ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Evaluation of the Synergistic Potential of the Combination of an Opioid and Non-Opioid Analgesic in Experimental Models of Pain.

Raja Chakraverty[*1], Amit Samanta[1], Amitava Ghosh[1], and Nilanjan Sarkar[2]

[1]Bengal College of Pharmaceutical Sciences & Research, B.R.B Sarani. Bidhannagar.Durgapur-713212. West Bengal
[2]NSHM College of Pharmaceutical Technology, 124, B.L Saha Road, Kolkata-700053. West Bengal

ABSTRACT

The purpose of this present work was to evaluate the antinociceptive efficacy of a combination of an opioid and a non-opioid analgesic in experimental models of nociceptive pain in swiss albino mice using established pharmacological models of pain. As of date, no single analgesic drug is considered perfect in the treatment of all types of pain. Each analgesic agent possesses some distinct advantages and disadvantages with respect to the others. Hence, the clinical outcomes might be improved in certain conditions with the use of a combination of two analgesics, rather than relying on a single one. A combination is most effective when the individual agents act through different mechanisms of analgesia and when they act synergistically. By activating multiple pain-inhibitory pathways, combination analgesics can provide more effective pain relief for a wider spectrum of pain, help in dose reduction and may also reduce adverse drug reactions. This work highlights the therapeutic potential of combining analgesic medications with different mechanisms of action, particularly a non- opioid analgesic like nimesulide with an opioid analgesic like pethidine in swiss albino mice. A total of 30 swiss albino mice (n=6) were chosen for this study. The models of pain employed in the study included the eddy's hot plate method, tail flick test using the analgesiometer and acetic acid induced writhing test in swiss albino mice. The findings point out to statistically significant ($P<0.05$) changes in response to a combined dose of the two analgesics using one way ANOVA followed by post hoc tests. This lead us to hypothesize that there is indeed some synergism that may be at play between these two types of analgesics in experimental models of nociception.

KEYWORDS: Nociception, Nimesulide, Pethidine, animal models, Synergistic effect.

Corresponding Author
E-mail: rchakraborty20@yahoo.com

ISSN: 0975-8585

INTRODUCTION

The study of a combination of two drugs with overtly similar effects is common in medical parlance. Prominent examples include analgesics agents, chemotherapy drug combinations, antihypertensive and antiemetic. The usual objective behind the combination is to treat the situation with drugs that have different underlying mode of action. Since painful stimulus involves multiple mechanisms the use of combinations of drugs with different mechanisms is logical. Besides, the use of two drugs almost always means a combination with lower doses of each (add-on therapy), thereby facilitating the minimization of the common adverse events that might be associated with higher doses of a single drug used in therapy. Quite often the drug combination and its effect is misinterpreted and described by the terms additive or synergistic interchangeably. Our aim here is to study the potential effect of a combination of an opioid and non-opioid analgesics in experimental models of pain in swiss albino mice using established models of pain like eddy's hot plate, tail flick method and acetic acid induced writhing response employing radiant or chemical stimulus in these animals [1-5].

The primary difference between opioids and non-opioids lies in the way how they produce their analgesic effects [6]. The opioid drugs reduce pain by working on specific pain receptors in the nervous system, primarily located in the brain and spinal cord. The non-opioids, on the other hand, work more directly on injured body tissues. The opioids decrease the brain's awareness to pain, whereas the non-opioids affect some of the chemical changes that normally take place wherever body tissues are injured or damaged in the process. These chemical changes at the site of the injury typically lead to inflammatory changes and increased pain sensitivity or algesia [7,8].

MATERIAL AND METHODS

Drugs and Chemicals

Nimesulide (crude powder) used for the study was obtained as a gift sample from Dristi Pharmaceuticals Ltd. Pethidine (2ml) was obtained as a gift sample from Bengal Chemicals & Pharmaceuticals Ltd. Acetic acid(1%v/v solution). used for this study was of analytical grade.

Experimental Animals

36 Swiss albino mice (Body wt. 20-40gms) were used for the entire study. Prior to the commencement of the study ethical clearance for the animal study was obtained from the institutional animal ethical Committee (**BCPSR/IAEC/2013/003**) and a copy of the permission was retained for future reference.

Methodology

Tail-flick method (Analgesiometer) [10,11]

18 mice weighing between 20-40 grams, of either sex were used for the experiment. Then the basal reaction time is taken by placing the tip (last 1-2 cm) of the tail on the radiant heat source. The tail withdrawal from the heat (flicking response) is taken as the end point. A cut off period of 10-12 sec was observed to prevent damage to the tail. Then at least 3 basal reaction reading were taken for each mouse at a gap of 5 minutes for more accurate result. Now, the test drug is injected i.p. and the readings at 10, 20, 30, 40, 50 minutes of time intervals was noted down.

Acetic acid induced Writhing test [11-14]

18 mice weighing between 20-40 grams, of either sex were used for the experiment. Then they were divided into two groups, consisting of three animals in control group (only acetic acid) and three animals in test group (acetic acid + drug) each, where the intraperitoneal (i.p.) dose is given. Then the onset of writhing response was noted down *i.e.* the number of abdominal contractions (AC), trunk twist response (TT) and hind limb extension (HLE) up to 10 minutes. Then the mean writhing scores in control and test group is calculated.

Hot plate method [11-14]

18 mice weighing between 20-40 grams, of either sex were used for the experiment. Then the basal reaction time is taken by placing on the hot plate which is the heat source. The paw licking or jump response from the heat is taken as the end point. A cut off period of 10-12 sec was observed to prevent damage to the paw. Then at least 3 basal reaction reading were taken for each mouse at a gap of 5 minutes for more accurate result. Now, the test drug is injected along i.p route and the readings at 10, 20,30,40,50 minutes of time intervals was noted down.

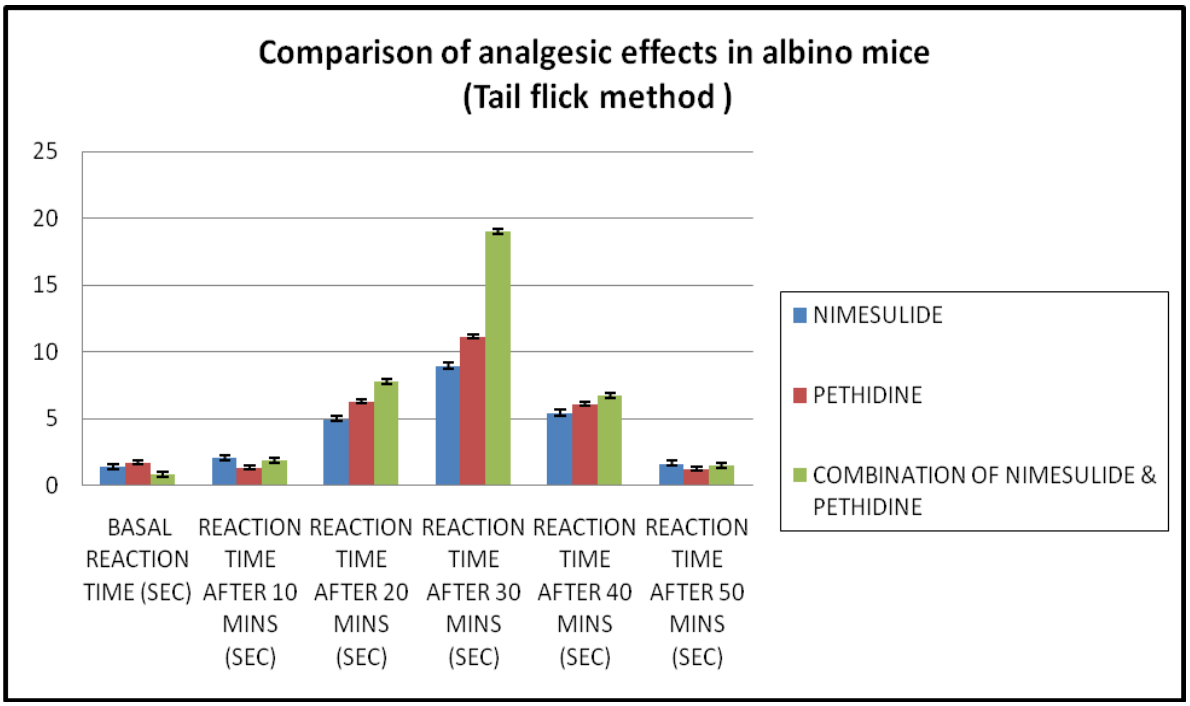
RESULTS AND DISCUSSIONS

This study was undertaken with the underlying objective to compare the analgesic efficacy of nimesulide and pethidine, alone and in combination in different animal models of nociceptive pain. The comparison was done in terms of degree of analgesia and time course of action. The findings emerging out of the present study indicates that the combination of the opioid and non-opioid analgesic exhibited synergism in these experimental models of nociception using models. The drug candidates selected for the study viz., Nimesulide and Pethidine are examples of an opioid and a non-opioid analgesic. The experimental combination of these drugs in the aforesaid models was tested in Swiss albino mice of both sexes. The level of significance of the study was assessed at ($P < 0.05$) using statistical software such as SPSS Version 17.1 using one way Analysis of variance (ANOVA) with post-hoc Tukey's test.

ISSN: 0975-8585

Tail flick test using Analgesiometer

Values are Mean ± Standard error of the mean (n=6)



Graph No. 1: The results of the tail flick test (Analgesiometer) in Swiss albino mice.

Acetic acid induced Writhing test

Table No. 1 Acetic acid induced writhing test results of Nimesulide in albino mice

Sl. No.	Body weight of mice (in gm)	Dose [acetic acid/drug]	Treatment	No. of writhing in 10 minutes	Mean wriths
1	28	1% soln.	Control {acetic acid}	78	79.666
2	26	1% soln.		74	
3	23	1% soln.		87	
4	40	1% soln. + 0.26mg/20gm	Test {acetic acid + Nimesulide}	60	60.333
5	30	1% soln. + 0.26mg/20gm		59	
6	39	1% soln. + 0.26mg/20gm		62	

Table No. 2: Writhing test results of Pethidine in albino mice

Sl. No.	Body weight of mice (in gm)	Dose [acetic acid/drug]	Treatment	No. of writhing in 10 minutes	Mean wriths
1	23	1% soln.	CONTROL {acetic acid}	89	90
2	26	1% soln.		97	
3	39	1% soln.		84	
4	28	1% soln. + 10mg/kg	TEST {acetic acid + Pethidine}	61	57.666
5	40	1% soln. +10mg/kg		59	
6	38	1% soln. +10mg/kg		53	

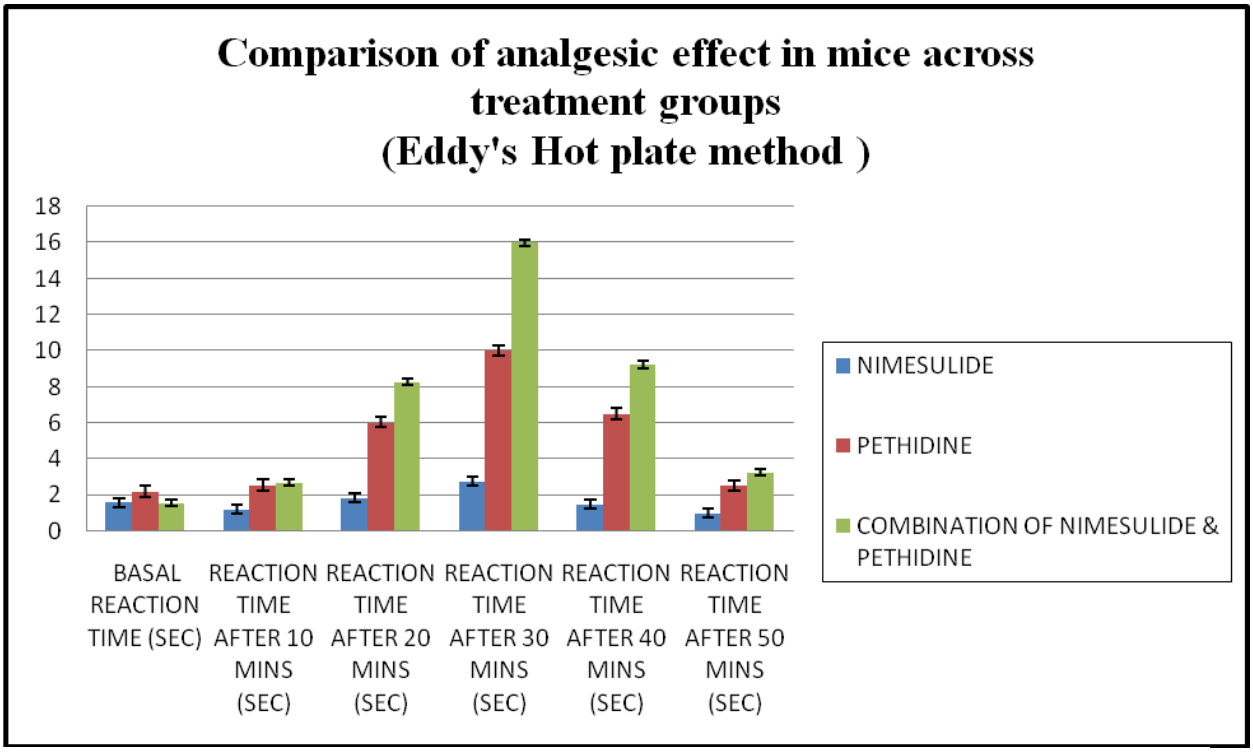
ISSN: 0975-8585

Table No. 3 Writhing test results of combination of Nimesulide and Pethidine

Sl. No.	Body weight of mice (in gm)	Dose [acetic acid/drug]	Treatment	No. of writhing in 10 minutes	Mean wriths
1	23	1% soln.	Control {acetic acid}	89	88.333
2	26	1% soln.		86	
3	39	1% soln.		90	
4	28	1% soln. + Combination dose	Test {acetic acid + drug combination}	38	38
5	40	1% soln. + Combination dose		36	
6	38	1% soln. + Combination dose		40	

Eddy's Hot plate method

Values are Mean ± Standard error of the mean (n=6)



Graph No. 2: The findings of the Eddy's hot plate test in swiss albino mice.

These study findings indicate towards statistical significance in the observed pre and post drug reaction times. These indicate a greater latency and tolerance to the pain stimulus (radiant heat or chemical). This leads us to hypothesize that the combination dose of an opioid and a non-opioid analgesic exhibit significant synergism in animal models of nociception as seen from the light of these results.

CONCLUSION

The present study is an insight into the hypothesized synergistic combination of an opioid (Pethidine) and a non-opioid (Nimesulide) analgesic in animal models of nociceptive pain utilizing both thermal and chemical stimulus for induction of pain in the experimental animals. The key findings of the study seem to indicate that the combination of an opioid and non-opioid analgesic exhibits statistically significant synergistic in the animal models of pain. However, the limitations of the present study lies in the limited number of animals of a single species were utilized and future studies are warranted with a larger sample size to corroborate the findings of the present pilot study .The underlying aim or future thrust area is to understand the mechanism and utility of such a synergism in opioids and to weigh its potential risk-benefit ratio to understand its plausible role in dose reduction and use as an add-on therapy for better therapeutical intervention of nociception.

REFERENCES

[1] Nicholas and Moore ND, Acute Pain, 11: 2009, 129-137.
[2] Parmar NS, Narosa publishing House, 2006, 225-226 & 232-233.
[3] Kulkarni SK, Vallabh Prakashan, 3: 2009, 123-125 & 127-128.
[4] Guyton H, Reeds Elsevier India Private Ltd., 11: 2007, 598-599.
[5] SusanneAbdulla, Regina Eckhardt, Ute Netter and Walied Abdulla. Anesth 21(4),2012.
[6] Howard S. Smith, Combination Opioid Analgesics Pain Physician 2008; 11:201-214.
[7] Paul F. White, Fanzca. Amnesty Analg 2002; 94:577-85.
[8] Avi A. Weinbroum, Pharmacological Research 65 (2012) 411-429.
[9] Eija Kalsoa, Jayne E. Edwards, R. Andrew Mooreb, Henry j. Mc Quayb, Pain 112(2004) 372-380.
[10] R.B. Raffa , Pharmacology of oral combination analgesics : rational therapy for pain , Journal of Clinical Pharmacy and Therapeutics (2001) 26,257-264.
[11] Ghosh MN. 3rd ed. Kolkata: Hilton and Company; 2005. p. 176.
[12] Ross D. Macpherson, Pharmacology & Therapeutics 88 (2000) 163-185.
[13] Torhild Warnckea. Audun Stubhaugb, Ellen Juruma,.2010.22-27
[14] Engelhardt G, Mauz AB, Pairet M. Arzneimittel Forschung.1997;47:917–27.
[15] Margareta Hakkein, Terhi Launiainen, Erkki Vuori, Ilkka Ojanpera, Forensic Science International 222 (2012) 327-331.