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Use of Second Generation Quinolones in Poultry

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Second generation quinolones form a promising family of new bactericidal antimicrobials. Drugs in this group are fluoroquinolones, derived from the quinolones mainly nalidixic acid. These were introduced in early 1990's in Pakistan are now widely used for the prevention and treatment of poultry diseases.

Available form(s): Various forms of second generation quinolones are available including norfloxacin, enrofloxacin, ciprofloxacin, enoxacin, benofloxacin, lomefloxacin, ofloxacin sarafloxacin, etc. Various countries have restricted some of these forms for use in human medicine only and registered other forms for use in veterinary medicine. In Pakistan, norfloxacin and enrofloxacin are extensively used in poultry; ciprofloxacin and danofloxacin are also in use.

Absorption: The gastro-intestinal absorption is rapid and substantial (plasma levels achieved within 30 min to 2 h).

Bioavailability through oral route

Drug	Bioavailability (%)
Ciprofloxacin	60-75
Enoxacin	87-98
Enrofloxacin	64-80
Ofloxacin	95-100
Norfloxacin	30-70

Distribution: Widely distributed in respiratory tract, bones, cartilage, and cerebrospinal fluid. Concentrations in tissues (lung, heart, liver, kidneys and intestine) are higher than concentration in blood or serum.

Mechanism of action: Act intracellularly in bacteria by changing the structure of an enzyme DNA-gyrase. The target site for bactericidal action is the type II topoisomerase. It results in synthesis of reduced and impaired DNA. The duration of action is long.

Excretion: The excretion is mainly through kidneys and partly biliary. Ciprofloxacin and norfloxacin crystallize in alkaline urine.

Indications: Broad spectrum antimicrobial activity. Active against Gram negative and Gram-positive bacteria (*E. coli*, *Past. multocida*, *Haemophilus*, Strep., Staph., *Salm. typhimurium*) and Mycoplasma (*M. gallisepticum*, *M. synoviae*). Anaerobic activity (*Cl. perfringens*) is weak.

Half-life (h) following oral administration

Drug	Normal kidney function	Impaired renal function
Ciprofloxacin	4	6-8
Danofloxacin	4	?
Enrofloxacin	3	?
Enoxacin	6	?
Norfloxacin	3-4	6-9
Ofloxacin	4.7-7	15-60

In vitro sensitivity test

	Norfloxacin	Enrofloxacin and ciprofloxacin
Disc potency (*u*g)	10	5
Resistant zone diameter (mm)	12	15
Intermediately susceptible zone (mm)	13-16	16-20
Susceptible zone (mm)	17	21

Minimum inhibitory concentration (μg mL^{-1})

Escherichia coli	0.06
Haemophilus spp.	0.02
Pasteurella multocida	0.008
Campylobacter	0.25
Staphylococcus aureus	0.12
Clostridium perfringens	0.5
Mycoplasma gallisepticum	0.1
Mycoplasma synoviae	0.1

Contra-indications: Should not be given to replacement birds within 14 days of commencement of laying.

Resistance: Does not develop rapidly but bacteria DO become resistant to these drugs. Resistance develops through chromosomal mutation inside the bacterial cells. Cross resistance occurs among fluoroquinolones.

Drug interactions: Non-steroidal anti-inflammatory drugs potentiate the CNS stimulant effects. May interfere with hepatic biotransformation of theophylline and warfarin.

Adverse reactions: Adverse effects are not severe when compared to the beneficial features. The target tissues for adverse effects are:

1. The juvenile cartilage (arthropathies such as lameness and erosion of articular cartilage in young animals).
2. Central nervous system.
3. Urinary tract.
4. Digestive tract.
5. Hypersensitivity can occur rarely (allergic).

Incompatibility: Incompatible with oxytetracycline, chloramphenicol, tylosin and erythromycin. Can be given with water soluble vaccines (Floxatril).

Safety: One of the safest antibiotics. LD50 2940 mg kg^{-1} body weight.

Recommended dosage and route of administration:
Norfloxacin:

Oral: 12 mg active drug per kilogram live body weight in drinking water.

Injection: 2.5 mg kg^{-1} body weight. Intramuscular or subcutaneous.

Do not use intravenous.

Enrofloxacin:

10 mg activity per kilogram live body weight.

Duration of treatment: 3-5 days

Withdrawal: 7 days. Do not use in birds producing eggs for human consumption.

Commercial preparations

The following commercial preparations are being marketed in Pakistan for poultry use.

Further readings

1. Bishop, Y.M., 1996. The Veterinary Formulary: Handbook of Medicines Used in Veterinary Practice. 3rd Edn., Royal Pharmaceutical Society of Great Britain, USA., ISBN: 9780853693451, Pages: 513.
2. Brander, G.C., D.M. Pugh, R.J. Bywater and W.L. Jenkins, 1991. Veterinary Applied Pharmacology and Therapeutics. 5th Edn., W.B. Saunders Co., Philadelphia, ISBN-13: 978-0702013669, pp: 486-488.
3. Wesley, G.C., D.Q. Craig, M.D. Brater and A.R. Johnson, 1990. Goth's Medical Pharmacology. 12th Edn., Galgotia Publication Ltd., New Dehli, India, pp: 640-787.

NORFLOXCIN

Brand name and manufacturer	Concentration	Dose
Water soluble products		
Agtrill 10% oral solution (Agrar, Holland)	100 mg mL^{-1}	1 mL/2 L drinking water (0.12 ml/kg body weight).
Agtrill 25% oral solution (Agrar, Holland)	250 mg mL^{-1}	1 mL/5 L drinking water
Doctorjin solution 20% (Dae Sung, Korea)	200 g L^{-1}	1 mL/4 L drinking water
Anflox 10% liquid (Anupco, England)	100 mg mL^{-1}	1 mL/2 L drinking water
Anflox gold 20% liquid (Anupco, England)	200 mg mL^{-1}	1 mL/4 L drinking water
Encure-20 (Nawan, Pakistan)	200 mg mL^{-1}	1 mL/4 L drinking water
Enrocin (Nawan, Pakistan)	200 mg mL^{-1}	1 mL/2 L drinking water
Floxatril 10% solution (Pantex, Holland)	100 mg mL^{-1}	1 mL/2 L drinking water
Floxatril Forte (Pantex, Holland)	? mg mL^{-1}	1 mL/5 L drinking water
Menorox liquid concentrate (Vetmark)	100 mg mL^{-1}	1 mL/2 L drinking water
Menorox soluble powder (Vetmark)	100 mg g^{-1}	1 g/2 L drinking water
Norflox 20% Liquid (ANI, England)	200 mg mL^{-1}	1 mL/4 L drinking water
Norfloxillin-200 (Shin-il, Korea)	200 mg mL^{-1}	1 mL/4 L drinking water
Nortril (Bremer, Germany)	100 mg mL^{-1}	1 mL/1.2-1.5 L drinking'water
Notrilaps soln. (SVPF, China)	50 mg mL^{-1}	1 mL L^{-1} drinking water
Quintox 3 (T, UK)	20%	1 mL/4 L drinking water
Feed premixes		
Anflox feed premix (Anupco, England)	100 g kg^{-1} premix	0.5 kg t^{-1} feed

Menorox feed premix (Vetmark)	100 g kg^{-1}	0.25-0.5 kg t^{-1} feed.
Injectable products		
Agtrill 10% injection (Agrar, Holland)	100 mg mL^{-1}	1 mL/10-15 kg body weight
Doctorjin inj. 10% (Dae Sung, Korea)	100 mg	0.5-1 mL/10 kg live body weight
Floxatril inj. (Pantex, Holland)	100 mg mL^{-1}	2.5-5 mg kg^{-1} live body weight.
Menorox sterile inj. (5%) (Vetmark)	50 mg mL^{-1}	2.5-5 mg kg^{-1} live body weight
Menorox sterile inj. (10%) (Vetmark)	100 mg mL^{-1}	2.5-5 mg kg^{-1} live body weight.
Norfloxillin 5% inj. (Shin-il, Korea)	50 mg mL^{-1}	0.05-0.1 mL kg^{-1} body weight
Norfloxacin 5% inj.(Shanghai)	50 mg mL^{-1}	5-10 mg kg^{-1} body weight.
Notrilaps inj. (SVPF, China)	50 mg mL^{-1}	2.5-5 mg kg^{-1} body weight.

ENROFLOXACIN

Brand name and manufacturer	Concentration	Dose
Water soluble products		
Avitryl oral solution (Avico, Jordan)	10 g/100 mL	1 mL/2 L drinking water
Baytril (Bayer)	10%	0.5 g L^{-1} drinking water (or active ingredient 50 mg L^{-1}).
Enroquin Forte 20% (Sinochem Ningbo, China)	20%	1 mL/4 L drinking water
Enrosol-S (Avico, Jordan)	100 mg mL^{-1}	1 mL/2 L drinking water
Floxivet solution (Medi-vet, Lahore)	10 g/100 mL	1 mL/2 L drinking water (or 0.1 mL kg^{-1} body weight).
Hipralona-Enro OS (Hipra, Spain)	100 mg mL^{-1}	1 mL/2 L drinking water
Quimiocoli oral suspension (Maymo, Spain)	10 g/100 mL	50 ppm (or 0.5 mL L^{-1}) in drinking water
SB Enrofloxacin (SB Pharma, Pakistan)	10%	1 mL/2 L drinking water
Vety-Enrox-20% (Vety-Care, Pakistan)	20%	1 mL/4 L drinking water
Injectable products		
Avitryl 5% inj. (Avico, Jordan)	50 mg mL^{-1}	1 mL/5 kg body weight intramuscular
Encur-10 (Nawan Labs., Pakistan)	100 mg mL^{-1}	1 mL/10 kg body weight intramuscular
Hipralona-Enro inj (Hipra, Spain)	50 mg mL^{-1}	1 mL/10 kg live body weight/intramuscular.

OTHER SECOND GENERATION FLUOROQUINOLONES

Brand name and manufacturer	Concentration	Dose
Cipryl-injection (Tarobina)	50 mg Ciprofloxacin Hcl/mL solution	0.05-0.1 mL kg^{-1} body weight. intramuscular
Advocin (Pfizer, Pakistan)	Danofloxacin 16.7%	1-7 days of age: active ingredient 50 ppm in drinking water. 7 days of age and older: 5 mg kg^{-1} day^{-1} in drinking water

Note: Authors accept omissions, if any, in the list of available products.

4. WHO., 1995. Evaluation of certain veterinary drug residues in food. Forty-third Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series No. 855, pp: 21-59.
5. Nakamura, S., 1995. Veterinary use of new quinolones in Japan. Drugs, 49: 152-158.

Study questions

1. Clearance of norfloxacin is decreased in kidney damage. Mycotoxin induced liver and kidney damage is very common under local conditions. What possible complications can arise during use of fluoroquinolones in nephrotoxicity and hepatotoxicity ?
2. Many poultry practitioners prescribe urine alkalinizers' such as 'citralka' as diuretic in poultry. What would be the outcome if fluoroquinolones are used along with?
3. How does the spectrum of action of nalidixic acid differ from those of the newer fluoroquinolones ?
4. How does the tendency for bacteria to develop resistance to fluoroquinolones compare with nalidixic acid ?
5. How do the sites of susceptible infections compare for nalidixic acid versus fluoroquinolones ?
6. What tissue is most susceptible to quinolone toxicity ? Are fluoroquinolones usually very toxic otherwise ?
7. Should quinolone derivatives be used in rapidly growing animals and humans (particularly pregnant women)?
8. On what is the manufacturer's claim based that fluoroquinolones cannot be cross-resistant with other anti-infective agents ?
9. What does it mean that killing of staphylococcus and *E. coli* is "concentration" dependent and not "time" dependent ?
10. Increased quinolone resistance in campylobacter and *E. coli* isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine has been reported from many other countries (Endtz *et al*., 1991. J Antimicrob Chemother 27: 199-208; Feierl *et al*., 1994. Int J Med Microbiol Virol Parasitol Infect Dis 281: 471-474; Griggs *et al*., 1994. J Antimicrob Chemother 33: 1173-1189). What can be implications of extensive use of fluoroquinolones in poultry to human health ?
11. Encircle correct.

☞ Cross-resistance between quinolones:
- ♦ Does not occur.
- ♦ Is almost complete.

☞ Resistance to quinolones occurs due to:
- ♦ Mutation in gyrA.
- ♦ Plasmids.

☞ Enrofloxacin (100 mg L^{-1} drinking water) given for 10 days in *Salmonella* pullorurn infection in laying chickens.
- ♦ Stops the mortality rate: Yes No
- ♦ Increases egg production: Yes No
- ♦ Reduces *salmonella* excretion. Yes No
- ♦ Prevents recurrence of the Yes No
- ♦ disease following end of treatment.

(Useful reading: Redman *et al*., 1989. DTW Dtsch Tierarztl Wochenschr 96: 137-138).

☞ What should be the daily frequency of oral administration (through drinking water) of enrofloxacin to poultry (encircle correct). (Useful reading: Intorre *et al*., 1997. Vet Res Comm 21:127-136).
- ♦ Once a day
- ♦ Twice a day.
- ♦ Throughout day.

☞ Indicate the main metabolites of enrofloxacin in poultry
- ♦ Sparfloxacin. ♦ Ciprofloxacin. ♦ Ofloxacin.
- ♦ Tosufloxacin. ♦ Enoxicin. ♦ Benofloxacin.
- ♦ Orbifloxacin.

☞ What percentage of Enrofloxacin is metabolized
- ♦ In chicken: Low Medium High
- ♦ In ducks: Low Medium High

☞ In Mycoplasma gallisepticum infection enrofloxacin is highly effective in
- ♦ Reducing level of egg transmission of the organism.
- ♦ Reducing number of dead-in-shell embryos.
- ♦ Rapid recovery of egg production.

☞ The quinolones should be indicated in poultry
- ♦ As first-choice. drugs.
- ♦ Only when first-choice drugs are ineffective.
- ♦ Only under the direction of veterinarian.
- ♦ Only for periods of less than 5 days.

☞ Indicate the main metabolite of danofloxacin:
- ♦ Ciprofloxacin
- ♦ 0-floxacin
- ♦ N-desmethyldanofloxacin
- ♦ Benofloxacin