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The role of fluoroquinolones for the treatment of brucellosis: An overview

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Abstract

The gram negative, non motile, intercellular bacterium is the *Brucella* bacterium which is named after the micro-biologist, David Bruce. Globally, brucellosis is a common zoonotic infection caused by the genus *Brucella*, which is transmitted to human from infected animals especially goats, sheep, and cattle. It is an ancient condition linked to the consumption of fluid-derived products, such as unpasteurized 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 environment and the first approach for the treatment is to prescribe antibiotics that have an acidic activity. Although anti-brucellosis treatment regimens include quinolones (fluoroquinolone) which are remarkable drug which may be able to act intracellularly under acidic conditions. So, the present review has undertaken to evaluate the efficacy, safety, and patient tolerability of fluoroquinolone regimens. Based on the outcomes, the potential role of fluoroquinolone as an anti-brucellosis has been established.

Keywords: Brucellosis, fluoroquinolones, treatment, efficacy, intracellular activity

Introduction

The genus *Brucella* consists of gram-negative coccobacilli which are strict intracellular parasites which infect both animals and human. *Brucella* bacterium is named after the microbiologist David Bruce [1]. This zoonotic bacteria has various species of which most pathogenic for human is *Brucella melitensis* which affect goat, sheep, camels. Again *Brucella abortus*, *Brucella suis*, *Brucella canis* infect cows, hogs, dogs respectively and transmitted to human by contact with infected animals or through ingestion of their products. These bacteria infect multi-system of the body especially respiratory, digestive, and genital system of the both animals and human [2]. The human diseases with various names like Mediterranean fever, Malta fever, undulant fever/remittent fever, Gibraltar fever, Cyprus fever are prevalent [3]. Brucellosis is a systemic infection observed in two forms like acute form and chronic form and that can affect any tissue and organs in human body [4]. Worldwide most of the chronic cases are caused by *Brucella melitensis* in human body [5]. *Brucella* is an intracellular pathogen which gets accumulated in the cells and organs of human being by microphage mechanism typically in liver and spleen. The general mechanism of phagocytosis occur in the human body can kill *Brucella* bacteria upto 90% but the remaining 10% which is alive in the body is enough for replication in to host cell. Among various species of *Brucella*, the species *abortus*, *suis*, and *melitensis* show prominent attack in the human host cells [6].

Major Transmission of *Brucella* bacteria in human

The common way to get infected is by eating or drinking unpasteurized or raw dairy products. When animals like sheep, goats, cows, hogs and camels are infected with these pathogenic bacteria and if anybody uses their milk and meat then the bacteria will get transmitted into their body system [7, 8]. Other mode of transmission of bacteria includes breathing of the bacteria during carrying out work in the laboratories. In addition, slaughterhouse and meat-packing employees have also been known to be exposed to the bacteria and ultimately infected. Veterinary doctors are also very much susceptible towards the infection especially during animal surgery. This bacterium is also transmitted into human's body through wounds on the skin or through mucous membrane.

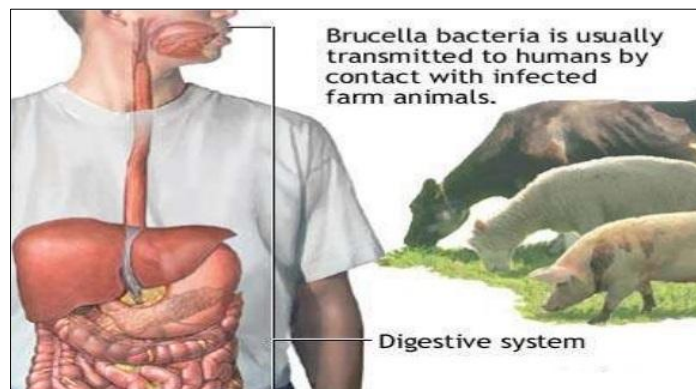


Fig 1: Major Transmission of Brucella in Human

Characteristics

Brucella species are small (0.5 to 0.7 by 0.6 to 1.5 μm) non-capsulated, non-motile and lacking a capsule, endospores, or native plasmids. They are intracellular parasite in the host cell, and show environmental persistence outside the host. The intracellular trafficking includes two or three main steps, starting with endosomal vacuoles, then endoplasmic reticulum-derived compartments and finally vacuoles having several markers of atypical autophagy [9]. Brucella is faintly stained gram-negative coccoid rods, with a microscopic appearance of 'fine sand', that lack endospores, capsules, or native plasmids [10]. They can live in high temperature, pH, and humidity. They infect many species, but with some specificity [11]. The brucella species belongs to the Rhizobiales group, in the Alpha-proteobacteria class [12].

Incubation Period

The general incubation period is highly variable, usually 2-4 weeks, can be 1 week to 2 months or longer. Initial presentation is nonspecific and includes fever, malaise, arthralgia, fatigue, headache, and night sweats. Focal

infections are common and can affect most organs in the human body. Osteo-articular involvement is the most common brucellosis complication, and reproductive system involvement is the second most common. Although rare, endocarditis can occur and is the principal cause of death among brucellosis patients [13].

Brucella species basically affect multi organ system in our body. These symptoms may show anytime from a few days to a few months after you've been infected. Primary symptom is flu and other includes pain in different areas abdomen, back, joints, or muscles. Whole body complications comprise of fever, chills, fatigue, loss of appetite, or night sweats. The commonest symptoms are coughing, headache, swollen lymph nodes, or weight loss [14].

Mechanism action of fluoroquinolones

The fluoroquinolones are the only direct inhibitors of DNA synthesis; by binding to the enzyme-DNA complex, they stabilize DNA strand breaks created by DNA gyrase and topoisomerase IV. Ternary complexes of drug, enzyme, and DNA block progress of the replication fork [15].

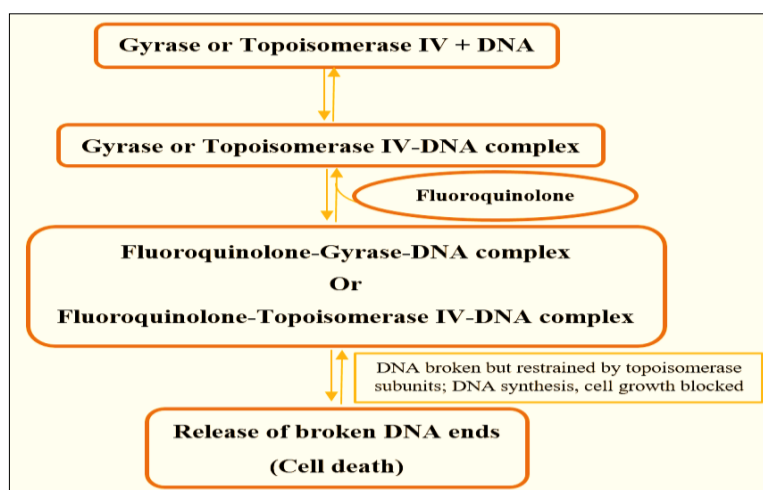


Fig 2: Mechanism of action of fluoroquinolone

Fluoroquinolones act by inhibiting two enzymes required in the synthesis of bacterial DNA, both of which are DNA topoisomerases that lack in human cells and that are necessary 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 trapped in which the DNA is broken, and the subunits of topoisomerase are covalently bound to broken DNA. Trapped complexes block the synthesis of DNA and the growth of the bacteria. From the figure 2, it is found that the release of broken DNA in the

complexes from the constraint imposed by the topoisomerases correlates with cell death [16].

Role of fluoroquinolones for the treatment of brucellosis

Earlier days a number of works have been carried out on various combination treatments with Doxycycline along with Streptomycin and Rifampicin or any amino glycosides act as first line therapy for the treatment of Brucellosis for first six weeks. Another combination therapy is Tetracycline – Streptomycin combination whose main route of administration is either intramuscular or intravenous route which shows patient in compliance [17]. Other series of adverse effects of Tetracycline includes liver and kidney damage, photo-toxicity reaction and for amino glycoside which covers serious ototoxicity especially vestibular & cochlear damage along with nephro- toxicity shows a decrease interest among the patient for the treatment of Brucellosis [18]. Even these combination therapies also show the relapsing of the fever which is up to 5-10% especially for pediatric and pregnant woman. Thus this type of long term therapy is not at all lead to patient compliance. Budaghabadi *et al.* prepared and evaluated nano carrier containing Rifampicin and Co-trimoxazole for the treatment against *Brucella melitensis*. The drug release rate is very much pH-dependent which 60% in the first 6 hours is. Even the nano- carrier approaches of these drugs offer resistance which decrease the efficacy of the drug regimen [19]. The relapse rate has not been decrease appreciably. Even the combination therapy offer less effective with about 15% failure in other types of disease. Hosseini *et al.* Manufacture Doxycycline encapsulated solid lipid nano particles against *Brucella melitensis* on the cell line J774A.

Till date, no combination drug therapy can cure the disease 100% since the infection is of intracellular level killing of pathogens is very much challenging. A serious disadvantage of solid lipid nanoparticles (SLNS) is the low drug loading capacities, the unstability of lipid physical state and an unpredictable release characteristics offers a resistance for the use of SLNS as carrier system [20]. Same has been found in Ghaderkhari *et al.* works where Rifampicin loaded nanoparticles were prepared [21]. Imbulizqueta *et al.* works on Gentamicine loaded nanoparticle also showed that the drug delivery has been successfully targeted to liver & spleen but the relapse rate of the disease cannot be minimized [22].

Fluoroquinolones belong to broad spectrum antibiotics having negligible adverse effect [23]. The important characteristics of fluoroquinolones are oral bioavailability, high tissue penetrability and localisation of drug intracellularly [24, 25]. *Brucella* is an intracellular pathogen which faces chemotherapeutic problems, but fluoroquinolones have the ability to be engulfed by the bacteria cell and can get localized within the phagocytic vacuoles [26]. There are various types of fluoroquinolones such as sparfloxacin, ciprofloxacin, ofloxacin which have minimal activity and cannot kill the bacteria under intracellular conditions [27] and therapeutic failures caused by the development of resistance by *Brucella melitensis* [28, 29]. On another hand newer fluoroquinolones such as levofloxacin, trovafloxacin, gatifloxacin shows low adverse effect, low toxicity, and minimal percentage of the relapse rate of disease occur [30].

In vitro studies of fluoroquinolones and other microbial agents against *Brucella* sp. isolates are tabulated in Table 1.

Table 1: *In vitro* studies examining the use of quinolones against *Brucella* species isolates

S. No.	Antibiotics used	MIC(mg/L)			Key Findings
		Range	MIC ₅₀	MIC ₉₀	
1	Ciprofloxacin	0.5-1	0.5	2	First report of <i>in vitro</i> testing of Ciprofloxacin against <i>B. melitensis</i> . ^[31]
	Norfloxacin	0.25-16	1	8	
	Nalidixic acid	64	64	64	
	Pipemidic acid	64	64	64	
2	Ofloxacin	0.02-0.03	0.02	0.02	Ofloxacin, tested for the first time <i>in vitro</i> against <i>B. melitensis</i> exhibited the highest activity amongst quinolones ^[32]
	Difloxacin	0.06-1.25	0.06	1.25	
	Ciprofloxacin	1.25-2.5	1.25	1.25	
	Tetracycline	0.001-0.6	0.005	0.04	
	Rifampicin	0.02-2.5	0.15	1.25	
	Streptomycin	0.15-5	0.6	2.5	
3	Trimethoprim-sulfamethoxazole	5-25	5	5	Three strains were resistant to Tetracycline and one to Rifampicin. No resistance was found to the other drugs ^[31]
	Ciprofloxacin	0.5-2	1	1	
	Netilmicin	0.25-1	0.5	1	
	Tetracycline	0.25->16	1	1	
	Streptomycin	1-4	2	4	
4	Rifampicin	0.25-16	2	4	Decreased activities (2–4 times) of quinolones at pH 5. Decreased bactericidal activities of quinolones were noted at both pH 5 and 7. ^[33,34]
	Trimethoprim-sulfamethoxazole	1->32	16	16	
	Sparfloxacin	0.125-0.5	0.25	0.25	
	Temafloxacin	0.125-0.5	0.25	0.25	
	Ciprofloxacin	0.25-0.5	0.5	0.5	
	Fleroxacin	0.5-1	0.5	1	
4	Ofloxacin	0.5-1	1	1	
	Lomefloxacin	1-2	2	2	

Conclusion

In conclusion, critical reviews considering the anti-brucellosis properties induced by fluoroquinolone have currently extended to a broader range of therapeutic regimens. Several studies on *in vitro* and clinical have been reported the potential role of fluoroquinolones in the treatment of human

brucellosis. Subsequently, further laboratory exploration may be of significance, focusing on *in vitro* studies of combinations of various quinolones with other antibiotics, especially with tetracycline and doxycycline. However, quinolone-based treatments seem to have a role in modern clinical practice as alternatives to standard therapy for patients

with relapse of brucellosis after treatment with another regimen, as well as in patients in whom toxicity has developed due to the use of some of the older agents. In these cases, it is important to choose the best solution, because ineffective brucellosis treatment can cause serious complications and the risk of relapse. This is also important to search for potential therapies for this patient group and provide new ideas for treatment.

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