Original Article

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Pharmacology Section

A Synergistic Approach to evaluate the Anti-Nociceptive Activity of a GABA Agonist with Opioids in Albino Mice

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ABSTRACT

Opioids constitute the first-line treatment for pain and they provide a potent analgesic effect, but they are also responsible for various adverse effects such as nausea, vomiting, sedation, constipation and respiratory depression, which seriously limit their use. The purpose of this study was to evaluate whether a GABA agonist which was given along with opioids at a minimal dose could elicit an anti-nociceptive activity in albino mice or not, as compared to morphine. Analgesia evaluation by using the acute pain model hotplate method was employed. The GABA agonists Gabapentin, Baclofen, Tiagabine and Vigabatrine with opioids Morphine and Tramadol, separately, at minimal doses, were given to mice and they were compared with a morphine analgesic dose. Morphine 3mg/kg showed a significant analgesic effect. This dose hot plate latency was taken as a standard and this was compared with all the test drugs which were used in this study. Morphine 1mg/kg (low dose) alone showed minimal antinociception, whereas in combination with a low dose GABA agonist, it showed significant antinociception. Tramadol 20mg/kg showed a significant analgesic effect and Tramadol 10mg/kg (low dose) showed a minimal analgesic effect, whereas the low dose Tramadol with the low dose GABA agonists in a combination showed a significant analgesic effect as that of Morphine 3mg/kg. The combination of a minimal dose of opioid and a GABA agonist has a significant anti nociceptive activity

Key Words: GABA, Opioids, Anti-nociceptive, Hot Plate

INTRODUCTION

Pharmacological treatments are undeniably the most common approach to treat pain. Earlier, mankind was dependent on herbs like Cichorium intybus and Solanum nigrum for hepatoprotection [1] and they were mostly dependent on opium for pain. Today, several pharmacological classes of drugs include a natural product prototype. Aspirin, atropine, ephedrine, digoxin, morphine, quinine, reserpine and tubocurarine are a few examples of the modern drugs which were originally discovered through the study of traditional cures and the folk knowledge of indigenous people [2]. Several peptide drugs are in the stages of preclinical and clinical development for the treatment of severe pain which is often associated with diseases such as cancer [3]. In the clinical practice, the recent advances have been based upon improved understanding of 'old' substances such as Morphine and at the same time, the research continues in the hope of finding the 'ideal' analgesic which is effective in most of the situations but without adverse effects [4]. The methods of treatment are different for acute and chronic pain. For acute pain, analgesics such as nonsteroidal anti-inflammatory drugs and opiates are commonly used, whereas chronic pain treatment constitutes a special category where drugs like tricyclic antidepressants, anti-convulsants, gamma-amino butyric acid agonists, local anaesthetic analogs and NMDA antagonists are employed [5]. The new GABA agonist anti-convulsant drugs increase the spectrum of the treatment and they represent the further steps with regards to the optimization of an individual's therapy [6].

Opioid analgesics are the drugs of choice for the treatment of severe pain. While treating patients with persistent pain, it is of particular interest whether the antinociceptive effect of the analgesic persists after its repeated administration. But the use of opioids in chronic pain treatment has led to the development of tolerance and dependence after its repeated administration. To overcome the tolerance to the analgesic effects of morphine, higher doses are necessary for adequate pain relief, but these are often accompanied by an undesirable physical dependence and side effects such as constipation, nausea and respiratory depression [7]. These problems limit the opioid dose and they result in inadequate analgesia. Therefore, non- opioid analgesics have been proposed to enhance the analgesic effect and to attenuate the side effects of opioids [8].

Hence, the present study was conducted to evaluate the synergistic anti-nociceptive activity of a GABA agonist with opioids in albino mice.

MATERIALS AND METHODS

This study was conducted in the Department of Pharmacology, Sri Ramachandra Medical College and Research Institute, Chennai, India. Prior permission was obtained from the institutional animal ethical committee.

ANIMALS

Male Swiss albino mice (25-30g) were housed at the Animal House, Sri Ramachandra University under 12h: 12h light: dark cycles at a controlled temperature with free access to pellet feed (Gold Mohar Ltd., Bangalore) and water. The experimental protocol was approved by the Institutional Animal Ethical Committee. The animals were divided into different groups, with each group comprising of six mice (n = 6). Each animal were used once for the experiment.

All the observations were made between 9 AM and 12 noon. The experiment was conducted in a noiseless room, with a room temperature of about 29-31^{0}C.

DRUG AND DOSAGE

All the drugs were obtained from the Ramachandra Hospital Pharmacy. They included Morphine, Tramadol Hydrochloride, Gabapentin, Baclofen, Tiagabine and Vigabatrine.

NOCICEPTIVE EVALUATION:

The hot – plate test:

The GABA agonist's analgesia evaluation by using the acute pain model hotplate method was preferred in this study because all the four limbs and even the tail of the animal are stimulated simultaneously [9]. Such heterotopic stimuli involving large body areas undoubtedly trigger diffuse noxious inhibitory controls with supraspinal origins [10,11]. So, it was decided that the nociceptive effect of the GABA agonists would be evaluated by using the hotplate method.

Before conducting the study, the Swiss albino mice were screened by sensitivity tests by placing the animals on the hot plate. Any animal that withdrew its hind paw or jumped in response in 5 seconds were rejected from the study. The animals were individually placed on a hotplate which was maintained at a constant temperature (52 ± 1^{o}C). The latency to the first sign of paw licking or jump response to avoid heat nociception was taken as an index of the nociceptive threshold with a cut off time of 15 sec. The nociceptive threshold was observed 0, 30, 60, 90 and 120 min after the drug administration.

The percentage of the maximum possible effect (MPE) of the antinociception was calculated as follows [12]:

$$\% \text{ MPE} = \frac{\text{Reaction time after treatment} - \text{Control reaction time}}{\text{Cut off time} - \text{Control reaction time}} \times 100$$

Experimental design:

Before their administration, Morphine and Tramadol were dissolved in 0.9% saline. Gabapentin, Baclofen, Tiagabine and Vigabatrin were tablet powdered and dissolved in distilled water. These solutions were diluted to the required strength and they were given orally by using a gastric tube, 30 min before Morphine 1mg/kg s.c or Tramadol 10mg/kg i.p were given and the antinociceptive effect was evaluated.

Test – I Analgesia Evaluation of Morphine and Tramadol

Group 1 Saline 1mL/kg (i.p) - Control

Group 2 Morphine 1mg/kg (S.C)

Group 3 Morphine 3 mg/kg (S.C)

Group 4 Tramadol 10 mg/kg (i.p)

Group 5 Tramadol 20 mg/kg (i.p)

Test – II Analgesia Evaluation of Morphine with Gabapentin

Group 1 Morphine 3 mg/kg (S.C)

Group 2 Gabapentin 10 mg/kg (Oral)

Group 3 Gabapentin 30 mg/kg (Oral)

Group 4 Gabapentin 90 mg/kg (Oral)

Test – III Analgesia Evaluation of Morphine with Baclofen

Group 1 Morphine 3 mg/kg (S.C)

Group 2 Baclofen 4 mg/kg (Oral)

Group 3 Baclofen 6 mg/kg (Oral)

Group 4 Baclofen 10 mg/kg (Oral)

Test – IV Analgesia Evaluation of Morphine with Tiagabine

Group 1 Morphine 3 mg/kg (S.C)

Group 2 Tiagabine 0.4 mg/kg (Oral)

Group 3 Tiagabine 0.8 mg/kg (Oral)

Group 4 Tiagabine 1.6 mg/kg (Oral)

Group 5 Tiagabine 2.4 mg/kg (Oral)

Test –V Analgesia Evaluation of Morphine with Vigabatrin

Group 1 Morphine 3 mg/kg (S.C)

Group 2 Vigabatrin 7.5 mg/kg (Oral)

Group 3 Vigabatrin 15 mg/kg (Oral)

Group 4 Vigabatrin 30 mg/kg (Oral)

Group 5 Vigabatrin 45 mg/kg (Oral)

Test – VI Analgesia Evaluation Morphine with GABA Agonists

Group 1 Morphine 3 mg/kg (S.C)

Group 2 Gabapentin 10 mg/kg (Oral) and Morphine1mg/kg (S.C)

Group 3 Baclofen 4 mg/kg (Oral) and Morphine 1mg/kg (S.C)

Group 4 Tiagabine 0.4 mg/kg (Oral) and Morphine 1mg/kg (S.C)

Group 5 Vigabatrin 7.5 mg/kg (Oral) and Morphine 1mg/kg (S.C)

Test -VII Analgesia Evaluation Tramadol with GABA Agonists

Group 1 Morphine 3 mg/kg (S.C)

Group 2 Gabapentin 10 mg/kg (Oral) and Tramadol 10mg/kg (i.p)

Group 3 Baclofen 4 mg/kg (Oral) and Tramadol 10mg/kg (i.p)

Group 4 Tiagabine 0.4 mg/kg (Oral) and Tramadol 10mg/kg (i.p)

Group 5 Vigabatrin 7.5 mg/kg(Oral) and Tramadol 10mg/kg(i.p)

RESULT

MORPHINE

Two doses were studied; Morphine 3 mg/kg showed a significant analgesic effect, which was taken as the standard for the hot plate latency and the results were compared with those of all the test drugs which were used in this study.

Morphine 1mg/kg showed minimal anti-nociception. This dose, in combination with a low dose GABA agonist showed significant antinociception.

TRAMADOL

Two doses were studied; Tramadol 20 mg/kg showed a significant

Dose	Morphine [13]	Tramadol [14]	Gabapentin [15]	Baclofen [16]	Tiagabine [17]	Vigabatrine [18]
I	1mg/kg(low)	10mg/kg(low)	10mg/kg	4mg/kg	0.4mg/kg	7.5 mg/kg
II	3mg/kg(high)	20mg/kg(high)	30mg/kg	6mg/kg	0.8mg/kg	15 mg/kg
III	-	-	90mg/kg	10mg/kg	1.6mg/kg	30 mg/kg
IV	-	-	-	-	2.4mg/kg	45 mg/kg

[Table/Fig-1]: Treatment Groups and Dose

analgesic effect which was also somewhat similar to that of Morphine 3 mg/kg. Tramadol 10 mg/kg showed a minimal analgesic effect as that of Morphine 1mg/kg. The low dose Tramadol with a low dose GABA agonist in combination showed a significant analgesic effect as that of Morphine 3 mg/kg.

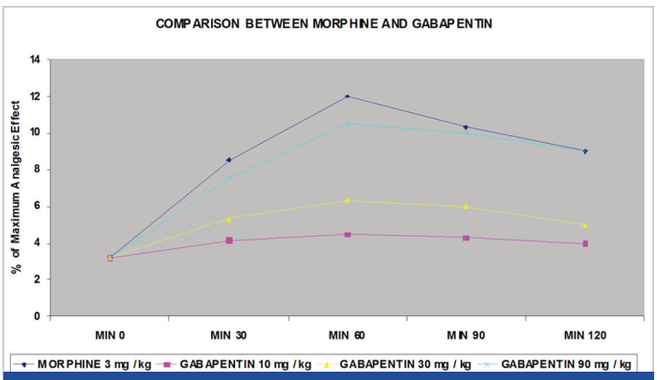
GABAPENTIN

Three doses were studied, 10mg (low dose), 30mg and 90mg and the results of these showed a dose dependent analgesic effect by using hotplate method. Gabapentin caused a dose dependent increase in the jumping or paw licking latency, which was significant at a 90 mg/kg dose level. This effect was comparable to that of Morphine 3 mg/kg.

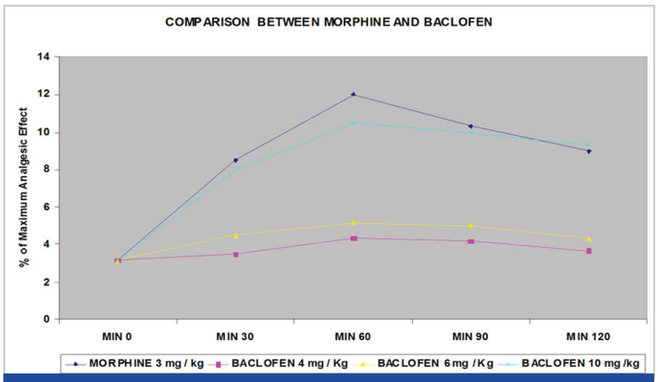
Low dose Gabapentin 10 mg/kg (Low Dose) with Morphine 1mg/kg (Low Dose) showed a significant analgesic effect as that of Morphine 3mg/kg. Low dose Gabapentin with Tramadol 10 mg/kg (low dose) showed a similar antinociceptive activity as that of Morphine 3 mg/kg.

BACLOFEN

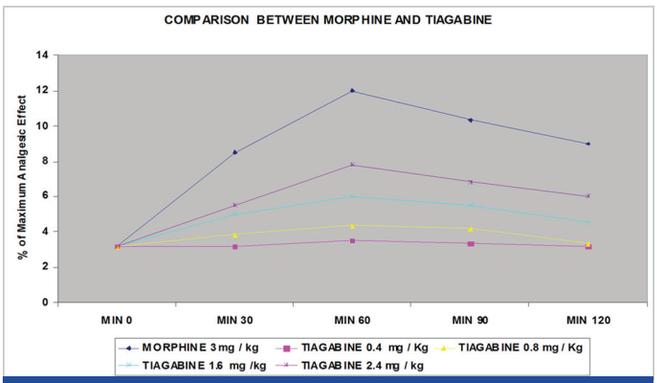
Three doses were studied, 4mg (low dose), 6mg and 10 mg/kg. The doses, 4mg and 6mg showed a minimal analgesic effect and Baclofen 10 mg/kg showed a significant analgesic effect. Baclofen showed a dose dependent analgesic effect and while



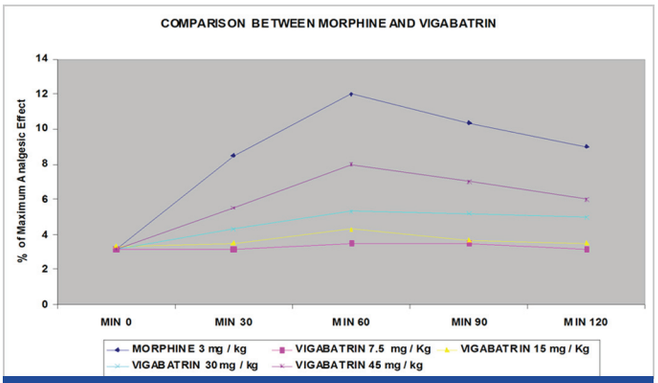
[Table/Fig-2]: Comparison between Morphine and Gabapenthin



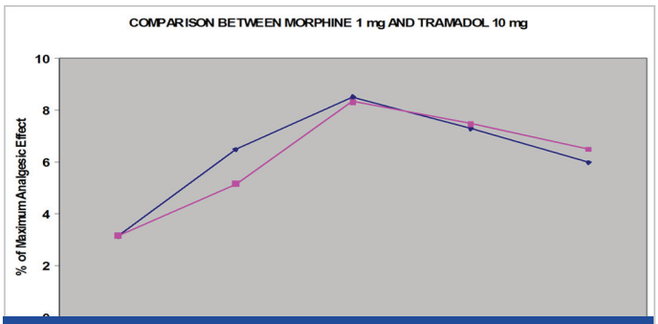
[Table/Fig-3]: Comparison between Morphine and Baclofen



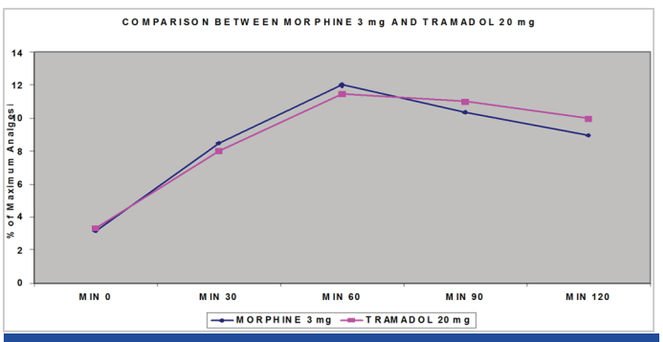
[Table/Fig-4]: Comparison between Morphine and Tiagabine



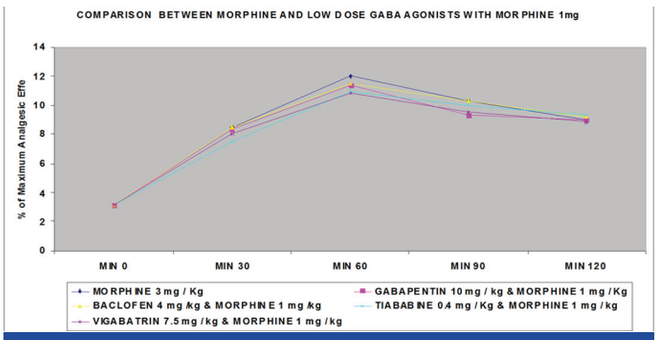
[Table/Fig-5]: Comparison between Morphine and Vigabatrine



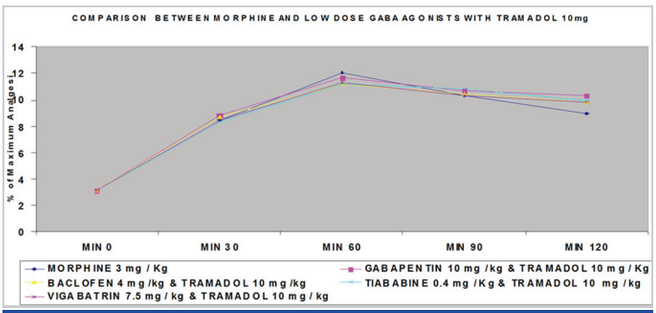
[Table/Fig-6]: Comparison between Morphine 1mg and Tramadol 10mg



[Table/Fig-7]: Comparison between Morphine 3mg and Tramadol 20mg



[Table/Fig-8]: Frequency of liver diseases



[Table/Fig-9]: Frequency of liver diseases

it was given in higher doses, the animal showed sedation and muscle weakness.

Low dose Baclofen 4 mg/kg with Morphine 1mg/kg showed a significant anti-nociceptive effect as that of Morphine 3 mg/kg. Low dose Baclofen with Tramadol 10 mg/kg showed a significant antinociceptive activity which was similar to that of Morphine 3 mg/kg.

TIAGABINE

Four doses were studied, 0.4 mg/kg, 0.8 mg/kg, 1.6 mg/kg and 2.4 mg/kg. Here, the doses, 0.4 mg/kg and 0.8 mg/kg showed no analgesic effect, but the higher doses of Tiagabine, 1.6 mg/kg and 2.4 mg/kg showed a minimal analgesic effect.

In case of a low dose combination, Tiagabine 0.4 mg/kg with Morphine 1mg/kg showed a significant anti-nociception which was similar to that of Morphine 3 mg/kg. Similarly, low dose Tiagabine 0.4 mg/kg with Tramadol 10mg/kg showed a significant antinociceptive activity as that of Morphine 3 mg/kg.

VIGABATRIN

Four doses were selected, the doses, 7.5 mg/kg and 15 mg/kg showed no analgesic effect. The higher doses of Vigabatrin, 30 mg/kg and 45 mg/kg showed a minimal antinociceptive activity in a dose dependent manner.

Low dose Vigabatrin 7.5 mg/kg with Morphine 1 mg/kg in combination showed a significant analgesic effect which was almost similar to that of Morphine 3 mg/kg. Low dose Vigabatrin with Tramadol 10 mg/kg showed a similar antinociceptive activity as that of Morphine 3 mg/kg.

DISCUSSION

Since anti-convulsants have been used for treating neuralgias, an interest has arisen to experimentally test the GABA agonists for their GABAergic mechanism of action of antinociception. Moreover, studies on Dextromethorphan and Midazolam alone or in combination have proven that they prevent the development of morphine induced tolerance and dependence. These effects can be related to the N-Methyl-D-Aspartate (NMDA) receptor antagonist behaviour of Dextromethorphan and the GABA-receptor agonist property of Midazolam [19]. In this study, acute pain evaluation by using the GABA agonists, Gabapentin, Baclofen, Tiagabine and Vigabatrin were studied by using the hotplate method. This study has shown that a maximum analgesic effect is present only at the basal time measurement of the hotplate method.

Morphine two doses 1mg/kg and 3 mg/kg showed an analgesic effect peak at 60mts, which was found to extend upto 120mts [Table/Fig 5].

Similarly, Tramadol 10 mg/kg and 20 mg/kg showed a significant analgesic effect as compared to that of Morphine and also the antinociceptive effect was more prolonged than that of Morphine, which helped in avoiding frequent dosing [Table/Fig 6]. The anti-nociceptive effect of Tramadol, in high doses, has shown a comparative effect with morphine in the hot-plate, formalin and the writhing analgesic models also [20].

Gabapentin is structurally related to GABA, a neurotransmitter that plays a role in pain transmission and modulation. Though Gabapentin does not bind to the GABA receptors, it has been shown recently, that it alters the release of GABA in the CNS [21]. The administration of oral Gabapentin 300 mg before ambulatory laparoscopic surgeries decreases the postoperative pain, analgesic requirement and the nausea [22]. Even though the real mechanism of action of these drugs was not known in this experiment, they showed a dose dependent, analgesic effect which could be compared to that of Morphine. Gabapentin caused a dose dependent increase in the jumping or paw licking latency, which was significant at a 90 mg/kg dose level ($P<0.05$). The effect started after 30 minutes of oral drug administration and it was maximum at 60 min. This effect was comparable to that of Morphine. The present study confirmed that Gabapentin had an analgesic action in an experimental acute pain model. A similar study was done on rats by Rakesh Dixit, et al., [15]. He compared the analgesic effect of Morphine with that of Gabapentin by using the hotplate method. Gabapentin and Morphine, in a low dose combination, showed a significant analgesic effect and the animals which were tested were quite normal. A similar effect was seen with low dose Tramadol in combination with Gabapentin. Such effects were reported in another study wherein an oral premedication with 300 mg Gabapentin reduced the postoperative pain and total morphine consumption [23]. Baclofen 4mg and 6mg did not exert an antinociceptive activity, while a higher dose, 10mg showed significant antinociception. Baclofen 4mg and 6mg did not produce motor incoordination, muscular hypotonia or ataxia. Baclofen 4mg and 6mg did not induce catalepsy, while a 10mg dose induced a state of mild sedation at 60min. A low dose combination with neither Morphine nor Tramadol, Baclofen 4mg did not have sedation.

A combination of low dose Morphine and low dose Baclofen showed a significant antinociceptive activity at 30 and 60 minutes. As both the drugs were in low doses, adverse effects were not seen. The animals were quite normal and there was no muscle weakness or sedation and they had a normal gait. The study by Cutting and Jordan (1975) reported that Baclofen exerted an antinociceptive activity and potentiate Morphine analgesia [24]. A similar effect was seen with Tramadol 10mg in combination with and the analgesic effect was prolonged.

This study determined that Tiagabine, a GABA uptake inhibitor, created a hot-plate allodynia effect in mice, which was significant in a dose-dependent manner. Similar reports were available from Laughlin T.M, et al., 2002 (A comparison of the anti-epileptic drugs tiagabine, lamotrigine, and gabapentin in mouse models of acute, prolonged and chronic nociception showed that gabapentin and lamotrigine produced antinociception in two mouse models of pain, an that an intra-thecal administration of tiagabine produced antinociception in all the three mouse models of pain) [17].

The higher the dose of Tiagabine, the animals were very active, while on testing, they showed only the jumping out of the hot plate effect. Low dose Tiagabine and Morphine showed a statistically significant antinociception. A similar effect was seen with Tramadol.

In this study, Vigabatrin showed a possible dose-dependent analgesic effect. A similar study was done by Alves ND; de Castro-Costa (1999) (a possible analgesic effect of vigabatrin in an animal experimental chronic neuropathic pain model) [18]. A combination of low dose Vigabatrin and low dose Morphine showed a significant analgesic effect. Low dose Tramadol with low dose Vigabatrin showed a statistically significant analgesic effect as that of Morphine 3 mg/kg.

The low dose GABA agonists with low dose Morphine [Table/Fig 7] and the synthetic opioid derivative, Tramadol [Table/Fig 8] also showed a significant analgesic effect.

The behaviour of the animals was quite normal in this low dose combination. The adverse effects of the opioid were not noticed in this dose and also, the GABA agonist's low doses did not have an analgesic effect; but in combination, it showed a significant anti-nociceptive effect and the adverse effect was expected to be minimal.

Tramadol appeared to produce less constipation and dependence than the equianalgesic doses of the strong opioids. Tramadol, in high doses, was found to increase the antinociception in mice, which is comparable to that of Morphine [20]. The analgesic potency of Tramadol is about 10% of that of Morphine, following its parenteral administration. Tramadol provides postoperative pain relief which is comparable to that of Pethidine, and the analgesic efficacy of Tramadol can further be improved by its combination with a GABA agonist, as per the present study. The subcutaneous administration of Tramadol also can provide a local anaesthesia which is equal to Lidocaine, with a longer pain-free period after the operation [25].

In this study, acute pain evaluation by using the hotplate method showed that the GABA agonists, Gabapentin, Baclofen, Tiagabine and Vigabatrin all had an anti-nociceptive effect in a dose-dependent manner. Even though these drugs had an anti-nociceptive effect individually, their clinical long term use and their adverse effects are yet to be studied. The combination of low dose Tramadol with a low dose GABA agonist showed a statistically significant antinociception and the effect was also sustained. Similar synergic studies of Gabapentin with Morphine which were done by Manzumeh-Shamsi Meimandi, et al., (2005) revealed an increased analgesic effect by the tail flick test. These results showed a less frequent dosing for chronic pain and lesser adverse effects than both groups of drugs individually [26].

CONCLUSION

All the GABA agonists which were used in this study (Gabapentin, Baclofen, Tiagabine and Vigabatrin) had an analgesic effect in a dose dependent manner. But the use of these drugs as analgesics for a long term clinical use for severe pain needs further studies.

Combinations of low dose GABA agonists with low dose Morphine or Tramadol showed a very good analgesic effect in mice. Tramadol has less adverse effects than Morphine and so, the low dose GABA agonists and Tramadol in a low dose combination can be tried for chronic or severe pain, but this needs further clinical trials to prove it.

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