COMMENT

β-Adrenergic receptor blockers and the treatment of vasovagal syncope: more nails in the coffin!

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ABSTRACT

β-Adrenergic receptor blockers are one of a number of therapeutic agents promoted as having beneficial effects in vasovagal syncope. In this issue of Clinical Science, Eldadah and co-workers have investigated the effect of the β-adrenergic receptor blocker propranolol in preventing syncope in a double-blind cross-over trial in eight subjects with a diagnosis based on tilt table testing and elevated plasma adrenaline levels during syncope. Of these, seven did not respond and the authors therefore suggest that this drug has no role in the management of vasovagal syncope. Their laboratory-based study, however, raises a number of issues regarding terminology, choice of subjects, the value and role of investigations directed towards diagnosis and in understanding pathophysiological mechanisms, and the relevance of such trials to individual subjects with vasovagal syncope.

β-Adrenergic receptor blockers are one of a number of therapeutic agents promoted as having beneficial effects in vasovagal syncope. This is a common condition that affects all age groups. It also is known as ‘common’ or ‘emotionally induced’ fainting. It falls under the umbrella of neurally mediated syncope (also referred to as reflex syncope), which is a condition characterized by intermittent dysfunction of the autonomic nervous system [1]. This causes withdrawal of sympathetic tone resulting in vasodilatation and thus hypotension, and an increase in parasympathetic (vagal) activity resulting in bradycardia. Vasodepression, cardio-inhibition or the combination of the two reduce cerebral blood flow thus causing syncope, especially in the upright position. The prognosis in vasovagal syncope usually is favourable even if untreated, unlike certain other causes of neurally mediated syncope, and especially in syncope caused by cardiac dysrhythmias. However, in vasovagal syncope, the uncertainty of attacks, the potential for trauma, possible difficulties with driving and limitations in pursuing certain jobs all contribute to concerns and morbidity.

A number of stimuli are often recognized as provoking an episode of vasovagal syncope [2]. These include fear of needles, blood and pain, in addition to situations predisposing to a fall in blood pressure when upright, such as intense heat, impaired fluid repletion and excessive fluid loss. The precise mechanisms resulting in vasovagal syncope, whether central, peripheral or both, often are unclear. Various humoral agents, and in particular those that cause vasodilatation, have been postulated as being causative or contributory. These include adrenaline, which in some studies is elevated during a syncopal episode. This has provided the theoretical basis for the use of β-adrenergic receptor blockers in vasovagal syncope. Thus it seems likely that blockade of vasodilatory β2 receptors with a non-selective blocker such as propranolol will be more effective than a cardioselective β1 blocker.

Key words: adrenaline, β-blocker, neurally mediated hypotension, tilt testing, vasovagal syncope.
Abbreviation: PoTS, postural tachycardia syndrome.
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In this issue of *Clinical Science*, the effect of propranolol in preventing syncope is reported [3] in a double-blind cross-over trial in eight subjects with a laboratory-confirmed diagnosis based on tilt table testing and elevated plasma adrenaline levels during syncope. Of these, seven did not respond, and the authors [3] therefore suggest that this drug has no role in their management. The study, however, raises a number of issues in vasovagal syncope regarding terminology, choice of subjects, the value and role of investigations directed towards diagnosis and in understanding pathophysiological mechanisms, and the relevance of such trials to individual patients.

Clarity in defining the disorder, and in the nomenclature used, is necessary. The term neurally mediated syncope has a major advantage as it indicates a neurogenic cause through the autonomic nervous system that affects blood vessels, the heart, or both, thus resulting in syncope [4]. It encompasses a number of disorders, including the most common of them, vasovagal syncope, that may present at any age. In infants and young children, reflex anoxic syncope [5], which has both similarities and differences to vasovagal syncope, needs to be considered. In the elderly, carotid sinus hypersensitivity is increasingly recognized [6]. Miscellaneous causes include micturition syncope and rarer disorders such as those associated with glossopharyngeal neuralgia and tumours [7]. In the study by Eldadah et al. [3], the term ‘neurocardiogenic’ was used synonymously with vasovagal syncope. This is misleading as it implies neural mechanisms affecting the heart only. There are three subtypes of vasovagal syncope: cardio-inhibitory (with vagal activation), vasodepressor (with vasodilatation secondary to sympathetic withdrawal) and combined (mixed). The combined form is the most common. Identification of the subtype is important as the management varies; when marked cardio-inhibition is present, a cardiac demand pacemaker is more likely to be of benefit.

Investigations in vasovagal syncope focus on confirming the diagnosis, determining the subtype and, ideally, understanding the pathophysiological mechanisms [8]. Tilt table testing is a key investigation. Alone it may not provoke an episode in the laboratory. In vasovagal syncope induced by needles or blood, head-up tilt in combination with venepuncture (or even pseudovenepuncture) [9] often induces an episode. Whether laboratory mimicry provides a measure of what occurs in real life remains unclear, but often is the basis of diagnosis and of therapeutic strategies. Head-up tilt even with needle provocation may not induce a vasovagal episode, especially when nausea or pain is the key initiating stimulus. Some therefore advocate supraphysiological measurements (such as lower body negative pressure), or a pharmacological stimulus (often a vasodilator), to induce an episode. This, however, raises questions about the relevance of laboratory-based testing to the real-life clinical situation. There also is a further issue about reproducibility of tilt table testing. Recent studies in subjects with an implanted loop recorder indicate differences with tilt table and drug challenge studies; with the loop recorder, however, a major deficiency is lack of blood pressure data [10].

Syncope sometimes may occur without a fall in either blood pressure or heart rate, as in patient 4 in the study by Eldadah et al. [3]. Some argue that this may result from cerebral vasoconstriction alone; hyperventilation may be a contributing factor in this response. Alternatively, it may indicate an ‘apparent’ loss of consciousness, as in pseudosyncope. This diagnosis is extremely difficult to confirm and may co-exist with vasovagal syncope, which complicates matters further [11].

The effect of the trial drug used by Eldadah et al. [3] on associated disorders that contribute to the condition needs consideration. One patient (patient 4) had a substantial tachycardia during head-up tilt of over 30 beats/min, consistent with PoTS (postural tachycardia syndrome). A recent study [12] indicates that approx. 25 % of subjects with PoTS have vasovagal syncope confirmed with a laboratory event. Some subjects with PoTS respond to β-adrenergic receptor blockers, presumably by reducing tachycardia, which precedes the vasovagal episode. Syncope also is more frequent in migraine sufferers [13]. β-Blockers, including propranolol, may reduce or prevent migrainous headaches [4], and in individual cases may reduce the frequency of syncopal episodes, consistent with clinical experience.

This study by Eldadah et al. [3] also emphasizes the possible errors that may result from meta-analysis. The studies included in such analyses may vary in the type of drug, the dosage, inclusion and exclusion criteria, and techniques to monitor benefit. There are likely to be difficulties especially in a heterogenous disorder such as vasovagal syncope. A previous meta-analysis of vasovagal syncope [14] suggested that non-selective β-blockers were more likely to be effective than cardioselective blockers, but this was not confirmed in the detailed study with propranolol [3]. Two other studies [15,16] also indicate that neither cardioselective nor non-selective β-blockers are effective.

In conclusion, therefore, the study by Eldadah et al. [3] has demonstrated clearly that the non-selective β-adrenergic receptor blocker propranolol was ineffective in preventing vasovagal syncope in a small group of subjects. Indirectly, it has raised a number of issues concerning diagnosis, investigation and management of this extremely common but complex disorder.

REFERENCES

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