Ivabradine and the SIGNIFY conundrum

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This editorial refers to ‘Bradycardia and atrial fibrillation in patients with stable coronary artery disease treated with ivabradine: an analysis from the SIGNIFY study’†, by K. Fox et al., on page 3291.

Stable angina is a prevalent and disabling condition that occurs in 10–14% of those aged 65–84 years,1 with population studies suggesting that almost a third of affected patients experience an angina episode at least once a week.2 Treatment focuses upon the alleviation of angina symptoms and the prevention of cardiac events. Although the development of cardioprotective agents has received considerable attention in recent years, there has been less progress with novel antianginal agents.

Ivabradine: an effective antianginal

Ivabradine is a novel antianginal agent that inhibits the sinus node If channel to produce a dose-dependent bradycardia and thus antiischaemic effects without significant direct effects on vasomotor tone, blood pressure, or myocardial contractility. Previous studies have shown it to be superior to placebo and non-inferior to first-line antianginal agents (beta-blockers and calcium channel blockers).1 However like the first-line agents, its cardioprotective benefit in patients with stable angina has not been confirmed,3,4 although its benefit in heart failure is well supported.5

The BEAUTIFUL3 and SIGNIFY4 studies evaluated the cardioprotective effects of ivabradine in patients with coronary artery disease with1 and without4 left ventricular systolic dysfunction, who had resting sinus rhythm rates ≥70 b.p.m. Although neither study reported an overall cardioprotective benefit, a post-hoc analysis of the BEAUTIFUL study observed a 42% reduction in myocardial infarct hospitalizations amongst patients with symptom-limiting angina.6 Consequently a pre-specified subgroup analysis of patients with Canadian Cardiovascular Society Class II–IV angina was undertaken in the SIGNIFY study [hereafter referred to as the ‘SIGNIFY Angina(II–IV)Subgroup’].

Astonishingly, ivabradine was associated with an 18% increase in the primary endpoint (cardiovascular death and non-fatal infarction) in the SIGNIFY Angina(II–IV) Subgroup. Thus although ivabradine is an effective antianginal agent, at best it has neutral cardioprotective effects but at worst it may increase major adverse cardiac events in symptomatic stable angina patients without heart failure. Hence those who would gain the most from its antianginal properties are also those most at risk from its apparent adverse cardiac effects. This conundrum warrants further investigation to explain these currently inexplicable findings.

Unravelling the SIGNIFY conundrum

The SIGNIFY Angina(II–IV) Subgroup analysis findings of increased cardiac events in those treated with ivabradine may have several potential explanations including: (i) statistical aberration; (ii) cardiac arrhythmias; (iii) drug interactions; and/or (iv) dose titration.

Statistical aberration

The surprising findings in the SIGNIFY Angina(II–IV) Subgroup analysis raise the possibility of an invalid result or a Type I error. This possibility is strengthened if no biological explanation for the findings can be derived; hence this should be explored before the statistical explanation is further considered.

Cardiac arrhythmias

Ivabradine use is associated with an increased frequency of emergent bradycardia and atrial fibrillation (see Figure 1). In this issue of the journal, Fox et al.7 compared the cardiac event primary endpoint in the ivabradine- and placebo-treated SIGNIFY patients with/without emergent bradycardia (resting heart rate <50 b.p.m., n = 3572) as well as those with/without emergent atrial fibrillation (n = 754). This subanalysis showed no difference in cardiac adverse events between placebo- and ivabradine-treated patients for both the overall and the SIGNIFY Angina(II–IV) Subgroup. Similarly, there was no difference in adverse cardiac events between treatment groups for
those with emergent atrial fibrillation in both the overall and the SIGNIFY Angina (II–IV) Subgroup. Thus, although emergent bradycardia and atrial fibrillation occur more often in the ivabradine-treated patients, these arrhythmias do not appear to account for the increased cardiac events reported in the SIGNIFY Angina (II–IV) Subgroup.

Early clinical studies utilizing doses up to 10 mg b.i.d. concluded that ivabradine prolongs the uncorrected QT interval by 18–30 ms in a dose-dependent fashion; however, when appropriately corrected for heart rate, this increase did not exceed 2 ms and thus should not have direct torsadogenic potential. Accordingly, although QT prolongation was observed in 114 (1.9%) patients on ivabradine and 42 (0.7%) patients on placebo in the SIGNIFY Angina (II–IV) Subgroup, this resulted in drug withdrawal in only three and two patients, respectively. It is also noteworthy that serious ventricular arrhythmias resulting in drug withdrawal were uncommon (4 vs. 1 patient, respectively) in this subgroup.

Despite the apparent safety of ivabradine in relation to QT prolongation, patients with a propensity for torsades de pointes (i.e. congenital or acquired long QT syndromes) have been excluded in the clinical trials and listed as contraindications in the drug product information. Recent clinical data has reinforced this concern with two case reports of ivabradine associated with torsades de pointes when co-administered with potentially torsadogenic medications. Furthermore a recent in vitro study has demonstrated that ivabradine at concentrations equivalent to the higher clinical dosage spectrum prolongs ventricular repolarization and alters electrical restitution, thereby potentially predisposing to torsades de pointes.

Drug interactions
Ivabradine has a plasma half-life of 2 h and a biological half-life of 11 h. It is extensively metabolized by the cytochrome P450 (CYP) enzyme, CYP-3A4, and although it does not influence the metabolism of CYP-3A4 substrates, its own metabolism is influenced by potent CYP-3A4 inhibitors. Consequently, concurrent use of strong CYP-3A4 inhibitors is contraindicated for ivabradine and excluded from clinical trials. Moderate CYP-3A4 inhibitors such as diltiazem or verapamil were discouraged in the earlier ivabradine studies but could be utilized in the SIGNIFY trial. Thus 4.6% of patients randomized to ivabradine therapy were receiving one of these agents.

Combining ivabradine with either verapamil or diltiazem not only increases ivabradine plasma levels three-fold via the above pharmacokinetic interaction, but also produces a pharmacodynamic interaction via the negative chronotropic actions of these non-dihydropyridine calcium channel blockers. The hazard of this interaction is exemplified by further analysis of the SIGNIFY Angina (II–IV) Subgroup data, where concurrent use of verapamil/diltiazem or other CYP-3A4 inhibitor with ivabradine was associated with a 62% increased trend in the primary endpoint ($P = 0.088$) and a significant 88% increase in non-fatal myocardial infarction ($P = 0.026$). This observation has prompted the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency to list the concurrent use of verapamil or diltiazem as a strong contraindication to initiating ivabradine therapy.

Dosage titration
In the SIGNIFY trial, ivabradine was initiated at a dose of 7.5 mg b.i.d. (or 5 mg b.i.d. in those ≥75 years) and titrated to 10 mg b.i.d. in order to achieve a target heart rate of 55–60 b.p.m. Consequently, 47% of the ivabradine study patients who were <75 years of age were receiving the 10 mg b.i.d. dosage. This contrasts with contemporary clinical practice, where ivabradine is initiated at 2.5–5.0 mg b.i.d. and titrated to a maximum of 7.5 mg b.i.d.

Figure 1 The SIGNIFY trial subanalysis findings. Cardiovascular endpoints in stable angina patients ($n = 12,049$) with moderate to severe angina (Canadian Cardiovascular Society Class II–IV) but without cardiac failure. CV, cardiovascular; MI, myocardial infarction.
primary endpoint occurred on the 10 mg b.i.d. dosage in 58% of the SIGNIFY Angina(II–IV) Subgroup patients. Considering the higher dose of ivabradine and the potential interaction with the concurrent use of verapamil/diltiazem, it is possible that the SIGNIFY trial may have inadvertently constructed the ‘perfect storm’, resulting in the disturbing findings in the SIGNIFY Angina(II–IV) Subgroup. Perhaps the high ivabradine levels unmasked a biological effect (such as QT prolongation) that is not a problem at the lower doses in routine clinical use.

The importance of resolving the SIGNIFY conundrum

The plight of ivabradine is further exemplified by the author’s own clinical experience in utilizing this agent for the treatment of angina in patients with coronary microvascular disorders. Its antianginal effect in these patients was remarkable, with some achieving good control despite failing to respond to proposed first-line treatments. However with the advent of the SIGNIFY Angina(II–IV) Subgroup findings, a decision to withdraw the ivabradine therapy from these patients was made on the basis of its ‘non-label use’ and an unclear explanation for the cardiac events in the symptomatic patients. Two of these patients with ivabradine-responsive angina subsequently developed a myocardial infarct shortly after discontinuing this agent. This appeared unrelated in one patient, since he experienced a peri-procedural myocardial infarct during stenting of his obstructive coronary artery disease, which had developed on a long background history of coronary microvascular dysfunction. However, the second patient experienced an unheralded myocardial infarct within 48 h of discontinuing ivabradine, despite a down-titration withdrawal over a week. These and several other microvascular angina patients in whom ivabradine was stopped are eager to recommence this medication considering the symptomatic benefits they derived from its use; however, their conservative physician remains reluctant until an adequate explanation for the SIGNIFY findings must continue so that ivabradine can be maintained as a useful tool in our very limited therapeutic antianginal armamentarium and avoid our previous errors of ‘throwing the baby out with the bath water’.

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References