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# ANALGESIC ACTIVITY OF CINNAMALDEHYDE *PER SE* AND IT'S INTERACTION WITH DICLOFENAC SODIUM AND PENTAZOCINE IN SWISS ALBINO MICE.

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**ABSTRACT:** Cinnamon is one of the best-known spices used as herbal medicine. Cinnamaldehyde is the most important constituents of cinnamon. The present study was aimed to evaluate the analgesic activity of Cinnamaldehyde *per se* and its interaction with diclofenac sodium and pentazocine in Swiss albino mice. Healthy mice of either sex weighing 20-30 grams were divided into 6 groups of 6 animals each. Peripheral analgesic activity was evaluated by acetic acid induced writhing test, and central analgesic activity was studied using Eddy's hot plate method. Cinnamaldehyde (100 and 200 mg/kg) and its combination (Cinnamaldehyde 100 + 2.5 mg/kg standard drug), diclofenac sodium (2.5 and 5 mg/kg) and pentazocine (2.5 and 5 mg/kg) were given orally. Acetic acid induced writhing model showed that diclofenac sodium at doses of 2.5 and 5 mg/kg reduces writhing 44% and 66% respectively as compared to control when administered alone. Cinnamaldehyde at 100 and 200 mg/kg showed dose-dependent decrease in writhes 54% and 81%, but when Cinnamaldehyde (100 mg/kg) was co-administered with diclofenac sodium (2.5mg/kg) showed a significant decrease in writhes 84.43% concerning control. While in Eddy's hot plate method Cinnamaldehyde not only showed hyperalgesia when given alone as compared to control but also decreases the analgesic effect of pentazocine when combined with pentazocine in comparison with pentazocine alone and control group. The findings suggest that the Cinnamaldehyde significantly increases the analgesic activity of diclofenac sodium, but decreases the analgesic activity of pentazocine.

**INTRODUCTION:** Pain is one of the most common and frequent complaints of a human being. It can be either defined to one specific area, or it can be generalized to the whole body. Perception of pain is a standard physiologic response of healthy nervous system [1] and is mediated by various mediators like prostaglandins, serotonin, substance P, *etc*.

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Currently, there are various medications available for pain. Depending on the type of pain, either NSAIDs or opioids can be used. But there are various adverse effects related to these medications.

NSAIDs has a high risk of gastric ulcers [2] similarly opioids has a wide range of CNS adverse effects like tolerance, dependence, CNS depression [3] *etc*. As an alternative to NSAIDs and opiates, newer analgesic drugs with lesser or negligible adverse effects along with high efficacy are being searched all over the world. According to WHO, about 80% of the world population still rely mainly on plant-based drugs [4]. Cinnamon is one of the oldest and best-known spices in the world and is used as

herbal medicine [5]. It belongs to family Laurence and is found in South India, Srilanka, Indonesia, Vietnam, Bangladesh, and Nepal and commonly known as dal-chini, darchini or dhall cheene in Hindi. The active component of commercial cinnamon is the dried inner stem-bark of aromatic evergreen tree 10-15 meters tall. The most important constituents of cinnamon are Cinnamaldehyde and eugenol, which are present in the essential oil of the bark thus contributing to the fragrance and the various biological activities observed with cinnamon [6].

Cinnamon has been investigated for antioxidant property [7], inhibition of tau aggregation [8], anti-inflammatory activity [9], anti-nociceptive activity [10], peptic ulcer protection effects [11, 12] effect on cardiovascular system [11, 13, 14] and hepato-protective effects [15], antihyperlipidemic activity [16] and antidiabetic [17]. The present study was planned to investigate whether Cinnamaldehyde has any analgesic activity *per se* and how does it interact with diclofenac sodium and pentazocine?

## MATERIALS AND METHODS:

**Drugs and Chemicals:** Cinnamaldehyde (CNM) was obtained from the Science center (Sunchem Pharma), Indore, Madhya Pradesh, India, having 98% purity. Tween twenty was purchased from the same and used as a vehicle. Acetic acid- Ranbaxy lab limited, Mumbai, diclofenac sodium (DICLO) (Voveron injection, 25 mg/ml- 3 ml ampoule-Novartis Pharmaceuticals) and pentazocine (PTZ) (Fortwin injection, 30 mg/ml – 1 ml ampoule, Ranbaxy Pharmaceuticals Ltd.) were purchased from their authorized representatives.

**Animals:** Swiss albino mice (20-30 gm) of either sex were used for the study. The animals were housed in polypropylene cages in the central animal house. The rooms were maintained at the temperature of 25 ± 5 ºC with 12 h light/dark cycles. All the animal experiments were carried out according to the Committee for Control and Supervision of Experiments on Animals (CPCSEA), India guidelines. The animals were fasted overnight before the experiment and were given only water *ad libitum*. The study was approved by the Institutional Animal Ethics Committee (IAEC), M.G.M. Medical College, Indore, India (IAEC-709/20/2010, dated 25/03/2015) and the work was conducted in the Department of Pharmacology.

**Preparation of Drugs for the Animal Experiment:** CNM and other drugs were dissolved in tween twenty 20% to maintain uniformity of the solvent.

**Experimental Design:** Animals were grouped in 6 groups comprising of 6 animals each. (N=6, n=6). All the drugs were administered orally as per the grouping is done to all animals at the stipulated doses. The grouping done as follows:- Group I - Tween-20 20% (10 ml/kg), Group II - Diclofenac sodium for peripheral activity and pentazocine for central activity (2.5 mg/kg), Group III - diclofenac sodium or pentazocine 5 mg/kg (as per the peripheral or central activity), Group IV- CNM (100mg/kg), Group V - CNM (200 mg/kg), and GroupVI – CNM + diclofenac sodium or pentazocine (100 + 2.5 mg/kg)

**Procedure and Experiment:** Two different models of nociception assessed antinociceptive activity.

### 1. Acetic Acid Induced Writhing Method to Demonstrate Peripheral Analgesic Activity:

**Principle:** Writhing method was used for the evaluation of the peripheral analgesic activity. Painful reactions can be produced in experimental animals by applying noxious stimuli using chemical irritants such as acetic acid and bradykinin. Acetic acid induces writhing after intraperitoneal administration in mice.

**Procedure:** Abdominal constrictions were induced, by 1% v/v glacial acetic acid solution (10 ml/kg, i.p.) [18], after 1 hour of group-wise drug treatments. The number of abdominal writhes was measured over 10 min after the intraperitoneal injection of acetic acid. Results are expressed as percentage inhibition of abdominal constrictions concerning control, the total number of writhes and onset time of writhes were recorded. Abdominal constriction followed by extension of at least one hind limb is considered as one writhe.

### 2. Eddy's Hot Plate Model to Demonstrate Analgesic Activity:

**Principle:** Painful reactions can be produced in experimental animals by applying noxious stimuli

such as thermal – using radiant heat as a source of pain, chemical – using irritants such as acetic acid and bradykinin and physical pressure – using tail compression.

In the Eddy's hot plate model, the animals are placed on Eddy's hot plate which consists of an electrically heated surface. The responses are jumping, withdrawal of the paws and licking of the paws. The time until these responses occur is prolonged after administration of centrally acting analgesics (opioid analgesics), whereas peripheral analgesics do not generally affect these responses.[19]

**Procedure:** Animals were weighed, dosed according to grouping and placed on the hot plate maintained at a temperature of 55 ± 1 ºC. Responses such as jumping, withdrawal, and licking of the paws were seen. The period (latency period), from when the animals were placed and until the responses occurred, was recorded using a stopwatch. To avoid tissue damage of the animals 10 sec was kept as a cut off time [20, 21].

The time obtained in all the untreated groups of animals was considered as basal reaction time. Increase in the basal reaction time was the index of analgesia. All the animals were screened at least three times initially in this way and the animals were showing a broad range of variation in the basal reaction time were excluded from the study.

After selecting the animals, the drugs were administered to all animals as per grouping. The reaction times of the animals were then noted at 0.5, 1, and 2 h interval after drug administration.

**Statistical Analysis:** SPSS-20.00 statistical computer software was used to evaluate the results. Results are expressed as mean ± SEM. One way ANOVA followed by Tukey's test was applied for multiple comparisons amongst different groups. $p<0.05$ was regarded as statistically significant.

## RESULTS:

### Analgesic Activity of Individual Drugs:

**(a) Cinnamaldehyde:** In acetic acid induced writhing method, CNM at the dose of 100 and 200 mg/kg showed a significant decrease in number and delayed onset of writhes in a dose-dependent manner ($p<0.05$) **Table 1.**

**TABLE 1: EFFECT OF CINNAMALDEHYDE (CNM) IN ACETIC ACID INDUCED WRITHING IN MICE**

| Drug treatment | Dose (p.o., mg/kg) | Number of writhes in 10 min | Percentage inhibition with respect to control | Onset of writhes in sec |
|---|---|---|---|---|
| Tween-20 20% | 10 ml/kg | 32.67 ± 1.74 | _ | 97.67 ± 5.85 |
| DICLO | 2.5 | 18.50 ± 0.76* | 43.38% | 181.67 ± 7.14* |
| DICLO | 5 | 11.00 ± 0.57*# | 66.33% | 276.67 ± 4.75*# |
| CNM | 100 | 15.33 ± 0.95* | 53.08% | 181.83 ± 3.55* |
| CNM | 200 | 6.17 ± 0.60*#† | 81.12% | 416.50 ± 4.51*#† |
| CNM+DICLO | 100+2.5 | 5.00 ± 0.70*#† | 84.70% | 402.33 ± 5.51*#† |

One way ANOVA followed by multiple Tukey's comparison tests.
Values are mean ± SEM, n= 6 in each group, df = 5, 30
* $p<0.05$, as compared to control.
# $p<0.05$ as compared to diclofenac 2.5 mg/kg.
† $p<0.05$ as compared to diclofenac 5 mg/kg.
Note: Percent reduction = [1 – (mean of writhes in test or standard group / mean of writhes in control group)] × 100

While on Eddy's hot plate it showed a hyperalgesic effect at the dose of 200 mg/kg as compared control and pentazocine during all time points of study ($p<0.05$). But with 100 mg/kg dose hyperalgesia was observed only at 0.5 hr as compared to control ($p<0.05$) and at all time point when compared with pentazocine (5mg/kg) **Table 2**.

**(b) Diclofenac Sodium:** Diclofenac sodium at a dose of 2.5 and 5 mg/kg produced a significant decrease in number and delayed the onset of writhes as compared to control ($p<0.05$) **Table 1**.

**(c) Pentazocine:** In Eddy's hot plate method, with a dose of 5 mg/kg of pentazocine, the significant antinociceptive effect was observed at 0.5 h after the treatment and persisted for the entire test period ($p<0.05$). With the sub-therepeutic dose of pentazocine (2.5 mg/kg) the antinociceptive effect was observed only at 2 h ($p<0.05$) **Table 2**.

**Analgesic Activity of Combinations:**

**(a) CNM and Diclofenac Sodium:** Diclofenac sodium (2.5mg/kg) in combination with CNM (100mg/kg) produced a significant decrease in some writhes when compared to control value or either of the treatment alone ($p$<0.05) **Table 1**.

**(b) CNM and pentazocine:** When CNM (100mg/kg) given in combination with pentazocine (2.5mg/kg) decreases the reaction time as compared to control and pentazocine 2.5 mg/kg significantly ($p$<0.05) **Table 2**.

No toxicity or mortality was observed during an observation period of seven days after the completion of the experiment.

**TABLE 2: EFFECT OF CINNAMALDEHYDE (CNM) ON EDDY'S HOT PLATE METHOD IN MICE**

| Drug treatment | Dose (mg/kg, p.o.) | Reaction time in seconds | | | |
|---|---|---|---|---|---|
| | | 0 h | 0.5 h | 1 h | 2 h |
| Tween-20 20 % | 10 | 3.14±0.08 | 4.52±0.12 | 4.05±0.48 | 3.03±0.12 |
| PTZ | 2.5 | 3.14±0.07 | 4.03±0.16 | 4.52±0.32 | 3.61±0.14$^{*}$ |
| PTZ | 5 | 3.04±0.05 | 5.87±0.28$^{*}$ | 5.81±0.80$^{*}$ | 4.59±0.06$^{*}$ |
| CNM | 100 | 2.89±0.21 | 3.41±0.15$^{*\#}$ | 3.32±0.29$^{\#}$ | 2.56±0.15$^{\#}$ |
| CNM | 200 | 2.73±0.07 | 3.00±0.06$^{*\#}$ | 3.05±0.39$^{*\#}$ | 2.34±0.06$^{*\#}$ |
| PTZ+CNM | 2.5+100 | 2.73±0.06 | 3.18±0.04$^{*\#}$ | 3.83±0.31$^{\#}$ | 3.74±0.05$^{*\#\dagger}$ |

One way ANOVA followed by multiple turkey's comparison tests.
Values are mean ±SEM, n= 6 in each group, df = 5, 30
* $p$<0.05 as compared to control
# $p$<0.05 as compared to pentazocine 5 mg/kg
† $p$<0.05 as compared to CNM 100 and 200 mg/kg

**DISCUSSION:** Thus in the present study, Cinnamaldehyde (CNM) was studied for its analgesic potential in both peripheral (non-narcotic) and central (narcotic) type of pain models. Diclofenac sodium (2.5 and 5 mg/kg, p.o.) and pentazocine (2.5 and 5 mg/kg, p.o.) were used as standard drugs for comparing analgesic effects at peripheral and central levels, respectively.

The study on peripheral analgesic activity using the glacial acetic acid (1%) induced writhing method showed that CNM has peripheral analgesic potential. CNM increases pain threshold in Swiss albino mice in a dose-dependent manner, *i.e.* 100 mg/kg and 200 mg/kg. There was a significant decrease in some writhes ($p$<0.05) and also delay in the onset time of writhes ($p$<0.05) with CNM 200 mg/kg concerning control and diclofenac 2.5 mg/kg and diclofenac 5 mg/kg.

The combination group (*i.e.*, CNM 100 mg/kg and diclofenac sodium 2.5mg/kg), showed significantly better analgesic activity as compared to control and standard drug groups (*i.e.*, half and a full dose of diclofenac sodium) ($p$<0.05).

On the contrary study for central analgesic activity reveals that CNM has a hyperalgesic effect in a dose-dependent manner and when it was given in combination with pentazocine it markedly decreased the analgesic effects of pentazocine. **Table 2**

CNM has the hyperalgesic effect, at both doses, i.e. 100mg/kg and 200 mg/kg and it remained for whole study period, *i.e.* 0 h, 1 h, 2 h, as compared to control and standard drug groups. ($p$<0.05) but there is no significant difference between the hyperalgesic effect of both CNM doses ($p>0.05$).

When CNM (100 mg/kg) was given in combination with pentazocine (2.5 mg/kg), we found a significant decrease in analgesic activity as compared to control and pentazocine (5 mg/kg) alone ($p$<0.05). The decreased analgesia, compared to the standard group pentazocine (5 mg/kg), was evident as early as 0.5 h and remained for the entire duration of the study.

If we analyze the above findings, we can say that the CNM showed hyperalgesic activity not only when given alone but also showed the same effects when it was combined with even subtherapeutic dose of the standard drug. The lowering of analgesic effect response of pentazocine probably can't be explained by peripheral pharmacokinetic interactions like lowered absorption of pentazocine by CNM or increased metabolism of pentazocine

by microsomal enzyme system because hyperalgesic activity was seen with incremental dose of CNM *per se* also, which could be due to antagonism of endogenous narcotic endopeptidases like endorphins, enkephalins, and dynorphins which are acting on various opiate receptors like mu, kappa, and delta. This activity is similar to narcotic antagonist drugs like naloxone and naltrexone. The hyperalgesic activity of CNM could be due to the stimulation of nociceptive receptors (NOP) or through agonistic action on Transient Receptor Potential Ankyrin 1 (TRPA1) which are involved in the process of nociception and hyperalgesia [22, 23].

Pain is a complex process mediated by many physiological mediators, *e.g.* prostaglandins, bradykinin, substance P, *etc*. In the acetic acid-induced writhing model the constrictions induced by acetic acid in mice results from an acute inflammatory reaction with the production of PGE2 and PGF2α in the peritoneal fluid [24, 25]. Therefore, it is likely that CNM might suppress the formation of these substances or antagonize their action for exerting analgesic activity. Nonsteroidal anti-inflammatory drugs inhibit COX and thereby inhibits production of prostaglandins [26]. The similar analgesic activity has been reported with CNM by Atta & Alkofahi in 1998 [10] and Annegowda HV in 2012 [7]. Against gastric ulceration [12] if we consider this as a principle mechanism of CNM, then like prostaglandin synthesis inhibitors it must impair the mucosal defense of GIT by increasing gastric acid secretion, reducing mucus formation and increasing mucosal permeability. However, the study of Alqasoumi S *et al.,* showed that CNM is protective against gastric ulceration [11]. Thus, it appears that the analgesic activity of CNM is due to some other mechanism rather than inhibition of prostaglandin synthesis.

The pharmacokinetic reasons may be responsible for the enhancement of analgesia of a low dose of diclofenac. This could be due to increased blood flow due to GIT irritation with consequently enhanced absorption. CNM may improve the absorption of drugs, perhaps by increasing GI blood flow by vasodialatation [11, 13].

Further studies are needed to reveal the exact mechanism of action responsible for the enhanced activity of diclofenac sodium and decreased activity of pentazocine. However, the study adds to our concept that CNM can improve the activity of diclofenac and inhibit the activity of pentazocine. So, the addition of CNM may reduce the required dose of diclofenac that may help in the reduction of toxicity. Contrastingly co-administration with pentazocine may cause the requirement of higher dose to lead to increased toxicity. Hence, further studies are required to acknowledge these facts.

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**CONFLICT OF INTEREST:** Nil

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