EFFECT OF PIPERINE AND QUERCETIN ADMINISTRATION ON PHARMACOKINETICS AND SAFETY PROFILE OF MARBOFLOXACIN IN BROILER CHICKENS

ABSTRACT

Key words: Marbofloxacin, Pharmacokinetics, Piperine, Quercetin, Safety profile, CYP3A37, MDR1 and Broiler chickens

Therapeutic and prophylactic use of antibiotics has allowed poultry production to achieve significant improvements by enhancing growth rate, feed efficiency and reduce mortality. Marbofloxacin is a 3rd generation fluorinated quinolone having broad spectrum of antimicrobial activity against gram-negative, gram-positive bacteria and mycoplasma spp. Pharmacokinetics of marbofloxacin after oral administration in chickens, reveals poor absorption and reduced bioavailability, which limits its therapeutic effectiveness. Several dietary constituents like piperine and quercetin have improved the bioavailability of co-administered drug by inhibiting efflux pumps (P-gp) or drug metabolizing enzymes CYP450 at intestine and liver. Hence, present study was planned to generate valuable information about effect of piperine and quercetin pretreatment (10 mg/kg, p.o., for 3 days) on pharmacokinetics and safety profile of marbofloxacin after single and repeated (5mg/kg, for 5 days) intravenous and oral administration in broiler chickens; and effect of on CYP3A37 and MDR1 mRNA expression levels in liver and duodenum of broiler chickens.

After repeated intravenous administration, the initial plasma concentration ($C_p^0$) marbofloxacin of 17.72 ± 5.28 μg/mL which was significantly higher than the respective value of 6.78 ± 0.28 μg/mL after single administration. Following single dose oral administration of marbofloxacin, the mean peak plasma concentrations ($C_{max}$) in normal, piperine pretreated, quercetin pretreated and both in combination pretreated broiler chickens were almost similar and achieved at $T_{max}$ 0.83 ± 0.11, 0.67 ± 0.11 h, 0.83 ± 0.25 and 1.50 ± 0.22 h, respectively. Thus, the piperine pretreatment has enhanced the marbofloxacin absorption after oral administration in chickens. Following single dose oral administration of marbofloxacin in combination pretreated broiler chickens, significantly higher elimination half-life (normal: 4.62 ± 0.42; combination pretreatment: 7.71 ± 0.59 h), volume of distribution (normal: 1.32 ± 0.10; combination pretreatment: 2.30 ± 0.27 L/kg), the mean residence time (normal:
7.03 ± 0.33; combination pretreatment: 10.71 ± 0.70 h) and bioavailability (normal: 60.22 ± 8.07; combination pretreatment: 75.39 ± 7.34 %) were observed as compared to normal chickens.

After repeated oral administration of marbofloxacin, significantly higher area under curve (single: 18.60 ± 1.31; repeated: 23.20 ± 2.30 µg.h/mL) and bioavailability (single: 75.39 ± 7.34; repeated: 89.60 ± 9.06 %) were observed as compared to single dose in combination pretreated broiler chickens. Piperine and quercetin pretreatment had no any significant effect on body clearance rate of marbofloxacin after single and repeated oral administration. After single oral administration of marbofloxacin AUC/MIC$_{90}$ ratios were higher in piperine (353.20 h), quercetin (367.20 h) and combination pretreatment group (372.00 h) as compared to normal chickens (302.30 h) at MIC value of 0.05 µg/mL.

After piperine and quercetin combination pretreatment, CYP3A37 mRNA expression was significantly down regulated in liver and duodenum by 24.35 and 17.59 fold, respectively and MDR1 by 7.65 and 21.59 fold, respectively in broiler chickens as compared to normal. Following multiple intravenous and oral administration of marbofloxacin, some of hematological and biochemical parameters were altered, but they were in the normal range for broiler chickens. Piperine and quercetin combined pretreatment has improved the pharmacokinetic profile and efficacy of marbofloxacin after single and repeated oral administration by inhibition of drug efflux protein (MDR1) and drug metabolizing enzyme (CYP3A37).