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Opioid mediated anti-nociceptive effect of domperidone and cisapride in mice

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KEY WORDS domperidone; cisapride; analgesics; acetic acids; naloxone

ABSTRACT

AIM: To study the anti-nociceptive effect of domperidone and cisapride in mice. **METHODS**: Initially, the effect of these drugs on motor activity was tested using rotarod. The anti-nociception was tested using chemical and mechanical assay. In the chemical assay, the number of abdominal constrictions either in the saline treated animals or in the domperidone/cisapride (1, 5, or 10 mg/kg either *po* or ip) treated mice, were recorded for a period of 30 min after acetic acid challenge (10 mL/kg, of 0.6 % acetic acid ip). In the tail clip assay, the time taken by the mouse to make attempts to dislodge the bulldog clamp placed at the tail (reaction time) was recorded with a cut off time of 30 s. The role of opioid pathways was examined by pretreating the animals with naloxone (1 mg/kg, ip) 30 min prior to domperidone and cisapride. **RESULTS**: Domperidone and cisapride, both reduced the number of abdominal constrictions when given orally or intraperitoneally. Domperidone (5 mg/kg) inhibited it to the extent of 57.0 % after *po* and 54.6 % after ip. The inhibition after cisapride (5 mg/kg) was 65.1 % (*po*) and 71.6 % (ip). Naloxone pretreatment reduced this inhibition (57.0 % *vs* 10.3 % for domperidone and induced hyperalgesia by antagonizing the inhibition and enhanced analgesia to the extent of 28.4 % for cisapride). The reaction time was increased by domperidone (10 mg/kg, ip) from 1.6 s ± 1.0 s to 14.8 s ± 0.5 s and cisapride (10 mg/kg, ip) from 3.3 s ± 1.0 s to 14.8 s ± 0.5 s. **CONCLUSION**: Domperidone and cisapride exhibited a significant anti-nociceptive activity after oral as well as intraperitoneal administration. A role for opioid pathways is indicated. Since domperidone is likely to exert less extrapyramidal effects, it can be substituted for metoclopramide, which is now widely used as an analgesic either alone or as an adjuvant.

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INTRODUCTION

Metoclopramide, a prokinetic drug, has been reported to exhibit anti-nociception in experimental models. This effect was found to be opioid mediated[1]. Besides, at the cellular level, it has also been suggested to modify the movement of calcium ions across the cell membranes to elicit anti-nociceptive action[2]. A combination of metoclopramide and paracetamol is commonly used clinically in acute migraine. The enhanced absorption of paracetamol was ascribed as the possible mechanism for this response. Since early 90 s, reports are available indicating the clinical utility of metoclopramide as an analgesic agent during labour[3], knee arthroscopy[4], termination of pregnancy[5,6], treatment of ureterolithiasis[7], and prosthetic hip surgery[8]. Evidence for an inherent analgesic action of metoclopramide in enhancing the opioid analgesic effect and decreasing the pain during prostaglandin induced termination of pregnancy is also available[7].

Metoclopramide elicits prokinetic action via dopaminergic mechanism and inherits extra pyramidal symptoms. This limitation has constrained its use as an analgesic agent.

Domperidone and cisapride are two other prokinetic agents used clinically. Domperidone acts via dopaminergic system with minimal access to central nervous system. Cisapride acts through serotonergic system and is independent of dopaminergic system[9].

The present study was designed to investigate the possible anti-nociceptive response of these prokinetic

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drugs, domperidone and cisapride, with an aim to explore the possibility of its substitution to metoclopramide clinically considering their lack of extra pyramidal side effects. An attempt to identify the mechanism of such action was also made.

MATERIALS AND METHODS

Animals Male Swiss Albino mice (25 – 30 g) were obtained from JIPMER animal house and acclimatized at the departmental animal house at least for a week prior to the experimentation. They had free access to food and water with a light/dark cycle of 12:12 h. The experiments were conducted during the light hour. The study protocol was approved by the Institute Animal Ethics Committee.

Drugs Torrent Pharmaceuticals, India, gifted cisapride and domperidone, while naloxone hydrochloride was purchased from Sigma (USA).

Rotarod The motor co-ordination of domperidone and cisapride-treated animals was tested by rotarod method (Inco Ambala, India, speed 1 revolution in 64 min). The animals were made to stay on the rotating rod. If they sustain on the rotating rod up to 2.5 min, it was considered that the motor activity was normal.

Assessment of anti-nociception In the chemical assay[10], 0.6 % of acetic acid (10 mL/kg, ip) was injected and the number of abdominal constrictions during the following 30 min period was noted. A significant reduction in the numbes of abdominal constrictions when compared with saline-treated animals was considered as anti-nociceptive response.

In the mechanical assay[11], a bulldog clamp with thin rubber sleeves was placed 2.5 cm from the base of the tail and the time taken by the mouse (reaction time) to make attempts to dislodge the clamp was recorded. A maximum of 30 s was allowed as the cut off time to avoid injury to the tail. A significant increase in the reaction time implies the presence of anti-nociceptive response. In both the assay procedures, each animal was subjected to analgesic test once only.

Drug treatment Animals receiving normal saline (equal volume to that of the drug) served as control. Domperidone or cisapride (1, 5 or 10 mg/kg, *po*/ip) was administered 30 min prior to the anti-nociceptive assay. For each concentration and for each route, separate group of animals were used. While the dose selection was made based on clinical adult doses (converted to per kg dose in animals) the time interval allowed between the drug administration and the analgesic assay was chosen based on earlier study[11].

Role of opioid system The possibility of opioid mechanism contributing to their anti-nociceptive response was investigated by exposing the animals to naloxone (1 mg/kg, ip) 30 min prior to domperidone or cisapride (5 or 10 mg/kg, *po*) administration.

Statistical analysis During the whole study, the animals were observed for the presence of any behavioral changes. The data was subjected to statistical analysis using analysis of variance (ANOVA) followed by Dunnet's t test. A level of $P < 0.05$ was considered statistically significant.

RESULTS

There was no significant difference in the motor activity of the domperidone/cisapride treated animals as tested by rotarod when compared with that of saline treated animals (data not shown).

In the chemical assay, treatment with oral domperidone (1 mg/kg) significantly reduced the number of acetic acid stimulated abdominal constrictions (Tab 1). A maximum of 60.1 % of inhibition of the abdominal constrictions was noticed, which did not alter significantly when the dose of domperidone increased from 5 to 10 mg/kg (Tab 1). A similar response was recorded after intraperitoneal administration of domperidone. However, the percentage inhibition was a little more, (65.8 % when compared with oral administration 60.1 %) (Tab 1).

Tab 1. Effect of domperidone and cisapride (*po* and ip) on acetic acid-induced abdominal constrictions in mice. $n = 6$. $\bar{x} \pm s$. $^cP < 0.01$ *vs* their corresponding saline treated group.

Treatment/ mg·kg^{-1}	Number of abdominal constrictions after		Percent inhibition after	
	po	ip	*po*	ip
Saline	42 ± 6	40 ± 5	00.0	00.0
Domperidone 1	17 ± 4^c	14 ± 7^c	60.1	65.8
Domperidone 5	18 ± 5^c	19 ± 6^c	57.0	54.6
Domperidone 10	17 ± 6^c	14 ± 3^c	58.6	66.9
Saline	46 ± 5	42 ± 5	00.0	00.0
Cisapride 1	21.8 ± 2.9^c	15 ± 6^c	52.9	68.0
Cisapride 5	16 ± 7^c	13 ± 9^c	65.1	71.6
Cisapride 10	19 ± 10^c	15 ± 6^c	59.0	67.0

In the tail clip assay, domperidone increased significantly the reaction time (from 1.6 s ± 0.9 s to 8 s ± 5 s after 1 mg and to 12 s ± 5 s and 12.8 s ± 2.4 s after 5 and 10 mg respectively) after oral administration. However, a comparable response was recorded after ip administration. A similar response was recorded for cisapride. However, the degree of increase was more after cisapride 1 mg (ip) when compared with domperidone (Tab 2).

Tab 2. Effect of cisapride and domperidone (*po* and ip) on tail clip assay in mice. $n = 5$. $\bar{x} \pm s$. $^cP < 0.01$ *vs* their corresponding saline treated group.

Treatment/mg·kg^{-1}	Reaction time/s	
	po	ip
Saline	1.6 ± 0.9	3.3 ± 1.0
Domperidone 1	8 ± 5^c	4.8 ± 2.3^c
Domperidone 5	12 ± 5^c	14.0 ± 1.3^c
Domperidone 10	12.8 ± 2.4^c	14.8 ± 0.5^c
Cisapride 1	4.2 ± 0.7^c	11 ± 3^c
Cisapride 5	13.4 ± 2.0^c	14.4 ± 1.2^c
Cisapride 10	3.8 ± 1.3^c	14.8 ± 0.5^c

Cisapride also inhibited the number of abdominal constrictions after both oral and interaperitoneal administration. Like domperidone, the inhibition was not dose-related but was comparatively a little higher (65.1 %) when compared with domperidone (Tab 1).

Naloxone *per se* in the dose employed, inhibited the acetic acid-induced abdominal constrictions in mice. However, its pretreatment attenuated the inhibitory effect of cisapride (5 or 10 mg/kg) or domperidone (5 or 10 mg/kg) on acetic acid-induced abdominal constrictions (Tab 3).

Tab 3. Effect of naloxone (1 mg/kg, ip) on domperidone and cisapride (5 or 10 mg/kg, *po*)-induced changes in the acetic acid-induced abdominal constrictions in mice. $n = 6$. $\bar{x} \pm s$. $^cP < 0.01$ *vs* saline treated value. $^fP < 0.01$ *vs* their respective drug treatment alone value.

Treatment/mg·kg^{-1}	Number of abdominal constrictions	Percent inhibition/%
Saline	42 ± 6	00.0
Naloxone	29.2 ± 1.4	24.0
Domperidone 5	18 ± 5^c	57.0
Domperidone 5 + Naloxone	26 ± 12^f	10.3
Domperidone 10	17 ± 6^c	58.6
Domperidone 10 + Naloxone	33 ± 6^f	− 12.3
Cisapride 5	17 ± 7^c	65.1
Cisapride 5 + Naloxone	38 ± 13^f	− 28.4
Cisapride 10	19 ± 10^c	59.0
Cisapride 10 + Naloxone	34 ± 9^f	− 15.8

DISCUSSION

The results of the present study indicate that prokinetic drugs, domperidone and cisapride exhibited significant anti-nociceptive effect when tested by two standard procedures in animal models. This effect was noticeable both after oral and interaperitoneal administrations. However, the difference in the degree of anti-nociception between these two routes was minimal. This observation appears to be advantageous since effective anti-nociception could be achieved even after oral route, which is convenient and economical. The absence of a dose-related anti-nociception could be attributed to the dose-range selected. The possibility that the minimal effective prokinetic dose elicited maximal anti-nociception can not be excluded. A detailed pharmacokinetic study on these lines is being contemplated.

Domperidone, a commonly used drug produces minimal extrapyramidal syndromes, when compared with metoclopramide. Since this drug has exhibited potent anti-nociceptive response in experimental studies, substitution of metoclopramide by domperidone may be clinically beneficial and deserves clinical trial.

In fact, cisapride exhibited a better anti-nociception. However, with the arrhythmogenic adverse effect reported for cisapride on the cardiac function[12] its possible clinical utility, as an analgesic agent remains debatable.

Like metoclopramide, domperidone might be acting via dopaminergic pathways, which ultimately utilizes opioid mechanism to produce anti-nociception. The observation in the present study, implied that the anti-nociceptive response of domperidone and cisapride was antagonized by naloxone suggest a definitive role for opioid mechanism.

Taken into consideration the analgesic action of metoclopramide[1] and the present information on domperidone and cisapride, it can be suggested that the prokinetic drugs possess anti-nociceptive response. One of the possible mechanisms is through opioid pathways. The possible association between the anti-nociceptive response of these prokinetic drugs and their effect on gastrointestinal motility deserves further studies.

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