Letter to Editor

Postoperative pharmacodynamic interaction of ondansetron; a 5-HT3 antagonist and paracetamol in patients operated in the ENT department under local anesthesia

Preclinical studies in incision pain models and healthy volunteers have demonstrated the central serotonergic analgesic mechanism of paracetamol.[1] This has been supported by some studies with evidence of raising serotonin concentrations in the brain following paracetamol administration.[2] Inhibition of this analgesia by ondansetron/tropisetron; the 5-HT3 antagonists suggest that this analgesia is 5-HT3-mediated.[3] However, in a few studies, these 5-HT3 antagonists themselves were found to have analgesic action.[4] These drugs are frequently co-administered, especially in cancer and postoperative patients. Hence, in this study, we have studied the pharmacodynamic interaction between paracetamol and ondansetron with reference to following parameters:

Pain scores calculated by visual analog scale (VAS),[5] face, legs, activity, cry, consolability (FLACC) behavior pain scale to assess the quality of analgesia,[6] postoperative requirement for rescue analgesic; its total dose required in 24 h and adverse effects.

A total of 20 patients who was undergoing elective surgeries in ENT Department under local anesthesia, like tympanoplasty (paracetamol plus NaCl, 0.9% n = 8, paracetamol plus ondansetron n = 9), septoplasty (paracetamol plus NaCl 0.9% n = 2, paracetamol plus ondansetron n = 1) were selected in this study.

The study population included patients of either sex, aged between 18 and 70 years, with American Society of Anesthesiologists (ASA) grade I and II.

Patients excluded from this were: ASA grade III and IV patients, patients with diabetes, IHD, stroke, malignancy, psychiatric diseases, and pregnancy-lactation.

This study was approved by the Institutional Ethics Committee (Ref. SKNMC No/Ethics/App/2013/139). This study was performed in accordance with the declaration of Helsinki. After obtaining written informed consent from each patient, the patients were randomly assigned to one of the study groups. Randomization was done with the help of OpenEpi software; version 2.3 (Andrew G.Dean and Kevin M. Sullivan, Atlanta, GA, USA). The drug was given by one investigator at the end of surgery and follow-up was done at awakening and every 30 min interval for the total period of 3 h by another investigator who was blinded. Postoperative level of analgesia was noted; when pain score noted was >4 on the VAS, rescue analgesic diclofenac or tramadol was given and postoperative analgesic consumption for 24 h was recorded.

Local anesthesia was given with xylocaine 2% and 1:200,000 adrenaline infiltration in the postaural groove and incisura terminals to block greater auricular, auriculotemporal, lesser occipital, and to a certain extent, part of vagus. Paracetamol in the dose of 1 g given intravenously to all patients and 1 ml NaCl, 0.9% as placebo, while ondansetron 4 mg as the test was given intravenously to either of study groups. Patients were observed for pulse, blood pressure, pain, sedation, and FLACC behavior pain scale scores at awakening and every 30 min for a period of 3 h. Rescue analgesic, oral diclofenac 50-100 mg or tramadol 50 mg was given when pain score was >4. Maximum dose of diclofenac was limited to 150 mg and for tramadol 400 mg in 24 h.

Statistical analysis was carried out using repeated measures ANOVA test and Mann–Whitney U-test (nonparametric test) using online Vassarstats (version 13.1) and SciStatCalc (version 1.3) software respectively. $P < 0.05$ were considered statistically significant. The significantly higher pain score was observed in the placebo group (paracetamol 1 g + NaCl, 0.9%) at awakening and further till 60 min ($P < 0.01$). The FLACC behavior scale score was observed apparently higher, but significantly higher score was observed only at 120 and 150 min with placebo group ($P < 0.01$) as compared to test group (paracetamol 1 g + ondansetron 4 mg) [Table 1]. Patients with placebo as well as test group were more or less

Access this article online	
Website: www.jbclinpharm.org	Quick Response Code
DOI: 10.4103/0976-0105.139732	

Uma A. Bhosale, Rahul Khobragade, Chetana Naik[1], Radha Yegnanarayan, Jyoti Kale[2]

Departments of Pharmacology, [1]ENT and [2]Anesthesia, SKNMC, Narhe (Ambegaon), Pune, Maharashtra, India

Address for correspondence:
Dr. Uma A. Bhosale,
Department of Pharmacology, SKNMC, Westerly Bypass Road, Narhe (Ambegaon), Pune - 411 041, Maharashtra, India.
E-mail: umabhosale2000@gmail.com

comfortable during the study; however, test group patients were more comfortable throughout the study as observed with FLACC scale and adverse effects in first 3 h. These results are in agreement with the study by Jokela *et al*. that states co-administration of ondansetron with paracetamol does not decrease the analgesic effect of paracetamol[7] whereas, contradictory to the results of Pickering *et al*.[2] analgesic requirement was significantly more with the placebo group as compared to test group [Table 2].

Postoperative pain management is very important because it is a decisive part of the patient's recovery. In the clinical practice, paracetamol is often used as a postoperative analgesic albeit its effects seem lower than those of morphine or ketoprofen.[5] The mechanism of action of paracetamol is still not clearly understood. Paracetamol has no known endogenous high-affinity binding sites like morphine. It is considered to be a weak prostaglandin (PG) synthesis inhibitor. Paracetamol is said to stimulate the activity of descending serotoninergic pathways that inhibit nociceptive signal transmission in the spinal cord.[1,2] Due to this reason, the interaction between paracetamol and 5-HT antagonists has been frequently evaluated in animals and humans. The selective 5-HT3 antagonists (tropisetron, granisetron) have been shown to completely block the analgesic effect of paracetamol in human.[3] This blockade occurs, as a result of a pharmacodynamic interaction, suggestive of the central serotoninergic system involvement in paracetamol induced antinociception.[2] However, our literature search revealed only one study describing an interaction between ondansetron and paracetamol, showing blockade of paracetamol antinociception by ondansetron.[5] In our study, the antinociceptive effect of paracetamol was instead seen to be increased when ondansetron was co-administered. This could be due to the reversal of the nociceptive effect of spinal 5-HT3 receptor activation by ondansetron.[4] The bulbospinal pathways descend to the spinal cord to either exhibit the antinociceptive or pronociceptive transmission of nociceptive inputs. Several studies have confirmed the contribution of supraspinal areas in the control of descending pronociceptive pathways. However, the spinal mediation of descending mechanisms of postincision pain has been emphasized scarcely. Ondansetron, a 5-HT3 antagonist, exhibited analgesic activity in some studies appears to be due to inhibition of this spinal descending pronociceptive pathway.[4]

Table 1: Postoperative pulse, BP, VAS, and FLACC behavior pain scale and adverse effects

Drugs given	Parameter	Time in minutes						
		0	30	60	90	120	150	180
Paracetamol 1 g plus NaCl, 0.9%	Pulse	79.5±11.6	82.5±11.8	81.7±11.2	84.5±15.9	85±8.5	82.2±9.9	82.3±10.5
	SBP	120.5±15	119.6±8.6	117.5±13.4	120.8±11.7	123.6±7.5	119.2±8.2	119.8±6.6
	DBP	69.75±9.2	72±7.7	74.5±8.09	76.16±10.2	76.5±10.5	73.6±8.04	73.3±8.2
	Pain score	4.4±3.5*	3.8±3.2*	3.7±3.3*	3.1±1.8	3.2±1.8	3.1±1.8	3.2±1.6
	FLACC score	1.7±1.7	1.1±1.4	0.5±0.7	0.3±0.5	0.7±1.3*	0.9±1.4*	0.8±1.3
	ADRs	Postoperative nausea=03, vomiting=01 and headache=01						
Paracetamol 1 g plus ondansetron 4 mg	Pulse	72.5±19.2	84±19.04	78.8±18.2	74.5±11.7	76±12.5	83.7±18.8	83.5±18.8
	SBP	119.6±8.6	119.4±8.1	118.6±5.6	118.6±9.6	120.5±8.2	116.6±4.6	118.6±5.8
	DBP	69±10.4	71.4±10.6	71.8±6.6	74.2±4.6	70.3±8.6	72.8±9.6	71.8±9.3
	Pain score	3.1±1.7	3.2±1.5	2.8±1.2	2±1.3	2.4±1.1	2.7±1.7	2.2±1.8
	FLACC score	1.8±1.2	1±0.7	0.5±0.7	0.2±0.07	0.3±0.07	0.3±0.5	0.6±1.1
	ADRs				Headache=01			

n=10, *P* values by ANOVA test for repeated measures. **P*<0.01 for pain score and FLACC score for paracetamol 1 g plus NaCl, 0.9% versus paracetamol 1 g plus ondansetron 4 mg groups. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ADRs: Adverse drug reactions, BP: Blood pressure, VAS: Visual analog scale, FLACC: Face, legs, activity, cry, consolability

Table 2: Postoperative rescue analgesic requirement in study subjects

Drug group (*n*=10)	Analgesic needed in 24 h mg	Per patient requirement median (Q1, Q3)	*P* value
Paracetamol 1 g plus NaCl, 0.9%	Diclofenac 600	50 (50, 100)*	0.0312*, 0.0412† (paracetamol 1 g+NaCl, 0.9% versus paracetamol 1 g+ondansetron 4 mg)
	Tramadol 200	25 (0, 25)†	
Paracetamol 1 g plus ondansetron 4 mg	Diclofenac 300	00 (0, 25)	
	Tramadol 050	00 (0, 0)	
Time of rescue analgesic administration	**0-4 h mg**	**4-12 h mg**	**12–24 h mg**
Paracetamol 1 g plus NaCl, 0.9%	Diclofenac 50	400	150
	Tramadol 50	100	050
Paracetamol 1 g plus ondansetron 4 mg	Diclofenac 00	200	100
	Tramadol 00	050	000

P values by Mann-Whitney U-test.**P*<0.05 for diclofenac and †*P*<0.05 for tramadol requirement in paracetamol 1 g plus NaCl, 0.9% versus paracetamol 1 g plus ondansetron 4 mg groups

Although activation of descending antinociceptive serotoninergic pathways reason central analgesic effect of paracetamol to some extent, other mechanisms are also involved, like PG synthesis inhibition or the indirect activation of cannabinoid 1 receptors.[5] Increased analgesic effect after paracetamol and ondansetron co-administration of our study is said to be the outcome of multifaceted antinociception imparted by them involving central and spinal mechanisms. However, tropisetron- and granisetron-induced antinociceptive blockade in earlier studies could be due to selective 5-HT3 antagonism at supraspinal areas.

A limitation of this study is that the interaction was studied only in patients operated under local anesthesia in the ENT department; patients operated under general anesthesia as well in various surgical departments need to be studied.

Hence, to conclude paracetamol and ondansetron co-administration pharmacodynamic interaction does not decrease the analgesia produced by paracetamol; on the contrary increase analgesic effect of paracetamol, reduce postoperative analgesic requirement, and improve postoperative comfort level. Hence, this study recommends the paracetamol and ondansetron co-administration in effective postoperative pain management.

Acknowledgments

The authors are thankful to Dr. A.V. Bhore, Dean SKNMC, and Dr. R. W. Naphade, HOD Anesthesia for providing facilities to carry out of the experiments of this work.

References

1. Anderson BJ. Paracetamol (Acetaminophen): Mechanisms of action. Paediatr Anaesth 2008;18:915-21.
2. Pickering G, Loriot MA, Libert F, Eschalier A, Beaune P, Dubray C. Analgesic effect of acetaminophen in humans: First evidence of a central serotonergic mechanism. Clin Pharmacol Ther 2006;79:371-8.
3. Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Ther 2005;12:46-55.
4. McCleane GJ, Suzuki R, Dickenson AH. Does a single intravenous injection of the 5HT3 receptor antagonist ondansetron have an analgesic effect in neuropathic pain? A double-blinded, placebo-controlled cross-over study. Anesth Analg 2003;97:1474-8.
5. Panah Khahi M, Yaghooti AA, Marashi SH, Nadjafi A. Effect of pre-emptive gabapentin on postoperative pain following lower extremity orthopaedic surgery under spinal anaesthesia. Singapore Med J 2011;52:879-82.
6. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nurs 1997;23:293-7.
7. Jokela R, Ahonen J, Seitsonen E, Marjakangas P, Korttila K. The influence of ondansetron on the analgesic effect of acetaminophen after laparoscopic hysterectomy. Clin Pharmacol Ther 2010;87:672-8.