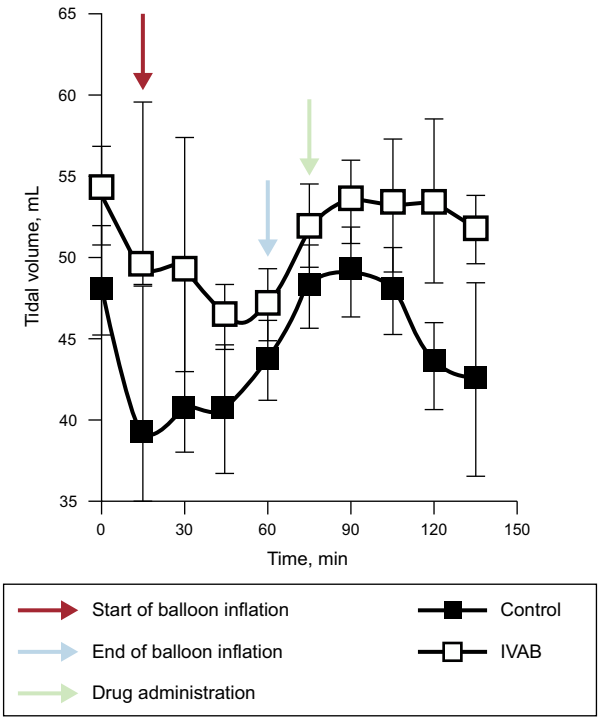

Figure 2. Change in tidal volume in ivabradine and control groups. IVAB, ivabradine.

CONFLICTS OF INTEREST

Servier provided ivabradine in powder for intravenous administration free of charge.

Marina Pascual Izco,[a] Borja Castejón,[b] María José Piedras,[b] José Luis Zamorano,[a] Marcelo Sanmartín,[a,*] and Carlos Zaragoza[b]

[a]*Servicio de Cardiología, Hospital Universitario Ramón y Cajal (IRYCIS)-Universidad de Alcalá de Henares, Madrid, Spain*
[b]*Servicio de Cardiología, Unidad de Investigación del Hospital Ramón y Cajal (IRYCIS)-Universidad Francisco de Vitoria, Madrid, Spain*

* Corresponding author:
E-mail address: msanfer@me.com (M. Sanmartín).

Available online 28 March 2017

REFERENCES

1. Núñez-Gil IJ, Martín-Reyes R, Bardají A, et al. Ischemic heart disease and acute cardiac care 2015: a selection of topical issues. *Rev Esp Cardiol.* 2016;69:408–414.
2. Roubille F, Lattuca B, Busseuil D, et al. Is ivabradine suitable to control undesirable tachycardia induced by dobutamine in cardiogenic shock treatment? *Med Hypotheses.* 2013;81:202–206.
3. Verrier RL, Silva AFG, Bonatti R, et al. Combined actions of ivabradine and ranolazine reduce ventricular rate during atrial fibrillation. *J Cardiovasc Electrophysiol.* 2015;26:329–335.
4. Pascual Izco M, Alonso Salinas G, Sanmartín Fernández M, et al. Clinical experience with ivabradine in acute heart failure. *Cardiology.* 2016;134:372–374.
5. Barillà F, Pannarale G, Torremeo C, et al. Ivabradine in patients with ST-elevation myocardial infarction complicated by cardiogenic shock: a preliminary randomized prospective study. *Clin Drug Investig.* 2016;36:849–856.
6. Bakkehaug JP, Naesheim T, Torgersen Engstad E, et al. Reversing dobutamine-induced tachycardia using ivabradine increases stroke volume with neutral effect on cardiac energetics in left ventricular post-ischaemia dysfunction. *Acta Physiol.* 2016;218:78–88.

http://dx.doi.org/10.1016/j.rec.2017.03.009
1885-5857/

Prevention of Cardiac Adverse Events Associated With the Use of Drugs in Patients With Severe Mental Illness: Case Report

Prevención de eventos adversos cardiacos relacionados con el uso de fármacos en pacientes con trastorno mental grave: a propósito de un caso

To the Editor,

Patients with severe mental disorders often have several comorbidities and are prescribed a large number of drugs, making them susceptible to the development of medication-related problems.[1] Care of their physical health should form part of the overall therapeutic approach used in this population. Preventive measures should be established to avert risk situations, such as the development of potentially life-threatening adverse events, including those associated with the use of medication that affects cardiac conduction. It is important for physicians to be aware of the adverse cardiovascular events associated with drugs used for cardiac and noncardiac diseases, as well as their potential interactions.[2]

Conduction changes can manifest as an acquired prolongation of the QT interval on electrocardiography (ECG), the most common cause of which is drug-related. This abnormality is a recognized risk factor for sudden death secondary to ventricular arrhythmias such as *torsade de pointes*.[3] In addition, conduction blocks can occur, as has been described with lithium use.[4] Complete left bundle branch block (LBBB) is a potential marker of severe heart disease, although in some cases it is not associated with recognizable structural abnormalities and shows a characteristic ECG pattern.

We describe the case of a 56-year-old man. Strict cardiac monitoring carried out in our center detected a new-onset LBBB during formoterol treatment that resolved following discontinuation of the drug. The ECG monitoring protocol used has been included in the 2015 Best Practice Guidelines of the Spanish Health System, approved by the SHS Interterritorial Council of April 13, 2016.[5]

The patient had no hypertension and no known heart disease. He was diagnosed with paranoid schizophrenia, hyperthyroidism, and chronic obstructive pulmonary disease, and was receiving treatment with clotiapine 40 mg/d, clorpromazine (40 mg/mL) 250 drops/d, levothyroxine 25 μg/d, omeprazole 20 mg/d, acetylcysteine 600 mg/d, calcium/vitamin D 600 mg/1000 IU in 1 tablet/d, and ipratropium bromide 18 μg/d. Follow-up ECGs since admittance had yielded normal results, with the last recordings showing sinus rhythm at 70 bpm, no atrioventricular or branch blocks, and QTc 399 ms.

At 7 months following admittance to our center, the patient was started on treatment with formoterol 12 μg/d because of poor control of his chronic obstructive pulmonary disease, with symptom improvement. At 7 days after initiation of this treatment, ECG examination detected a new-onset LBBB, with sinus rhythm at 70 bpm and QTc 438 ms (Figure). In addition, the patient reported chest pain at rest of 5 minutes' duration on various occasions

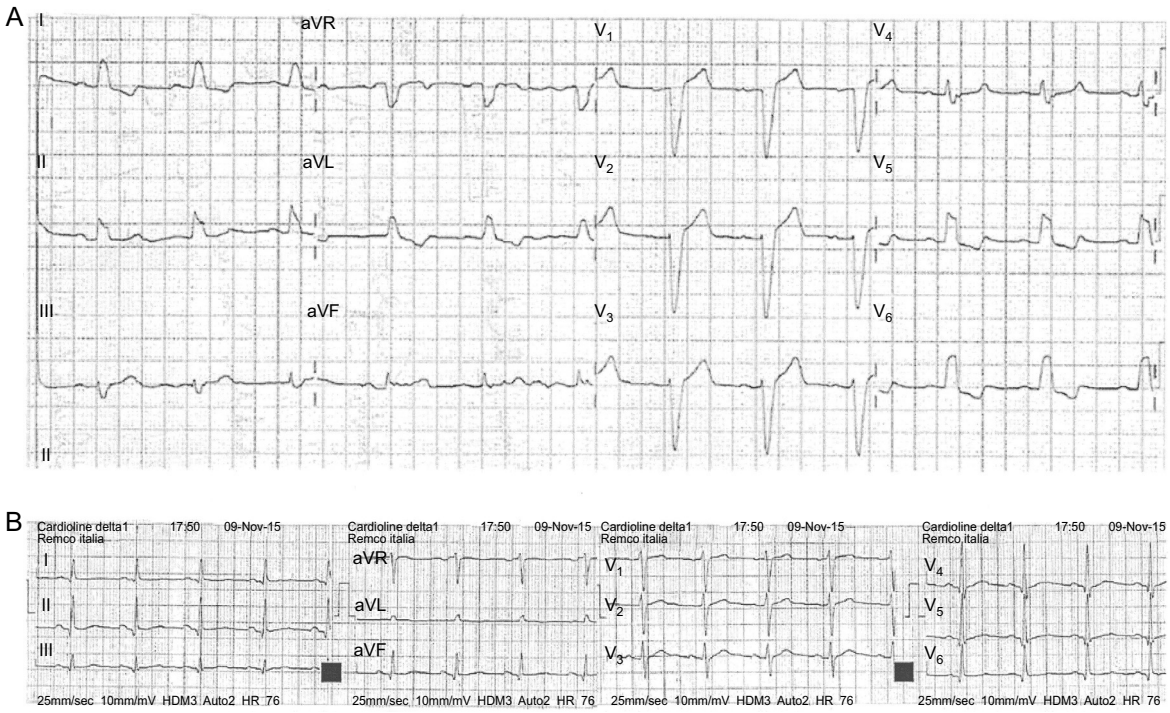

Figure. A: Electrocardiogram performed following initiation of formoterol treatment, showing sinus rhythm and complete left bundle branch block. B: Electrocardiogram following discontinuation of formoterol, showing sinus rhythm without left bundle branch block.

during the previous 4 days, which prompted his urgent referral to the reference center. Serial troponin T determinations were negative and stress transthoracic echocardiography disclosed no relevant structural heart disease, thereby excluding an acute coronary syndrome. The patient was discharged with a diagnosis of mechanical chest pain and a recommendation for cardiologic follow-up. Upon his return to our center, formoterol treatment was stopped. At 10 days after discontinuation of the drug, a new follow-up showed resolution of the LBBB with QTc measuring 433 ms and heart rate at 78 bpm.

On application of the Naranjo[6] algorithm to analyze the causal relationship between formoterol administration and the appearance of the adverse reaction, the relationship was deemed "probable". The case was notified to the Spanish Drug Surveillance System.

The José Germain Psychiatric Institute of Mental Health Services is a publically-funded health center that provides specialized mental health care. Since 2013, an internal protocol has been in operation to prevent iatrogenic sudden death secondary to pharmacological treatment. At admission, all patients undergo a systematic evaluation, including ECG, by internal medicine specialists. The QT interval value is corrected according to the heart rate (corrected QT [cQT]), using the Bazzet formula in patients whose heart rate is 40 to 80 bpm and the Friedericia formula for other rates.[3] After the baseline examination, periodic ECG monitoring is carried out, according to the characteristics of the individual patients and the pharmacological treatment they are receiving. The aim is to monitor QT segment prolongation and other heart rhythm abnormalities.

Since implementation of ECG monitoring of patients admitted to our center, several cases of drug-related QT interval prolongation have been identified and reported to the Spanish Drug Surveillance System. However, this is the first time new-onset LBBB has been detected in association with administration of a drug.

Although an acute coronary syndrome was ultimately excluded in the case described, we believe it is important for psychiatric centers to have protocols designed to detect cardiac risk situations that may have a fatal outcome. It is recommended to include ECG monitoring in patients with severe mental disorders to improve the safety of their health care. All patients receiving several medications are at higher risk of experiencing potentially serious adverse events due to drug interactions that may go unnoticed by the treating clinician.[2]

Elena López-Lunar,[a,*] Cristóbal Manuel Rodríguez-Leal,[b] Rosa María Provencio-Arranz,[a] José Manuel Carrascosa-Bernáldez,[c] and Álvaro Rivera-Villaverde[c]

[a]*Servicio de Farmacia Hospitalaria, Instituto Psiquiátrico Servicios de Salud Mental José Germain (IPJG), Leganés, Madrid, Spain*
[b]*Servicio de Medicina Interna, Instituto Psiquiátrico Servicios de Salud Mental José Germain (IPJG), Leganés, Madrid, Spain*
[c]*Departamento de Dirección, Instituto Psiquiátrico Servicios de Salud Mental José Germain (IPJG), Leganés, Madrid, Spain*

* Corresponding author:
E-mail address: elopezlunar@gmail.com (E. López-Lunar).

Available online 9 March 2017

REFERENCES

1. Kukreja S, Kalra G, Shah N, Shrivastava A. Polypharmacy in psychiatry: a review. *Mens Sana Monogr.* 2013;11:82–99.
2. Romero-León JM, Gálvez-Contreras MC, Díez-García LF. Bradicardia sintomática e insuficiencia cardiaca precipitadas por ivabradina a una paciente que recibe tratamiento antirretroviral. *Rev Esp Cardiol.* 2016;69:529.

3. Fanoe S, Kristensen D, Fink-Jensen A, et al. Risk of arrhythmia induced by psychotropic medications: a proposal for clinical management. *Eur Heart J*. 2014;35:1306–1315.
4. Ficha técnica. Centro de Información online de Medicamentos de la AEMPS – CIMA [accessed 1 Jun 2016]. http://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=buscar.
5. Buenas prácticas en el Sistema Nacional de salud 2015. "Prevención de la muerte cardiaca súbita yatrogenica" [accessed 7 Dec 2016]. http://www.msssi.gob.es/organizacion/sns/planCalidadSNS/pdf/BBPP_2015/Estrategia_Cardiopatia/BBPP_CARDIO_Madrid_1.pdf.
6. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–245.

http://dx.doi.org/10.1016/j.rec.2017.02.022
1885-5857/

Saxagliptin and Heart Failure in the SAVOR-TIMI 53 Trial: Reflections on the Bradford Hill Criteria

Saxagliptina e insuficiencia cardiaca en el estudio SAVOR-TIMI 53: bajo la lupa de Bradford Hill

To the Editor,

The association between saxagliptin use and an increased risk of hospitalization for heart failure (HF) has generated considerable controversy.[1,2] One reason is that the mechanisms of the potential deleterious effect are mainly unknown and speculative. Second, to make the scenario even more complex, we recently pointed out a high risk of type 1 error (chance finding) in the SAVOR-TIMI 53 trial due to an insufficient Bonferroni correction and an apparent deviation from the initial statistical analysis planned by the authors.[3]

Give the controversy surrounding the relationship between saxagliptin and HF and in an effort to help resolve it, the present article aims to provide a summarized review of the association using the Bradford Hill criteria of causation.

As described by Hill, the criterion *strength of association* attempts to determine whether there is a relationship between the putative causal factor and the effect under study. The more distant the relative risk is from 1, the larger is the strength of the association. With saxagliptin, the hazard ratio (HR) was 1.27 and the 95% confidence interval (95%CI), 1.07-1.51 (P = .007).[1] A subsequent analysis including all HF hospitalizations (analysis of recurrent events or Andersen-Gill analysis) showed a slight attenuation of this relationship (HR, 1.26) as well as a reduction in the lower limit of the 95%CI to 1.02, that is, very close to the null hypothesis.[1] This attenuation was produced because the greater risk of HF in saxagliptin-treated patients was only observed in the first 314 days, being virtually neutral thereafter (HR, 1.05; 95%CI, 0.81-1.35).[1] An analysis "excluding the first hospitalization for HF" as part of a sensitivity analysis using another approach, known as the Prentice-Williams-Peterson model, did not find a higher associated risk (HR, 1.06; 95%CI, 0.75-1.50).[1] Thus, different statistical models yielded distinct, even contradictory results. In addition, we should not overlook that HF hospitalization was a secondary endpoint, understood therefore, as exploratory, which would increase the probabilities of chance. Because of all these considerations, the strength of the association is likely to be weak.

Hill considered an association *consistent* if the relationship between the 2 variables were upheld in more than 1 study, in different populations and circumstances. For saxagliptin, the relationship shows little consistency, as it has not been confirmed by recent retrospective observational studies[4] (although this is not true of all[5]) and there is no robust experimental evidence.

The criterion of *specificity* refers to an effect being attributable to a single cause. With regard to the excess HF risk in the saxagliptin group, one might speculate that it could be due to chance because of the multiplicity of secondary variables (up to 10),[3] or to the fact that there were more deaths (nonsignificantly) in the saxagliptin group, which could lead to a smaller number of patients at risk and therefore, an upward bias in the HF incidence rate.[3]

Temporality, as related to an association, is essential to ensure that the risk factor appeared before the putative effect, which is verified in the study.[1]

The *biological gradient* or dose-response relationship encompasses the concept that increased exposure or dose increases the incidence of a disease. Currently, there is no evidence of a dose-response relationship for the association between saxagliptin and HF.

With regard to *biological plausibility*, the biological context should logically explain the etiology by which a cause produces an effect. This concept is closely related to reproducibility and experimental evidence. In this regard, it should be mentioned that the finding was completely unexpected, as previous studies did not show a greater risk of edema or water retention.[1] Endothelial dysfunction and increased left ventricular volumes have been cited as potential mechanisms,[1] although other studies indicate benefits.[6]

Coherence refers to an association being in line with previous knowledge regarding biological mechanisms. Again, the association was unexpected, in disagreement with later studies[4] (although not all[5]), and did not have a constant mechanism relating cause and effect.

Lastly, *analogy* is based on established cause-effect relationships, whereby if one risk factor produces an effect, another with similar characteristics should have the same impact. In this line, previous data from the same family of drugs (alogliptin) indicate that there could be a nonsignificant numerical trend toward a higher risk of HF.

In conclusion, on application of the Bradford Hill criteria to evaluate the relationship between saxagliptin use and the risk of HF hospitalization, a robust association was not found. However, as safety is a priority, it is essential to carry out new, specific, prospective studies to confirm or rule out this association.

Ana M. Cebrián Cuenca,[a] Domingo Orozco Beltrán,[b] Jorge Navarro Pérez,[c] Fernando Álvarez-Guisasola,[d] Julio Núñez Villota,[c] and Luciano Consuegra-Sánchez[e,*]

[a]*Centro de Salud San Antón, Cartagena, Murcia, Spain*
[b]*Centro de Salud Cabo Huertas, San Juan de Alicante, Alicante, Spain*
[c]*Instituto de Investigación Sanitaria INCLIVA, Valencia, Spain*
[d]*Centro de Salud de la Ribera del Órbigo, Benavides de Órbigo, León, Spain*
[e]*Servicio de Cardiología, Hospital General Universitario de Santa Lucía, Cartagena, Murcia, Spain*

[*] Corresponding author:
E-mail address: lconsue@gmail.com (L. Consuegra-Sánchez).

Available online 9 March 2017