± 44.7 mg/day, and 310 patients (35.5%) received pilsicainide temporarily. The mean eGFR was 68.0 ± 22.3 mL/min; 154 patients (17.6%) had an eGFR of < 50 mL/min, and 12 (1.4%) were on hemodialysis. DIPs were detected in 10 patients (1.1%). These baseline characteristics are listed in Table 1.

Out of 874 patients administered with pilsicainide, the drug serum concentration was assessed only in 202 (23.1%). Fig. 1 shows the distribution of pilsicainide serum concentration according to the dose administered.

3.2. Risk factors of DIP

In DIP patients, the eGFR was significantly lower than that in non-DIP patients (32.2 ± 15.1 *vs.* 68.4 ± 22.1 mL/min, $p < 0.001$, Table 2). Although clinical factors, such as age, renal dysfunction (eGFR < 50 mL/min), use of angiotensin receptor blockers (ARBs), and diuretics had a significant association with DIPs, a multivariate analysis showed that only renal dysfunction (eGFR < 50 mL/min) was significantly associated with DIPs (OR 44.6; 95% CI 5.61–335.0, $p < 0.001$, Tables 2 and 3).

3.3. Characteristics and follow-up of DIP patients

Among the 874 patients, DIPs were observed in 10 (1.1%). All DIP patients had AF, and they all displayed renal dysfunction. The pilsicainide serum concentrations were high with only one exception. The serum potassium level was between 3.1 and 7.2 mM. The 10 DIP patients' characteristics are listed in Table 4.

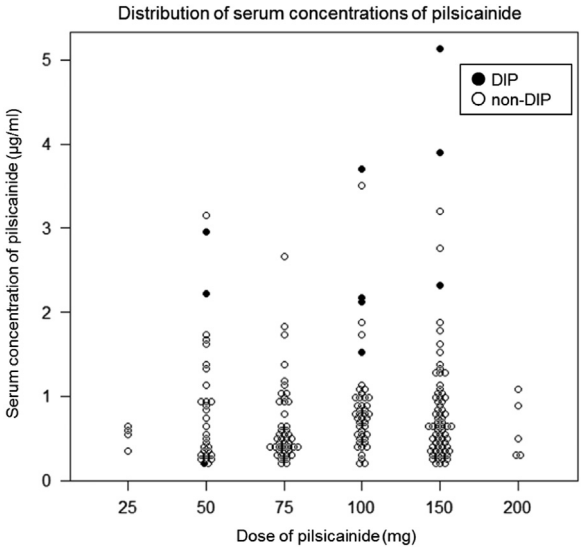

Fig. 1. Distribution of the serum concentrations of pilsicainide. Serum pilsicainide concentrations were plotted against the administrated dose in DIP (black dots) and non-DIP (white dots) patients.

Table 2
Comparison of the patients' characteristics between DIP and non-DIP groups.

	non-DIP (864)	DIP (10)	*p* Values
Male (%)	538 (62.3)	5 (50.0)	0.516[a]
Age (years)	63.4 ± 15.3	75.7 ± 6.7	0.012[a]
Height (cm)	157.7 ± 27.3	154.4 ± 9.9	0.697[b]
Weight (kg)	58.0 ± 16.6	50.8 ± 7.2	0.166[b]
BMI (kg/m^2)	22.7 ± 3.9	21.3 ± 2.3	0.238[b]
Cr (mg/dL)	0.94 ± 0.83	2.1 ± 2.1	< 0.001[b]
eGFR (mL/min)	68.4 ± 22.1	32.2 ± 15.1	< 0.001[b]
Hemodialysis (%)	11 (1.3)	1 (10.0)	0.130[a]
ARBs (%)	268 (31.0)	7 (70)	0.014[a]
Diuretics (%)	119 (13.8)	5 (50)	0.007[a]

BMI, body mass index; ARBs, angiotensin receptor blockers. Data are expressed as the means ± SD or numbers (%).

[a] The *p* values were determined by Fisher's exact test.

[b] The *p* values were determined by unpaired Student's *t*-test.

Table 3
Predictors of DIPs detected by a logistic regression analysis.

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p* Values	OR (95% CI)	*p* Values
Sex	0.61 (0.14–2.66)	0.516	0.82 (0.23–3.00)	0.761
Age > 75	4.78 (1.12–23.26)	0.016	1.60 (0.42–6.03)	0.823
eGFR < 50	44.4 (6.07–1937)	< 0.001	44.6 (5.61–355)	< 0.001
ARBs	5.18 (1.17–31.3)	0.014	3.54 (0.89–14.2)	0.074
Diuretics	6.24 (1.41–27.5)	0.007	2.65 (0.72–9.77)	0.143

OR, indicates odds ratio; CI, confidential intervals.

Table 5 shows the ECG findings on admission and the treatment received by the 10 DIP patients. The ECG findings revealed that 8 patients lacked P waves, 4 had ventricular tachycardia/ventricular fibrillation (VT/VF), and 6 had bradycardia. All the QRS and QTc intervals tended to be prolonged. Five patients were treated with continuous hemodiafiltration (CHDF), 2 needed percutaneous cardiopulmonary support (PCPS), and 4 needed temporary pacemakers. Table 6 shows the follow-up of DIP patients. One patient died; the remaining 9 were discharged, as their QRS and QTc intervals normalized.

3.4. Correlation between pilsicainide concentration and ECG parameters

Regarding the correlation between the ECG parameters in DIP patients and their pilsicainide blood level, as the drug concentration increased, both QRS and QTc intervals prolonged (Fig. 2). The QRS interval in DIP patients was longer than that of non-DIP patients (223.0 ± 135.9 ms *vs.* 108.2 ± 23.6 ms, $p < 0.001$). The JT and QTc intervals in DIP patients was also longer than that in non-DIP patients (JT; 374.7 ± 38.2 ms *vs.* 322.4 ± 28.7 ms, $p < 0.001$, QTc; 555.8 ± 37.6 ms *vs.* 430.7 ± 32.6 ms, $p < 0.001$). However, the correlation between the JT interval and the pilsicainide blood concentration was weak.

4. Discussion

4.1. Main findings

First, 18% of patients had renal dysfunction (eGFR < 50 mL/min), including 1.4% with hemodialysis. The eGFR of DIP patients was significantly lower than that of non-DIP patients, and renal dysfunction (eGFR < 50 mL/min) was the only parameter significantly associated with DIPs. Second, as the pilsicainide serum concentration increased, both QRS and QTc intervals prolonged.

4.2. Pharmacokinetics of pilsicainide

According to the Vaughan–Williams classification, pilsicainide is a class IC antiarrhythmic agent, and it is mostly excreted in the urine. Therefore, the appropriate dose should be determined with great care in patients with renal dysfunction, since renal insufficiency would obviously prolong the drug elimination half-life [6–9]. Although after 0.5 mg/kg pilsicainide administration, the drug elimination half-life at beta-phase is 5.74 hours (h), in patients whose creatinine clearance (CCr) is 20–50 mL/min, it increases to 10 h, and in patients whose CCr is < 20 mL/min, it increases further to 25 h [8,9]. Pilsicainide is a basic drug, and it binds to serum proteins and in particular to an alpha-1-acid glycoprotein [10,11]. Its plasma protein binding ratio is about 27% in normal subjects, but the ratio has been reported to increase to 37% in patients with renal dysfunction [6,9,10]. Although the protein binding ratio elevates in patients with renal dysfunction, the total concentration of pilsicainide also elevates and, as a result, pilsicainide adverse effects may be induced.

It has been reported that pilsicainide elimination rate is low in patients on hemodialysis [6,12]. Therefore, these patients have an increased risk of developing DIP.

4.3. Mechanisms of proarrhythmias associated with pilsicainide

In general, the pilsicainide effective serum concentration is 0.2–0.9 μg/mL. Although the effective concentration is known, the precise toxic threshold has not been defined. Torsade de pointes induced by class IA or III antiarrhythmic drugs is caused by a prolongation of the QT interval. It is suggested that inhibiting the K^+ channel current may prolong the repolarization phase and induce early afterdepolarizations. The proarrhythmic potential of a particular drug is increased by concomitant electrolyte disturbances, such as hypokalemia or hypomagnesemia. These factors result in the prolongation of the action potential duration, and refractoriness at the cellular level [13].

On the other hand, class IC antiarrhythmic drugs inhibit the Na^+ channel current and delay the depolarization, which induces reentrant ventricular tachycardia based on localized depolarization disturbances [13,14].

Table 4
Characteristics of patients with DIPs.

No	Sex	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Rhythm	BUN (mg/dL)	Cr (mg/dL)	K (mM)	PLS concentration (μg/mL)	Time after administration (h)	PLS dose (mg/day)
1	Female	68	142	45	22.3	AF	30	2.03	5.6	5.13	48	150
2	Male	83	158	56	22.4	AF	45	2.44	4.4	2.95	7	50
3	Male	77	161	62	23.9	AF+DDD	44	2.27	4.7	3.7	17	100
4	Female	88	150	46	20.4	AF	42	2.87	7.2	3.91	12	150
5	Female	75	155	53	22.1	AF	64	3.53	6.7	2.32	27	150
6	Male	69	173	59	19.7	AF	40	2.81	4	2.22	2	50
7	Male	76	160	43	16.8	AF	34	2.39	6.8	2.17	24	100
8	Male	67	158	53	21.2	AT	31	7.63	4.7	2.12	120	100
9	Female	80	141	40	20	AF	58	1.65	5.6	1.54	24	100
10	Female	74	145	52	24.7	AF+DDD	21	1.33	3.1	0.26	12	50

BMI, body mass index; AF, atrial fibrillation; DDD, DDD is the type of generic pacemaker code; AT, atrial tachycardia; BUN, blood urea nitrogen; Cr, creatinine; PLS, pilsicainide; time after administration, time at which PLS concentration was measured, after the administration.

Table 5
ECG findings and treatment.

No	ECG findings	Absent P waves	PQ Interval (ms)	QRS interval (ms)	QTc interval (ms)	CHDF	PCPS	TPM
1	VT+PEA	+	–	206	540	+	+	+
2	VT	+	–	196	568	+	–	–
3	Pacemaker rhythm	+	–	600	–	+	–	–
4	Junctional rhythm	+	–	188	528	+	–	–
5	Junctional rhythm	+	–	136	552	+	+	+
6	Tdp+VF	–	212	146	541	–	–	–
7	Junctional rhythm	+	–	234	625	–	–	+
8	Sinus bradycardia	–	240	202	548	–	–	–
9	AF bradycardia	+	–	160	600	–	–	+
10	VF	+	–	162	538	–	–	–

ECG, electrocardiogram; CHDF, transient hemodiafiltration; PCPS, percutaneous cardiopulmonary support; TPM, temporary pacemaker; VT/VF, ventricular tachycardia/ventricular fibrillation; Tdp, torsades de pointes; AF, atrial fibrillation; PEA, pulseless electric activity.

Table 6
Follow-up of DIP patients.

No	Prognosis	Rhythm	PQ interval (ms)	QRS interval (ms)	QTc interval (ms)	BUN (mg/dL)	Cr (mg/dL)
1	Survive	Sinus	144	92	422	46	1.02
2	Survive	AF	–	106	441	36	2.08
3	Survive	Sinus	168	134	448	27	1.61
4	Survive	AF	–	96	445	14	1.09
5	Dead	–	–	–	–	–	–
6	Survive	Sinus	184	146	524	–	–
7	Survive	AF	–	90	413	33	1.29
8	Survive	Sinus	184	120	440	41	7.85
9	Survive	AF	–	96	431	14	0.68
10	Survive	PM	178	158	502	24	0.59

PM, pacemaker; AF, atrial fibrillation; BUN, blood urea nitrogen; Cr, creatinine.

These drugs also cause sinus arrest or sinoatrial block. Their cardiac Na^+ channels blocking action with slow recovery kinetics suppresses the transmission of the sinus impulse to the atrium and prolongs the PQ, and QRS, AH and HV intervals [4].

In our study, the mean serum K^+ concentration of DIP patients was 5.3 mM, suggesting that this hyperkalemia might have induced proarrhythmias (Table 4). However, although hyperkalemia could be induced by renal dysfunction, the extent at which the serum K^+ concentration affected DIP patients' proarrhythmias is unknown. Other drugs, such as β-blockers or calcium channel blockers, and other antiarrhythmic drugs (AADs) also have a proarrhythmic effect, but we failed to observe significant differences in the use of these drugs between DIP and non-DIP patients.

Among DIP patients, two were implanted with a pacemaker (Table 4, patient nos. 3 and 10). This suggests that the Na^+ channel blocking action of pilsicainide may have been responsible for the delayed depolarization, therefore causing proarrhythmias in patients with potential sinus node dysfunction or atrioventricular block. This is probably because pilsicainide may increase the depolarization disturbances due to the myocardial dysfunction caused by heart disease or renal failure, and induce proarrhythmias regardless of its serum concentration.

4.4. K^+ channel blocking action and pilsicainide

Pilsicainide is a class IC AAD that exerts its action by selectively blocking Na^+ channels, with generally no effect on the K^+ channels or alpha- or beta-receptors, at clinically relevant concentrations. The pharmacodynamic effects of pilsicainide are characterized by slow recovery kinetics, for the onset and offset of its Na^+ channel blocking action [1,8]. Okishige et al. reported the results of the PSTAF-II study, in which an oral dose of 50 mg of pilsicainide, administered three times daily increased the QRS interval from 91 ms at baseline to 98 ms, but failed to change the QT interval [15]. Pilsicainide prolongs not only the intra-atrial and proximal His

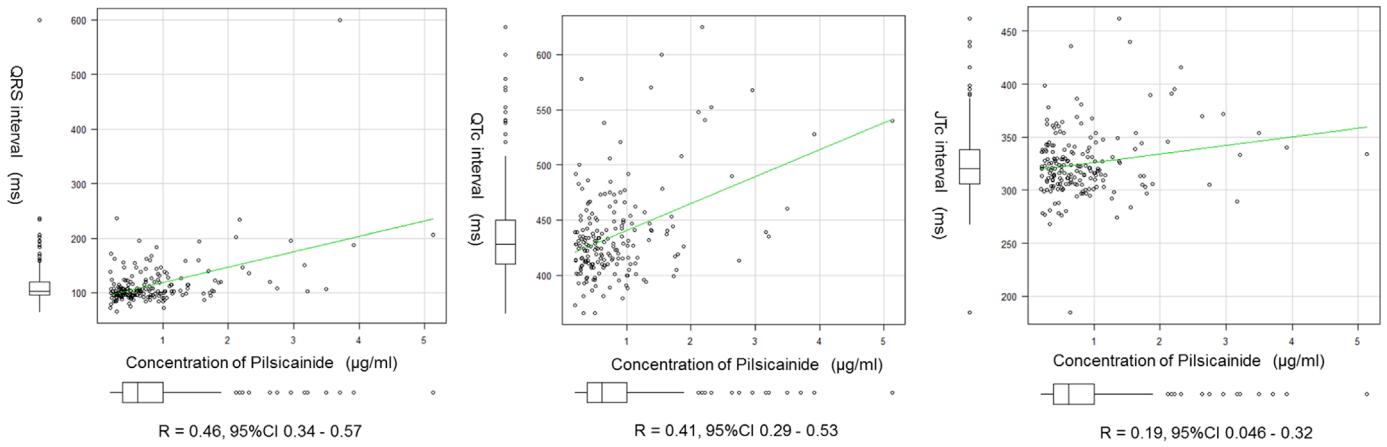

Fig. 2. ECG parameters and the serum concentration of pilsicainide. As the concentration of pilsicainide increases, both QRS and QTc intervals prolong.

region conduction times, which are Na^+ channel-dependent, but also the PQ interval [16].

Some case reports demonstrated that a high dose of pilsicainide prolongs the QTc interval, and concomitantly decreases the heart rate [17]. The authors of the study concluded that the prolongation of the QRS interval might contribute to the prolongation of the QTc interval [17]. However, in basic studies, pilsicainide was shown to block also the K^+ channels. Pilsicainide blocks the K^+ channel current in the human ether-a-go-go-related gene (HERG) with a preferential affinity for the open state of the channel, and shows a fast access to the binding site [18–20]. As a result, the K^+ channel blocking action of pilsicainide prolonged the QTc interval in patients presenting with very high pilsicainide concentrations.

There are some factors responsible for prolonging the QTc interval in general. In our study, the QTc interval positively correlated with the QRS interval, and both intervals prolonged significantly. Although there was a weak correlation between the JT interval and the plasma concentration of pilsicainide, the JT and QTc intervals in DIP patients were longer than those in non-DIP patients. Prolonged QTc intervals might be caused not only by a prolonged QRS interval (secondary effect), but also by high levels of pilsicainide, blocking K^+ channels (direct effect). Other factors, such as the serum K^+ concentration and the concomitant use of other drugs, were not significantly associated with the prolonged QTc interval. Pilsicainide may not only have a Na^+ channel blocking action, but also a K^+ channel blocking action in the high concentration.

4.5. Preventing DIPs – renal dysfunction and elderly patients

Although there are some reports investigating the administration of pilsicainide in patients with renal dysfunction, and elderly patients [6,9,11], the rate of developing acute renal failure or side effects in those patients remains unknown.

In our study, 18% of the patients had renal dysfunction (eGFR $<$ 50 mL/min) including 1.4% patients on hemodialysis. In patients whose eGFR was $<$ 50 mL/min, the pilsicainide concentration was assessed only in 53 (34.4%). DIPs caused by pilsicainide administration were strongly associated with renal dysfunction; therefore, assessing renal function would be necessary prior to and/or during the administration of pilsicainide. If the renal function worsens, clinicians should try to reduce the dose or terminate the administration of pilsicainide while monitoring the patient general condition, heart rate, and ECG.

Although age was not associated with DIPs, special attention should be given when administering pilsicainide in elderly patients. Because these patients are usually administrated with ARBs or diuretics, it is likely that their eGFR worsens due to dehydration or drug-induced renal injury. In our study, the use of ARBs or diuretics showed a significant association with DIPs in the univariate analysis. Hence, not only the renal function, but also medications including diuretics, ARBs, and other AADs should be assessed.

Moreover, it is also important to control the patients' pilsicainide serum concentration. However, there were cases where, although pilsicainide serum concentration was in the normal range, patients still developed DIPs (Table 4, patient no. 10).

4.6. Study limitations

This study had some potential limitations: it was a retrospective and observational study done in a single institute, and the number of DIP patients was limited, which may result in a statistical bias. Further research, possibly with a larger number of patients, is therefore necessary.

5. Conclusions

DIPs caused by pilsicainide were strongly associated with renal dysfunction, particularly a reduced eGFR. Therefore confirmation of renal function would be necessary prior to and/or during the administration of pilsicainide. We should be careful when prescribing pilsicainide in patients whose eGFR is $<$ 50 mL/min or in elderly patients, since their eGFR is more likely to become aggravated ($<$ 50 mL/min). ECG parameters, such as the QRS and QTc intervals could be useful markers to prevent DIPs.

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Conflict of interest

All authors declare no conflict of interest related to this study.

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