Cardiovascular events related to the use of macrolides in an intensive care unit

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Abstract

Introduction and objectives: macrolides are widely used antibiotics for which a greater frequency of cardiovascular events related to increased arrhythmias has been reported. This study seeks to describe some cardiovascular complications of the use of macrolides in ICU patients.

Materials and methods: this was a descriptive cross-sectional study which included adult patients admitted to the Medical Intensive Care Unit at the Fundación Cardioinfantil who received antibiotic treatment with clarithromycin in 2013 and 2015.

Results: the collected sample was 38 patients. The median age was 64 years, and clarithromycin was most frequently used for treating community-acquired infections, with pneumonia being the most common diagnosis. The frequency of atrial fibrillation or flutter was 7.89%, and ventricular tachycardia 2.63%. The most frequently used concomitant medication was quetiapine at 28.95%. The main cause of death was respiratory failure.

Conclusions: the frequency of arrhythmias was high in our study, although the most frequent cause of death was respiratory failure. (Acta Med Colomb 2020; 45. DOI: https://doi.org/10.36104/amc.2020.1336).

Key words: *macrolide, clarithromycin, pneumonia, atrial fibrillation, cardiovascular diseases*.

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Introduction and objectives

Macrolides are antibiotics which are widely used in the treatment of various diseases, including respiratory infections. The prototype of this group is erythromycin, whose first clinical use in upper respiratory tract infections took place in the 50s (1).

In addition to the macrolides´ antimicrobial effects, they have been shown to have anti-inflammatory and immunomodulatory properties (1, 2). Given the widespread use of this group of antibiotics over the last 15 years, cardiovascular events related to their use have been reported. These include prolonged QT interval, arrhythmias like *torsades de pointes* and ventricular tachycardia, and sudden cardiac death (3-5).

In the medical intensive care unit at the Fundación Cardioinfantil - Fundación Neumológica Colombiana, pulmonary sepsis was the principal reason for admission in 2012, and community acquired pneumonia made up 33% of the cases. Clarithromycin is indicated for treating this disease, according to the national treatment guidelines. The possible cardiovascular effects for this population are unknown, which is why it is necessary to ascertain the complications associated with cardiovascular events related to the use of macrolides in this group of patients.

Methods

A cross-sectional descriptive study was performed, which included patients over the age of 18 who were admitted to the medical intensive care unit (MICU) at the Fundación Cardioinfantil and who received clarithromycin antibiotic treatment during 2013 and 2015.

Selection criteria

- Inclusion criteria**:** patients over the age of 18, MICU admission, treatment with clarithromycin.
- Exclusion criteria**:** acute cardiovascular event on admission to the MICU, "do not resuscitate" criteria, severe liver disease, post solid organ transplant, requiring two or more vasopressors or inotropes.

All patients who met the selection criteria underwent daily electrocardiographic follow up from admission to the MICU until the fifth day, and in the event of an episode of acute tachyarrhythmia.

Data analysis plan

Following data collection, the recorded data was reviewed to ensure that it matched the type of variable, its corresponding unit and the coding, if applicable. The sample was described using measures of central tendency

for the quantitative variables, as well as proportions for qualitative variables. Data analysis was performed using the STATA 11 statistical software.

Ethical considerations

The protocol was approved by the Research Ethics Committee of the Fundación Cardioinfantil.

Results

During the study period, a sample of 38 patients was collected, of whom 50% were women, and the median age was 64 years. With regard to the distribution of comorbidities, respiratory disease was the most frequent, with 63.16% of the patients, followed by arterial hypertension with 47.37% and heart disease with 31.58%. The least common comorbidity was cancer, which was only reported in one patient (Table 1).

The most frequent diagnosis was pneumonia (97.37%), and in 37 cases the infections were community acquired. The median APACHE II score on patient admission was 10.5 (interquartile range 5-17) and the median initial SOFA score was 5 (interquartile range 3-9). Inpatient mortality in our patient sample was 21.05%, which corresponds to eight patients.

With regard to management during the intensive care unit stay, the median length of stay in the ICU was 4.5 days, 57.89% of patients required vasopressor support, and 65.79% required mechanical ventilation. An analysis of cardiovascular events showed that the median initial corrected QT interval was 447 milliseconds, which was similar to the median final corrected QT interval of 452 milliseconds. Altogether, 7.89% of the patients had atrial fibrillation or flutter, and one patient had sustained ventricular tachycardia (Table 2).

The first-line combination antibiotic treatment used with clarithromycin was ampicillin/sulbactam (55.26%), piperacillin/tazobactam (21-05%) and cefepime (15.79%). The least used antibiotics were meropenem, vancomycin and moxifloxacin (Table 3).

The serum electrolyte values of 36 patients were available during their ICU stay. A total of 30.56% had hyperkalemia, 58.33% hyponatremia, 66.67% hypomagnesemia and 19.44% hypocalcemia. Concomitant medications were also analyzed: quetiapine was used in 28.95% of patients, fluoxetine in 21.05%, amiodarone in 15.79% and quinolones were only used in two cases (Table 4).

A detailed analysis of the characteristics of the 11 patients who received concomitant quetiapine treatment showed no significant differences in the median initial and final corrected QT interval, and there were no cases of atrial or ventricular arrhythmias. An analysis of serum electrolytes in the 10 patients in this group for whom data was available showed that 50 to 70% had potassium, magnesium and calcium within normal limits. Forty percent of these patients were hyponatremic and 30% had sodium levels within the normal limits (Table 5).

The variables of greatest interest were analyzed in the four cases who presented some type of arrhythmia during their ICU stay. The four patients had underlying heart disease and they all had both initial and final QTc intervals above the normal limit. Only two cases were being treated with concomitant medications and most of them had hypokalemia (Table 6).

Finally, the causes of death of the eight patients who died as inpatients were analyzed, with the most frequent cause being respiratory failure (50%). Only one case died due to a ventricular arrhythmia, which was the same patient who presented sustained ventricular tachycardia during the ICU stay and whose relevant information is presented in Table 6, case 4. Deaths were also reported due to multiple organ dysfunction and hypovolemic shock (Table 6).

Discussion

Macrolides are antibiotics produced by fungi from the *Streptomyces* genus and some bacteria such as *Arthrobacter,* and they are made up of a macrocyclic lactone ring. The prototype of this group is erythromycin, whose first clinical use in upper respiratory tract infections occurred in the 50s (1).

Table 1. Initial patient characteristics.

Characteristic	n = 38
Age in years, median (Q1 , Q3)	64 (52, 77)
Women, No. (%)	19 (50)
Comorbidities	
Respiratory disease, No. (%)	24 (63.16)
Arterial hypertension, No. (%)	18 (47.37)
Heart disease, No. (%)	12 (31.58)
Kidney disease, No. (%)	7 (18.42)
Diabetes mellitus, No. (%)	7 (18.42)
Neurological disorder, No. (%)	4 (10.53)
Autoimmune disease, No. (%)	2 (5.26)
Cancer, No. (%)	1 (2.63)
Diagnosis	
Pneumonia, No. (%)	37 (97.37)
Tracheobronchitis, No. (%)	1 (2.63)
Source of the infection	
Community acquired, No. (%)	37 (97.37)
Nosocomial, No. (%)	1 (2.63)
Patients' condition on admission	
APACHE II score, median (Q1, Q3)	10.5 (5, 17)
Initial SOFA score, median (Q1, Q3)	5 (3, 9)
Outcomes	
Mortality, No. (%)	8 (21.05)

Besides the antimicrobial effects of the macrolides through protein synthesis inhibition by binding to the 50s subunit of the bacterial ribosome, they have been documented to have anti-inflammatory and immunomodulating properties. This occurs by altering the production of mucus; interfering in the function of neutrophils and macrophages in the respiratory tract; altering chemotactic, migration and cellular activation processes; and decreasing the production of proinflammatory cytokines (1,2).

Among the approved indications for macrolides is the treatment of community acquired pneumonia (CAP), where it has been reported to have immunomodulating effects independent of the antibacterial activity (6). In retrospective studies, treatment with macrolides in addition to beta-lactams versus monotherapy with beta lactams has been noted to have increased survival in these patients (7). In addition, hospital stay was seen to decrease with treatment with this group of antibiotics (8).

This study describes our experience with the use of clarithromycin in critically ill patients, mainly to treat CAP. The average age and distribution by sex are similar to previous publications analyzing the risk of cardiovascular events related to the use of clarithromycin in this type of patients. In our study, the presence of prior heart disease and prior kidney disease was greater than that reported in previous studies (9, 10). In addition, the APACHE II score, SOFA score, and need for ventilatory and vasopressor support in the ICU were high, which could suggest that our population had a high burden of comorbidities and a greater disease severity.

Table 2. *ICU treatment characteristics.*

Variable	n = 38
Intensive care unit stay, in days, median (Q1, Q3)	4.5 (2 , 12)
Vasopressor support required, No. (%)	22 (57.89)
Mechanical ventilation required, No. (%)	25 (65.79)
Elevated lactate, No. (%)	13 (34.21)
Initial corrected QT interval, median (Q1, Q3)	447 ms (438 , 453)
Final corrected QT interval, median (Q1, Q3)	452 ms (442 , 481)
Atrial fibrillation/atrial flutter, No. (%)	3 (7.89)
Sustained ventricular tachycardia, No. (%)	1 (2.63)

Table 3. *First-line antibiotics used.*

Antibiotic	n = 38
Ampicillin/sulbactam, No. (%)	21 (55.26)
Piperacillin/tazobactam, No. (%)	8 (21.05)
Cefepime, No. (%)	6 (15.79)
Meropenem, No. (%)	1 (2.63)
Vancomycin, No. (%)	1 (2.63)
Moxifloxacin, No. (%)	1 (2.63)

Table 4. Serum electrolyte levels and concomitant medications.

Serum electrolytes	n = 38
Hyperkalemia, No. (%)	11 (30.56)
Hypokalemia, No. (%)	5 (13.89)
Hypernatremia, No. (%)	8 (22.22)
Hyponatremia, No. (%)	21 (58.33)
Hypermagnesemia, No. (%)	8 (22.22)
Hypomagnesemia, No. (%)	4 (11.11)
Hypercalcemia, No. (%)	10 (27.78)
Hypocalcemia, No. (%)	7 (19.44)
Medication	**n = 38**
Amiodarone, No. (%)	6 (15.79)
Fluoxetine, No. (%)	8 (21.05)
Quetiapine, No. (%)	11 (28.95)
Quinolones, No. (%)	2 (5.26)

Table 5. *EKG and electrolyte data with concomitant use of clarithromycin and quetiapine.*

Electrocardiographic data	n = 11
Initial corrected QT interval, median (Q1, Q3)	441.5 ms (420 , 447)
Final corrected QT interval, median (Q1, Q3)	446.5 ms (430 , 481)
Atrial fibrillation/Atrial flutter, No. (%)	0 (0)
Sustained ventricular tachycardia, No. (%)	0 (0)
Serum potassium	**n = 10**
High, No. (%)	3 (30)
Low, No. (%)	2 (20)
Normal, No. (%)	5 (50)
Serum sodium	**n = 10**
High, No. (%)	3 (30)
Low, No. (%)	4 (40)
Normal, No. (%)	3 (30)
Serum magnesium	**n = 10**
High, No. (%)	2 (20)
Low, No. (%)	1 (10)
Normal, No. (%)	7 (70)
Serum calcium	**n = 10**
High, No. (%)	2 (20)
Low, No. (%)	2 (20)
Normal, No. (%)	6 (60)

Table 6. *Cases with arrhythmias in the ICU*

	Age (Years)	Arryhthmia	Underlying heart disease	Initial QTc interval	Final QTc interval	Sodium	Potassium	Magnesium	Calcium	Concomitant medications
Case 1	72	Atrial fibrillation	Yes	520 ms	534 ms	High	Normal	High	Normal	Amiodarone, fluoxetine and quinolone
Case 2	78	Atrial flutter	Yes	471 ms	471 ms	Normal	Low	Normal	High	None
Case 3	74	Atrial fibrillation	Yes	495 ms	480 ms	Normal	Low	Normal	High	Amiodarone
Case 4	81	Nonsustained ventricular tachycardia	Yes	540 ms	480 ms	High	Low	High	High	None

* Case 4 corresponds to the patient who died during the study.
ms: milliseconds

Table 7. *Causes of death.*

Causes of inpatient deaths	n = 8
Respiratory failure, No. (%)	4 (50)
Multiple organ dysfunction, No. (%)	2 (25)
Hypovolemic shock, No. (%)	1 (12.5)
Ventricular arrhythmia, No. (%)	1 (12.5)

Over the last 15 years, cardiovascular events related to the use of macrolides have been reported. These include prolonged QT interval, increased arryhthmias like *torsades de pointes* and ventricular tachycardia, and a greater risk of cardiac sudden death (3-5). These effects have been reported more frequently with erythromycin, clarithromycin and azithromycin (3, 11-13). The factors related to the potential arrhythmogenic effect of the macrolides are secondary to delayed ventricular repolarization which is a process mediated by the intracellular outflow of potassium (14, 15).

Adverse cardiovascular events associated with the use of macrolides have been reported to be more frequent when they are simultaneously administered with other medications which prolong the QT interval, as well as when other factors related to a prolonged QT interval are present, such as female sex, advanced age, electrolyte disturbances such as hypokalemia and hypomagnesemia, and a history of heart failure and bradycardia, among others (15, 16). An analysis adjusted for comorbidities and patient characteristics documented a 24 to 68% decrease in the risk of cardiovascular events related to the use of clarithromycin (17).

Our study reported hypokalemia in 13.89% of patients and hypomagnesemia in 11.11%. The most frequently used concomitant medication with clarithromycin was quetiapine at 28.95%. These two medications have been associated with a prolonged QTc interval, which may be greater than 60 milliseconds in critically ill patients; and, when used together, they facilitate arrhythmias like *torsades de pointes* (18, 19).

Finally, the frequency of atrial fibrillation or flutter arrhythmias in our study was 7.89%, with ventricular tachycardia at 2.63%. Only 12.5% of the patients who died had ventricular arrhythmia as the cause of death. In previous studies, the frequency of arrhythmias was 6.5% in patients treated with clarithromycin, which is lower than that found in our patients, and in a meta-analysis this was not associated with a greater risk of cardiovascular mortality (9, 13).

Conclusions

Macrolides are antibiotics which, in addition to their antibacterial activity, may have other beneficial effects for the treatment of infectious diseases. In our experience, the use of macrolides was related to a greater frequency of arrhythmias compared to previous publications, but the cardiovascular complications were not the main cause of death.

The presence of multiple comorbidities, the severity of underlying diseases and the pharmacological combinations the patients in our study were receiving could explain the increased frequency of arrhythmias.

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