Efficacy of theophylline in patients affected by low adenosine syncope

Michele Brignole, MD,[*] Diana Solari, MD,[*] Matteo Iori, MD,[†] Nicola Bottoni, MD,[†] Regis Guieu, MD,[‡§] Jean Claude Deharo, MD[‡§]

From the [*]Department of Cardiology, Ospedali del Tigullio, Lavagna, Italy, [†]Department of Cardiology, Arcispedale S. Maria Nuova, Reggio Emilia, Italy, [‡]UMR MD2, Aix Marseille University, Marseille, France and [§]Institute of Biological research of the French Army (IRBA), Marseille, France.

Introduction

Patients with unexplained syncope of sudden onset, normal heart, and normal electrocardiogram (ECG; so-called unexplained syncope, no prodrome, and normal heart) have been shown to be different from patients with vasovagal syncope.[1,2] Rather, their clinical and biological features are close to those observed in patients affected by idiopathic paroxysmal atrioventricular (AV) block.[3] Patients with syncope without prodrome and normal heart and patients with idiopathic paroxysmal AV block have an adenosine profile that is opposite to that observed in patients with vasovagal syncope and is characterized by low plasma adenosine values, low expression of A2A adenosine receptors, and a high induction rate of transient complete heart block during exogenous injections of adenosine.[4] Unlike in patients with vasovagal syncope, tilt testing is usually negative.[4] Adenosine is suspected to be involved in the mechanism of syncope in such patients. These forms of syncope have been labeled *low adenosine syncope*,[1] and this terminology is used throughout this article.

Since patients with low plasma adenosine levels are highly susceptible to exogenous and endogenous adenosine,[2–6] we wanted to investigate whether treatment with theophylline, a nonselective adenosine receptor antagonist, should result in the prevention of syncopal recurrences. We found the opportunity to test this hypothesis in a highly selected subset of patients who will be described in this article.

Description of patients

We report the prolonged clinical observation of 6 patients with low-adenosine syncope (mean age 50 ± 20 years; 4 (67%) women) treated with oral theophylline within the serum therapeutic range of 12–18 μg/mL. The patients had common major clinical features: (1) a long-standing history (median 8 years; range 3–30 years) of recurrent unexplained syncope without prodrome, normal heart, and normal ECG and (2) baseline values of plasma adenosine (0.11 ± 0.03 μmol/L) well below the 5th percentile of the value of normal subjects (0.40 μmol/L).[4] Multiple episodes of paroxysmal AV block and sinus arrest were documented at the time of (pre) syncope in 4 and 1 patients, respectively; in another patient, documentation of the mechanism was lacking, as no ECG monitoring was active at the time of symptoms. Patient characteristics are listed in Table 1.

We had the opportunity to perform an intrapatient comparison between a period with and a period without theophylline therapy with the support of prolonged ECG monitoring in the majority of them (Table 2). The follow-up of all patients was updated to July 2015.

Specifically,

- patient 1 was seen in 1995 and followed up for 20 years. In 1995, Holter monitoring fortuitously recorded idiopathic paroxysmal AV block, which was reproduced on the adenosine triphosphate test. For the next 10 years, she underwent theophylline therapy, during which time she had no syncopal recurrences. In 2005, soon after discontinuing theophylline, she had a syncopal recurrence, for which she received an implantable loop recorder (ILR); over the next 3 years, 2 further episodes of syncope due to idiopathic paroxysmal AV block with long asystolic pauses up to 22 seconds were documented. Overall, she had 4 syncopes in the 36 months of monitoring off therapy and no recurrence during the previous 120 months on theophylline therapy. In 2008, she received a permanent pacemaker and has remained asymptomatic since that time.
- patient 2 participated in a 4-period crossover trial (off-on-off-on therapy) under ILR monitoring: overall he had 19 episodes of idiopathic paroxysmal AV block (maximum pause 7 seconds) in the 11 months off therapy but only 4 episodes (maximum pause 3 seconds) in the 14 months on therapy (Online Supplemental Figures 1 and 2A–2C).
- patient 3 had 8 syncopes in the 2 years off therapy and no recurrence during the subsequent 2 years on therapy.

KEYWORDS Syncope; Theophylline; Adenosine; Xanthine; Implantable loop recorder; Atrioventricular block; Sinus arrest (Heart Rhythm 2016;13:1151–1154)

Address reprint requests and correspondence: Dr Michele Brignole, Department of Cardiology, Ospedali del Tigullio, via don Bobbio 25, 16033 Lavagna, Italy. E-mail address: mbrignole@asl4.liguria.it.

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Table 1 Characteristics of the 6 patients with low adenosine syncope who were treated with theophylline

Patient no., sex, age	ECG documentation of the index event (total duration/longest pause)*	Adenosine plasma level (μmol/L) (normal range 0.40–0.78 μmol/L)	A2A adenosine receptor expression (AU) (normal range 0.40–0.80 AU)	Adenosine intravenous test, maximum pause	Tilt table testing	Carotid sinus massage	Electro physiology study
1, F, 50 y	Idiopathic AVB (34/22 s)	0.12	0.20	11 s	Negative	Negative	Negative
2, M, 72 y	Idiopathic AVB (11/7 s)	0.09	0.50	Negative	Negative	Negative	Negative
3, F, 20 y	None (ILR only with theophylline)	0.09	0.55	5.4 s	Negative	np	Negative
4, F, 71 y	Idiopathic AVB (24/7 s)	0.10	Np	7 s	Positive mixed	Negative	np
5, M, 41 y	Sinus arrest (18/6 s)	0.18	0.80	7.4 s	Positive cardioinhibitory	Negative	np
6, F, 52 y	Paroxysmal AVB (–/9 s)	0.10	0.45	7.6 s	Negative	Negative	Negative

Adenosine plasma level was evaluated using high-performance liquid chromatography, as described previously.[2] Adenosine A_2 receptor expression was evaluated with the Western blot, as described previously.[7] The normal ranges are between 5th and 95th percentiles of the values recorded in healthy control subjects.[4]

AU = arbitrary units; AVB = atrioventricular block; ECG = electrocardiographic; ILR = implantable loop recorder; F = female; M = male; np = not performed.

*Documentation with prolonged monitoring using an ILR in patients 1, 2, 4, and 5 and Holter monitoring in patient 6.

Only when she started receiving theophylline therapy did she receive an ILR, which never recorded any arrhythmias.

- patient 4 had 27 episodes of idiopathic paroxysmal AV block (maximum pause 7 seconds) in the 13 months off therapy but no episodes in the 6 months on therapy (Figure 1).
- patient 5 had 1 syncope documented with an ILR off therapy in a 2-month period: 2 consecutive pauses due to sinus arrest of 3 and 6 seconds were preceded by a few beats of slowing of sinus rate; he remained free of symptoms and arrhythmias during the 20 months of theophylline therapy.
- we also report the case of a woman (patient 6) who had frequent (daily) presyncopes during a 3-year observation period; on several occasions, she underwent 24-hour Holter monitoring, which, on each occasion, detected multiple episodes of paroxysmal asystolic AV block preceded and followed by PR interval prolongation and second-degree AV block (Online Supplemental Figure 3). Since the patient refused pacemaker implantation, she was treated with oral theophylline 600 mg/d for 1.5 months. Although her symptoms persisted, the episodes of asystolic AV block declined from 14 (longest pause 9.2 seconds) on pretherapy Holter monitoring to 7 (longest pause 6.7 seconds) on monitoring during theophylline therapy. She discontinued theophylline and refused pacemaker implantation; she is still symptomatic with no change in symptoms.

To summarize, in 5 patients, symptoms disappeared and the number of prolonged asystolic pauses detected by the

Table 2 Comparative effect of outcomes in 5 patients who responded to theophylline and the 1 patient who did not

	History of syncope before diagnosis		Observation without therapy			Observation during theophylline therapy		
Patient no.	Duration (y)	No. of episodes	Months	Episodes of syncope	Episodes of asystole ≥3 s*	Months	Episodes of syncope	Episodes of asystole ≥3 s*
1	30	20	36	4	3	120	0	Np
2	12	2	11	0	19	14	0	4
3	18	40	24	8	np	24	0	0
4	1	2	13	0	27	6	0	0
5	3	5	2	1	1	20	0	0
Median (IQR)	12 (3–18)	5 (2–20)	13 (11–24)	0.11 (0–0.33)	1.11 (0.4–1.8)	20 (14–24)	0 (0–0)	0 (0–0.7)
6	2.5	Frequent presyncopes	6	Frequent presyncopes	14 per day (maximum pause 9.2 s)	1.5	Frequent presyncopes	7 per day (maximum pause 6.7 s)

Wilcoxon matched-pairs signed rank test: too few cases to use this test.

IQR = interquartile range; np = not performed.

*Observation with prolonged monitoring using an implantable loop recorder in patients 1–5 and Holter monitoring in patient 6.