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Efficacy of theophylline in patients with syncope without prodromes with normal heart and normal ECG☆,☆☆

Michele Brignole [a,*], Matteo Iori [b], Diana Solari [a], Nicola Bottoni [b], Giulia Rivasi [c], Andrea Ungar [c], Jean Claude Deharo [d], Regis Guieu [d,e]

[a] Department of Cardiology, Ospedali del Tigullio, Lavagna, GE, Italy
[b] Department of Cardiology, Arcispedale S. Maria Nuova, Reggio Emilia, Italy
[c] Department of Geriatrics and Geriatric Intensive Care Medicine, University of Florence and Azienda Ospedaliero Universitaria Careggi, Florence, Italy
[d] Department of Cardiology, Hopital La Timone Adultes, Marseille, France
[e] UMR MD2, Aix Marseille University, Institute of Biological research of the French Army (IRBA), Marseille, France

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ABSTRACT

Background: Patients affected by syncope without or with very short (≤5 s) prodrome with normal heart and normal ECG have been seen to present low plasma adenosine levels. We investigated whether chronic treatment of these patients with theophylline, a non-selective adenosine receptor antagonist, results in clinical benefit.
Methods: In a consecutive case-series of 16 patients (mean age 47 ± 25 years, 9 females) who had ECG documentation of asystolic syncope, we compared the incidence of syncopal recurrence during a period without and a period with tailored theophylline therapy.
Results: During a median of 60 months before ECG documentation of the index episode, the patients had a median of 2 syncopes per year. During the 6 months of the study phase without therapy, the patients had a median of 2.6 syncopes per year, $p = 0.63$. During the 23 months of the study phase with theophylline, the patients had a median of 0.4 syncopes per year, $p = 0.005$ vs history and $p = 0.005$ vs no therapy. In the 13 patients who had an implantable loop recorder during both study phases, the incidence of asystolic episodes > 3 s decreased from 9.6 per year to 1.1 per year, $p = 0.0007$. During theophylline treatment, syncope recurred in 1/5 (20%) patients who had an idiopathic atrioventricular block as the index event versus 9/11 (81%) patients who had a sinus arrest, $p = 0.005$.
Conclusion: Theophylline is effective in reducing syncopal burden in patients with syncope without prodromes with normal heart and normal ECG. Its efficacy is greater in those with idiopathic atrioventricular block.

1. Introduction

Patients affected by syncope without or with very short (≤5 s) prodrome with normal heart and normal ECG have been seen to present low plasma adenosine levels (so-called "*Low-adenosine syncope*") [1]. Adenosine is suspected to be involved in the mechanism of syncope through the activation of A_1 adenosine receptors which are known to be located within the atrioventricular (AV) node and the sinus node; their activation causes AV block and/or sinus bradycardia [2,3]. These patients have an adenosine profile which is opposite to that observed in vasovagal syncope and is characterized by very low plasma adenosine values, low expression of A_{2A} adenosine receptors and a high induction rate of transient complete heart block during exogenous injections of adenosine [1,2]. The typical mechanism of syncope is an idiopathic paroxysmal AV block [4,5]; however, sinus bradycardia, most often followed by sinus arrest, is as frequent as idiopathic AV block, and some patients do not have rhythm variations at the time of syncope [6]. These latter findings suggest some overlap with other forms of reflex syncope.

Since patients with low plasma adenosine levels are highly susceptible to exogenous and endogenous adenosine [1,2,5,7], we investigated whether chronic treatment of these patients with theophylline, a non-selective adenosine receptor antagonist, results in prevention of syncopal recurrences.

2. Methods

The study population consisted of a consecutive case-series of 16 patients affected by syncope without prodromes, with normal heart (including normal echocardiogram) and normal ECG, in whom syncope with asystolic pause/s had been documented by means

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* Corresponding author at: Department of Cardiology, Ospedali del Tigullio, via don Bobbio 25, 16033 Lavagna, Italy.
E-mail address: mbrignole@asl4.liguria.it (M. Brignole).

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of prolonged ECG monitoring (implantable loop recorder in 13 cases, external loop recorder in 3 cases). In these patients, a decision not implanting a pacemaker was taken because of the young age of some patients (6 patients were below the age limit for pacing of 40 years, according to guidelines [8,9]) or because the patients were reluctant to embarking in a definitive therapy and preferred to delay such intervention.

2.1. Study design

We compared the yearly incidence of syncopal recurrence during a period without and a period with tailored theophylline therapy. Theophylline was started at a dose of 600 mg b.i.d. and was subsequently titrated to the maximum dosage that was tolerated by the patient without side effects. The actual dose during the study period, after titration, was 520 ± 185 mg (range 300–900). The period without therapy started at the beginning of prolonged monitoring and ended at the date when a decision to start theophylline therapy was taken, at the discretion of the attending physician. The period with theophylline therapy started when therapy was initiated and ended at the time of discontinuation of the therapy or at the end of follow-up. The study protocol was approved by the institutional review boards.

2.2. Statistical analysis

In all analyses, we used a two-sided type-1 error alpha = 0.05. Continuous data are shown as means ± standard deviations or medians (25th–75th percentile), as appropriate. The Wilcoxon matched-pairs signed-rank test was used to compare the incidence of syncope and of asystolic events.

The Kaplan-Meier product-limit method was used to assess the time to the first syncopal recurrence. The effect of clinical variables on the outcome was analyzed by means of the Cox proportional-hazards regression. Analyses were performed by means of MedCalc version 15.8 (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Population

The study population consisted of 16 patients (mean age 47 ± 25 years, range 8–80 years), 9 of whom were females. They had a history of recurrent syncope lasting, on average, 5 years. Syncopal episodes had occurred without prodromes in 6 patients, and sometimes with very short (≤5 s) prodromes in the others; however, 3 patients (pts no 6, 11 and 13 in Tables 1 & 2) had some episodes triggered by typical situations (instrumentation, micturition) and one had typical vasovagal syncopes during adolescence.

The ECG at the time of the documented index syncope showed: 1) an idiopathic AV block (defined as paroxysmal third-degree AV block with abrupt onset and absence of other rhythm disturbances before or during the block [5]) in 5 patients (pts no 1–5); 2) brief (a few seconds) progressive sinus bradycardia, usually followed by one or more consecutive episodes of sinus arrest/s in 11 patients (pts no 6–16): one of these (pt no 6) also had blocked P waves during the episode (sinus bradycardia plus AV block) and one (pt no 16) had sinus bradycardia (30 bpm) without sinus arrest. This latter patient had already received a permanent pacemaker after documentation of bradycardic syncope, but this had failed to prevent recurrences: the mechanism of syncope was therefore presumed to be adenosine-mediated hypotension (via vascular adenosine A_2 receptors). The median duration of the pauses was 11 s (6.8; 20). The patients with idiopathic AV block were older than those with sinus bradycardia (65 vs 39 years, p = 0.05).

The median value of plasma adenosine was 0.11 μM/L (0.09; 0.17): all except 3 patients (pts 5, 10 and 12) had a value well below the lowest 5th percentile of the values of normal subjects (0.40 μmol/L) [2]. Adenosine testing (20 mg adenosine bolus injection) was positive in 4/6 patients in whom it was performed. Tilt testing was positive in 3/10 patients in whom it was performed.

3.2. Outcome

During a median of 60 months before ECG documentation of the index episode, the patients had a median of 2 syncopes per year (Table 1 and Fig. 1). During the 6 months of the study phase without therapy, they had a median of 2.6 syncopes per year, p = 0.63. During the 23 months of the study phase with theophylline, the patients had a median of 0.4 syncopes per year, p = 0.005 vs history and p = 0.005 vs no therapy.

In the 13 patients who had an implantable loop recorder during both study phases, the incidence of asystolic episodes > 3 s decreased from 9.6 per year to 1.1 per year (Table 2 and Fig. 1), p = 0.0007. Fairly good reproducibility of ECG findings was observed: the patients with idiopathic AV block continued to have AV block and those with sinoatrial block continued to have sinoatrial block.

During theophylline treatment, syncope recurred in 1/5 (20%) patients who had an idiopathic AV block as the index event, versus 9/11 (81%) of patients who had a sinus arrest, p = 0.005 (Fig. 2). Among baseline clinical variables (sinus arrest vs idiopathic AV block, plasma adenosine value, age, gender, and number of syncopes during history) only sinus arrest vs idiopathic AV block was independently predictive of syncope recurrence on Cox proportional-hazards regression, with a p value of 0.02.

3.3. Adverse events

In two patients (#4 and #9), theophylline was discontinued owing to side effects (i.e., palpitations and insomnia) after 10 and 24 months, respectively; these received a pacemaker. Another two patients (cases

Table 1
Burden of syncopal episodes before and during the study period.

Pts number	History of syncope before monitoring			Observation without therapy			Observation during theophylline therapy		
	Months	Episodes of syncope	Incidence/year	Months	Episodes of syncope	Incidence/year	Months	Episodes of syncope	Incidence/year
1	360	20	0.7	36	4	1.3	120	0	0.0
2	144	2	0.2	11	0	0.0	40	0	0.0
3	12	2	2.0	13	0	0.0	37	0	0.0
4	60	8	1.6	6	1	2.0	10	0	0.0
5	Multiple pre-syncopes			12	2	2.0	162	1	0.1
6	72	27	4.5	24	8	4.0	22	2	1.1
7	226	50	2.7	2	2	12	54	1	0.2
8	2	4	24	1	1	12	2	1	6.0
9	144	5	0.4	22	4	2.2	24	1	0.5
10	96	6	0.8	2	2	12	11	1	1.1
11	60	20	4.0	6	1	2.0	34	3	1.1
12	120	10	1.0	24	1	0.5	13	0	0.0
13	48	20	5.0	4	1	3.0	9	1	1.3
14	Few VVS at the age of 15			1	3	36	10	0	0.0
15	36	6	2.0	5	4	9.6	14	2	1.7
16	48	12	3.0	2	1	6.0	23	2	1.0
Median	60	8	2.0	6	1.5	2.6	22	1	0.4
IQR	48;144	5;19	0.8;3.0	2.0;15	1;3	1.8;10.2	11;38	0;1.3	0;1.1

VVS: vasovagal syncope.

Table 2
Burden of asystolic episodes > 3 s documented by prolonged ECG monitoring during the two study periods.

Pts number	Observation without therapy			Longest asystole, s	Observation during theophylline therapy			Longest asystole, s
	Months	Episodes of asystole ≥ 3 s*	Incidence/year		Months	Episodes of asystole ≥ 3 s*	Incidence/year	
1	36	3	1.0	22	120	na	na	na
2	11	19	20.7	7	40	6	1.8	6
3	13	27	24.9	7	37	0	0.0	–
4	6	1	2.0	13	10	1	1.2	8
5	12	1	1.0	6	162	na	na	na
6	24	8	4.0	35	22	2	1.1	20
7	2	2	12.0	15	54	1	0.2	40
8	1	1	12.0	4	2	1	6.0	15
9	22	4	2.2	30	24	1	0.5	7
10	2	2	12.0	20	11	2	2.2	15
11	6	1	2.0	13	34	3	1.1	11
12	24	1	0.5	7	13	0	0.0	–
13	4	9	27.0	9	9	0	0.0	–
14	1	3	36.0	30	10	0	0.0	–
15	5	4	9.6	6	14	2	1.7	19
16	2	PM	na	2	23	PM	na	na
Median	60	3	9.6	11	22	1	1.1	13
IQR	48;144	1;6	2;16	6.8;20	11;38	0;2	0.0;1.7	7;18

Patient no 16 had a permanent pacemaker (PM) implanted.

#7 and #10) received a pacemaker because of syncopal recurrences during theophylline therapy. No injuries due to syncope relapse occurred during the study period.

4. Discussion

The main finding of this study is that chronic oral theophylline therapy was effective in reducing syncopal burden in patients with syncope without prodromes with normal heart and normal ECG. Its efficacy was greater in those with idiopathic AV block. Several patients with sinoatrial arrest continued to have some recurrence of syncope, but the decrease in syncopal burden was >80% in both subgroups.

Like other methylated xanthine derivatives, theophylline is a nonselective A_1 and A_2 adenosine-receptor antagonist [10]. Adenosine exerts important actions on cardiac conduction tissue, i.e., AV node and sinus atrial node, and on vascular smooth muscles [7,11]. In cardiac conduction tissue, adenosine binds to high-affinity A_1 adenosine receptors located within the AV node and, to a lesser extent, in the sinus node, the activation of which may cause syncope as a result of prolonged asystolic pauses due to AV block or sinus arrest [2,5,6,7,12]. A_1 receptors undergo up- and down-regulation, depending on their chronic exposure to adenosine. When plasma adenosine values are low, the subsequent A_1 receptor up-regulation exposes patients to AV block and sinus bradycardia. Theophylline is able to saturate A_1 receptors, thus preventing their activation in the event of an acute increase in endogenous plasma adenosine (e.g., in the case of hypoxia, inflammation or during reflex beta-adrenergic stimulation) [7,12]. The effect of adenosine is synergic with that of acetylcholine at the level of muscarinic effectors. In addition, adenosine exerts an indirect antiadrenergic action by opposing the effect of sympathetic nervous activation and β_1 stimulation.

In vascular smooth muscles, adenosine binds to A_{2A} adenosine receptors and causes relaxation by increasing cAMP levels via a G protein, leading to K_{ATP} channel activation, and by strongly inhibiting L-type calcium channels (calcium inhibitor-like effect). Theophylline is also an almost equally potent antagonist of A_2 receptors; thus, it might also have a potential role in counteracting a vasodepressor reflex, as in the case of our patient no 16.

However, the magnitude of efficacy of theophylline depends on the relative contribution to syncope of the adenosine pathway (more active in patients with no prodromes, normal heart and normal ECG) compared with that of the sympatho-vagal pathway (more active in patients with vasovagal syncope); this explain the variable efficacy of theophylline therapy reported in the literature in the absence of plasma adenosine assay [13,14,15,16]. Because theophylline competes with adenosine for binding to adenosine receptors, when the extracellular

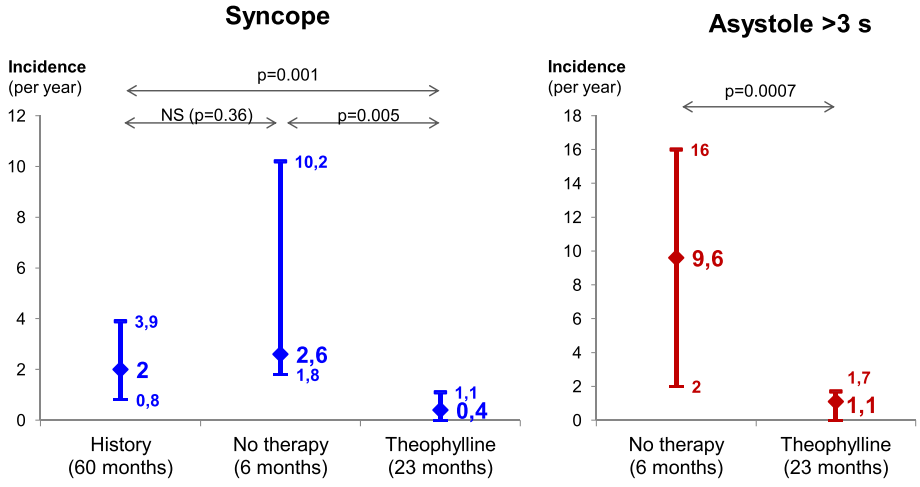

Fig. 1. ***Panel A***. Yearly incidence of syncopal episodes in the history and during the two study periods (no therapy and therapy with theophylline). ***Panel B***. Yearly incidence of asystolic episodes > 3 s during the two study periods (no therapy and therapy with theophylline). Each bar shows the median value with its interquartile range.

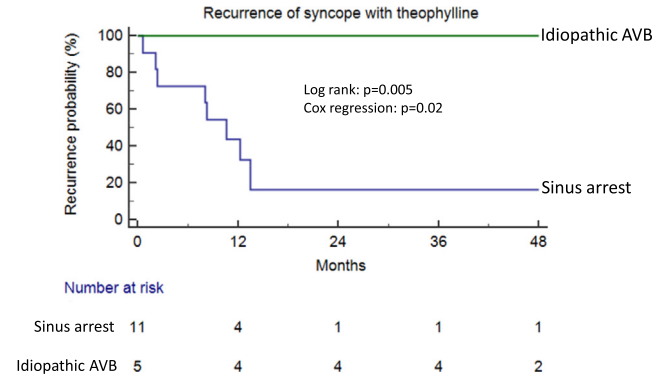

Fig. 2. Kaplan-Meier product-limit estimated time to first syncope recurrence during theophylline therapy in patients who had an idiopathic AV block and in those who had a sinus bradycardia/sinus arrest.

adenosine level is low, theophylline will be more effective, as it will prevent adenosine from binding to free receptors during an increase in the adenosine level. Conversely, in vasovagal syncope, in which the extracellular adenosine level is high [17,18], most adenosine receptors are occupied by adenosine, and theophylline may fail to displace adenosine from the binding sites. However, these two situations probably overlap in most patients.

4.1. Limitations

The main limitations are the small size of the study population and the lack of a parallel controlled prospective study design. The natural history of reflex syncope is often characterized by a spontaneous decrease in recurrences. It is known that syncopal recurrence is not constant, but fluctuates over time, peaking at the time of evaluation. In general, many patients do not have syncopal recurrences after evaluation and, in those with recurrences, the burden of syncope decreases [8]. The effect of education and reassurance, the expectation effect [19,20] and even purely statistical explanations [21,22] have been advocated. Thus, owing to the small size and to the design of this study, the efficacy of theophylline cannot be considered established and future trials are needed before such therapy can be recommended in the guidelines. Nevertheless, these results seem quite robust. Indeed, the total observation period was very long, lasting >7 years, with 28 months of prospective observation during ECG monitoring. The burden of syncope during theophylline therapy decreased greatly, by 80% and 85%, in relation to no-therapy periods, and the burden of asystolic episodes > 3 s decreased by 89%. It seems unlikely that these results could have been achieved without theophylline playing at least a partial role.

4.2. Which patients may benefit more from chronic oral theophylline therapy?

These are patients in whom an asystolic pause is documented at the time of syncope and an adenosine-mediated mechanism is presumed to be responsible for that pause. A low plasma adenosine value identifies patients who may benefit from theophylline, achieving good resolution, with some exceptions. If the plasma adenosine level is not known, patients with syncope without prodromes, or with very short (≤5 s) prodromes, with normal heart and normal ECG are very good candidates. Indeed, approximately 80% of these patients showed a low value of plasma adenosine in this and in previous studies [1,5,6].

Patients in whom asystolic syncope is documented are usually considered for pacemaker implantation. However, when a cardiac etiology is excluded, cardiac pacing is not indicated in patients aged < 40 years by both ESC and American guidelines [7,8]. Six of our patients belonged to this category. Even in patients > 40 years of age guidelines are quite conservative in pacing indication with a low class IIb in American guidelines [9] and class IIa in ESC guidelines [8]. Our patients were reluctant to embarking in a definitive therapy or preferred to delay such intervention in case of further recurrences. Thus, in these patients, theophylline therapy was intended as a temporary ("bridge") therapy during the "hot" phase of the disease, in order to delay the definitive therapy, i.e., pacemaker implantation, in the case of long-term persistence of the disease.

Theophylline seems to be more effective in patients with idiopathic AV block than in those with sinus bradycardia/sinus arrest probably because high-affinity A_1 adenosine receptors are located more in the AV node than in the sinus node. In patients with sinus arrest, we should expect syncope to recur, but at a much lower rate. Owing to the overlap of action of the adenosine and sympatho-vagal pathways, theophylline could also have partial efficacy in patients with situational or vasovagal syncopes, who typically have normal or high adenosine values [17,18], but this issue has never been investigated.

In conclusion, theophylline (and xanthine derivatives in general) is effective in reducing syncopal burden in patients with syncope without prodromes with normal heart and normal ECG. The exact magnitude of its effect and the identification of suitable candidates remain largely to be assessed.

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