Ivabradine in treatment of sinus tachycardia mediated vasovagal syncope

Richard Sutton1,2*, Tushar V. Salukhe2,3, Ann-Christine Franzen-Mcmanus2,3, Andrea Collins2,3, Phang Boon Lim1,2, and Darrel P. Francis1,2

1St Mary’s Hospital, Imperial College Healthcare NHS Trust, London, UK; 2National Heart Lung Institute, Imperial College London, London, UK; and 3Department of Electrophysiology, Royal Brompton Hospital, Royal Brompton and Harefield NHS Foundation Trust, London, UK

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Aims
Ivabradine, an I(f) current blocker, has shown promising results in treatment of postural orthostatic tachycardia syndrome (POTS). There is a subgroup of vasovagal syncope (VVS) patients, who demonstrate sinus tachycardia before collapse on tilt testing mimicking some features of POTS. These patients may also respond to ivabradine therapy. University Hospital Syncope Clinic where ivabradine was prescribed in a prospective fashion on humanitarian grounds between October 2008 and December 2011.

Methods and results
Twenty-five patients of mean age 33 ± years presenting syncope in all and palpitation in 23, duration 9 ± years underwent tilt testing with reproduction of usual symptoms including tachycardia preceding collapse. Ivabradine was prescribed in doses of 5–20 mg/day, mean 10.7 mg, as once or twice daily medication. The response to treatment was classified as deterioration in none, no change in 5, improvement in 10, and symptoms abolished in 8 patients. Side effects were minimal; one patient required discontinuation.

Conclusion
In this pilot study of ivabradine, in patients with VVS, of patients who demonstrated sinus tachycardia before collapse on tilt, 72% reported a marked benefit or complete resolution of symptoms. The drug was well tolerated. A randomized controlled trial against placebo is justified.

Keywords
Vasovagal syncope • Postural orthostatic tachycardia syndrome • Ivabradine • Tilt testing • Syncope Clinic

Introduction
Ivabradine, an I(f) current blocker acting in the sino-atrial node to slow the heart, has been shown to offer benefit to some patients with postural orthostatic tachycardia syndrome (POTS). A subgroup of patients with vasovagal syncope (VVS) has been identified to show sinus tachycardia prior to collapse on tilt testing.1,2 These two groups of patients share some common haemodynamic features, notably sinus tachycardia > 120 b.p.m. at onset of symptoms. Sinus tachycardia in VVS is associated with epinephrine release,3 which may be a trigger for vasovagal collapse. A minority of patients with POTS also has VVS.4–6 The hypothesis for the study was formed on the basis of these data.

No study has specifically targeted VVS patients who have documented sinus tachycardia prior to collapse, with a drug effective in limiting this sinus tachycardia. There have been studies of drugs that have wide action including heart rate (HR) reduction, in broadly drawn VVS populations,7 but most of these studies have been negative for any benefit of the selected drug or limited by sub-optimal protocols. Beta-blockers are poorly tolerated by these highly symptomatic patients.

The advent of ivabradine, a specific agent to limit sinus tachycardia, permits its exploration in VVS patients who are most likely to be helped, namely those who show a marked tachycardia response before syncope on tilt testing.8 Ivabradine is licensed for reduction of sinus HR in treatment of angina pectoris and in heart failure in the UK. It is not specifically licensed for attenuation of sinus tachycardia in patients with VVS, and treatment in this cohort was, therefore, undertaken on humanitarian grounds. The study was a clinical series
and no attempt was made to calculate the likely success rate of therapy at its inception.

Patients and methods

Patients were selected for treatment after a full initial evaluation. These patients were already compliant with fluid intake increase to about 3 L/day, salt intake increase to about 6 g/day, and use of physical counter measures to ameliorate symptoms. The patients meeting the criteria for inclusion were selected consecutively by one of the four physician authors. From October 2008 to December 2011, 25 patients with syncope, of whom 23 also reported palpitation, and a positive tilt test reproducing the presenting symptoms, received treatment with ivabradine. The 25 patients constituted 3.3% of the patients seen in the Syncope Unit during the recruitment period.

Tilt tests were conducted using the Italian protocol, 20 min passive upright phase, followed by sublingual administration of 400 mcg nitroglycerine continuing upright for a further 15 min unless syncope occurred. All 25 patients met modified HR criteria for POTS on tilt.10 There were minor deviations from the criteria of Grubb’s group as follows: those over 19 years old had a HR rise of >35 b.p.m. with a peak >115 b.p.m., while those under 19 had HR rise >40 b.p.m. and a peak >130 b.p.m. This was done to be able to include two needy patients who fell marginally outside the criteria of Grubb,10 but were clinically of the same type.

Ivabradine (Servier Laboratories) was prescribed in standard adult doses beginning with 5 mg/day in one or two doses up to a maximum of 20 mg/day. Dosage titration was conducted on clinical grounds, where upward dosage was used for lack of response to the maximum or to side effects and occurrence of side effects prompted dosage reduction, if necessary to discontinuation. Repeat tilt testing while the patients were taking the drug was not performed and no checks were carried out to ascertain if the drug was actually being taken. The resting HR was checked at every clinic attendance (never below 60 b.p.m.) and there was no evidence of symptomatic bradycardia. Follow-up was conducted in the Syncope Clinic and was completed in all patients by telephone in April 2012. The mean duration of follow-up was 15 (range 4—40) months. Response to medication was classified as: deterioration, no change, improvement in symptoms without abolition, or abolition of symptoms. Non-response to ivabradine involved the highest tolerable dose in all.

Statistical comparisons were made using Fisher’s exact test in all comparisons except that of ivabradine dosage (Table 1) when unpaired Student’s t-test was selected.

Results

The 25 patients included comprised of 21 females and 4 males. Twenty-three of them also complained of palpitation, both at the time of syncope and at other times. Their mean age was 33 [standard

| Table 1 | Comparison of clinical features of responders and non-responders to ivabradine therapy |
|---------|----------------------------------|------------------|--------|
|         | Responders (20)                  | Non-responders (5) | P value |
| Ivaradine daily dose, mg (mean, SD) | 9, 2.9                  | 15, 2.9           | 0.001  |
| Males   | 3                                  | 1                       | 0.455  |
| Age >30 years | 8                          | 3                       | 0.282  |
| Age <30 years | 12                               | 2                       | 0.283  |
| Sinus tachycardia on tilt >140 b.p.m. | 8                      | 2                       | 0.121  |
| Sinus tachycardia on tilt <140 b.p.m. | 9                      | 1                       | 0.253  |
| Duration of symptoms >3 years | 14                        | 4                       | 0.403  |
| Duration of symptoms <3 years | 6                        | 1                       | 0.403  |
| Syncope on tilt | 10                               | 3                       | 0.355  |
| Pre-syncope on tilt | 10                        | 2                       | 0.355  |
| Blood pressure >20 mmHg | 12                        | 2                       | 0.283  |
| Blood pressure <20 mmHg | 6                        | 3                       | 0.19   |
| Blood pressure oscillation during tilt | 12                      | 4                       | 0.308  |
| No blood pressure oscillation during tilt | 6                       | 1                       | 0.403  |
| Midodrine | 10                               | 3                       | 0.355  |
| No midodrine | 10                        | 2                       | 0.355  |
| Follow-up duration >1 year | 10                        | 2                       | 0.355  |
| Follow-up duration <1 year | 10                        | 3                       | 0.355  |

No significant differences were identified except for drug dosage (Fisher’s exact test was used for all comparisons except for drug dosage when Student’s unpaired t-test was used.) Blood pressure (lines 11 and 12) = blood pressure fall on tilt.
deviation (SD) 11.4 years, range 17–70 years, and their symptom duration prior to inclusion was 9 (SD 11.2) years, range 1–55 years. Thirteen patients were taking midodrine at inclusion. No dosage changes were made in midodrine during the study except that it was possible to discontinue the drug in three. Twelve patients had previously taken beta-blocking agents but all had experienced intolerable side effects, mainly extreme tiredness, and had requested discontinuation.

On tilt, the supine HR was 76 (SD 13.3) b.p.m. and peak HR was 145 (SD 24.4) b.p.m. (Figure 1). All patients had pre-syncope and palpitation on tilt and 12 went on to experience frank syncope. Sixteen patients showed profound oscillation of blood pressure 30 mmHg peak to trough. A typical example is shown in Figure 2 and a positive tilt without excessive tachycardia response is shown for comparison in Figure 3. Three patients had no blood pressure fall when the severity of symptoms necessitated the termination of tilt and five others showed only a fall of blood pressure of <20 mmHg.

Ivabradine was taken by all 25 patients. The mean dosage was 10.7 mg/day, duration 15 (SD 10.9) months, range 2–40 months. Eight patients reported complete abolition of syncope, 10 experienced a great improvement in syncope occurrence and well-being. Five patients had no benefit and discontinued the drug after 15 (SD 10.9) months, range 2–40 months. One patient stopped the drug 2 months after commencement because she became pregnant. One stopped the drug because of side effects which she described as ‘severe’ but were not specific in nature. Nine of the 18 patients who improved have continued on midodrine in unaltered doses. No clinical parameter was found which identified responders to ivabradine (Table 1). The eight asymptomatic patients were not found...
different from the 10 who only reported improvement. Two patients experienced the retinal side effects of ivabradine early during use but, on continuing the drug, these side effects resolved. The graphics from the tilt tests were missing in three patients but the clinical record was sufficient to indicate that sinus tachycardia >120 b.p.m. was present on tilt but absence of exact HRs on tilt precluded these three from appearing in the sinus tachycardia >140 vs. <140 b.p.m. comparison in Table 1.

Thus, 72%, or 18 of 25 of these patients with severe and long-lasting symptoms gained benefit from ivabradine with 32% becoming completely asymptomatic. Ivabradine was generally well tolerated.

Discussion
This single-centre experience of the use of the specific sinus node modulator ivabradine to control severe symptoms of syncope and palpitation, in a tachycardiac subset of vasovagal patients, has been encouraging. Nearly three-quarters of the patients reported either improvement or complete resolution of their symptoms.

Ivabradine is a drug which has been gaining prominence since its introduction. Its action as an I(f) current blocker largely confines its effects to the sino-atrial node, where it delays Phase 4 depolarization resulting in bradycardia. Ivabradine also has inhibitory effects on I(h) current, which may promote luminous visual phenomena or phosphenes.12 Its specificity makes it possible for it to be relatively benign in its side effects. It is used as an anti-anginal by reducing HR during activity and thereby reducing myocardial oxygen consumption.13 It is presently considered as an alternative to beta-blockers in this regard. Reduction in HR has received attention in treatment of heart failure, where ivabradine is also considered to be an alternative or additional drug to beta-blockers.14

In the field of diseases of the autonomic nervous system, where tachycardia is involved, ivabradine has also been used with some success in inappropriate sinus tachycardia,15 POTS1 and mixed autonomic disturbances.16 All these clinical complexes are likely to be related despite their multifactorial aetiologies. The common feature is sinus tachycardia permitting ivabradine to be effective in treatment.

Drugs have a disappointing record in treatment of VVS. Many have shown promise in small observational studies but once they are submitted to the rigour of a randomized controlled trial they are found wanting.7 Only midodrine has trial evidence in its favour,7 albeit weak. The ideal drug for VVS would be one that has few side effects, is known to be free of teratogenic effects and is required only once daily. Midodrine fails on all these counts as it has many side effects, its teratogenicity is unknown, and it has to be administered three or more times daily. Ivabradine has few side effects and can be taken once daily.

Limitations
This is a single-centre observational study.

The patients reported that they were taking ivabradine, with the two exceptions mentioned, discontinuation for pregnancy and side
effects, but no checks were carried out to confirm concordance with the medication regime.

Up-titration of ivabradine was performed on symptomatic grounds with no target resting HR. Follow-up Holter monitoring was not routinely performed. The last European Society of Cardiology Guidelines expressly advised against repeat tilt testing as a means of qualifying drug efficacy in treatment of VVS. However, given the results of this cohort, future studies might benefit from repeat tilt tests to examine whether ivabradine effectively blocked HR rise provoked by tilt, as long as there is a placebo control arm.

In a randomized controlled trial, the dose escalation protocol might include a target resting HR, assessment of symptom response, Holter monitoring, and repeat tilt testing.

Conclusions

These outcomes in 25 patients suggest that a randomized controlled trial is warranted, of ivabradine vs. placebo, in patients with VVS and excessive HR response to tilt testing.

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