Ivabradine in the Treatment of Vasovagal Syncope

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## Ivabradine in Tachy VVS

### Disclosure Statement of Financial Interest

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<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tr>
<td>Grant/Research Support</td>
<td>Medtronic Inc Research Grant</td>
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<td>Consulting Fees/Honoraria</td>
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<td>Major Stock Shareholder/Equity</td>
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<tr>
<td>Other Financial Benefit</td>
<td>Medtronic Inc Patents</td>
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<td>Abbott Labs Patent</td>
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Ivabradine has been proposed in the treatment of Postural Tachycardia Syndrome. Newton’s group Europace 2011; 13: 427-430.

Vasovagal Syncope has an identifiable subgroup, which has sinus tachycardia before the collapse.


Postural Tachycardia Syndrome

**Definition**

POTS is characterized by a sustained heart rate increment of ≥30 bpm within 10 min of standing or head-up tilt in the absence of orthostatic hypotension. The standing heart rate for all subjects is often ≥120 bpm. These criteria may not be applicable for individuals with low resting heart rates. For individuals aged 12-19 years the required increment is at least 40 bpm. The orthostatic tachycardia may be accompanied by symptoms of cerebral hypoperfusion (brain fog) and autonomic overactivity that are relieved by recumbency.

The symptoms do not include Syncope but syncope is reported to occur in 30% which is widely held also to be a population figure.
Postural Tachycardia Syndrome

Definition

The symptoms do not include Syncope.

BUT recent reports suggest that syncope may occur in 10-38% of POTS patients.

Various explanations have been suggested including exhaustion of norepinephrine stores, relative sympathetic withdrawal and parasympathetic surge.

**POTS + VVS**

**POTS** has multiple causes

An overlap with **VVS** should not surprise as **VVS** is a very common condition.

Grubb's group found 18 with **VVS** from a database of 300 **POTS** patients.  

Kanjwal K et al PACE 2011; 34: 549-554.

A trigger for **VVS** may be a rapid heart rate.

This has been the rationale for use of Beta-blockers in treatment of **VVS**. However no longer tenable ESC Class III.

Treatment of **VVS** with Beta-blockers has not been successful perhaps because the trials have not addressed the patient group with tachycardia before syncope and, also, because of side-effects.
Ivabradine is an If current blocker that acts in the sinoatrial node to inhibit Phase 4 depolarization. This drug was introduced in the last decade by Servier Laboratories. It has found use in treatment of relative sinus tachycardia in heart failure and inappropriate sinus tachycardia. It has been proposed as a ‘longevity’ drug. It is a very specific drug as it only affects the SA node and colour vision cells in the retina.
Early use of Ivabradine in POTS was reported by Ewan V et al Europace 2007; 9: 1220.

This was followed by several reports on its use in Inappropriate Sinus Tachycardia.


The series of patients with VVS and ‘excessive heart rate response’ was inspired by the original description of tilt-test collapse patterns, known as the VASIS collapse patterns Sutton R et al. Eur J Cardiac Pacing Electrophysiol 1992; 2: 180-183.

This work was intended to offer a classification of autonomic behaviour in VVS but it has not proved reliable from the point of view of reproducibility of pattern or its ability to predict effective therapy. It was subsequently revised by Bartoletti et al. Europace 2000; 2: 339-342.

Despite the possible criticism, there is no doubt that a subgroup of VVS patients has an excessive heart rate response to upright posture before collapse. These are the patients to be considered for Ivabradine therapy.
Ivabradine Study Design and Setting

Key points:

- This was a Prospective Observational Study.
- Performed in a University Hospital Syncope Clinic.
- Patient inclusion began in October 2008.
- All suitable patients were included until December 2011.
- Patients had to present with both syncope and palpitation.
- Tilt tests were performed in all (data unavailable for analysis in 3 patients).
- The tilt test had to be considered positive for the reproduction of typical symptoms.
- Patients >19 years had to have a heart rate rise of >35 bpm on tilt and a peak HR of >115 bpm.
- Patients <19 years (2) had to have a HR rise of >40 bpm on tilt and a peak HR of >130 bpm.
Ivabradine Study Methods

Key points:

- Patients underwent an initial evaluation despite most of them being tertiary referrals. This consisted of history, physical examination and 12 lead ECG, plus an echocardiogram if clinically indicated.

- Tilt test by the Italian protocol, which is a 20 min passive phase followed by sublingual nitroglycerine 400mcg and a further 15 min.

- Ivabradine was commenced in all suitable patients in a starting dose of 5–10mg daily in two doses with an increase to 20mg daily if necessary.

- Response to medication was classified as none (no benefit), improved (marked reduction in occurrence of syncope) and elimination of syncope. Telephone follow-up was performed at the end of the study.
Ivabradine Study Results

Key points:

- 28 patients were initially included.
- ~750 patients in toto were seen in the Syncope Clinic during the recruitment period.
- 3 patients were subsequently excluded because 2 did not adequately fulfill the entry criteria and one was diagnosed as having epilepsy and successfully treated with anti-epileptic medication.
- 25 patients were available for analysis with final follow-up by telephone interview.
- There were 21 females and 4 males.
- Their ages were a mean of 33+/−11.4 years (17–70).
- Their symptom duration was 9+/−11.2 years (1–55).
- Thirteen patients were already taking Midodrine.
Ivabradine Study Results

Key points:

- On tilt, the resting HR was 76+/-13.3 bpm (55–100), the peak HR was 145+/-24.4 bpm (117–195).
- On tilt, 12 patients had frank syncope with the remainder having symptoms of severe dizziness and palpitation reproduced.
- On tilt, 16 of the available 22 for analysis had profound oscillation of blood pressure, a pathognomonic feature of vasovagal syncope.
- On tilt, 3 of the available 22 showed no appreciable fall in blood pressure when severity of symptoms determined cessation of the test. The fall in blood pressure was minor < 20mmHg in another 5 patients.
Ivabradine Study Results

Key points:

- **Ivabradine** was taken by all patients in a mean dosage of 10.7mg daily (5–20mg) for a mean duration of 15+/-10.9 months (2–40)
- 5 patients received no benefit from **Ivabradine** and discontinued it after a mean of 13.3 months (3–29 months).
- 1 patient discontinued the drug on advice because she was pregnant. She had improved up to that point.
- 1 patient who received no benefit discontinued the drug because of side-effects, which were non-specific but ‘intolerable’.
- 2 patients experienced briefly the retinal side-effects but neither discontinued the drug on these grounds.
- 8 patients experienced a **complete elimination of syncope** and palpitations.
- 10 patients had a **marked reduction in occurrence of syncope** and continued on the drug.
Ivabradine Study Interpretation

Ivabradine improved 18/25 (72%) of patients for whom it seemed suitable. This result was obtained in a very severely symptomatic group.

Complete elimination of syncope occurred in 8/25 patients (32%).

Ivabradine had few side-effects and was well tolerated for extended periods. Retinal side-effects did not prove to be problematic.

This study should be considered to be the pilot study that justifies a Randomized Double-blind Controlled Trial.
Ivabradine is considered the nearest that the pharmaceutical industry has yet come to produce a drug for a subset of VVS, which can be prescribed in a once daily dosage, is both effective and has few side-effects. It, however, does not yet have reliable studies showing a lack of teratogenic effect, which is a necessity in this group of mainly young female patients.
Ivabradine Study Interpretation

This study was single centre and non-randomized, albeit prospective. Thus, it cannot be regarded as a definitive study in the use of Ivabradine in patients with VVS and excessive HR response or POTS and VVS.

Ivabradine was prescribed for these patients on humanitarian grounds as it was not currently licensed for use in the treatment of syncope in the UK.

No checks were conducted on patients as to their actual consumption of Ivabradine other than history-taking.
Conclusions

1. Ivabradine is effective treatment for a high percentage of very symptomatic patients with VVS + excessive HR rate response (POTS+VVS).

2. Ivabradine is well tolerated by these patients.

3. A Randomized Double-blind Controlled Trial is now justified. But not supported by Servier.