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Can promethazine in combination with sub-analgesic doses of fentanyl offer an alternative to pethidine in pain management? – An experimental study

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Abstract

Introduction: Narcotics like morphine or pethidine are neither widely prescribed, nor readily available as analgesic drugs. Availability of fentanyl is relatively easier, but has tolerability issues and dependence liability. In post-operative setting, fentanyl and promethazine are frequently co-administered. This study aimed at determining the analgesic potential of promethazine in suitable mice models and at studying if combining it with fentanyl could produce analgesia comparable to pethidine, while reducing the dose requirement of fentanyl.

Materials and Method: Dose escalation studies were done to determine subanalgesic doses of fentanyl and analgesic potential of promethazine. Subsequently, analgesia by promethazine in combination with sub-analgesic fentanyl was compared to that caused by pethidine. Five groups of mice were evaluated before and after analgesic dosing. Group I served as vehicle control, Group II received pethidine, Group III and IV received combination treatments with promethazine and sub- analgesic doses of fentanyl, Group V received fentanyl. Evaluation of analgesia were done by tail flick analgesiometer and formalin test.

Results: Formalin test ratings showed equivalent scores in the pethidine group and fentanyl-promethazine combination groups. Tail-flick latency in the fentanyl-promethazine combination groups was significantly increased in comparison to the pethidine group. When promethazine was combined to sub-analgesic fentanyl, Tail-flick latency was also found to be similar to that of full analgesic dose of fentanyl.

Conclusion: The study showed that promethazine had notable analgesic activity in mice. When combined to sub-analgesic doses of fentanyl, promethazine produced better analgesia as compared to pethidine. Combining promethazine to fentanyl reduced the dose requirement of fentanyl without compromising the analgesic efficacy.

Keywords: Analgesic, Promethazine, Fentanyl, Pethidine, Pain Management

Introduction

Despite immense advances in the understanding and management of pain over last few decades, efforts to unveil its mystery or to allay the sufferings caused by it have remained a challenge. Pharmacotherapy remains the mainstay of pain management, comprising of nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, anesthetics, antihistamines, antidepressants and antiseizure medications.[(1)]

A post-operative setting is a tricky situation where adequate analgesia invariably associates with untoward drug effects. Doses of NSAIDs are limited by gastrointestinal disturbances and renal dysfunction whereas respiratory depression and dependence oftentimes accompany higher doses of opioids. Following the enactment of Narcotic Drugs and Psychotropic Substances Act, 1985, the use of morphine, pethidine and related opioids in clinical practice has been grossly restricted, currently limited mostly to pain palliation in malignancies.[(2,3)] Impelled by such limitations in pharmacotherapy of pain, the search for more efficacious vis-à-vis safe alternatives, targeting novel pain pathways, continues.

Histaminergic systems are thought to play an important role in central nociception. Experimental and clinical data suggest that antihistamines like phenyltoloxamine, promethazine, methdilazine, and tripelennamine may possess selective analgesic efficacy, exact mechanisms being overtly unknown. It is hypothesized that H-antagonists may produce these effects by peripheral mechanisms or by central actions.[(4)] There are considerable evidences suggesting roles of histaminergic and serotonergic central pathways in nociception.[(5)]

Promethazine has established antihistaminic, antiemetic and anticholinergic actions and is widely used in treating nausea and vomiting subsequent to chemotherapy or radiation therapy for malignancies.[(6)] A combination therapy using pethidine and promethazine has been widely in use in clinical practice.[(7)] However, pethidine, due to its existing stigmata in usage, is neither widely prescribed, nor readily available in India. Availability of fentanyl is relatively easier and is a safer alternative to pethidine. But a higher dose of fentanyl invariably invites opioid-related adversities. In pre and post-operative setting, fentanyl and promethazine are frequently co-administered for varied indications. However, a careful search of relevant literature could not reveal any study exploring the analgesic potential of such combination.

We intended to see if an antihistamine-fentanyl combination could be a substitute to pethidine in the management of pain. We studied the analgesic potential of promethazine and determined the ceiling analgesic dose of fentanyl in suitable mice models. We subsequently determined if combining promethazine with fentanyl could produce analgesia comparable to pethidine, while reducing the fentanyl dose requirement.

Materials and Method

A thermal-stimuli induced and a chemical-stimuli induced pain model in mice were selected for the study, namely Tail-Flick Test and Formalin Test - so as to include both short duration "phasic" pain and long duration "tonic" pain states while taking into account both somatic and visceral pain components.[8]

Healthy male Swiss albino mice weighing between 25-30 grams were procured from a recognized breeder and allowed a period of acclimatization of atleast 14 days. Animals were fed pellet diet and water ad-libitum. Humidity, temperature, light and other housing conditions, care of the animals and application of experimental procedures were done in accordance with CPCSEA guidelines, after obtaining due approval from the institutional animal ethics committee.

Injection fentanyl 50 mcg/ml (Trofentyl, Troikaa Pharmaceuticals Ltd.), injection pethidine 100 mg (Pethitroy, Troikaa Pharmaceuticals Ltd.) and tablet promethazine 25 mg (Phenergan, Abbott Healthcare Pvt. Ltd.) were procured locally. Formalin (S.D. Fine Chem. Pvt. Ltd.) was diluted with distilled water to obtain 1% formalin solution. 2% solution of carboxy-methyl cellulose (CMC) was used as a vehicle. The Tail-flick Analgesiometer (INCO, India) was used after due calibration.

The experimental procedures were divided into three parts (Part A, Part B & Part C) as follows:

Part A: Dose escalation study to determine analgesic and sub-analgesic doses of fentanyl: Each of the seven selected mice received single dose of the test drug. Starting from a dose of 0.025 mg/kg subcutaneously, the dose of fentanyl was gradually increased to 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, 0.6 mg/kg & 0.75 mg/kg. These doses were arbitrarily selected based on human dose ranges of fentanyl and subsequent dose extrapolation in mice. Evaluation of analgesia at each dose level was done by tail-flick analgesiometer and formalin test. The minimum dose that produced the ceiling analgesic effect was considered as the full analgesic dose. Sub-analgesic doses were arbitrarily selected at 50% and 75% of the full analgesic dose.

Part B: Dose escalation study to determine analgesic potential of promethazine: Eight groups of four mice in each were selected. Based on prior studies,[9] the lower limit of human oral analgesic dose range of promethazine was seen to be 25mg/dose. Multiplying by a conversion factor of 0.0026, the extrapolated equivalent dose was 0.065mg/20gm mice, i.e. 3.25mg/kg. Mice in group I received single 3 mg/kg dose of promethazine in CMC vehicle orally. Subsequently, remaining seven groups received single doses of 3.5mg/kg, 4mg/kg, 4.5mg/kg, 5 mg/kg, 5.5 mg/kg, 6 mg/kg and 6.5 mg/kg respectively. Evaluation of analgesia at each dose level was done by tail-flick analgesiometer and formalin test separately.

Part C: Comparing the analgesic potential of pethidine to that of promethazine in combination with sub-analgesic doses of fentanyl: Six weeks after completion of Parts A and B, five groups (Groups I to V) of 6 healthy mice in each, were selected. All groups received single doses of the corresponding drugs. **Group I** served as vehicle control receiving 2% CMC orally. **Group II** received pethidine at a dose of 6.5 mg/kg subcutaneously (equivalent dose in mice was deduced from the usual subcutaneous human analgesic dose of 50mg/dose, by multiplying with conversion factor of 0.0026). **Group III** received a combination treatment with full analgesic dose of promethazine (as obtained from Part B) and half of the full analgesic dose of fentanyl (as obtained from Part A). **Group IV** received a combination treatment with full analgesic dose of promethazine and 3/4th the full analgesic dose of fentanyl. **Group V** received fentanyl at a dose of 0.6 mg/kg s.c which was the ceiling analgesic dose as deduced from Part A.

Evaluation of analgesia in all the groups in parts A, B and C were done by tail-flick analgesiometer and formalin tests separately.

Measuring Analgesic activity by Tail-flick Analgesiometer: The distal third of the tail was exposed to radiant heat generated from a wire heated by passing a current of 6mA. The time taken for the withdrawal of the tail was recorded as tail-flick latency (TFL) in seconds.[10,11] While determining the TFL, an auto cut-off value of 40 seconds was preset in the instrument to avoid undue tissue injury.[10]

All mice included in the study were first screened for activity testing using an Actophotometer, to rule out hyper or hypoactivity. Mice with normal activity were subjected to a preliminary tail-flick screening test (any animal that withdrew its tail in 5 seconds was rejected from the study). Screen positive mice were allotted to respective groups and received the desired dose.

During the dose-finding study of fentanyl (Part A), the basal reaction time was measured initially (10 minutes before dose administration) and another set of seven measures were taken at 10, 20, 40, 60, 80, 110 and 140 minutes after drug administration to measure respective post-drug tail-flick latencies. In the dose-finding study of promethazine (Part B), the baseline measurement for tail-flick latency was taken just before dose administration and another set of four measures taken at 30, 60, 90 and 120 minutes post-dose. During Part C of the study, three measures for tail-flick latency were taken after 30, 60 and 90 minutes after dose administration in all five groups. Summative values of the three respective TFL scores for each mice (TFL_30+TFL_60+TFL_90) were expressed as **Σ(**TFL). Mean Σ(TFL) values for each group were compared.

Measuring Analgesic activity by Formalin Test: Each mouse was allowed 15 minutes to explore the

chamber before injection and its behavior was rated according to Dubuisson and Dennis scale (1977)[12] described below. Mice were administered 25µl of 1% formalin (intra-dermally) into the dorsal portion of right fore paw. The test drug where applicable, was administered simultaneously either subcutaneously or orally. Pain intensity was rated according to the following numerical scale:

Scale 0.	Both forepaws are placed on the floor and weight is evenly distributed
Scale 1.	The injected paw rests lightly on the floor or on another part of the animal's body and little or no weight is placed upon it
Scale 2.	The injected paw is elevated and not in contact with any surface. The uninjected paw is placed firmly on the floor.
Scale 3.	The injected paw is licked, bitten or shaken, while the uninjected paw is not.

For each reading, mice were observed for three consecutive minutes and the amount of time (in seconds) spent in each scale (0, 1, 2, and 3) during those three minutes were recorded. The pain score, designated as Formalin test rating is given as: FTR = (T1+ 2T2 + 3T3)/180, where T1, T2 and T3 are the durations (in seconds) spent in scales 1, 2 or 3, respectively during each 3-minute block. In this study, the baseline FTR was measured 10 minutes post-formalin administration. Test drug was immediately administered and another set of four measures were observed at 30, 35, 40 and 45 minutes post-test drug administration. The entire process for each mouse was completed within 60 minutes of formalin administration. For the purpose of comparison, the four post-drug FTR scores were summated for each mouse and expressed as Σ(FTR).

Σ(TFL) in seconds and Σ(FTR) scores were compared between the test and control groups where applicable. Numerical data were expressed as Mean±Standard Deviation and Range. Between groups comparison was done using ANOVA followed by post-hoc Tukey's test. A two-tailed p value <0.05 was considered as statistically significant.

Results

Part A: Full-analgesic and sub-analgesic doses of fentanyl were evaluated using Tail-flick latency and Formalin test ratings (FTR) scores. When fentanyl was injected subcutaneously in mice in escalating doses starting from 0.025 mg/kg upto 0.75 mg/kg, the degree of analgesia as evidenced by TFL demonstrated a ceiling effect at a dose of 0.6 mg/kg. On further increment of doses to 0.75 mg/kg, no change in analgesic effect was observed. No visible signs of toxicity were noted with any of the doses of fentanyl. (Table 1; Fig. 1)

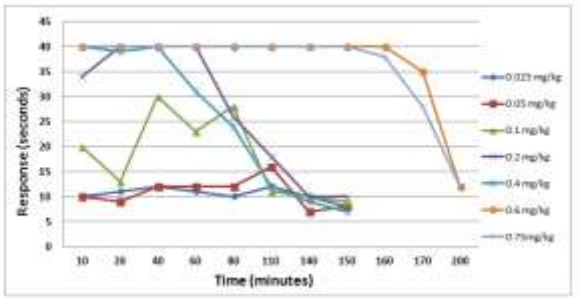

Fig. 1: Dose Escalation Study of fentanyl: Tail Flick Latency in seconds (y-axis) at different time points (x-axis) after administration of various increasing doses of fentanyl

Table 1: Tail Flick Latency (TFL in seconds) with increasing doses of Fentanyl:

Dose	Pre-treatment TFL (seconds)	Post-Treatment TFL (seconds)										
		10 mins	20 mins	40 mins	60 mins	80 mins	110 mins	140 mins	150 mins	160 mins	170 mins	200 mins
0.025 mg/kg	8	10	11	12	11	10	12	10	8	-	-	-
0.05 mg/kg	7	10	9	12	12	12	16	7	8	-	-	-
0.1 mg/kg	8	20	13	30	23	28	11	10	9	-	-	-
0.2 mg/kg	6	34	40	40	40	26	18	10	10	-	-	-
0.4 mg/kg	6	40	39	40	31	24	12	9	7	-	-	-
0.6 mg/kg	5	40	40	40	40	40	40	40	40	40	35	12
0.75mg/kg	8	40	40	40	40	40	40	40	40	38	28	12

NB*: For all mice that did not flick the tail at the prespecified cut off span of 40 seconds, the time to flick has been taken as 40 seconds for the purpose of statistical analysis. For all other mice whose response did not exceed 40 seconds, the exact time in seconds has been considered. No further readings were taken when two consecutive TFL readings were 10 or less.*

Similar results were obtained while testing in formalin test model where ceiling analgesic response was obtained at a dose of 0.6 mg/kg of fentanyl. The effect sustained at the subsequent dose of 0.75 mg/kg. (Table 2)

Table 2: Formalin Test Rating (FTR) Scores with increasing doses of fentanyl

Dose (mg/kg)	Formalin Test Ratings	
	Pre drug screening FTR	Post drug Σ(FTR) (summation of four observations)
0.05	2.375	8.89
0.1	2.648	9.55
0.2	2.366	5.466
0.4	1.833	2.73
0.6	1.133	0
0.75	2.216	0

Therefore 0.6 mg/kg was considered as the maximum analgesic dose of fentanyl. The sub-analgesic dose of fentanyl were calculated as 50% & 75% of this maximum analgesic dose. Accordingly, the two subanalgesic doses of fentanyl used in the subsequent experiment were 0.3 mg/kg and 0.45 mg/kg.

Part B: Promethazine was used in escalating doses from 3 mg/kg upto 6.5 mg/kg in 8 groups of albino mice bearing 4 mice per group. Analgesic potential of promethazine was evaluated over this dose range using TFL and FTR scores. However, no difference was evident on tail-flick latency even at 120 minutes after oral administration of the drug.

On formalin test, promethazine in escalating doses demonstrated increasing levels of analgesia (reduction in pain score) and reached a ceiling effect at dose of 6 mg/kg. Further escalation of dose to 6.5 mg/kg reproduced similar pain scores. Thus, oral dose of 6 mg/kg b.w. of promethazine was taken as reference standard dose for further comparison with other analgesic agents. (Table 3)

Table 3: Analgesic potential of promethazine in different doses evaluated as TFL in seconds (Mean ± SD [Minimum-Maximum]) and ΣFTR score (Mean ± SD [Minimum-Maximum])

Groups (n=4 in all groups)	Tail Flick Latency Mean ± SD (min-max)					Formalin Test Ratings Mean ± SD (min-max)	
	Base_TFL	TFL_30	TFL_60	TFL_90	TFL_120	Pre-drug FTR Score	Summation of 4 Post-drug FTR Scores
Gr. 1 (3 mg/kg)	7.75±1.258 6-9	9.75±1.50 8-11	9.25±2.06 7-11	9.50±1.291 8-11	8.75±0.500 8-9	1.694±1.020 0.312-2.87	1.15±0.47 0.50-1.78
Gr. 2 (3.5mg/kg)	6.50±0.577 6-7	8.75±0.957 7-10	8.25±0.957 7-9	8.50±1.291 7-10	8.50±0.577 8-9	2.438±0.385 2.002-2.991	0.77±0.74 0.06-1.66
Gr. 3 (4 mg/kg)	7.00±0.816 6-8	8.25±1.50 7-10	8.50±0.577 8-9	9.00±0.81 8-10	8.50±0.577 8-9	2.122±0.515 1.537-2.927	0.088±0.05 0.04-0.15
Gr. 4 (4.5 mg/kg)	7.25±0.957 6-8	9.25±0.957 8-10	8.50±0.577 8-9	9.00±0.816 8-10	8.50±0.577 8-9	2.350±0.227 2.015-2.762	0.24±0.37 0.033-0.80
Gr. 5 (5 mg/kg)	6.25±0.50 6-7	7.50±0.57 7-8	8.00±1.41 7-10	8.50±1.29 7-10	8.75±0.50 8-9	1.976±.512 1.295-2.741	0.67±0.34 0.22-1.07
Gr. 6 (5.5mg/kg)	6.75±0.957 6-8	7.5±0.577 7-8	8.00±1.41 7-10	8.50±1.29 7-10	8.75±0.50 8-9	1.780±0.415 1.227-2.289	0.03±0.01 0.01-0.05
Gr. 7 (6mg/kg)	7.25±0.50 7-8	9.00±0.81 8-10	9.75±1.25 8-11	9.25±0.95 8-10	8.75±0.50 8-9	2.280±0.473 1.917-2.966	0.01±0.002 0.011-0.016
Gr. 8 (6.5mg/kg)	6.50±0.57 6-7	7.50±1.29 6-9	8.25±1.25 7-10	8.50±1.29 7-10	8.75±0.50 8-9	2.214±0.306 1.862-2.787	0.01±0.002 0.011-0.016

Part C: Following the dose escalation studies for fentanyl and promethazine, tail-flick and formalin test were performed between the five groups and the results were compared. Σ(TFL) in all four drug-treatment groups (Groups II, III, IV, V) were seen to be increased significantly ($p<0.001$) in comparison to Group I (vehicle treated group). Among the drug-treatment groups, Σ(TFL) was significantly ($p<0.001$) increased in Groups III (promethazine-fentanyl combination), IV (promethazine-fentanyl combination) and V (fentanyl group) with respect to Group II (pethidine group). Groups IV & V showed significantly ($p<0.001$) increased TFL as compared to Group III. However, there was no significant difference in TFL between Groups IV & V. (Table 4, Fig. 2)

On comparing Σ(FTR) scores between five different groups, all four drug-treatment groups (Groups II, III, IV, V) showed significantly decreased FTR ($p<0.001$) in comparison to Group I (vehicle-treated group). However, no significant difference was detected in Σ(FTR) scores between Groups II, III, IV and V. (Table 4, Fig. 2)

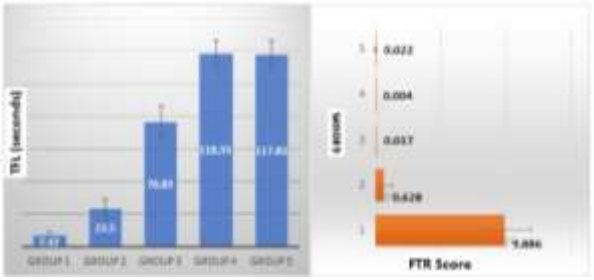

Fig. 2: Comparison of Mean Tail Flick Latency and Mean Formalin Test Score between different Groups

Table 4: Comparison of Tail Flick Latency Scores and Formalin Test Scores between different groups

Groups	Summation of tail flick latencies at 30, 60 & 90 Minutes **Σ(TFL) Mean ± Standard Deviation (Minimum - Maximum)**	Summation of 4 post-drug FTR Scores **Σ(FTR) Mean ± Standard Deviation (Minimum - Maximum)**
I (n=6) Vehicle control	7.33 ± 0.816 (6 – 8)	9.88683 ± 1.024793 (5.8222 - 11.483)
II (n=6) Pethidine 6.5mg/kg subcutaneously	23.50 ± 2.950* (21 – 28)	0.62833 ± 0.296995* (0.305 - 1.016)
III (n=6) 6 mg/kg promethazine & 0.3 mg/kg fentanyl	76.83 ± 4.875*# (72 – 86)	0.01717 ± 0.010704* (0.005 - 0.033)
IV (n=6) 6 mg/kg promethazine & 0.45 mg/kg fentanyl	118.33 ± 4.082*#€ (110 – 120)	0.00350 ± 0.006442* (0 - 0.016)
V (n=6) Treatment with 0.6 mg/kg fentanyl	117.83 ± 4.401*#€ (109 – 120)	0.0220 ± 0.02901* (0 - 0.07)
*p<0.001 in comparison to Group 1value (One way ANOVA followed by post hoc Tukey's test) #p<0.001 in comparison to Group 2 value (One way ANOVA followed by post hoc Tukey's test) € p<0.001 in comparison to Group 3 value (One way ANOVA followed by post hoc Tukey's test)		

Discussion

Despite availability of multiple classes of analgesics including opioids and NSAIDs, pharmacotherapy of pain remains far from satisfactory. Tolerability issues tend to downsize analgesic doses, thus compromising their efficacy. Concomitant use of different adjuvant drugs have been shown to potentiate the analgesic efficacy of NSAIDs and opioids. Histamine plays an important role in nociception. Some H_1 and H_2 antagonists were reported to potentiate antinociceptive effects of morphine and fentanyl.[13,14] In a study in mice, promethazine (4 and 6 mg/kg) produced a significant inhibition of the second phase response in the formalin pain model.[15] Further, it is not an uncommon clinical practice in short surgical procedures to use promethazine-pethidine analgesic combinations. Thus, while animal and clinical data suggest that antihistamines may have efficacy in pain management, the mechanism of such analgesia remains obscure.[16]

Pethidine, is one of the few opioids actually used in clinical practice. It is efficacious but has its limitations. It is a controlled substance and its availability is unreliable. Prolonged use may lead to dependence of the morphine-type; withdrawal symptoms appear more rapidly than with morphine and are of shorter duration.

Hence, there is a strong case for finding an opioid substitute for pethidine that can be used in combination with the more commonly available antihistamines. This can reduce the opioid dose-requirement and thus its related adverse effects, while effectively managing pain. It is from such rationale that the present study was planned. Fentanyl is a fast acting potent synthetic μ-opiate receptor agonist, typically used to treat severe pain conditions like post-operative pain. Disagreeable opioid related side-effects like respiratory depression limit its use to the fullest. We intended to see if promethazine showed sufficient analgesic activity in suitable pain models. We additionally explored the analgesic potential of promethazine and low-dose fentanyl combination by comparing it to pethidine.

Among the experimental pain models, chemical stimuli has been shown to closely mimic acute clinical pain. Our experiments were conducted using two commonly used pain models, the radiant heat-based tail-flick method and chemical stimuli-based formalin test method. Formalin injection into rodent hind paws is one of the commonly employed pain assays. The resulting nocifensive behaviors can be divided into two phases differing in timing, duration and underlying mechanisms. An intense first (early) phase of hind paw shaking and licking subsides approximately five minutes after formalin injection, while the second (late) phase of the formalin response, that we have seen in these experiments, is referred to as the "inflammatory phase," and has classically been ascribed to inflammation.[17]

Dose finding studies were done for fentanyl and promethazine in the two experimental pain models to arrive at respective ceiling analgesic doses. For fentanyl, the ceiling dose in either pain models were found to be 0.6mg/kg. In this study, promethazine could not produce discernible analgesia in the tail-flick test in mice though it was found to have satisfactory analgesic effect in the formalin test model. The TFL response is governed predominantly by a central pain pathway[18] whereas promethazine is known to cause analgesia by peripherally-acting pathways. As such, promethazine failing to produce discernible effects on tail-flick response in albino mice is justifiable.

In the final part of the experiment, when promethazine was combined with subanalgesic doses of fentanyl, analgesia caused by the combination in both the models were found to be satisfactory and probably synergistic. Promethazine combined with two sub-analgesic doses of fentanyl (namely 0.3mg/kg and 0.45mg/kg), demonstrated highly significant analgesic effect as compared to vehicle treatment. 0.45mg/kg fentanyl with 6mg/kg of promethazine showed analgesia similar to the ceiling analgesic effect of fentanyl in both the pain models. Further, these combinations clearly demonstrated to have an edge over analgesic effects of usual doses of pethidine.

A careful perusal of the literature revealed a few studies highlighting additive effects of promethazine on opioid induced analgesia.[19] Another clinical study revealed that promethazine in conjunction with meperidine premedication eliminated the need of supplementary anesthesia before diagnostic procedures.[20] Whereas, we didn't come across any studies focusing the analgesic actions of fentanyl and promethazine combinations, despite a diligent literature search. This study is therefore unique in its attempt to establish the analgesic efficacy of promethazine - fentanyl combination.

We did a preliminary experimental study to explore whether combining a first generation antihistamine with low doses of fentanyl could yield analgesic effects comparable to full analgesic doses of fentanyl as well as usual analgesic doses of pethidine. We however didn't focus on the tolerability issues of such combinations. To what extent, using full analgesic dose of promethazine is feasible, needs to be tested in both experimental and clinical set-up. We contemplate further studies to look upon the actual therapeutic implications of this study in clinical setting. Additionally, if this combination is seen to be synergistic through further studies, it may prove to be an useful drug interaction whereby, dose requirement for fentanyl may reduce when co-administering it with promethazine in actual practice.

Conclusion

The present study was conducted in two animal models of analgesia - Tail-flick Method and Formalin Test in mice. While promethazine used alone failed to demonstrate sufficient analgesia in Tail-flick model, it showed notable analgesic property in Formalin Test model. Promethazine in 6mg/kg dose showed satisfactory analgesic property when combined with low sub-analgesic doses of fentanyl - in both the animal models of pain. Analgesia caused by the 6mg/kg promethazine - 0.45 mg/kg fentanyl combination in both the models clearly surpassed the anti-nociception induced by a moderate dose of pethidine. Combining promethazine to fentanyl reduced the dose requirement of fentanyl while not compromising the analgesic efficacy.

Pethidine being a controlled substance has its own limitations in pain management. It may therefore be suggested that promethazine-fentanyl combination in appropriate proportion may be considered a potential candidate as an alternative to pethidine in pain management, and hence, this combination deserves further investigation. We contemplate detailed studies in future to throw more light on the unconcluded issues.

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