Review Article

The role of fluoroquinolones in the treatment of brucellosis: an overview

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Abstract

Globally, Brucellosis is a common zoonotic infection caused by the genus *Brucellae*, which is transmitted to humans from infected animals especially goats, sheep, and cattle. It is an ancient condition linked to the intake of fluid-derived products, such as raw milk and milk products. As a systemic disease, it can affect any host body organ or organ system. Human brucellosis exhibits multiple clinical signs and making it difficult to diagnose. Therapeutic options for brucellosis are predominantly based on uncontrolled, non-randomized, non-blinded trials. *Brucella sp*. changes the level of pH in the intracellular domain and the first approach for the therapy is to prescribe antibiotics that have an acidic activity. Although anti-brucellosis treatment regimens include quinolones (fluoroquinolone) are remarkable drug which may be able to act intracellularly under acidic conditions. So, the present review was undertaken to evaluate the efficacy, safety, and patient tolerability of fluoroquinolone regimens and we tried to compile clinical studies utilizing quinolones for the treatment of brucellosis. Based on our outcomes, we enlighten the potential role of fluoroquinolone as anti-brucellosis.

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Introduction

Brucellosis is a chief multisystemic zoonotic disease caused by facultative intracellular Gram-negative bacteria of the genus Brucellae and although complete eradication of the microorganism leading to chronic, recurrent infections and relapses are being reported many years after the initial infection [1]. Worldwide, in humans and domesticated animals, brucellosis remains a major cause of morbidity. In animals, bovine brucellosis is still the most widespread form, caused mainly by Brucella abortus. In humans, Brucella melitensis-induced ovine/caprine brucellosis is by far the most common form of the disease [2]. Brucellosis was an emerging infection after Bruce discovered Brucella melitensis in 1887. Consequently, with the discovery of Brucella abortus, Brucella canis, Brucella neotomae, Brucella ovis, Brucella suis, and more recently, forms that infect marine mammals, a progressively complex form of strains emerged. Since each type has distinctive epidemiological characteristics, the sophistication of the human experience has increased with each new type. With new strains emerging and existing types adapting to changing social and agricultural practices, the depiction remains unfinished [3]. The disorder has a wide variety of clinical causes and can affect various organs and systems. Localized and complex forms of brucellosis result in severe morbidity and require extensive medical treatment. Fortunately, mortality is relatively low and is mostly due to complications of the disease in the central nervous and cardiovascular systems. However, some scrutinizes have been lead over the past half-century, the optimal

antibiotic therapy for brucellosis does not have conclusive evidence. Relapse of the ailment is also one of the most imperative therapeutic obstacles [4]. Brucellae demonstrates heavy tropism of the tissue and replicates dendritic cells (DCs), macrophage, and placental trophoblasts within vacuoles. The pathogen, however, can reproduce in a varied range of mammalian cell types, comprising endothelial cells, epithelial cells, fibroblasts, and microglia [5]. During infection, (as shown in figure 1) Brucella first invades the host cells (a), forms brucella-containing vacuoles (BCVs) (b), and undergoes guided fusion with the lysosome (c). About 90 percent of the Brucella are degraded in this stage, and the remaining 10 percent survive (d). Then, the BCV traffic to and reach endoplasmic reticulum (ER) (e) and the replicative site (f) is created. The Brucella traffic toward the autophagy-like vacuoles (g) after ER replication persists inside these compartments (h) and eventually leaves the host cells to facilitate cell-to-cell spreading (i). T4SS (type IV secretion system) potentially targets the following molecular events involved in these steps: excluding late endosome or lysosome markers, acquiring ER markers, interacting with secretory pathways, acquiring autophagosome markers, resisting the intolerant intracellular condition, and modulating the stimulation of essential immune pathways [6]. The cure remains challenging due to side-effects from the antibiotics, period of therapy, and deprived compliance. Also, clinicians may face therapeutic failures and relapses that are linked to the antibiotic pharmacokinetic and pharmacodynamics properties used. These problems have steered to the exploration of novel drugs for brucellosis treatment [7]. The fluoroquinolones have successful and excellent bactericidal activity against a diversity of bacteria. Moreover, they penetrate well into leukocytes and macrophages, which makes them suitable agents in the treatment of intracellular infections [8]. Countless clinical and microbiological studies of the prospective use of quinolones in human brucellosis care have been performed by laboratory scientists and clinicians since the mid-1980. The key benefits of utilizing quinolones in this condition are activity against intracellular bacteria, reduced threat of nephrotoxicity, strong pharmacokinetic properties, and insufficiency of a product level monitoring requirement. Besides, the requirement for a treatment that would prevent relapse of the infection also necessitated quinolone use [9]. However, this forthcoming randomized survey reviewed the existing in-vitro and clinical records at the time and analyses the principle, as well as the consequences, of quinolone use for brucellosis.

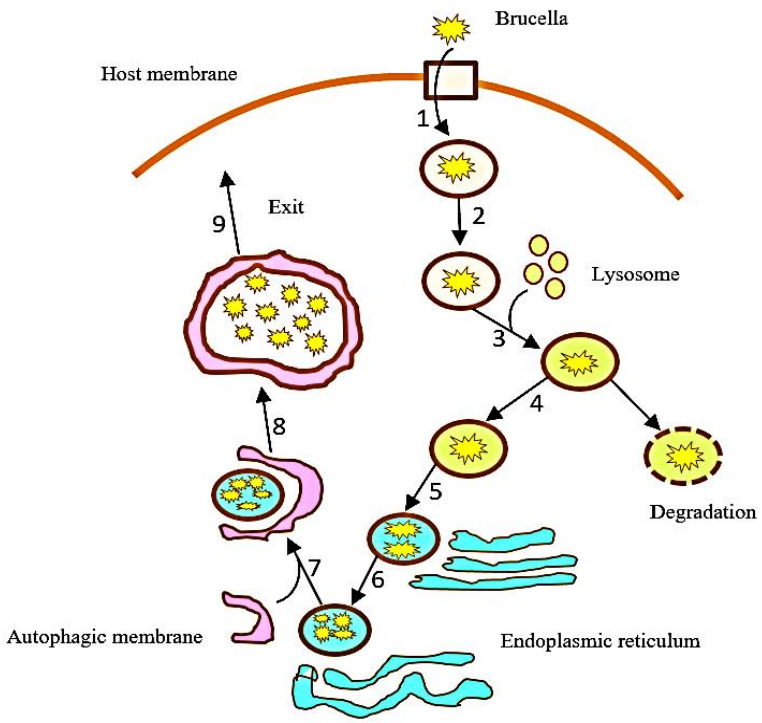

Figure 1: Life cycle of Brucella within host cells

Comparative activity of different classes of antibiotics on the treatment of brucellosis are summarized in tabular form in Table 1.

Sl No.	Class	Activity	Example	References
1	Tetracyclines	Doxycycline exhibits excellent activity in the acidic phagolysosomal environment	Doxycycline Minocycline	[10]
2	Aminoglycosides	Does not survive in the acidic phagolysosomic environment, but proven that it is the only compound exhibiting bactericidal activity in the first 24 h	Streptomycin	[11]
3	Rifamycins	Rifampicin survives in the acidic environment of the infected macrophages and exhibits bactericidal activity 48 h after administration	Rifampicin	[12]
4	Macrolides	Azithromycin does not survive in the acidic environment of the infected macrophages. Erythromycin was used instead of tetracycline in combination with streptomycin and the high doses necessary for achieving a clinical response	Azithromycin Erythromycin	[2]
5	Fluoroquinolones	Lack of synergistic activity with the older antibiotics. Recent studies with the combination of ofloxacin and rifampicin have yielded promising results	Ofloxacin Ciprofloxacin Moxifloxacin	[13]
6	Sulfonamides	Studied in the paediatric population, and its clinical efficacy, when compared to in vitro studies of Brucellae susceptibility, underlines the inconcordance between in vitro studies and clinical reality	Trimethoprim–sulfamethoxazole	[12]
7	β-Lactams	There are reports of excellent in vitro activity of cefotaxime and meropenem but not tested clinically	Ampicillin Ceftriaxone Cefotaxime	[14]

Table 1: Comparative activity of different classes of antibiotics on the treatment of brucellosis

Fluoroquinolones

Fluoroquinolones are a class of antimicrobial broad-spectrum agents that have been used more widely in present days and will continue to be used even in the next decade, therefore they are extremely active against both Gram-positive and Gram-negative aerobic organisms. Fluoroquinolones are synthetic fluorinated analogs of nalidixic acid, a 1, 8-naphthyridine, and possess a 4-quinolone nucleus [15]. Fluoroquinolones act by inhibiting two enzymes necessary in the synthesis of bacterial DNA, both of which are DNA topoisomerases that lack in human cells and that are needed for replication of bacterial DNA, thereby facilitating these agents to be both specific and bactericidal. DNA topoisomerases are accountable for splitting the strands of duplex DNA of bacteria, inserting another strand of DNA through the disruption, and then resealing the initially separated strands. Fluoroquinolones are antibacterial agents that attack DNA gyrase and topoisomerase IV on chromosomal DNA. When DNA gyrase and DNA topoisomerase IV bind to DNA, both DNA strands break down at the site of interaction. If fluoroquinolones are present, an intermediate reaction is confined in which the DNA is fragmented, and the subunits of topoisomerase are covalently attached to fragmented DNA. Confined complexes restrict the synthesis of DNA and the growth of the bacteria. The release of fragmented DNA in the complexes from the restriction enforced by the topoisomerases correlates with cell death (Figure 2) [16].

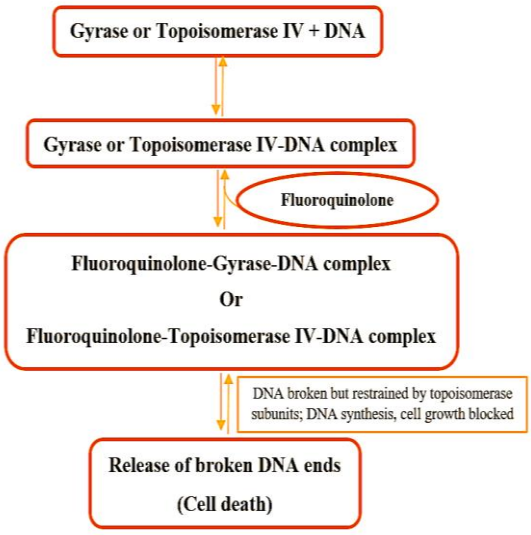

Figure 2: Mechanism of action of fluoroquinolone

Fluoroquinolones: an anti-brucellosis

The progression of fluoroquinolones and the effective usage of these compounds in several infections, including certain zoonotic diseases and various intracellular pathogens, contributed to the progress of what became a scientific interest in demonstrating their effectiveness in the treatment of brucellosis. Clinical and experimental studies on the usage of quinolone in the treatment of human brucellosis recommend that there is a lack of evidence in the primary therapeutic regimen to sustenance the use of quinolones. In vitro studies show that quinolone activity decreased at pH 5 relatively to pH 7, and synergistic activity is absent against brucellosis with the former antibiotics. Clinical trials with ciprofloxacin as a single agent for the brucellosis treatment have produced insufficiently high percentages of failing the therapy. However, recent studies with the combination of ofloxacin and rifampicin have brought promising results [10]. While numerous trials have been performed over the past 2 decades, the ideal antibiotic cure for brucellosis does not have conclusive proof. The relapse of the state is also one of the most imperative medicinal issues. The WHO's latest recommendation for the therapy of acute brucellosis in adults was reported in 1986 and advised 600 to 900 mg of rifampin and 200 mg of doxycycline day-to-day for a minimum of 6 weeks [2].

Alternatively, the WHO recommended replacing rifampin with 15 mg/kg of streptomycin, administered intramuscularly for just 2 weeks. However, a meta-analysis as well as a potential randomized case, both approved out by Solera et al., revealed that the "good old" combination of streptomycin-tetracycline leads to less relapses than the combination of doxycycline-rifampin [17,18]. A controlled study of clinical cases with other antibiotics, comprising trimethoprim-sulfomethoxazole, new macrolides, and β-lactams, showed poorer results or had less number of patients involved in a proper assessment. And the two aforementioned variations suggested by the WHO are the most frequently used regimens. Furthermore, rifampin monotherapy is the core selection for brucellosis during pregnancy, while its combination with trimethoprim-sulfomethoxazole is the treatment suggested for brucellosis in infancy [19, 20]. Two recent studies were based upon the brucellosis treatment regimens containing fluoroquinolone [2, 21]. Although using different perspectives, both reviews determine that combinations with fluoroquinolones can be acceptable, but do not suggest them as first-line treatment options for human brucellosis. The limited appropriate randomized trials present on the subject do not show the superiority or even non-inferiority of

fluoroquinolone-containing regimens, as per the first review. The second analysis records a cumulative response rate above 85%, which is an acceptable comeback; but the currently higher cost of fluoroquinolone-containing regimens and the possibility of increasing the production of the overall population fluoroquinolone tolerance argue against the prevalent use of fluoroquinolones for brucellosis in humans. The authors feel that if older fluoroquinolones are less costly in the future, more properly planned randomized trials can explore their potential in the combined cure of brucellosis. There are no records on the efficiency of the newer fluoroquinolones in brucellosis apart from occasional case reports, but the authors do not recommend their routine use in brucellosis despite their limited efficacy against respiratory pathogens. These antibiotics should also only be administered in the sense of appropriately planned prospective clinical trials.

Effect of different antibiotics examining the usage of quinolones against Brucella sp isolates are recapitulated in Table 2.

Sl No.	Antibiotics used	Key Findings	References
1	Ciprofloxacin Norfloxacin Nalidixic acid Pipemidic acid	First study of in vitro testing of ciprofloxacin against *B. melitensis*.	[22]
2	Ofloxacin Difloxacin Ciprofloxacin Tetracycline Rifampin Streptomycin Trimethoprim-sulfamethoxazole	Ofloxacin, tested for the first time *in vitro* against *B. melitensis* exhibited the highest activity among quinolones.	[23]
3	Ciprofloxacin Netilmicin Tetracycline Streptomycin Rifampin Trimethoprim-sulfamethoxazole	3 strains were resistant to tetracycline and one to rifampin. No resistance was found to the other drugs.	[24]
4	Sparfloxacin Temafloxacin Ciprofloxacin Fleroxacin Ofloxacin Lomefloxacin	Decreased activities (2–4 times) of quinolones at pH 5. Decreased bactericidal actions of quinolones were noted at both pH 5 and 7.	[25]
5	PD 131628 Clinafloxacin Lomefloxacin Ciprofloxacin Fleroxacin Pefloxacin Norfloxacin Sparfloxacin Temafloxacin Gentamicin Tetracycline Rifampin	One isolate showed resistance to all quinolones (cross-resistance) after analysis with Ciprofloxacin, except for PD 131628, which retained favourable activity and inhibited the isolate at a conc of 2.0 mg/litre (no cross-resistance). All strains were susceptible to gentamicin, rifampin and trimethoprim-sulfamethoxazole PD 131628 did not exhibit synergy with any of the conventional drugs.	[26]

	Trimethoprim-sulfamethoxazole		
6	BAYy3118 Sparfloxacin Ciprofloxacin Tetracycline Rifampin Streptomycin	-----	[27]
7	Sparfloxacin Ciprofloxacin Norfloxacin Pefloxacin Fleroxacin Rufloxacin Tetracycline Gentamicin Rifampin Trimethoprim-sulfamethoxazole	Cross-resistance of one isolate to all quinolones noted after therapy with Ciprofloxacin MIC_{99} for Sparfloxacin was 0.12 mg/L.	[28]
8	Levofloxacin Ciprofloxacin Rovafloxacin Moxifloxacin	-------	[29]
9	Sparfloxacin Levofloxacin Ciprofloxacin Ofloxacin Gentamicin Gatifloxacin	------	[30]
10	Doxycycline Tetracycline Ciprofloxacin Moxifloxacin Rifampin Streptomycin Trimethoprim-sulfamethoxazole	Ranges of MICs were lowest for the 2 quinolones (0.5 mg/L).	[31]

Table 2: Effect of different antibiotics examining the utilization of quinolones against Brucella sp isolates

Conclusion

In conclusion, critical reviews considering the anti-brucellosis properties persuaded by fluoroquinolone have currently extended to a broader range of therapeutic regimens. Several studies on in vitro and clinical have been documented the potential role of fluoroquinolones in the treatment of human brucellosis. Consequently, more laboratory exploration may be of significance, centre of attention on in vitro studies of combinations of several quinolones with other antibiotics, specifically with tetracyclines. On the contrary, quinolone-based medicaments give the impression to have a role in modern medical practice as substitutes to most accepted therapy for patients with relapse of brucellosis after treatment with another process, as well as in patients in whom noxious has thrived due to the utility of some of the older agents. In these circumstances, it is important to choose the best solution, because ineffective brucellosis treatment can cause serious complications and the possibility of relapse. This is also important to search for potential therapies for this patient group and provide new ideas for treatment.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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