Letters to the Editor

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

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

To the Editor,

We read with interest the joint document of the Section on Geriatric Cardiology of the Spanish Society of Cardiology related to the geriatric emergency and coronavirus infectious disease-19 (COVID-19).[1] Based on data published by the Spanish Ministry of Health, up to May 24, 2020, 235 772 confirmed cases of COVID-19 had been diagnosed in Spain, of which 86% of the deceased were older than 70 years.[2] We would like to make some important points about melatonin, elderly patients, and COVID-19.

Excellent reviews have noted that melatonin has significant beneficial effects against ischemia-reperfusion injury, myocardial chronic intermittent hypoxia injury, pulmonary hypertension, hypertension, valvular heart diseases, vascular diseases, and lipid metabolism.[3,4] Melatonin is synthesized from tryptophan in the pineal gland and by almost all the organs of the body, since its production is associated with mitochondria. It is noteworthy that high levels of melatonin play positive roles in health and aging.[3] Melatonin, a well-known chronobiotic, is also a promising adjunct drug for viral infections due to its anti-inflammatory, antiapoptotic, immunomodulatory, and powerful antioxidant properties. Melatonin binds to M1 and M2 receptors that can be found in the retinae and in the brain, as well as in the heart, gut, lymphocytes, and liver.[3]

Melatonin levels change during the life span. Nocturnal melatonin levels are highest in young children, approximately 325 pg/mL and then decline gradually with age. For example, levels are between 50 and 55pg/mL in 15 to 50-year-olds, approximately 27 pg/mL in 50 to 70-year-olds and approximately 15 pg/mL in persons $>$ 70 years.[3] COVID-19 infection attacks the melatonin synthetic pathway resulting in reduced melatonin levels at a time when melatonin is most needed. This often leads to altered immune responses, specifically, with the overreaction of the innate immune response. The uncontrolled innate immune response promotes a massive inflammatory reaction and causes irreversible tissue damage and mortality.[5,6] Our group recently published a review on how the various medical comorbidities (diabetes mellitus, hypertension, obesity, and cardiovascular disease) can affect the melatonergic pathway and its relationship with COVID-19. In addition, we suggest melatonin doses for treatment and prophylactic use.[6]

When a vaccine is developed, it may not be as effective in elderly patients. A limited immune response to vaccines has been previously reported in older patients due to immunosenescence.[7] Thus, adjuvant therapy to enhance vaccine efficacy in the elderly is urgently needed amidst the COVID-19 crisis and melatonin may be a suitable candidate.[6] Melatonin is an inexpensive product with scalable production. It has a long shelf life, the simplest mode of transportation, and can be self-administered orally in remote areas.

Under normal circumstances, the conclusion of this Letter to the Editor would be to initiate elderly prophylactic prospective clinical studies dividing patients into case-control groups with one group receiving the standard of care alone, and the other group receiving the standard of care supplemented with melatonin. Let's assume that we conduct exactly this type of study and then conclude that melatonin reduces rates of hospitalization and the incidence of irreversible postinfection complications. Under the current COVID-19 crisis, there is a serious ethical problem with this otherwise correct approach. Because melatonin is known as a safe, inexpensive, readily-available over-the-counter product, how could we justify its nonuse to millions of people not benefitting from it at the time of a deadly crisis?[8] Therefore, we propose to immediately inform physicians, nurses, health care providers, and the general public of the potential benefits of melatonin in COVID-19 patients.

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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.

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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]

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