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CLINICAL STUDY

Theophylline in the prevention of vasovagal syncope recurrences

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ABSTRACT

OBJECTIVES: The present work aimed to study the efficacy and patient compliance of oral theophylline treatment in the prevention of vasovagal syncope recurrences.

BACKGROUND: High blood adenosine may trigger vasovagal syncope. Theophylline is an adenosine receptor antagonist.

METHODS: In 44 patients with vasovagal syncope (8 men and 34 women, age 46.4±3.2 years) with an average 4.8±0.74 syncopal episodes (range 1–20, median 4,5 episodes) oral theophylline therapy was started with dose 2x100/200 mg, which was further increased if necessary. All patients were treated by non-pharmacological measures which were not effective. Patients were followed in regular intervals on an outpatient basis in 6-month intervals.

RESULTS: After the start of treatment patients were followed for the mean of 17.1±2.1 months (2–51 months, median 12 months). The total number of syncopal episodes decreased from 4.8±0.74 to 1.73±0.45 (p=0.0006). The occurrence of syncopal episodes per year decreased from 4.07±0.80/year to 1.50±0.54 /year during the treatment period (p=0.001). After a gradual increase in theophylline dosage, in 34 patients no syncopal recurrences were observed. In 10 persons syncopal recurrences persisted despite treatment. Side effects leading to discontinuation of treatment were present in 14 patients – gastrointestinal intolerance (7 patients), palpitations (6 patients) and headache (3 patients).

CONCLUSION: The addition of oral theophylline preparation to non-pharmacological treatment led to a marked reduction of syncopal recurrence in patients with vasovagal syncope. About one-third of study subjects discontinued therapy because of side effects *(Tab. 2, Fig. 4, Ref. 22)*. Text in PDF www.elis.sk

KEY WORDS: theophylline, adenosine, vasovagal syncope, treatment.

Introduction

In patients with frequent episodes of vasovagal syncope patient's quality of life is significantly affected. Management of individuals with recurrent vasovagal syncope can be difficult and pharmacotherapy is one of the possible options. Up to now, no large multicenter randomized placebo-controlled clinical trial is available for the pharmacological therapy of vasovagal syncope. Only small placebo-controlled trials are available with conflicting results. The search for novel strategies of pharmacotherapy is based on our evolving knowledge of the pathogenetic mechanisms of vasovagal syncope.

The activation of mechanoreceptors in the heart by myocardial contractions (Bezold-Jarisch reflex) is considered to be the triggering mechanism of vasovagal syncope. The reason for the activation of mechanoreceptors is central hypovolemia. During the first 10–180 seconds of orthostasis, 500–1000 ml of blood moves into the venous system of lower extremities which leads to a reduced return of venous blood to the heart and increased torsion of underfilled ventricles and subsequent irritation of cardiac mechanoreceptors. Reflex activation results in a sudden decrease in sympathetic activity and an increase in parasympathetic activity with the consequent decrease in cardiac output and peripheral vasodilation.

The efferent hemodynamic mechanism of vasovagal syncope is a drop in blood pressure 30-60 seconds before syncope (systolic blood pressure usually drops by about 50 mmHg). The decisive mechanism of hypotension is a decrease in cardiac output by approximately 35–48%. The role of peripheral vasodilatation in hypotension is less important during sympathetic inhibition, the total peripheral vascular resistance does not change, and it may even rise slightly (1).

Other mechanisms also contribute to the pathogenesis of vasovagal syncope: failure of baroreflex blood pressure control, humoral mechanisms (adrenaline, vasopressin, serotonin adenosine, and others), receptor mechanisms (reduced sensitivity of alpha receptors), paradoxical vasoconstriction of cerebral vessels and also genetic mechanisms (polymorphisms of serotonin receptor gene, serotonin transporter gene, gene for catechol-o-methyltransferase and other) (2).

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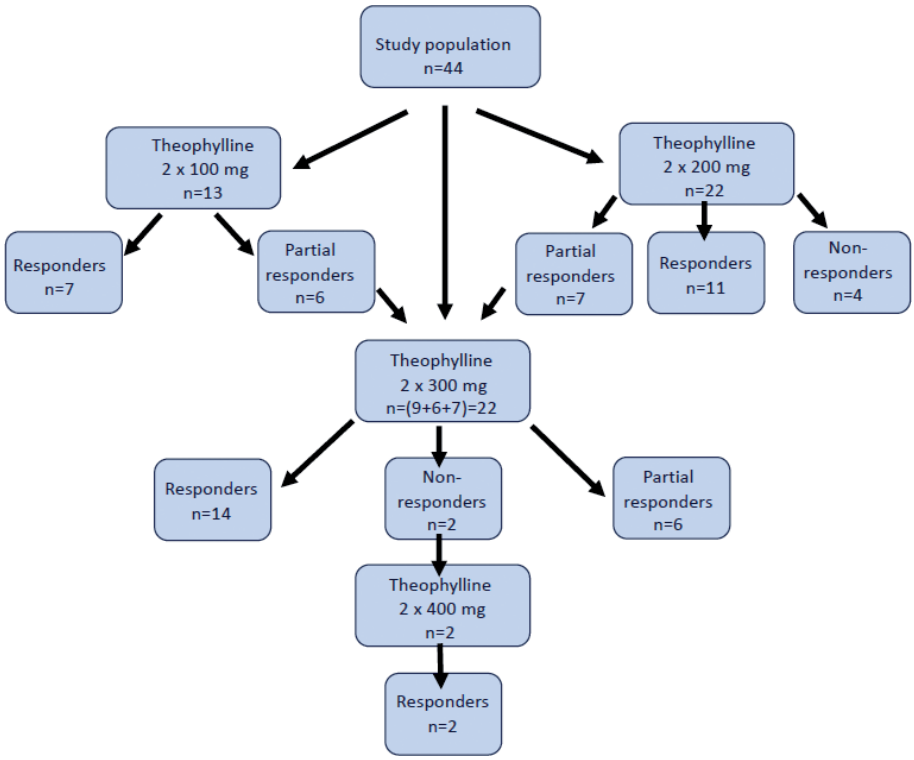

Fig. 1. Flow-chart of the study.

In recent years our knowledge has broadened with the role of adenosinergic mechanisms in the pathogenesis of vasovagal syncope. Adenosine may play a role in the pathogenesis of vasovagal syncope. In patients with positive head-up tilt test increased levels of adenosine in the blood were observed in comparison to control subjects (3). This is a rationale for a novel therapy with adenosine receptor antagonists. Theophylline is a non-selective adenosine receptor antagonist. Several clinical trials about the beneficial effect of theophylline in the treatment of syncope in patients without structural heart disease and low plasma adenosine are available (4, 5). On the other hand, the role of theophylline in the treatment of vasovagal syncope (high-adenosine syncope) was examined in only one small study.

The present study aimed to test the hypothesis that the pharmacological blockade of the adenosine receptor by theophylline may decrease syncopal recurrences in patients with vasovagal syncope.

Tab. 1. Study group clinical characteristics.

Men	8 patients
Women	34 patients
Age	46.4 + 3.2 years
Arterial hypertension	14 patients
Bronchial asthma	11 patients
Thyroid gland disease	1 patients
Diabetes mellitus	1 patients
ACE inhibitor/ Sartan	11 patients
Beta blocker	5 patients
Calcium channel blocker	2 patients
Diuretics	3 patients

Patients and methods

The study was was conducted in 44 patients (with recurrent vasovagal syncope 8 men and 34 women, average age 46.4±3.2 years) (Fig. 1). Patients in the study group experienced on average 4.8±0.74 syncopal episodes (range 1–20, median 4,5 episodes) (Tab. 1). The research was approved by the local ethics committee.

The diagnosis of vasovagal syncope was based on the typical clinical history and was confirmed by a head-up tilt test (HUT). Feelings of the warmth, sweating, nausea or vomiting, and pallor before and after syncope were considered typical clinical features of vasovagal syncope, as well as occurrence of syncope after prolonged standing, in a crowded and warm environment, or after medical instrumentation. HUT was performed at a 60-degree angle on a tilt table test with a motorized footboard. The initial phase was conducted for 20 minutes and if negative followed by 15 minutes pharmacological phase without lowering the patient to supine position. Sublingual nitroglycerine spray in the dose of 0,4 mg was used for pharmacological stimulation.

Other possible causes of syncope were excluded by additional diagnostic methods. They included 12 lead ECG, echocardiography, ambulatory ECG monitoring, and basic laboratory tests. Study patients exhibited no serious cardiovascular comorbidities.

Inclusion criteria were diagnosis of typical vasovagal syncope (based on clinical criteria and positivity of HUT test), negative work-up for other possible causes of syncope, and signed informed consent.

All patients were treated by non-pharmacological measures (increased water and salt intake, avoidance of triggers, horizontalization, and/or isometric countermaneuvers at the time of presyncope. The reason for the addition of pharmacological therapy with theophylline was the non-effectivity of the non-pharmacological management.

Exclusion criteria were the presence of structural heart disease, cardiac arrhythmias, resistant hypertension, neurological diseases, untreated thyroid disorders, anemias, active malignancy, clinical features of suspected low-adenosine syncope (small number of syncopal episodes with trauma and absence of prodromal symptoms) and inability to complete at least one follow-up visit.

The patients were medicated with oral preparations of theophylline in doses of 2x100 mg, 2x200 mg, 2x300 mg or 2x400 mg. The standard initial dose was by choice 200 mg twice a day. In young patients, patients with a low body weight, and patients with a tendency to higher resting heart rate, the initial dose was reduced to 2x100 daily. In patients with higher body weight, the initial dose was increased to 2x300 mg. According to the effectiveness, the dose was individually increased, taking into account patient compliance and possible adverse effects. Treatment with theophylline preparations was terminated in case of intolerance.

After the initialization of the treatment patients were followed in regular intervals on an outpatient basis. Follow-up visits were scheduled after 2 months, after 6 months, and then in 6-month intervals. In addition, patients were instructed to visit our center in the case of syncope recurrence.

Patients with no syncopal recurrences after pharmacological therapy were labeled as responders. Patients in whom no decrease in syncopal episodes was observed during the follow-up period were labeled as non-responders. Patients with syncopal recurrences but a decreased number of syncopal episodes were labeled as partial responders.

Statistical analysis

The MedCalc software (MedCalc Software Ltd, Ostend, Belgium) was used for statistical analysis. Values are shown as mean±standard error of the mean (SEM). All data were tested for the normality of distribution. The comparison of continuous variables was carried out by Student's T-test or Wilcoxon test based on data distribution. The chi-square test was used for the comparison of non-continuous variables. p value of less than 0.05 was considered statistically significant.

Results

All patients had a positive HUT test, 16 patients had mixed type vasovagal syncope (VASIS I), 5 patients had cardioinhibitory type without asystole (VASIS IIa), 5 patients had cardioinhibitory type with asystole (VASIS IIb) and 18 patients had a vasodepressor type of vasovagal reaction (VASIS III).After the initialization of treatments, patients were followed for the mean of 17.1±2.1 months (2–51 months, median 12 months)

The average number of syncopal episodes before treatment was 4.8±0.74 (range 1–20, median 4.5 episodes). A significant decrease in the recurrence of syncope, during long-term treatment with theophylline preparations was observed in the study. The total number of syncopal episodes decreased from 4.8 0.74 to 1.73±0.45 (p=0.0006). The average occurrence of syncopal episodes decreased from 4,07 0.80/year to 1.50±0.54 /year during the treatment period (p=0.001).

After a gradual increase in theophylline dose 34 patients were responders to treatment – no syncopal recurrence was observed. In 4 persons partial response was observed (decrease in syncopal episodes) and in 6 persons no decrease in syncopal recurrence rate was observed (non-responders).

The efficacy of different theophylline doses is shown in Figures 2–4. The occurrence of syncopal episodes per year is shown in Table 2.

Theophylline treatment was started with a dosage of 2x100 mg in 13 patients. 7 patients were responders (53%) and 6 patients were partial responders. There was no non-responder in this subgroup of patients. In 6 patients (partial responders) dosage was increased to 2x300 mg.

An initial dosage of 2x200 mg was used in 22 patients. From these patients in 11 patients (50%) no syncope occurred during

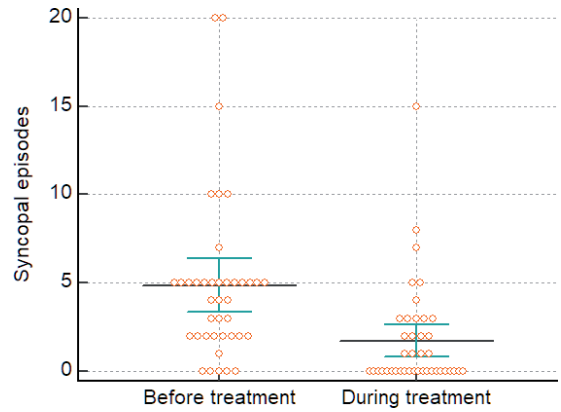

Fig. 2. Syncopal recurrence – theophylline dosage 2x100 mg (n=13).

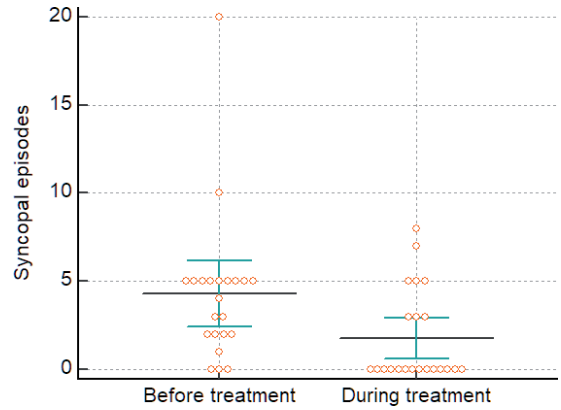

Fig. 3. Syncopal recurrence – theophylline dosage 2x200 mg (n= 22).

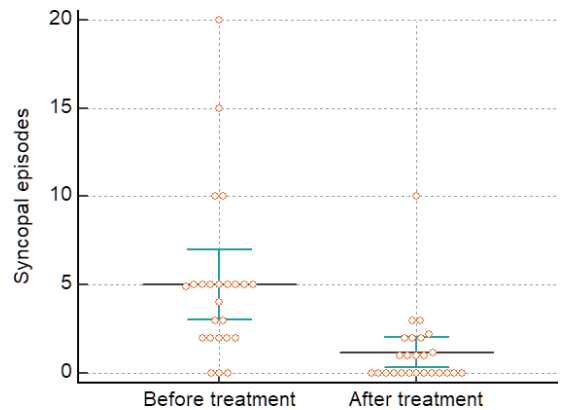

Fig. 4. Syncopal recurrence – theophylline dosage 2 x 300 mg (n= 22).

Tab. 2. Syncopal episodes/year before and during theophylline treatment.

	Episodes/year before treatment	Episodes/year during treatment	Statistical significance (p)
2x100 mg (n =13)	4.07±0.76	1.23±0.54	0.0008
2x200 mg (n =22)	4.09±1.23	3.01±1.13	0.03
2x300 mg (n =22)	5.1±1.18	1.04±0.41	0.0003
2x 400 mg (n =2)	3.75±1.25	0.25±0.25	0.17

Syncopal recurrence – theophylline dosage 2x300 mg (n= 22)

follow-up (responders). In 7 patients decrease in syncopal episodes was observed (partial response). In 4 patients no decrease in syncopal recurrences was present (non-responders). In 7 patients dosage was increased to 2x300 mg

Dosage 2x300 mg was used as initial treatment in 9 patients. In 13 patients this dosage was used in case of not adequate effectivity of lower doses (2x100 mg or 2x200 mg). 14 patients were responders to treatment (70%), in 6 patients partial response was observed. In 2 patients no response was present. In these 2 patients dosage was increased to 2x400 mg, with no further syncopal recurrences (Fig. 1).

There was no significant difference in response to treatment in different hemodynamic types of vasovagal syncope. In patients with VASIS I type the total number of syncopal episodes decreased from 4.87±1.30 to 1.41±1.01 episodes. In patients with VASIS II type the total number of syncopal episodes decreased from 5.1±1.64 to 1.43±1.21 episodes. In patients with VASIS III type the total number of syncopal episodes decreased from 4.86±1.00 to 1.74±1.18 episodes. From 16 subjects with VASIS I type were 12 responders (75%), from 10 subjects with VASIS II type were 6 responders (60%) and from 18 patients with VASIS III type were 16 responders (88%). The trend to the highest efficacy was noted in the vasodepressor type of syncope (VASIS III) and the lowest efficacy in the cardioinhibitory type of syncope (VASIS IIa +IIb). However, these differences were not statistically significant (p=0.2)

Side effects leading to discontinuation of treatment were present in 14 patients. Side effects were most frequent in patients receiving 2x300 mg of theophylline (8 patients), followed by dose 2x200 mg (5 patients). Only one patient on treatment dose 2x100 mg experienced side effects. The most common side effect was gastrointestinal intolerance (7 patients), palpitations (6 patients), and headache (3 patients). Overall, nearly one-third of patients (31%) discontinued treatment because of side effects.

Discussion

In this study, we determined the effectiveness of treatment with oral preparations of theophylline in patients with recurrent vasovagal syncope. In most patients, syncope was reduced or completely disappeared while using this treatment.

Adenosine is a purine nucleoside that plays a role in a wide range of physiological processes. It is present in almost all cells as well as in the extracellular space and plays a role in the energy transfer process in the macroergic phosphate cascade (ATP, ADP, AMP). Adenosine is also involved in pathological processes including inflammation, ischemia, necrosis, and neoplasmic changes. Adenosine is produced from adenosine monophosphate (AMP) by the enzyme ecto-5-nucleotidase and is metabolized to inosine (by adenosine-deaminase) and further to uric acid (by the action of xanthin oxidase). Adenosine acts on 4 types of receptors: AR1 (predominant in the heart), AR2A and AR2B (in blood vessels), and AR3 (in cells of the immune system, CNS, and elsewhere) (6).

The possible role of adenosine in the pathogenesis of syncope is mediated through A1 receptors in the heart and A2 receptors in blood vessels. Activation of A1 receptors has a negative chrono-, dromo- and inotropic effect. Activation of A2 receptors has a vasodilatory effect.

Both low and high adenosine levels seem to be involved in the pathogenesis of syncope**.** Groppelli observed a larger distribution of adenosine values in syncopal patients than in control subjects. High adenosine values (defined as more than 0,8 umol/l) were present in 19% and low adenosine (less than 0,4 umol/l) was present in 18% of syncopal patients. In general, higher values of adenosine blood levels in patients with likely reflex syncope compared to healthy control subjects with no history of syncope were observed (7).

Patients with low plasma adenosine show different clinical characteristics compared to patients with high adenosine levels. Patients with high adenosine levels have typical clinical features of vasovagal syncope, high ratio of head-u tilt test positivity high expression of A2A receptors, and the predominance of the CC variant in the single nucleotide c.1364 C>T polymorphism of the A2A receptor gene. On the contrary patients with low adenosine levels often exhibit syncope without prodromes, have low expression of A2A receptors, and the predominance of the TC variant in the single nucleotide c.1364 C>T polymorphism of the A2A receptor gene. The typical mechanism of syncope is paroxysmal atrioventricular block which is frequently manifested after intravenous administration of exogenous adenosine (6, 8, 9).

In patients with low baseline adenosine levels (low-adenosine syncope), an up-regulation and hypersensitivity of cardiac A1 receptors is present. Activation of A1 receptors has a negative chrono-, dromo- and inotropic effect. An increase in adenosine during orthostasis by acting on hypersensitive receptors causes significant bradycardia and asystole. The density of A1 receptors is greater in the area of the AV node than in the area of the SA node, therefore paroxysmal AV block is a typical manifestation of adenosine-sensitive syncope. Low-adenosine syncope is clinically, usually manifested by infrequent syncopal episodes, which, however, often have traumatic consequences due to the absence of prodromal symptoms (6). The diagnosis is evidenced by the finding of an asystolic pause during syncope (usually documented

by an implantable loop recorder and a low level of adenosine (below 0.5 umol/l). However, the determination of adenosine in the blood under the conditions of common clinical practice is difficult. Therefore, an alternative way of identifying this group of patients was proposed. These are patients without organic heart disease, with absent or short prodromes (less than 5 seconds) and a normal ECG. 80% of the patient population defined in this way has a low level of adenosine (4).

Although cardiac pacing is an effective method of treating this type of syncope, the possibility of pharmacological therapy with adenosine antagonists, especially theophylline, is also being considered. Candidates for theophylline therapy are patients with non-cardiac syncope under the age of 40 who are not indicated for permanent pacing according to current guidelines (10) Theophylline therapy can also be considered in patients over 40 years of age if they do not agree to the implantation of a pacemaker or as a bridge to pacemaker insertion. In a pilot study with theophylline therapy in 16 patients selected in this way, there was a significant reduction in the number of syncopal episodes and asystolic events (5). In a subsequent multicenter study, a group of 76 patients treated with theophylline at a dose of 2x300 mg per day and 58 patients in the control group were compared. In patients in the theophylline group, syncope recurred less often than in the control group (33% vs 47%). Greater effectiveness was observed in patients with paroxysmal AV block than SA block (11). Although a relatively large number of patients (39%) had to discontinue therapy due to adverse effects, theophylline therapy represents a possible treatment alternative for a selected group of patients with syncope (12).

In patients with vasovagal syncope, higher levels of adenosine are observed compared to the normal population. Saadjian reported higher levels and a significant rise in adenosine during the HUT (13). In addition to higher levels of adenosine, Franscheschi also described a reduced expression of AR2, which can be interpreted as a consequence of their downregulation (14). Vasovagal syncope can be induced by exogenous administration of adenosine during HUT and this approach was also adopted as an alternative method of pharmacological stimulation during HUT (15).

The affinity of A1 receptors to adenosine is higher compared to A2 receptors. The rise of adenosine levels in the emerging vasovagal syncope (high-adenosine syncope) leads predominantly to the activation of vascular AR2 receptors with resulting vasodilation. All available A1R receptors are already saturated at baseline (because of their higher affinity to adenosine), the bradycardic effect is relatively milder, and variable, and asystole occurs only in some patients (16).

Our recently published study showed that in patients with vasovagal syncope higher levels of adenosine are present at baseline as well as at the time of tilt-induced syncope compared to tilt-negative controls. We also described higher adenosine levels in the vasodepressor type compared to cardioinhibitory and mixed types of vasovagal syncope. These findings point to the fact that the vasodepressive effect of adenosine on vascular A2R receptors may play a pathogenetic role in vasovagal syncope. Another finding of our study is that the rise of adenosine levels in vasovagal syncope is a consequence of insufficient adenosine clearance by adenosine deaminase. In patients with a positive HUT, the adenosine-deaminase level does not rise in contrast to patients with a negative HUT (3).

The vasodilatory effect of adenosine was shown in experimental animals as well as in humans. Adenosine infused into the brachial artery increased forearm blood flow by more than 500%. This response was significantly attenuated by concomitant intra-arterial infusion of theophylline but not by enprofylline (xanthine derivate with very low affinity to purinergic receptors)(17).

The use of oral theophylline was focused mainly on patients with low–adenosine syncope up to now (9). However, there is a theoretical basis for the administration of theophylline also in high adenosine (vasovagal) syncope which is supported by favorable results of the present observational study.

The present study showed that theophylline may be an effective drug in the prevention of vasovagal syncope recurrences in patients who do not respond to standard non-pharmacological treatment. This effect may be related to the blockade of vascular AR2a receptors, the activation of which leads to vasodilation and hypotension. To the best of our knowledge, only one work has been published in the available literature, which followed the effect of long-term treatment with theophylline in patients suffering from vasovagal syncope. Nelson administered theophylline at a dose of 6–12 ug/kg/day and demonstrated a reduction in spontaneous syncopal episodes in patients with vasovagal syncope. From the treated group, 82% of patients did not experience syncope during the control HUT, and 18% had a longer overall tolerated time. However, the study included only 20 patients (18).

The main limitation of the study was the absence of the control group. After head-up tilt test, the frequency of syncopal spells decreases without any treatment. Syncope likelihood decreases in both observational studies and the control arms of randomized trials for vasovagal syncope (19). It was reported that syncope recurred only in 30–87% of patients with no therapy (20,21) and the total number of syncopal spells decreased during one–year follow-up by 9% (22). In our study, we observed a much greater reduction in syncopal recurrences after theophylline treatment than an expected spontaneous decline in syncope occurrence.

Another important limitation is the absence of adenosine plasma level vales in study participants which would confirm the anticipated high plasma adenosine levels. However, for the majority of treating physicians, these data will be unavailable soon due to the lability of adenosine in blood samples and the complicated laboratory method of plasma level determination. Their diagnosis will be similar to in the present study based on clinical characteristics and results of HUT

Conclusion

The addition of the oral theophylline preparation to non -pharmacological treatment led to a marked reduction of syncopal recurrence in patients with typical clinical features of vasovagal syncope and positive head-up tilt test. Side effects were relatively

frequent in the study group. About one-third of study subjects discontinued therapy because of side effects.

The results of the study should be interpreted with caution because the placebo effect of the medication cannot be excluded due to the study one one-arm non-randomized design. This study should be considered far more as hypothesis generating, rather than seen as a definitive allegation of theophylline efficacy. However, there is a pathophysiological rationale behind this treatment, and in our opinion results of the present non-randomized study generate the need for further studies with a larger participant number and placebo-controlled design.

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