Ivabradine for inappropriate sinus tachycardia: another piece of evidence

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This editorial refers to ‘Metoprolol succinate vs. ivabradine in the treatment of inappropriate sinus tachycardia in patients unresponsive to previous pharmacological therapy’ by P. Ptaszynski et al., on page 116

Prevalence of inappropriate sinus tachycardia (IST) defined by heart rate criteria is estimated to be 1.2% in the middle-aged population. Its clinical presentation with polymorphic symptoms of variable intensity, sometimes including debilitating palpitations and general incapacity, is fortunately much less common.

Pathophysiological background of this infrequent entity remains poorly understood and several investigations led to rather controversial results. Enhanced intrinsic automaticity of the sinus node and/or impairment of cardiac autonomic regulation were suggested. Inappropriate sinus tachycardia has also been linked to the presence of beta-receptor stimulating autoantibodies. The clinical features of IST significantly overlap with postural orthostatic tachycardia syndrome, so that extracardiac autonomic system abnormalities may play an important role. For all these reasons, a multidisciplinary model in managing IST patients was proposed.

Beta-blockers are the cornerstone of pharmacological therapy for IST that may be replaced by or combined with nondihydropyridine calcium channel blockers. Since this therapy is ineffective or associated with intolerable side effects in approximately one-third of patients, radiofrequency catheter modification of sinus nodal region has been proposed. This approach should be reserved for highly symptomatic patients who are refractory to medical therapy because ablation has no clear acute endpoint and may be associated with significant complications. Also long-term outcomes were disappointing. Due to the ‘systemic’ nature of IST, invasive procedure may, however, identify a considerable proportion of associated non-IST arrhythmias that can be cured by radiofrequency ablation more successfully.

Ivabradine is a novel, highly selective If ‘funny’ channel blocker, i.e. the inhibitor of the most important ionic current in regulating pacemaker activity in the sinoatrial node. By slowing down the diastolic cellular depolarization, it can, unlike conventional heart rate-lowering agents, reduce the heart rate without affecting myocardial contractility, ventricular repolarization, or intracardiac conduction. While initially its efficacy has been shown in large populations of patients with stable angina pectoris or with heart failure, ivabradine soon attracted the attention of physicians challenged by patients with resistant IST.

Several case reports, and three series of patients with IST (including a total of 41 subjects), were published recently (the most recent by Calò et al.) in which the effect of ivabradine was investigated prospectively. In this issue of the journal, Ptaszynski et al. report the results of a prospective, single-centre study of 20 patients with IST in whom treatment with ivabradine was compared with slow-release metoprolol. The study is a welcome addition to the published research on this topic. It had a non-randomized, cross-over, open-label design with treatment periods of 4 weeks. The dose of ivabradine was titrated from 5 to 7.5 mg twice daily. The initial single dose of metoprolol succinate of 47.5 mg was gradually increased up to 190 mg if tolerated (50% of patients), but had to be subsequently reduced in 30% patients because of hypotension, so that the mean final dose of 157 ± 38 mg was reached.

Both drugs had highly significant and comparable effects on resting and Holter-based heart rate, as well as on exercise tolerance (a treadmill stress test by standard Bruce protocol) and subjective perception of symptoms [the authors used the European Heart Rhythm Association (EHRA) symptom classification for atrial fibrillation]. Ivabradine overpowered metoprolol in the reduction of mean heart rate during daily activities and in the reduction of symptomatic episodes during 24-h Holter monitoring. Ivabradine also significantly prolonged the maximum exercise duration compared with metoprolol. There was also a trend for superiority of ivabradine in EHRA score improvement; 70% patients appeared asymptomatic on ivabradine compared with 45% patients on metoprolol.

Several study limitations were already mentioned by the authors. The study was obviously limited by the open-label design that might have influenced the results due to patients’
past experience and expectations especially when some study endpoints were of a highly subjective nature. All patients were previously treated by widely available heart rate-lowering agents (55% with beta-blockers; of them 45% with metoprolol, although in the immediate-release formulation) so that the anticipation of a greater effect of the brand-new ‘experimental’ drug compared with a more or less conventional drug may have biased the results of the study. Similarly, exercise tolerance and duration may have been influenced by the motivation of patients in the open-label trial as well as by a ‘learning’ effect, when exercise testing on ivabradine was the last (third) assessment in all patients. Both blinded design and a randomized sequence of treatment allocations would have eliminated these confounding factors.

A relatively short pre-treatment washout period (4 weeks) might have set slightly worse baseline characteristics (perhaps because of a still subsiding rebound phenomenon) and, consequently, may have resulted in apparently greater effect of both treatments. Also, treatment periods were relatively short for dose titration. In the case of ivabradine, this process was quite straightforward, while for metoprolol the dose was first up-titrated and then reduced in a considerable proportion of patients. One may speculate that in some patients the metoprolol dosage was fully optimized at the very end of the treatment period. In such a situation, the assessment of symptoms may have been distorted in favour of ivabradine depending on how the investigated subject projected their recent symptoms into the final assessment.

On the other hand, a relatively simple scoring system (EHRA score) was used for the subjective perception of symptoms. It cannot be ruled out that differences between both drugs would have become significant if the authors had used a broadly validated European Quality of Life Group Instrument (EQ-5D) that is able to project their recent symptoms into the final assessment.

What was most exciting for me is that the authors did not find any relationship between the baseline heart rate and the magnitude of heart rate reduction on ivabradine. They did not disclose the method used for this analysis and discussed vaguely their result that contrasted with the positive findings in previous studies. Caló et al.7 reported a highly significant correlation between the baseline heart rate and its reduction on ivabradine. This finding was also discussed in the corresponding editorial8 and explained by specific properties of ivabradine-induced block of the native funny channel, specifically by facilitation of block during repetitive open/closed channel cycling. As reviewed by DiFrancesco,6 such feature of ivabradine implies that the drug effect might be stronger at high (tachycardic) rates and, consequently, could have explained an intriguingly safe therapeutic profile.

Similar statements concerning ivabradine have been reverberated in the literature in recent years although no clear evidence has been provided apart from simple correlation analysis. Why was such an analysis misleading? This can be explained by a ubiquitous statistical phenomenon, known as ‘regression to the mean’, that can make natural variation in repeated data look like a real change.10 It is principally based on the fact that extreme measurements tend to be followed by measurements that are closer to the true (mean) value. The significant correlation between a baseline variable and its change after intervention (either effective or ineffective) is a nice example of how this phenomenon may lead to erroneous inference.

In conclusion, Ptaszynski et al.8 are to be congratulated on an important study contributing to the growing literature on ivabradine use in patients with IST which showed that ivabradine was better tolerated at the maximum recommended dose and somewhat more effective in head-to-head comparison with standardized metoprolol treatment. It is clear that more research is needed. In particular, I would welcome the results of a much larger, placebo-controlled study in IST patients investigating the long-term benefit from ivabradine treatment when given on top of tolerable beta-blocker medication. The study by Ptaszynski et al.8 provided pilot data for designing such trials.

Conflict of interest: none declared.

References