

Quinolones

Subjects: **Pharmacology & Pharmacy**

Contributor: Anthony Maxwell

Fluoroquinolones (FQs) are arguably among the most successful antibiotics of recent times. They have enjoyed over 30 years of clinical usage and become essential tools in the armoury of clinical treatments. FQs target the bacterial enzymes DNA gyrase and DNA topoisomerase IV, where they stabilise a covalent enzyme-DNA complex in which the DNA is cleaved in both strands. This leads to cell death and turns out to be a very effective way of killing bacteria. However, resistance to FQs is increasingly problematic, and alternative compounds are urgently needed.

Quinolones

Fluoroquinolones

quinolone antibiotics

1. Introduction

The quinolone antibiotics (Figure 1) are the most successful class of topoisomerase inhibitors to date. They are synthetic antimicrobials with the initial compound, nalidixic acid, being discovered as a by-product of chloroquine synthesis in 1962^{[1][2]}. They are used to treat bacterial infections caused by both Gram-positive and Gram-negative bacteria, including, but not limited to, urinary tract infections (UTIs), pyelonephritis, gastroenteritis, sexually-transmitted diseases, such as Gonorrhoea, tuberculosis^[3], prostatitis, community-acquired pneumonia and skin and soft-tissue infections^{[4][5]}. However, due to an increase in resistance and issues surrounding toxicity, their use in the treatment of mild infections has been contraindicated^[6]. The global rise in antibiotic resistance has galvanised research into new antibiotics against both well-established targets and new targets. It has also sparked further research into antibiotics whose mode of killing is less well-established, as well as how bacteria become resistant to them. This is certainly true in the case of quinolones.

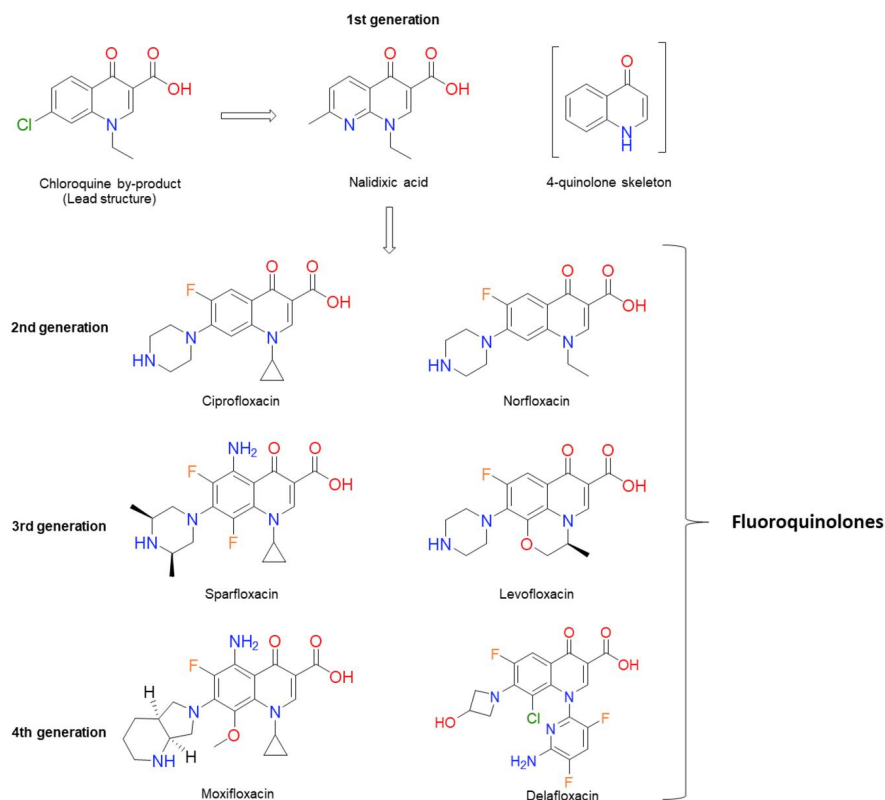


Figure 1. Chemical structures of several significant fluoroquinolones. Nalidixic acid (the first “quinolone”) is shown, along with the chloroquine by-product inspiring its synthesis. Note that nalidixic acid lacks the 4-quinolone core and instead contains a 1,8-naphthyridine nucleus.

2. Quinolone-Induced AMR

Along with the increase in FQ resistance that is seen with FQ use, there is also evidence that FQs may increase resistance to non-FQ antibiotics^{[7][8][9][10][11]}, particularly under sublethal or sub-MIC exposure. Treatments with sublethal FQs have been shown to increase mutation, recombination and persister formation rates, often leading to an increase in the frequency of resistance to non-quinolone antibiotics.^{[12][13][14][15][16][17][18]}

2.1. Treatment with Quinolones Increases Resistance to Non-Quinolone Antibiotics (QIAR)

There is growing evidence, particularly from the livestock and veterinary sectors, that FQ use can lead to an increase in antibiotic-resistant isolates^[19]. This resistance can be FQ resistance, resistance to non-FQ antimicrobials or multidrug resistance. Pereira et al.^[9] looked at the resistance profiles of *E. coli* isolates from pre-weaned calves that were treated with enrofloxacin or the cephalosporin ceftiofur for diarrhoea and respiratory diseases. They found that 77% of the isolates from the FQ-treated calves showed resistance to three or more antimicrobials, including ciprofloxacin, streptomycin, tetracycline, ampicillin, ceftiofur and chloramphenicol. In the study, only the calves treated with the FQ were significantly more likely to have non-susceptible *E. coli* isolates^[9]. Similarly, a study on healthy chickens found an increase in the number of isolates resistant to doxycycline,

amoxicillin and enrofloxacin in the commensal *E. coli* populations after treatment with enrofloxacin^[7]. This was mirrored in more recent studies on commensal *E. coli* isolates from chickens and turkeys that were treated with enrofloxacin^{[10][11]}. In the former study, multidrug resistance was identified in *E. coli* isolates from chickens treated with the FQ for *Salmonella* sp. infections^[11], whilst, in the latter, *E. coli* isolates from turkeys treated with enrofloxacin were found to be resistant to ampicillin, despite ampicillin not being used in the study^[10]. Further evidence comes from *Sa. Typhimurium* clinical isolates from pigs, which showed multidrug resistance following a single treatment of marbofloxacin below the mutant prevention concentration^[20]. This phenomenon is not peculiar to isolates from livestock; a strain of multidrug resistant *Sa. enteritidis* was isolated after a patient with a splenic abscess was treated with ciprofloxacin^[21]. One of the first studies done in vitro looked at the resistance profiles of *Salmonella* spp. after repeated exposure to FQs and β -lactams. They found that mutants generated after treatments with various FQs showed reduced susceptibility to a wide range of the antibiotics tested (seven different antibiotics). This was in contrast to mutants generated under treatment with β -lactams, which showed reduced susceptibility to fewer antibiotics (five antibiotics)^[22]. Similarly, it has been shown that the treatment of methicillin-resistant *St. aureus* with sublethal FQ further enhances methicillin resistance^[12]. A similar effect is seen with *E. coli*, as cells become resistant to quinolone and non-quinolone antibiotics after exposure to sublethal FQ^[23]. Alongside these studies that show increases in resistance to non-quinolone antibiotics after FQ treatment, there is also evidence that sublethal treatment with quinolones increases mutation rates, mutation frequencies and recombination.^{[13][14][15][16][17][18]}

2.2. Sublethal FQ Treatment Increases Mutation Rate

Quinolones are potent inducers of the SOS response^{[24][25][26][27]}. As mentioned above, the SOS response is the bacterial response to DNA damage. It is regulated by RecA, a recombinase that is activated when there is DNA damage, and LexA, the repressor of the SOS regulon that autocleaves when RecA is active. The autocleavage of LexA results in the derepression of the SOS regulon that controls the expression of ~50 genes in *E. coli*, including three error-prone polymerases (Pol II, Pol IV and Pol V) that can introduce mutations^[28]. Thus, it is not that surprising that quinolones could potentially increase the mutation rate. Indeed, many studies have shown that after the treatment with sublethal concentrations of FQs, there is an increase in mutation rate and mutation frequency.^{[12][13][14][15][16][17][27][29][30][31][32]}

Ysern et al.^[27] were the first to show that the quinolones increase mutagenesis through the induction of the SOS response. They suggested that the mutagenic effect was through the upregulation of Pol V. In 2005, Gillespie et al.^[17] demonstrated that the treatment of *Mycobacterium fortuitum* with sub-MIC ciprofloxacin was able to increase the mutation rate by 72–120-fold. A more systematic study of the role of SOS in the mutagenic effect of quinolones was performed by Cirz et al.^[29]. Using a neutropenic murine thigh infection model, they found that, in pathogenic *E. coli*, LexA, the repressor of the SOS response, was required for the evolution of the resistance induced by treatment with ciprofloxacin. They concluded that the homologous recombination pathway was important in the repair of ciprofloxacin-induced DNA damage and that LexA cleavage was induced during the repair. This then caused the upregulation of the three error-prone polymerases, which, together, generated the mutations that conferred resistance^[29]. The same group went on to show that this was also the case in *P. aeruginosa*^[16] and *St. aureus*.^[15] LexA, RecA and error-prone DNA polymerases were also found to be upregulated in *M. tuberculosis*

when treated with sublethal doses of ciprofloxacin^[18]. Some groups, however, have suggested that upregulation of the error-prone polymerases is not the only mutagenic pathway induced by treatments with sublethal quinolones. Song et al.^[33] showed that, when all three of the error-prone polymerases were deleted, ciprofloxacin-induced deletions still occurred. Long et al.^[34] suggested that the increased mutagenesis observed with norfloxacin was not only due to the error-prone polymerases but, also, by indirect effects of the antibiotic on the mismatch-repair system and DNA-oxidative repair mechanisms. Oxidative stress has also been suggested as the main mutagenic pathway of a range of antibiotics, including norfloxacin, by Kohanski et al.^[8]. They demonstrated that treating *E. coli* MG1655 with sublethal concentrations of norfloxacin in vitro caused multidrug resistance, which was abolished by the use of the ROS scavenger thiourea.

2.3. Sublethal FQ Treatment Stimulates Recombination

Sub-MIC treatment with quinolones have also been shown to increase genetic recombination. Ciprofloxacin has been demonstrated to stimulate homologous recombination in *E. coli*^[13]. This was shown to be RecA-dependent and only partially reliant on induction of the SOS response; an uncleavable LexA mutant reduced the recombination but did not abolish it^[13]. Sublethal ciprofloxacin was also demonstrated to induce nonhomologous recombination. This recombination was surprisingly independent of the SOS response but did require the other recombination pathways, RecBCD or RecFOR^[14]. This study also looked at the effect of sublethal ciprofloxacin on conjugative transfer. Although they found no significant increase in the transfer of a conjugative plasmid, they did see an increase in horizontal gene transfer of an antibiotic-resistance gene from the plasmid to the genome^[14]. Along these lines, three different FQs were shown to stimulate generalised transduction in *Sa. Typhimurium*. This was demonstrated through the transfer of a kanamycin resistance gene from a multidrug-resistant strain to susceptible strains through a P22-like bacteriophage^[35].

2.4. Sublethal FQ Stimulates the Formation of Persisters

Another factor is how sublethal FQs has been shown to increase the presence of persister cells in the population^{[36][37][38][39][40]}. Persisters are cells that can survive lethal concentrations of antibiotics due to phenotypic (but not genetic) changes. How persisters manage to survive antibiotic action is not clear, though it has been suggested that they do it by inactivating the drug target or lowering the drug uptake^[41]. Persister cells have been demonstrated to form as a result of induction of the SOS response^{[36][38][39]} or through a cellular response to starvation^[40]. This persister population has also been shown to allow long-term survival to the exposure to the quinolone by allowing mutations to accumulate within the population that are then selected for by the antibiotic^{[36][37]}.

How sublethal FQs induce mutation appears to be complex, much like the lethality of quinolones and the repair of quinolone-induced DNA damage. There appear to be several pathways that lead to an increase in mutation. However, mutation seems to be a consequence of repair, and this mutagenesis does not increase the evolvability of the bacteria^[42]. More work is needed to understand the role FQs play in mutagenesis, as a better understanding

of how these drugs induce mutation may enable strategies to be put in place that will reduce their role in the acquisition of antibiotic resistance.

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