

## Effects of non-selective (piroxicam) and selective (meloxicam) cyclo-oxygenase inhibitors on the intestinal contractility of rabbits

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### ABSTRACT

**Background:** To shed some light on full characterization and utilization of non-steroidal anti-inflammatory drugs (NSAIDs) in veterinary medicine, this study, therefore, was designed to clarify the pharmacological effects of two NSAIDs (one selective, that is meloxicam, and the other is non-selective, that is piroxicam) on intestinal contractility of rabbit as a farm animal species.

**Methods:** Rabbits were humanely slaughtered, and segments from different parts of intestinal tracts were dissected out and an intestinal segment of about 2 cm long was fixed in an organ bath containing warm oxygenated Tyrode's solution at 37°C. The tissue was subjected to a resting tension of 2 g and allowed to equilibrate for 30 min and then the effects of graded increased concentrations of piroxicam and meloxicam were demonstrated on the normal rhythmic motility of the isolated intestinal segments. The sites of action of piroxicam and meloxicam were tried.

**Results:** Piroxicam and meloxicam exhibited concentration-dependent relaxations of intestinal smooth muscle segments with minimal and maximal effects of more potency by piroxicam than meloxicam. Calculated inhibitory concentration 50% were 15.45 and 23.10 µg/ml bath for piroxicam and meloxicam, respectively. Effects of either piroxicam or meloxicam did not involve cholinergic, adrenergic, histaminergic, nitregeric, or purinergic pathways as the application of the corresponding agonists/antagonists did not affect the inhibitory response of piroxicam and meloxicam. It was assumed that the effects of the drugs were attributed to the direct effects of the drugs on the intestines in addition to inhibiting endogenous prostaglandin synthesis activity via their cyclo-oxygenase inhibiting properties.

**Conclusions:** Data of the present study may indicate that piroxicam and meloxicam could be used effectively and safely in rabbits for their anti-inflammatory actions in small therapeutic doses. However, in large doses, they (particularly, piroxicam) may produce depressant effects on gastrointestinal tract motility that should be taken in consideration in the case of introducing these drugs in therapy with larger doses.

**Keywords:** Non-steroidal anti-inflammatory drugs, Piroxicam, Meloxicam, Anti-inflammatory, Intestinal contractility, Autonomic pharmacology

### INTRODUCTION

Cyclo-oxygenase- (COX-) inhibitors are those drugs which can inhibit the activity of COX enzymes (1 and 2) resulting in inhibition of prostaglandin (PG) synthesis.<sup>1</sup> There are two types of COX-inhibitors, the traditional non-selective non-steroidal anti-inflammatory drugs (NSAIDs) which block both types of COX. The second type is selective COX-2 inhibitors which have no or minimal affinity, and thus, no effect on COX-1. The development of the COX-2 selective inhibitors was intended to provide drugs that would offer the same pain-relieving and anti-inflammatory effects as the traditional NSAIDs without causing the gastric ulcers that have been associated with the pioneer drugs.<sup>2</sup>

NSAIDs can be categorized into many classes, including, salicylic acid derivatives (as aspirin), acetic acid derivatives (as indomethacin and diclofenac), propionic acid derivatives (as naproxen and ibuprofen), oxicams (as piroxicam and meloxicam), pyrazolones (as phenylbutazone), and fenamic acids (as mefenamic acid). All groups of NSAIDs exert their effects by inhibiting one or both of the COX enzymes, COX-1, and COX-2.<sup>3</sup>

Application of NSAIDs has been utilized on a large scale in human therapeutics. However, it is still of less interest in veterinary practice in spite of its great importance. COX-inhibitors are very important in the symptomatic treatment of disease conditions and for specific treatment

as well. In symptomatic treatment, they are prescribed in most cases together with the specific remedies to relieve a variety of inflammatory symptoms such as fever, pain, swelling, congestion, and edema. Moreover, they are the main or specific drugs used for the treatment of chronic inflammatory conditions including rheumatism, rheumatoid, tendinitis, osteoarthritis, muscle aches, back aches, bursitis, and menstrual cramps. In addition, they have special role post grafting to avoid graft rejection.

This study, therefore, was designed to demonstrate the pharmacodynamic profile of two NSAIDs (one selective, that is meloxicam, and the other is non-selective, that is piroxicam) in rabbit as a farm animal species, on the isolated intestinal smooth muscle preparations (duodenum, jejunum, ileum, and colon). This may shed some light to full characterization and utilization of this important group of drugs in veterinary medicine. The comparative profiles of piroxicam and meloxicam from the pharmacodynamic aspect of view have been also elucidated.

## METHODS

### Drugs

Piroxicam was obtained as the patent preparation Feldene® (Pfizer, USA) that is an intramuscular therapy for inflammatory conditions in man, formulated as 1 ml ampoules equivalent to 20 mg piroxicam.

Meloxicam was obtained as the patent preparation Mobic® (Boehringer Ingelheim, Germany) that is an intramuscular therapy for inflammatory conditions with minimal gastric side effects, formulated as 1.5 ml ampoules equivalent to 15 mg meloxicam.

For organ bath studies, two-fold serial dilutions (from 0.5 to 200 µg/ml bath of piroxicam and 0.5-100 µg/ml bath of meloxicam were made from the stock drugs using an appropriate physiological salt solution.

### Experimental animals

Male New Zealand white rabbits were used for studying the comparative effects of piroxicam and meloxicam on motility patterns of isolated intestinal preparations. Adult animals were purchased from a local farm in Tripoli, Libya and were of body weight ranging between 1.8 and 2 kg. Animal care was in accordance with Guidelines for Care and Use of Laboratory Animals in Biomedical Research of the National Institutes of Health of the United States,<sup>4</sup> and approved by our Institutional Committee of Experimentation Ethics on Animal Use.

### Chemicals

Adrenaline was purchased from Aguettant (Lyon®, France); acetylcholine (ACh) chloride, atropine sulfate, cibacron

blue, histamine dihydrochloride, and Nω-Nitro-L-arginine methylester hydrochloride were purchased from Sigma-Aldrich® (Saint Louis, USA); phenylephrine from Sterop® group (Anderlecht, Belgium); propranolol hydrochloride from MIBE GmbH Arzneimittel® (Sandersdorf-Brehna, Germany); and PGF2α was purchased from Virbac® (Carros, France). All other classical chemicals were purchased from local distributors and were of analytical grade.

### Glass jar bath

In the present study, an organ bath (model GRAZ, type 846, Hugo Sachs Elektronik, HSE®, D-79232 March, Germany) was used. The Graz organ bath consists of a plexiglass base plate with 2 vertical columns, each of which carries organ vessel, tissue carrier and lever transducer (B40, type 373, serial number 07416, HSE), amplifier (TAM-A type 705/1, HSE) and digital recording unit (Data translator, DT 9800 BNC translator, Box 16SE serial no. 20072401, HSE) with data acquisition software for measuring the contraction forces. Organ vessels were of 10 ml capacity. The organ vessels carry a drain cock for draining the solution. The fresh solution which must be pre-warmed and aerated was introduced into the vessel with a syringe of appropriate size. A frit was fused into the base of each organ vessel for aerating the solution. A needle valve was provided for separately adjusting the aeration rate of each vessel. The standard tissue carrier was suitable for mounting different tissue specimens.

### Physiological salt solution

Tyrodé's physiological salt solution was prepared as indicated by Department of Pharmacology, University of Edinburgh<sup>5</sup> with the following composition: sodium chloride (8.00 g), potassium chloride (0.20 g), calcium chloride (0.20 g), magnesium chloride (0.10 g), sodium dihydrogen phosphate (0.05 g), sodium bicarbonate (1.00 g), glucose (1.00 g), and distilled water (to 1000.00 ml).

### Tension recording technique

The method modified after Department of Pharmacology, University of Edinburgh,<sup>5</sup> and Valeri et al.<sup>6</sup> was used for studying the effects of piroxicam and meloxicam on the isolated rabbit's duodenum, ileum, jejunum, and colon. A rabbit was humanely slaughtered, and segments from the intestines were dissected out, flushed, and kept in warm oxygenated Tyrodé's solution at 37°C. An intestinal segment of about 2 cm long was fixed in the organ bath containing warm oxygenated Tyrodé's solution at 37°C by attaching it at one end by a thread with the tissue carrier and the other end was tied by a thread to an isotonic lever transducer connected to amplifier, digital data translator and display unit with data acquisition software. The tissue was subjected to a resting tension of 2 g and allowed to equilibrate for 30 mins during which the tissue was washed three times, after that the normal rhythmic motility of the isolated strip of intestine was

recorded, and the effects of graded increased concentrations of piroxicam and meloxicam were demonstrated. The sites of action of piroxicam and meloxicam were determined after recording their effects on intestinal motility.

### Statistical analysis

Data were expressed as the mean±standard error of mean of "n" observations, where "n" represents the number of tissues studied in each experiment (triplicates). The data were analyzed using one-way analysis of variance (ANOVA) followed by least significant difference *post-hoc* test for multiple comparisons among the untreated tissue segments and those treated with different drug concentrations (0.5~200 µg/ml bath). Differences were considered significant at  $p \leq 0.05$ . Percentage of drug-induced inhibitions and median inhibitory concentration ( $IC_{50}$ ) were also calculated. All statistical procedure were calculated using GraphPad Prism software version 6 for Windows (GraphPad Software, La Jolla, California, USA).

## RESULTS

The effects of graded increased concentrations of piroxicam and meloxicam on the contractility of rabbit's intestinal preparations, including duodenum, jejunum, ileum, and colon were almost similar; therefore we presented only those of the duodenum, which are recorded in Table 1 and shown in Figure 1. Piroxicam at concentrations up to 1 µg/ml bath had no effect on the duodenal contractility. The minimal effect of piroxicam was observed at concentration of 2 µg/ml bath that produced 16% inhibition of duodenum contractility. Complete relaxation of duodenum smooth muscle was established after the addition of piroxicam at concentration of 128 µg/ml bath. While meloxicam at

concentrations up to 2 µg/ml had no effect on the duodenal contractility. The minimal effect of meloxicam was recorded at concentration of 4 µg/ml bath that produced 12% inhibition of duodenum contractility. Complete relaxation of duodenal smooth muscle was evident after addition of meloxicam at concentration of 100 µg/ml bath.  $IC_{50}$  of piroxicam and meloxicam were 15.45 and 23.10 µg/ml bath, respectively.

Trials were performed to locate the site of action of piroxicam and meloxicam on the rabbit's duodenum. Concentrations of the drugs that produced submaximal or maximal inhibitory effects were used in such experiments. To investigate the hypothesis that piroxicam and meloxicam produce their inhibitory effects on rabbit's duodenum *via* blocking of muscarinic receptors, ACh (2.5 µg/ml bath) was added to the duodenal preparation in presence of either piroxicam or meloxicam; and its effect was compared to the effect of ACh alone. Both piroxicam and meloxicam failed to decrease the effect of ACh on the duodenal preparations (Figure 2).

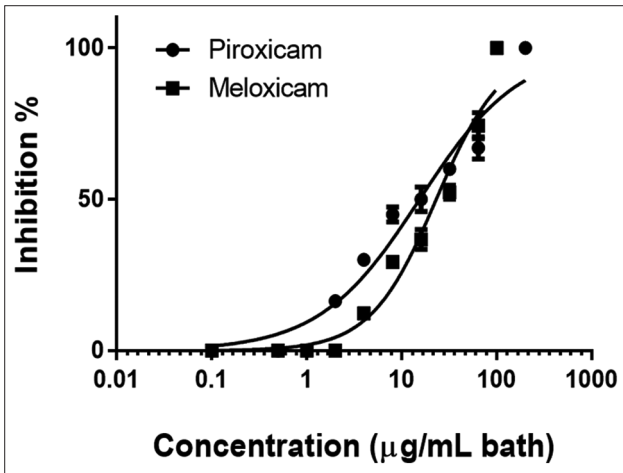
After pre-addition of either piroxicam or meloxicam to the duodenal tissue and establishment of their almost complete inhibitory effects, nicotine at a small concentration (1 µg/ml bath) was able to produce its stimulatory effect (Figure 3).

To investigate the hypothesis that piroxicam and meloxicam produce their inhibitory effects on rabbit's duodenum *via* stimulating neuronal nitric oxide synthase (nNOS) and synthesis of the inhibitory transmitter, nitric oxide, the drugs have been added to the duodenal preparations after pre-incubation with L-NAME (NOS blocker, 200 µM) and their effects were compared to those recorded in absence of L-NAME. The inhibitory effects of both drugs were evident in spite of the presence of L-NAME (Figure 4).

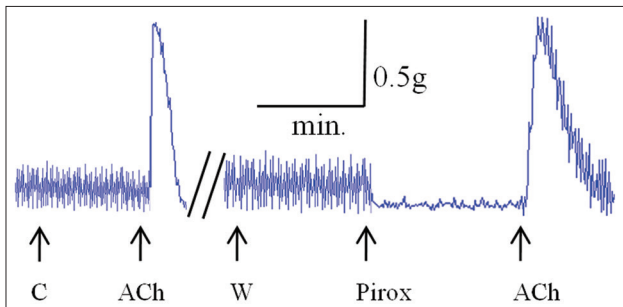
**Table 1: Effects of graded concentrations (0.5~200 µg/ml bath) of piroxicam and meloxicam on isolated rabbit's duodenum (mean±SEM; n=3).**

Concentrations (µg/ml bath)	Response of rabbit's duodenum			
	Piroxicam (amplitude, g)	Piroxicam (inhibition %)	Meloxicam (amplitude, g)	Meloxicam (inhibition %)
Pretreated	0.667±0.033	0.000±0.000	0.667±0.033	0.000±0.000
0.5	0.667±0.033	0.000±0.000	0.667±0.033	0.000±0.000
1	0.667±0.033	0.000±0.000	0.667±0.033	0.000±0.000
2	0.567±0.033*	16.333±1.856*	0.667±0.033	0.000±0.000
4	0.467±0.033*	30.000±2.000*	0.567±0.033*	12.333±1.452*
8	0.367±0.033*	45.000±2.517*	0.467±0.033*	29.333±0.667*
16	0.300±0.033*	50.000±4.041*	0.400±0.000*	36.667±3.333*
32	0.267±0.033*	60.000±4.000*	0.300±0.000*	52.333±2.333*
64	0.200±0.000*	67.333±3.667*	0.230±0.0338	74.333±4.3338*
100	-	-	0.000±0.000*	100.000±0.000*
128	0.000±0.000*	100.000±0.000*	-	-
200	0.000±0.000*	100.000±0.000*	-	-

\*Significantly different from pretreated ( $p \leq 0.05$ ; ANOVA followed by LSD test). - Not applied. SEM: Standard error of mean



**Figure 1: Inhibition % produced by graded concentrations (0.5~200 µg/ml bath) of piroxicam and meloxicam on isolated rabbit's duodenum (mean±standard error of mean; n=3).**



**Figure 2: Effect of 2.5 µg/ml bath acetylcholine (ACh) alone and after 128 µg/ml bath piroxicam (pirox.) on rabbit's duodenum; (meloxicam produced similar effect).**

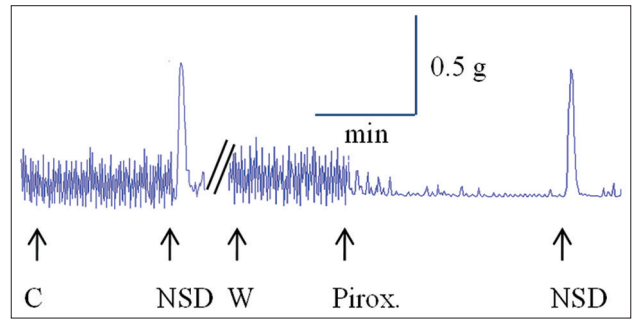
PGnF2 $\alpha$  at a concentration of 1 µg/ml bath was able to evoke its stimulatory effect in spite of the presence of either piroxicam or meloxicam onto the duodenal preparations (Figure 5).

Similarly, histamine (200 µM) was able to evoke its stimulatory effect in spite of the presence of either piroxicam or meloxicam onto the duodenal preparations (Figure 6).

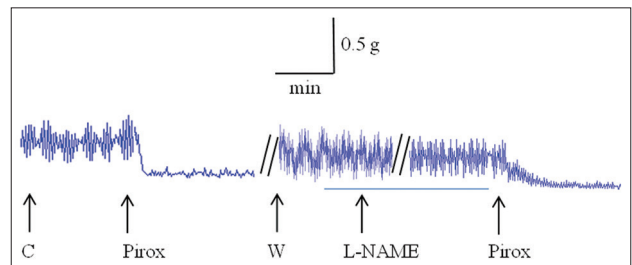
To investigate the possibility of involvement of adrenergic pathway in the inhibitory effects of piroxicam and meloxicam on rabbit duodenal preparations, the drugs were added after pre-addition of propranolol (non-selective beta blocker, 2.5 µg/ml bath). The drugs produced their inhibitory effects despite blocking the inhibitory  $\beta$ 2 adrenergic receptor (Figure 7).

Phenylephrine ( $\alpha$ -agonist, 1 µg/ml bath) was able to produce its weak stimulatory effect on the duodenal preparation in the presence of either piroxicam or meloxicam (Figure 8).

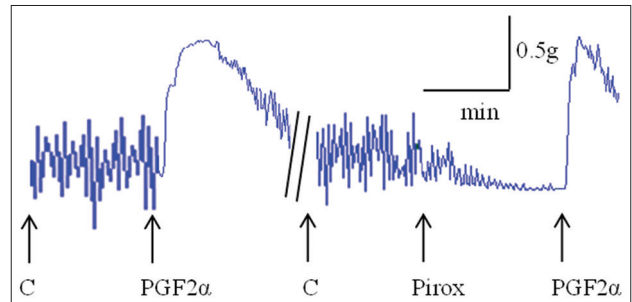
The inhibitory actions of both piroxicam and meloxicam on isolated duodenal preparations were also evident in spite of



**Figure 3: Effect of 1 µg/ml bath of nicotine (NSD) alone and after 128 µg/ml bath piroxicam (pirox.) on rabbit's duodenum; (Meloxicam produced similar effect).**



**Figure 4: Effect of piroxicam (pirox.; 200 µg/ml bath) alone and after the neuronal nitric oxide synthase blocker, L-NAME (200 µM) on rabbit's duodenum; (Meloxicam produced similar effect).**



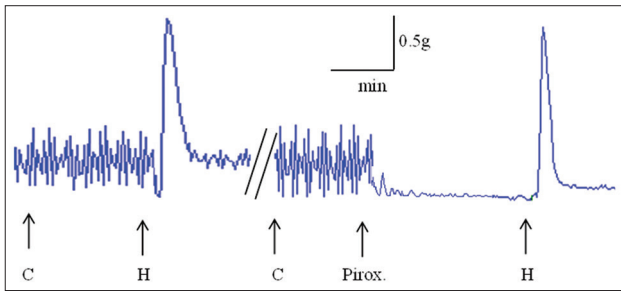
**Figure 5: Effect of prostaglandin F2 $\alpha$  (1 µg/ml bath) alone and after 128 µg/ml bath piroxicam (pirox.) on rabbit's duodenum; (Meloxicam produced similar effect).**

the presence of the P2Y purinergic receptor blocker, cibacron blue (200 µM) (Figure 9).

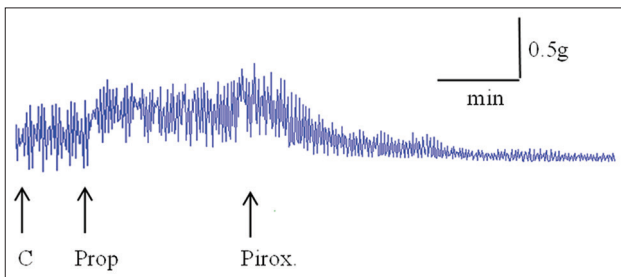
## DISCUSSION

Due to their anti-inflammatory, analgesic, and anti-pyretic properties, NSAIDs have become one of the most widely used classes of drugs in the world. NSAIDs are generally weak organic acids, making them well absorbed when taken orally, highly bound to plasma proteins and excreted by tubular or glomerular routes.<sup>7</sup>

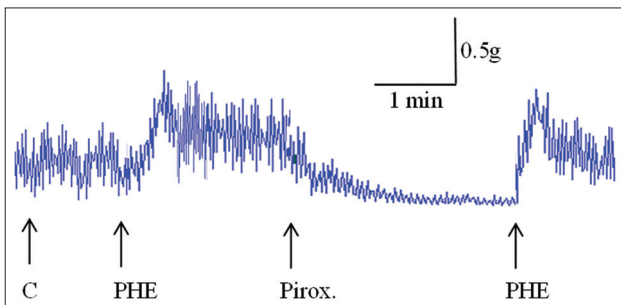
In veterinary use, there is a support to the use of NSAIDs for the control of pain-associated veterinary procedures



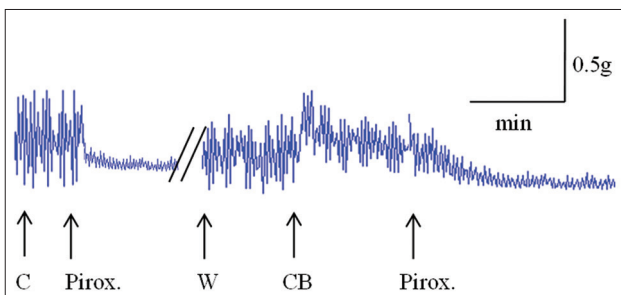
**Figure 6: Effect of histamine (H., 200  $\mu$ M) alone and after 128  $\mu$ g/ml bath piroxicam (pirox.) on rabbit's duodenum; (Meloxicam produced similar effect).**



**Figure 7: Effect of piroxicam (pirox., 128  $\mu$ g/ml bath) alone and after propranolol (prop., non-selective  $\beta$ -blocker; 2.5  $\mu$ g/ml bath) on rabbit's duodenum; (Meloxicam produced similar effect).**



**Figure 8: Effect of phenylephrine (PHE, 1  $\mu$ g/ml bath) alone and after piroxicam (pirox., 128  $\mu$ g/ml bath) on rabbit's duodenum; (Meloxicam produced similar effect).**



**Figure 9: Effect of piroxicam (pirox., 128  $\mu$ g/ml bath) alone and after cibacron blue (CB, P2Y purinergic receptor blocker; 200  $\mu$ M) on rabbit's duodenum; (Meloxicam produced similar effect).**

such as dehorning and castration. However, as different species have varying reactions to different medications in

the NSAID family, little of the reported research data can be extrapolated to animal species other than those specifically studied. For example, ketoprofen effects have been studied in horses more than in ruminants but, due to controversy over its use in race horses, veterinarians who treat livestock in the United States more commonly prescribe flunixin meglumine, which, while labeled for use in such animals, is not indicated for post-operative pain. In the United States, meloxicam is approved for use only in canines, whereas (due to concerns about liver damage) it carries warnings against its use in cat.<sup>8</sup> In spite of these warnings, meloxicam is frequently prescribed "off-label" for non-canine animals.

Among most important NSAIDs that have been used extensively in human filed and not yet applied in parallel manner in veterinary filed are piroxicam (long acting non-selective COX blocker), and meloxicam (intermediate acting selective COX-2 blocker). It is important from the pharmacological point view to describe different actions including either pharmacological or side ones in different animal species.

The present work, therefore, was performed to investigate some pharmacodynamic effects of piroxicam and meloxicam in rabbits as a farm animal model *in vitro*, namely, the effects of piroxicam and meloxicam on isolated gastrointestinal tract (GIT) preparations.

The present investigation showed that, piroxicam and meloxicam, *in vitro*, inhibited the contractility of rabbits' duodenum, jejunum, ileum, and colon. The inhibitory effect of piroxicam and meloxicam was proportional to the graded tested concentrations. The maximal inhibitory responses were recorded at 200  $\mu$ g/ml bath piroxicam and 100  $\mu$ g/ml bath meloxicam.

Addition of ACh (2.5  $\mu$ g/ml bath) as a muscarinic cholinergic agonist in the presence of either piroxicam or meloxicam produced its stimulant action indicating that the inhibitory effect of both tested drugs at the tested concentrations did not involve muscarinic receptors.

Similarly, addition of nicotine at a small concentration (1  $\mu$ g/ml bath) as a nicotinic cholinergic (ganglionic) agonist in the presence of piroxicam and meloxicam produced its characteristic stimulant action indicating that the inhibitory effects of piroxicam and meloxicam on GIT did not involve ganglia.

Application of standard adrenergic receptor agonists (phenylephrine for  $\alpha$ 1) and antagonists (propranolol for  $\beta$ ) did not affect the inhibitory responses of GIT preparation to piroxicam and meloxicam, indicating that involvement of adrenergic pathway in the action of piroxicam and meloxicam is unlikely.

Likewise, application of cibacron blue, the P2Y purinergic receptor antagonist, did not affect the inhibitory responses

of GIT preparation to piroxicam and meloxicam indicating that the involvement of purinergic pathway in the action of piroxicam and meloxicam is also unlikely.

The addition of histamine as H1-receptor agonist in the presence of piroxicam and meloxicam produced its stimulant action indicating that the inhibitory effect of both tested drugs do not involve H1-receptors and is not attributable to blocking histaminergic transmission.

Application of L-NAME as NOS inhibitor did not affect the inhibitory response of the tested drugs on GIT, excluding the involvement of nitric oxide in their action.

Taken all the aforementioned trials together, the inhibitory action of piroxicam and meloxicam on GIT preparations, therefore, may be attributed to inhibiting endogenous PG synthesis (that produce GIT stimulation) *via* their established action on COX. This fact should not be confused with the excitatory response of the exogenously applied PG on the GIT preparations in presence of piroxicam and meloxicam; as the tested drugs can inhibit endogenous synthesis of PGs, yet are not able to block the action of already synthesized, exogenously applied PGs. The direct mode of action of piroxicam and meloxicam on cell plasma membranes could not be also excluded.

These findings may be in accordance with Lichtenberger et al.<sup>9</sup> who concluded that both NSAIDs (indomethacin) and proton pump inhibitors (omeprazole) treatment suppressed contractile activity in the distal regions of the small intestine. The suppression of intestinal contractility was associated with increased inflammation in both cases; however, indomethacin and omeprazole appear to affect intestinal motility by different mechanisms.

Data of the present study may be partially inconsistent with Shahbazian et al.<sup>10</sup> who reported that the COX-1 inhibitor SC-560, the COX-2 inhibitor NS-398 (both at  $0.1 \pm 1 \mu\text{M}$ ) and the isoform-non-selective inhibitors furbiprofen ( $0.01 \pm 10 \mu\text{M}$ ), and piroxicam ( $0.1 \pm 50 \mu\text{M}$ ) were without major influence on peristalsis, whereas indomethacin and etodolac ( $0.1 \pm 10 \mu\text{M}$ ) disturbed the regularity of peristalsis by causing non-propulsive circular muscle contractions.

Again, Herbert et al.<sup>11</sup> reported that peristalsis in the guinea pig small intestine *in vitro* is impaired by acetaminophen but not aspirin and dipyron. They added that the inhibition caused by acetaminophen involves transmitters acting via small conductance  $\text{Ca}^{2+}$ -activated potassium channels, endogenous opioidergic pathways, and presumably inhibition of COX-3.

In another study, Menozzi et al.<sup>12</sup> studied the effects of non-selective and selective COX inhibitors on small intestinal motility in the horse. At that purpose, samples of equine ileum were put in isolated organ baths for the motility experiments. Non-selective COX inhibitors were devoid

of major effects on motility, except for an inhibition of tonic contraction shown by flunixin meglumine. SC-560, selective COX-1 inhibitor, was devoid of significant effects on ileal motility. Selective COX-2 inhibitors reduced both tonic contraction and spontaneous phasic contractions while PG receptor antagonists were ineffective. Intestinal samples submitted to the histological investigation or reverse transcription polymerase chain reaction revealed the presence of an inflammatory reaction and the presence of both COX isoforms mRNAs. They concluded that their data support the hypothesis that the effects of COX inhibitors on horse small intestinal motility are not linked to PG depletion.

These discrepancies among the results of the present study and those of other studies may be attributed to different NSAIDs used, concentrations, methodologies and different environmental conditions as well as different experimental animals that have been used.

These data may support the effective and safe use of both piroxicam and meloxicam in rabbits, however, larger doses may be associated with depression of both small and large intestines; these effects should be monitored and managed in large dose/long term therapies with such NSAIDs in rabbits.

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*Ethical approval: The study was approved by the Institutional Animal Ethics Committee*

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