MANAGEMENT OF ACUTE VERTIGO WITH BETAHISTINE

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ABSTRACT : *This open, prospective study was carried out in 29 outpatients of vertigo with Betahistine treatment at a dose of 16 mg three times daily for a maximum treatment period of 6 weeks or earlier until remission of vertigo attacks. The evaluations were carried out based on three parameters such as frequency, duration, and severity of vertigo attacks. Betahistine showed a significant improvement in the three parameters of frequency, duration and severity of vertigo attacks. Associated symptoms such as tinnitus, nausea, vomiting, headache, faintness showed a significant improvement with the therapy. Subgroup analysis showed a significant improvement of patients with severe and incapacitating vertigo attacks at baseline. Thus, this study proves excellent efficacy and good tolerability of Betahistine as an anti-vertigo drug at a dose of 16 mg three times daily and gives a new insight for controlling acute or severe vertigo attacks without causing sedation.*

INTRODUCTION

Vertigo is always a symptom and never a disease Vertigo is a very common complaint in clinical practice seen in 10-15% of patients reporting to Otorhinolaryngologists Vertigo is referred to various terms such as giddiness, dizziness, imbalance etc Atleast 80 different disorders are reported to have vertigo as a possible symptom (Oosterveld 1985) So it is not very surprising that in about 40% of cases, a definite and clear diagnosis of vertigo is not possible inspite of modern diagnostic procedures

True vertigo is an unpleasant sensation of imbalance, spinning and disorientation Nausea and vomiting are commonly associated and during an acute attack, many patients are understandably terrified

Management of a vertigo patient is one of the challenges to the medical practitioners There are various ways of management of vertigo, which includes pharmacotherapy, surgery and vestibular rehabilitation therapy

Pharmacotherapy There are various drugs available to treat vertigo Betahistine is one of the most widely used drugs for vertigo It acts as a partial agonist at H1 receptors and as antagonist at H3 receptors (Arrang 1985, Venkataraman 1998) Various animal and human studies have shown that Betahistine increases cochlear blood flow (Suga 1969) as well as cerebral blood flow (Rivera, 1974) The efficacy of Betahistine compared with that of placebo for the treatment of vertigo has been demonstrated by various controlled clinical studies (Canty 1981, Legent 1988, Oosterveld 1989)

The most interesting aspect of this drug is its dose-dependent effect proved by various clinical studies Unemoto et al (1982) investigated the effects of Betahistine in an electrophysiological study in cats and investigated that Betahistine produced a dose-dependent inhibition of induced spike generation of polysynaptic neurons in lateral vestibular nucleus

Oosterveld (1987) studied the effects of various doses (8, 16, 32 mg) of Betahistine on induced vestibular nystagmus in a double-blind study in 10 normal subjects The study showed that Betahistine reduced the duration of induced nystagmus in a dose-dependent manner Higher the dose, better was the effect of Betahistine

This was the basis of our present study that Betahistine has a dose-dependent effect Till past few years the most commonly prescribed dosage of Betahistine was 8 mg three times daily It is expected from its dose-dependent effect that a dosage of 16 mg three times daily will have a better effect Hence this open, prospective study of Betahistine was undertaken to establish the efficacy and tolerance of Betahistine as an antivertigo drug at a dosage of 16 mg three times daily

METHOD

Patient selection :

Inclusion Criteria :

Patients under the age of 65 years who suffered from an average of atleast one episode of vertigo in the preceding

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month were eligible for study Females stabilized on a reliable form of contraception were included Stabilized hypertensive and diabetic patients were included

Exclusion Criteria

Following patients were excluded Patients with middle or inner ear infection, who required surgery, suffering from Parkinson's disease, brain tumor, head trauma, epilepsy, multiple sclerosis, and paralysis of eye muscles, psychological problems, pregnant and lactating women, peptic ulcer, bronchial asthma, pheochromocytoma, those with concurrent treatment by systemic antihistamines Regular users of excessive amount of alcohol or drugs were excluded

All patients complying with the patients' selection criteria were included in the study

Study Design

This was an open, prospective study of Betahistine carried out as an out-patient trial Informed consent was received from all patients prior to inclusion in the study

All patients received Betahistine 16 mg three times a day after meals (#Vertin 2 tablets three times daily, 1 tablet containing 8 mg of Betahistine) for a maximum treatment period of 6 weeks or earlier than 6 weeks until remission of vertigo attacks

Any other antivertigo medication was stopped Patients were included in the trial one week after stoppage of such medication Stabilized hypertensive and diabetic patients were allowed to continue with their usual medication

Assessment

At baseline, all patients underwent a clinical examination including mainly disease history and any illness currently suffering from Past duration for which the patient was suffering from vertigo attacks was recorded Also number of attacks in the preceding month was recorded Patients on any earlier antivertigo medication were given a washout period of 1 week

Demographic data was ascertained On entry into the study all patients underwent baseline investigations such as routine blood investigations, audiogram readings, special audiological tests or radiological testing if any

The follow-up evaluations were done weekly during Betahistine treatment period The three major parameters of frequency, duration and severity of vertigo attacks were assessed

-The frequency of vertigo attacks was evaluated as the number of vertigo attacks per week

-Duration of vertigo attacks was recorded as seconds/ minutes/hours

-Severity of vertigo attacks was assessed on a scale as -

-incapacitating (confined to bed)

-severe (disruption of daily routine)

-mild (some interference with daily routine)

-absent (no interference with daily routine)

-no attack (free from vertigo attack)

The patients were classified depending on description of symptoms of vertigo attacks as -

-sudden, serious, short lasting

-sudden severe gradually diminishing

-brief spells

-chronic not severe, persistent

Number of patients suffering from associated symptoms like tinnitus, hearing loss, nausea, vomiting, faintness, headache was noted Other parameters such as B P, sugar, (blood, urine) were recorded

Side effects if observed were recorded at each assessment Patients were questioned on experience of drowsiness and effect on quality of lifestyle by the drug treatment

Global Evaluation

Patients as well as clinicians assessed the overall efficacy, tolerance and effect on associated symptoms of the study medication using a four-point scale such as excellent, good, fair or poor

RESULTS

Twenty nine patients entered the study No patient dropped out and results were analyzed in all the 29 patients Demographic data of the patients is as given in table 1 On entry into the study, the average past history of illness was 19 12 + 38 25 weeks

Table 1

Demographic data

	Total Number
Males	15
Females	14
Total	29

Average past history of illness was 19 12 + 38 25 weeks

Average number of attacks in the preceding month 41 24 + 62 13

Mean age in years 42 86 + 14 44

Current health status and associated illnesses were recorded Two patients had diabetes, 4 had hypertension while 3 were suffering from spondylosis

Audiogram showed that 15 patients had bilateral hearing loss, 3 had unilateral hearing loss while 11 patients showed normal audiogram No primary treatable cause of vertigo was identified in these patients

At baseline, 11 patients had sudden, serious short lasting vertigo attacks, 10 had sudden, severe, gradually diminishing vertigo attacks Three patients had brief spells while 5 patients had chronic, not severe, persistent vertigo attacks

At baseline, the mean frequency of vertigo attacks was 14 66+20 18 per week and the mean duration of vertigo attacks in minutes was 33 81+56 1 The mean severity score was recorded to be 2 9+0 62 (Table 2)

Frequency of vertigo attacks

The average frequency of vertigo attacks at baseline was 14 66 attacks per week which reduced statistically significantly by 61 66% to 5 62 attacks per week (p<0 05)

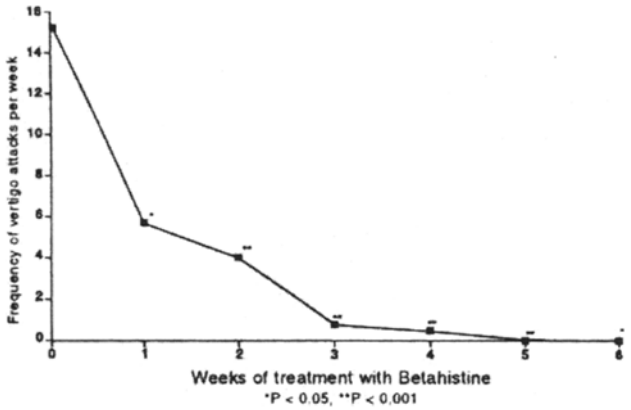

Fig I Reduction in frequency of vertigo attacks with Betahistine therapy

on completing 1 week of therapy On completing 3 weeks of therapy the frequency reduced by 95 29% to 0 69 attacks per week, which was highly significant (p< 0 001) (Table 2) (Fig 1)

Duration of vertigo attacks

The average duration of vertigo attacks on entry into the study was 33 81 minutes This reduced by 53 18 % (p< 0 05) to 15 83 minutes on completing 1 week of therapy While on completing 3 weeks of therapy, the duration reduced by 93 88 % to 2 07 minutes which was highly

Table 2

Mean Symptom Score (ñS D) Before and After Starting the Treatment (n=29)

Weeks of treatment	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Parameters							
Frequency of	14 66	5 62*	3 9**	0 69**	0 41**	0**	0**
attacks per week	+20 18	+8 65	+11 86	+2 58	+ 1 64		
Duration of	33 81	15 83*	6 4**	2 07**	1 04**	0**	0**
attack in min	+ 56 1	+35 04	+24 51	+11 14	+5 57		
Severity score #	2 9	1 83*	0 69**	0 14**	0 14**	0**	0**
	+0 62	+1 14	+1 04	+0 52	+0 52		

* Significant p<0 05, ** highly significant p<0 001

Severity score Incapacitating - confined to bed, 4, Severe - complete disruption of daily routine, 3,

Mild - sometimes interferes with daily routine, 2, Absent - does not interfere with daily routine, 1,

No vertigo attack - complete relief from vertigo attacks, 0

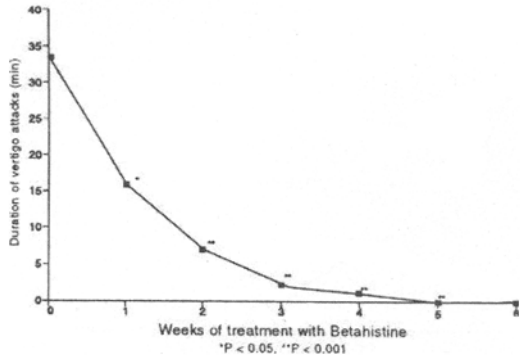

FIg II Reduction in duration of vertigo attacks with Betahistine therapy

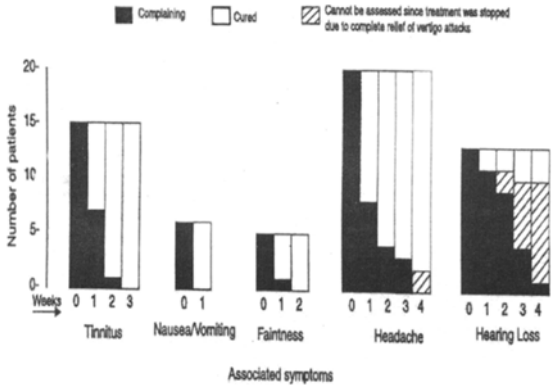

Fig III Reduction in severity of vertigo attacks with Betahistine therapy

significant ($p < 0.001$) (Table 2) (Fig 2)

Severity of vertigo attacks

At baseline the average severity score was 2 9 On completing 1 week of treatment, this was reduced by 36 9% to 1 83 On completion of 3 weeks of treatment, the severity score was reduced by 95 17 % to 0 14 (Table 2) (Fig 3)

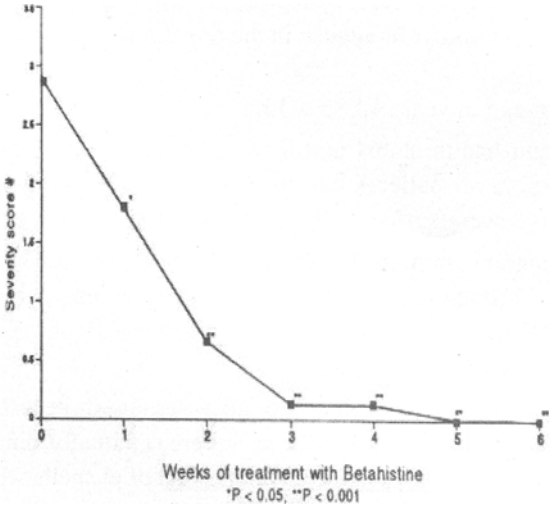

Fig IV Number of patients with associated symptoms before and after treatment with Betahistine

On completion of 5 weeks of Betahistine (Vertinr tablets) therapy, all the patients were completely relieved of vertigo attacks The average frequency, duration as well as severity of vertigo attacks were reduced to zero Effect on associated symptoms (Table 3) (Fig 4)

Fifteen patients suffered from tinnitus Fourteen patients improved on completing 2 weeks of treatment On completion of 3 weeks of therapy, no patient was complaining of tinnitus

Six patients complained of nausea/vomiting Treatment with Betahistine relieved these associated symptoms in all the patients on completing just 1 week of therapy Five

Table 3

No of patients with associated symptoms

Weeks of treatment	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Associated symptoms							
Tinnitus	15	7*	1**	0**	0**	0**	0**
Nausea /vomiting	6	0**	0**	0**	0**	0**	0**
Faintness	5	1**	0**	0**	0**	0**	0**
Headache	20	8*	4**	3**	2+	+	+
Hearing loss	13	11$	11$	10$	10$	+	+
			9+2+	4+6+	1+9+		

\+ Cannot be assessed since treatment was stopped due to complete relief of vertigo attacks

* Significant, p<0 05, ** Highly significant p<0 001, $ non significant

patients were complaining of faintness on entry into the study On completing 1 week of therapy, 4 patients were relieved of faintness while fifth patient was relieved of faintness on completing 2 weeks of treatment with Betahistine

At baseline, 20 patients were complaining of headache After treatment with Betahistine, 18 patients were relieved of headache We cannot assess the remaining two patients for this symptom since treatment was stopped due to complete relief from vertigo

At baseline, 13 patients were complaining of hearing loss 3 patients showed improvement during Betahistine treatment We can not comment on improvement of hearing in remaining 10 patients, since treatment was stopped early due to complete relief of vertigo attacks

Table 4 shows the number of patients with vertigo attacks classified as incapacitating, severe, mild, absent based on severity at each week of assessment

Table 6

Global Evaluation - Clinicians' Evaluation

	No. of patients (%)		Rating as	
	excellent	**good**	**fair**	**poor**
Parameters				
Efficacy (n=29)	21 (72 41%)	8 (27 59%)	0 (0%)	0 (0%)
Tolerance (n=29)	22 (75 86%)	7 (24 24%)	0 (0%)	0 (0%)
Effect on associated symptoms (n=21)	19 (90 48%)	1 (4 76%)	1 (4 76%)	0 (0%)

No adverse signs or symptoms were noted in any patient Gastrointestinal side effects such as gastro-intestinal upset, hyperacidity were not noted with this dose No patient experienced drowsiness No patient expressed that the quality of lifestyle was hampered by the treatment

Table 4

No of Patients With Different Severity Score Before and After Starting the Treatment

Weeks of treatment	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Type of vertigo attack based on severity (score) Incapacitating (4)	4	1	0	0	0	0	0
Severe (3)	18	7	2	0	0	0	0
Mild (2)	7	13	6	2	2	0	0
Absent (1)	0	2	2	0	0	0	0
Total number of patients with vertigo attacks (n)	29	23	10	2	2	0	0

Table 5

Global Evaluation - Patients' Evaluation

	No. of patients (%)		Rating as	
	excellent	**good**	**fair**	**poor**
Parameters				
Efficacy (n=29)	20 (68 97%)	9 (31 03%)	0 (0%)	0 (0%)
Tolerance (n=29)	21 (72 41%)	8 (27 59%)	0 (0%)	0 (0%)
Effect on associated symptoms (n=21)	17 (80 95%)	3 (14 29%)	1 (4 76%)	0 (0%)

GLOBAL ASSESSMENT

After completion of therapy, 100% patients rated the efficacy as well as tolerance of treatment as excellent to good 95% patients rated the effect on associated symptoms as excellent to good (Table 5)

After completion of Betahistine treatment clinicians rated the efficacy as well as tolerance of treatment as excellent to good in 100% of patients Clinicians rated the effect on associated symptoms as excellent to good in 95% patients (Table 6)

Sub group analysis

Also patients with severe vertigo attacks at baseline were analyzed separately (n=18) (Table 7)

Mean frequency of vertigo attacks in this group was 14 39 This was reduced on completing 2 weeks of treatment by 73% to 3 89 Mean duration of vertigo attacks was 23 19 minutes This was reduced by 99 4% to 0 15 minutes on completing 2 weeks of therapy Mean severity score was 3 0 This was reduced by 77 7% to 0 67 on completing 2 weeks of treatment

A clinically significant improvement was seen in these patients with severe vertigo attacks since all of them were completely free of vertigo attacks on completion of 3 weeks of treatment

Patients with incapacitating vertigo attacks at baseline were analyzed separately (n=4) (Table 8)

Mean frequency of vertigo attacks in this group was 3 75 per week This was reduced on completing 2 weeks of treatment by 93 3% to 0 25

Mean duration of vertigo attacks was 82 75 minutes This was reduced by 63 8% to 30 0 minutes on completing 2 weeks of therapy

Mean severity score was 4 0 This was reduced by 93 75 % to 0 25 on completion of 2 weeks of treatment

All these patients with incapacitating vertigo attacks in the beginning were completely free of vertigo attacks on completing 3 weeks of Betahistine treatment

DISCUSSION

Various clinical studies had shown that Betahistine effectively provides relief of vertigo attacks It reduces frequency of vertigo attacks thus providing prophylactic effect It also offers symptomatic relief by lowering the severity and duration of vertigo attacks

In this study, Betahistine was given in a dose of 16 mg three times daily A statistically significant improvement was seen on completing 1 week of therapy itself More than 93% reduction in frequency, duration and severity of vertigo attacks was seen on completing 3 weeks of treatment with Betahistine All the patients were completely relieved of vertigo attacks on completion of 5 weeks of Betahistine treatment Both clinicians as well as patients expressed the efficacy as well as tolerance to be excellent to good in 100% of patients

The most interesting aspect of the analysis is the sub-group analysis of patients with severe and incapacitating (n=18+4)

Table 7

Mean Symptom Score (ñS D) of Patients with Severe Vertigo Attacks at Baseline Score (n=18)

Weeks of treatment	**0 (n=18)**	**1 (n=14)**	**2 (n=5)**	**3 (n=0)**	**4**	**5**	**6**
Parameters							
Frequency of attacks per week	14 39 +23 04	4 94* +8 5	3 89** +14 06	0**	0**	0**	0**
Duration of attack in min	23 19 +49 22	6 27** +15 20	0 15** +0 33	0**	0**	0**	0**
Severity score #	3 0 +0 0	1 94* +1 16	0 67** +1 14	0**	0**	0**	0**

* Significant p<0 05, ** highly significant p<0 001

Severity score Incapacitating - confined to bed, 4, Severe- complete disruption of daily routine, 3,

Mild - sometimes interferes with daily routine, 2, Absent - does not interfere with daily routine, 1,

No vertigo attack - complete relief from vertigo attacks, 0

n represents total number of patients with vertigo attacks, each patient with different severity score

Table 8

Mean Symptom Score (± S D) of Patients with Incapacitating Vertigo Attacks at Baseline (n=4)

Weeks of treatment	**0 (n=4)**	**1 (n=3)**	**2 (n=1)**	**3 (n=0)**	**4**	**5**	**6**
Parameters							
Frequency of attacks per week	3 75 +1 26	1 00* +0 82	0 25** +0 50	0**	0**	0**	0**
Duration of attack in min	82 75 +82 28	32 75** +58 34	30 00* +60 00	0**	0**	0**	0**
Severity score #	4 0 +0 0	1 75* +1 71	0 25** +0 50	0**	0**	0**	0**

* Significant p<0 05, ** highly significant p<0 001

Severity score Incapacitating - confined to bed, 4, Severe - complete disruption of daily routine, 3, Mild - sometimes interferes with daily routine, 2, Absent - does not interfere with daily routine, 1, No vertigo attack - complete relief from vertigo attacks, 0

n represents total number of patients with vertigo attacks, each patient with different severity score

vertigo attacks at baseline On completion of 2 weeks of therapy 72% of patients with severe vertigo and 75% of patients with incapacitating vertigo were relieved of their symptoms On completion of 3 weeks of Betahistine treatment all the patients with severe and incapacitating vertigo attacks were completely free of attacks

Another aspect, which is of concern in the management of vertigo patient, is the tolerance of the drug therapy In this study, it was observed that with the therapy of Betahistine at a dose of 16 mg three times daily, no adverse signs and symptoms were observed as emerges from patients' experience The drug was specifically advised after meals No patient discontinued the treatment due to side effects Both clinicians as well as patients rated the tolerance of the treatment to be excellent to good in 100 % of patients Thus Betahistine was very well tolerated in a dose of 16 mg three times daily

Associated symptoms such as tinnitus, nausea and vomiting are commonly associated with vertigo attacks They are very disturbing to already frightened vertigo patients An interesting finding of this study is that all the patients who complained of nausea and vomiting as associated symptoms were completely relieved of the same on completion of 1 week of Betahistine therapy Other associated symptoms such as tinnitus, faintness, headache showed a statistically significant improvement with Betahistine treatment

Most patients with vertigo tend to hold their head and neck rigid in an attempt to prevent aggravation of attacks The resultant spasm of neck muscles is one of the major causes of headache associated with vertigo Relief of vertigo attacks tends to release this spasm and thus alleviate headache as well Since hearing loss observed in these cases was a chronic, non-fluctuant type, it is not surprising that this symptom did not show marked improvement

Till recently, there was trend to control very severe vertigo attacks or acute attacks with labyrinthine sedatives such as Cinnarizine or Prochlor-perazine Sedation or drowsiness is the common side effect of these drugs which delays vestibular compensation (Kirtane, 1999) But with the experience of this study, there is new insight for management of such severe or acute attacks of vertigo Betahistine in dose of 16 mg three times daily is a better choice to control acute or severe vertigo cases

In acute vertigo which is essentially due to the imbalance in the firing activity of the vestibular nuclei of both sides, there is a tendency during the acute phase for the cerebellum to inhibit the vestibular nuclei and thus alleviate the symptoms This is very graphically called the 'cerebellar clamp' Gradually over a period of weeks the vestibular nuclei on the unaffected side take over the function of the affected vestibular nuclei This occurs through the establishment of cross synapses and leads to a balance

in the firing activity of the nuclei of both sides As this happens, the vestibular nuclei are gradually released from the effect of the cerebellar clamp The entire process is called 'compensation', whereby an acutely giddy individual gradually regains his sense of balance even though the original pathology may not have been reversed Most antivertiginous drugs produce sedation and CNS depression This delays the process of compensation which is so necessary in rehabilitation of the patient As betahistine does not produce CNS depression it does not affect compensation

Betahistine being non-sedative, does not hamper the normal lifestyle of patients In fact, it has a facilitatory effect on vestibular adaptation, which is very vital for speedy rehabilitation of patients with acute peripheral vestibular failure (Biswas 1998 Tighilet et al (1995) observed that oral Betahistine (50 or 100 mg/kg bodyweight) significantly accelerated recovery in posture and balance following transection of left side vestibular nerve in cats and thus significantly facilitated vestibular compensation in cats

CONCLUSION

Thus the results of this study establish the excellent efficacy of Betahistine treatment at a dose of 16 mg three times daily in the management of vertigo patients Even acute or severe vertigo cases can be managed well with this therapy The results of this study also established the excellent tolerance of Betahistine therapy given as 48 mg/ day in divided doses (16 mg three times a day) in Indian patients without causing sedation

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