Comparative Evaluation of the Analgesic Effect of Brand and Generics of Meloxicam tablets Available in markets

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ABSTRACT

Meloxicam is one of non-steroidal anti-inflammatory drugs (NSAIDs) used for relief of pain and inflammation. It works by inhibition of cyclooxygenase enzymes which are responsible for Prostaglandins synthesis. The purpose of this study was to assess analgesic effects of brand (Mobic®) and three generics (Neoxicam®, Coxicam®, Oximal®) of meloxicam in rats. Fifty-four male albino rats were divided into nine groups equally and randomly allocated to receive oral Mobic, Neoxicam, Coxicam or Oximal at same doses (10 mg/kg) and one group received vehicle orally (positive control). Anti-nociception was evaluated using hot plate test at 30 minutes, 1st, 2nd, 4th and 8th hour after drug administration and formalin test at phase1 (within this time the first 5 minutes), phase 2A (from 10 to 39 min) and phase 2B (from 40 to 60 min). The result of this study in hot plate test shown that the analgesic effect of Oximal at 2nd and 4th hours was statistically significant ($p<0.05$) compared to Mobic; also Coxicam significantly increased the percentage of the maximum possible effect than the brand at 4th hour. However, there was no significant difference between the band and all generics at 30, 60 and 480 min. In formalin test, all treatment groups significantly reduced the frequency of flinching compared to positive control group, but there was no significant difference between the brand and generics at all time-points. Moreover, the reduction in the duration of licking was not significant between treatment groups and positive control group in phase1 and 2A. Nevertheless, the brand and generics significantly reduced the duration of licking in phase 2B compare to control group and there was no significant difference between the all treatment groups at the same phase. In conclusion, according to these results, the analgesic effect of the generics (Neoxicam, Coxicam, Oximal) proved to be as good as the brand (Mobic).

Key Words: *meloxicam, hot plate test, formalin test, brand, generic.*

eIJPPR 2019; 9(3):73-79

HOW TO CITE THIS ARTICLE: Yasir A. Alshehry, Hassan M. Ghonaim, Mohammed S. Khalid (2019). "Comparative Evaluation of the Analgesic Effect of Brand and Generics of Meloxicam tablets Available in markets", International Journal of Pharmaceutical and Phytopharmacological Research, 9(3), pp.73-79.

INTRODUCTION

Meloxicam is an important non-steroid anti-inflammatory (NSAID) drug with a different pharmacokinetic and pharmacodynamic profile compare to conventional NSAIDs. It is FDA-approved to relief pains and inflammations of Rheumatoid Arthritis, Osteoarthritis and Juvenile Rheumatoid Arthritis in patients with 2 years of age or older [1-4]. Also, it can be used for management of postoperative pain, gout, and acute flares [5-7]. Like other NSAID, meloxicam demonstrates anti-inflammatory, analgesic, and antipyretic properties through inhibition of prostaglandins synthesis. Prostaglandins are important inflammatory mediator synthesized by two isoforms of cyclooxygenase enzymes (COX) which are COX 1 and COX 2 [4, 8]. In general, cyclooxygenase is an enzyme found in many tissues in the body, additionally within neurons of the spinal cord and brain [9]. Meloxicam, compare with other NSAID, is characterized by more

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 22 December 2018; **Revised:** 05 June 2019; **Accepted:** 11 June 2019

selectivity to inhibit COX 2, but it is weak inhibitor for COX 1 which leads to improve gastrointestinal tolerability profile compared with other NSAID [10-12]. However, the common adverse reactions of meloxicam include hypertension, cardiac arrhythmia, edema, insomnia, skin rash, nausea and increase liver enzyme. It is contraindicated for relief of postoperative pain after coronary artery bypass graft surgery or in patient with hypersensitivity to meloxicam [4].

Meloxicam is an oxicam derivative (figure 1) and it has different dosage forms such as tablets, oral suspensions and capsules. In Saudi Arabia, it marketed as tablet under brand name Mobic and generic names Neoxicam, Coxicam, and Oximal.

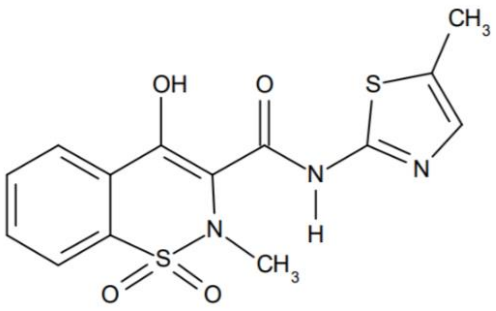

Figure 1: meloxicam chemical structure

In 2012, the total budget of healthcare in Saudi Arabia was 23 billion dollars [13], while the total drug expenses were between 3.5 and 4 billion dollars. Of this total, 84% was spent on brand names and only 16% on local generics [14]. Published studies in USA [15] and Saudi Arabia [16] demonstrate 78% to 79% of physicians supported generic drugs and 17% to 16% of them prescribed generic drugs in all cases when it is available, and only 5% of physicians didn't believe that the generic medication is comparable to the brand. A study conducted in Cyprus and Greece in 2007 [17] showed that 60% of physicians in Cyprus versus 51% in Greece rated the generic medications compared to brand medications to be excellent or satisfactory. Only 25% of Greece physicians prescribed generic drugs instead of brand in most cases compared to 67% of physicians in Cyprus. Toklu et al. [18] conducted a survey in 2010 in Turkey and showed that 32% and 31% of physicians and pharmacists believe that generic drugs are similar to brand in term of safety and efficacy. Eighty-two percent of the prescribers and 40% of the pharmacists were unconfident about the bioequivalence of generics. Twenty-six present of the patients stated that they will accept to substitute the brand by generic when the physician prescribes it, whereas 10% accepted the generic if it substituted by the pharmacists.

The aim of the present study was to compare the efficacy of generic products of meloxicam tablets versus its brand (Mobic®) in a rat model, using hot plate and formalin tests.

MATERIALS AND METHODS

Drug administration:

Male albino Wistar rats weighing 90-140g were used in this study. They were obtained from Research and Medical Consultation (IRMC) Institute of Imam Abdulrahman Bin Faisal University.

Rats were maintained at 22 ± 1ºC (humidity 60%) on a 12 hours light-dark cycle and given standard laboratory diet and water ad libitum. In all tests, the ethical guidelines were followed in conscious animals for examination of experimental pain [19]. All procedures were followed according to the Animal Experimentation Ethics Committee of the University. The allocation of rats to nine groups were randomized. *In-vivo*, the experimental protocol of this study had the approval of the Institutional Review Board (IRB) **IRB-UGS-2018-05-054**; dated: 13-03-2018.

Before the experiments start, all rat groups were housed separately in wire mesh in standard plastic cages to avoid eating of faeces or dung (coprophagy) under controlled environment conditions. all groups were kept without food for 12hr and they only had water ad libitum [20].

Forty-eight rats divided into groups of six animals, received orally (p.o), 10mg per body weight of Mobic, Neoxicam, Oxicam and Coxicam dissolved in vehicle (distilled water) in a volume of 10ml/kg, 30 minutes before hot plate or formalin test, as described in Tables 1 and 2 [8]. One additional group of animals (positive control), tested regarding to their behavioral profile and received only formalin solution in formalin test in our experimental design. The groups were then tested in hot plate and formalin tests with the above-mentioned experimental design.

Hot-plate test:

Eddy et al. developed the hot plate latency experiment in 1950 [21]. Anti-nociceptive effect of meloxicam was evaluated by hot plate consisted of aluminum plate which is electrically heated (Ugo Basile Hot Plate 35100) at the constant temperature of 55 ± 0.5°C. The rat was placed in a glass cylinder on the hot plate and the response time between placement and jumping or liking of paws was recorded. The baseline for rat to show response in the hot-plate test was recorded. The data for analgesic effect of the drug was presented as a percentage of the maximum possible effect, according to the following formula:

$$\%MPE = \frac{test\ latency - baseline\ latency}{45 - baseline\ latency} \times 100$$

where 45 indicate cut off time, in seconds [20].

In this test, the experimental groups (A, B, C and D) were given 10mg per kg of meloxicam, orally as described in table 1 after 12 hours of fasting [22, 23]. Each rat was placed in the hot plate 30 min after oral administration of brand and generics of meloxicam preparation and the reaction time was taken as Hot Plate Latency. The reaction time was recorded at 0 (baseline), 30 min and at 1^{st},2^{nd},3^{rd},4^{th} and 8^{th} hour after oral administration of the product.

In order to prevent tissue damage, the rat doesn't allow to stay on the hot plat longer than 60 seconds. The mean %MPE for each group was calculated [20].

Formalin test.

Rats were placed individually in standard cages, divided into five groups (6 rats /group) and fasted for 12 hours. On the day of experiment, the animals in the treatment groups (B, C, D and E) were given 10mg per kg of meloxicam, orally as described in table 2 whereas, group A which was used as positive control received vehicle orally. Before testing the animals, 50 µl of 2.5% (v/v) formalin injected subcutaneously into right hind paw (dorsal surface) of the rat by using a micro syringe needle (26-gauge). Pain behavior observed over 60 min after formalin injection, the frequency of spontaneous flinching or duration of licking of the injected paw were summed at phase 1 and 2. Phase 1 began immediately after formalin injection up to 5 minutes (1^{st}-5^{th}) and this phase considered as early phase. Phase 2 started at time 10 minutes and pain behavior was observed for 50 minutes. Furthermore, the second phase was divided into two phases due to data analysis purpose. Phase 2A was started at 10 min and ended at 39 min (10^{th}-39^{th}) and phase 2B began at 40 min up to 60 min (40^{th}-60^{th}) [24]. The experiment was performed at room temperature (22±1) to avoid interference between skin and room temperatures [25]. The time was counted by using a stopwatch. In the end of the experiment, the rats were anaesthetized immediately after observation phases.

Statistical Analysis:

The data for hot plate and formalin test was expressed as means ± SEM. The data obtained from the formalin and hot plate test experiments was evaluated by one-way analysis of variance followed by Tukey's post-hoc test for comparisons between the brand group (Mobic) and rats treated with the generic groups. The data were analyzed by using SPSS 21 software program and the results with P values less than 0.05 were considered significant during this study.

Table 1: experimental design of meloxicam for hot plate test

Groups (n= 6)	Treatment	Batch No.	Dose (mg/kg; p.o)
A	Mobic (Brand)	97-68-73	10
B	Neoxicam (Generic 1)	08-584-7	10
C	Oximal (Generic 2)	07-171-61	10
D	Coxicam (Generic 3)	04-225-127	10

n = Number of rats; p.o.: per oral.

Table 2: experimental design of meloxicam for formalin test

Groups (n= 6)	Treatment	Batch No.	Dose (mg/kg; p.o)
A	Positive control	-	Vehicle
B	Mobic (Brand)	97-68-73	10
C	Neoxicam (Generic 1)	08-584-7	10
D	Oximal (Generic 2)	07-171-61	10
E	Coxicam (Generic 3)	04-225-127	10

n = Number of rats; p.o.: per oral.

RESULTS AND DISCUSSION

Results:

Hot plate test:

The %MPE of rats treated with Mobic, Neoxicam, Oxicam and Oximal at 10mg/kg are shown in figure 2. Significant analgesia was seen in all the three generic groups as compared to brand group. Analgesia in groups treated with generics were much greater than that treated with Mobic (brand). However, Oximal was found to be more significant at 2^{nd} and 4^{th} hr and regarding to Coxicam at 4^{th} hr was moderately significant. Whereas, Neoxicam was the least significant compared to the brand.

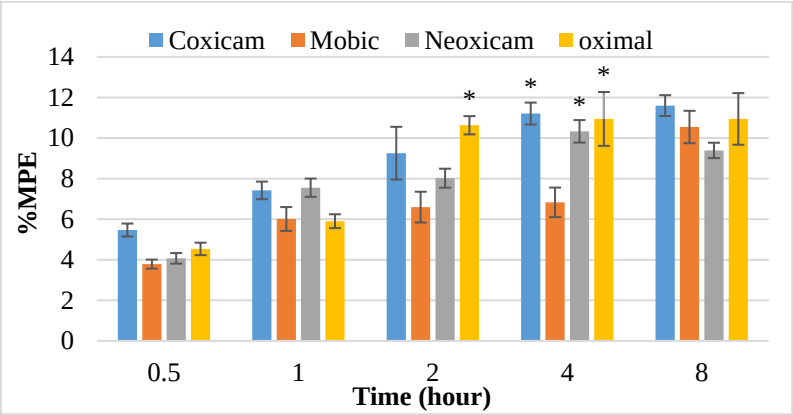

Figure 2. hot plate test. percentage of the maximum possible effect (%MPE) after oral administration of Mobic, Neoxicam, Oximal, Coxicam in rats (10mg/kg). Data are expressed as mean values ± SEM (each group contain 6 rats). *P < 0.05, compared with brand-Mobic (one-way analysis of variance followed by Tukey's post-hoc test).

Formalin Test:

The effects of per oral (p.o) administration of meloxicam (Mobic-brand) and its three generics were observed in phase 1 and 2. In both phases, the pain behaviors were evaluated as frequency of filching or jerking as well as the duration of licking. The time course of the licking response of rats treated with generics Neoxicam, Coxicam and Oximal (10mg/kg) and brand Mobic (10 mg/kg) was compared with control values in figure 4 and total jerking frequency in figure 3.

In phase 1 of formalin test, the frequency of flinching was significantly lowered in treatment groups than that of the positive control group (pd"0.05). Furthermore, the values obtained by Coxicam, Neoxicam and Mobic groups were lower compared to Oximal, and this difference wasn't statistically significant (Figure 3). However, there is no significant difference between treatment groups and control group in the duration of licking (Figure 4).

As shown in Fig. 3, Coxicam induced a significant reduction in the frequency of flinching and jerking in all phases compare to the positive control group and in phase 2A & 2B, it was better than Mobic. Mobic at the dose of 10 mg/kg, orally, shows less reduction in phase 2A as well as Oximal. In phase 2A, Neoxicam shown less numbers of flinches and jerks compared to Mobic. Oximal has reduced flinches and jerks but not better than Mobic. Thus, Coxicam and Neoxicam were effective in all phases of the formalin test, proving as smellier or more efficacious than the brand Mobic. However, the total duration of licking wasn't significantly lowered in treatment groups as compared to control group in phase 2A (Figure 4).

Furthermore, in the phase 2B of formalin test, the treatment groups showed reduction in pain behaviors compared to positive control group. however, Neoxicam and Oximal were found to be much better in reducing the licking response than Coxicam when compared to Mobic mainly in phase 2A (Figure 4).

Thus, in observation period of formalin test, Neoxicam is said to be highly potent, Coxicam is moderately potent and Oximal equally potent to Mobic by significantly reducing the number of flinching and the total duration of licking compared to positive control (Figure 3 & 4).

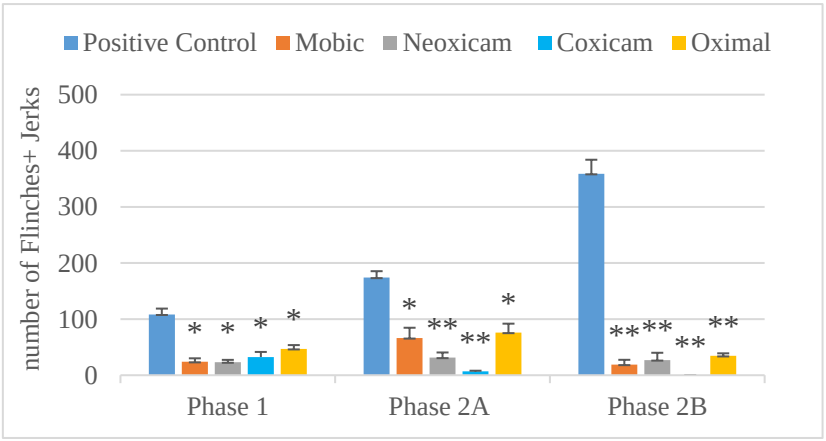

Figure 3. Formalin test. Number of Flinches + Jerks in formalin test with different group of rats given during 60 min (phase 1 and 2), as indicated. Data are express as the mean values ± SEM (each group contain 6 rats). *=p<0.05, **=p<0.001, compared to positive control (formalin2.5%). (one-way analysis of variance followed by Tukey's post-hoc test).

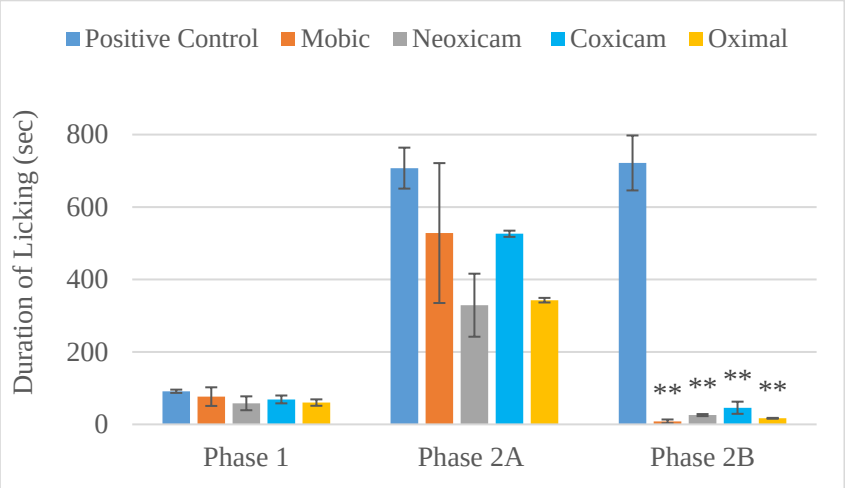

Figure 4. Formalin test. Duration of Licking (sec) in formalin test with different group of rats given during 60 min (phase 1 and 2), as indicated. Data are express as the mean values ± SEM (each group contain 6 rats). **=p<0.001, compared to positive control (formalin2.5%). (one-way analysis of variance followed by Tukey's post-hoc test).

DISCUSSION

The difference between brand and generics is considered as one of the major issues for governments, physicians, pharmacists, and patients. In addition to the difference in cost, there are variety of opinions support the efficacy of generics versus brand [15-18]. With this view, the present experiments have been undertaken to evaluate the efficacy of the brand (Mobic®) and generics (Oximal®, Neoxicam®, and Coxicam®) of meloxicam.

Meloxicam is used frequently as anti-nociceptive in laboratory animals [8, 26-29]. In this study, administration of meloxicam orally (10 mg/kg) demonstrated analgesic activities on hot plate and formalin test. The hot plate test used to assess supraspinal anti-nociceptive effects and it reflects activity in afferent nerve fibers for thermal sensitivity and activity of C and Aδ fibers [30]. In our study, we demonstrated that Neoxicam, Coxicam, and Oximal were comparable to the brand of meloxicam (Mobic) in hot plate test as has been seen in figure 2. However, the analgesic activity of Oximal at 2nd and 4th hour was significantly ($p<0.05$) more than Mobic. Also, it was found that all the three generics suppressed nociceptive effects more potently ($p<0.05$) compared to Mobic at 4th hour but after 4 hours, the analgesic activity of Mobic increased and there is no significant ($p>0.05$) difference between Mobic and the other generics, also at 30 minutes and 1st hour. The variation in the results between these products may be related to difference in pharmaceutics parameters or bioavailability of the drugs.

The formalin test is a dependable technique to evaluate analgesic and anti-inflammatory activity in rat models, moreover it's sensitive for different classes of drugs with anti-inflammatory or analgesic activities [31]. This test has three different phases which are early phase (from 0 to 5 min), interphase (from 11 to 39 min), and late phase (from 40 to 60 min). The early phase (phase 1) of formalin test shows direct activation of nociceptors, whereas interphase (phase 2A) reflects the stimulation of central analgesic system, and the late phase (phase 2B) reflects inflammation [32]. In the present study, we demonstrated that oral administration of the brand and the generics of meloxicam had significant analgesic effect in formalin test compared to positive control group. Despite that, there were no significant difference between Mobic, Oximal, Coxicam, and Neoxicam in all phases of formalin test, thus the result of this study supports the theory that have been reported in different studies which is generic drugs did not differ from their brand in term of efficacy [15-17]. In the early phase of formalin test, it was found that all study groups significantly reduced the number of flinching and jerking (pd"0.05) compared to control group (figure 3), but the duration of licking was not significant in all groups of meloxicam versus control group except in phase 2B (figure 4). Rosland et al. [33] reported that anti-inflammatory drugs didn't affect the initial phase of formalin test even with a very low concentration of formalin. Our findings support these results as well. Again, in the phase 2A, the results of licking duration were not significantly lowered in treatment groups compared to the control group ($p>0.05$), but the difference between these groups in the frequency of jerking were statistically significant. Furthermore, in the late phase of formalin experiment, it was found that the administration of brand and generics of meloxicam reduced both the frequency of flinching and the total duration of licking in comparison to the positive control group. Therefore, these results reveal that the analgesic

effect of the brand (Mobic) are comparable to the generics (Oximal, Coxicam, and Neoxicam).

This study had highlighted that Neoxicam showed better analgesic effect compared to other groups in formalin test. However, the anti-nociceptive effect at late phase (phase A & B) was noticeably higher for both Mobic and Coxicam compared to other groups. In hot plate test, Coxicam and Oximal had higher anti-nociceptive effect compared with Mobic and Neoxicam (at the 2-, 4-, 8-hour time points), whereas Mobic was more potent than Neoxicam at 8th hour and less potent than other groups. With our data, we can say both the brand and generics of meloxicam are comparable. However, no studies have compared the anti-nociceptive effects between Mobic, Neoxicam, Coxicam, and Oximal.

CONCLUSION

According to the formalin and hot plate tests, the analgesic effects of the generics (Neoxicam, Coxicam, Oximal) proved to be as good as the brand (Mobic). Furthermore, bioequivalent studies must be performed in rats and humans to conform these results.

ACKNOWLEDGEMENTS

The authors would like to thank clinical pharmacy college at Imam Abdulrahman Bin Faisal University for providing library facility and e-journal free access facility to write this article.

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