5. Reiter RJ, Sharma R, Ma Q, Dominquez-Rodriguez A, Marik PE, Abreu-Gonzalez P. *Melatonin Inhibits COVID-19-induced Cytokine Storm by Reversing Aerobic Glycolysis in Immune Cells: A Mechanistic AnalysisMed Drug Discov.* 2020;6:100044.
6. Reiter RJ, Abreu-Gonzalez P, Marik PE, Dominguez-Rodriguez A. Therapeutic algorithm for the use of melatonin in patients with COVID-19. *Front Med.* 2020;7:226.
7. Chen WH, Kozlovsky BF, Effros RB, Grubeck-Loebenstein B, Edelman R, Sztein MB. Vaccination in the elderly: an immunological perspective. *Trends Immunol.* 2009;30:351–359.
8. Shneider A, Kudriavtsev A, Vakhrusheva A. Can melatonin reduce the severity of COVID-19 pandemic? *IntRev Immunol.* 2020. http://dx.doi.org/10.1080/08830185.2020.1756284.

https://doi.org/10.1016/j.rec.2020.06.005
1885-5857/

Melatonin, coronavirus, cardiovascular disease, and the geriatric emergency: let's use everything we have! Response

Melatonina, coronavirus, enfermedad cardiovascular y emergencia geriátrica: ¡usemos todo lo que tenemos! Respuesta

To the Editor,

We read with interest the Letter to the Editor by Domínguez-Rodríguez et al. concerning our article[1] and suggesting that melatonin treatment may be useful in elderly patients with COVID-19. The authors propose that this treatment could prevent the infection or lessen its severity, which is more pronounced among the elderly.[2] Melatonin has anti-inflammatory and antioxidant activity, thus attenuating the proinflammatory cytokine storm and neutralizing the production of free radicals to help preserve cell integrity and prevent lung damage.[3] Melatonin levels drop significantly with age, an effect that has been related to the development of chronic inflammatory processes, including some cardiovascular diseases. Consequently, its use in elderly patients may be particularly relevant. Exogenous supplementation has been shown to be safe and to have few adverse effects, although these effects are diminished when melatonin is administered consistent with its circadian rhythm of production.[3] Nevertheless, there are a paucity of data on its clinical benefit in various situations, and no evidence is available on how it affects established prognostic variables.[4]

We agree with the authors on the need to design and implement new therapies rapidly and effectively in the context of this pandemic. However, we should not neglect the perspective gained from a formal evaluation of any potential treatments. The pathophysiologic plausibility and the available experimental and clinical data are promising, and studies could be designed to evaluate the potential efficacy of melatonin in COVID-19. However, they are insufficient to recommend routine clinical use as proposed by the authors. In our opinion, ethical considerations require that the therapies we administer to our patients be supported by sufficient rigorous evidence, even during emergencies.

SEE RELATED CONTENT:
https://doi.org/10.1016/j.rec.2020.06.005

Sergio García-Blas,[a] Pablo Díez-Villanueva,[b] Francisco Tarazona-Santabalbina,[c] and Clara Bonanad[a,*]

[a]*Servicio de Cardiología, Hospital Clínico Universitario de Valencia, Valencia, Spain*
[b]*Servicio de Cardiología, Hospital Universitario La Princesa, Madrid, Spain*
[c]*Servicio de Geriatría, Hospital de la Ribera, Alzira, Valencia, Spain*

* Corresponding author:
E-mail address: clarabonanad@gmail.com (C. Bonanad).

Available online 5 August 2020

REFERENCES

1. Bonanad C, García-Blas S, Tarazona-Santabalbina FJ, et al. Coronavirus: la emergencia geriátrica de 2020, Documento conjunto de la Sección de Cardiología Geriátrica de la Sociedad Española de Cardiología y la Sociedad Española de Geriatría y Gerontología. *Rev Esp Cardiol.* 2020;73:569–576.
2. Bonanad C, García-Blas S, Tarazona-Santabalbina F, et al. The effect of age on mortality in patients with Covid-19: a metanalysis with 611,583 subjects. *J Am Med Dir Assoc.* 2020. http://dx.doi.org/10.1016/j.jamda.2020.05.045.
3. Reiter RJ, Sharma R, Ma Q, Dominquez-Rodriguez A, Marik PE, Abreu-Gonzalez P. Melatonin inhibits COVID-19-induced cytokine storm by reversing aerobic glycolysis in immune cells: a mechanistic analysis. *Med Drug Discov.* 2020;6:100044.
4. Zhang R, Wang X, Ni L, et al. COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci.* 2020;250:117583.

https://doi.org/10.1016/j.rec.2020.06.024
1885-5857/

Do we have a new drug for heart rate control in patients with permanent atrial fibrillation?

¿Hay un nuevo fármaco disponible para el control de la frecuencia cardiaca de pacientes con fibrilación auricular permanente?

To the Editor,

We have read with great interest the article by Fontenla et al.[1] describing the design of the BRAKE-AF project, which will analyze the safety and efficacy of ivabradine for heart rate control in patients with permanent atrial fibrillation.

Ivabradine has shown beneficial effects in patients with ischemic heart disease and in patients with heart failure and reduced ejection fraction.[2] The drug has a good safety profile, as it does not affect cardiac contractility or blood pressure due to its selective I_f current inhibition. Until recently, the negative chronotropic effect of the drug was considered the result of its selective effect in the sinus node and, therefore, it was not recommended for heart rate control in patients with atrial fibrillation. However, recent studies have suggested that ivabradine slows atrioventricular (AV) conduction and may be beneficial in these patients.[3] Fontenla et al.[1] have proposed this study, as this effect is biologically plausible (the AV node does have I_f currents) and this hypothesis is supported by several experimental animal studies[4] and small human trials.[5]

SEE RELATED CONTENT:
https://doi.org/10.1016/j.rec.2020.08.016
https://doi.org/10.1016/j.rec.2020.09.004

The BRAKE-AF project is a promising undertaking, as the therapeutic armamentarium available for heart rate control in patients with permanent atrial fibrillation is scant and insufficient in a significant percentage of patients. In fact, beta-blockers, which are the most effective drugs in this context, do not achieve adequate heart rate control in 30% of patients.[6] Furthermore, calcium channel blockers are contraindicated in the presence of severe ventricular dysfunction, and digoxin has a narrow therapeutic margin and is associated with higher mortality.[7] As a result, some patients require pacemaker implantation and AV node ablation to achieve adequate heart rate control.[8] New drugs with negative chronotropic effects could add to current therapeutic options and may help minimize invasive treatment.

The project is based on a sound design with 2 differentiated arms: an experimental arm to analyze the effect of the drug on the action potential of the AV node and a noninferiority clinical trial. The aim of the clinical trial, which compares the efficacy of digoxin with ivabradine, is rational, as digoxin is less successful in controlling heart rate than beta-blockers or L-type calcium channel blockers. The trial has several limitations. In particular, it uses an unblinded approach, in view of the effects of digoxin on the surface electrocardiogram, and includes patients with and without ventricular dysfunction. Ivabradine could have a different effect in patients with ventricular dysfunction; therefore, based on the results of the trial, a second study could be undertaken in this subgroup.

We look forward to the publication of the results of the BRAKE-AF project to learn the therapeutic possibilities of ivabradine in this context.

Nuria Rivas-Gándara[a,b,c,d,*] and Jaume Francisco-Pascual[a,b,c,d]

[a]*Unidad de Arritmias, Servicio Cardiología, Hospital Universitario Vall d'Hebron, Barcelona, Spain*
[b]*Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain*
[c]*Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain*
[d]*Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*

[*] Corresponding author:
E-mail address: nrivas@vhebron.net (N. Rivas-Gándara).

Available online 18 September 2020

REFERENCES

1. Fontenla A, Lopez-Gil M, Tamargo-Menendez J, et al. Ivabradine for chronic heart rate control in persistent atrial fibrillation Design of the BRAKE-AF project. *Rev Esp Cardiol.* 2020;73:368–375.
2. Hidalgo F, Carrasco F, Castillo JC, et al. Effect of early treatment with ivabradine plus beta-blockers on long-term outcomes in patients hospitalized with systolic heart failure. *Rev Esp Cardiol.* 2018;71:1086–1088.
3. Giuseppe C, Chiara F, Giuseppe R, et al. Addition of ivabradine to betablockers in patients with atrial fibrillation: Effects on heart rate and exercise tolerance. *Int J Cardiol.* 2016;202:73–74.
4. Verrier RL, Bonatti R, Silva AFG, et al. If inhibition in the atrioventricular node by ivabradine causes rate-dependent slowing of conduction and reduces ventricular rate during atrial fibrillation. *Heart Rhythm.* 2014;11:2288–2296.
5. Wongcharoen W, Ruttanaphol A, Gunaparn S, et al. Ivabradine reduced ventricular rate in patients with non-paroxysmal atrial fibrillation. *Int J Cardiol.* 2016;224:252–255.
6. Olshansky B, Rosenfeld LE, Warner AL, et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. *J Am Coll Cardiol.* 2004;43:1201–1208.
7. Turakhia MP, Santangeli P, Winkelmayer WC, et al. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. *J Am Coll Cardiol.* 2014;64:660–668.
8. Ibáñez-Criado J, Quesada A, Cózar R, et al. Registro Español de Ablación con Catéter XVIII Informe Oficial de la Sección de Electrofisiología y Arritmias de la Sociedad Española de Cardiología (2018). *Rev Esp Cardiol.* 2019;72:1031–1042.

https://doi.org/10.1016/j.rec.2020.07.013
1885-5857/

Do we have a new drug for heart rate control in patients with permanent atrial fibrillation? Response

¿Hay un nuevo fármaco disponible para el control de la frecuencia cardiaca de pacientes con fibrilación auricular permanente? Respuesta

To the Editor,

We thank Drs Rivas-Gándara and Francisco-Pascual for their interest shown in the BRAKE-AF project.[1]

There is indeed evidence to suggest that ivabradine could be effective for rate control in permanent atrial fibrillation (AF). Following publication of its efficacy in a patient with poorly-controlled AF,[2] we were aware that to "make this hypothesis a reality" we would need to conduct a clinical trial.[3]

Permanent AF is the most common form of AF yet, surprisingly, new drugs for rate control have not been developed in the past 30 years. The industrial development of antiarrhythmic drugs is increasingly uncommon, probably because it involves investment that is risky and/or with small profit margins; this means that clinicians must assess the antiarrhythmic effect of drugs that are marketed for other indications, as is the case with ranolazine.[4] We would like to point out that the BRAKE-AF project was undertaken with public funding only and thanks to the generous effort of independent investigators: cardiologists from several hospitals and pharmacologists from the *Universidad Complutense de Madrid.*

Our trial is currently in the recruitment phase, and bears the difficulties inherent to any clinical trial with the added impact of the recent COVID-19 outbreak. Like Rivas-Gándara and other authers,[5] we hope that the BRAKE-AF trial will answer the question of whether there is a new drug for rate control in AF. If so, the next question will be, "Could ivabradine improve prognosis in patients with permanent AF?"

Adolfo Fontenla,[a,*] Juan Tamargo-Menéndez,[b] María López-Gil,[a] and Fernando Arribas[a,c]

[a]*Servicio de Cardiología, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (i+12), Madrid, Spain*
[b]*Departamento de Farmacología, Facultad de Medicina, Universidad Complutense, Madrid, Spain*
[c]*Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*

[*] Corresponding author:
E-mail address: drfontenla@gmail.com (A. Fontenla).

Available online 14 October 2020

SEE RELATED CONTENT:
https://doi.org/10.1016/j.rec.2020.07.013