ARTYKUŁ POGLĄDOWY/REVIEW PAPER
Otrzymano/Submitted: 11.02.2016 • Zaakceptowano/Accepted: 11.03.2016

Levofloxacin – its practical application in the treatment and pharmacokinetics

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Summary

Levofloxacin is a third generation of fluoroquinolones representative. It is characterized by a wide spectrum of bactericidal activity. Due to its properties it can be applicated in community acquired pneumonia and tuberculosis treatment. In case of tuberculosis is a second line drug often combined with other antituberculotic drugs. In *Helicobatcer pylori* eradication it can be combined with two or three other drugs when other therapies fail (so called triple therapy or quadruple therapy respectively). Due to its high concentration in urine it can be applied in urinary tract infections. It premeats well to prostatic tissue and it is first line drug used in prostatitis. The pharmacokinetics of levofloxacin is described by two-compartment model. It is absorbed after oral administration and it permeats tissues very well. The elimination of levofloxacin is age-dependant process. Levofloxacin is also glycoprotein-P inhibiting agent and it may lead to the increase of the blood levels of other drugs. Levofloxacin is a quite safe drug however man should be aware in treatment of elderly patients. *(Farm Współ 2016; 9: 1-7)*

Keywords: pharmacokinetics, tuberculosis, Helicobacter pylori, levofloxacin, community acquired pneumonia

Introduction

Levofloxacin is a representative of the third generation of fluoroquinolones. It is S-(-) enantiomer of racemic ofloxacin. Levofloxacin is characterized by a wide spectrum of bactericidial activity against Gram-positive and Gram-negative microorganisms such as *Staphylococcus aureus, Streptococcus pneumonie, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Clostridium perfringens* [1]. The conducted *in vitro* study showed synergistic activity of levofloxacin and piperacylin with tazobactam on fluoroquinolone restistant strains of *P. aeruginosa* [2].

Levofloxacin in community-acquired pneumonia and tuberculosis treatment

Infectious Diseases Society of America (IDSA) recommends levofloxacin in the treatment of community-acquired pneumonia (CAP). The recommended dose is 750 mg. Fluoroquinolones are active towards most pathogenes that cause CAP including penicillin and macrolide-resistant *S.pneumoniae*. Levofloxacin is dosed once daily and it delivers effective therapy to the wide range of patients. The European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases recommend fluoroquinolones as a first-line drug in monotherapy for hospitalized non-ICU patients with CAP. For the treatment of the patients in the Intensive Care Units, the IDSA guidelines recommend the combination of a fluoroquinolone with extended-spectrum of cephalosporin (cefotaxime or ceftriaxone) or a beta-lactam or beta-lactamase inhibitor. In spite of the proven efficacy in CAP the new fluoroquinolones like levofloxacin can be applied in the management of tuberculosis (TB). The dose is 750-1000 mg/day. WHO recommends levofloxacin as a second line drug in TB treatment. It should be used only in case multidrug resistant TB (MDR-TB) or when the toxicity of the standard therapy reduce the range of the drugs that can be used. Standard TB therapy consists of 2-months of initial intensive isoniasid, rifampicin, ethambutol and pyrazinamide phase. It is followed by 4 months of isoniasid and rifampicin. MDR-TB is considered when the resistance for at least isoniasid and rifampicin is observed with only a maximum of

two drugs of the standard regimen remaining available. In case of MDR-TB the following drugs are included: pyrazinamid or ethambutol, one injectable agent (kanamycin capreomycin, amikacin and streptomycin), one fluoroquinolone (ofloxacin, gatifloxacin, levofloxacin or moxifloxacin) and cycloserine or p-aminosalycilic acid (if cycloserine can not be applied). Fluoroquinolones permeat the tissues well contrary to aminoglycosides. The *in vitro* study conducted by Rey-Juardo et al. showed that combination of levofloxacin-amikacin-ethambutol inhibits the growth of the colonies more than levofloxacin in monotherapy. Moreover, the combination including linezolid and levofloxacin showed less activity than levofloxacin alone. The mechanism of this antagonism in not known. Levofloxacin is an inhibitor of topoisomerase II and IV. *Mycobacterium tuberculosis* lacks of topoisomerase IV and DNA gyrase is the only target point for levofloxacin. The resistance is caused by spontaneous chromosome mutation in the *gyr*A and *gyr*B gene that encodes the units of topoisomerase II. Food and drug administration (FDA) recommends the fluoroquinolones in the treatment of acute bacterial sinusitis, however they should not be used as a first – line drug because of the potential bacterial resistance. Levofloxacin treatment of acute bacterial bronchitis is effective if the pathogens are *Haemophilus influenzae* and *Moraxella catarrhalis* [3-11].

Levofloxacin in eradication of *H.pylori*

Levofloxacin can be used in eradication of *Helicobacter pylori*. The standard triple therapy proposed on Maastricht conference comprises PPI (proton pump inhibitor), clarithromycin and amoxicillin and it takes from 7 to 14 days. The other option is the sequential therapy (PPI and amoxicillin 5-7 days, clarithromycin and metronidazole (5-7 days)). Metronidazole is used instead of amoxicillin when penicillin allergy is observed. The standard triple therapy is not recommended when clarithromycin resistance is observed. In this case the quadruple bismuth therapy is recommended. It involves PPI, bismuth, tetracycline and metronidazole. In case of failure of standard therapy, the levofloxacin--based rescue therapy is recommended unless there is fluoroquinolone resistance. It is more effective and better tolerated than bismuth quadruple therapy and 10-day regimen is superior to 7-day treatment. The levofloxacin-based triple therapy comprised PPI, levofloxacin and amoxicillin (7-14 days). The other option is sequential therapy i.e. PPI and amoxicillin (5 days) followed by PPI, levofloxacin and metronidazole (5 days) or 10-day quadruple therapy containing PPI, bismuth salt, tetracycline and levofloxacin. The eradication rate of the latter therapy is 95.8%. Levofloxacin-based quadruple therapy is a promising when other therapies fail. The dose of levofloxacin is 750 mg and it should be validated for *H. pylori* eradication [12-15].

Other applications of levofloxacin

Due to the high concentration in urinary tract and renal clearance levofloxacin is used as a bactericidial agent in urinary tract infections, acute uncomplicated pyelonephritis. Given in three- to ten-day courses can be as effective as trimethoprim-sulfamethoxazole combination. Levofloxacin permeats to prostatic tissue and high concentration of the drug are observed there. The eradication rate is 67-91%. Levofloxacin is a first-line agent in prostatitis treatment.

Levofloxacin, in case of use of biological weapon, can be effective as prophylactic agent after exposure to *Bacillus anthracis* spores. The ophthalmic solution of the drug can be used in ophthalmic infections such as conjunctivitis. The fluorquinolones in drops are also used in keratitis caused by *Staphylococcus* sp. and *Streptococcus* sp. Standard monotherapy with fluoroquinolones ophthalmic solutions used to be effective however the resistant strains of bacteria may occur. Suzuki et al. in his study investigated the combined activities of levofloxacin and nonfluoroquinolone antibacterial eye drops. He suggested that levofloxacin should be combined with cefmenoxime or tobramycin. The therapy should be selected to causative bacteria. The combined activity of fluoroquinolone and additional antimicrobial drug is reported against *P. aeruginosa*. In this case the synergistic action was observed for cefepime and gentamycin. The combination of levofloxacin (and other fluoroquinolones) with other antimicrobial agents is important from clinical point of view. Schimel et al. compared the resistance of bacteria that cause endophtalmitis. He demonstarated that levels of resistance of *Staphylococcus* sp. to commercially available fluoroquinolones increased over 15 years from 1990 to 2005. In 2005 only 41.4% (*vs.* 100% in 1990) *Staphylococcus* sp. isolates were susceptible to levofloxacin [16-18].

Dosing of levofloxacin

Levofloxacin is available in the market in the following formulations: tablets, infusions and ophthalmic

solutions. The intravenous administration is applied at patients with severe infections or when there are contraindications for *per os* administration. The time of the infusion should for be 30, 60 or 90 minutes for the doses 250 mg, 500 mg and 750 mg respectively. Due to the high bioavailability of levofloxacin, the intravenous therapy can be replaced with oral administration of the drug after few days of *i.v.* treatment without the dose change. Pediatric patients require the change in the dosing regimen. The application of levofloxacin is limited only for anthrax and pestis treatment in this group of patients [19].

The pharmacokinetics of the levofloxacin

The pharmacokinetics of levofloxacin is linear, best described by two-compartment model. However it can be described by non-compartmental analysis.

▪ Absorption

Levofloxacin is totally absorbed after oral administration (bioavaiability > 99%). The study on 23 healthy volunteers after administration of levofloxacin in tablets from two different manufacturers and the 60-minutes infusion of the same dose was conducted. The pharmacokinetic parameters after oral administration such as C_{max}, t_{max}, AUC and half-life were similar with the ones after infusion [17,20]. The stationary state is reached after 48h of administration of 500 mg/24 h or 750 mg/24 h. The simultaneous administration with a meal delay the absorption of levofloxacin and prolong the time to reach the maximum plasma concentration at about 1 hour. It also decreases the plasma concentration at about 14%. The fat rich meals does not change the bioavailability. FDA recommends the administration of the drug 1 hour before or 2 hours after the dinner. It is acceptable to take the drug with a meal [1,19-21].

The absorption may be impaired by cations. Fluoroquinolones chelate with cations such as aluminium, magnesium, zinc, calcium and iron. The complexes can not be absorbed and it results in both lower plasma concentration and lower AUC [8].

▪ Distribution

Levofloxacin permeats the tissues very well. The volume of distribution after single or multiple dose 500 mg and 750 mg administration is 74-112 l. The target tissue concentration is higher than in plasma and few times higher than MIC for most pathogens. The high concentrations are observed in lung tissue. The maximum concentration after administration 500 mg of the drug and it is 2-5-fold higher than in the plasma [19]. It ranges from 2.4 to 11.3 mg/l. Levofloxacin permeats the central nervous system only in 16%, however in meningitis it changes to 60% [22]. After single dose 500 mg the urine concentration is 128-343 mg/l, and in blood is 4.5 -5.2 mg/l. The concentration prostate: plasma ratio is 2.96:1 [23].

The concentration of levofloxacin in lacrimal fluid after single dose (1 drop of 0.5% levofloxacin solution) reach the concentration much above MIC (2 μg/ml) for most pathogens and remains about 6 hours at healthy volunteers, at some of them it is observed even after 24 hours [24].

The concentration of levofloxacin in tissues like bronchi, lungs and prostate are higher than those ones observed for ciprofloxacin [25]. Levofloxacin binds to plasma proteins in 40-60 %. The *in vitro* study proved that it can change with the drug concentration [26].

▪ Metabolism and elimination

Levofloxacin is stereochemically stable and it can not be conversed to R isomer both in urine and in plasma. The half life is 6-8h and it is not dose dependant. It is metabolized in low extent. 79-87% of the dose is excreted in urine as a parent drug during 48 hours. 4% of the dose is metabolized to N-oxy and desmethyl metabolites. They are the only metabolites found in human body and they are pharmacodynamically inactive. The total and renal clearance are 144-226 ml/min and 96-142 ml/min respectively indicates low elimination in non-renal excretion. The renal clearance is higher than creatinine clearance and it indicates the excretion to renal tube. The simultaneous administration of cimetidine or probenecid with levofloxacin results in the reduction of renal clearance at 24% and 35% respectively. It implies that in this case levofloxacin is excreted in proximal tube [17,19].

The study on pharmacokinetic of levofloxacin was conducted at pediatric patients between 6 month of life and 16 year-old ones. They were divided into five age groups. The dose 7 mg/kg b.w. was administered three times in intravenous or in oral way. The results were compared with those for adults group. Both the absorption (C_{max}, t_{max}) and distribution phase are similar at adults and in children. The elimination parameters ($t_{0.5}$, Cl) depend on age. Children below 5-year-old eliminate the drug 2-fold faster than adults and the AUC

is a half value of AUC of adults. The AUC at children after oral and intravenous administration are similar. It proves the total bioavailability at pediatric patients. The recommend dose for children between 6-month and 5-year-old is 10 mg/kg/12 h. The children above 5-year-old should be treated with the dose 10 mg/kg/24 h [27].

Levofloxacin is excreted mainly with urine in 80%. In case of renal failure the dose should be changed. The clearance of creatinine is required in such cases. In elderly patient the dosing rate is not required to be changed on condition that there is no renal disorders. The liver failure is not a contraindication for administration of levofloxacin [28]. Race, sex, age above 65 year-old, HIV do not influence the pharmacokinetic parameters [22,29-31].

At patients with renal impairment the renal clearance decreases and the half-life is longer: Cl_{cr} = 70-40 ml/min, $t_{0.5}$ = 6.4 h, Cl_{cr} = 39-20 ml/min, $t_{0.5}$ = 11.1 h, Cl_{cr} < 20 ml/min, $t_{0.5}$ = 28.2 h. The dosing rate should be modified in order to avoid toxic concentrations.

Contraindications

Levofloxacin can't be administered to patients with allergy to the fluoroquinolones [19].

Levofloxacin is classified in C category. It means that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks [32,33].

Cahill et al. reported that at breastfeeding women the concentration of levofloxacin in milk is similar to the one in plasma. It implies that infant is exposed to the drug [34].

Man should be careful in case of elderly patients. There is a risk of tendons damage at these patients. Patients with myasthenia gravis or with the central nervous system diseases should be careful. The QT-prolongation, unbalanced hypokalemia or the treatment with I A-class antiarrythmic drugs (quinidine, procainamide) and III-class (amiodarone and sotalol) are contraindications for the treatment with levofloxacin. Moreover, the glucose levels should be monitored in diabetic patients [35,36].

Interactions with other drugs

Levofloxacin interacts with antacids containing aluminium, magnesium, calcium and iron. They form complexes and it leads to the decrease of bioavailability of levofloxacin. It should be two hours break between administering these drugs [19].

Probenecid and cimetidine decreases the renal clearance of levofloxacin at about 24 and 34% respectively. However this interaction is highly unlikely to occur when therapeutic doses are administered. Only patient with renal impairment should be aware of this interaction [4]. Levofloxacin decreases the renal clearance and prolongates the half-life of both procainamide and its active metabolite N-acetylprocainamide (NAPA). This interaction might be the result of the interaction with organic cation transporters (OCT) which may be the carriers for both procainamide and NAPA and levofloxacin. Moreover procainamide, NAPA and levofloxacin are excreted via active secretion in proximal tube and it may lead to the mutual competition [37].

During clinical trials the interaction of levofloxacin with theophylline and nonsteroid anti-inflammatory drugs was not stated. However they lower the seizure threshold and there is an increasing risk of the seizures as a side effect. Levofloxacin influences the pharmacokinetics of the other drugs. Simultaneous administration of levofloxacin and cyclosporine inhibits the metabolism of the latter drug. It increases the C_{max}, AUC_{12h}, C_{trough} and $C_{average}$. The administration with witamin K antagonists (warfarine) leads to increasing values of the coagulation factors. Glycoprotein P (P-gp) is the protein that prevents the permeation of the xenobiotics to human body. It pumps the chemical substances out of cells. It can be found in intestinal epithelium, liver and kidneys. Levofloxacin is an inhibitor of P-gp and may lead to the increase of the compounds that are the substrates of it such as erythromycin, cyclosporin, imatinib [38-40].

Side effects

Levofloxacin is concerned as a safe and well tolerated drug. The most frequent side effects were nausea, headaches, diarrhea, sleeplessness, constipation and dizziness [36,41]. Levofloxacin can increase the risk of tendon rupture or tendinitis. According to MEDLINE database in the years 1966-2011 11 cases of tendon rupture were reported. The most frequent concerned Achilles tendon. This side effect can occur during the pharmacotherapy or several months after therapy. Not only tendon rupture can occur but also arthropathies. They are characterized by pain, joint stiffness and swelling. The first symptoms can be observed after a

few days of therapy and can be observed during couple of days or weeks after the treatment [42]. Patient with *myasthenia gravis* should be careful because levofloxacin can block the neuromuscular transmission [28].

The other side effects are the results of allergic reaction to levofloxacin. They may occur after taking the first dose. We may observe hypotension, convulsions, loss of consciousness, angioedema, bronchoconstriction, dyspnoea, hives and itch [19,43].

The severe reactions were reported after multiple doses. The following symptoms were observed: fever, rash and other skin reaction (Stevens-Johnsons disease), serum sickness, pneumonia, interstitial nephritis, acute renal failure, hepatitis, acute necrosis of liver or kidneys, hematological diseases.

The drug should be withdrawn right after the first symptoms of rash, jaundice or any other symptoms of allergy [19].

Due to the risk of cartilage damage proved on the animal model levofloxacin administration at pediatric patients is limited only to anthrax and plague. Fluoroquinolones can accumulate cartilages and form the complexes with calcium and magnesium ions which may lead to functional deficiency of these elements [44,45].

Fluoroquinolones can cause both hyperglycaemia and hypoglycaemia. Levofloxacin can cause this metabolic disfunction however in much lower extent than gatifloxacin and temafloxacin. It can be observed at diabetic patients treated simultaneously with oral hypoglycaemic agents and insulin. The hypoglycaemic effect can be caused by blocking the ATP-sensitive potassium channels in beta islet cells. It leads to the excretion of insulin. The mechanism of hyperglycaemia is not known [19,46,47].

Conclusions

Levofloxacin is a third generation fluoroquinolone. It is characterized by wide range of antimicrobial activity. It can be applied also in community-acquired pneumonia and tuberculosis treatment as a second line drug. Due to the resistance increase in *Helicobacter pylori* levofloxacin with bismuth salt is introduced when other therapy schemes occur to fail. Levofloxacin can also be applied in ophthalmology as drops. Levofloxacin is a quite safe drug, however man should be aware of the risk of cartilage and tendon damage at elderly patients. The incidents of hypo- and hyperglycaemia may also occur. Its pharmacokinetics is linear. Levofloxacin permeats the tissues very well and the concentration in target tissue is higher than in plasma and few times higher than MIC. The dose of levofloxacin should be changed at children below 5 year old because of faster elimination and also should be reduced if renal impairment is observed.

Conflict of interes
None

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