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CIPROFLOXACIN;
THE FREQUENT USE IN POULTRY AND ITS CONSEQUENCES ON HUMAN HEALTH

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ABSTRACT… Fluoroquinolones are bactericidal agents that exhibit AUC/MIC dependent killing. In general, they are effective against Gram-negative organisms and some mycobacteria. Ciprofloxacin is the members of this group and its bactericidal action involves the impeding of enzyme topoisomerase II and IV. In human beings, this drug is recommended for a variety of infections including typhoid fever,chronic bacterial prostatitis, lower respiratory tract infections, skin infections, urinary tract infections, acute exacerbations of chronic bronchitis, complicated intra-abdominal infections, infectious diarrhea, and uncomplicated cervical as well as urethral gonorrhea.The drug is as effective in animals as in humans, and is therefore used in animals as well. According to European health law and National Office of Animal Health (NOAH), UK, the statutory withdrawal period for veterinary medicinal products must not be less than 28 days for meat from poultry. The chicken used for meat purpose usually is of the age between 6 to 8 weeks, therefore the use of the drug must be discontinued by the age of 2 weeks. Whereas the age of chick at which it usually develops indicated diseases, is 3 weeks. In this situation, it is not possible to attain a withdrawal period of 28 days. Based on these observations, ciprofloxacin use may not be recommended in poultry for treatment of diseases as it may cause unnecessary exposure to humans while utilizing poultry meat and may lead to the development of drug resistance.

Key words: Ciprofloxacin, Withdrawal, Fluoroquinolones, Poultry, Drug resistance

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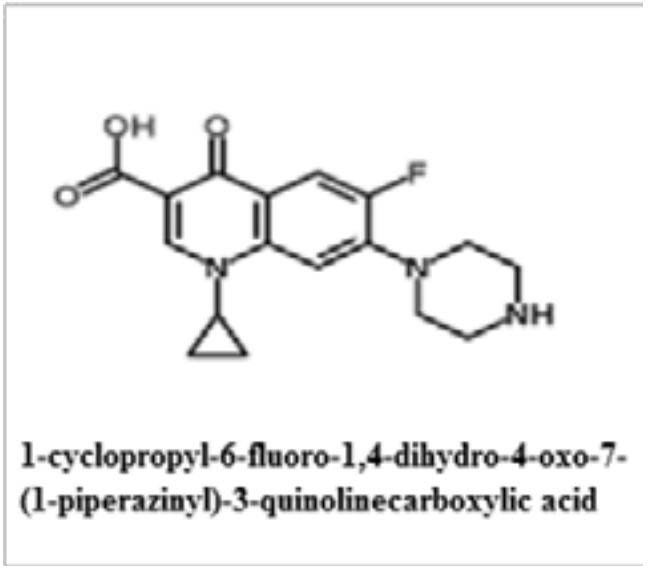
INTRODUCTION

Ciprofloxacin belongs to the group of drugs called fluoroquinolones[1]. Introduction of the first fluorinated quinolone, norfloxacin lead to the development of other members of this group[2], such as ciprofloxacin, which has wide clinical applications, better safety profile and good in vitro effectiveness against resistant pathogenic organisms as compared to other classes of antibiotics[3]. Fluoroquinolones are bactericidal agents and exhibit AUC/MIC dependent killing.In general, they are effective against Gram-negative organisms and some mycobacteria[4]. The molecular formula of Ciprofloxacin is $C_{17}H_{18}FN_3O_3$ having a molar mass of of 331.4g/mol. Chemically it is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid[5]. Physically the drug exists in crystalline form at room temperature with a light yellow color[6]. The structural formula of ciprofloxacin is[7]



1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

Pharmacokinetic properties of ciprofloxacin

Ciprofloxacin is well absorbed from gastrointestinal tract after oral administration with a serum protein binding of about 20 to 40%. The absolute bioavailability of the drug is almost 70% and it is not affected by first pass metabolism[8].

The drug is distributed through out the body after oral administration. The tissue concentration generally exceeds serum concentration especially in genital tissuesincluding prostate. The drug is found in active form, in nasal and bronchial secretions, skin blister fluid, mucosa of the sinuses, sputum, saliva, lymph, prostatic secretions, peritoneal fluid and bile[9,10]. A deep analysis reveals the noticeable amounts of ciprofloxacin incartilage, and bones, fats, lungs, skin and skeletal muscles[11], while less amount of drug has been detected in vitreous humor of the eyes[12].This feature of deep penetration makes the use of this drug questionable in meat producing animals.

Upon urine analysis, four metabolites (approximately 15% of oral dose) of ciprofloxacin have been identified[13]. It is observed that ciprofloxacin impedes human cytochrome P450 1A2 (CYP1A2) mediated metabolism, therefore co-administration of this drug with other drugs which are primarily metabolized by CYP1A2 may result in increased plasma concentrations of the later drugs and has the potential to cause clinically significant adverse events[14].

In individuals with normal renal function, ciprofloxacin's elimination half-life in the serum is about 4 hours. Approximately 40 to 50% of oral dose of the drug is excreted in the urine as unchanged[15]. Concurrent use of ciprofloxacin with probenecid (a drug to treat gout and hyperuricemia)can lead to 50% increase in concentration of ciprofloxacin in systemic circulation because of its reduced renal clearance[16,17].

Pharmacodynamic properties of ciprofloxacin

Antibacterial (bactericide) action of ciprofloxacin is exhibited by deterring the enzymes topoisomerase IV and topoisomerase II (DNA gyrase). These enzymes are the basic requirements of bacteria for DNA repair, transcription, recombination, and replication[18].

Antimicrobial spectrum

Antibacterial spectrum of ciprofloxacin includes; Streptococcus pneumoniae (penicillin susceptible isolates only), Enterococcus faecalis (vancomycin-susceptible isolates only), Staphylococcus epidermidis (methicillin-susceptible isolates only), Staphylococcus saprophyticus, Staphylococcus aureus (methicillin-susceptible isolates only), Streptococcus pyogenes, Gram-negative bacteria, Citrobacterkoseri (diversus), Proteus mi rabilis,Citrobacterfreundii,Enterobacter cloacae, Escherichia coli, Neisseria gonorrhoeae,Morgan ellamorganii,Haemophilusinfluenza,Haemophilus para influenzae,Klebsiella pneumonia, Moraxella catarrhalis, Campylobacter jejuni, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Pseudomonas aeruginosa, Salmonella typhi, Serratia marcescens, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei.[19]

Drug Resistance

Microorganisms resistant to penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines may be susceptible to fluoroquinolones, including ciprofloxacin because of different bactericidal mechanism[20]. Even then, resistance to fluoroquinolones is possible either by decreased outer membrane permeability, mutations in the DNA gyrases, or drug efflux. In vitro studies have shown that, resistance develops slowly with the prolong exposure to low doses of ciprofloxacin by multiple step mutations[21].

Clinical Uses In humans

Besides the prophylactic use, ciprofloxacin is indicated for the treatment of infections like; typhoid fever (enteric fever), urinary tract infections, chronic bacterial prostatitis, for the treatment of acute exacerbations of chronic bronchitis, skin and skin structure infections, complicated intra-abdominal infections, acute uncomplicated cystitis in females, lower respiratory tract infections, acute sinusitis, bone and joint infections, infectious diarrhea, as well as

uncomplicated cervical and urethral gonorrhea caused by neisseria gonorrhoeae[22-27].

Uses in Poultry

In veterinary medicines, ciprofloxacin is often recommended for respiratory tract infections, gastrointestinal tract infections and urinary tract infections caused by Campylobacter, E. coli, Haemophilus, Mycoplasma, Pasteurella and Salmonella species[28]. These diseases start appearing in poultry from the age of three days to several months, on an average the most vulnerable age is 3 weeks for respiratory diseases[29] and 4 to 6 weeks for gastrointestinal diseases[30].

Dose of ciprofloxacin in poultry

Different manufacturers recommend different doses of the drug ranging from 1mg/ml to 1 mg/15ml in drinking water, on an average a young chick consumes 250ml water per day which means the intake of the drug is from 17mg to 250mg per day[31,32,33].

Withdrawal period:

Withdrawal period is the time required after the administration of a drug to an animal to assure that drug residues in the marketable/saleable product are below a determined maximum residue limit (MRL). Withdrawal period is of most concern during the administration of drug to any edible product or food animal for meat or eggs. According to European health law and National Office of Animal Health, UK, the statutory withdrawal period for Veterinary Medicinal Products must not be less than 28 days for meat from poultry and mammals[34]. However ciprofloxacin has a withdrawal period of 12-15 days in absolute conditions[35].The recommended duration of the therapy is 5-7 days and may be prolonged upto 2 weeks depending upon the severity and type of disease.

Administration of ciprofloxacin to animals (produced for commercial purpose) with a serious impaired hepatic and/or renal function can alter (increase) the protein binding of the drug leading to an increased withdrawal time period of up to 23 days which is actually 12-15 days in normal considerations.

CONCLUSIONS

From this study, it is clear that extensive use of ciprofloxacin in poultry is most likely to develop complications/ resistance in pathogenic organisms to human because of following reasons;

Normal withdrawal period of the drug in animal is 12-15 days from the time of last administered dose. Administration of ciprofloxacin to animals (produced for commercial purpose) with seriously impaired hepatic and/or renal function can alter (increase) the protein binding of the drug leading to an increased withdrawal time period (up to 23 days).

The usual age of the poultry chicken used for meat purpose is 6-8 weeks (42-56 days), which means that the therapy of ciprofloxacin must be stopped at the age of 19th day in order to complete the withdrawal period of 23 days.

The usual age at which the respiratory diseases affect the chicken is 21 days (at the age of 3 weeks) while the use of ciprofloxacin must be stopped before the age of 19th day, therefore its use must be discouraged.

Furthermore its use may cause abnormal delivery of drug to humans which may cause toxicity in patients having probenecid therapy as co-current use of ciprofloxacin with probenecid (a drug to treat gout and hyperuricemia) can lead to 50% increase in concentration of ciprofloxacin in systemic circulation because of its reduced renal clearance. It is observed that Ciprofloxacin impedes human cytochrome P450 1A2 (CYP1A2) mediated metabolism.

Co-administration of ciprofloxacin (even in a very minute quantity) with other drugs which are primarily metabolized by CYP1A2 particularly the drugs which already have very narrow therapeutic window like theophylline and tizanidine may cause serious adverse events.

Similarly some other drugs of very common and often long term use like,terbinafine,

warfarin, clopidogrel,ondansetron, propafenone, leflunomide,propranolol, verapamil, naproxen, zileutin, olanzapine, imipramine and mexiletine may also show an increased plasma concentration when used with ciprofloxacin and have the potential danger to cause clinically significant adverse events.

Overall, it is not possible to attain the complete withdrawl period with the use of ciprofloxacin in poultry animals used for meat purpose within the age of 6-8 weeks.While the unnecessary exposure of ciprofloxacin with a low dose for a long period may also has its drawbacks regarding the development of resistance in humans.

Conflict of no interest statement

All the authors of this manuscript declare no conflict of interest to any individual or manufacturer or company or organization.

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