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ANTINOCICEPTIVE ACTIVITY OF NON-ANALGESIC AGENTS AND THEIR INTERACTIONS WITH TRAMADOL AND DICLOFENAC IN RATS

DR. RAJANISH KUMAR SANKDIA* AND DR. SHILPA N. KAORE

Department of Pharmacology, Peoples College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh 462037

ABSTRACT

Objective of this work is to study the antinociceptive activity of haloperidol, metoprolol, metoclopramide, venlafaxine and their interactions with tramadol and diclofenac. Antinociceptive action of haloperidol (1, 2 mg/kg), metoprolol (3, 5 mg/kg), metoclopramide (2, 5 mg/kg) and venlafaxine (5, 10 mg/kg) were studied in rats (tail flick and tail immersion tests). The sub-analgesic doses of haloperidol, metoprolol, metoclopramide and venlafaxine were combined with sub-analgesic doses of tramadol, diclofenac to further study their antinociceptive effects. The antinociceptive action of test drugs were found only at higher doses, for haloperidol (2 mg/kg), metoprolol (5 mg/kg), metoclopramide (5 mg/kg) and venlafaxine (10 mg/kg); that was statistically significant. When a sub-analgesic dose of test drugs were combined with sub-analgesic doses of tramadol, diclofenac, the combination resulted in a significant antinociceptive effect. Observations from our study indicate that various non-analgesic drugs may prove as alternative strategies for pain management in practice; possibly for adjuvant use.

KEY WORDS: **Antinociceptive activity, tail flick method, tail immersion test**

DR. RAJANISH KUMAR SANKDIA
Department of Pharmacology, Peoples College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh 462037

***Corresponding author**

INTRODUCTION

Pain is the most common symptom experienced by mankind. International association for the study of pain defines pain as an "unpleasant sensory and emotional experience with actual or potential tissue damage[1]." Every individual experiences pain in one or various forms in their life time. Pain is frequently classified as physiological and pathological pain which includes inflammatory and neuropathic pain. Acute pain has a sudden onset and recedes during the healing process. According to Woolf, there are three classes of pain : nociceptive pain, inflammatory pain which is associated with tissue damage and the infiltration of immune cells, and pathological pain which is a disease state caused by damage to the nervous system (neuropathic pain) or by its abnormal function (dysfunctional pain, like in fibromyalgia, irritable bowel syndrome, tension type headache)[2, 3]. The principal objective of alleviating pain is to remove the cause of pain, but it is not always possible to do so, hence, analgesics are used for the symptomatic treatment or relief of pain[4]. Anti-inflammatory, antipyretic, and analgesic agents like NSAIDs (non-steroidal anti-inflammatory drugs) and opioids are most common analgesic agents available for pain management. Opioids are very effective in acute pain, their effectiveness is limited under chronic pain conditions, including chronic inflammatory pain, due to its ability to cause physical and psychological dependence, as well as drug abuse[4]. Chronic pain is troublesome because it persists long after recovery from an injury and is often refractory to common analgesic agents, including NSAIDs and opiates[5]. Various non-analgesic drugs like antipsychotics[6], adrenergic receptor antagonists[7], prokinetic[8] and antidepressants[9] have shown antinociceptive action, in addition. Thus, this study was undertaken to explore antinociceptive action of some antipsychotic (haloperidol), beta blocker (metoprolol), and prokinetic agent (metoclopramide), antidepressant (venlafaxine) and their interactions with tramadol and diclofenac.

MATERIALS & METHODS

The study was carried out on rats of either sex 150-250 gm, maintained under standard laboratory conditions. The experimental protocol was approved by the Institutional Animal Ethics Committee and executed according to the CPCSEA guidelines (Committee for the Purpose of Control and Supervision of the Experiments on Animals). The doses of these drugs were concluded by trial and error method taking the drugs in varying dose range. The doses explored for the antinociceptive action of drugs were as follows: haloperidol (1, 2 mg/kg), metoprolol (3, 5 mg/kg), metoclopramide (2, 5 mg/kg) and venlafaxine (5, 10 mg/kg) for tail flick and tail immersion tests in rats. Further, the sub-analgesic doses of haloperidol (1 mg/kg), metoclopramide (2 mg/kg), metoprolol (3 mg/kg), venlafaxine (5 mg/kg) were combined with sub-analgesic doses of tramadol (10 mg/kg) and diclofenac (5 mg/kg) for further exploration of their antinociceptive effects using the mentioned in-vivo techniques.

The pre - screened animals were divided into groups of 6 rats each for antinociceptive activity (n=6).

Group I	: Control	(distilled water, i.p.)
Group II	: Haloperidol	(1, 2 mg/kg bw, i.p.)
Group III	: Metoprolol	(3, 5 mg/kg bw, i.p.)
Group IV	: Metoclopramide	(2, 5 mg/kg bw, i.p.)
Group V	: Venlafaxine	(5, 10 mg/kg bw i.p.)
Group VI	: Diclofenac	(5, 10 mg/kg bw, i.p.)

Group VII : Tramadol (10, 25 mg/kg bw, i.p.)

Determination of analgesic activity

In all the groups the antinociceptive test were performed and recorded as baseline (0 min) and at time intervals of 15, 30, 60, 120 min after the administration of drugs for further analysis. Antinociceptive activity was measured by using two methods.

1. Tail flick method

Analgesic activity was measured by the tail flick method, using the analgesiometer as described by D'Armour and Smith[10]. Six rats weighing 150-250 grams were selected and the reaction time (tail flick response) noted for all rats. Rats not exhibiting any response till 10 seconds were excluded to avoid any injury to its tail[11].

2. Tail immersion test

After intraperitoneal injection of the test substance, the animal tail was immersed in the hot water bath at a temperature of 55^0 C. The time until a typical reaction- a violent jerk of the tail, was noted[12].

Statistical analysis

The results were expressed as Mean±SD, paired't' test were employed for comparison between the two means as a measure of significance. One-way ANOVA followed by Tukey-HSD test of significance was applied for multiple comparisons amongst different groups. P Value of <0.05 was regarded as a statistically significant value.

RESULTS

In the distilled water treated animals there were no significant changes in hot water immersion test or tail flick method during the entire test period of 2 hrs.

1. Effect of test drugs on tail flick latency in tail flick method

Haloperidol (1 mg/kg), metoclopramide (2 mg/kg), metoprolol (3 mg/kg) and venlafaxine (5 mg/kg) showed no statistically significant increase in tail flick latency period as compared to the baseline value in rats, on the tail flick method. But at higher doses, these drugs significantly increased tail flick latency period as compared to the baseline value in rats. This was noted at dose described in parenthesis; for haloperidol (2 mg/kg), metoprolol (5 mg/kg), metoclopramide (5 mg/kg) and venlafaxine (10 mg/kg); that was statistically significant. Onset of analgesic activity was at 30 min. and duration of action 2 hrs for haloperidol (2 mg/kg), metoclopramide (5 mg/kg) and venlafaxine (10 mg/kg) while metoprolol (5 mg/kg) showed analgesic activity at 15 min. that continued for duration 1 hr that was statistically significant.

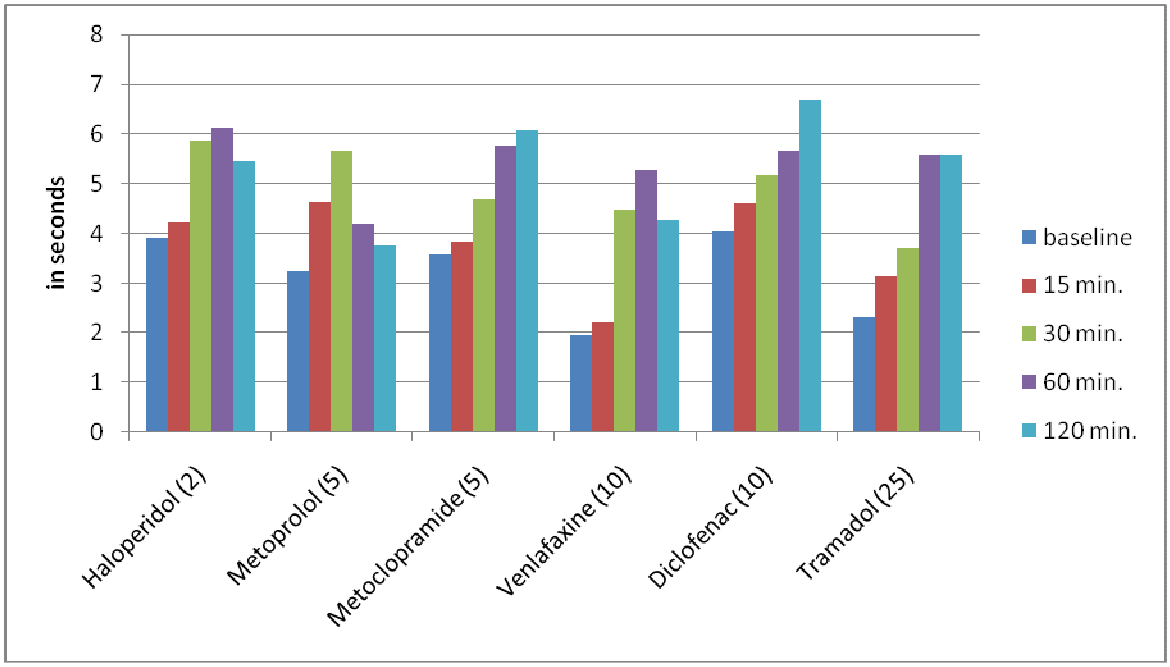
Table1

Effect of different test drugs on tail flick latency at different time intervals at varying doses of drugs

Drug & dose (mg/kg)	Tail flick latency in seconds Post drug time (in min)					P Value
	0	15	30	60	120	
Haloperidol (1)	3.87± 0.50	3.95± 0.48	3.93± 0.49	3.92± 0.49	3.83± 0.50	0.993
Haloperidol (2)	3.92± 0.49	4.23± 0.32	5.87± 0.72*	6.11±0.48 *	5.45± 0.48*	0.000**
Metoprolol (3)	4.2± 0.41	4.3± 0.42	4.1± 0.39	3.9± 0.38	3.8± 0.37	0.191
Metoprolol (5)	3.23± 0.66	4.62± 0.42*	5.65± 0.38*	4.2± 0.25*	3.75± 0.39	0.000**
Metoclopramide (2)	4.1± 0.39	3.9± 0.38	3.7± 0.36	3.8± 0.37	3.9± 0.38	0.461
Metoclopramide (5)	3.57± 0.55	3.82± 0.45	4.68± 0.46*	5.75± 0.39*	6.08± 0.40*	0.000**
Venlafaxine (5)	4.32± 0.42	4.35± 0.42	4.38± 0.42	4.4± 0.41	4.4± 0.41	0.996
Venlafaxine (10)	1.95± 0.55	2.2± 0.59	4.47± 0.66*	5.28± 0.61*	4.26± 0.55*	0.000**
Diclofenac (5)	3.4± 0.33	3.6± 0.35	3.3± 0.32	3.2± 0.31	3.2± 0.31	0.206
Diclofenac (10)	4.03± 0.39	4.6± 0.46	5.18± 0.49*	5.65± 0.38*	6.7± 0.43*	0.000**
Tramadol (10)	3.38± 0.32	3.4± 0.33	3.36± 0.32	3.4± 0.33	3.4± 0.33	0.999
Tramadol (25)	2.32± 0.57	3.15± 0.51	3.7± 0.45*	5.58± 0.53*	5.57± 0.53*	0.000**

** p value < 0.05, ** p value < 0.005*

Figure 1
Effect of test drugs on tail flick latency in tail flick method



2. Effect of test drugs on reaction time in tail immersion method

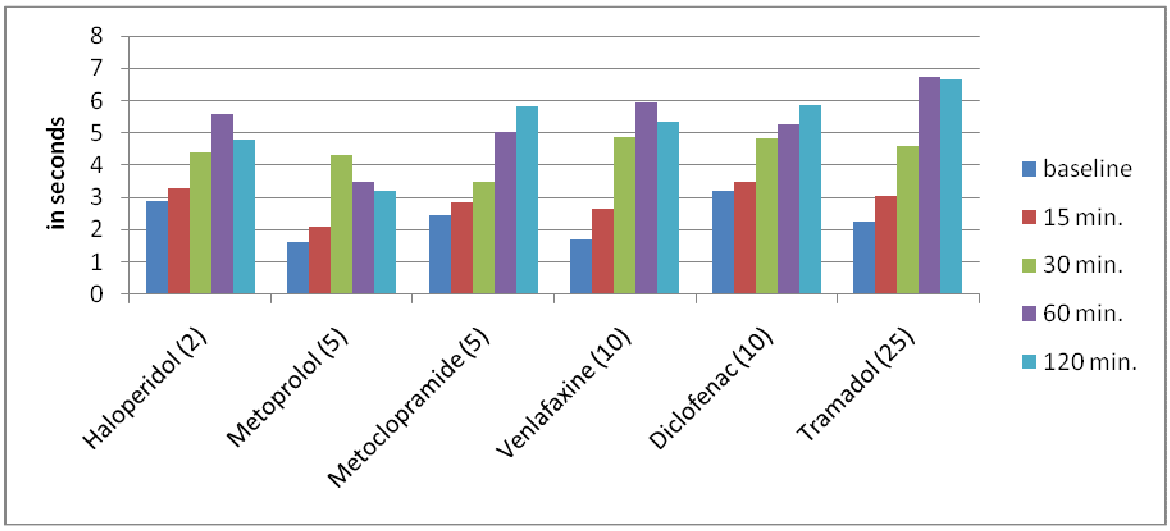
Haloperidol (1 mg/kg), metoprolol (3 mg/kg), metoclopramide (2 mg/kg) and venlafaxine (5 mg/kg) showed no statistically significant increase in reaction period as compared to the baseline value in rats, in the tail immersion method. Haloperidol (2 mg/kg), metoprolol (5 mg/kg), metoclopramide (5 mg/kg) and venlafaxine (10 mg/kg) showed significant increase in reaction time as compared to the baseline value in rats that was statistically significant. Onset of analgesic activity was at 30 min. and duration of action 2 hrs for haloperidol (2 mg/kg), metoclopramide (5 mg/kg) and venlafaxine (10 mg/kg) and metoprolol (5 mg/kg)); that was statistically significant.

Table2
Effect of different test drugs on reaction time in tail immersion method at different time intervals in varying drug doses

Drug & dose (mg/kg)	Tail flick latency in seconds Post drug time (in min)					P value
	0	15	30	60	120	
Haloperidol (1)	4.2± 0.41	4.1± 0.4	3.9± 0.38	3.78± 0.36	3.8± 0.37	0.260
Haloperidol (2)	2.9± 0.53	3.29± 0.49	4.4± 0.47*	5.6± 0.46*	4.8± 0.45*	0.000**
Metoprolol (3)	3.92± 0.38	3.75± 0.36	3.54± 0.34	3.87± 0.37	3.32± 0.32	0.430
Metoprolol (5)	1.61± 0.53	2.1± 0.58	4.32± 0.63*	3.5± 0.44*	3.2± 0.50*	0.000**
Metoclopramide (2)	3.9± 0.38	3.9± 0.38	3.4± 0.33	3.7± 0.36	3.8± 0.37	0.135
Metoclopramide (5)	2.46± 0.54	2.87± 0.62	3.47± 0.64*	5.01± 0.47*	5.82± 0.51*	0.000**
Venlafaxine (5)	3.75± 0.36	3.93± 0.38	3.86± 0.37	3.72± 0.36	3.84± 0.37	0.861
Venlafaxine (10)	1.72± 0.53	2.65± 0.61	4.87± 0.67*	5.93± 0.63*	5.34± 0.61*	0.000**
Diclofenac (5)	4.42± 0.43	4.51± 0.44	4.43± 0.43	4.52± 0.44	4.5± 0.44	0.990
Diclofenac (10)	3.2± 0.66	3.5± 0.64	4.84± 0.37*	5.28± 0.46*	5.85± 0.51*	0.000**
Tramadol (10)	3.85± 0.37	3.87± 0.37	3.76± 0.36	3.81± 0.37	3.74± 0.36	0.966
Tramadol (25)	2.26± 0.59	3.06± 0.52	4.59± 0.55*	6.75± 0.34*	6.64± 0.33*	0.000**

**** p value < 0.05, ** p value < 0.005***

Figure 2
Effect of test drugs on reaction time in tail immersion method



3. Effect of combined treatment on tail flick latency in tail flick method

Sub-analgesic dose of haloperidol (1 mg/kg), metoprolol (3 mg/kg), metoclopramide (2 mg/kg) and venlafaxine (5 mg/kg) and subanalgesic dose of tramadol (10 mg/kg) and diclofenac (5 mg/kg) were explored further. With subanalgesic dose of tramadol (10 mg/kg), all test drugs in subanalgesic doses showed analgesic activity and were statistically significant. While with subanalgesic dose of diclofenac (5 mg/kg), all test drugs in subanalgesic doses exhibited no analgesic activity; except metoprolol that showed significant analgesic activity in combination.

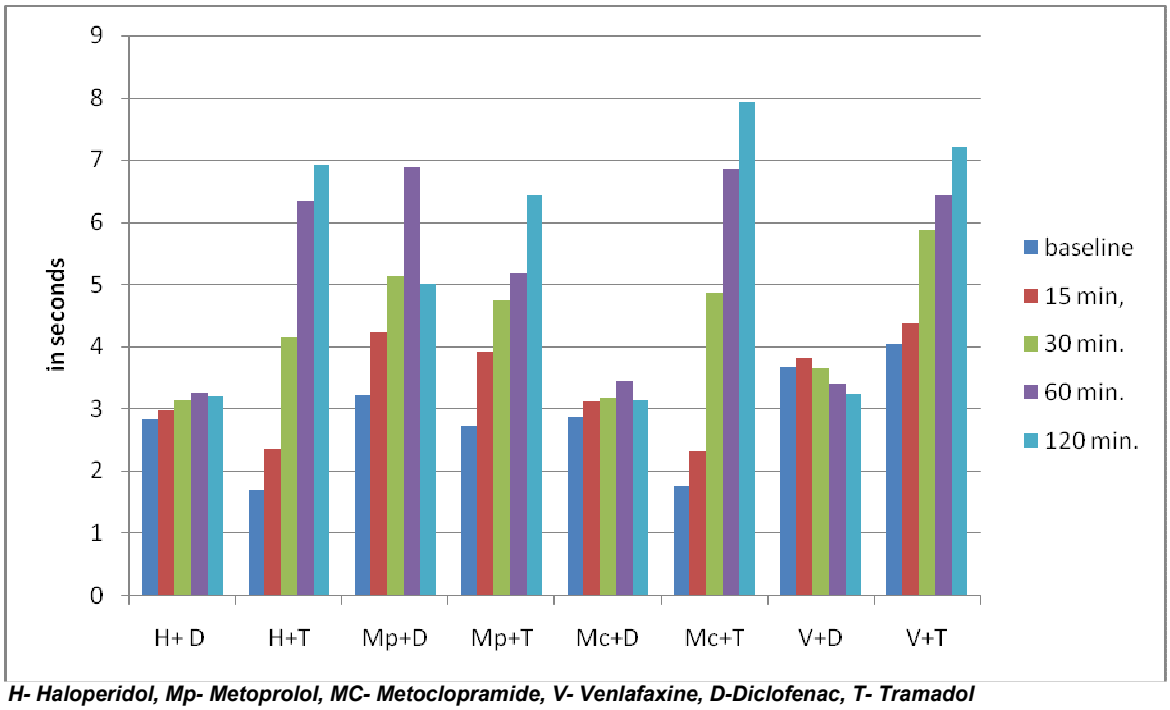
Table 3
Effect on tail flick latency after combined treatment of test drugs with diclofenac and tramadol at different time intervals

Drug (mg/kg)	Tail flick latency in seconds Post drug time (in min)					P
		15	30	60	120	
H+ Diclofenac	2.82± 0.53	2.97± 0.52	3.14± 0.5	3.25± 0.49	3.19± 0.5	0.586
H+Tramadol	1.69± 0.55	2.35± 0.59	4.13± 0.42*	6.35± 0.35*	6.93± 0.3*	0.000**
M+ Diclofenac	3.21± 0.49	4.23± 0.39*	5.12± 0.51*	6.87± 0.35*	5.01± 0.49*	0.000**
M+Tramadol	2.71± 0.54	3.91± 0.43*	4.73± 0.41*	5.16± 0.51*	6.43± 0.36*	0.000*
MC+ Diclofenac	2.87± 0.53	3.12± 0.50	3.17± 0.5	3.43± 0.45	3.14± 0.50	0.446
MC+Tramadol	1.76± 0.56	2.31± 0.59	4.87± 0.42*	6.85± 0.33*	7.93± 0.25*	0.000**
V+ Diclofenac	3.66± 0.41	3.81± 0.44	3.64± 0.4	3.39± 0.38	3.24± 0.39	0.138
V+Tramadol	4.03± 0.43	4.36± 0.42	5.87± 0.47*	6.43± 0.35*	7.21± 0.27*	0.000**

**** p value < 0.05, ** p value < 0.005***
H- Haloperidol, M- Metoprolol, MC- Metoclopramide, V- Venlafaxine

Figure 3

Effect on tail flick latency after combined treatment of test drugs with diclofenac and tramadol at different time intervals



H- Haloperidol, Mp- Metoprolol, MC- Metoclopramide, V- Venlafaxine, D-Diclofenac, T- Tramadol

4. Effect of combined treatment on reaction time in tail immersion method

Sub-analgesic dose of haloperidol (1 mg/kg), metoprolol (3 mg/kg), metoclopramide (2 mg/kg) and venlafaxine (5 mg/kg) and subanalgesic dose of tramadol (10 mg/kg) and diclofenac (5 mg/kg) was explored further. With subanalgesic dose of tramadol (10 mg/kg), all test drugs in subanalgesic doses showed analgesic activity that was statistically significant. While with subanalgesic dose of diclofenac (5 mg/kg), all test drugs in subanalgesic doses exhibited no analgesic activity; except metoprolol that showed significant analgesic activity in combination.

Table4

Effect on reaction time in tail immersion method after combined treatment of test drugs with diclofenac and tramadol at different time intervals

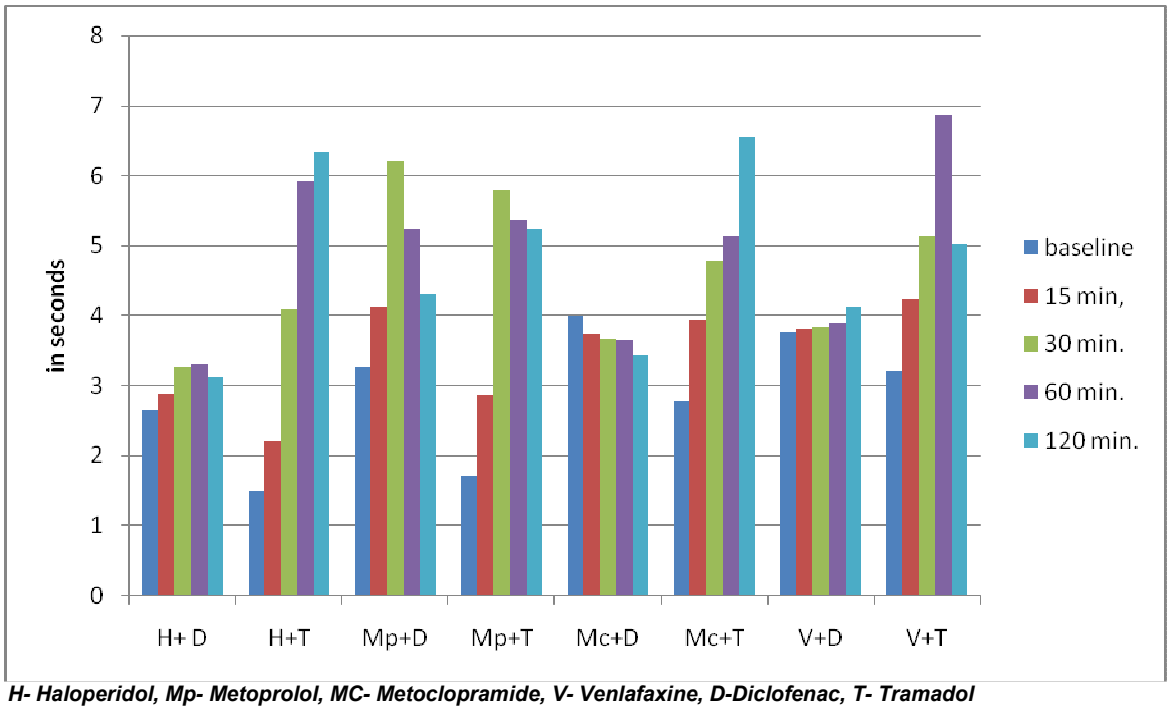
Drug (mg/kg)	Tail flick latency in seconds Post drug time (in min)					P
		15	30	60	120	
H+ Diclofenac	2.63± 0.54	2.87± 0.52	3.26± 0.50	3.3± 0.49	3.12± 0.51	0.156
H+Tramadol	1.49± 0.51	2.2± 0.66	4.08± 0.48*	5.92± 0.55*	6.34± 0.35*	0.000**
M+ Diclofenac	3.25± 0.65	4.12± 0.49	6.2± 0.37*	5.23± 0.51*	4.3± 0.45*	0.000**
M+Tramadol	1.71± 0.53	2.86± 0.62*	5.78± 0.66*	5.36± 0.61*	5.23± 0.35*	0.000**
MC+ Diclofenac	3.99± 0.39	3.73± 0.37	3.66± 0.31	3.65± 0.36	3.43± 0.34	0.138
MC+Tramadol	2.76± 0.52	3.94± 0.44*	4.78± 0.67*	5.13± 0.60*	6.55± 0.37*	0.000**
V+ Diclofenac	3.76± 0.39	3.81± 0.38	3.83± 0.37	3.89± 0.35	4.11± 0.33	0.511
V+Tramadol	3.21± 0.66	4.23± 0.31*	5.12± 0.62*	6.87± 0.36*	5.01± 0.59*	0.000**

**** p value < 0.05, ** p value < 0.005***

H- Haloperidol, M- Metoprolol, MC- Metoclopramide, V- Venlafaxine

Figure 4

Effect on reaction time in tail immersion method after combined treatment of test drugs with diclofenac and tramadol at different time intervals



H- Haloperidol, Mp- Metoprolol, MC- Metoclopramide, V- Venlafaxine, D-Diclofenac, T- Tramadol

DISCUSSION

In the present study, we had explored the antinociceptive actions of non-analgesic drugs for their antinociceptive action in two models of pain in experimental animals. Our findings suggest that haloperidol (antipsychotic), metoprolol (antiadrenergic), metoclopramide (prokinetic agent) and venlafaxine (antidepressants) exhibited antinociceptive action in experimental models. Our observations are in accordance with the results of various clinical and animal studies[6, 7, 8, 9]. Exploration of test drugs suggest that the onset of analgesic activity was at 30 min. and duration of action 2 hrs for haloperidol (2 mg/kg), metoclopramide (5 mg/kg) and venlafaxine (10 mg/kg) while metoprolol (5 mg/kg) showed onset analgesic activity at 15 min. that persisted for 1 hour. Haloperidol exhibited statistically significant antinociceptive effect at 2 mg/kg dose that was in accordance with other study by Cendan et al.[6], 2005. Subanalgesic dose of haloperidol produced additive antinociceptive effect when combined with subanalgesic dose of tramadol. Observations from a study reported haloperidol to potentiate antinociception of morphine in the rat, possibly by acting as sigma receptor antagonist[13]. σ1 receptors directly associate with opioid receptors and that through this association, σ-selective antagonists can potentiate opioid-induced cell signaling[13]. Further, a study found haloperidol to disrupt antinociceptive tolerance and physical dependence of opioid by inhibiting Ca2 /calmodulin-dependent protein kinase II (CaMKII) (Yang et al.[14] 2011). Evidences from other studies also suggest that supraspinal and spinal inhibition of CaMKII, not only prevented but also reversed opioid-antinociceptive tolerance and physical dependence in several rodent models[15, 16] . These data support a critical role of CaMKII in the development and maintenance of opioid tolerance and dependence. Furthermore, inhibiting CaMKII by chemical inhibitors, small interfering RNA, and gene deletion methods

attenuated opioid-induced hyperalgesia, a clinical and experimental phenomenon that is highly relevant for tolerance[17]. CaMKII can phosphorylates the NMDA receptor[18, 19], leading to enhanced NMDA receptor activity and influx of Ca^{2+} through the channels[20]. The latter, in turn, results in more activation of calmodulin[21, 22] and autophosphorylation of CaMKII at position Thr286[23]. This positive feedback between CaMKII and NMDA receptor can serve as one mechanism for sustained activation of CaMKII and NMDA receptors in opioid tolerance and dependence. Experimentally, by combining opioids (morphine, pentazocine) with NMDA receptor antagonists (ketamine, memantine), tolerance is impaired and analgesia is enhanced without an increase in the dose of opioid[24]. Hence therapeutically memantine may serve to dissociate analgesic action of morphine from tolerance and dependence that contribute to its abuse potential[25].

Analgesic dose of metoprolol is very low as compared to its anti-adrenergic dose range (5-10 mg/day), and hence may justify use as an adjuvant analgesic. Studies indicate the possible mechanisms for the role of β -adrenergic receptors in nociception[26, 27], based on decrease of the adenylyl cyclase activity[28], reduction of intracellular cAMP and inhibition of voltage sensitive calcium and sodium channels activity[26, 27, 29], that may lead to a decrease of neuronal excitability. Additionally, β -blockers are able to suppress IL-6[30], TNF α[31] release and to inhibit the phospholipase A[32], which could be strongly linked to analgesia[33]. While with subanalgesic dose of diclofenac (5 mg/kg), all test drugs in subanalgesic doses exhibited no analgesic activity; except metoprolol that showed significant analgesic activity in combination. Subanalgesic dose of metoprolol (3 mg/kg) showed significant analgesic activity in combination with subanalgesic dose of diclofenac (5 mg/kg), supported by other studies, showing similar results (Patel et al., 2009)[7]. Also subanalgesic dose of metoprolol (3 mg/kg) showed significant analgesic activity in combination with subanalgesic dose of tramadol (10 mg/kg), supported by other studies, showing decrease in hepatic metabolism of opioids by β-blockers to extend the analgesic effect, and a reduction in opioid tolerance[34]. Metoclopramide was found to exhibit antinociceptive effect at 5 mg/kg, that was in accordance with the reported analgesic effect by Ceyhan et al.[35], 2005. The antinociceptive action at 5 mg/kg was significantly higher than other study groups and comparable with antinociceptive action of tramadol that may possibly justify its use as an alternative to tramadol and possibly due to reduction in adverse drug reactions as compared to opioids. The pharmacological actions of metoclopramide are mediated centrally by antagonizing dopamine D2 receptors[36, 37, 38, 39] . The drug also possesses serotonergic effects[40] and indirect cholinergic activity[41]. It has been suggested that the analgesic effect of metoclopramide is mediated through the release of prolactin hormone[42]. This action could also be mediated centrally as most of the pharmacological effects of metoclopramide such as anti-emesis and sedation are of central origin[36, 37, 38, 39, 43, 44] . As far as the mechanism of antinociception for metoclopramide is understood, it may be possibly be due to the interaction with D2 receptors, and not 5-HT3 receptors as shown in study by Kamerman et al 2007[8].

Subanalgesic dose of Metoclopramide produced additive antinociceptive effect when combined with subanalgesic dose of tramadol (metoclopramide 2 mg/kg with tramadol 10 mg/kg), as subanalgesic dose of both will have less side-effects and effectiveness for preventing pain. Ceyhan et al.[35] 2005, also showed the same effects in animal models (metoclopramide 2.5 mg/kg with tramadol 22.5 mg/kg), thus supporting metoclopramide as an alternative to tramadol in management of pain. Several antidepressants are known to possess intrinsic analgesic acitivity[45, 46]. Venlafaxine, a widely used newer generation antidepressant, has been cited as a promising drug for neuropathic pain control[47, 48]. Venlafaxine mainly block reuptake of the NA and 5-HT in descending pain pathways[49], that possibly dictates the antinociceptive action. As

chronic pain is usually associated with symptoms of depression, venlafaxine is likely to prove more beneficial in such patients for exerting both analgesics as well as antidepressant action[50]. In our study, venlafaxine showed an antinociceptive effect at 10 mg/kg, supported by other studies, showing similar results (Jha, et al.[9] 2006) and also mitigated thermal hyperalgesia in rats (Lang et al.[51] 1996). Analgesic dose of Venlafaxine is very low as compared to antidepressant dose range (75-375 mg/day) and adverse drug reactions are minimal, thus justifying its use as an adjuvant analgesic. Studies have shown that tramadol activates monoaminergic spinal inhibition of pain by inhibiting noradrenaline and serotonin uptake and, to a lesser extent, dopamine uptake[52,53]. Venlafaxine exhibited additive antinociceptive effect when combined with tramadol.

CONCLUSION

Observations from our study indicate that various non-analgesic drugs may prove as alternative strategies for pain management in practice; possibly for adjuvant use. Antidepressants may be a boon, when used as an analgesic especially in chronic pain. Evidence from studies suggests involvement of opioid pathways or interaction with opioid receptors as mechanism for analgesia even for drugs not belonging to typical opioids e.g. haloperidol. In addition, haloperidol is found to disrupt antinociceptive tolerance and physical dependence of opioid by inhibiting Ca2/calmodulin-dependent protein kinase II (CaMKII). Metoprolol, also is linked to analgesia, the plausible mechanisms underlying may be decrease in adenylyl cyclase activity, reduction of intracellular cAMP and inhibition of voltage sensitive calcium and sodium channels, suppression of IL-6, TNF α release and inhibition of phospholipase A. Also decrease in hepatic metabolism of opioids by β-blockers to extend the analgesic effect, and a reduction in opioid tolerance. Thus, further studies are required to explore these drugs for analgesia and its utility to overcome tolerance and dependence of opioid analgesic and could possibly prove a drug with better tolerable profile.

REFERENCES

1. Terry J. Baumann : Pain management : Joseph T. Dipiro et al :Pharmacotherapy – A pathophysiologic approach, 6th edition, McGraw HILL, Newyork, 2005, Chapter 58 : 1089-1090.
2. Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E. Towards a mechanism-based classification of pain?. Pain. 1998;77(3):227–9.
3. Woolf CJ. What is this thing called pain? . Journal of Clinical Investigation. 2010; 120(11):3742–4.
4. Yadlovskyi oleh. Antinociceptive activity of a new non—opioid analgesic pyrodazol and ketorolac. Int J Pharm Bio Sci 2014 Jan; 5(1): (P) 219 - 224
5. Barett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 23 rd ed. New Delhi: Tata McGraw Hill Education Private Limited; 2010. p . 168.
6. Cruz M. Cendán, José M. Pujalte,Enrique Portillo-Salido,José M. Baeyens Antinociceptive effects of haloperidol and its metabolites in the formalin test in mice. Psychopharmacology. November 2005, Volume 182, Issue 4, pp 485-493
7. Patel S, Shah J, Mistry K, Contractor R, Nagda C, Patel V. Antinociceptive activity of tadalafil and adrenergic agents in the writhing test in mice. Pharmacologyonline 1: 533-539 (2009)
8. Kamerman PR, Becker N, Fick LG.Interactions between metoclopramide and morphine: enhanced antinociception

and motor dysfunction in rats. Clin Exp Pharmacol Physiol. 2007 Jan-Feb;34(1-2):106-12.
9. Jha PK, Mazumdar B, Bhatt JD. Analgesic activity of venlafaxine and its interaction with tramadol, celecoxcib and amlodipine in mice. Indian J Pharmacol. 2006; 38(3): 181-184.
10. D'Armour FE, Smith DL. A method for determining loss of pain sensation. J Pharmacol Exp Ther 1941;72:74-9.
11. Ramabadran K, Bansinath M. A critical analysis of the experimental evaluation of nociceptive reactions in animals. Pharmaceutical Res 1986;3:263-70.
12. K.V.Shivanand Reddy1, J.Balaji, Umakant Patil. Antinociceptive Activity of Selective Serotonin Reuptake Inhibitorsin Albino Rats. International Medical Journal of Students' Research, October 2011, Volume 1, Issue 1
13. Felix J. Kim, Ivanka Kovalyshyn, Maxim Burgman, Claire Neilan, Chih-Cheng Chien, and Gavril W. Pasternak. σ1 Receptor Modulation of G-Protein-Coupled Receptor Signaling: Potentiation of Opioid Transduction Independent from Receptor Binding. Mol Pharmacol. Apr 2010; 77(4): 695–703.
14. Yang C, Chen Y, Tang L, Wang ZJ. Haloperidol Disrupts Opioid-Antinociceptive Tolerance and Physical Dependence. The Journal Of Pharmacology And Experimental Therapeutics.2011.sep;338(1):164-172.
15. Wang ZJ, Tang L, and Xin L (2003) Reversal of morphine antinociceptive tolerance by acute spinal inhibition of Ca(2_)/calmodulin-dependent protein kinase II. Eur J Pharmacol 465:199–200.
16. Tang L, Shukla PK, Wang LX, and Wang ZJ (2006a) Reversal of morphine antinociceptive tolerance and dependence by the acute supraspinal inhibition of Ca(2_)/ calmodulin-dependent protein kinase II. J Pharmacol Exp Ther 317:901–909.
17. Chen Y, Yang C, and Wang ZJ (2010) Ca2_/calmodulin-dependent protein kinase II alpha is required for the initiation and maintenance of opioid-induced hyperalgesia. J Neurosci 30:38–46.
18. McGlade-McCulloh E, Yamamoto H, Tan SE, Brickey DA, and Soderling TR (1993) Phosphorylation and regulation of glutamate receptors by calcium/calmodulindependent protein kinase II. Nature 362:640–642.
19. Lau LF and Huganir RL (1995) Differential tyrosine phosphorylation of N-methyl- D-aspartate receptor subunits. J Biol Chem 270:20036–20041.
20. Kitamura Y, Miyazaki A, Yamanaka Y, and Nomura Y (1993) Stimulatory effects of protein kinase C and calmodulin kinase II on N-methyl-D-aspartate receptor/ channels in the postsynaptic density of rat brain. J Neurochem 61:100–109.
21. Klee CB, Crouch TH, and Richman PG (1980) Calmodulin. Annu Rev Biochem 49:489–515.
22. Shifman JM, Choi MH, Mihalas S, Mayo SL, and Kennedy MB (2006) Ca2_/ calmodulin-dependent protein kinase II (CaMKII) is activated by calmodulin with two bound calciums. Proc Natl Acad Sci USA 103:13968–13973.
23. Strack S and Colbran RJ (1998) Autophosphorylation-dependent targeting of calcium/ calmodulin-dependent protein kinase II by the NR2B subunit of the N-methyl-D-aspartate receptor. J Biol Chem 273:20689–20692.
24. Malec D, Mandryk M, Fidecka S. Interaction of memantine and ketamine in morphine- and pentazocine-induced antinociception in mice. Pharmacol Rep. 2008 Mar-Apr;60(2):149-55.
25. Grande LA, O'Donnell BR, Fitzgibbon DR, Terman GW. Ultra-low dose ketamine and memantine treatment for pain in an opioid-tolerant oncology patient. Anesth Analg. 2008 Oct;107(4):1380-3.
26. Matthews JC, Baker JK. Effects of propranolol and a number of its analogues on sodium channels. Biochem Pharmacol 1982; 31:1681-1685.
27. Akaike N, Ito H, Nishi K, Oyama Y. Further analysis of inhibitory effects of propranolol and local anaesthetics on the

calcium current in Helix neurones. Br J Pharmacol 1982; 76:37-43.
28. Taussing R, Gilman AG. Mammalian membrane-bound adynylyl cyclase. J Biol Chem 1995; 270:1-4.
29. Brown AM, Birnbaumer L. Direct G protein gating of ion channels. Am J Physiol 1988; 254:H401-H410.
30. Soszynski D, Kozak W, Conn CA, Rudolph K, Kluger MJ. Beta-adrenoceptor Vol. 51(1): 77 - 86, 2010 antagonists suppress elevation in body temperature and increase plasma IL-6 in rats exposed to open field. Neuroendocrinology 1996; 63:459-467.
31. Bloksma N, Hofhuis F, Benaissa-Trouw B, Willers J. Endotoxin-induced release of tumour necrosis factor and interferon in vivo is inhibited by prior adrenoceptor blockade. Cancer Immunol Immunother 1982; 14:41-45.
32. Trotz M, Jellison EJ, Hostetler KY. Propranolol inhibition of the neutral phospholipase A of rat heart mitochondria, sarcoplasmic reticulum and cytosol. Biochem Pharmacol 1987; 36:4251-4256.
33. Millan MJ. The induction of pain: an integrative review. Prog Neurobiol 1999; 57: 1-164.
34. Yoon Hee Kim. The antinociceptive effect of esmolol. Korean J Anesthesiol. 2010.sep;59(3):141-143.
35. Ceyhan A, Ustun H, Altunatmaz K, Ide T, Unal N.Is metoclopramide an alternative to tramadol in management of post-operative pain? An experimental study. J Vet Med A Physiol Pathol Clin Med. 2005 Jun;52(5):249-53.
36. Aiello SE, Ed.: Merck Veterinary Manual. Merck & Co., Inc., Whitehouse Station, NJ, 1998.
37. DiPiro JT, Schwinghammer TL: Gastrointestinal disorders. In: Pharmacotherapy Handbook, 7th edn., Eds. Wells BG, DiPiro JT, Schwinghammer TL, DiPiro CV, McGraw Hill Co., Inc., New York, 2009, 239–320.
38. Kosecki SM: Metoclopramide: dopamine receptor antagonist, antiemetic, gastroprokinetic agent. Compend Contin Educ Pract Vet, 2003, 25, 826–900.
39. Rang HP, Dale MM, Ritter JM, Moore PK: Pharmacology, 7th edn., Churchill Livingstone, Edinburgh, 2011.367.
40. Fisher AA, Davis MW: Serotonin syndrome caused by selective serotonin reuptake-inhibitors: metoclopramide interaction. Ann Pharmacother, 2002, 36, 67–71.
41. Chemnitius JM, Haselmeyer KH, Gonska BD, Kreuzer H, Zech R: Indirect parasympathomimetic activity of metoclopramide: reversible inhibition of cholinesterases from human central nervous system and blood. Pharmacol Res, 1996, 34, 65–72.
42. Ramaswamy S, Bapna SJ: Analgesic effect of metoclopramide and its mechanism. Life Sci, 1986, 38, 1289–1292.
43. Al-Zubaidy MHI, Mohammad FK: Metoclopramide induced central nervous system depression in chickens. BMC Vet Res, 2005, 1, 6 [cited 2011 July 10] Available from http://www.biomedcentral.com/1746–6148/1/6.
44. Mohammad FK, Al-Zubaidy MHI, Alias AS: Sedative and hypnotic effects of combined administration of metoclopramide and ketamine in chickens. Lab Anim, 2007, 36, 35–39.
45. Jung AC, Staiger T, Sullivan M. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. J Gen Intern Med 1997;12: 384-9.
46. Singh VP, Jain NK, Kulkarni SK. On the antinociceptive effect of fluoxetine, a selective serotonin reuptake inhibitor. Brain Res 2001;915:218-26.
47. Kiayias JA, Vlachou ED, Lakka-Papadodima E. Venlafaxine HCl in the treatment of painful peripheral diabetic neuropathy. Diabetes Care 2000;23:699.
48. Pernia A, Mico JA, Calderon E, Torres LM. Venlafaxine for the treatment of neuropathic pain. J Pain Symptom Manage 2000;19:408-11.

49. Rang HP, Dale MM, Ritter JM. Pharmacology. 7 th ed. Edinburgh: Churchill Livingstone; 2011. 576-77.
50. Rafieian-Kopaei M, Sewell RDE. Newer antidepressants: analgesic and relative monoamine reuptake inhibitory potency. J Pharm Pharmacol 1994;46:1088.
51. Lang E, Hord AH, Denson D. Venlafaxine hydrochloride relieves thermal hyperalgesia in rats with an experimental mononeuropathy. Pain. 1996;68:151–5.
52. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther 1992;260: 275-85.
53. Driessen B, Reimann W, Giertz H, Grunenthal G. Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine in vitro. Br J Pharmacol 1993;108:806-11.