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EFFECT OF ENROFLOXACIN ON HEPATIC MICROSOMAL MIXED FUNCTION OXIDASES IN CAMEL

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ABSTRACT

Administration of enrofloxacin at a dose of 5 mg/kg intramuscularly for 3 days has resulted in a significant decrease in aminopyrine-N-demathylase and aniline-4-hydroxylase in liver of camel compared to saline treated (controls). It is suggested that co-administration of drugs metabolised by phase-I reaction with enrofloxacin should be avoided in camels.

Key words: Camel, enrofloxacin, hepatic, oxidases

The fluoroquinolones are an increasingly important and relatively new class of antimicrobials for use in veterinary medicine (Giguere *et al*, 1996). They are characterised by low minimum inhibitory concentration values for many Gram-negative and Gram-positive bacteria including many of the important veterinary pathogens. They are potent against mycoplasma and achieve high tissue concentrations (Orsini *et al*, 1989; Papich and Riviere, 2001).

The presence of a unique bacterial enzyme DNA gyrase (topoisomerase type II) and its necessary influence on DNA negative surpercoiling provides key to fluoroquinolone activity (Birmingham *et al*, 2000). The action of this enzyme in breaking double strands of DNA during protein synthesis and of subsequent re-sealing the breaks to allow re-establishment of the supercoil is an essential function of bacterial DNA replication. The effect of fluoroquinolones in inhibiting DNA gyrase is therefore, bactericidal by virtue of their ability to prevent the correct reconstruction of the true DNA helix and supercoil. The compromised DNA formation then results in the production of endonucleases producing permanent double stranded gaps in the DNA compliment leading ultimately to bacterial death. The requirement of oxygen for quinolones to actively kill bacteria, also provides a reason for their failure to adversely effect normal commensal anaerobic gut flora during therapy (Bertone *et al*, 2000).

Enrofloxacin has been used in horses more than any other fluoroquinolones and its pharmacokinetics and tissue concentrations have been reported (Orsini *et al*, 1989; Moore *et al*, 1992). Pharmacokinetics largely involves phase I metabolism in the liver mediated by enzymes, collectively called mixed function oxidases (MFO). The activity of the MFO can be elevated or depressed after exposure to many xenobiotics, and the metabolism of certain drugs given concomitantly or thereafter, might also be changed (Elshiekh *et al*, 1991).

Quinolones have been shown to inhibit N-demethylation in human (Staib *et al*, 1987) and in laboratory animals (Mizuki *et al*, 1996) and chicken (Shlosberg *et al*, 1995), but no such studies have been published on this promising group of antimicrobial which are now used in camels. This study is designed to assess the effect of the fluoroquinolone antibiotic enrofloxacin on the activity of MFO inhibitor in camels.

Materials and Methods

Healthy adult camels (n=10) were used in this study. Food and water were available *adlibitum*. Five animals (Group 1) were injected intramuscularly with enrofloxacin (Baytril, Bayer, Germany) at a dose 5 mg/kg for 3 days. Group 2, animals were treated similar to group 1 but with saline. Camels were then immedately slaughtered. The livers were removed and determination was made of aniline hydroxylase, aminopyrine N-demethylase (Elsheikh *et al*, 1988), cytochrome P-450 (Omura and Sato, 1964) and protein (Lowry *et al*, 1951) in the 9000 g supernatant liver

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fraction. The significance of difference between means shall be estimated by student *t-test*.

Results and Discussion

Results of the effect of enrofloxacin and saline on mixed function oxidases (MFO) activity in livers of camels are shown in table 1. Administration of enrofloxacin to camel has resulted in a significant ($P < 0.05$) decrease in aminopyrine-N-demethylase and aniline-4-hydroxlase compared to saline treated controls. Similar effects on MFO can be produced by grisofulvin in sheep (Haisah *et al*, 2003), latex in goats (Elsheikh *et al*, 1991) and flukes in sheep (Elsheikh *et al*, 1992). Enrofloxacin was also a potent inhibitors of aminopyrine-N-demethylase and aniline-4-hydroxylase in chicken (Shlosberg *et al*, 1995). Furthermore, quinolones have been shown to inhibit N-demethylation in humans (Staib *et al*, 1987) and in laboratory animals (Mizuki *et al*, 1989). In this experiment and in others (Shlosberg *et al*, 1995) enrofloxacin was unable to reduce the activity of cytochrome P-450, another phase-I metabolising enzyme. One possible explaination is that the mixed function oxidase enzyme system is heterogenous and consists of several isozymes of cytochrome P-450 mediating defferent metabolic pathways (Elsheikh *et al*, 1991). Those responsible for the hydroxylation of aniline might be inhibited by enrofloxacin. In view of these facts, co-administration of drugs metabolised by phase-I reactions with enrofloxacin should be avoided in camels. As the enzymes necessary for their metabolic interaction are impaired. Such effect may result in toxicity too.

Table 1: Mixed function oxidase activity in liver of camels treated either with enrofloxacin (5mg/kg) or saline.

Parameter	Saline (n=5)	Enrofloxacin (n=5)
Cytochrome P-450	0.231 ± 0.016	0.233 ± 0.017
Aminopyrine-N-demethylase (1)	6.21 ± 0.431	3.612 ± 0.25*
Aniline-4-hydroxylase(1)	0.396 ± 0.019	0.121 ± 0.016*
Protein (mg/gm of liver homogenate)	160.4 ± 3.1	164.2 ± 3.2

(1) Enzyme activity expressed as nmol product formed/mg microsomal protein/minute

(*) A significant ($P < 0.05$) compared to control

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