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RESEARCH ARTICLE
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Effect of meloxicam and its combination with levofloxacin, pazufloxacin, and enrofloxacin on the plasma antioxidative activity and the body weight of rabbits

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Abstract

Aim: Evaluation of meloxicam, levofloxacin, pazufloxacin, and enrofloxacin for their effect on the plasma antioxidative activity (AOA) and the body weight in rabbits.

Materials and Methods: Thirty two male Soviet Chinchilla rabbits were divided to eight groups of four rabbits each. Group A, serving as control, was administered 5 % dextrose. Group B, C, E and G were gavaged meloxicam, levofloxacin, pazufloxacin and enrofloxacin, respectively, in 5% dextrose. Levofloxacin and pazufloxacin were administered at the dose rate of 10 mg/kg body weight b.i.d 12h, whereas the meloxicam and enrofloxacin were administered at 0.2mg/kg body weight o.i.d and 20 mg/kg body weight, respectively. Groups D, F and H were co-gavaged meloxicam with levofloxacin, pazufloxacin, and enrofloxacin, respectively, at the above dose rates. All these drugs were administered for 21 consecutive days. The plasma AOA and body weight was determined on 0, 7, 14, and 21 day of treatment.

Results: The plasma AOA of meloxicam treated group was significantly lower than the control from 7th day of treatment. On the 14th day of treatment, the levofloxacin treated group had values significantly higher than the enrofloxacin-meloxicam co-treated group. Except for the levofloxacin treated group, a significant decrease in the antioxidative activity was observed in all treatment groups when compared to the control group on 21st day of treatment. The body weight of all groups differed non-significantly throughout the study period.

Conclusion: The results from this study indicate that although these drugs have no effect on the body weight, a decrease in the plasma AOA is observed, especially when the duration of treatment is increased.

Key words: enrofloxacin, levofloxacin, meloxicam, pazufloxacin, plasma antioxidant activity

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used drugs in both veterinary and human medicine for various inflammatory conditions of infectious or non-infectious origin [1]. NSAIDs act by inhibiting the pro-prostaglandin enzymes, cyclooxygenase-2 (COX-2), and cyclooxygenase-1(COX-1). The COX-2 inhibition is considered to mediate the therapeutic actions of NSAIDs, while the COX-1 inhibition usually results in unwanted side-effects, particularly in the gastrointestinal tract [1]. Meloxicam is a NSAID that has an apparently greater selectivity towards inhibition of inducible COX-2 isoform, than the constitutive isoform COX-1 [1].

Fluoroquinolones (FQs) are the quinolones with fluorine atom attached to the central ring system, typically at the C-6 position or C-7 position. These are bactericidal drugs that inhibit the bacterial enzymes DNA gyrase and topoisomerase IV and possess a broad spectrum of anti-bacterial activity against a range of bacteria, including the ones resistant to other anti-microbial drugs [2]. Despite the basic similarity in the core structure of these molecules, their physiochemical properties, pharmacokinetic characteristics, and anti-microbial activities vary markedly across compounds [3]. Levofloxacin, the active L-isomer of the racemate ofloxacin, has nearly 100% oral bioavailability and is thus preferred over FQs that have broad spectrum of activities, but limited oral bioavailability [4]. It is used alone or in combination with other antibacterial drugs to treat certain bacterial infections, including pneumonia, urinary tract infections, and abdominal infections. Pazufloxacin, a fused tricyclic quinolone, has a 1-aminocyclopropyl substituent at C-10 position, a unique feature of the molecule contributing the potent broad spectrum activity to this drug [5]. It may be used as the drug of choice in community acquired infections, acute exacerbation of chronic bronchitis and post-abdominal infection sepsis [6]. Enrofloxacin, a 6-fluoro-7-piperazinyl-4-quinolone approved for veterinary use, has been evaluated as a method to eliminate *Salmonella* infections in cattle and poultry and manage several bacterial diseases in lagomorphs, from *Pasteurella multocida* to *Mycoplasma* spp. [7]. Oral dosing with enrofloxacin does not appear to develop antibiotic dysbiosis, which is common with

penicillins and cephalosporins [7].

Although fluoroquinolones (FQs) are relatively safer drugs, certain adverse effects such as gastro-intestinal discomfort, hepatotoxic reactions, central nervous system effects, juvenile joint toxicity, phototoxic and retinopathic effects, although rare, have been reported in association with their use [8]. In 2004, the FDA requested new warning labels to be added to all of the FQs, about irreversible peripheral neuropathy, rhabdomyolysis, tendon damage, pseudomembranous colitis, heart problems (prolonged QT Interval/ Torsades de pointes), Stevens - Johnson syndrome, as well as concurrent usage of NSAIDs contributing to the severity of these reactions [9]. Some of the side effects of FQs, like phototoxicity [10] and cartilage defects [11] have been incriminated to the production of reactive oxygen species (ROS) [12]. Although, NSAIDs including meloxicam improve oxidative imbalance [1, 13, 14], alteration of antioxidant levels has been reported with several NSAIDs [15] with studies demonstrating oxidative stress as the mechanism of their toxicity [16, 17]. An imbalance between the pro-oxidant and antioxidant moieties represents oxidative imbalance/ stress. Complete antioxidant profile of body fluids cannot be fully reflected by any single component of antioxidant complex, due to interactions that occur in vivo among different antioxidant components [18]. Total antioxi-dative activity (AOA) considers the cumulative effect of all antioxidants present in body fluids [19]. It could be used to assess the real change in antioxidant status in patients with severe infection and can thus make the treatment effective [20]. Complicated infections require weeks of antibiotic therapy and protracted course of NSAIDs to manage various associated inflammatory conditions like pyrexia and pain [21, 22]. Taking the above facts into consideration and the lack of sufficient toxicological data regarding the simultaneous exposure of FQs and NSAIDs, we evaluated meloxicam, levo-floxacin, pazufloxacin and enrofloxacin for their effect on the plasma AOA that could give some insight of their basic toxicological profile. Since prolonged treatment of some drugs (zonisamide, topiramate, caffeine, etc) leads to body weight loss, drugs like antipsycotics, on the other hand, produce obesity in humans [23,24]. The assessment of body weight parameter would indicate general impact on metabolism in addition to generating data regarding the above cited effects of drugs on the body weight. This will also help in considering dosage corrections of these drugs when used for prolonged durations.

The availability of data on body weight with the co-administration of NSAIDs and FQs is also lacking. Thus, we also evaluated the effect of these drugs on body weight and correlated the body weight with AOA to determine any relation between the two parameters.

Materials and Methods

Animals: Thirty two male adult Soviet Chinchilla rabbits of 6 months of age, weighing around 3 Kg, were kept under normal ambient conditions, with an average day length of 11.5 hours, in a well-lighted experimental house. The animals were maintained on standard rabbit feed and *ad libitum* water.

Ethical approval: The experimental protocol was approved by the University Animal Ethics Committee under order No.VMC/13/17/86-1806 dated 4/4/13.

Experimental design: Rabbits were randomly divided to eight groups of four rabbits each. Group A, serving as control, was administered 5 % dextrose. Group B, C, E and G were gavaged meloxicam, levofloxacin, pazufloxacin, and enrofloxacin, respectively, in 5% dextrose. Levofloxacin and pazufloxacin were administered at the dose rate of 10 mg/kg body weight b.i.d 12h, that was extrapolated from the therapeutic dose in humans [6, 25], whereas the meloxicam (0.2mg/Kg body weight o.i.d.) and enrofloxacin (20 mg/kg body weight o.i.d.) were used at their recommended therapeutic doses in rabbits [26,27]. Groups D, F and H were co-gavaged meloxicam with levofloxacin, pazufloxacin, and enrofloxacin, respectively, at the above dose rates.

Drugs: The drugs used were meloxicam (Melonex® Intas Pharma, India), levofloxacin hemihydrate (Levoflox®, Cipla Pharma, India) pazufloxacin mesylate (Pazumac®, Macleoids Pharma, India) and enrofloxacin (Enrocin™, Pfizer Animal Health, India).

Disclaimer about the drugs: The drugs used in the study are for information purpose only. Authors or institute of authors do not recommend the use of these drugs.

Plasma antioxidant activity analysis: Blood samples were collected from the ear vein of these animals in heparinized vials on 0, 7, 14 and 21 day of treatment. The plasma AOA was determined by the method of Koracevic et al. [28] based on the principle that a standardized solution of Fe-EDTA complex reacts with hydrogen peroxide by a Fenton-type reaction, leading to the formation of hydroxyl radicals that degrade benzoate, resulting in the release of thio-barbituric acid reactive substances (TBARS). Antioxidants from the added plasma suppress TBARS production. This reaction was measured spectrophotometrically and the inhibition of color development is defined as the total antioxidant activity.

Body weight: Body weight was determined with an electronic weighing balance at 0, 7, 14 and 21 days of treatment. These weekly body weight values were also used to make the necessary corrections in dose of the above drugs administered. The weekly determined body weight of each animal was expressed as the percentage of its zero day body weight to determine the trend in the body weight pattern.

Statistical analysis: All these results were subjected to analysis of variance carried in completely randomized design, and the significance was tested using Duncan's

Table-1. Effect of meloxicam (group B), levofloxacin (group C), levofloxacin+meloxicam (group D), pazufloxacin (group E), pazufloxacin+meloxicam (group F), enrofloxacin (group G) and enrofloxacin+meloxicam (group H) on the plasma antioxidant activity (mmol/L) in rabbits.

Group	Day 0	Day 7	Day 14	Day 21
Group A (Control)	1.24±0.056^{a}	1.18±0.035^{bcd}	1.17±0.049^{bc}	1.13±0.050^{c}
Group B	1.22±0.114^{a}	1.01±0.092^{a}	1.00±0.033^{a}	0.84±0.080^{a}
Group C	1.24±0.028^{a}	1.09±0.060^{ab}	1.22±0.058^{c}	1.09±0.014^{bc}
Group D	1.23±0.038^{a}	1.11±0.007^{abc}	1.10±0.031^{abc}	0.87±0.072^{ab}
Group E	1.33±0.041^{a}	1.12±0.016^{abc}	1.12±0.035^{abc}	0.80±0.086^{a}
Group F	1.28±0.017^{a}	1.15±0.035^{abcd}	1.15±0.026^{bc}	0.81±0.083^{a}
Group G	1.35±0.021^{a}	1.28±0.004^{d}	1.12±0.022^{abc}	0.76±0.063^{a}
Group H	1.26±0.038^{a}	1.25±0.050^{cd}	1.07±0.049^{ab}	0.70±0.131^{a}

Values given are mean ± standard error of mean for 4 animals
Means, in a column, with different superscript do not differ significantly

Table-2. Effect of meloxicam (group B), levofloxacin (group C), levofloxacin+meloxicam (group D), pazufloxacin (group E), pazufloxacin+meloxicam (group F), enrofloxacin (group G) and enrofloxacin+meloxicam (group H) on body weight (Kg) in rabbits.

Group	Day 0	Day 7	Day 14	Day 21
Group A (Control)	3.21±0.04^{a}	3.33±0.04^{a}	3.43±0.05^{a}	3.56±0.05^{a}
Group B	3.07±0.07^{a}	3.18±0.08^{a}	3.31±0.09^{a}	3.25±0.09^{a}
Group C	3.08±0.08^{a}	3.19±0.07^{a}	3.23±0.06^{a}	3.20±0.06^{a}
Group D	3.06±0.08^{a}	3.22±0.07^{a}	3.24±0.07^{a}	3.23±0.06^{a}
Group E	3.13±0.08^{a}	3.40±0.08^{a}	3.36±0.10^{a}	3.37±0.09^{a}
Group F	3.23±0.09^{a}	3.33±0.12^{a}	3.36±0.12^{a}	3.31±0.13^{a}
Group G	3.09±0.11^{a}	3.26±0.12^{a}	3.30±0.13^{a}	3.43±0.10^{a}
Group H	3.22±0.01^{a}	3.24±0.01^{a}	3.34±0.01^{a}	3.55±0.01^{a}

Values given are mean ± standard error of mean for 4 animals
Means, in a column, with one common superscript do not differ significantly

multiple range test [29]. The results for AOA were correlated with body weight with Pearson's correlation. The significance was assayed at 5 % ($p<0.05$) levels. These statistical calculations were carried out with SPSS 16.0 software.

Results and Discussion

The results for the effect of meloxicam, levofloxacin, pazufloxacin and enrofloxacin on the plasma antioxidative activity in rabbits are presented in the Table-1. On the day 7 of treatment, the AOA of group B was significantly lower than the groups A, G and H with group G having significantly higher values compared to groups C, D and E and group H having significantly higher values than the group C. The values of group B were significantly lower than the groups A, C and F on the 14th day of treatment, with group C also having the values significantly higher than the group H. When compared to the two non-significantly different groups, A and C, a significant decrease in the AOA was observed in the other treatment groups on the 21st day of treatment. However, the AOA values of group C differed non-significantly from the group D. The alterations in various parameters of antioxidant status/oxidative stress have been reported with FQs [30-32] or NSAIDs [15], although only a few studies are available about the effect of these drugs on AOA [15,33,34]. There are paucity of literature on the concurrent exposure of FQs and NSAIDs.

Elimination of xenobiotic requires ATP as the energy source. During the ATP synthesis from mitochondrial electron transport chain, a premature leakage of small number of electrons to oxygen forms reactive oxygen species (ROS) [35]. The biological outcome of mitochondrial ROS production and its potential involvement in physiological (signal transduction) versus pathological processes (oxidative stress induced disorders) depends on the balance between their production and detoxification [36]. Plasma AOA includes both enzymatic and nonenzymatic antioxidant systems [37], the measurement of which provides a holistic picture of antioxidant status than the measurement of individual antioxidant indices and is thus considered as a better marker of antioxidant status [36, 38] that could also help in assessment of oxidative status *in vivo* [39].

An initial response of body to ROS is the expression of Nrf-2, a transcription factor that increases the expression of genes mediating antioxidant response [40]. The significantly higher values of AOA in some of the treatment groups (group G versus groups B, C, D and E on day 7 of treatment and group C versus groups B and D on day 14 of treatment) could be attributed to this mechanism. However, consistently increasing exposure of pro-oxidative xenobiotics overwhelms the antioxidant status, by inhibiting the activity or sufficient synthesis of antioxidants, predisposing the cells to oxidative damage [41]. This might be incriminated as a reason for the significantly decreased levels of AOA observed in this study, especially at the 21st day of treatment when all treated groups, except group C, had significantly lower levels of AOA compared to the control group.

The results for the effect of meloxicam and the

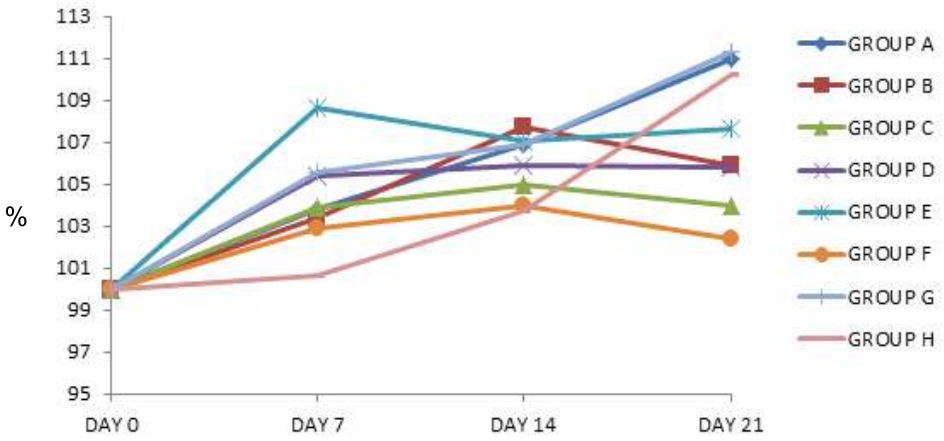

Figure-1. Comparative trend of body weight of control rabbits (Group A) *versus* rabbits administered meloxicam (group B), levofloxacin (group C), levofloxacin + meloxicam (group D), pazufloxacin (group E), pazufloxacin + meloxicam (group F), enrofloxacin (group G) and enrofloxacin + meloxicam (group H)

above FQs on body weight are presented in Table-2 and Figure-1. The body weight of all the groups differed non-significantly from each other throughout the study period. A non-significant correlation was observed between AOA and body weight of each group which indicates that the predisposition to the pathological implications oxidative/antioxidant imbalance [1,14, 15,30,42-44] predicted from the estimation of parameters related to oxidative/anti-oxidant status [32, 42, 45] cannot be predicted from body weight.

Conclusion

The results from this study indicate that meloxicam, pazufloxacin, and enrofloxacin reduce the body's AOA. Significant reduction in body's AOA also occurs when levofloxacin is co-treated with meloxicam. The body weight alterations induced by these drugs are non-significant. Since the alterations in antioxidant status is both predisposing and precipitating factor in the pathogenesis of several diseases and toxicities, these drugs should be used with caution for prolonged periods of time, especially, when the slow rate of elimination due to compromised hepatic and renal clearances, as seen in geriatric patients, enhances their plasma levels and hence the toxicity.

Authors' contributions

Both authors contributed equally. Both authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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