BJP British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2011.01818.x
www.brjpharmacol.org

COMMENTARY

Verapamil as an antiarrhythmic agent in congestive heart failure: hopping from rabbit to human?

Thom RG Stams*, Vincent JA Bourgonje*, Marc A Vos and Marcel AG van der Heyden

Department of Medical Physiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence
Marcel AG van der Heyden, Department of Medical Physiology, Division of Heart & Lungs, University Medical Center Utrecht, Yalelaan 50, 3584 CM Utrecht, The Netherlands. E-mail: m.a.g.vanderheyden@umcutrecht.nl

*Both authors contributed equally.

Keywords
heart failure; torsade de pointes; arrhythmia; calcium channel; verapamil; rabbit model; repolarization reserve

Received
21 October 2011
Revised
5 December 2011
Accepted
5 December 2011

Repolarization-dependent cardiac arrhythmias only arise in hearts facing multiple 'challenges' affecting its so-called repolarization reserve. Congestive heart failure (CHF) is one such challenge frequently observed in humans and is accompanied by altered calcium handling within the contractile heart cell. This raises the question as to whether or not the well-known calcium channel antagonist verapamil acts as an antiarrhythmic drug in this setting, as seen in arrhythmia models without CHF. According to the study of Milberg *et al.* in this issue of *BJP*, the answer is yes. The results of this study, using a rabbit CHF model, raise important questions. First, given that the model combines CHF with a number of other interventions that predispose towards arrhythmia, will similar conclusions be reached in a setting where CHF is a more prominent proarrhythmic challenge; second, what is the extent to which other effects of calcium channel block would limit the clinical viability of this pharmacological approach in CHF? *In vivo* studies in large animal CHF models are now required to further explore this interesting, but complex, approach to the treatment of arrhythmia.

LINKED ARTICLE

This article is a commentary on Milberg *et al.*, pp. 557–568 of this issue. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2011.01721.x

Abbreviations

CHF, congestive heart failure; EAD, early after depolarization; $I_{Ca\text{-}L}$, L-type calcium current; I_{Kr}, rapid delayed rectifier channel; TdP, torsade de pointes

In cardiac ventricular myocytes, an imbalance between inward and outward currents may prolong action potential duration. This makes the heart vulnerable to the occurrence of so-called torsade de pointes (TdP) arrhythmias, which are life-threatening ventricular tachycardias that create rapid fluctuations of QRS complexes around the isoelectric line on the human ECG. In patients, there are several independent risk factors or 'challenges' for TdP arrhythmias, including hypokalaemia, bradycardia, genetic and drug-induced long QT syndromes and chronic congestive heart failure (CHF) (Roden, 2004). A single 'challenge' to cardiac ventricular repolarization, for example, the reduction of a single membrane ion current, usually does not result in repolarization-dependent arrhythmias. Apparently, the heart has a reserve, commonly referred to as 'repolarization reserve' (Varró and Baczkó, 2011), and multiple challenges are therefore usually required in order to provoke arrhythmia. Often, QT-prolonging drugs associated with TdP arrhythmias are the final challenge that exceeds the reserve, resulting in proarrhythmia. Quantification of the repolarization reserve, however, remains difficult. Although a number of surrogate parameters have been suggested (Thomsen *et al.*, 2006), such as temporal or spatial dispersion of action potential duration, optimal quantification of repolarization reserve still requires testing of susceptibility to arrhythmias, where the cumulative severity of the challenges required to exceed the reserve then provides an estimation of the reserve. Interestingly, some drugs, including those that block the inward L-type calcium current ($I_{Ca\text{-}L}$), have been shown to be effective against drug-induced arrhythmias, by

counteracting one or more of the predisposing challenges (Oros *et al.*, 2010).

Only a few experimental large animal models mimicking CHF have been developed. Currently, the efficacy in which $I_{Ca\text{-}L}$ inhibition prevents or suppresses early after depolarizations (EAD) and polymorphic ventricular tachycardia in CHF is not clear and difficult to predict since calcium-handling disturbances are apparent in this disease (Janse, 2004). Moreover, in a setting of CHF, this apparent simple antiarrhythmic approach has to deal with conflicting imperatives such as antiarrhythmic action versus haemodynamic tolerance. In this issue of the *BJP*, Milberg *et al.* (2012a) report the outcome of $I_{Ca\text{-}L}$ block by verapamil, a well established antiarrhythmic compound, on arrhythmic end points in a rabbit model of non-ischemic CHF with long-QT characteristics (Milberg *et al.*, 2012a). CHF was generated by continuous right ventricular rapid pacing and, subsequently, Langendorff-perfused sham and CHF hearts were subjected to a number of additional challenges in order to provoke arrhythmias: bradycardia, ectopic ventricular activation, severe hypokalaemia and erythromycin-mediated I_{Kr} block. Repolarization was prolonged to some extent in CHF but spatial dispersion was not affected at baseline. Only after I_{Kr} block, especially transmural dispersion was increased to a larger extent in CHF. Arrhythmias were observed, but their number in hearts from sham animals (four of 11 hearts; 36%) was not significantly different from rabbit hearts with CHF (eight of 11; 73%; P = NS). Unfortunately, surrogate parameters were only reported for normokalemic circumstances, when the repolarization reserve was challenged less severely and thus could not directly be associated with the arrhythmic end point. Remarkably, the findings of the same group published recently (Frommeyer *et al.*, 2011), in which the rabbit hearts were used to analyse the proarrhythmic effect of the I_{Kr} blocker sotalol were in favour of the CHF model used here . In this CHF group, sotalol induced EADs (as estimated from monophasic action potential morphology) and TdP in 16 of 18 (89%) hearts compared with seven of 14 (50%) hearts in the sham group. When we solely compare arrhythmia incidence based on these numbers, a P-value of 0.023 is obtained (two-tailed Fisher exact test). However, in both studies, and yet another [seven of 14 (50%) Milberg *et al.*, 2012b], the pronounced incidence of arrhythmias in the sham hearts represents a potential limitation. Nevertheless, verapamil was demonstrated to be an efficient antiarrhythmic drug in this setting, and importantly, we may thus conclude that effectiveness of $I_{Ca\text{-}L}$ block as antiarrhythmic treatment persists in an isolated rabbit heart model where CHF is added. The next hurdle will be to reach similar conclusions in an *in vivo* model where CHF is a more prominent proarrhythmic factor.

Mechanisms of the antiarrhythmic potential of verapamil against repolarization-dependent arrhythmias have been ascribed to shortening of the QT interval and decreases in beat-to-beat variability of action potential duration (Oros *et al.*, 2010; Bourgonje *et al.*, 2011), and now Milberg *et al.* (2012a) show that it counteracts spatial dispersion in a CHF heart too. Promising as it seems, verapamil is contraindicated in CHF, especially in cases with severe systolic dysfunction and reduced fractional shortening (Chew *et al.*, 1981). As verapamil inhibits the systolic calcium flux and, consequently, contractility, it is negatively inotropic, and this makes verapamil probably a poor choice in the clinic; certainly, when considering that the concentration used by Milberg *et al.* (0.75 μM) was unable to suppress arrhythmias completely. In the *in vivo* complete atrial-ventricular block dog model, verapamil plasma levels of around 0.5 μM clearly were antiarrhythmic but also lowered left ventricular pressure (Oros *et al.*, 2010). Upon titrating verapamil, antiarrhythmic activity could not be observed without a drop in left ventricular pressure (Bourgonje *et al.*, 2011). Other calcium channel antagonists might be a better option, however, and the authors themselves advocate second-generation $I_{Ca\text{-}L}$ blockers. Take, for instance, nifedipine that more strongly affects smooth than striated muscle (Millard *et al.*, 1983), where lowering peripheral resistance would compensate for negative inotropy. This may still have a major drawback because, in order to preserve blood pressure where contractility is reduced and vessels are dilated, heart rate must increase, which is also unfavourable for an already weakened heart. Obviously, it would be hard to predict the individual effects on vasodilatation and cardiac contractility, and where they would counterbalance each other in a haemodynamically challenged heart under neurohumoral influence. This should be approached experimentally. Furthermore, while inhibiting systolic calcium may be worrisome, in the case of diastolic dysfunction, calcium channel antagonism might be beneficial by improving coronary flow and muscle relaxation. As answering these questions is beyond the opportunities offered by the model of Milberg *et al.* (2012a), other models should be employed to address these intriguing possibilities.

In conclusion, the study of Milberg *et al.* (2012a) demonstrates the efficacy of verapamil as an antiarrhythmic agent in the setting of CHF and provides basic science insights into its mechanism of action of reducing spatial dispersion. Further studies are required to pinpoint the contribution of CHF to arrhythmogenesis in this model, to recapitulate the findings in models where CHF is a more pronounced proarrhythmic challenge and to validate the antiarrhythmic efficacy and demonstrate clinical feasibility, of $I_{Ca\text{-}L}$ block in *in vivo* models of CHF.

Acknowledgements

We thank Rebecca Burton, Department of Physiology, Anatomy, and Genetics, University of Oxford, for careful reading of the manuscript. This work received funding from the European Community's Seventh Framework Programme FP7/2007–2013 under grant agreement no. HEALTH-F2-2009-241526 EUTrigTreat and by a grant from the Fondation Leducq and the Alliance for Calmodulin Kinase II Signaling in Heart Disease.

Conflict of interest

The authors declare they have no conflicts of interest.

References

Bourgonje VJ, Vos MA, Ozdemir S, Doisne N, Acsai K, Bito V *et al.* (2011). SEA0400 provides anti-arrhythmic actions against dofetilide-induced torsade de pointes (TdP) without a negative inotropic effect. Heart Rhythm 8: S330–S331.

Chew CY, Hecht HS, Collett JT, McAllister RG, Singh BN (1981). Influence of severity of ventricular dysfunction on hemodynamic responses to intravenously administered verapamil in ischemic heart disease. Am J Cardiol 47: 917–922.

Frommeyer G, Milberg P, Witte P, Stypmann J, Koopmann M, Lücke M *et al.* (2011). A new mechanism preventing proarrhythmia in chronic heart failure: rapid phase-III repolarization explains the low proarrhythmic potential of amiodarone in contrast to sotalol in a model of pacing-induced heart failure. Eur J Heart Fail 13: 1060–1069.

Janse MJ (2004). Electrophysiological changes in heart failure and their relationship to arrhythmogenesis. Cardiovasc Res 61: 208–217.

Milberg P, Fink M, Pott C, Frommeyer G, Biertz J, Osada N *et al.* (2012a). I_{Ca} block leads to suppression of early afterdepolarizations and reduction of transmural dispersion of repolarization in a whole heart model of chronic heart failure. Br J Pharmacol 166: 557–568.

Milberg P, Frommeyer G, Uphaus T, Kaiser D, Osada N, Breithardt G *et al.* (2012b). Electrophysiologic profile of dronedarone on the ventricular level: beneficial effect on post repolarization refractoriness in the presence of rapid phase-III-repolarization. J Cardiovasc Pharmacol 59: 92–100.

Millard RW, Grupp G, Grupp IL, DiSalvo J, DePover A, Schwartz A (1983). Chronotropic, inotropic, and vasodilator actions of diltiazem, nifedipine, and verapamil. A comparative study of physiological responses and membrane receptor activity. Circ Res 52: I29–I39.

Oros A, Houtman MJ, Neco P, Gomez AM, Rajamani S, Oosterhoff P *et al.* (2010). Robust anti-arrhythmic efficacy of verapamil and flunarizine against dofetilide-induced TdP arrhythmias is based upon a shared and a different mode of action. Br J Pharmacol 161: 162–175.

Roden DM (2004). Drug-induced prolongation of the QT interval. N Engl J Med 350: 1013–1022.

Thomsen MB, Matz J, Volders PG, Vos MA (2006). Assessing the proarrhythmic potential of drugs: current status of models and surrogate parameters of torsades de pointes arrhythmias. Pharmacol Ther 112: 150–170.

Varró A, Baczkó I (2011). Cardiac ventricular repolarization reserve: a principle for understanding drug-related proarrhythmic risk. Br J Pharmacol 164: 14–36.