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ORIGINAL ARTICLE

Ceftriaxone: rational use by the Pediatric's department of the Santa Casa's Hospital of Belo Horizonte, MG

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Ceftriaxone,
Drug Resistance,
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Abstract

Objective: The present study had as main objective to evaluate the use of ceftriaxone in the Pediatric's Department of the Santa Casa's Hospital of Belo Horizonte, MG, as well as the bacterial resistance profile of nosocomial infections in the same period. **Methods:** The study was based on the analysis of 160 antimicrobial forms of patients taking ceftriaxone and containing the main medical indication, as well as other variables: age, time of use and microbial growth in cultures. **Results:** Regarding the total antibiotics prescribed, only 0.12% corresponded to the use of the cephalosporin, evidencing the low rate of use and the importance of a conscious and directed use of this drug. **Conclusion:** The study shows the rational use of ceftriaxone in the Pediatric's Department of the Santa Casa's Hospital of Belo Horizonte, MG, when compared to other antimicrobials, evidencing its importance in pediatric clinical practice, mainly in relation to the reduction of bacterial resistance.

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INTRODUCTION

Ceftriaxone is a third generation semi-synthetic cephalosporin, part of a group of broad-spectrum antimicrobials. This includes gram-positive and gram-negative aerobic bacteria, as well as minimal anaerobic action.[1] It is mainly known for its bactericidal action against gram-negative pathogens, specifically all Haemophilus influenzae (including beta-lactamase producing strains), Moraxella catarrhalis, most Escherichia coli, Klebsiella pneumoniae, Morganella, Neisseria, Proteus, Enterobacter sp, Serratia marcescens and Acinetobacter sp. It is also active against all group A and B streptococci, almost all Streptococcus pneumoniae, including non-sensitive penicillin streptococcus outside the cerebrospinal fluid (CSF). Staphylococcus epidermidis, other coagulase negative staphylococci, methicillin-resistant Staphylococcus aureus (MRSA) and all enterococci are considered resistant.[1,2]

Ceftriaxone's half-life clearance (6 to 9 hours) is much longer than most cephalosporins due to its high affinity for plasma proteins, allowing for one or two daily doses. There is a peculiarity, in relation to neonates in which the half-life of this drug is longer (9 to 16 hours), this may be associated with factors such as reduced glomerular filtration and altered protein binding[2]. As ceftriaxone actively displaces bilirubin from albumin, most professionals avoid its use in newborns. According to the Food and Drug Administration (FDA), ceftriaxone is contraindicated in premature babies up to 41 weeks of age and in term neonates younger than 28 days of age, especially if there is associated hyperbilirubinemia, or if they are receiving calcium replacement. There are reports of neonatal deaths associated with the precipitation of a ceftriaxone-calcium salt in the lungs and/or kidneys.[2,3]

In its intravenous administration, this antimicrobial diffuses rapidly into the interstitial fluid, where the bactericidal concentration against sensitive organisms is maintained for 24 hours. It has good penetration into the bones, joints, muscles, skin and middle ear, with approximately 10% reaching the CSF through inflamed meninges. The main ways of eliminating ceftriaxone are urine (40 to 60%) and bile secretion (11 to 65%).[2,4]

Adverse effects that occur in less than 5% of patients include thrombocytosis, transient elevations in liver function tests, allergic reactions and leukopenia. There is an increasing risk of neutropenia or thrombocytopenia from the second week of use, which can reach 15%. Candida superinfection and diarrhea occur in 10% to 15% of patients, accompanied by eosinophilia in 6% of cases, in addition to Clostridium difficile colitis. Bile sludge and pseudolithiasis appear more commonly in young patients, are dose-dependent and occur mainly with fluid restriction or biliary stasis. An important, rare and potentially fatal adverse effect is immune-mediated hemolysis, which can occur despite safe and previous treatment with the drug.[4] Almost all records of this adverse effect reported in the literature were in immunocompromised patients. It can also lead to an increase in infections due to organisms producing broad spectrum beta lactamase (BSBL).[7]

Pediatric doses for the treatment of meningitis are 100 mg/kg once daily, or divided every 12 hours. Outside the meninges, the dose is 50 to 75 mg/kg once a day. For intramuscular use, dilution in 1% lidocaine reduces the pain caused by the injection[5].

Ceftriaxone is effective in complicated and uncomplicated urinary tract infections, lower respiratory tract infections, skin, soft tissue, bone and joint infections, bacteremia/septicemia and meningitis in pediatrics. However, it is important to note that no third generation cephalosporin is a first-line agent for methicillin-sensitive Staphylococcus aureus (MSSA) and none is suitable as a monotherapy for penicillin-resistant Streptococcus pneumoniae infections.[5,6] The development of resistance and/or bacterial superinfection with the use of this drug is already described in the literature (for example, due to Streptococcus faecalis, Pseudomonas aeruginosa, Enterobacter, Serratia and Bacteroides fragilis species).[5] The main mechanisms by which bacteria develop resistance to cephalosporins include mutations of the antibiotic target such as penicillin-binding proteins (PBPs) or inactivation of the drug by beta-lactamases.[6] The development of bacterial resistance may be linked to the indiscriminate, empirical and daily use of antimicrobials, especially those with a broad spectrum, such as ceftriaxone.[6] In order for this to be avoided, there is a need for vigilance in rationalizing the use of antibiotics in general, as well as an adequate medical prescription. For this reason, the characterization of the bacterial incidence and its resistance profile is the basis for targeted and safe antibiotic therapy. Undoubtedly, if this does not occur, the selection of resistant strains will be favorable, which is the main cause found in the hospital environment, where the use of these drugs is more common.[7]

A very common resistance mechanism is the production of beta-lactamase, a bacterial enzyme that breaks down the nucleus of the beta-lactam ring, leaving the antibiotic unable to bind to PBP. An example is a beta-lactamase called TEM-1 (present in an untyped Haemophilus influenzae), which inactivates cefaclor and cefprozil for example, and is stable in relation to ceftriaxone. However, BSBL and beta-lactamases from Amp-C, found mainly in nosocomial gram-negative pathogens, inactivate all currently available cephalosporins.[6,7]

Therefore, the present study aims to show the use of Ceftriaxone in the Pediatrics department of the Santa Casa Hospital in Belo Horizonte-MG, and that targeted and careful antibiotic therapy can contribute positively to the reduction of bacterial resistance.

METHODS

This is a descriptive retrospective, cross-sectional, uncontrolled study, carried out from January 1, 2015 to December 31, 2017 at the Santa Casa Hospital - Belo Horizonte-MG, a reference in highly complex public healthcare in the entire country. We surveyed the data from all pediatric

patients who used ceftriaxone, the mean time of use, age, growth in cultures and what was the main clinical indication in the pediatric units of the hospital: Pediatric Clinic (ward A), Pediatric Surgery (ward B), Pediatric Cardiology (ward B), Pediatric Oncology (ward C) and Pediatric Intensive Care Unit (ward D). In addition, we analyzed the hospital's bacterial resistance profile and the pathogens most frequently isolated in nosocomial infections.

The study included 160 children, all of whom were hospitalized on the 3rd floor of the Santa Casa Hospital - Belo Horizonte-MG, in all the wards mentioned above. The inclusion criteria included all age groups, regardless of gender. The patients whose antimicrobial forms were not properly filled out by the attending physician were excluded from the study.

Data analysis was computed manually using antimicrobial forms; standardized documents used by the Hospital Infection Control Service (SCIH), and processed using the Excel 2016 spreadsheet.

After obtaining the data, we analyzed all the variables and compared the quantity of ceftriaxone used with all the antibiotics used in the period. Regarding bacteria isolated in cultures, we compared the result with the nosocomial bacterial resistance profile of the hospital.

This study was authorized by the infectious disease specialist at the Hospital Infection Control Service (SCIH), accompanied by the head/coordinator of the Pediatrics department and the clinical pharmacist responsible for the sector.

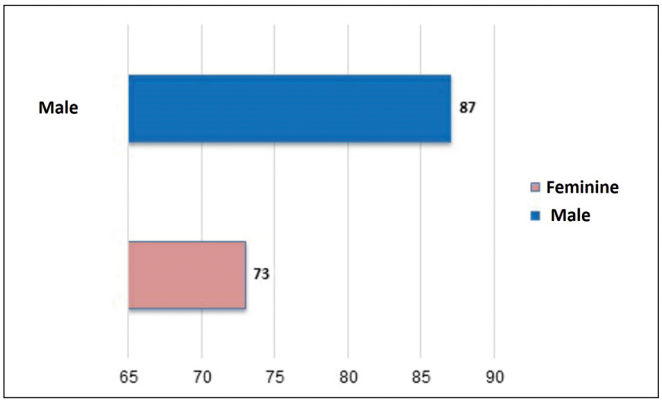
Because this is a retrospective study, which involved a large number of patients who had already been discharged from the service, the ICF (free and informed consent term) was not applied. However, confidentiality concerning the information contained in the patients' medical records was carefully maintained.

RESULTS

We broke the sample down into four age groups: neonatal age group (7 to 26 days of life), totaling 6 patients (3.7%), infants (1 month to 1 year), totaling 63 patients (39.4%), schoolchildren and preschoolers (2 to 10 years), totaling 59 patients (36.9%); and finally teenagers (11 to 17 years), totaling 32 patients (20%). Of the total number of patients evaluated, 87 (54%) were males and 73 (46%) were females (graph 1).

Of the 160 patients who used ceftriaxone in this period, 93 were from ward A (58.3%), 34 from ward B (21.2%), 7 from ward C (4.3%) and 26 from ward D (16.2%). The average prescribed use of this antimicrobial was 8.4 days, with a minimum of 1 day and a maximum of 21 days.

Regarding the clinical indication for the use of ceftriaxone, the most frequent were orbital cellulitis, corresponding to 19 patients in the sample (12%); urinary tract infection 23 (14%); bacterial meningitis 13 (8%) and simple pneumonia

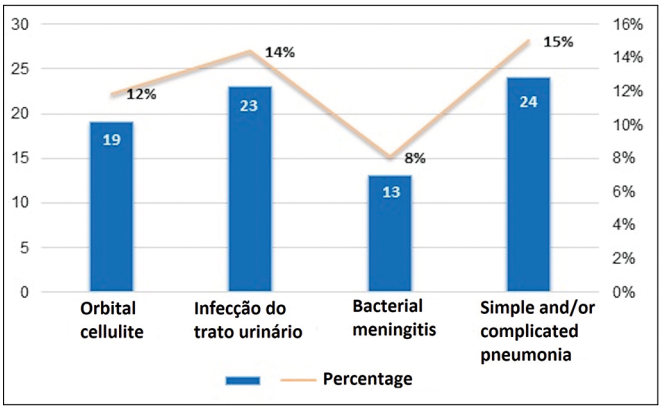


Graphic 1. Relationship between the use of Ceftriaxone between the sexes.

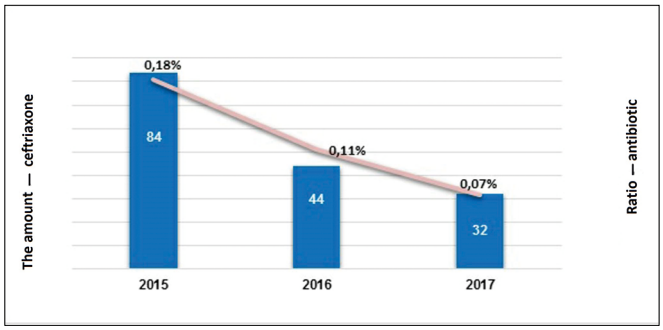
and/or complicated 24 (15%) as seen in Graph 2. This includes patients who have already been transferred from other services using the antibiotic and it was maintained and/or those who had some associated comorbidity that justified its use. In addition, other medical indications for the use of the antibiotic in question were found, but to a lesser extent, such as: lung abscess (1 patient), brain abscess (1 patient), perianal abscess (1 patient), tonsillar abscess (3 patients), appendicitis (1 patient), periorbital cellulitis (7 patients), cellulitis refractory to common antibiotics (1 patient), septic shock (2 patients), cholangitis (2 patients), acute cholecystitis (2 patients), gonococcal conjunctivitis (3 patients), endocarditis (3 patients), hemorrhagic fever (1 patient), fever without localizing signs (1 patient), fever and seizure crisis (1 patient), infectious gastroenteritis (2 patients), DVP-associated central nervous system infection (3 patients), nonspecific lymphadenitis (1 patient), otomastoiditis (8 patients), febrile neutropenia in the absence of cefepime (2 patients), acute otitis media (2 patients), osteomyelitis (1 patient), peritonitis (2 patients), pyelonephritis (2 patients), aspiration pneumonia (2 patients), surgical prophylaxis (9 patients), sepsis (9 patients), acute chest syndrome in sickle cell anemia (3 patients), recurrent sinusitis (1 patient), tracheitis (1 patient) and ventriculitis (1 patient).

All antibiotics prescribed at the time passed the approval of the SCIH, of which 128 were approved and for 32, a change in the antimicrobial scheme was advised.

Regarding germ growth in cultures, 20 samples were being analyzed at the time of the medical prescription, 13 were not requested, and in 115 there was no microbial growth. Regarding the sample group, 12 showed microbial growth, which corresponds to 7.5% of cases. The isolated germs included Streptococcus pneumoniae (8.3%), Streptococcus viridans (16.6%), Klebsiella pneumoniae (16.6%), Klebsiella ESBL (8.3%), Staphylococcus aureus (8.3%), Escherichia coli (25%), unidentified gram-negative rods (16.6%) and Enterobacter cloacae (8.3%). This result corroborates with the data provided by the hospital's SCIH showed in this period, considering all cases of nosocomial



Graphic 2. Most frequent clinical indications for the use of Ceftriaxone.



Graphic 3. Use of Ceftriaxone in relation to the total number of antibiotics prescribed.

infections evaluated, and the most frequent germs found in the service were: Klebsiella pneumoniae in 13 cases (15.29%), Pseudomonas aeruginosa in 11 cases (12.94%), Staphylococcus epidermidis in 7 cases (8.24%), Staphylococcus aureus in 7 cases (8.24%), Escherichia coli in 7 cases (8.24%) and Enterobacter cloacae in 4 cases (4.71%).

During the study period, 46,745 antibiotics were prescribed in 2015, of which, ceftriaxone corresponded to 84 cases (0.18%). In subsequent years, we found an even greater reduction (graph 3), as in 2016, in which the prescription of antimicrobials totaled 38,951, and ceftriaxone corresponded to 44 cases (0.11%); and in 2017 of the 45,997 prescriptions, ceftriaxone represented 32 cases (0.07%). This shows the conscious and rational use of this third generation cephalosporin, by the Pediatrics department of Santa Casa de Belo Horizonte hospital-MG and its importance in terms of bacterial resistance.

DISCUSSION

In recent years, resistance to antimicrobial agents is increasing within some bacterial species, particularly resistance to third generation cephalosporins. An example of this is Enterobacter cloacae, which emerged as an important nosocomial pathogen, and is included in the resistance profile of ceftriaxone as we can see in a study carried out in France, at Besançon Hospital, published in May 2004.[7,8] The proportion of E. cloacae isolates resistant to third generation cephalosporins increased between 1999 and 2002, from 24.3% to 29.6% (p = 0.03). This study demonstrated a specific correlation between the use of ceftriaxone and the development of resistance among clinical isolates of E. cloacae. That is, for each additional patient treated with ceftriaxone, resistance to E. cloacae increased by 0.34% compared to other cephalosporins. This can be explained by the high bile elimination of the drug compared to others, which may be responsible for a greater impact of this antibiotic on the digestive flora. Another explanation for this resistance would be that ceftriaxone may, more often than other cephalosporins, lead to inactivation of the cephalosporinase gene. This possibility is consistent with the study by Fung-Tomc et al who reported that, in vitro, the development of resistance was faster, after exposure to ceftriaxone, than to other antimicrobials of the same class.[8] All of this corroborates the study in question that showed the isolation of E. cloacae in 8.3% of the analyzed samples, whose patients were using ceftriaxone.

Monitoring this antimicrobial resistance is important, because it has been associated with increased patient morbidity and mortality, prolonged hospitalization and increased hospital expenditure, particularly for bacteremia and pneumonia associated with mechanical ventilation.[8] There are two basic ways of spreading antimicrobial resistance: dissemination of multidrug-resistant strains by cross-transmission, and acquisition of resistance by susceptible strains.[8] The causes of the emergence and spread of pathogens resistant to antimicrobials are multifactorial, but the excessive and inappropriate use of antimicrobials is clearly the main determinant.[8,9]

There is a report in the literature of significant resistance (> 90%) of P. aeruginosa in relation to third generation cephalosporins: Cefotaxime and Ceftriaxone. The study by Gräf et al. (2008) emphasizes the current results, as they found multidrug-resistant strains of P. aeruginosa, due to the synthesis of a group of beta-lactamases - metallo-β-lactamase - one of the most relevant resistance mechanisms today.[9] Although during the analysis period at Santa Casa hospital, no resistant P. aeruginosa was isolated from patients who used ceftriaxone, such resistance has already been described.

In addition to the importance of a targeted and adequate medical prescription, the non-suspension of use, when treatment with antimicrobials is unnecessary, is of great relevance, as it contributes to the overuse of antimicrobials and induces resistance in the same way. In this sense, it is worth mentioning the study by Cotten et al,[9,7] which reported on the increase in the occurrence of necrotizing enterocolitis and death among 4,093 extremely low birth weight newborns, who empirically received an antimicrobial treatment, for a period greater than or equal to 5 days. Due to the risk of resistance induction, the empirical use of third and fourth generation cephalosporins should be avoided, being recommended in the treatment of meningitis, infection in newborns

with renal failure and in infections by bacteria resistant to aminoglycosides[9].

It is worth mentioning that one of the biggest causes of the excessive use of antimicrobials is the treatment of colonization.[10] Clinical and laboratory criteria can help distinguish between infection and colonization. Improving the specificity of the diagnostic criteria for infection can help reduce the unnecessary use of antimicrobials.

The widespread use of third generation cephalosporins has also been associated with the worrying emergence of broad-spectrum beta-lactamase-producing enterobacteria (BSBL), capable of hydrolyzing cefotaxime, ceftriaxone, ceftazidime and aztreonan. Among the BSBL-positive species are Klebsiella pneumoniae, Escherichia coli, Enterobacter sp, non-fermenting gram-negative bacilli such as Pseudomonas aeruginosa and Acinetobacter baumanii[10]. It has also been reported that BSBL-mediated resistance to third generation cephalosporins has appeared among neonatal pathogens. In a report from India, 22% of Gram negative bacilli isolated from blood cultures of neonates with septicemia were BSBL producers[2,10]. In another report also from India, more than 80% of neonatal septicemia isolates were resistant to ceftriaxone and were probably BSBL producers[2,10]. At Santa Casa hospital, a case of BSBL Klebsiella (8.3%) was isolated in an 11-month-old child; which, even though not corresponding to the neonatal age group, is consistent with data in the literature regarding ceftriaxone resistance.

The appropriate and individualized antimicrobial therapy includes the correct choice of the antimicrobial or a combination of them at the appropriate time, in the appropriate dosage, route of administration and duration of treatment. After culture results, it may be necessary to adapt the antibiotic used, according to the identified microorganism and resistance profile[10]. The precise indication for the use of antibiotics is essential to minimize the risk of inducing bacterial resistance and the appearance of multi-resistant species, as well as to reduce the occurrence of adverse events associated with drug use[7,10], as is the case of ceftriaxone.

Studies like this are very important so that you can control the rates of bacterial resistance with the correct use of antimicrobials and guide the appropriate medical therapy. The hospital's SCIH must be closely associated with the clinical staff in this regard. Our results emphasize the need for antibiotic policies and surveillance for the emergence of bacterial resistance in order to avoid scenarios, as described above.

CONCLUSION

The present study demonstrated that for 3 years (between 2015 and 2017) ceftriaxone was prescribed for 160 pediatric patients. This corresponds to 0.12% of a sample of admissions to Santa Casa Hospital - Belo Horizonte - MG, when compared to other children who received antibiotics of the most varied classes in the same period. As we can see, this rate is relatively low, showing that there is a rational use by the Department of Pediatrics. Indirectly, the benefit of this study in pediatric clinical practice is associated with the importance of the appropriate use of antibiotics and what this reflects in the reduction of bacterial resistance.

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