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## **Beta adrenergic receptor blockers and the treatment of vasovagal syncope – more nails in the coffin!**

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## ABSTRACT

$\beta$ -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  $\beta$ -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 trial to individual subjects with vasovagal syncope.

Beta-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 characterised by intermittent dysfunction of the autonomic nervous system<sup>(1)</sup>. This causes withdrawal of sympathetic tone resulting in vasodilatation and thus hypotension, and an increase in parasympathetic (vagal) activity resulting in bradycardia. Vasodepression, cardioinhibition or the combination, reduce cerebral blood flow thus causing syncope, especially in the upright position. The prognosis in vasovagal syncope 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 often are recognised as provoking an episode of vasovagal syncope<sup>(2)</sup>. 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 beta-adrenergic receptor blockers in vasovagal syncope. Thus, it seems likely that blockade of vasodilatory beta-2 receptors (with a non-selective blocker such as propranolol), will be more effective than cardioselective beta-1 blockers.

In this issue the effect of propranolol in preventing syncope is reported in a double-blind crossover trial in 8 subjects with a laboratory confirmed diagnosis based on tilt table testing and elevated plasma adrenaline levels during syncope<sup>(3)</sup>. Of these 7 did not respond and the authors therefore suggest that this drug has no role in their management. Their 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. 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<sup>(4)</sup>. It encompasses a number of disorders, including the most common, vasovagal syncope that may present at any age, often in the teenage years. In infants and young children, reflex anoxic syncope<sup>(5)</sup>, which has both similarities and differences to vasovagal syncope needs to be considered, while in the elderly, carotid sinus hypersensitivity increasingly is recognised<sup>(6)</sup>. Miscellaneous causes include micturition syncope, and rarer disorders such as associated with glossopharyngeal neuralgia and tumours<sup>(7)</sup>. In the study by Eldadah et al. <sup>(3)</sup>, the term 'neurocardiogenic' was used, synonymously with vasovagal syncope. This is misleading, as it implies neural mechanisms affecting the heart only. There are three sub-types 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 sub-type is important as the management varies; in the cardioinhibitory form a cardiac pacemaker is more likely to be of benefit.

Investigations in vasovagal syncope focus on confirming the diagnosis, determining the sub-type and ideally understanding the pathophysiological mechanisms<sup>(8)</sup>. 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 pseudo puncture)<sup>(9)</sup> 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 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 measures (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<sup>(10)</sup>.

Syncope sometimes may occur without a fall either in blood pressure or heart rate, as in Patient 4<sup>(3)</sup>. 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<sup>(11)</sup>.

The effect of the trial drug 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 bpm, consistent with the postural tachycardia syndrome (PoTS). A recent study indicates that approximately 25% of PoTS subjects have vasovagal syncope confirmed with a laboratory

event<sup>(12)</sup>. Some PoTS subjects respond to beta adrenergic receptor blockers, presumably by reducing tachycardia which precedes the vasovagal episode. Syncope also is more frequent in migraine sufferers<sup>(13)</sup>. Beta blockers, including propranolol, may reduce or prevent migrainous headaches<sup>(4)</sup>, and thus may reduce the frequency of syncopal episodes, consistent with clinical experience.

This study<sup>(3)</sup> also emphasises 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<sup>(14)</sup> suggested that non-selective beta blockers were more likely to be effective than cardioselective blockers, but this was not confirmed in the detailed study with propranolol<sup>(3)</sup>. Two other recent studies also indicate that neither cardio-selective nor non-selective beta blockers are effective<sup>(15,16)</sup>.

In conclusion therefore, this study has demonstrated clearly that the non-selective beta adrenergic receptor blocker propranolol was ineffective in preventing vasovagal syncope in a small group of subjects. It indirectly has raised a number of issues concerning diagnosis, investigation and management of this extremely common but complex disorder.

## References

- 1) Mathias CJ. To stand on one's own legs. *Clin Med* 2002; **2**: 237-245
- 2) Ganzeboom KS, Colman N, Reitsam JB, Shen WK, Wieling W. Prevalence and triggers for syncope in medical students. *Am J Cardiol*, 2003; **91**: 1006-1008
- 3) Eldadah BA, Pechnik SL, Holmes CS, Moak JP, Saleem AM, Goldstein DS. Failure of propranolol to prevent tilt-evoked system vasodilatation, adrenaline release and neurocardiogenic syncope. *Clin Sci* 2006 (in press).
- 4) Mathias CJ. Orthostatic hypotension and orthostatic intolerance. In: *Endocrinology*. 5<sup>th</sup> ed. Eds. LJ DeGroot, JL Jameson, D de Kretser, AB Grossman, JC Marshall, S Melmed, JT Potts, GC Weir. Elsevier Saunders, Philadelphia PA, USA 2006, 2613-2632
- 5) Stephenson JBP, Whitehouse W, Zuberi SM. Paroxysmal non-epileptic disorders: differential diagnosis of epilepsy. In: Wallace SJ, Farrell K (eds). *Epilepsy in Children*. Arnold, London. P4-20
- 6) McIntosh SJ, Lawson J, Kenny RA. Clinical characteristics of vasodepressor, cardioinhibitory and mixed carotid sinus syndrome in the elderly. *Am J Med* 1993; **95**: 203-208
- 7) PF Worth, JC Stevens, F Lasri, S Brew, MM Reilly, CJ Mathias, P Rudge. Syncope associated with pain as the presenting feature of neck malignancy: failure of cardiac pacemaker to prevent attacks in two cases. *J Neurol Neurosurg Psychiatry* 2005, **76**:1301-1303
- 8) Mathias CJ. Role of autonomic evaluation in the diagnosis and management of syncope. *Clin Auton Res* 2004, **14**; S1, 45-54
- 9) Mathias CJ, Deguchi K, Schatz I. Observations on recurrent syncope and presyncope in 641 patients. *Lancet* 2001, **357**; 348-353
- 10) Deharo J-C, Jegou C, Lanteaume A, Djiane P. An implantable loop recorder study of highly symptomatic vasovagal patients: The heart rate rhythm observed during a spontaneous



syncope is identical to the recurrent syncope but not correlated with the head-up tilt test or adenosine triphosphate test. *J Am Coll Cardiol* 2006; **47**: 587-593

11) Mathias CJ, Deguchi K, Bleasdale-Barr K, Smith S. Familial vasovagal syncope and pseudosyncope: observations in a case with both natural and adopted siblings. *Clin Auton Res* 2000, **10**; 43-45

12) Hajdinjak M, Harris S, Corridan M, Scott H, Watson L, Stivali G, Mathias CJ. Diagnosing postural tachycardia syndrome – head-up tilt or standing? *Clin Auton Res* 2006, **16**; 156-157

13) Thijs RD, Kruit MC, van Buchem MA, Ferrari MD, Launer LJ, van Dijk JG. Syncope in migraine. *Neurology* 2006, **66**; 1034-1037

14) Dendi R, Goldstein DS. Meta-analysis of non-selective versus beta-1 adrenoceptor-selective blockade in prevention of tilt-induced neurocardiogenic syndrome. *Am J Cardiol* 2002, **89**; 1319-1321

15) Flevari P, Livanis EG, Theodorakis GN, Zarvalis E, Mesiskli T, Kremastinos DR. Vasovagal syncope: a prospective, randomized, crossover evaluation of the effect of propranolol, nadolol and placebo on syncope recurrence and patients' wellbeing. *J Am Coll Cardiol* 2002, **40**; 449-504

16) Sheldon R, Connolly S, Rose S, Kingenheben T, Krahn A, Morillo C, Talajic M, Ku T, Fouad-Tarazi F, Richie D, Koshman ML: POST Investigators. Prevention of Syncope Trial (POST): A randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. *Circulation* 2006; **113**: 1164-70