WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 4, 1873-1882. Research Article ISSN 2277 – 7105

PHARMACOLOGICAL SCREENING COMBINATION OF PARACETAMOL AND SUCROSE

Sandhya sree.M*, B.Rohitreddy, A.Mary Navaneetha, CH. Mounika, A.Rajashekar Reddy, Karthik.M, A Salomy Monica Diyya, J.Gautami.

*Assistant Professor, Department of pharmacology, Bharat Institute of Technology, Ibrahimpatnam,India, 501510.

Article Received on
30 April 2014,
Revised on 25 May 2014,
Accepted on 18 Jun 2014

***Correspondence for Author**
Sandhya Sree.M
Assistant Professor,
Department of pharmacology,
Bharat Institute of Technology,
Ibrahimpatnam,India, 501510.

ABSTRACT

Analgesic drugs act in various ways on the peripheral and central nervous systems. Pharmacological screening combination of Paracetamol and sucrose on mice and rats using Tail immersion method, Carrageenan induced rat paw edema method and Antipyretic activity was performed. Test group with paracetmol + sucrose 35% showed maximum analgesic and anti-inflammatory activity with the use of tail immersion and carrageenan method. Prostaglandin analogue like Misoprostol in tail immersion method, the analgesic response was reduced when compared with standard& test groups without prostaglandin analogues. The paracetmol coated with sucrose can be formulated which decreases the rejection of paracetmol for its bitter taste.

KEY WORDS: Analgesic, sweet, prostaglandin.

INTRODUCTION

An analgesic, or painkiller, is any member of the group of drugs used to achieve analgesia — relief from pain. Previous studies report that the ingestion of highly concentrated sweet solutions produces a morphine-like analgesia in rats, human infants, and in adult males. To determine whether sweet-induced analgesia occurs with more commonly consumed substances, 30 adult males (Mage = 22.4 years) were exposed to a cold pressor test and pain responsivity was assessed both before and after consuming either an 8% sucrose solution, water, or nothing. Between-groups compari- sons revealed that relative to the Sucrose or Nothing groups, the Water group showed increased pain tolerance. Neither pain thresholds nor ratings of pain intensity and unpleasantness on a visual analogue scale differed among

groups. The results support previous findings in both humans and animals that the palatability or hedonic value of food or drink may be the key predictor of its analgesic effect. The efficacy of paracetamol when used in combination with weak opioids (such as codeine) was assessed in data studies in 1996 and 2009, which found improved efficacy for approximately 50% of patients but increases in the number of patients experiencing adverse effects. Combination drugs of paracetamol and strong opioids like morphine reduce the amount of opioid needed and improve analgesic effect.

Animal profile: Animal: Albino mice and Wistarrats, Gender: Male, Body weight: Mice—(35g-40g) of 2 months old, Rats --- (250g-300g) of 1 year old

Dose calculations

150 mg/Kg body weight of paracetmol was administered in a constant volume of 0.2 ml using oral Gavage. Standard drug (S) of 150 mg/Kg body weight of paracetmol suspended in water and administered in a constant volume of 0.2ml.

Test drug preparations

Paracetmol 150mg/kg body weight and sucrose 35% combination (T1) was prepared

Paracetmol 150mg/kg body weight and sucrose 30% combination (t1) was prepared

S.No	control	Test (t1)	Test (T1)	Standard (S)
Number of animals	3	3	3	3
Dose	0.2ml	0.2ml	0.2ml	0.2ml
Drug	Water	Paracetmol150mg/kg+sucrose 30%	Paracetmol150mg/kg+ sucrose 35%	Paracetmol150 mg/kg

Screeningmethod:1.tail immersion method

1. Weight the animals and number them
2. Each rat is kept in individual cylindrical rat holders such that the tail hangs freely
3. Mark the tail at 5cm from tip. Immersed in hot water(55^{o}C)
4. Animal immediately withdraws its tails and the time taken is recorded by using stopwatch
5. The test substance administered.
6. Note the reaction time 0,30,60,90,120min
7. 2.carrageenin induced rat paw edema method
8. Weight the animal and number them

9. Make a mark on both hind paws (right & left)so that every time the paw is dipped in the mercury column up to the fixed mark to ensure constant paw volume
10. Note the individual paw volume (both right &left)of each rat by mercury displacement method
11. Divided the animals in four groups it should be at least three rats in one group inject the Test drug (35%sucrose+150mg/kgparacetmol)
12. Noted readings before carrageen & after carrageen
13. Thirty minutes later the rats are challenged by S.C injection of 0.05 ml of 1% solution of carageenin on the plantar surface of left hind paw.
14. Note the reaction time 0^{th}min,1hr,2hr
15. 3.antipyretic activity
16. In rats subcutaneous injection of brewer's yeast suspension produces significant pyrexia which can be counteracted by clinically effective antipyretic drugs.

METHODS

Wistar rats are divided in groups of three animals each. Their initial temperature is recorded by insertion of a thermo couple to a depth of 2cm into the rectum..A 15% susupension brewer's yeast in 0.9%saline is injected subcutaneously in back below the nape of the neck in a dose of 10 ml/kg. The site of injection is massaged inorder to spread the suspension beneath the skin. The room temperature is maintain between 22-24^{0}c immediately of the yeast injection the food is withdrawn and at 18h post challenge the rise in rectal temperature is recorded the observation is repeated after 30min.Only animals with a body temperature of at least 38^{0}c are included in this test .This animals received the test compounds or standard drug by oral administration and their rectal temperature are recorded at 30,60,120,180min thereafter. The maximum reduction in average rectal temperature in comparison with the control hyperpyrexicgrop is calculated and the results are compared with the effect of a standard drug like paracetamol

TABLES AND GRAPHS

Table 1:Tail immersion method

Test:- 35%sucrose+ 150MG/kg of paracetamol ;test:- 30%sucrose+ 150mg/KG paracetmol; Standard:-150mg/KG of paracetmol;Control:- water

Treatment groups	Mean reaction time				
	0^{th} min	30^{th} min	60^{th} min	90^{th} min	120^{th} min
Test(T)	2sec	5.6sec	4.6sec	5sec	4.6sec
test(t)	1.3sec	3.3sec	4.45sec	4.3sec	4.3sec
Standard	1sec	2.3sec	3sec	3.6sec	4.2sec
Control	1.6sec	2.3sec	2.6sec	2.3sec	2.3sec

TABLE 2:Carrageenan induced rat paw edema method

s.no	Treatment groups	Mean paw volume in ml			
			0^{th} min	1hr	2hr
1	Control	c	0.3	0.29	0.26
2	Standard	s	0.29	0.17	0.14
3	Test	T	0.3	0.15	0.14
4	Test	t	0.3	0.17	0.14

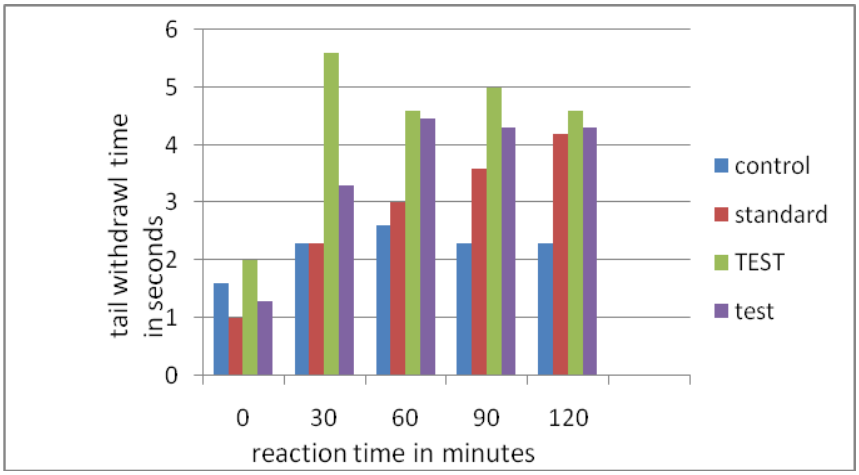
TABLE 3: Antipyretic activity

S.NO	Treatment groups	Before yeast injection (temperture ^{o}c)	After yeast injection (temperture ^{o}c)				
			0	30	60	120	180
1	C	35	40	39	38	38	38
2	S	34	39	38	36	34	34
3	T	35	40	38	36	35	34
4	t	34	40	38	37	33	33

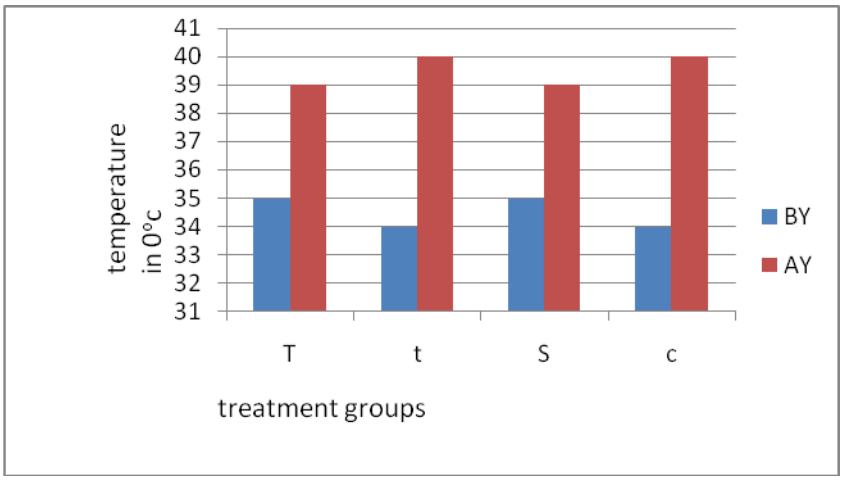
TABLE 4:Effect of prostaglandin analogues on paracetmol and paracetmol+sucrose combination using tail immersion method.

Groups	Dose of drug	Time(sec)			
		0	30	60	90
C_1	Misoprostal	3	3	2	2
C_2	Water	3	3	3	3
T	Paracetmol+sucrose(35%)+M	4	4	3	2
t	Paracetamol+sucrose(30%)+M	4	4	3	3
S	Paracetamol+M	4	5	4	4

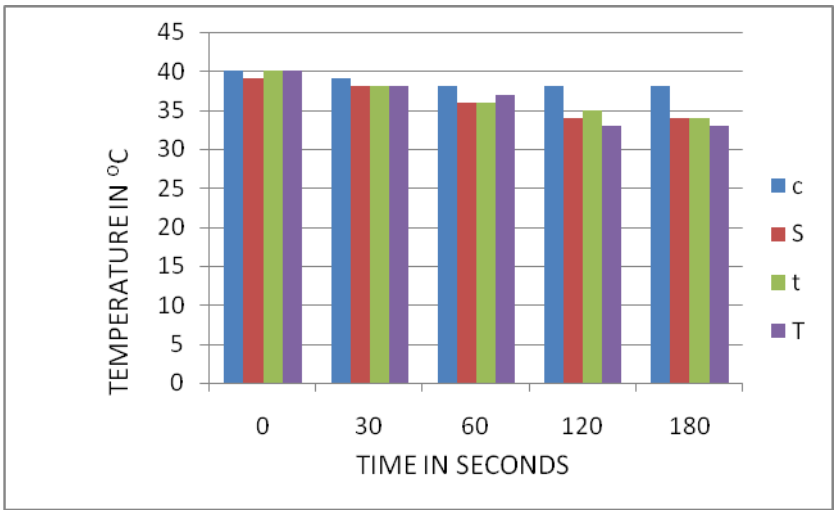
M-Misoprostil



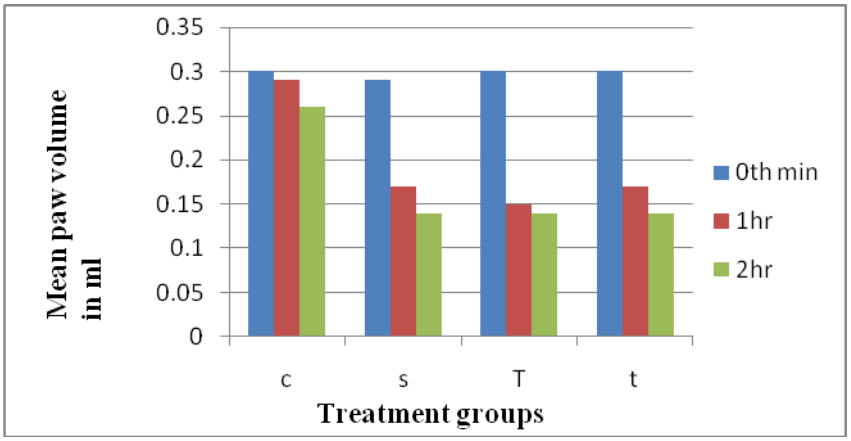
GRAPH-1 Tail immersion method



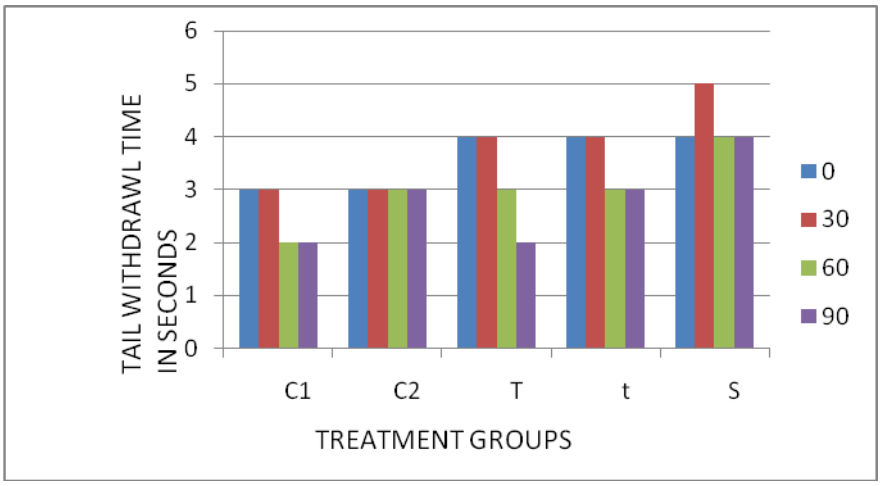
GRAPH-2 Antipyretic activity



GRAPH-3



GRAPH-4 Carrageenan induced rat paw edema method



GRAPH-5. Effect of prostaglandin analogues on paracetmol and paracetmol+sucrose combination using tail immersion method.

CONCLUSION

Maximum analgesic response at 60 min in case of T and t for standard drug at 120min .Maximum analgesic response with Test(T)when compared to t& S. Maximum reduction in 2hrs and sudden reduction from 0.3to 0.15 Test(T) has shown more reduction in paw edema when compared with test(t) and standard(S) Reduction in temperature with S,T&t was observed .test group (t) maximum reduced temperature at 120°c almost all groups have shown similar reduction in temperature. With prostaglandin analogue like Misoprostol in tail immersion method. The analgesic response was reduced when compared with standard& yeast groups without prostaglandin analogues. The above results indicate prostaglandins presence is suppressing the analgesic response of standard and test drugs. The underlying mechanism under the synergistic effect

can be through this inhibition of prostaglandin levels further studies on with different screening methods and with opioid antagonists can be performed.

It is concluded that the test group with paracetmol + sucrose 35% showed maximum analgesic and anti-inflammatory activity with the use of tail immersion and carrageenan method.

The combination on further screening on different analgesic, anti-inflammatory and antipyretic methods is encouraged to further analyse the combinational effect of paracetmol and sucrose from the above results the paracetmol coated with sucrose can be formulated which decreases the rejection of paracetmol for its bitter taste. It is also concluded from the above results that this sucrose coated paracetmol not only improves palatability of bitter drug paracetmol but also improves pharmacological activity of paracetmol. It is also concluded from the results that prostaglandin level reduction mechanism underlying pharmacological activity of combinational drugs.

REFERENCES

1. Conaghan PG (June 2012). "A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity". *Rheumatol. Int.* 32 (6): 1491–502.doi:10.1007/s00296-011-2263-6. PMC 3364420. PMID 22193214
2. Driessen B, Reimann W (January 1992). "Interaction of the central analgesic, tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain in vitro". *British JournalofPharmacology*105 (1):147 doi:10.1111/j.145381.1992.tb14226.x. PMC . PMID 1596676.
3. Bamigbade TA, Davidson C, Langford RM, Stamford JA (September 1997). "Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus". *British Journal of Anaesthesia* 79 (3): 352–6. doi:10.1093/bja/79.3.352. PMID 9389855.
4. Sandhyasree.M*, “Evaluation of antipyretic activity of polyphyto leaf extract of cocculushirusitus and maytenusemarginata”..ISSUE NO : 3/4825-4830.
5. Reimann W, Schneider F (May 1998). "Induction of 5-hydroxytryptamine release by tramadol, fenfluramine and reserpine". European Journal of Pharmacology 349 (2–3): 199–203.doi:10.1016/S0014-2999(98)00195-2. PMID 9671098.
6. Gobbi M, Moia M, Pirona L, *et al.* (September 2002). "p-Methylthioamphetamine and 1-(m-chlorophenyl)piperazine, two non-neurotoxic 5-HT releasers in vivo, differ from

neurotoxic amphetamine derivatives in their mode of action at 5-HT nerve endings in vitro". Journal of Neurochemistry 82 (6): 1435–43. doi:10.1046/j.1471-4159.2002.01073.x. PMID 12354291

7. Oxford Textbook of Palliative Medicine, 3rd ed. (Doyle D, Hanks G, Cherney I and Calman K, eds. Oxford University Press, 2004).
8. Kornhuber J, Bleich S, Wiltfang J, Maler M, Parsons CG (1999). "Flupirtine shows functional NMDA receptor antagonism by enhancing Mg2+ block via activation of voltage independent potassium channels. Rapid communication". *J Neural Transm* 106 (9-10): 857–67. PMID 10599868.
9. A. S. Levine and C. J. Billington, "Opioids. Are They Regulators of Feeding?" *Annals of the New York* Acad- emy of Sciences, Vol. 575, No. 1, 1989, pp. 209-220. doi:10.1111/j.1749-6632.1989.tb53244.x
10. S. A. Czirr and L. D Reid, "Demonstrating Morphine's Potentiating Effects on Sucrose-Intake," *Brain Research Bulletin*, Vol. 17, No. 5, 1986, pp. 639-642. doi:10.1016/0361-9230(86)90195-4
11. M. J. Fantino, J. Hosotte and M. Apfelbaum, "An Opiate Antagonist, Naltrexone Reduces Preference for Sucrose in Humans," *American Journal of Physiology*, Vol. 251, No. 1, 1986, pp. R91-R96.
12. J. Dum, C. Gramsch and A. Herz, "Activation of Hypo- thalamic Beta-Endorphin Pools by Reward Induced by Highly Palatable Food," *Pharmacology Biochemistry and Behaviour*, Vol. 18, No. 3, 1983, pp. 443-447. doi:10.1016/0091-3057(83)90467-7
13. T. Yamamoto, N. Sako and S. Maeda, "Effects of Taste Stimulation on Beta-Endorphin Levels in Rat Cerebro- spinal Fluid and Plasma," *Physiology and Behavior*, Vol. 69, No. 3, 2000, pp. 345-350. doi:10.1016/S0031-9384(99)00252-8
14. T. Yamamoto, "Brain Mechanisms of Sweetness and Pa- latability of Sugars," *Nutrition Reviews*, Vol. 61, No. 5, 2003, pp. S5-S9. doi:10.1301/nr.2003.may.S5-S9
15. J. C. Melchior, D. Rigaud, N. Colas-Linhart, A. Petiet, A. Girard and M. Apfelbaum, "Immunoreactive Beta-Endor- phin Increases after an Aspartame Chocolate Drink in Healthy Human Subjects," *Physiology and Behavior*, Vol. 50, No. 5, 1991, pp. 941-944. doi:10.1016/0031-9384(91)90418-N
16. E. M. Blass, E. Fitzgerald and P. Kehoe, "Interactions between Sucrose, Pain and Isolation Distress," *Pharma- cology Biochemistry and Behaviour*, Vol. 26, No. 3, 1987, pp. 483-489. doi:10.1016/0091-3057(87)90153-5

17. V. C. Anseloni, H. R. Weng, R. Terayama, D. Letizia, B. J. Davis, K. Ren, *et al*., "Age-Dependency of Analgesia Elicited by Intraoral Sucrose in Acute and Persistent Pain Models," *Pain*, Vol. 97, No. 1-2, 2002, pp. 93-103. doi:10.1016/S0304-3959(02)00010-6
18. M. D. Holder, "Responsivity to Pain in Rats Changed by the Ingestion of Flavoured Water," *Behavioral and Neu- ral Biology*, Vol. 49, No. 1, 1988, pp. 45-53. doi:10.1016/S0163-1047(88)91207-1
19. F. N. Segato, C. Castro-Souza, E. N. Segato, S. Morato, and N. C. Coimbra, " Sucrose Ingestion Causes Opioid Analgesia," *Brazilian Journal of Medical and Biological Research*, Vol. 30, No. 8, 1997, pp. 981-984. doi:10.1590/S0100-879X1997000800011
20. R. G. Barr, M. S. Pantel, S. N. Young, J. H. Wright, L. A. Hendricks and R. Gravel, "The Response of Crying New- borns to Sucrose: Is It a 'Sweetness' Effect?" *Physiology and Behavior*, Vol. 66, No. 3, 1999, pp. 409-417. doi:10.1016/S0031-9384(98)00294-7
21. E. M. Blass and L. B. Hoffmeyer, "Sucrose as an Analge- sic for Newborn Infants," *Pediatrics*, Vol. 87, No. 2, 1991, pp. 215-218.
22. B. A. Smith, T. J. Fillion and E. M. Blass, "Orally-Me- diated Sources of Calming in One to Three-Day-Old Hu- man Infants," *Developmental Psychology*, Vol. 26, No. 5, 1990, pp. 731-737. doi:10.1037/0012-1649.26.5.731
23. B. Stevens, J. Yamada and A. Ohlsson, "Sucrose for An- algesia in Newborn Infants Undergoing Painful Proce- dures," *Cochrane Database of Systematic Reviews*, Vol. 1, No. 1, 2010, Article ID: CD001069.
24. Miller, R. G. Barr and S. N. Young, "The Cold Pressor Test in Children: Methodological Aspects and the Anal- gesic Effect of Intraoral Sucrose," *Pain*, Vol. 56, No. 2, 1994, pp. 175-183. doi:10.1016/0304-3959(94)90092-2
25. M. Y. Pepino and J. A. Mennella, "Sucrose-Induced An- algesia Is Related to Sweet Preferences in Children but Not Adults," *Pain*, Vol. 119, No. 1, 2005, pp. 210-218. doi:10.1016/j.pain.2005.09.029
26. T. Kakeda and T. Ishikawa, "Gender Differences in Pain Modulation by a Sweet Stimulus in Adults: A Random- ized Study," *Nursing and Health Sciences*, Vol. 13, No. 1, 2011, pp. 36-40. doi:10.1111/j.1442-2018.2010.00573.x
27. T. Kakeda, "Potential of Sucrose-Induced Analgesia to Relieve Pain in Male Adults: A Preliminary Study," *Ja- pan Journal of Nursing Science*, Vol. 7, No. 2, 2010, pp. 169-173. doi:10.1111/j.1742-7924.2010.00150.x
28. T. Kakeda, M. Ito, T. Matsui and T. Ishikawa, "The Evi- dence for Sweet Substance-Induced Analgesia in Adult Human," *Pain Research*, Vol. 23, No. 3, 2008, pp. 159- 166.

29. M. D. Lewkowski, B. Ditto, M. Roussos and S. N. Young, “Sweet Taste and Blood Pressure-Related Analgesia,” *Pain*, Vol. 106, No. 1, 2003, pp. 181-186. doi:10.1016/S0304-3959(03)00333-6