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EVALUATION OF ADDITION OF PARACETAMOL AS ADD ON THERAPY TO LOW DOSE ETORICOXIB FOR ANALGESIA IN ACUTE PAIN: AN EXPERIMENTAL STUDY

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Keywords:

Etoricoxib, Paracetamol, Low dose, Writhing, Hot plate method, Cost effective

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ABSTRACT: Objective: To study the influence of paracetamol on analgesia when given separately with low dose etoricoxib for treatment of acute pain in mice. **Materials and methods:** Animals were divided into 6 groups consisting of six animals in each group. Dose was calculated by using conversion factor for mice from human dose. Group I, II, III and IV received 2% Gum acacia 10ml/kg, paracetamol 84.5mg/kg, etoricoxib 3.9 mg/kg and 7.8 mg/kg respectively. Group V and VI received etoricoxib 3.9 mg/kg + paracetamol 42.25mg/kg and etoricoxib 3.9 mg/kg + Paracetamol 84.50 mg/kg respectively. Group II, V and VI were administered rescue paracetamol at 6 h. Acetic acid induced writhing test and hot plate method were used to evaluate immediate and delayed analgesic activity respectively. **Results:** After 1 h low dose paracetamol in combination with low dose etoricoxib showed significant (P<0.05) analgesic activity as compared to etoricoxib low and paracetamol high dose when used alone and comparable analgesia as compared to etoricoxib high dose when used alone. High dose paracetamol with low dose etoricoxib showed better analgesic activity as compared to high dose etoricoxib when used alone. Delayed analgesic activity in paracetamol treated group were significant at 7th h as compared to 6th h. **Conclusion:** Addition of paracetamol increases the analgesic efficacy of low dose etoricoxib and is cost effective as compared to high dose etoricoxib when used alone.

INTRODUCTION: Pain is a warning signal that causes discomfort, and patient visits to a physician or takes medicine over the counter. An increasing trend for analgesic use has been observed for pain relief, and patients are often consuming more than the recommended dose. Classical non-steroidal anti-inflammatory drugs which act by inhibiting both cyclo-oxygenases (COX I and COXII) enzymes are the most commonly prescribed analgesics, but gastrointestinal (GIT) toxicity is a problem with their use. They inhibit the production of prostaglandins that helps in the relief of pain but also inhibit gastroprotective effect [1].

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Selective COX-II inhibitors were found promising drugs for relief of pain without any GIT toxicity [2]. Later two of the COX-II inhibitors rofecoxib and valdecoxib were banned because of their involvement in causing serious adverse effects on the cardiovascular system, which is more than the classical or non-selective COX inhibitors [3]. Recently the use of classical NSAIDs increased in combination with proton pump inhibitors to protect against GIT toxicity with increased treatment cost [4].

Paracetamol is a weak analgesic as compared to non-selective and selective COXII inhibitors but has widespread use as it is cheaper and devoid of GIT toxicity. It was combined with non-selective COX inhibitors for better analgesic efficacy, but this combination needs to be administered three to four times a day, and it could not prevent GIT toxicity [5].

Adverse effects of drugs are often dose-related. One way to reduce the dose of a drug is to use it with a lower dose of another drug that acts synergistically. Such lower doses of two drugs which act synergistically if given together, may have better efficacy than their alone use [6]. Administration of those two drugs in low doses having better treatment profile for relief of pain and which do not add to adverse effects is the need of hour for the treatment of pain in chronic illnesses. Etoricoxib is a selective COX-II inhibitor, and paracetamol is both COX-I and COX-II inhibitor and both do not cause gastric toxicity [7, 8]. Etoricoxib is long-acting and used once a day, whereas paracetamol is short-acting and has to be given four times a day [9]. Due to the difference in pharmacokinetic profile present study is planned to compare the analgesic effect of lower dose and high dose of paracetamol when administered three to four times separately to mice suffering from acute pain treated with a lower dose of etoricoxib and this is compared with high dose etoricoxib treatment when used alone.

MATERIALS AND METHODS:

Chemical and Drugs: Etoricoxib (Abbott) and paracetamol (Glaxo Smithkline) were purchased from the market. Distilled water, Acetic acid 0.6% and gum acacia 2% of standard quality were used.

Experimental Animals: Healthy Swiss Albino male mice (40-45 grams) of 6-8 weeks age available in animal house under Department of Pharmacology Gajra Raja Medical College, Gwalior were used in the study. All animals under the experiment were kept in at 25 ±1 ºC and fed with a standard pellet diet (Aashirwad, Mohali Punjab) and water *ad libitum*. The experimental protocol was approved by the institutional Animal Ethics Committee (IAEC) vide registration no.846/GO/ Ere/S/04/CPCSEA

Selection of Dose: Animal doses for etoricoxib and paracetamol were calculated from absolute human dose by using conversion factor for mice, *i.e.*, 0.0026, which is developed according to body surface area.[10]

1. Etoricoxib 30mg×0.0026 = 0.078mg absolute mice dose = 3.90mg/kg
2. Etoricoxib 60mg×0.0026 = 0.156mg absolute mice dose = 7.80mg/kg
3. Paracetamol 325mg×0.0026 = 0.845mg absolute mice dose = 42.50mg/kg
4. Paracetamol 650mg×0.0026 = 1.69mg absolute mice dose = 84.50mg/kg

Experimental Protocol: Animals were divided into six groups consisting of six animals in each group. Group1 received 2% Gum acacia aqueous suspension 10ml/kg, GroupIIreceived paracetamol 84.5mg/kg, Group III and IV received etoricoxib 3.9 mg/kg and 7.8 mg/kg respectively, Group V and VI received etoricoxib 3.9mg/kg + paracetamol 42.25 mg/kg and etoricoxib 3.9 mg/kg + Paracetamol 84.50 mg/kg respectively. Animals were fasted for 12 h before each study. Paracetamol was administered at 0 and at 6 h as rescue analgesia, whereas etoricoxib was administered once in animals of respective groups by gavage orally. Immediate analgesic activity after 1h was studied using the writhing test, whereas delayed analgesic activity was studied using hot plate in the second set of animals at 6^{th} and 7^{th} h.

Writhing Test: The study drugs were given orally by gavage 60 minutes before the start of the study. Acetic acid solution (0.6% v/v) 10 ml/kg was injected intraperitoneally, and abdominal constriction with stretching of the hind limbs defined as writhe was cumulatively counted over a period of 30 min just after acetic acid injection [11]. Antinociceptive activity was expressed as the percentage inhibition of abdominal constrictions between control animals and mice pre-treated (n=6) with the different test drugs using the ratio: (Control mean – Treated mean) × 100 / Control mean.

Hot Plate Test: Fasted animals were placed individually on a hot plate maintained at a temperature of 55 ± 0.5 ºC. The latency to lick the paw or jumping was considered as the reaction time. The cut-off time was set at 20 sec to avoid damage to the skin [12]. Paw licking or jumping responses were recorded in all groups at 6^{th} and 7^{th} h, respectively. Only groups II, V, and VI were administered rescue paracetamol after recording analgesic activity at 6^{th} h.

Cost-Effective Analysis: The cost of the single-day treatment was evaluated individually for all single and combined treatments. Monthly treatment

cost was calculated for chronically ill patients. Low dose etoricoxib with either low or high single dose of paracetamol was compared with a low and high dose of etoricoxib when used alone.

RESULTS:

Analgesic Efficacy of Drug Treatments on Writhing Response after One Hour:

Effect of Etoricoxib and Paracetamol when used alone: Etoricoxib low dose when used alone showed a decrease in writhing as compared to control, which was statistically significant (P<0.05) and justifies its analgesic efficacy. It was comparable with high-dose paracetamol when used alone. Etoricoxib high dose showed significant (P<0.05) analgesic activity as compared to control, low dose etoricoxib, and high dose paracetamol alone, suggesting dose-dependent better efficacy of etoricoxib high dose **Table 1**.

TABLE 1: EFFECT OF PARACETAMOL AND ETORICOXIB ALONE AND IN COMBINATION BY WRITHING METHODS AT 1 h

Treatment	No of writhes in 30 min (mean ±SEM)	Inhibition (%)
Control	72.17±2.31	--
PCM-H	56.67±3.14*	21.48
ETO-L	53.00±3.83*	26.56
ETO-H	44.00±1.71^{*a}	39.03
ETO-L+ PCM-L	39.50±2.37^{*ab}	45.27
ETO-L+ PCM-H	30.83±1.66^{*abc}	57.28

PCM-H = paracetamol 84.50mg/kg, ETO-L = etoricoxib 3.9 mg/kg, ETO-H = etoricoxib 7.8mg/kg PCM-L = paracetamol 42.25 mg/kg. All values are presented as mean ±SEM. $^{*}P$<0.05 when compared to control, ^{a}P<0.05 compared to PCM-H, ^{b}P<0.05 compared to ETO-L, ^{c}P<0.05 compared to ETO-H.

Effect of Combinations of Low Dose Etoricoxib with Low Dose of Paracetamol: Efficacy of low dose paracetamol when added to low dose etoricoxib showed decrease in writhing as compared to control, etoricoxib low dose and paracetamol high dose when used alone and was statistically significant (P<0.05). Combination of low doses of the two drugs have shown comparable efficacy in reducing writhes with etoricoxib high dose when used alone **Table 1**.

Effect of Combinations of Low Dose of Etoricoxib with High Dose Paracetamol: Effect of low dose etoricoxib with that of high dose paracetamol showed significant (P<0.05) decrease in writhing numbers as compared to control, etoricoxib low and high dose and paracetamol high dose when used alone. This combination also showed dose-dependent better analgesic efficacy as compared to the addition of low dose paracetamol to low dose etoricoxib. It was better than the etoricoxib high dose when used alone but was not significant statistically (P>0.5).

Delayed Analgesic Efficacy of Drug Treatments using Hot Plate at 6th and 7th h:

Comparison of Analgesic Efficacy at 6th h with 7th hour within the Group: Significant (P<0.5) increase in jumping latency was seen in rescue paracetamol treated Group V and VI at 7th h as compared to 6th h suggestive of restoration of synergistic activity of etoricoxib and paracetamol. There was little increase in jumping latency in etoricoxib alone treated Groups III and IV at 7th h as compared to 6th h **Fig. 1**.

Comparison of Intergroup Analgesic Efficacy at 7th h: Group II showed comparable jumping latency with Group III (P>0.5) whereas Group V showed a significant (P<0.5) increase in jumping latency as compared to Group III and was comparable with Group IV, suggesting better efficacy of combined treatments. Group VI showed a significant (P<0.5) increase in jumping latency as compared to Group III and Group V and was also better than Group IV **Fig. 1**. These results suggest that after the addition of paracetamol, high dose to low dose etoricoxib treated animals analgesic efficacy at 7 h is more than high dose etoricoxib when used alone.

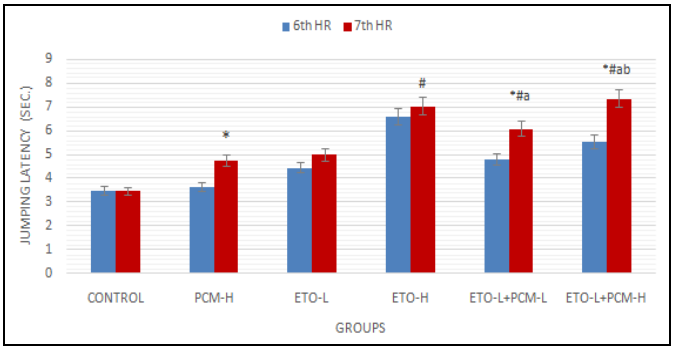

FIG. 1: DELAYED ANALGESIC EFFECTS OF PARACETAMOL AND ETORICOXIB ALONE AND IN COMBINATION BY HOT PLATE METHOD AT 6th AND 7th h. RESCUE PARACETAMOL ADMINISTERED AT 6 h. PCM-H = paracetamol 84.50mg/kg, ETO-L = etoricoxib 3.9mg/kg, ETO-H = etoricoxib 7.8mg/kg PCM-L = paracetamol 42.25mg/kg. All values are presented as mean ±SEM. $^{*}P$<0.05 when compared to latency at 6th h in paracetamol treated groups, $^{\#}P$<0.05 compared to PCM-H, ^{a}P<0.05 compared to ETO-L, ^{b}P<0.05 compared to ETO-L+PCM-L at 7th h

Cost-Effective Analysis: Patients taking single low dose of etoricoxib for pain will costs approximately Rs 5 per day only. For effective analgesia supplementation of low dose paracetamol, 6 hourly to etoricoxib low dose will cost approximately Rs 7 day only. The cost of etoricoxib high dose, when used alone, is approximately Rs 10 and is comparable in efficacy as compared to a combination of low doses of paracetamol and etoricoxib. Thus per day Rs 3 can be saved with exposure of patients to a lesser dose of etoricoxib. **Table 2** suggestive of lesser chances of cardiovascular adverse effects also.

TABLE 2: COST-EFFECTIVE ANALYSIS OF PARACETAMOL AND LOW DOSE ETORICOXIB WHEN USED ALONE AND IN COMBINATION

Drugs and dose to be used clinically	No. of tablets required/day	Approximate Cost of one day treatment (Rs)	Approximate Cost per month for chronic diseases (Rs) (cost of 1 day dose × 30)
Etoricoxib30mg	1	5	150
Etoricoxib60 mg	1	10	300
Etoricoxib30mg+ paracetamol325mg	1+4	5+2 =7	210
Etoricoxib30mg+ paracetamol650mg	1+4	5+4=9	270

Statistical Analysis: The results are expressed as mean± standard error of mean and one-way analysis of variance (ANOVA) followed by Tukey's Multiple Comparison Test. GraphPad Prism 5.01 software used for statistical analysis. Values of $P< 0.05$ were considered to be statistically significant.

DISCUSSION: Standard and test drugs showed antinociceptive activity in both the models used in the present study: hot plate and writhing test indicating the action of these drugs through central as well as peripheral mechanism.[13] Acetic acid-induced inflammatory pain is due to increase capillary permeability and release of arachidonic acid and prostaglandin biosynthesis *via* cyclo-oxygenase. In the present study, low-dose etoricoxib showed better analgesic activity than high dose paracetamol when used alone; this confirms increased COX-II expression at inflammation site, and etoricoxib is a selective COX-II inhibitor suppressing prostaglandin synthesis at sites of inflammation [14].

When a low dose of paracetamol is added to low dose etoricoxib it showed better analgesic activity as compared to low dose etoricoxib alone, which might be due to additional COX-I inhibition with paracetamol along with COX-II inhibition [15]. This combination is showing comparable efficacy with high dose of etoricoxib, which might be because inhibition of both the COX enzyme produces better analgesic activity as compared to COX-II inhibition alone [16]. Furthermore, it is also reported that paracetamol inhibits COX-III centrally, which is a variant of COX -I [17].

In the present study, the addition of a high dose of paracetamol to low dose etoricoxib showed better analgesic activity than high dose etoricoxib alone, suggesting that paracetamol act through some other mechanisms that add to analgesia [18]. Studies have revealed paracetamol stimulates serotonergic descending neuronal pain pathways which are involved in inhibition of pain sensations. The L-arginine/NO pathway activated by substance P and NMDA receptors leads to NO synthesis, which is an important neurotransmitter in the nociceptive processes of the spinal cord. Paracetamol inhibits nitrogen oxide (NO) formation l. It also increases the activity of the endocannabinoid system [9, 15, 18].

The present study suggests that per day treatment with low dose etoricoxib along with low dose paracetamol cost only Rs 7 whereas cost of high dose etoricoxib is Rs 10 and is inferior as efficacy; thus, it suggests that the addition of paracetamol is a cost-effective addition to increasing etoricoxib analgesia and can be used for a longer period for the patients of chronic arthritis. The result of the present study indicates that if paracetamol alone added with low dose etoricoxib will produce analgesia for 5-6 h only owing to its short half-life so it can be supplemented subsequently alone every 6 hourly as per need for continuous analgesia and etoricoxib having long half-life given once only and need not to be repeated before 24 h. Thus, it will be a suitable regime to control pain for 24 h at the expense of Rs 3 per day less as compared to Rs 10 per day for etoricoxib high dose.

Fixed-dose combination of high dose etoricoxib with low dose paracetamol which is available as

different brands in the market, costs approximately Rs 12 per day and exposes the patients to increased cost, dose, and adverse effects unnecessarily. Results of the present study suggest that low dose paracetamol can be supplemented with low dose etoricoxib separately 6 hourly and can be cost-effective, safe and rational treatment regime for pain [19].

This is a single-day study in animals, but the results are encouraging to conduct a study of long duration in patients suffering from acute or chronic pain to confirm the results.

CONCLUSION: Paracetamol can be a good and safe adjuvant as well as a subsequent rescue analgesic to low-dose etoricoxib. Cost calculation indicates that there will be handsome saving in overall treatment cost with increased analgesic efficacy and minimal adverse effect profile than etoricoxib high dose when used alone.

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CONFLICTS OF INTEREST: Nil

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