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PREDICT THE EFFICACY OF THREE MOTION SICKNESS MODELS IN HUMAN VOLUNTEERS BEFORE AND AFTER THE ADMINISTRATION OF ANTI-EMETIC DRUGS

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ABSTRACT

Motion sickness is a common problem which is evoked in a susceptible person, when they are subjected to the movements which have certain characteristics. Although the symptoms of motion sickness may vary somewhat in number and intensity from individual to individual, it can be stated that on an average, they are, drowsiness, facial pallor, cold sweating, salivation, nausea and vomiting. Although good guidelines may be established by animal experiments, this information cannot reliably predict the effects in man due to species differences. Therefore, the important problem is to select a method of study that reduces human variants to a minimum to obtain precise observations and avoid bias and pure psychic response. Three motion sickness models are used to predict more accurately the anti-emetic effect of two anti-emetic drugs, Metoclopramide & Cinnarizine, from two different pharmacological classes. Three motion sickness models such as, Model A-Head movements in yaw axis rotation and Model B-Chair rotation with head movements and eyes closed and Model C-Chair rotation with head movements and obscured field of vision were used in this study. Twenty healthy human volunteers were divided into two test groups. Tab. Cinnarizine 25 mg was given to one group and Tab. Metoclopramide 10 mg was given to another group. At the end of each test seven motion sickness symptoms such as dizziness, bodily warmth, headache, sweating, stomach awareness, increased salivation, nausea and one sign-pallor were graded as mild, moderate and severe. The response scores were added to give an overall symptom score using 1-10 scale for each test. Motion sickness symptoms were assessed before and 2 hours after administration of drugs. All 3 methods provide an excellent situation for observing the progression of motion sickness symptoms as the subjects become more sick. The waxing and waning of the symptoms was very clear. All these motion sickness provocation tests were technically easy and no special instrument except a rotating chair was required which can be rotated manually. It appeared that there is increased tolerance to almost all symptoms of motion sickness induced by head movements and chair rotation with cinnarizine as compared to metoclopramide.

Key words Motion sickness, Cinnarizine, Metoclopramide, anti-emetic.

INTRODUCTION

Vomiting is a common problem in clinical practice. It is always associated with motion sickness which is a specific disorder evoked in susceptible persons when they are subjected to movements. On exposure to an effective type of motion, sense organs of the non-auditory labyrinth discharge impulses repetitively to the brain. They contain neural mechanisms which are involved in the genesis of motion sickness. Slight reduction in cerebral blood flow during rotation occurs indirectly through the reflex vasomotor changes in circulation as a result of labyrinthine stimulation . Nodulus, flocculi and uvula comprise the vestibular portion of cerebellar cortex. The visceral changes are mediated through the autonomic efferent pathway and finally the integrated somatic nervous discharges to the skeletal muscle which causes retching and vomiting.

Following stimulation of vomiting centre emesis is mediated by various efferent pathways including the vagus, phrenic nerves and spinal innervations of the abdominal musculature. The initial manifestation often involved nausea in which gastric tone is reduced, gastric peristalsis is reduced or absent. Tone of upper jejunum and duodenum is increased, such that gastric reflux occurs. Ultimately, upper part of stomach relaxes while pylorus constricts, followed by co-ordinated contraction of diaphragm and abdominal muscles leads to expulsion of gastric contents.

Usual symptoms include anorexia, drowsiness, pallor, epigastric awareness, malaise, cold sweat, nausea, vomiting,retching,salivation,fatigue,headache,increased intestinal peristalsis and mental depression may also occur. The sequence, number and intensity of symptoms may vary considerably depending upon the individual and the kind and severity of the motion experienced .Many of the symptoms are subjective sensations and virtually impossible to quantitate. Facial pallor, frequently serves as an indication of approaching nausea and vomiting. The symptomatology of motion sickness is a matter which is important not only for the evaluation of prophylactic and curative measures but also for the standardization of the procedures used in experimental production of motion sickness.

Normally visual, vestibular and somatosensory-these three streams of inflammation are combined in brain to form an estimate of head and body orientation and motion. When there is mismatch between the information carried on two or more senses, motion sickness is perceived associated with neuro-vegetative symptoms like nausea and vomiting. Sensory information from eyes, vestibular apparatus together with proprioceptive information from the neck and limbs passes into central nervous system, where at the level of vestibular nuclei, it is integrated and modulated by the activity arising in the cerebellum, extrapyramidal system and the cortex. This in turn allows awareness of head and body position in space together with compensatory occulomotor and motor activity thus, there is very close association between the vestibular apparatus, vestibular nuclei and cerebellum. Experimental methods of motion sickness include various artificial devices like assault crafts, fast petrol boats, life rafts with artificial waves, vertical accelerator, swings, rotating chairs, tables, etc.But these models showed variations in interval between medication and exposure to motion, in duration and type of motion, mode of administration and dosage levels of the drug and certain subjective symptoms of varying severity to dehydration and prostration from repeated vomiting could not be accurately recorded or measured. Thus, Head movements during yaw axis rotation model, Chair rotations with head movements and eyes closed model, Chair rotation with head movements and obscured field of vision model are used to predict the efficacy since they are technically easy, cheap and can indicate different neurological pathway involved in the generation of nausea and vomiting.

Dopamine and serotonin, these are the specific neurotransmitters and mediators of the emetic signals and of motor reflexes in the stomach. Serotonin (5-HT) acting at 5HT3 receptors is an important emetic signal and transmitter in the afferent pathway from stomach and small intestine, in CTZ and in solitary tract nucleus. Dopamine acting at D2

receptors is implicated in emetic signaling through the CTZ and solitary tract nucleus. Dopamine receptors in the stomach appears to mediate the inhibition of gastric motility that occurs during nausea and vomiting. These receptors may provide a site of action for anti emetic dopamine receptor antagonist. Acetylcholine acting through muscarinic receptors in the solitary tract nucleus. Histamine and H1 receptors are concentrated in the solitary tract nucleus as well. Antagonism of transmission through these pathways contributes to the anti emetic effects of D2 and 5-HT3 receptor antagonists. Cholinergic and histaminergic synapses seem to be involved in transmission from the vestibular apparatus to the emetic centre suggesting a basis for the utility of H1 receptor directed anti histamines and muscarinic cholinergic antagonists in motion. Dopamine receptor antagonist-Metoclopramide is a substituted benzamide and histamine receptor antagonist-Cinnarizine is a piperazine derivative with H1 receptor and calcium channel blocking activity are anti-emetic drugs for motion sickness. For motion sickness a dose of 25-30 mg may be taken two hours before start of journey and 15 mg every eight hours during the journey. These drugs are used in these three human models.

MATERIALS AND METHODS

A) HEAD MOVEMENTS IN YAW AXIS ROTATION

This study was conducted in 20 healthy human volunteers

Written informed consent was taken prior to this test. Subjects with a previous history of vertigo or symptoms of neuro-otological disease or currently taking any medication were excluded from the study.

Subjects were instructed to avoid alcohol for 24 hours before each test.

Following drugs were used in this model :

1) Tab. Cinnarizine (Cinzan – FDC Limited) – 25 mg.

2) Tab. Metoclopramide (Reglan – Fluford) – 10mg.

This study was carried out in four test sessions at the same time of the day at weekly intervals.

The first session was used to familiarize the subject with test procedure and allow subject to experience the progression of motion sickness symptoms induced by the head movement during lateral rotation through 90□.

METHOD

Subjects were instructed to do the head movements during lateral rotation through 90□.At the end of the test, subject was asked to rate the overall level of malaise using a number scale from (1-10), in which,

1 = Complete well being

10 = Level of malaise at which the subject wished to stop the test.

No attempt was made to standardize the end-point of the test between the subjects.Subjects were instructed in the 1st session to choose a level of malaise to which they would be willing to progress in the three subsequent tests.

At the end of each test, a list of seven symptoms such as- dizziness , bodily warmth, headache , sweating, stomach awareness, increased salivation , nausea and one sign – pallor were graded as-

Absent = 0

Mild = 1

Moderate = 2

Severe = 3

The response scores were added to give an overall symptom score for each test. The subjects were divided into two test groups.

One group was given Tab. Cinnarizine – 25 mg orally

The subjects of the other group were given tab. Metoclopramide- 10 mg orally.At the end of 2 hours,the subjects underwent the same test as described above. Motion sickness symptoms were assessed as mentioned above.

B) CHAIR ROTATION WITH HEAD MOVEMENTS AND EYES CLOSED

This study was conducted in 20 healthy human volunteers.

Written informed consent was taken prior to the test.

The criteria for exclusion of volunteers were same as test A of motion sickness model.

Drugs dosage schedule in this model was same as used in test A.

METHOD

The subject was seated on a rotating chair with eye closed.

The chair was rotated manually and the rotation was started in clockwise manner through 3600 as one rotation in every four seconds. This speed was maintained throughout the test.

During the rotation of the chair, the subject was instructed to make 600 head movements to the left and right in roll and forwards and backwards in pitch.

The sequence of head movement was so arranged that the subject made a head movement to and from each of the four directions in a random order over a 30 seconds period.

The subject reported the motion sickness symptoms using 1-10 scale as used in test A. The test was discontinued either after 40 mins or when the subject reached a malaise score of 10.

The response score were added to give an overall symptom score for each test. The subjects were divided into two test groups.

One group was given Tab.Cinnarizine 25 mg orally.

The subjects of the other group were given Tab. Metoclopramide 10 mg orally. At the end of 2 hours, the same test was repeated as described above. Motion sickness symptoms were assessed as mentioned above.

C) CHAIR ROTATION WITH HEAD MOVEMENTS AND OBSCURED FIELD OF VISION

This study was conducted in 20 healthy human volunteers

Written informed consent was taken prior to the test.

The criteria for exclusion of the subjects were same as Test A & Test B of motion sickness models.

Drugs and dosage schedule in this model was same as used in Test A and Test B.

METHOD

The subject was seated on a rotating chair. The field of vision was obscured with enclosure. The enclosure was fitted over the head and tied below the chin.

Chair was rotated manually in a clockwise manner through 3600 as one rotation in every four seconds. This speed was maintained throughout the test.

During the chair rotation, the subject was instructed to make 600 head movements to the left and right in roll and forwards and backwards in pitch.

The sequence of head movement was so arranged that the subject made a head movement to and from, each of the four directions in a random over a 30 sec. period.

The subject was instructed to report the symptom using 1-10 scale as used in Test B.

The test was discontinued either after 40 mins or when the subject reached a malaise score of 10.

The response scores were added to give an overall symptom score for each test. The subjects were divided into two groups and were given the drugs, Tab. Cinnarizine -25 mg. and Tab. Metoclopramide-10 mg orally.

At the end of 2 hours, the same test was repeated as described above. Symptoms of motion sickness were assessed as mentioned above.

Results of all three tests of motion sickness model were tabulated and analysed by using unpaired ‘t’ test.

RESULTS AND DISCUSSION

TABLE A

HEAD MOVEMENTS DURING YAW AXIS ROTATION

Sr.No	Symptoms	A Before Drug	B After Drug	C After Drug	Comparison Between		
		Mean	Mean	Mean	A & B	A & C	B & C
1.	Dizziness	2.6 +/- 0.51	1.2 +/- 0.42	1.3 +/- 0.67	6.64**	4.83**	0.39
2.	Bodily warmth	1.2 +/- 1.03	0.3 +/- 0.48	0.3 +/- 0.48	2.49*	2.49*	0

3.	Headache	1.6 +/- 0.84	0.4 +/- 0.51	0.8 +/- 0.42	3.83**	2.68*	1.89
4.	Sweating	1.8 +/- 1.03	0.2 +/- 0.42	0.6 +/- 0.69	4.53**	3.04*	1.54
5.	Stomach awareness	1.6 +/- 0.69	0.2 +/- 0.42	1.9 +/- 0.31	5.42**	1.23	10.20**
6.	Increased salivation	1.5+/- 0.70	0.4 +/- 0.51	1.4 +/- 0.69	3.97**	0.31	3.63**
7.	Nausea	1.4+/- 1.07	0.4 +/- 0.69	1.8 +/- 0.42	2.46*	1.09	5.42**
8.	Pallor	0.7 +/- 0.67	0.1 +/- 0.31	0.5 +/- 0.52	2.54*	0.73	2.05*
9.	Total symptom score	2.4 +/- 3.47	3.3 +/- 1.63	8.6 +/- 1.34	7.49**	3.22*	7.9**

A= Symptom score before drugs

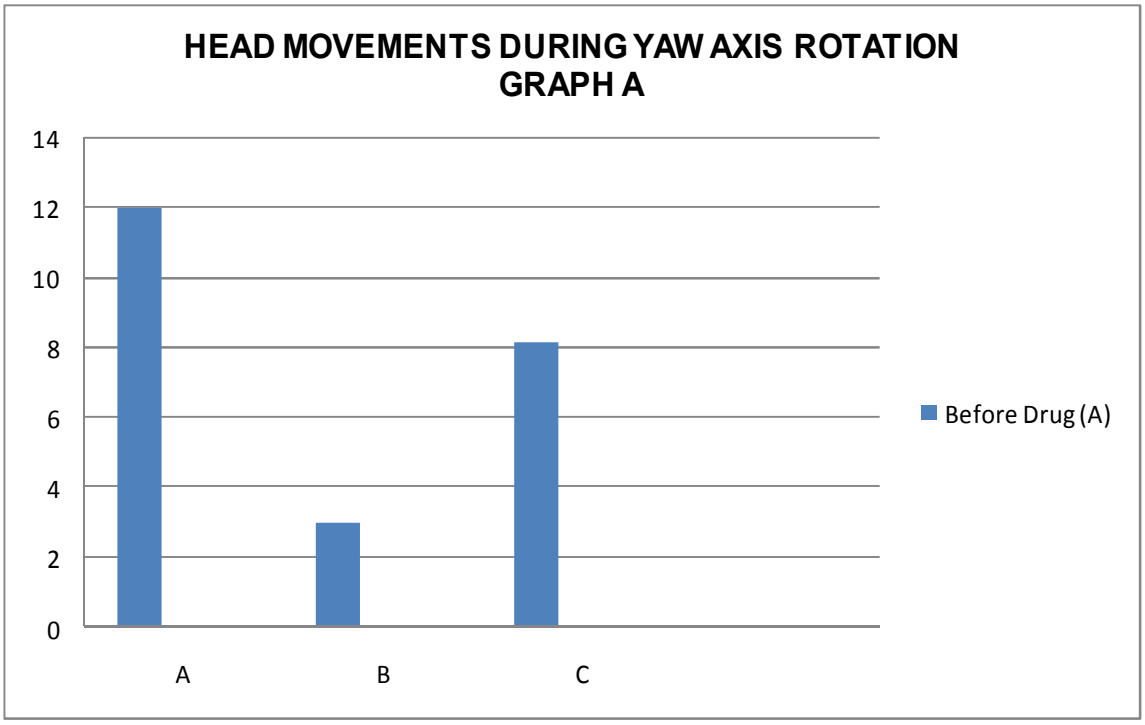
B = Symptom score after Cinnarizine

C = Symptom score after Metoclopramide

** = P < 0.001

*= P < 0.05

Results are expressed as Mean +/- S.D.



RESULT

1) There was increased tolerance to all the symptoms of motion sickness such as dizziness , bodily warmth , headache , sweating , stomach-awareness , salivation , nausea as well as pallor with prophylactically given cinnarizine.(Table -A, Graph -A)

2) Increase in tolerance was also observed to some extent for the few symptoms such as dizziness , bodily warmth , headache and sweating with prophylactically given metoclopramide.

3) Most of the symptoms of motion sickness such as stomach awareness , salivation , nausea as well as pallor , were not decreased when metoclopramide was given prophylactically.

4) When the overall prophylactic effects to motion sickness symptoms of both drugs were compared , it was observed that there is statistically significant reduction in stomach-awareness , salivation , nausea and pallor ($P < 0.001$) mainly due to cinnarizine. The main adverse effects of these two drugs were drowsiness and sedation , observed almost in all subjects.

TABLE B

Sr.No	Symptoms	A Before drug	B After Drug	C After Drug	Comparison between		
		Mean	Mean	Mean			
1.	Dizziness	7.4 ± 1.64	4.9 ± 2.76	6.8 ± 2.09	A&B	A&C	B&C
2.	Bodily warmth	4.7 ± 2.40	1.8 ± 1.98	3.1 ± 2.68	2.45*	0.71	1.73
3.	Headache	4.1 ± 1.91	0.6 ± 0.84	2.9 ± 2.28	2.93*	1.40	1.23
4.	Sweating	4.1 ± 3.03	2.8 ± 2.65	2.5 ± 1.90	5.29**	1.27	2.98*
5.	Stomach-awareness	6.7 ± 1.63	2.0 ± 2.49	5.1 ± 3.21	1.01	1.41	0.29
6.	Increased salivation	4.8 ± 2.57	1.5 ± 2.01	3.3 ± 2.98	4.98**	1.40	2.41*
7.	Nausea	7.1 ± 2.13	1.9 ± 2.46	5.4 ± 3.06	3.19**	1.20	1.58
8.	Pallor	1.3 ± 0.48	0.2 ± 0.42	0.8 ± 0.78	5.04*	1.44	2.81*
9.	Total symptom score	40.2 ± 9.71	15.7 ± 10.04	29.9 ± 12.82	5.54**	2.02	2.75*

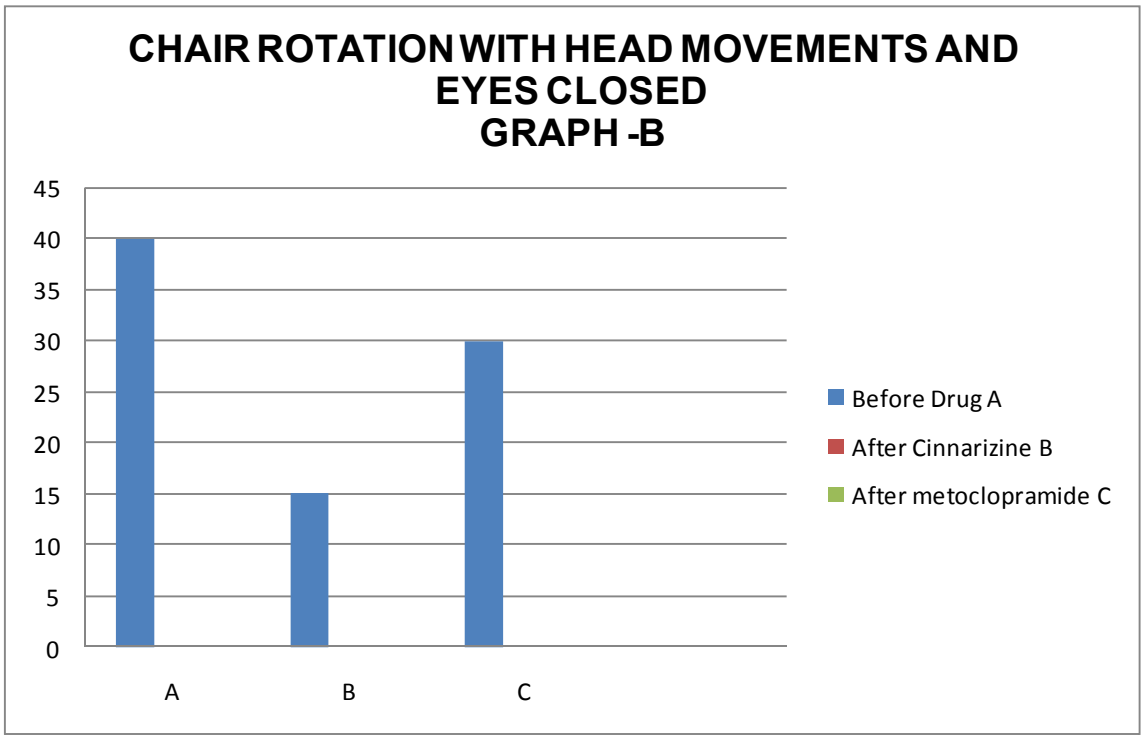
A = Symptom score before drug

B = Symptom score after Cinnarizine

C = Symptom score after Metaclopramide

** = P < 0.001

* = P < 0.05



RESULT

1) There was statistically significant (P < 0.001) increase in the tolerance to almost all the symptoms of motion sickness with prophylactically given cinnarizine.

2) Tolerance to any symptom of motion sickness was not observed with prophylactically given metoclopramide.

3) When the overall prophylactic effects of both the drugs, i.e. cinnarizine and metoclopramide were compared, a statistically significant (P <0.05) reduction in motion sickness symptoms such as headache , stomach-awareness , nausea as well as pallor was observed mainly due to cinnarizine.

4) Mild adverse events such as drowsiness and sedation were experienced by almost all the subjects.

TABLE C

Sr.No	Symptoms	A Before drug	B After Drug	C After Drug	Comparison between		
		Mean	Mean	Mean	A&B	A&C	B&C
1.	Dizziness	6.3 ± 2.16	3.40 ± 2.41	6.5 ± 2.01	2.80*	0.21	3.11
2.	Bodily warmth	4.1 ± 2.96	2.70 ± 1.88	3.5 ± 2.95	1.26	0.45	0.72
3.	Headache	3.2 ± 2.04	2.3 ± 3.09	3.1 ± 2.13	0.76	0.10	0.67
4.	Sweating	4.6 ± 2.63	2.5 ± 2.22	4.1 ± 2.23	1.92	0.45	1.60
5.	Stomach-awareness	6.2 ± 1.31	3.7 ± 2.40	6.7 ± 1.63	2.88*	0.75	3.26*
6.	Increased salivation	3.7 ± 1.94	1.6 ± 1.83	4.3 ± 1.63	2.48*	0.74	3.46*
7.	Nausea	6.7 ± 1.49	2.3 ± 1.05	7.3 ± 2.16	7.59**	0.72	6.56**
8.	Pallor	1.2 ± 0.63	0.1 ± 0.31	1.0 ± 0.81	4.91**	0.61	3.25*
9.	Total symptom score	36.0 ± 9.83	18.6 ± 8.92	36.5 ± 10.26	4.14**	0.11	4.16**

A = Symptom score before drugs

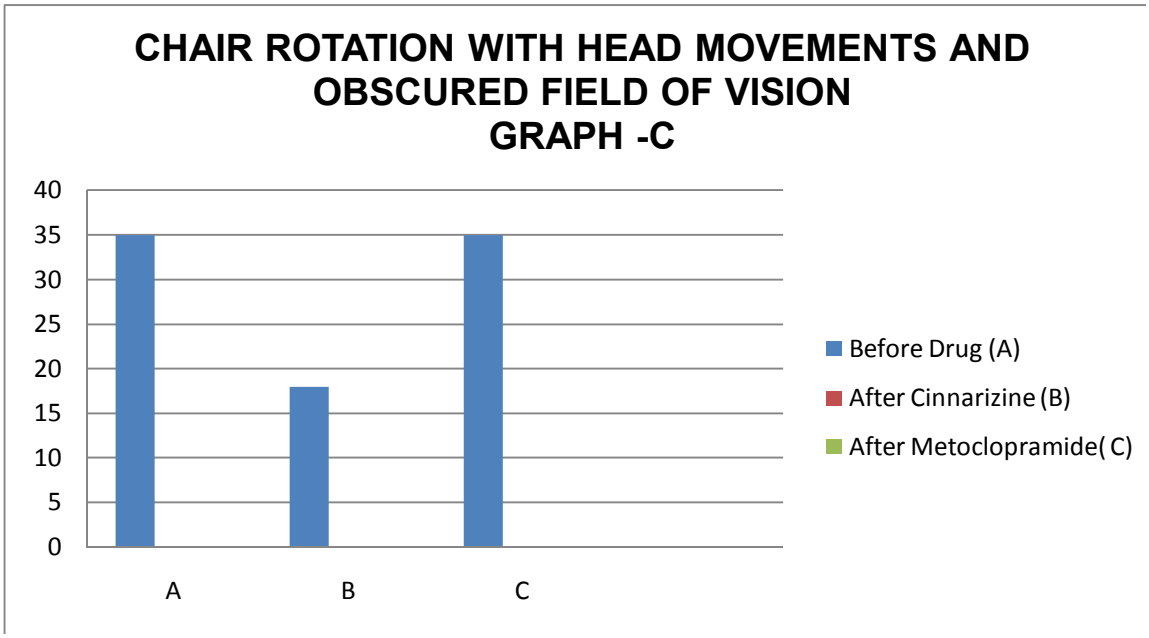
B = Symptom score after cinnarizine

C = Symptom score after metoclopramide

**= P < 0.001

*=P < 0.05

Results are expressed as Mean ± S.D.



RESULTS

1) It was observed that prophylactically given cinnarizine causes statistically significant reduction increase in tolerance to the motion sickness symptoms such as dizziness , sweating, stomach awareness,salivation,nausea as well as pallor.

2) Tolerance to the symptoms of motion sickness was not observed with prophylactically given metoclopramide.

3) When the overall prophylactic effects of both the drugs such as cinnarizine and metoclopramide were compared, a statistically significant ($P < 0.001$) reduction in motion sickness symptoms such as dizziness , stomach awareness , salivation , nausea and pallor was observed.

4) Mild adverse effects such as sedation and drowsiness were experienced by all the subjects.

DISCUSSION

From the observation of all 3 motion sickness models, it appeared that there is increased tolerance to almost all symptom of motion sickness induced by head movements and chair rotation with cinnarizine as compared to metoclopramide.

From this study, it can be said that , reduction in motion sickness symptom and increase in tolerance with the antihistaminic cinnarizine may be due to its central and peripheral action as well as calcium channel blocking action. Intracellular Ca++ is regarded as the physiological link between excitation-response coupling. Cinnarizine dampens this by inhibiting influx of Ca++ into the cells of Crista and vestibular neurons. Thus, it acts as vestibular suppressant (end organ), anticholinergic and sedative agent (Ghosh and Rohatgi , 1989 and Olivier Rascol et al,1995).

It was also observed that metoclopramide a dopamine receptor antagonist appeared to increase the tolerance to few symptoms of motion sickness in model A (Head movements in yaw axis rotation) while in subsequent tests, i.e. B & C, metoclopramide failed to give prophylactic benefit to motion sickness symptoms. It can be said that in the subsequent tests the intensity of stimulus to produce motion sickness symptoms was comparatively high which may be responsible for its failure to give prophylactic benefit. Harrington and Hamilton, in 1983 reviewed that metoclopramide is thought to have anti-emetic effect at both peripheral (gastrointestinal) and central (chemoreceptor trigger zone) sites, raising its threshold of activity and also decreases the sensitivity of visceral nerves which transmit afferent impulses from gastro-intestinal tract to emetic centre.

Metoclopramide also had an inhibitory action on vestibular nuclei, indicating a possible antivertigo effects (Harrington, 1983).Hence, it can be said that there was tolerance to few motion sickness symptoms in model A with metoclopramide.

In this study, it was observed that motion sickness symptoms can be easily evoked by all 3 methods in short duration, i.e. within 10-15 mins to malaise score of 10 (i.e. endpoint). This is the main advantage of this model.

All 3 methods provide an excellent situation for observing the progression of motion sickness symptoms as the subjects becomes more sick. The waxing and waning of the symptoms was very clear. The subject was flushed , then becomes pale , mouth becomes dry , or there was increased salivation , stomach awareness built up to nausea.Some minor symptoms such as slight pallor can be detected (WOOD and Graybiel,1970). Same results were observed in our study of motion sickness models.

All these motion sickness provocation tests were technically easy and no special instrument except a rotating chair was required which can be rotated manually.

Prevention of motion sickness symptoms by cinnarizine was clearly observed as compared to metoclopramide as shown in Tables A,B,C and Graphs A,B and C.

Mild adverse effects were experienced by most of the subjects such as drowsiness and sedation.

So, considering all the above mentioned facts, it can be said that for studying the anti-emetic drugs,this model is very useful because of its greater simplicity and tolerability.

CONCLUSION

In motion sickness models, cinnarizine actively prevents most of the symptoms of motion sickness like dizziness, stomach awareness, salivation, nausea, sweating and pallor as compared to metoclopramide.

All three methods provide an excellent situation for observing the progression of motion sickness symptoms as the subjects becomes more sick. The waxing and waning of the symptoms was very clear. The subject was flushed , then becomes pale , mouth becomes dry , or there was increased salivation , stomach awareness built up to nausea.

All these motion sickness provocation tests were technically easy and no special instrument except a rotating chair was required which can be rotated manually.

Motion sickness models has both the advantages such as greater simplicity and excellent tolerability.For the evaluation of anti-histaminics or anti-motion sickness drugs, motion sickness model is the useful model. Thus one can choose the effective model accordingly.

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