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Case Study

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Total or Sub-Total Correction of a Marked and Long-standing Cardiac Dysrhythmia after Sofosbuvir/Ledispavir Treatment

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Abstract

Cardiac dysrhythmias (atrial and/or ventricular fibrillation) represent a major medical problem, with possibly life-threatening complications, necessitating costly, life-long treatments or complicated procedures. We report here a case of a sustained correction of a severe and long-standing atrial dysrhythmia (hyperexcitability) and at a lesser degree, a ventricular hyperexcitability, occurring after treatment with a combination of sofosbuvir plus ledispavir administered to treat a chronic Hepatitis C virus infection (HCV). The correction appeared within the first days of anti-HCV treatment and was totally maintained 3 months after drug cessation and still noticeable 3 more months. The mechanism of such an antiarrhythmic action has still to be elucidated. If confirmed, the potential antiarrhythmic effect of sofosbuvir combined with another antiviral drug, could represent a real advance in atrial and maybe ventricular hyperexcitability treatment.

Keywords: Cardiac arrhythmia; Atrial fibrillation; Extrasystoles; Sofosbuvir; Ledispavir; HCV

Background

In the general population, severe atrial dysrhythmia, particularly atrial fibrillation (AF), is a major health problem. AF could be responsible for life-threatening complications. [1] Ventricular fibrillation most often threatens post-myocardial infarction state with risk of sudden death [2]. Permanent AF preceded by electro-cardiographic signs of atrial dysrhythmia is often (extrasystoles; SVES). Available drugs are not always efficient, with few rates of severe side effects, particularly when administrated with Flecainide or Amiodarone. In any case, these drugs are only suspensive of the disturbance and should permanently be taken.

Sofosbuvir and Ledipasvir are both direct-acting antiviral (DAA) drugs used to treat chronic hepatitis C infection (HCV). On March 24, 2015, the US Food and Drug Administration (FDA) reported a drug safety announcement of serious slowing of heart rate, when sofosbuvir and ledipasvir were both administrated with amiodarone, an antiarrhythmic drug [3].

We report a case of an asymptomatic long-standing atrial hyperexcitability (numerous SVES), associated with less severe polymorphic ventricular extrasystoles (VES).

Case Report

A 76 years old male patient was known to have a severe dysrhythmia for several years (Table 1). A clinical, biological and cardiovascular exploration ruled out an underlying cause for this trouble. In addition, the patient has been taken metformin (2 g), Saxagliptin (5 mg) for type-2 diabetes and irbesartan (150 mg), Amlodipine (10 mg) for hypertension, Tamsulodin (0.4 mg) and, occasionally, Pantoprazole (40 mg) daily.

A treatment of a non-cirrhotic chronic active HCV infection combining Sofosbuvir (400 mg) and Ledispavir (90 mg) (Harvoni®, 1 cap once a day, Gilead Laboratories) was started for 12 weeks in January 6th, 2016 (Month 0, Mo). Within the first days following the treatment initiation, the patient noticed a total normalization of his pulse frequency. This improvement, both on atrial and ventricular levels, was authentified on 10 hours Holter, the last day of the HCV treatment (M3) and more completely verified in June 2016 (M5): at this time, the correction was total; a slight deterioration was observed at M9 on atrial excitability and still total on the ventricular level. The electrocardiographic modifications were documented on a sequence of 24-hour EKG Holter recordings before, during and after the antiviral treatment. Table 1 shows the progressive deterioration of the atrial hyperexcitability with a number of 24H SVES at 12,593 / 108 800 and VES at 420 on pre-treatment; this pre fibrillation state was totally corrected at M3 and M5. A slight reappearance of atrial hyperexcitability was observed at M9, when the correction of ventricular hyperexcitability was still maintained.

Parameters				**Dates**		
(Mo, Yrs)	**10.201**	**11.2014**	**9. 2015**	**Month 3* 4.2016**	**Month 5* 6.2016**	**Month 9* 10.2016**
	B	B	B	D**	A	A
Effective Recording Duration (hrs)	20	23	22	10	24	24
Total Number of Complexes Analyzed (X 103)	98.3	90.3	108.8	49.4	111.4	XX
Heart Rate						
Min	54	55	52	64	52	47
Max	112	91	107	101	122	108
Ventricular Extrasystoles	229	1 215	420	246	96	0
Total number Doublets	0	279	4	0	0	0
Supraventricvular Extrasystoles						
Total Number	3 306	3 827	12 593	48	90	1412
Number of ESSV/hour	165	166.4	572.4	4.9	3.7	58.8
Doublets	8	279	530	0	0	6
Triplets	4	28	0	0	0	7
Bigem.	0	0	0	0	0	0
Trigem.	0	0	0	0	0	0

Table 1: Main Characteristics of Ekg Holter Recorded Before (B), During (D) And After (A) Antiviral Drug Therapy.
*The HCV treatment started in January 6th 2016 for 12 weeks: Month 3 (April, 2016): the last day of the HCV treatment. Month 5 (June, 2016): 2 months after the HCV treatment. Month 9 (October 2016): 6 months after the HCV treatment.
D** : Recording the last day but during the treatment with antiviral drugs; notice that for technical reasons, only 10 hours of recording were analyzable.

Discussion

Our case report is the first observation showing an almost immediate and sustained regression of a pre-AF state under and after treatment combining sofosbuvir and ledispavir. This improvement was total within the first days of antiviral drug initiation and remained so 3 months after antiviral drug cessation. At M9, a slight reappearance of atrial excitability was observed still largely below the pretreatment values when correction of the ventricular hyperexcitability remained total.

This observation raises numerous questions. The first one consists in examining the possible cause/effect relationship of the combined antiviral treatment on the EKG modification, even if it needs to be confirmed by prospective studies. A causal effect is likely since dysrhythmia was present for more than five years. The cardiac pulse effect was observed within a few days after starting the combined HCV-treatment. Associated medications did not change during and after the anti HCV treatment except for an abstention of pantoprazole intake. Back and Burger take the very short period between the DAA treatment initiation and the unexpected effect as a good indicator of a causal effect [4]. Another indirect argument can be found in the recent warnings put on the effects of sofosbuvir and antiviral drugs on intracardiac conduction. Many cases of severe and permanent bradycardia occurring after sofosbuvir-based regimen have been published indicating a possible direct toxic effect of these antiviral drugs on the myocardium [4].

In the present observation, the suspected beneficial effect of the antiviral association on cardiac dysrhythmia cannot be attributed to the disappearance of the viral infection as such cardiac abnormalities have not described in HCV infection. The administration of sofosbuvir and ledispavir did not modify the mean cardiac frequency, but significantly accelerated the intra-cardiac electrical conduction (Table 2); we observed a significant reduction in the mean P wave value durations over 24 hours; we also observed an atrio-ventricular conduction acceleration (mean PR values), but only significant during nighttime. The intra-ventricular conduction was also accelerated (significant decrease in mean QRS duration values) over 24 hours.

The molecular mechanism by which sofosbuvir and DAA may act on cardiac conduction or excitability is not known [4,5] and, if confirmed by further investigations, has to be elucidated. A putative cardio-toxicity of polymerase inhibitors has been previously reported [5]. In the severe cases of bradycardia, Back and Burger [4] do not exclude sofosbuvir to be the "victim" of an interaction with amiodarone, the latter being considered as the "aggressor". It should be noticed however that amiodarone was not constantly co-administered in the sofosbuvir-associated bradycardia. In our case, we cannot exclude a favorable interaction between the antiviral drugs and the

chronic treatment taken by the patient. In addition, Back and Burger [4] do not exclude a possible genetic predisposition for such interaction: this hypothesis could also be valid in our case.

Item		Before Tt 9/25/2015	After Tt 6/13/2016	p value
Heart Rate, bpm	overall*	74 ± 10	76 ± 14	0.4
(mean ; bpm)	daytime**	78 ± 10	83 ± 12	0.052
	nightime***	67 ± 5	63 ± 5	0.03
P wave duration, ms	overall*	139 ± 7	120 ± 11	<0.001
	daytime**	138 ± 8	116 ± 11	<0.001
	nightime***	140 ± 4	127 ± 6	<0.001
Mean PR space duration,	overall*	194 ± 9	193 ± 18	0.57
msms				
ms	daytime**	192 ± 10	186 ± 19	0.07
	nightime***	198 ± 7	206 ± 5	0.001
Mean QRS duration, ms	overall*	102 ± 8	86 ± 4	<0.001
	daytime**	102 ± 9	86 ± 4	<0.001
	nightime***	102 ± 5	86 ± 4	<0.001

Table 2. Characterization of the intracardiac (atrial, atrionodal, and intraventricular) conduction before and after treatment by Sofosbuvir.
* calculated on 48 samples, one taken every 30 minutes over 24 hours
**calculated on 32 samples taken every 30 minutes over 16 hours daytime.
*** calculated on 16 samples, one taken every 30 minutes over 8 hours nighttime.
Bpm: beats per min, milliseconds
Daytime (8 am-12 pm)
Nighttime (12 pm-8 am)

Conclusion

Our unique observation of a long-standing cardiac dysrhythmia following administration of a sofosbuvir plus ledispavir combined treatment, raises the possibility of an unexpected favorable effect on cardiac hyperexcitability. Extensive results obtained in more patients under the same clinical context would support this hypothesis. If confirmed, this treatment, with largely well-tolerated drug(s) would be an important advancement in cardiac hyperexcitability prevention and treatment, particularly atrial fibrillation. This would be the first long-acting oral treatment of cardiac rhythm diseases, to be compared with daily actual oral treatments, not free of deleterious side effects [2-5]. If a favorable antiarrhythmic effect is confirmed, then indicators are to be defined to determine in which patients the favorable effect is to be expected.

Conflict of Interest

- Gérard Slama: No conflict of interest concerning this paper.
- Laurence Slama serves as a member of advisory Board meeting for Gilead, ViiV outside the submitted work.
- Jacques Blacher: No conflict of interest concerning this paper.
- Yves El Bèze: No conflict of interest concerning this paper.
- Serge Gryner: No conflict of interest concerning this paper.
- Stanislas Pol is speaker or board member for GSK, BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Novartis, Abbvie and received grants from BMS, Gilead, Roche, MSD.

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