Quinolones and bacterial resistance

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Abstract

Fluoroquinolones are antimicrobial agents introduced in clinical practice, at the beginning of the 80s. Their broad spectrum against bacterial species, like *Pseudomonas aeruginosa* and methicillin resistant strains of *Staphylococcus aureus*, orally absorbed and a favorable side-effect profile have rapidly made them a widely prescribed antibiotic. But in 1989-90 some information reported that the development of resistant bacterial strains. The authors based on the literature and the hospital data warn against the empirical use of quinolones and their negative implications on infection control.

Keywords: quinolones, resistant bacterial strains.

Introduction

Fluoroquinolones, or simply quinolones, are a group of antimicrobial broad-spectrum agents having been introduced into clinical practice at the beginning of the 80s. Structurally related with nalidixic acid, sharing its pharmacological action mechanism – DNA--gyrase inhibition, an enzyme responsible for keeping DNA double-helix resulting in uncontrolled protein synthesis. Its broad spectrum of antibacterial activity is extremely wide, covering aerobic microorganisms both Gram positive and Gram negative, including *Staphylococcus aureus* methicillin resistant, *Pseudomonas aeruginosa* and *Mycobacterium spp.* [1] Once the available pharmaceutical forms enable its oral administration, after being introduced in the market for the first time, possible to administer orally an antibiotic intended to treat any infections due to *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus*.

Surely such fact, along the excellent pharmacokinetic features of quinolones, in particular its optimum bioavailability and tissue diffusion (including bone tissue) explained, on one hand, the big investment made in the pharmaceutical industry in such group of drugs and on the other hand the great interests and enthusiasm that clinicians have always expressed regarding its use. *In vitro,* ciprofloxacin is quinolone presenting a higher antibacterial activity and most probably the most used quinolone in a hospital environment.[2]

Quinolones have emerged as unique antimicrobial – broad spectrum of antibacterial activity, possibility of oral administration to cover *Pseudomonas aeruginosa* and *Staphylococcus aureus* methicillin resistant and a very favorable profile of adverse effects.

However, in 1989 – 90, fewer years after being introduced in the clinic of such antimicrobials, emerged in the literature the first worrying data, concerning not only its weak activity *in vivo* against *Streptococcus pneumonia,* [3,4] as will as the quick development of resistant strains, in particular strains of *Staphylococcus aureus*, with a multiple resistance pattern observed not only in a hospital environment but also in a practice suggesting here a non appropriate use.[5]

Can we be before an issue relating to the selection of resistant mutants, identical to the one verified with the nalidixic acid?

The bacterial resistance to quinolones is mainly resulting of chromosomal mutants – changing to a DNA- gyrase subunit and a lipopolysaccharide making part of the cell wall responsible for the permeability or non-permeability of the antimicrobial bacteria. Due to an increase of the number in bacterial strains resistant to quinolones, during or after therapy with such drugs in several clinical situations is widely described in literature.[1,6] Globally, the emergency of resistance to quinolones is, among Gram negative bacteria, relatively rare with Enterobacteriaceae but relatively frequent with *Pseudomonas aeruginosa,* while in the group of Gram positives the development of resistant strains is quick and very frequent in particular with *Staphylococcus aureus, Staphylococcus epidermidis,* negative *Staphylococcus coagulase* and *enterococcus*.[1,6,7] Regarding *Streptococcus pneumoniae*

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quinolone basic bacterial activity is very variable (minimum inhibition concentrations ranging from 0.5 and 4.0 mcg/ml ciprofloxacin) such as the *Mycoplasma pneumonia,* several examples of bacteremia due to *Streptococcus pneumonia* occurred during the treatment of respiratory infections due to Pneumococcus or other microbial agents are described in the literature.[3,4,6]

Why a quinolone should then be used in the treatment of breathing infections, being *Streptococcus pneumonia*, still the bacterial agent responsible for the highest number of breathing infections acquired in the community?

In a hospital environment, the increase in the incidence of infections by *Enterococcus* is in reality, partly due to an increase of using broad spectrum antimicrobials, many of which with a minimum activity for such microorganisms. Quinolones are one of these antimicrobial agents and super infections by *Enterococcus* during therapy with quinolones are well-documented in the literature.[7] Such fact is particularly relevant because Enterococcus resistant to all available antimicrobial agents, including vancomycin and teicoplamine, have already been isolated in several hospitals units.[8]

And if *Staphylococcus* acquires resistance to vancomycin, what will happen then?

As it is mentioned on editorial published on the N Engl J Med of 28 April 1994 – "Can antibiotic resistance be controlled?" – In spite of emerging resistance being an unavoidable consequence of using antimicrobials agents, the pattern of using antimicrobials have an important role on the development of resistance to antimicrobials themselves. For example, it is mentioned that although no *E. coli* was resistant to quinolones from 1983 to 1990, the same did not happen from 1991 to 1993 in which 28% of E. coli became resistant in this period, and the quinolone rate of use went from 1.4% in 1983 -1985 to 45% from 1991- 1993.[9]

In our hospital, there are rules relating to the use of quinolones, namely: hematology patients, selective decontamination of the digestive tract, cystic fibrosis patients and in clinical situations where there is no appropriate alternative therapy. However in 1994 while only 3.4% of isolated E. coli were resistant to quinolones, 87.4% of *Staphylococcus aureus* methicillin resistant, 48.7% of *Staphylococcus epidermidis* and 16.4% of *Pseudomonas aeruginosa* isolated showed resistance to ciprofloxacin. Regarding this last percentile of *Pseudomonas aeruginosa* strains, when we considered the isolated exclusively from patients in cystic fibrosis and hematology units, it is verified that the percentage of resistance goes respectively from 34% to 80%. In 1988, date when ciprofloxacin was for the first time used in our hospital, only 15.1% of *Staphylococcus aureus* methicillin-resistant were resistant to such quinolone. Also important is the fact that it 8.1% of *Enterococcus faecium* isolated during the year of 94 had presented resistance to vancomycin (results from the movement of the Bacteriology Laboratory of Santa Maria Hospital in the year of 1994).

To reflect upon this problem becomes compulsory and enables us, undoubtedly, to understand that the clinic use of quinolone, globally can only be recommended in literature when there are no appropriate political alternatives.[6] The same way we will understand the recently taken measures by the "Centres for Disease Control and Prevention" (Atlanta, USA), regarding the development control of resistant strains to vancomycin in hospitals. [10] What is actually been done when using a quinolone? ■

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References

1. Rosentiel N, Adam D. Quinolone Antibacterials – An Update of their Pharmacology and Therapeutic use. Drugs 1994:47:872 – 901.

2. Ciprofloxacin. Drug monographs. In: Micromedex Inc. vol. 84, 1995

3. Cooper B, Lawlor M. Pneumococcal bacteremia during Ciprofloxacin Therapy for Pneumococcal Pneumonia. Am J Med 1989: 87:475.

4. Frieden TR, Mangi RJ. Inappropriate Use of Oral Ciprofloxacin. JAMA 1990, 264: 1438 – 1440.

5. Pane FJ, Ringer L, Child JA, Miller DM. Ciprofloxacin Staphylococcus Aureus resistance. DICP, the Annals of Pharmacotherapy 1990: 24: 439.

6. Joshi N, Milfred D. The Use and Misuse of New Antibiotics. Arch Intern Medicine 1995: 155 : 569 – 577

7. Fish DN, Rodvold KA. Fluoroquinolone Treatment of Enterococcus Infection. Ann Pharmacother 1992:26:498 – 499

8. Anonymous. Intensive care units see increase in resistant enterococci. Clin Pharm 1993 :12 :797.

9. Murray BE. Can antibiotic resistance be controlled? N Engl J Med 1994:330:1229 – 1230.

10. Anónimo. CDC releases draft plan for controlling vancomycin resistance in hospitals. Am J Hosp Pharm 1994:51:1846 – 1849