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Ranolazine — a new drug for patients with recurrent antiarrhythmic therapy-refractory ventricular arrhythmias?

Ranolazyna — nowy lek w nawracających opornych na leczenie arytmiach komorowych?

Błażej Kusz[1], Artur Filipecki[1], Wojciech Kwaśniewski[1], Witold Orszulak[1], Dagmara Urbańczyk-Świć[1], Artur Chmiel[1], Andrzej Swinarew[2], Krzysztof Szydło[1], Katarzyna Mizia-Stec[1]

[1]First Department of Cardiology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland
[2]Institute of Material Science, Faculty of Computer Science and Material Science, University of Silesia, Katowice, Poland

Lekarz Błażej Kusz jest absolwentem Wydziału Lekarskiego Śląskiego Uniwersytetu Medycznego w Katowicach. Obecnie odbywa szkolenie specjalizacyjne w I Katedrze i Klinice Kardiologii pod kierownictwem prof. dr hab. n. med. Katarzyny Mizi-Stec. Jest uczestnikiem studiów doktoranckich Wydziału Lekarskiego Śląskiego Uniwersytetu Medycznego w Katowicach oraz kierownikiem projektu „Szybka screeningowa analiza fazy wydechowej i osocza u pacjentów z tętniczym nadciśnieniem płucnym", realizowanego w ramach konkursu 'Preludium' Narodowego Centrum Nauki. Zainteresowania pozamedyczne dr. Kusza obejmują muzykę, literaturę oraz grę w tenisa. W wolnych chwilach uwielbia podróżować.

Abstract

Introduction. The pharmacological treatment of ventricular arrhythmias (VA) has significant limitations. Ranolazine is a relatively new drug with documented antianginal and anti-ischaemic mechanisms and where preclinical data provides evidence of additional antiarrhythmic properties.

The aim of this article was to evaluate the safety and efficacy of ranolazine in patients with recurrent antiarrhythmic therapy-refractory VA.

Material and methods. This prospective evaluation included 30 patients (pts) (male/female: 26/4; mean age: 65 ± 10 years; coronary artery disease/dilated cardiomyopathy: 20/10; New York Heart Association class I/II/III/IV: 2/14/12/2, left ventricular ejection fraction: 27 ± 10%; implantable cardioverter-defibrillator (ICD): 15 pts, implantable cardioverter-defibrillator with cardiac resynchronisation therapy (CRT-D): 14 pts with recurrent significant VA [ventricular fibrillation, sustained ventricular tachycardia (VT) and/or non-sustained VT, multiple ventricular premature complexes > 1,000/day, biventricular stimulation (BiV) < 95%] and where standard treatment options, *i.e.* pharmacotherapy, coronary revascularisation, and percutaneous ablation, had proved ineffective. The severity of the arrhythmia was assessed by 24-hour electrocardiographic (ECG) Holter monitoring and in ICD/CRT-D memory recording. The patients received, in addition to the standard pharmacotherapy (amiodarone: 18 pts, beta-blocker: 26 pts) ranolazine 375 mg twice daily for three months. Baseline data was compared to the data obtained after the three months of ranolazine treatment.

Address for correspondence: lek. Błażej Kusz, I Katedra i Klinika Kardiologii, Śląski Uniwersytet Medyczny w Katowicach, ul. Ziołowa 45/47, 40–635 Katowice, Poland, e-mail: kuszblazej@gmail.com

Results. We observed a significant reduction of total ventricular extrasystoles determined by ECG Holter monitoring (median: 1,737 vs. 1,260, p = 0.04). Similarly, significant VA in ICD/CRT-D memory recording was diminished (67.7 vs. 35.5%, p = 0.03). The number of ICD interventions in terms of both antitachycardia pacing (9 pts vs. 2 pts, p = 0.01), and shock delivery (8 pts vs. 2 pts, p = 0.01), was lower after the three-month observation. The therapy was ineffective for nine (29%) patients — two were hospitalised during the three-month follow-up because of recurrent arrhythmia and in seven pts there was no noticeable reduction in the amount of VA. Adverse effects, in the form of gastrointestinal symptoms (diarrhoea: two, constipation: one), occurred in three (10%) patients.

Conclusions. Authors observed no significant QT prolongation in any patient. There were no differences between the baseline and the post-ranolazine patient clinical characteristics. Ranolazine seems to be a safe and effective second-line therapy in the reduction of VA and ICD interventions in patients with recurrent antiarrhythmic therapy-refractory events.

Key words: ranolazine, ventricular arrhythmias, therapy-refractory arrhythmias

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Introduction

Ventricular arrhythmias remain a complex and challenging problem. Treatment comprises pharmacotherapy, which however has significant limitations, as well as invasive procedures such as coronary artery revascularisation and catheter ablation.

Therefore, there is a clear need to seek new anti-arrhythmic drugs that could be implemented into therapy.

A potential option could be ranolazine. This is a relatively new, well-tolerated drug with proven antianginal activity [1–3] and with a biochemical structure similar to that of lidocaine. As ranolazine is an inhibitor of ion channels, it can modify the excitability of atrial and ventricular myocardium cells. It inhibits both extracellular (depolarising) currents: sodium (Na^+) along with L-type calcium channels (Ical), as well as cellular (repolarising) potassium (K^+) currents. The clinical effects of ranolazine, which are based on the protection of the myocardium during ischaemia/reperfusion (an antianginal effect), an improvement in mechanical dysfunction, and an 'electrical' stabilisation of cells, are mainly associated with the inhibition of sodium channels.

The anti-arrhythmic activity of ranolazine has been recorded among patients with atrial fibrillation [4–6], but its role in the treatment of ventricular arrhythmias has not yet been fully investigated. It appears that the drug could primarily be used in the treatment of such arrhythmias in patients with coronary artery disease (CAD), but potentially also in other groups, *i.e.* dilated cardiomyopathy (DCM).

Thus, the aim of our study was to evaluate the safety and efficacy of ranolazine in patients with the highest risk of sudden cardiac death (SCD) — in patients with recurrent antiarrhythmic therapy-refractory ventricular arrhythmias.

Material and methods

This prospective evaluation included a group of 30 patients enrolled into the study between 2013 and 2018 (26 male/4 female, mean age: 65 ± 10 years; CAD/DCM: 20/10; New York Heart Association (NYHA) class: I/II/III/IV: 2/14/12/2, left ventricular ejection fraction (LVEF): 27 ± 10%; implantable cardioverter-defibrillator (ICD): 15 pts, cardiac resynchronisation therapy with defibrillator (CRT-D): 14 pts) (Table 1), all of whom had recurrent significant antiarrhythmic therapy-refractory ventricular arrhythmias.

The inclusion criteria were: ventricular fibrillation (VF), sustained (sVT) and/or non-sustained ventricular tachycardia (nsVT), and multiple ventricular premature complexes (VEs) obtained after exhausting the standard treatment options, *i.e.* pharmacotherapy, coronary revascularisation and percutaneous ablation.

The exclusion criteria were: acute coronary syndrome, severe heart failure decompensation, current infection of potential significance for the occurrence of ventricular arrhythmias, thyroid function abnormalities, hypokalemia, implanted device without Holter monitoring, liver failure, chronic kidney disease with GFR < 30 ml/min., neurological diseases/conditions such as a past history of clinically apparent ischaemic stroke, and active subarachnoid haemorrhage.

Of the 30 patients enrolled into the study, 20 suffered from coronary artery disease (LVEF: 28 ± 12%, ICD: 9; CRT-D: 10) and 10 from dilated cardiomyopathy (LVEF 25 ± 6%, ICD: 6; CRT-D: 4). In all patients, standard pharmacotherapy administered according to the current ESC guidelines as well as invasive procedures including coronary artery revascularisation and catheter ablation had proved ineffective. All patients had been re-hospitalised due to recurrent arrhythmia. They were on stable therapy.

Table 1. Clinical characteristics

Parameter	All patients N = 30	Patients with CAD N = 20	Patients with DCM N = 10
		Mean value ± SD N (%)	
Age [years]	65 ± 10	68 ± 7	60 ± 13
Height [cm]	173 ± 9	171 ± 10	176 ± 4
Weight [kg]	87 ± 15	83 ± 14	95 ± 16
BMI [kg/m^2]	29 ± 5	29 ± 5	31 ± 5
LVEF [%]	27 ± 10	28 ± 12	25 ± 7
LV EDD [mm]	70 ± 11	69 ± 10	72 ± 12
LV ESD [mm]	58 ± 11	56 ± 11	61 ± 11
ICD	15 (50%)	9 (45%)	6 (60%)
CRT-D	14 (47%)	10 (50%	4 (40%)
DDDR	1 (3%)	1 (5%)	0

All modifications/interventions were done during the previous hospitalisation.

These patients received ranolazine 375 mg twice daily for three months in addition to their standard pharmacotherapy. Eighteen patients were on chronic amiodarone therapy.

Clinical assessment, resting ECG, ECG Holter monitoring, ICD/CRT-D memory recording, transthoracic echocardiography as well as standard laboratory examinations were obtained at baseline and again after three months of ranolazine treatment. The severity of the arrhythmia was assessed by 24-hour ECG Holter monitoring (significant ventricular arrhythmia was defined as: nsVT/VT/VEs > 1,000/day) and in ICD/CRT-D memory recording (significant ventricular arrhythmia was defined as: nsVT/VT/VF, BiV < 95%).

Baseline data was compared to data obtained after the three-month ranolazine treatment.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee. All patients gave their written consent for participation in the study prior to enrollment.

Statistical analysis

Statistical analysis was performed using Statistica 10.0 (StatSoft Poland) software. Continuous variables were presented as median, and categorical as absolute counts and percentages. The type of distribution was verified using a Shapiro-Wilk test. In cases of normally-distributed variables, Student's t test for unpaired samples was used, while Mann–Whitney U test was implemented in non-normally distributed parameters. Wilcoxon test was used for paired samples. A p-value of less than 0.05 was considered statistically significant.

Clinical characteristics

Comparison of the baseline clinical data and the data obtained after the three-month ranolazine therapy did not reveal any significant changes in the patients' clinical status. We observed no significant improvement in effort tolerance expressed in the NYHA scale. In several cases we found an improvement in CCS scale (5 pts) as well as a reduction of the subjective sensation of palpitations (5 pts). The echocardiographic parameters remained similar after the treatment, including LVEF (28% ± 12 vs. 29% ± 12, p = NS). The level of potassium remained normal, at a stable level (avg. 4.4 mEg/L). Serum NT-proBNP level did not significantly change during the observation (median value 412 vs. 365 pg/mL).

Efficacy of ranolazine treatment

Significant ventricular arrhythmia determined via Holter monitoring was reduced after ranolazine therapy (77.4 vs. 48.4%, p = 0.01). A significant reduction of total VEs was observed in the Holter monitoring (median: 1,737 vs. 1,260, p = 0.04) (Table 2).

Table 2. Efficacy of ranolazine treatment

Parameter	Baseline	Post--ranolazine	p value
Total VEs in Holter ECG (median)	1,737	1,260	0.04
Ventricular arrhythmia in ICD/CRT-D memory recording [%]	67.7	35.5	0.03
ATP, N [%]	9 (30)	2 (7)	0.01
Shock delivery, N [%]	8 (27)	2 (7)	0.01

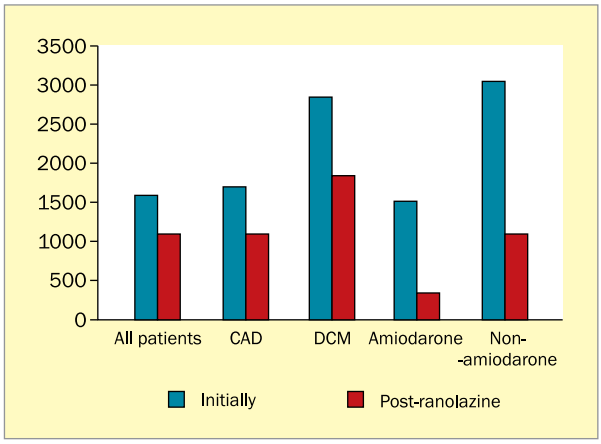

Figure 1. Median value of total ventricular extrasystoles in electrocardiographic Holter monitoring before and post-ranolazine treatment; CAD — coronary artery disease; DCM — dilated cardiomyopathy

Similarly, significant ventricular arrhythmia in ICD/ /CRT-D memory recording was diminished (67.7 vs. 35.5%, p = 0.03). The number of ICD interventions in terms of both antitachycardia pacing (9 pts vs. 2 pts, p = 0.01) and shock delivery (8 pts vs. 2 pts, p = 0.01) was lower after the three-month observation (Table 2).

The therapy was ineffective for nine (29%) of the pts — two were hospitalised during the three-month follow-up, and in seven pts there was no noticeable reduction in the amount of ventricular arrhythmia.

Ranolazine treatment: CAD vs. DCM

The total value of VEs in Holter ECG in patients with CAD was insignificantly higher at baseline than in cases of DCM (median value 1,864 vs. 3,074).

After the ranolazine treatment, we observed a significant reduction in total VE values determined via Holter ECG in the CAD patients (median value 1,864 vs. 1,271, p < 0.05).

In the group of patients with DCM, a reduction in total VE values was observed in five cases (50%, median value 6,460 vs. 500), although the result was statistically non-significant for the whole subgroup (median value 3,074 vs. 2,000) (Figure 1).

Ranolazine treatment: amiodarone vs. non-amiodarone

The total value of VEs determined via Holter ECG in patients treated with amiodarone was insignificantly lower than the value in subjects without amiodarone at baseline (1,529 vs. 4,100).

In the group of patients treated with amiodarone, we observed a significant reduction in total VEs in Holter ECG (median value 1,529 vs. 500, p < 0.05).

In the group of patients treated with ranolazine without amiodarone, we observed reduced total VEs in Holter ECG in five cases (42%, median value 5,000 vs. 1,281), but the efficacy of the drug was statistically insignificant for the whole subgroup (median value 4,100 vs. 1,281).

Safety of ranolazine treatment

Adverse effects in the form of gastrointestinal symptoms (diarrhoea: two, constipation: one) occurred in three (10%) pts. We observed no significant QT prolongation in any patient, and no significant changes in the average heart rate (66 ± 8 vs. 63 ± 9 bpm, p = 0.31).

Discussion

The crucial finding of our research is that ranolazine can be used effectively as a second-line therapy in ventricular arrhythmias.

The drug was effective with statistical significance in patients with CAD. Perhaps this was due to its better effect in people with this disease; however, due to the small number of patients in the study group, further research is needed to objectify this claim.

It should be noted that we analysed a very specific group of patients. Our study group consisted of patients with the highest risk of SCD — patients with recurrent antiarrhythmic therapy-refractory ventricular arrhythmias. Both standard pharmacotherapy and invasive procedures had proved ineffective. Ranolazine was administered over and above the current available therapy.

Additionally, all subjects presented symptoms of chronic heart failure with a reduced ejection fraction. Regardless of their stable haemodynamic status, the LVEF was below 30% in most of the patients. All these figures underline the clinical importance of our findings.

Whereas until now the efficacy of the drug has been proved in atrial fibrillation [4–6], studies are still ongoing regarding its possible use in ventricular arrhythmias. A recently completed RAID trial in which a comparable group of patients was enrolled into the study showed however that in high-risk ICD patients, treatment with ranolazine did not significantly reduce the incidence of the first VT or VF or death.

But, in prespecified secondary endpoint analyses similar to our study, ranolazine administration has been associated witha significant reduction in recurrent VT or VF requiring ICD therapy, without evidence for increased mortality [7]. Another study, conducted by Yeung E et al., showed a significant reduction in median premature ventricular complexes burden, as well as the elimination of VT in chosen patients and the prevention of recurrent defibrillator therapy, something which was also found in our study [8]. The efficacy of ranolazine in the treatment of ventricular arrhythmias has also been observed in patients with symptomatic non-obstructive hypertrophic cardiomyopathy. Olivotto et al. [9] examined a group

of 80 patients who were treated with ranolazine 1,000 mg bid for five months. However, their primary endpoint was to observe possible changes in peak VO_2 compared to baseline using a cardiopulmonary exercise test. The severity of the ventricular arrhythmia was also assessed, and a significant reduction was observed in the 24-hour burden of premature ventricular complexes compared to a placebo [9].

It is worth mentioning that several studies have demonstrated the additional efficacy of ranolazine treatment in combination with amiodarone or dronedarone. Although differences have been observed in atrial fibrillation, from our study it appears that a similar relationship exists in the case of severe ventricular arrhythmias [5, 10, 11].

Overall, in the vast majority of studies, ranolazine has proved to be safe and well tolerated.

We are aware of some limitations of our study, of which the most important remains the relatively small group of patients enrolled. This was because the study included patients with both advanced cardiac insufficiency and an exhausted option of standard therapy. It seems safe to assume that this is inherently a rare group. It should probably be contemplated using higher doses of the drug to investigate possible intensification of its action.

Conclusion

Ranolazine seems to be an effective and safe second-line therapy in reducing the number of ventricular arrhythmia episodes and ICD interventions in patients with recurrent antiarrhythmic therapy-refractory events. Further research is however needed in order to provide more evidence.

Funding

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Conflict(s) of interest

All authors declare no conflict of interest.

Streszczenie

Wstęp. Farmakologiczne leczenie komorowych zaburzeń rytmu (VA) jest ograniczone. Ranolazyna to stosunkowo nowy lek o udokumentowanym działaniu przeciwdławicowym i przeciwniedokrwiennym oraz z danymi przedklinicznymi wskazującymi na dodatkowe właściwości antyarytmiczne.

Celem pracy była ocena bezpieczeństwa i skuteczności ranolazyny u pacjentów z nawracającymi opornymi na leczenie VA.

Materiał i metody. Prospektywną oceną objęto 30 pacjentów (pts) (mężczyźni/kobiety: 26/4, średnia wieku: 65 ± 10 lat; choroba wieńcowa/kardiomiopatia rozstrzeniowa: 20/10, klasa I/II/III/IV według *New York Heart Association*: 2/14/12/2, frakcja wyrzutowa lewej komory: 27 ± 10%; kardiowerter-defibrylator [ICD]: 15 pts, terapia resynchronizująca serce z funkcją defibrylacji [CRT-D]: 14 pts) z nawracającymi istotnymi VA (migotanie komór, utrwalony częstoskurcz komorowy [VT] i/lub nieutrwalony VT, liczne pojedyncze ekstrasystolie komorowe > 1000/d., stymulacja biwentrikularna (BiV) < 95%) i z wyczerpaną standardową opcją leczenia, tj. farmakoterapią, rewaskularyzacją wieńcową i przezskórną ablacją. Nasilenie arytmii oceniano w 24-godzinnym monitorowaniu elektrokardiograficznym (EKG) metodą Holtera oraz w pamięci holterowskiej ICD/CRT-D. U pacjentów do standardowej farmakoterapii (amiodaron: 18 pts, beta-adrenolityk: 26 pts) dołączono ranolazynę w dawce 375 mg 2 razy/dobę przez 3 miesiące. Wyjściowe dane porównano z danymi uzyskanymi po 3-miesięcznym leczeniu.

Wyniki. Autorzy zaobserwowali istotną redukcję liczby ekstrasystolii komorowych w monitorowaniu EKG metodą Holtera (mediana: 1737 *v.* 1260; p = 0,04). Podobnie odnotowano istotne zmniejszenie częstości istotnej VA w zapisie pamięci ICD/CRT-D (67,7 *v.* 35,5%; p = 0,03). Liczba interwencji ICD zarówno pod względem stymulacji antyarytmicznej (9 pts *v.* 2 pts; p = 0,01), jak i wyładowań (8 pts *v.* 2 pts; p = 0,01) była niższa po 3-miesięcznej obserwacji. Terapia była nieskuteczna u 9 (29%) pacjentów — 2 hospitalizowano w trakcie 3-miesięcznej obserwacji z powodu nawrotu VA, a u 7 nie stwierdzono zauważalnego zmniejszenia występowania VA. Działania niepożądane pod postacią dolegliwości żołądkowo-jelitowych (biegunka: 2, zaparcie: 1) wystąpiło u 3 (10%) chorych. U żadnego z pacjentów nie obserwowano istotnego wydłużenia odstępu QT. Nie obserwowano istotnych różnic w charakterystyce klinicznej pacjentów wyjściowo i po podaniu ranolazyny.

Wnioski. Ranolazyna wydaje się bezpiecznym i skutecznym lekiem drugiego rzutu, który może być stosowany w redukcji VA i liczby interwencji ICD u pacjentów z nawracającymi opornymi na leczenie VA.

Słowa kluczowe: ranolazyna, arytmie komorowe, arytmie oporne na leczenie

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