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Early bradycardia in patients with COVID-19 and triple therapy

Bradicardia temprana en pacientes con COVID-19 y triple terapia

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Keywords:
Bradycardia, COVID-19, hydroxychloroquine, azithromycin, lopinavir-ritonavir drug combination.

Palabras clave:
Bradicardia, COVID-19, hidroxicloroquina, azitromicina, combinación de fármacos lopinavir/ritonavir.

ABSTRACT

Because there is still no effective medical treatment for COVID-19, off-label drugs have been used such as hydroxychloroquine or chloroquine, lopinavir/ritonavir and/or azithromycin, whose safety information is limited with the risk of developing potential cardiac adverse effects. In order to contribute with the safety information about combined drugs used in COVID-19, we used the CARE Guidelines: Consensus based Clinical Case Reporting Guideline Development by EQUATOR Network (Enhancing the Quality and Transparency of Health Research) to present four patients, without known cardiac pathology or evidence of cardiac rhythm disorders, who developed early sinus bradycardia, 1 to 3 days after the concomitant use of triple therapy with hydroxychloroquine, lopinavir/ritonavir and azithromycin, which solved after the suspension of one or more of the mentioned medications. These cases contribute to improving the awareness of safety concerns about the past use of off-label drugs for COVID-19. The risk of bradycardia with the triple therapy presented should be considered.

RESUMEN

Debido a que aún no hay un tratamiento médico efectivo para la COVID-19, se han utilizado medicamentos fuera de indicación como la hidroxicloroquina o cloroquina, lopinavir/ritonavir y/o azitromicina, cuya información de seguridad es limitada con el riesgo de la presencia de efectos adversos cardiacos potenciales. Con la finalidad de contribuir con la información de seguridad del uso de combinación de medicamentos para COVID-19, seguimos la Guía «Consensus based Clinical Case Reporting Guideline Development» desarrollada por la Red EQUATOR (Enhancing the Quality and Transparency of Health Research) para presentar cuatro pacientes, sin patología cardiaca conocida o evidencia de trastornos del ritmo cardiaco, que desarrollaron bradicardia sinusal temprana uno a tres días posteriores al uso concomitante de la triple terapia con hidroxicloroquina, lopinavir/ritonavir y azitromicina, la cual remitió tras la suspensión de uno o más de los medicamentos mencionados. Estos casos contribuyen a mejorar el conocimiento de los problemas de seguridad sobre el uso pasado de medicamentos no aprobados para la COVID-19. Se debe considerar el riesgo de bradicardia con la triple terapia presentada.

INTRODUCTION

In the absence of an effective treatment against the infection by the new SARS-CoV-2 coronavirus, multiple pharmacological options that over the years have shown effectiveness for the management of other viral infections have been evaluated. For example, the combination lopinavir/ritonavir (L/R) is used in patients with HIV/AIDS infection. It has been shown to have inhibitory activity *in vitro* against the virus that causes Severe Acute Respiratory Syndrome (SARS) in humans.[1] Hydroxychloroquine (HCQ), known for its immunomodulatory properties, has shown *in vitro* its potential beneficial effect by limiting the entry of the virus into cells and its replication,[2] likewise, an experimental study reported that the combination of HCQ with azithromycin, macrolide antimicrobial with immunomodulatory properties, has the ability to decrease viral loads more quickly.[3]

The American Heart Association (AHA) has listed HCQ among the agents that can cause direct myocardial toxicity or exacerbate underlying myocardial lesions.[4] While the CredibleMeds database, an online resource

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that promotes the safe use of medications, classify azithromycin and HCQ in the category of drugs with known risk, and to L/R as a possible risk, in relation to the ability to prolong the QT interval.[5]

The term bradycardia refers to a heart rate less than 60 beats per minute. Its etiology can be intrinsic (ischemic heart disease, acute myocardial infarction, acute and chronic coronary disease, sick sinus syndrome, radiotherapy, myocarditis, among others) or extrinsic (endotracheal aspiration by vasovagal reflex, β-blockers, digoxin, blockers of calcium channels, class I to IV antiarrhythmic, hypothyroidism, sleep apnea, hyperkalemia, etc.).[6] Only some patients present symptoms such as fatigue, exercise intolerance, dizziness, syncope, worsening of cardiac pathologies or cognitive deceleration,[6] which require interventions for their correction.

Recently, it has been reported that there is a tropism of SARS-CoV-2 for cardiac tissue, and viral load and particles have been found in the myocardium of infected patients.[7]

Until now, only potential cardiac rhythm disturbances derived from the combination of HCQ and azithromycin as part of the treatment for patients with SARS-CoV-2 infection have been reported in the literature, without mentioning the association of these drugs with L/R. Using the CARE Guidelines: Consensus based Clinical Case Reporting Guideline Development by Equator Network, we present the case of four patients with confirmed COVID-19 infection, in whom sinus bradycardia was identified during the first week, after exposure to the triple therapy based on HCQ, L/R and azithromycin.

RESULTS. PRESENTATION OF CASES

I. Patient information

a) Demographic and clinical information of the cases *(Table 1)*
b) Medical, family and psychosocial history including relevant genetic information

Case 1:

- Family history: genetic load for DM2.
- NPPI: recent immunizations: influenza and pneumococcus in November 2019.
- PPI: traumatic: Fracture of the 5th metatarsal 30 years ago, conservative treatment. Previous hospitalizations: in 2019, with a

Table 1: Demographic and clinical information of the cases.

Variable	Case 1	Case 2	Case 3	Case 4
Age (years)	55	54	67	73
Sex	Male	Male	Female	Male
Non cardiac comorbidity	No	DM2 Hypertriglyceridemia	DM2	No
Cardiac comorbidity	No	No	No	No
BMI category (BMI kg/m^2)	Normal (23.5)	Overweight (29.6)	Overweight (28.3)	Normal (22.8)
Bradycardia onset after use of HCQ, azithromycin and L/R (days)	2	1	3	3
Corrected QT interval on bradycardia day by Bazett (ms)	s/d	429	490	365
Tisdale score on bradycardia day	9/moderate	10/moderate	11/high	11/high
Length of hospital stay (days)	65	49	46	79
Survivor	No	Yes	No	No

BMI = body mass index, DM2 = type 2 diabetes mellitus, HCQ = hydroxychloroquine, L/R = lopinavir/ritonavir, ms = milliseconds.

diagnosis of influenza pneumonia. Smoking: suspended 30 years ago, positive for 10 years at the rate of 3 cigarettes per day. Smoking index (SI): 1.5 packages a year.

Case 2:

- Family history: mother: alive, 82 years old, diagnosed with breast cancer, DM2 under treatment. Father: 83 years old deceased, due to acute myocardial infarction, history of chronic obstructive pulmonary disease. Four living siblings, two with a diagnosis of DM2 and systemic arterial hypertension (SAH).
- NPPI: immunization against influenza in November 2019. Exposure to chemical dusts and/or solvents for 30 years.
- PPI: DM2 for 12 years, on treatment with insulin NPH 15 IU in the morning and 25 IU at night, metformin 850 mg every 8 hours, in apparent good control. Familiar hypertriglyceridemia being treated with 400 mg bezafibrate every 24 hours. Allergies: penicillin. Surgical: strabismus correction at age 9, without complications.

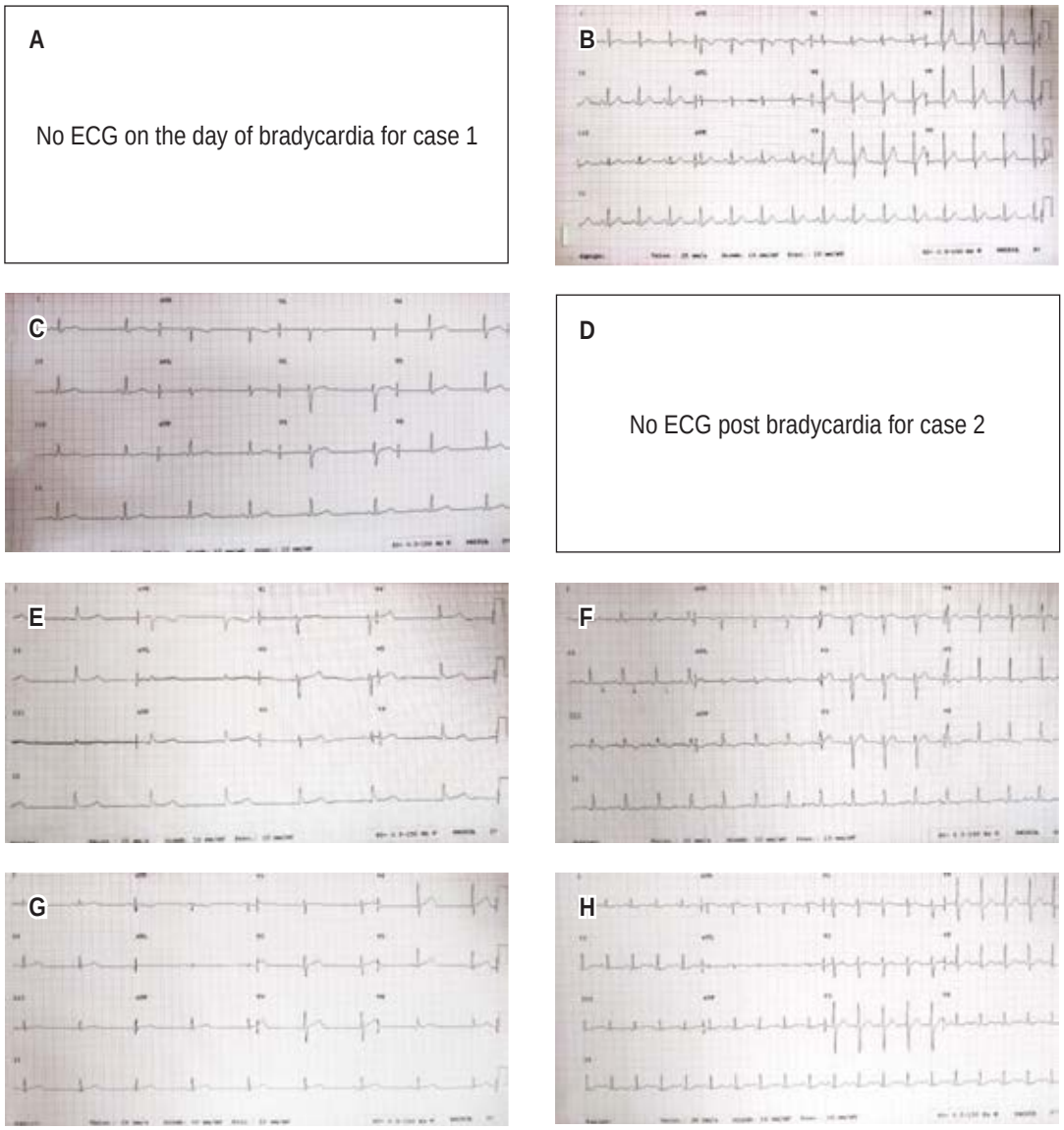


Figure 1:

Electrocardiograms (ECGs) of the cases. Electrocardiograms (ECGs) are shown for each case. The left column represents ECGs at the day of the event (bradycardia), and the right column represents ECGs days after the event (bradycardia). **A, B:** Case 1. **C, D:** Case 2. **E, F:** Case 3. **G, H:** Case 4.

Case 3:

- Family history: father died at 68 years old with history of SAH and DM2. Mother died at 71 years old due to complications of DM2 with history of SAH as well. Five living siblings, diagnosed with DM2 and SAH (systemic arterial hypertension). Five children alive, apparently healthy.
- NPPI: denies immunization against influenza.
- PPI: diagnosis of DM2 for 18 years, with regular adherence to unspecified oral treatment. Second hand smoking, by her husband, suspended 15 years ago.

Case 4:

- Family history: unknown.
- NPPI: contact with a co-worker with a diagnosis of COVID-19.
- PPI: smoking: positive from 20 to 60 years old at the rate of 20 cigarettes a day. SI: 40 packages a year. Rest denied.

II. Admission diagnostics

Case 1. Septic shock of pulmonary origin. Community acquired pneumonia (CAP) of atypical presentation. SARS-CoV-2 infection.

Case 2. CAP due to SARS-CoV-2. Uncontrolled DM2.

Case 3. SARS-CoV-2 infection. Multisegmental CAP of viral etiology by SARS-CoV-2. DM2.

Case 4. Pulmonary focus septic shock. Moderate acute respiratory distress syndrome. Atypical pneumonia due to SARS-CoV-2. Type 1 respiratory failure.

III. Clinical findings and timeline

To determine the medications used concomitantly that prolong the QT interval, we considered that in approximately seven half lives (t ½) the totality of the drug is eliminated from the body, and therefore, the following times were established:[8]

- Azithromycin t ½: 72 hrs, approximately in 21 days the drug is eliminated from the body.
- Hydroxychloroquine t ½: 40 days, approximately in 9 months.
- Lopinavir t ½: 6 hrs and ritonavir t ½: 5 hrs, approximately in 2 days.
- Dexmedetomidine t ½: 3 hrs, approximately in 21 hrs.
- Furosemide t ½: 2 hrs, approximately in 14 hrs.

IV. Diagnostic evaluation

a) Electrocardiograms (ECGs) of the cases at the day of the bradycardia (on the left) and days after the bradycardia (on the right) in *figure 1*.
b) Diagnosis

Sinus bradycardia confirmed by ECG (all cases).

V. Therapeutic intervention

The intervention in all cases was the suspension of some of the medications involved, see the suspension dates on the pharmacotherapy timeline in *Figures 2 to 5*.

VI. Monitoring and results

a) Clinical results

For all cases, the sinus bradycardia was transient, with spontaneous resolution within 1 to 5 days after discontinuation of some of the suspected medications.

b) Follow-up of important diagnostic tests or other

Follow-up ECG.

c) Discharge diagnosis

Case 1. Acute myocardial infarction. Acute respiratory illness due to SARS-CoV-2.

Case 2. Severe acute respiratory illness due to SARS-CoV-2. Remitted acute respiratory distress syndrome. Tracheostomy status. Remitted acute kidney injury AKI III. DM2.

Case 3. Severe acute respiratory illness due to SARS-CoV-2. Severe acute respiratory distress syndrome. Septic shock. DM2. Acute kidney injury.

Case 4. Severe acute respiratory illness due to SARS-CoV-2. Severe acute respiratory distress syndrome. Septic shock. Ventilator associated pneumonia. Acute kidney injury. DM2.

DISCUSSION

a) Strengths and limitations of case management

The strength of the study lies in the fact that no patient had a history of previous cardiovascular disease or electrolyte imbalances during bradycardia that could explain it. Likewise, the heart rhythm disorder reversed after the suspension of some of the medications involved.

The main limitation identified is that during the approach it was difficult to carry out complementary diagnostic studies for the intentional search for silent cardiovascular disease, as well as the lack of measurement of other variables because the patients were not enrolled in a research protocol and the number of patients involved.

b) Discussion of relevant medical literature

As a result of the limited scientific evidence on the efficacy and safety profiles of the use of drug combinations such as L/R, HCQ and azithromycin, some authors emphasize the role that identification of adverse events plays through spontaneous notification systems in pharmacovigilance to ensure the safety of new therapeutic options or those redirected for COVID-19.[9]

This report included four critical patients, three men and one woman, without known

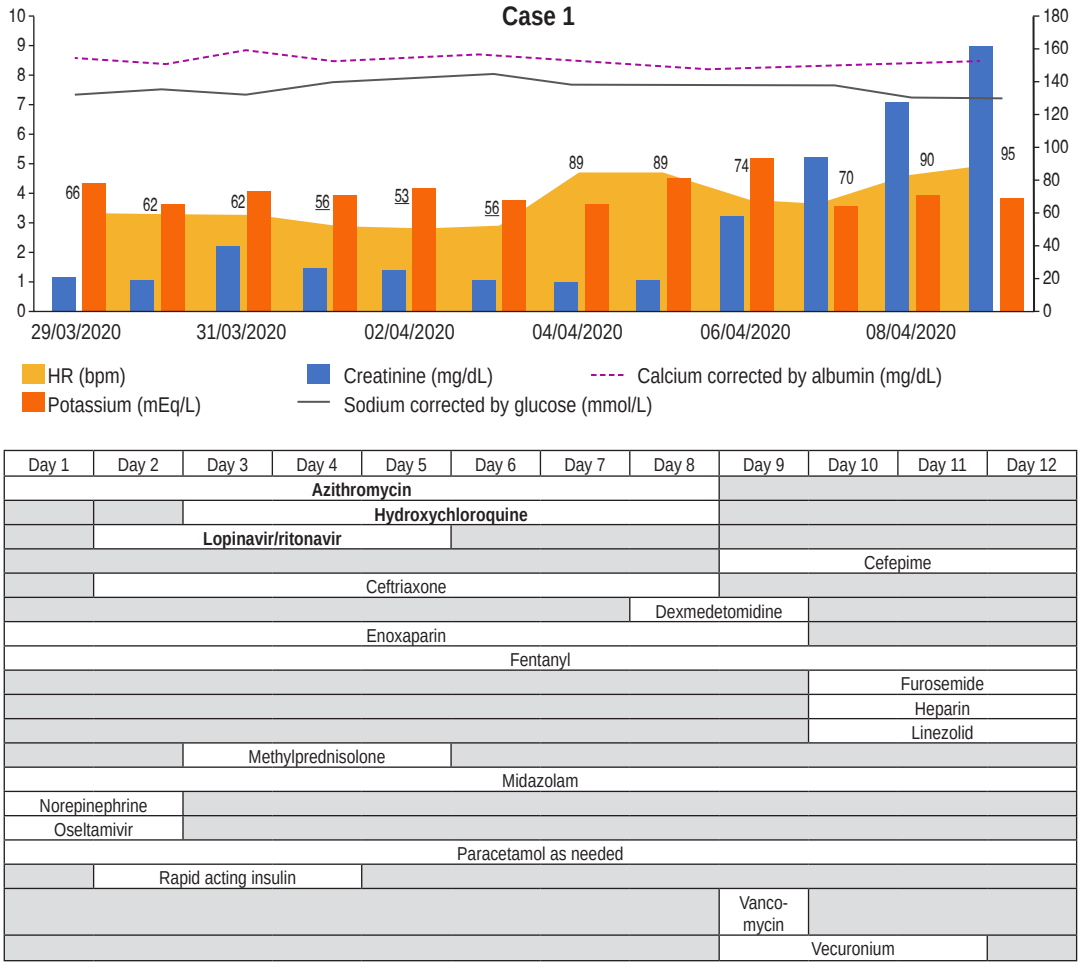
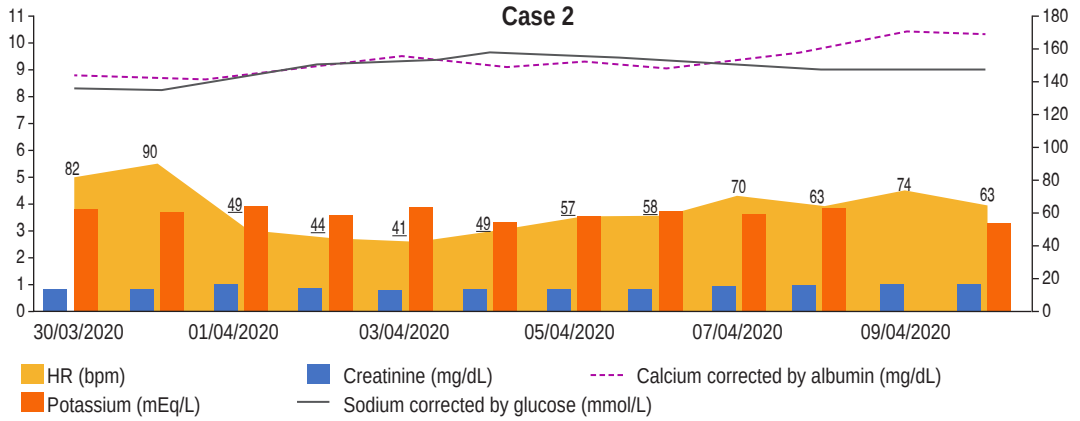


Figure 2:

Relevant clinical variables and pharmacotherapy timeline. Represents clinical variables (heart rate, creatinine, potassium, calcium corrected by albumin and sodium corrected by glucose) and drugs used in the first 12 days of hospitalization to observe their evolution before, during and after the development of bradycardia of each case. Case 1. For each case, the heart rate (HR) is represented in beats per minute (bpm) and underlined those with bradycardia.



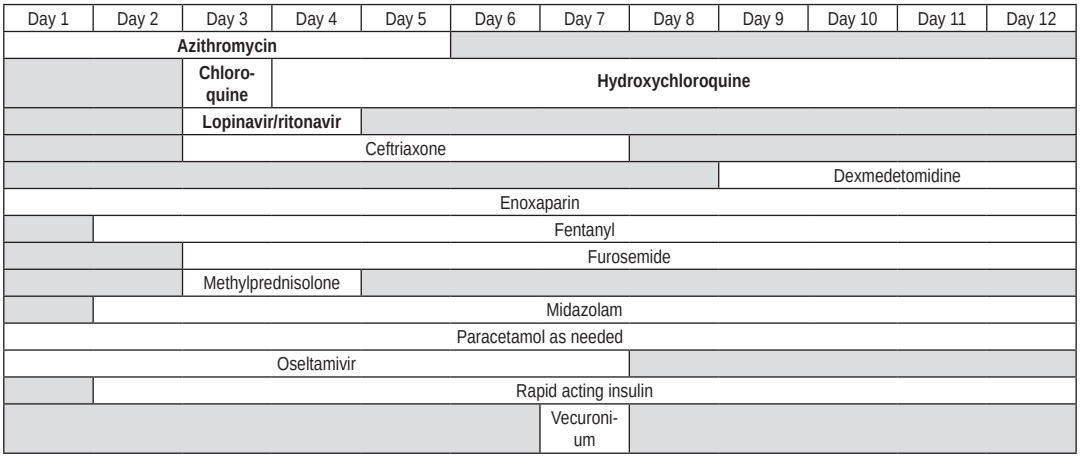


Figure 3:

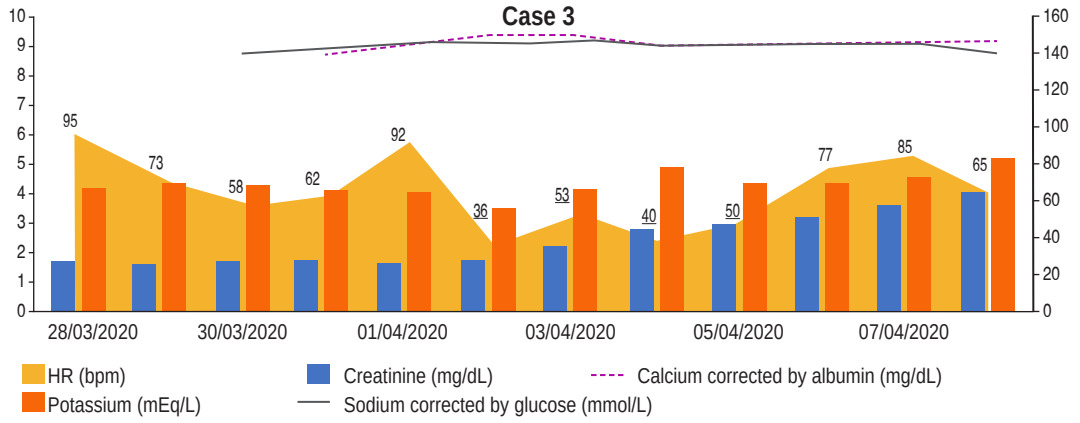
Case 2.

heart disease or evidence of heart rhythm disorders upon admission who developed sinus bradycardia. Although there are no reports that describe the type of arrhythmia,[10] they were present in 16.7% of a Chinese cohort of 138 hospitalized patients with COVID-19, and they were more frequent in critical patients than in non critical patients (44.4 vs 6.9%).[11]

The time interval since the triple therapy was started and the development of bradycardia was between 1 to 3 days. However, it must be taken into consideration that, due to the half-life of the medications involved, it is expected to find plasma concentrations in the body after their suspension, with the risk of triggering potential drug interactions.[12] Among the medications with a potential negative chronotropic effect, it was identified that all patients had fentanyl-based analgesia, and only one patient was being administered dexmedetomidine at the time of bradycardia onset.

Because there was not enough evidence about the efficacy of triple therapy, and when the benefit-risk balance of its continuity was evaluated, especially concerning potential cardiovascular events, it was decided to stop the administration of one or more of the medications involved, observing in all patients a return to normal heart rate in an average of 4 days (2, 5, 4 and 5 days respectively for each case).

Amaratunga et al. suggest that the development of bradycardia in this group of patients could be a manifestation directly related to COVID-19 due to alterations in the pacemaker cells' heart rhythm dynamics or due to limiting their response capacity derived from the pro-inflammatory cytokine cascade,[13] while Hu et al. attribute bradycardia to the inhibitory effect of the virus on the activity of the sinus node.[14] However, the temporality among the event (bradycardia) and the medication exposure,



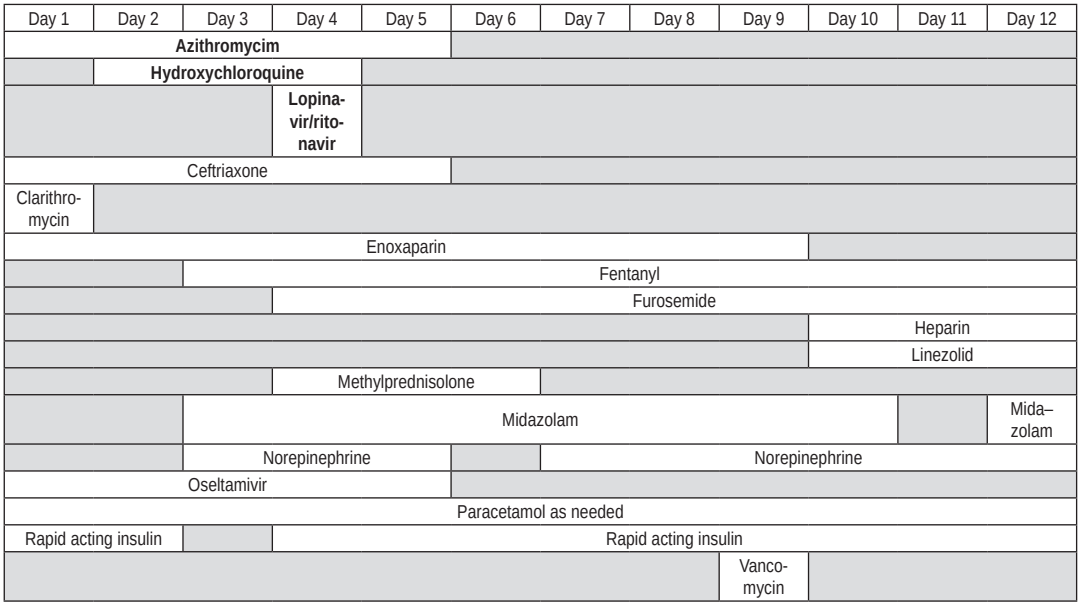


Figure 4:

Case 3.

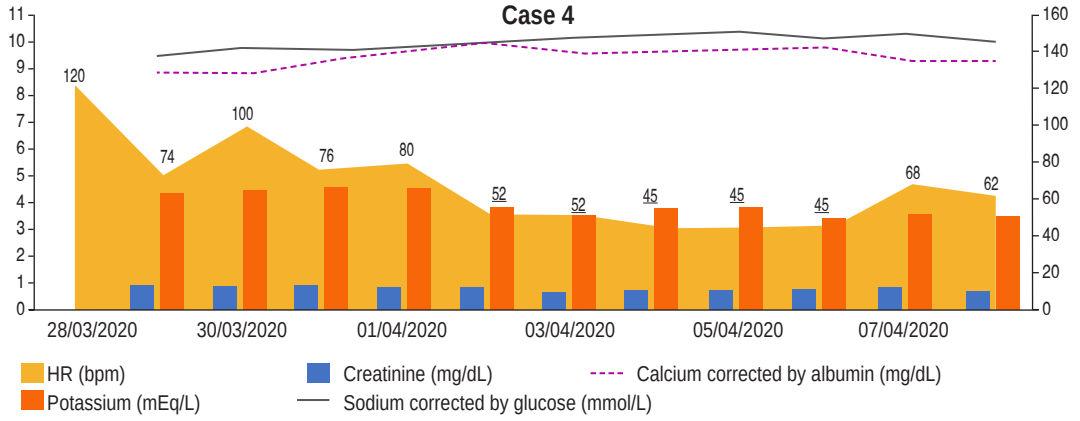
the response to its discontinuation and the knowledge of its arrhythmogenic potential, are three of the Bradford Hill causality criteria that strongly support the establishment of the causal relationship between medications and bradycardia.

Evidence from studies in patients who usually use HCQ for autoimmune diseases such as lupus or rheumatoid arthritis, report that the observed heart rhythm disturbances, prolongation of the QT interval/torsades de pointes (TdP), are attributed to azithromycin more than to the combination of azithromycin and HCQ or HCQ alone (lower value of the 95% CI of the proportional reporting ratio 3.80 vs 1.80 vs 1.29),[9] likewise, Lane et al. suggest that the use of HCQ is safe as they do not find an increased risk of serious adverse events after 30 days of use, including myocardial infarction, stroke, transient ischemic attack, cardiac arrhythmias, among others, however, when azithromycin was added to HCQ treatment, an increased risk of cardiovascular mortality was observed after 30 days of use (HR 2.19 [95% CI 1.22-3.94]), chest pain/ angina (HR 1.15 [95% CI 1.05-1.26]), and heart failure (HR 1.22 [95% CI 1.02-1.45]), thus suggesting that the increased risk of cardiovascular mortality with the combined therapy could arise through the synergistic effect (drug interaction) for the induction of lethal arrhythmias (TdP) or as an adverse effect of azithromycin alone, however

the design of the afore mentioned study did not allow this evaluation.[15]

Some authors even recommend serial ECG for patients who require a combination of medications with proarrhythmic risks, such as HCQ, favipiravir, L/R, macrolides, fluoroquinolones and/or piperacillin/tazobactam; however, it is reported that drug interactions are usually underestimated when drugs are used off label for the treatment of new diseases.[12] A preliminary report showed that the maximum change in the QT interval in patients diagnosed with COVID-19 treated with HCQ and azithromycin occurred between 3 and 4 days,[16] so in an environment with limited resources, this monitoring could be carried out every 3-4 days.[12] Among the patients involved in the present report, the QT interval was only prolonged in case 3 at the time of the development of bradycardia.

Finally, only one patient (case 1) presented fever during the reported bradycardia event. On days 6 and 7 the patient had relative bradycardia, having heart rate (HR) < 100 bpm despite fever (38-38.5 ºC), but on day 8 the relative bradycardia remitted since the patient had HR > 100 bpm during fever. On day 5, lopinavir/ritonavir was suspended, continuing with azithromycin and hydroxychloroquine, and by day 8 the bradycardia had already remitted, so it continued meeting causality criteria



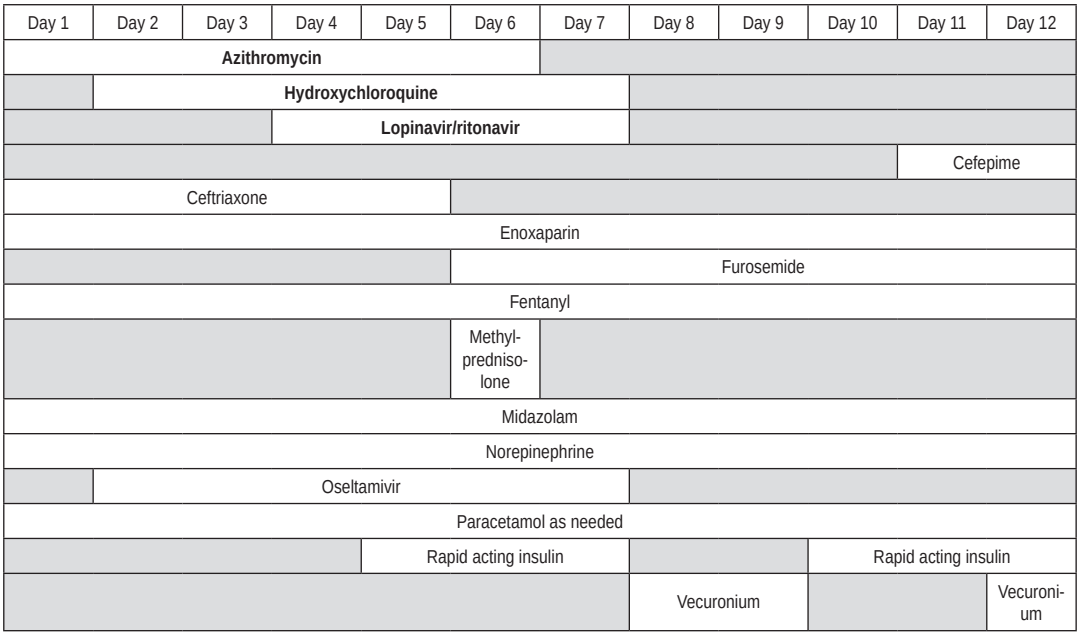


Figure 5:

Case 4. For each case, the heart rate (HR) is represented in beats per minute (bpm) and underlined those with bradycardia.

between bradycardia and exposure to drugs, such as the appearance of the event after the beginning of the medications and the response to stopping one of them.

CONCLUSIONS

Efficacy and safety of COVID-19 treatment are still evolving, so it is important to provide information, in this case regarding the use of triple therapy with HCQ, L/R and azithromycin, where no information was found.

Multiple factors could contribute to the development of sinus bradycardia in addition to the triple therapy for COVID-19, such as sedation or the probable presence of viruses in the myocardium, so the monitoring of the patients' heart rate should be strengthened during treatment of severe COVID-19 pneumonia and do not forget to consider the presence of relative bradycardia to identify it correctly.

It is recommended to establish early monitoring guidelines for patients to assess the benefit-risk of treatments in conditions where there are no established pharmacological guidelines with an evaluation of the efficacy and safety and even more when the pharmacokinetics of these medications in Mexican people with COVID-19 is still unknown.

The main lesson learned from this case report is that the risk of bradycardia with triple therapy (HCQ, L/R, and azithromycin) should be considered to improve the awareness of safety concerns about the past use of off-label drugs for COVID-19.

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