The effect of atropine in vasovagal syncope induced by head-up tilt testing

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Aims This single-blinded, randomized, placebo-controlled study was designed and undertaken to assess the efficacy of intravenous atropine administration on haemodynamic impairment induced by head-up tilt testing in patients with vasovagal syncope.

Methods and Results One hundred and thirteen consecutive patients (62 male and 51 female, mean age 46·3 years) with recurrent syncope, no evidence of cardiac, neurological or metabolic disease and a positive head-up tilt test were included in the study. Within 2 weeks of the first head-up tilt test all patients underwent a second tilt test. During this second test, all patients were randomized to receive a bolus of either atropine (0·02 mg . kg\(^{-1}\)) or placebo (isotonic saline solution). The administration of atropine or placebo was performed at the onset of the haemodynamic modifications (heart rate and/or blood pressure fall) in conjunction with typical vasovagal prodromal symptoms. Treatment was taken as effective when symptoms aborted and the test was completed. In 29 of 113 patients the second tilt test was negative and these patients were excluded from final data analysis. Forty-one patients received placebo, which was effective in nine cases (21·9%). Atropine was administered to 43 patients and was effective in 30 cases (69·7%, \(P<0·01\) vs placebo). The effects of treatment were analysed further to consider the haemodynamic patterns of tilt-induced vasovagal reflex. In the cardio-inhibitory form, placebo was never effective (15 cases), while atropine was effective in 15 of 18 cases (83·3%, \(P<0·001\) vs placebo). In the vasodepressor form, placebo was effective in nine of 26 patients (34·6%), while atropine was effective in 15 of 25 cases (60·0%, no significant difference vs placebo).

Conclusions Atropine is fully effective in the cardio-inhibitory form of tilt-induced vasovagal reflex, but is limited in the vasodepressor form.

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Introduction

Vasovagal syncope appears to result from a circulatory disturbance in which both an inappropriate heart rate response (cardio-inhibition) and a reduction in systemic vascular tone (vasodepression) lead to inadequate cerebral perfusion and fainting\(^{[1,2]}\). While bradycardia is thought to be the result of increased efferent parasympathetic activity, hypotension is possibly related to sudden sympathetic withdrawal\(^{[1,2]}\).

Head-up tilt testing has recently become a widely used method for the clinical assessment of patients with recurrent syncope of unknown origin, as it provides evidence of the possible vasovagal nature of a syncopal episode\(^{[3,4]}\). Moreover, during such a procedure a controlled orthostatic stress is delivered and detailed observations on the pathophysiological events taking place during a vasovagal spell can be performed. Therefore, this methodology has been used as an experimental model for the assessment of acute therapeutic interventions in the setting of vasovagal syncope\(^{[5]}\). The introduction of tilt testing in clinical practice has enabled the two main forms of vasovagal compensation to be identified\(^{[6,7]}\): (1) a vasodepressor form, in which a sudden reduction of arterial blood pressure without significant bradycardia, represents the main haemodynamic feature; (2) a cardio-inhibitory form, in which a relevant bradycardia is associated with hypotension.

The treatment of recurrent vasovagal syncope is still a matter of dispute, as neither pharmacological interventions nor cardiac pacing have proven clearly effective in all instances\(^{[8,9]}\). Both dual chamber cardiac pacing and chronic oral therapy, with several different drugs (beta-blockers, disopyramide, anticholinergic agents, alpha-agonists, theophylline, fludrocortisone)\(^{[8,9]}\) have been...
proposed for the prevention of vasovagal syncope. Cardiac pacing is expected to relieve syncope symptoms in those patients with a predominant cardio-inhibitory form of vasovagal syncope, but has been less effective in treating the vasodepressor variant of the syndrome[10,11]. On the other hand, the pharmacological therapy currently employed in the treatment of vasovagal syncope is possibly more effective in vasodepressor forms, but has several limitations[12]: (1) it is usually empirically prescribed, with unpredictable efficacy; (2) treatment should be long term, even if vasovagal episodes seem to appear in clusters; (3) treatment is often withdrawn owing to side effects or adverse reactions. Consequently, the limitations of the available therapies have prompted further studies aimed at developing new options for the long-term treatment of recurrent vasovagal syncope. A combined device-pharmacological approach may theoretically represent an effective new opportunity. In particular, ad hoc implantable drug delivery devices are currently under investigation, as such infusion systems may allow an automatic ‘on demand’ administration of a bolus of an active drug in the course of a vasovagal spell[13,14]. However, no data are available about the correct timing and the possible efficacy in contrasting a vasovagal reflex of such mode of drug administration. Even if several agents have been proposed for this use, no available drug has ever been tested[13,14].

The anticholinergic agent atropine is regularly and effectively used in several clinical settings for the immediate relief of vagal symptoms, without significant side effects or adverse reactions[15,16]. However, since the original report from Lewis[17], atropine has been considered only partially effective in treating vasovagal spells, as such a drug is expected to resolve the bradycardia, but not the hypotension, in the course of a vasovagal episode[18]. On the other hand, available data concerning the efficacy of atropine in the treatment of vasovagal syncope are far from conclusive, owing to the limited number of patients studied[19,20].

In a single-blinded, randomized, placebo-controlled clinical investigation we studied the efficacy of intravenous atropine in the haemodynamic impairment induced by head-up tilt testing in patients with vasovagal syncope.

Methods

Patient selection

Patients from the outpatient department of our institution were considered eligible for inclusion in the study if all the following criteria were met: (1) recurrent unexplained syncope (at least two syncopal spells in the preceding 6 months); (2) no clinical or laboratory evidence of cardiac, neurological or metabolic disease; (3) a positive head-up tilt table test. One hundred and thirteen consecutive patients (62 females and 51 males; mean age 46.3 ± 16.7 years) fulfilled the inclusion criteria and provided written informed consent to take part in the study.

Study protocol

The study protocol was submitted to the ethical committee of our institution and approved. Within 2 weeks of the first positive head-up tilt table test, all included patients underwent a second tilt table test; both tests were performed according to the Westminster protocol (passive tilt without any pharmacological provocation at 60° for 45 min[21]). The tests were performed in the morning in fasting state; no pharmacological therapy had been started. An electronically controlled tilt table with a foot-board for weight-bearing and restraining belts was used for the procedures. Continuous electrocardiographic monitoring of heart rate and rhythm was performed, while blood pressure was measured non-invasively beat-to-beat by means of an Ohmeda Finapress 2300 (Louisville, Colorado, U.S.A.) photoplethysmographic device. In all patients a 20G heparin-cathed cannula was inserted in the antecubital vein before the procedure. During the second head-up tilt test, patients were randomized to receive a bolus of either atropine sulphate (1% solution, 0.02 mg . kg \(^{-1}\)) as active treatment, or isotonic saline solution (5 ml) as placebo via the previously cannulated antecubital vein. The administration of atropine or placebo during the tilt test was performed by a physician at the onset of the haemodynamic modifications (heart rate and/or blood pressure fall) in conjunction with typical prodromal vasovagal symptoms (nausea, light-headedness, vertigo, epigastric discomfort, diaphoresis). Patients were unaware of which substance was intravenously injected during the test. Intravenous treatment was taken as effective when symptoms aborted and the test was completed.

In accordance with previous reports[6,7], two main forms of positive response to the tilt table test were identified: (1) a vasodepressor form (syncope associated with a decrease in systolic blood pressure to 60 mmHg or less, but without significant heart rate reduction); (2) a cardio-inhibitory form (syncope associated with a decrease in systolic blood pressure to 60 mmHg or less, and a heart rate reduction to less than 40 beats . min \(^{-1}\))

Statistical analysis

All collected data are expressed as mean ± SD and analysed by Fisher’s exact test.

Results

In 29 out of 113 patients (25.6%, 12 males and 17 females; mean age 45.8 ± 12.8 years) the second tilt table
test performed after inclusion in the study was negative, thereby giving a short-term positive tilt table test reproducibility of 74.4%. In these cases, no intravenous treatment was administered and these subjects were excluded from the final data analysis.

**Placebo group**

Forty-one patients received intravenous placebo during the second tilt table test (19 males and 22 females; mean age 46.3 ± 16.4 years). Placebo was effective in nine cases (21.9%; four males and five females, mean age 45.5 ± 9.8 years), while the remaining 32 patients (78.1%; 15 males and 17 females, mean age 47.7 ± 17.1 years) experienced syncope after placebo administration (Fig. 1).

When considering the different forms of tilt-induced vasovagal reflex, the following results were noted:

1. Twenty-six patients (63.4%, 11 males and 15 females) had a vasodepressor vasovagal reflex: in nine patients (34.6%, four males and five females) the placebo was effective, while the remaining 17 patients (65.3%, seven males and 10 females) experienced syncope (Fig. 2).

2. Fifteen patients (36.6%, eight males and seven females) developed a cardio-inhibitory vasovagal reflex and all of them experienced syncope despite the administration of placebo (Fig. 3).

**Active treatment group**

Forty-three patients received intravenous atropine during the second tilt table test (20 males and 23 females, mean age 45.8 ± 12.9 years). The drug was effective in 30 cases (69.7%, 15 males and 15 females, mean age 46.1 ± 13.7 years), while the remaining 13 patients (30.3%, five males and eight females, mean age 45.9 ± 9.7 years) had syncope despite atropine administration (P<0.01 vs placebo) (Fig. 1). When considering the different forms of vasovagal reflex during the tilt table test the following results were noted:

1. Twenty-five patients (58.1%, 11 males and 14 females) had a vasodepressor vasovagal reflex: in 15 subjects (60.0%, seven males and eight females) atropine was effective, while the remaining 10 (40.0%, four males and six females) experienced syncope despite treatment (no significant difference vs placebo) (Fig. 2).

2. Eighteen patients (41.9%, nine males and nine females) developed a cardio-inhibitory vasovagal reflex: in 15 subjects (83.3%, eight males and seven females) atropine was effective, while the remaining three (16.7%, one male and two females) experienced syncope despite treatment (P<0.001 vs placebo) (Fig. 3).

**Haemodynamic modifications after atropine administration during tilt-induced vasovagal reflex**

1. Vasodepressor vasovagal reflex.

When effective in resolving vasovagal symptoms (15 patients), atropine administration was followed by a rapid increase in heart rate (mean peak heart rate of 157.8 ± 29.8 beats . min⁻¹, reached within 43.7 ± 13.9 s of atropine administration, mean heart rate increase of 53.6 ± 17.9 beats . min⁻¹; mean percentage in heart rate increase of 58.6 ± 8.7%) and minor variations in blood pressure (Fig. 1). On the other hand, in patients who experienced syncope (10 cases), severe hypotension developed despite atropine administration (mean reduction in systolic blood pressure of 74.8 ± 11.8 mmHg), together with a less relevant heart rate increase (mean peak heart rate of 129.6 ± 37.4 beats . min⁻¹, reached within 41.9 ± 11.9 s; mean heart rate increase of 23.7 ± 12.9 beats . min⁻¹; mean percentage in heart rate increase of 26.5 ± 11.4%) (Fig. 4).
(2) Cardio-inhibitory vasovagal reflex.
When atropine was effective (15 patients), a sudden increase in heart rate was noted (mean peak heart rate of 136·8 ± 27·8 beats . min⁻¹, reached within 39·4 ± 13·8 s; mean increase of 67·8 ± 23·9 beats . min⁻¹; mean percentage in heart rate increase of 87·5 ± 27·9%), in conjunction with minor variations in blood pressure. When syncope developed (three cases), a severe bradycardia (mean reduction in heart rate of 59·5 ± 17·7 beats . min⁻¹) and hypotension (mean reduction in systolic blood pressure of 63·8 ± 21·6 mmHg) were noted despite atropine administration (Fig. 5).

Haemodynamic modifications after placebo administration during tilt-induced vasovagal reflex

(1) Vasodepressor vasovagal reflex.
Placebo administration was associated with a mild increase in heart rate (mean increase of 17·6 ± 11·8 beats . min⁻¹; mean percentage in heart rate increase of 18·6–14·7%) and a reduction in blood pressure (mean reduction in systolic blood pressure of 27·8 ± 13·7 mmHg) in patients who did not experience syncope (nine patients). While severe hypotension (mean reduction in systolic blood pressure of 69·5 ± 26·8 mmHg) without relevant variations in heart rate, was noted in those patients who had a syncopal spell (17 cases) (Fig. 4).

Figure 3 Efficacy of atropine and placebo in tilt-induced cardio-inhibitory vasovagal syncope. □=syncope; □=no syncope.

Figure 4 Heart rate (HR) and systolic blood pressure (SBP) behaviour (mean values) after the administration of atropine or placebo in patients with tilt-induced vasodepressor vasovagal syncope (— ● — = atropine effective; — ■ — = atropine not effective; — ▲ — = placebo effective; — □ — = placebo not effective).
All patients with a cardio-inhibitory vasovagal reflex who received placebo experienced syncope in conjunction with severe bradycardia (mean reduction in heart rate of $63.7 \pm 25.7$ beats min$^{-1}$) and hypotension (mean reduction in systolic blood pressure of $73.7 \pm 34.9$ mmHg).

**Discussion**

In clinical practice, atropine is constantly and effectively used to treat abnormal vagal reflexes inducing bradycardia and hypotension$^{[15,16]}$. This drug has a pure anticholinergic action, which is responsible for its parasympatholitic effect$^{[15]}$ and is therefore expected to antagonize the bradycardia due to the sudden increase of efferent vagal activity during a vasovagal reflex$^{[15,16]}$. Furthermore, as active cholinergic vasodilatation of the peripheral vascular bed may have a role in the genesis of vasovagal fainting, atropine could also contribute to relieve vasovagal vasodepression$^{[22]}$. Previous experiences employing atropine in the treatment of vasovagal syncope have been disappointing, but should not be taken as conclusive, owing to the limited number of patients studied and the absence of controls$^{[15,16,19,20]}$. In this study, the efficacy of the anticholinergic agent atropine in contrasting and resolving a vasovagal episode was tested in a controlled setting, using a tilt-induced vasovagal reflex as an experimental model. In the overall study population, atropine proved significantly more effective than placebo in causing the resolution of a tilt-induced vasovagal spell ($P<0.01$). However, when the effects of active treatment were analysed, taking into account the specific haemodynamic patterns of the tilt-induced vasovagal reflex, atropine efficacy was found to be related mainly to the positive effect shown in those patients with a cardio-inhibitory form ($P<0.001$). In patients with a vasodepressor form of vasovagal reflex, the difference between atropine and placebo in the reflex did not reach statistical significance, despite a trend in favour of atropine.

Assessment of the haemodynamic modifications following both atropine and placebo administration at the onset of the tilt-induced vasovagal reflex allowed further considerations. While placebo was never effective in modifying the course of a cardio-inhibitory tilt-induced vasovagal reflex, atropine was almost fully effective in such a condition. In fact, in these cases the anticholinergic drug determined a striking increase in heart rate of more than 80%, which maintained cerebral perfusion despite the possible concomitant vasodepression. Furthermore, in the vasodepressor form of tilt-induced vasovagal reflex, atropine was found to be effective only when it succeeded in inducing an increase in heart rate of more than 50%. In general, atropine appeared to be effective when it caused a relevant tachycardia, possibly providing a sufficient cardiac output to overcome the effects of vasodepression. Such observations on atropine efficacy are in keeping with reported clinical experiences on the effects of cardiac pacing employing high rates of pacing intervention in vasovagal syndromes$^{[23,24]}$. Inappropriate cardiac slowing, due to a sudden increase in efferent vagal activity, and diffuse arteriolar dilatation by a reduction of sympathetic outflow, are considered the pathophysiological hallmarks of a vasovagal reflex$^{[1,2]}$. Consequently, the ideal treatment of recurrent

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*Figure 5*  Heart rate (HR ■) and systolic blood pressure (SBP ▲) behaviour (mean values) in the 15 patients with cardio-inhibitory syncope abortion after atropine administration.

(2) Cardio-inhibitory vasovagal reflex.
vasovagal syncope has been aimed at reversing both neuromediated circulatory disturbances. In clinical practice, the appropriate treatment of recurrent vasovagal syncope markedly differs among patients. In most individuals, especially those with sporadic episodes, reassurance and instructions regarding avoidance of potential traumatic injuries represent the only interventions warranted. However, additional therapeutic interventions are necessary when syncope recurrence impairs quality of life and imparts increased risk in everyday activity[1,2]. At present, treatment options for recurrent vasovagal syncope may be broadly classified as chronic oral pharmacological therapy and cardiac pacing[3,4]. Such therapeutic approaches have different aims, a drug therapy should be effective in preventing the development of the vasovagal reflex, while cardiac pacing is expected to eliminate the reflex just after its appearance. Despite the existence of a substantial number of publications on both pharmacological and pacing treatments for vasovagal syncope, the efficacy of any specific option is still uncertain[5]. In particular, a major limitation of all employed options is represented by the fact that vasovagal syncope tends to recur in clusters, leaving long periods free of symptoms, while severely disturbing short but significant periods of life[1,2,5]. Consequently, the possibility of a specific intervention limited to a single vasovagal episode is appealing. When provided with an effective diagnostic algorithm for the recognition of impending syncope and employed in carefully selected patients, cardiac pacing may represent a valuable therapeutic approach[6]. However, cardiac pacing is unlikely to be fully effective when a relevant vasodepression dominates the clinical picture of a vasovagal spell[7].

The limits of the available therapies have therefore prompted further studies aimed at the development of new options for the long-term treatment of recurrent vasovagal syncope. In particular, specific implantable devices are currently under investigation and should ideally couple the best available cardiac pacing mode with the possibility of delivering an active drug in the course of a vasovagal attack[8,9]. This particular combined therapeutic strategy should be effective in resolving both the cardio-inhibition and the vasodepression taking place during the vasovagal episode. These new devices should have several different features (1) a diagnostic element allowing automatic detection of an incipient vasovagal attack; (2) the possibility of patient-activated treatment intervention; (3) a drug delivery element allowing automatic administration of an intravenous bolus of an active drug; (4) a dual chamber cardiac pacemaker; (5) a data storage unit to record interventions.

Several different sensors have been proposed for reliable early recognition of an imminent vasovagal spell[10,11], while no data are currently available as to the most appropriate drug to be used in these new evolving implantable devices[12]. The appropriate drug should be effective in resolving the vasovagal reflex, but should also demonstrate specific chemical and pharmacological features. The ideal compound has to be stored in low-capacity implanted reservoirs for long periods of time, so it has to be chemically stable for long periods of time at body temperature in high concentrations. Moreover, this drug has to be fast-acting to relieve symptoms immediately, while showing a brief duration of action to minimize possible side effects and adverse reactions[13]. Few agents effective in inhibiting vasovagal events have these properties. However, the anticholinergic agent atropine has all the previously described chemical and pharmacological features (long-term stability in high concentrations at body temperature, immediate onset of action, brief duration of action) and is therefore theoretically suitable for use in an implantable infusion pump[14]. Moreover, as shown in this study, when correctly delivered in appropriate doses during a vasovagal episode, this drug may induce a relevant increase in heart rate, and is possibly effective in maintaining cerebral perfusion, despite the concomitant hypotension.

In our opinion, this study provides clear evidence that a drug can be effectively delivered, on the basis of both prodromal symptoms and haemodynamic modifications, to prevent a vasovagal reflex at its onset. However, the limited effectiveness of atropine, in inhibiting the vasodepressor component of the vasovagal reflex, makes this drug a possible second-line option for future use in drug-delivery devices. Consequently, further investigations are needed to assess the possible use of other agents that should share the specific pharmacological properties owned by atropine, but also have a wider range of effectiveness in the setting of vasovagal syncope.

References


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