Anti vertigo Drugs-Revisited

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Abstract : Vertigo is a sense of whirling and rotation and is frequently associated with nausea and vomiting. Vertigo is a cardinal manifestation of vestibular disorders. Pharmacotherapy is required for symptomatic treatment of vertigo and motion sickness irrespective of the aetiology. Drugs like cinnarizine, betahistine and scopolamine are time honoured drugs. Antihistaminics and phenothiazines are also useful agents. Surprisingly, very few newer agents have shown undisputed efficacy against vertigo. This review describes the neurotransmitters involved in the genesis of vertigo and current status and evolution of appropriate pharmacological options for the treatment. [Khilnani AK et al NJIRM 2013; 4(4) : 118-128]

Key Words: Anticholinergic drugs for vertigo, Antihistaminics as antivertigo drugs, Pharmacotherapy of vertigo

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Introduction: Our body remains static due to interaction of three systems- the somatosensory, the visual and the vestibular system. The vestibular system is the most important in maintaining spatial orientation and posture. The semicircular canals transduce angular acceleration, otoliths in saccule and urticle transduce linear acceleration, and static gravitational forces provide the sense of head-position in space. Dysfunction in any of these systems may cause vertigo. Cerebellum functions as regulator of movement and posture. A mismatch of incoming sensory inputs (erratic input due to motion or disease) and conceptual internal model is perceived as vertigo. The cerebellar flocculus makes adjustments for vestibulo-ocular reflex while inferior olivary neurons carry information of voluntary body movements. Destruction of this nucleus prevents compensation after unilateral labyrinthectomy in animals[1].

The severity of vertigo varies from mild spinning sensation to tumbling down. Vertigo should be differentiated from presyncope, dizziness associated with postural hypotension and unsteadiness due to cerebellar dysfunction. Vestibular vertigo is usually of sudden onset and may or may not be associated with auditory symptoms. A number of brainstem lesions are associated with vertigo, which must be differentiated from peripheral vestibular lesions for proper management.

Motion sickness (Travel sickness, Sea sickness) is an important cause of vertigo and vomiting. It occurs during passive transportation by car, train, air or sea. Nausea, vomiting, salivation, yawning, malaise, reduced gastric motility, impaired digestion and hyperventilation characterize it. Labyrinthine stimulation and mismatch between anticipated and actual inputs appear to be the cause during travel. Other important causes are benign paroxysmal positional vertigo (BPPV) and cervical vertigo. Uncommonly, vertigo may be an adverse effect of drugs.

This review describes the neurotransmitters involved in the genesis of vertigo and current status and evolution of appropriate pharmacological options for the treatment.

Neurotransmitters in vestibular pathway: The vestibular system includes end organs which are the bony labyrinths (three semicircular canals) for linear motion and the utricle and saccule for angular motion. The vestibular hair cells generate receptor potential by movement induced disturbance. The chief excitatory neurotransmitter in type-II hair cells of vestibular nuclei is glutamate and histamine acts as a regulatory transmitter in median vestibular nuclei (MVN). Histamine is released during vestibular disturbance and excites MVN cells. Acetylcholine is considered to be main neurotransmitter in efferent vestibular system[2]. Neurotransmitters that mediate induction of vertigo and vomiting include acetylcholine, histamine, dopamine and serotonin and these are found in different parts of central vestibular connections. The corresponding receptors for above neurochemicals are histaminic (H_1) and cholinergic-muscarinic (M_1) in the labyrinth, and

serotoninergic ($5HT_3$), dopaminergic (D_2), M_1 and H_1 in area postrema. *Histamine* is found diffusely in central vestibular structures and centrally acting antihistamines modulate symptoms of motion sickness[3]. GABA acts as inhibitory neurotransmitter in vestibular neurones. Norepinephrine and dopamine are involved in compensation and adaptative responses to persistent vertigo. Noradrenaline (NE) facilitates neuronal plasticity following acute insult. Thus, NE enhances vestibule-ocular and vestibulospinal reflexes[4]. Serotonin is involved in mediating emetogenesis, potentiates rapid reactions to external stimuli and dynamic vestibular responses. Highest density of muscarinic receptors is found in area postrema and vagal nuclei[5]. Neuronal fibres from purkinje cells of cerebellum and vestibular nuclei also have an inhibitory neurotransmitter-GABA. Stimulation of the two types of GABA receptors, GABA-A and GABA-B, have similar effects on vestibular pathways[6], but specific GABA-B agonists, such as baclofen, decreases the duration of vestibular responses in animal models[7]. GABA-B receptors remain down regulated for longer period of time during compensation after acute vertigo whereas rapid functional restoration of GABA-A receptors is noted in MVN[8]. There is a close anatomical cooperation of vomiting centre, area postrema and various vestibular nuclei. Serotonin was found to inhibit the MVN neuronal activities via the $5\text{-}HT_{1A}$ receptors. Glutamate exists in the vestibular nerve and is released from the nerve besides the presence of glutamate receptor subtypes in the Vestibular nuclei [9].

Since several neurotransmitters and their receptors are involved in mediation of vertiginous syndrome, several different types of drugs are used as antivertigo agents. Many of these drugs are in clinical use for over a decade and some newer agents have been investigated. The efficacy of these drugs was not tested vigorously and even now in careful conducted studies some of the drugs are found to be as good as placebos. Some of these agents affect favourably or adversely the compensation and this may help selection of a particular drug. Those which adversely affect compensation should be used for a short period, for usually 1-2 weeks only. Patients who are susceptible to motion sickness are also sensitive to other emetogenic stimuli and hence many antiemetic agents are also required. This articles focusses on pharmacotherapy only and the specific treatment of different disorders manifesting as vertigo need to be undertaken

Experimental Evaluation of Antivertigo Drugs:

Animal models: A number of animal models for the study of motion sickness have been used over the years. Cats are very useful because of a wealth of neuroanatomic, neurochemical, and neurophysiologic information about them. Rat models are unique in that these animals do not vomit in response to coriolis stimulation, but they do demonstrate observable behavioral changes such as pica (eating nonnutritive substances such as kaolin). Rats are generally easier to handle than larger animals, and they require less stimulation time than do dogs and cats. Squirrel monkeys are the only primates commonly used in animal studies of motion sickness. They are highly susceptible to motion sickness induced by coriolis stimulation, and their response to anti-motion sickness drugs is similar to that of humans[10].

1. Anticholinergic agents : These are commonly used in motion sickness and other forms of vertigo. High density of muscarinic receptors is found in vagal nucleus, area postrema and vestibular nuclei. The central antimuscarinic action of these drugs is responsible for antivertigo effects.

Scopolamine (Hyoscine) is a time honoured vestibular sedative for the treatment of motion sickness and is considered to be the gold standard to test the efficacy of other agents. It can be given orally but only 10% is bioavailable. Its usual dose is 0.3 mg to be taken 30 minutes before journey and then same dose repeated every 6-8 hourly. Although a parenteral preparation containing scopolamine butyl bromide 20 mg/ml is available for IM use but being a quaternary compound it does not penetrate the blood brain barrier and thus lacks significant antimotion sickness activity. Scopolamine can also be used as a buccal tablet (1 mg) in hydroxypropyl methyl cellulose base[11]. A

transdermal patch (Transderm-V) contains 1 mg of drug and is effective for about 3 days. It must be applied 4 hours before the journey is begun. Scopolamine nasal spray is a quick acting measure in motion sickness[12]. Scopolamine can be used with ephedrine (25 mg) to counteract sedation and add the antivertigo effect. Similarly, addition of d-amphetamine in a dose of 5 mg has a synergistic effect[13]. Scopolamine was found to be more effective than cinnarizine in motion sickness[14].

There are limitations to the use of scopolamine. It delays adaptation to new environmental stimuli. There are unacceptable central (sedation, impaired psychomotor performance, amnesia) and peripheral (dry mouth, tachycardia, blurring of vision, urinary retention in elderly, and precipitation of glaucoma) antimuscarinic adverse effects. No impairment of psychomotor performance was reported in a randomised cross over trial[15]. In some patients contact dermatitis develops upon application of dermal patch for over a month. Scopolamine may also cause some dependence and psychosis and withdrawal may be difficult[16-18].

Other anticholinergics such as *atropine* , *glycopyrrolate* and *dicyclomine* have least antivertigo action*. Zamifenacin,* an agent used for irritable bowel syndrome, has more selective actions on M_3 (& M_5) receptors and is reported to be as effective as scopolamine in prevention of motion sickness[19]. These observations suggest that selective M_3 antagonists could be developed as antivertigo agents.

2. Antihistaminics: As a group these agents have moderate efficacy in the vertigo and motion sickness. In fact they are time-tested medications for acute episodes of vertigo in meniere's disease, vestibular neuronitis, and motion sickness. However, they are less effective in motion sickness than in other disorders.

The histaminergic receptors are found in central vestibular pathways including vestibular nuclei, area postrema (H_2), CRTZ (H_3), cerebellum (H_1) and nucleus tractus solitarius. H_1 and H_2 are postsynaptic whereas H_3 receptors are located pre-synaptically and have modulatory role. Conventional antihistaminics with anticholinergic and sedating activity are used as vestibular suppressants[20]. These agents enter blood brain barrier effectively. Newer nonsedating antihistaminics such as *fexofenadine*, *levocetirizine*, *loratidine, desloratidine*, *rupatadine* are devoid of anticholinergic activity and thus lack significant antivertigo actions. *Astemizole* may be an exception as it has been found useful in chronic vertigo and in meniere's disease[21]. However, its use is discouraged because of its arrhythmogenic potential. Antihistaminics are not only effective when used prophylactically but also when symptoms have occurred.

Promethazine: It is a potent antihistaminic, sedative and anticholinergic agent. It is found to be an effective vestibular suppressant in a dose of 12.5-25 mg, 3-4 times a day. In prevention of vomiting and nausea in motion sickness it must be used as 25 mg 1-2 hours before journey. It also hastens adaptation to motion stimuli and thus helps in compensation. It causes marked sedation which interferes with day time activities. Sedation can be reduced by addition of small dose (10 mg) of amphetamine. The latter has antivertigo effect on its own also. Promethazine (25 mg) is found to be equally or less effective but has a longer action as compared to scopolamine (0.6 mg) [22].

Diphenhydramine: It has pharmacological properties similar to promethazine. Its half-life is about 8 hours and is well absorbed orally (bioavailability is 86%). It is found in cough mixtures and antiallergic expectorants. It has significant antivertigo effect which is marred by daytime sedation and dry mouth. It may impair motor activity, cause blurred vision, constipation and urinary retention in elderly. The sedative effect of CNS depressants is potentiated[23].

Dimenhydrinate: The 8-chlorotheophylline derivative of dimenhydrinate is about 60% as potent as parent compound but has considerably less sedating activity. Therefore, it is a preferred agent for prevention and treatment of motion

sickness in dose of 50-100 mg taken 30 minutes before travelling and half the dose repeated every 6-8 hours thereafter. Children (> 2 years dose is 5mg/kg) in the age group 2-6 years may require 12.5-25 mg 2-3 times (maximum 75 mg) and 6-12 years require 25-50 mg 2-3 times a day with a maximum dose of 150 mg. A parenteral preparation contains 50 mg/ml and can be used by intramuscular route in meniere's disease[24]. It shares the adverse effects with diphenhydramine. A greater relative efficacy of dimenhydrinate (50 mg) over *meclizine* (50 mg) is reported in some studies[25].

Meclozine (Meclizine): Meclozine is effective in inhibiting the symptoms of motion sickness such as nausea, vomiting, and dizziness. The drug possesses anticholinergic activity also. It depresses labyrinth excitability and vestibular stimulation. The recommended dose is 25–50 mg orally, taken 1 hour before travel. The dose may be repeated every 24 hours as needed.

Cyclizine: It is a piperazine derivative having antimotion sickness effect similar to dimenhydrate and is considered to have less sedative effect[26].

Betahistine: It is considered to be an important drug useful in control of vertigo of various aetiology. In normal persons betahistine and cinnarizine show strong vestibular suppressant effects on nystagmus testing by cold calorie test. It is a histamine analogue which stimulates H_1 and H_2 receptors in vestibular nuclei and brain stem. In addition, it acts as an antagonist on H_3 presynaptic autoreceptors found in CRTZ and NTS in brain stem. Betahistine increases microcirculation in the vestibules and stria vascularis of cochlea. The drug is found to be effective in vertigo due to meniere's disease and vestibulitis. The effect is modest and dose dependent. Antivertigo effect is apparent in doses 8 mg thrice a day but full effect requires 16 mg thrice a day. It does not cause sedation and facilitates compensation/adaptation[27]. Unlike phenothiazines, it does not cause abnormal movements. It is also recommended for vertigo in elderly people. It is found to be moderately effective (v/s placebo) in meniere's disease in a dose of 16 mg twice a day[28.] In comparative trials it is found to be as effective as flunarizine[29]. In a metanalysis of 6 Randomized controlled trials, it was concluded that none of the trials showed any effect of betahistine on the hearing loss and most of the trials showed a reduction in the severity of vertigo and tinnitus[30,31]. There were sources of bias in these trials. Therefore, there is insufficient evidence to show that betahistine is really effective in meniere's disease. Analysis of the sub-groups in another meta analysis denoted a maximum efficacy after doses of 32 to 36 mg and with a period of treatment of 3-8 weeks[32]. It is contraindicated in active peptic ulcer and pheochromocytoma.

3. Neuroleptics: Phenothiazines have antihistaminic action have been discussed earlier. Among the other neuroleptics, *droperidol* has been investigated and found to have some antivertigo effect[33]. L-sulpiride (selective D_2 antagonist) was shown to have potent anti-motion sickness effect in monkeys[34]. Droperidol with fentanyl (an opioid analgesic) is currently used in the treatment of acute severe vertigo[35].

Prochlorperazine : A potent neuroleptic, it acts as D_2 blocker in chemoreceptor trigger zone (CTZ) and has anticholinergic effects also. It is used mainly in nausea & vomiting but is also effective in vertigo due to labyrinthine disorders & migraine in a dose is 5-10mg thrice a day. It can also can be given intramuscularly (12.5mg/ml) in acute vertigo. A sublingual tablet 5mg or a suppository (25mg) may also be used. However, it is less effective than meclizine & scopolamine[36]. Parenteral prochlorperazine causes some impairment of psychomotor performance and arousal. It may cause abnormal movements particularly in elderly & potentiates sedative action of CNS depressants and may cause arrhythmias with antihistaminics. It is avoided in epileptics.

4. Calcium Channel Blockers : Vestibular hair cells have calcium channels which are blocked by certain calcium channel blockers such as nifedipine, cinnarizine and flunarizine.

Cinnarizine : The mechanism of vestibular sedative effect is not known exactly. It is a calcium channel blocker and has some antihistaminic (H_1 blocking), anticholinergic & local anesthetic activity resulting in labyrinthine sedative effect. It has more selective action on vascular smooth muscles, which relax causing vasodilatation. As such cinnarizine blocks all types of calcium channels (voltage sensitive- L, T and N types and receptor-sensitive Ca++ channels). It is a highly lipid soluble agent and reaches brain adequately. Cinnarizine may inhibit Ca++ movement across vestibular sensory cell in ampulla and prevent constriction of the stria vascularis by inhibition of Ca^{++} channels[37].

After absoption, cinnarizine is well distributed in various body organs. It is extensively metabolized & then only small amount of active drug is excreted in urine and faeces. Because it has a short half-life of 3 hrs, it must be given 3 times a day after meals.

In clinical testing, the agent has demonstrated reduction in the duration of post-rotational nystagmus & post-rotational turning sensation. It reduces the intensity of nystagamus induced by cold caloric stimulation. It is moderately effective in controlling nausea and vertigo in meniere's disease and other vestibular disorders. It was found to be as effective and safe as nimodipine in 12 week double blind cross over study[38.] It effectively suppresses vertigo due to peripheral vestibular lesions & due to vertebrobasilar insufficiency in older patients. Cinnarizine is also used for prevention of motion sickness and should be used 2 hours before travelling[39]. Cinnarizine effectively prevents vertigo of motion sickness when given alone or along with domperidone, 30mg to be taken 2 hours before journey & then 15mg every 8 hourly during journey (child 5-12 years should receive half the adult dose). The combination with domperidone is supra-additive[40]. Because of rheological & vasodilatory actions, cinnarizine is useful in peripheral vascular insufficiency also. A dose of 75mg thrice a day reduces symptoms of intermittent claudication and increases walking distance.

Adverse effects: It is fairly well tolerated but occasionally, it may produce extrapyramidal effects [dyskinesia] in elderly. This unwanted effect is due to a reduction in Ca^{++} movement in strial neurones and its antidopaminergic effect. Therefore, the symptoms of parkinsonism may worsen. Severe mental depression if taken for longer time, weight gain, drowsiness (30 mg/day) and allergic reactions are other effects.

Flunarizine: It is a difluorinated derivative of cinnarizine & has shown strong vestibular suppression action due to its antihistaminic and Ca^{++} channel blocking actions. It is used as a prophylactic agent in migraine, motion sickness and in management of vertigo due to central vestibular disorders and peripheral vascular disease. Its usual dose is 5-10mg given once daily in night as it causes drowsiness. A higher dose of 30mg is more effective in reducing caloric response as compared to 5mg prochlorperazine[41]. It has a long life so given once daily and residual concentration is detected up to 4 months. It shares the adverse effects with cinnarizine.

Nimodipine : It is a lipophilic dihydropyridine type of Ca^{++} channel blocker (CCB) is currently used to counteract the cerebral vasospasm following subarachnoid hemorrhage in a dose of 30 mg three to four times daily. It crosses the blood-perilymph barrier. It may have a role in meniere's disease when conventional agents fail[42]. Its mechanism of antivertiginous effect is not exactly known but may be attributed to inhibition of calcium influx into vestibular hair cell. A central neuromodulation in response to pheripheral vestibular input is also contributory. It was found be as effective as cinnarizine a double blind cross over trial for 12 weeks[38].

5. Anticonvulsants : A source of stimulation causing neural mismatch may result in hyper-excitability of neurons in motion sickness and therefore, anticonvulsant with sodium blocking action may stabilize such excitable neurons. Phenytoin, an agent widely used in tonic-clonic seizures is shown to increase tolerance to motion stimuli as compared to placebo. Phenytoin also

reduces gastric motility in motion sickness[43]. *Gabapentin, oxcarbazepine, carbamazepine* are also shown some effect in anecdotal reports. Gabapentin also suppressed nystagmus of central origin[44].

Benzodiazepines: These are commonly used for their anxiolytic, sedative and hypnotic properties. As a group the benzodiazepines effects are mediated by GABA-ergic modulation of GABA-A receptors which is inhibitory in nature.

Diazepam suppresses neuronal activity in vestibular nuclei of cats[45]. In humans, when motion stimuli are provided by rotation and head tilt, diazepam increases tolerance to these tests when used 2 hours before. The effects come in doses smaller (2 mg two to three times a day) than antianxiety doses (20-30 mg daily). These small doses have less adverse effects such as sedation, altered alertness, memory impairment and benzodiazepine dependence. Small doses also do not impair vestibular compensation[46]. Parenteral *lorazepam* 1-2 mg is an effective agent to suppress severe acute vertigo. It is used in smaller doses of 0.5 mg twice a day in chronic vertigo. *Clonazepam*, an anticonvulsant benzodiazepine, is also found to be as effective as lorazepam in chronic vertigo but not in acute severe vertigo. It is a slower acting agent as compared to lorazepam[47]. *Alprazolam* is another benzodiazepine derivative tried but there is a greater risk of dependence and withdrawal syndrome with its use.

6. Adrenergic agents : *Dextroamphetamine* and *ephedrine* are older agents used as adjuncts in the management of motion sickness and vertigo. In some studies amphetamine is reported to be as effective as antihistaminics[48]. The antimotion sickness effects are probably due to raised dopaminergic activity in the brain. Unfortunately it has dependence liability.

Ephedrine alone is not useful in vertigo but when given with scopolamine it reduces impairment in alertness. An advantage of using adrenergic agents is that these drugs increase compensation.

7. Antidepressants: The antidepressants with sedative effects such as *doxepin* and *imipramine* have been shown to exert antimotion sickness action. Doxepin (10mg, 25mg, 75 mg tablet) has additional antihistaminic action which contributes to its antivertigo effect. Subjects exposed to rotation with head tilt manoeuvres daily for 5 days were given doxepin (75mg per day) and the effects were compared with scopolamine. Both drugs were found to be equally effective[49].

8. Glucocorticoids : Meniere's disease is considered to be an autoimmune reaction and hence there is a role of glucocorticoids. In acute vertigo, glucocorticoids reduce inflammatory oedema of endolymphatic sac. These also modulate central vestibular pathways which mediate vertigo and vomiting. Evoked vertigo in healthy volunteers is consistently associated with an increase in steroid serum levels and accompanying decreases in the plasma levels of glutamate, aspartate, and GABA[50].

There is some evidence to show that steroids improve compensation in vertigo. A high dose initially for about a month and then tapered gradually is reported to improve vertigo and hearing in meniere's disease. Topical administration of dexamethasone, via tympanostomy tubes, provides higher concentration and better results with lower systemic adverse effects[51.] Intratympanic injection of 16 mg methylprednisolone and 16 mg IV dexamethasone for 3 days followed by oral dexamethasone is shown to improve hearing (35.4%) and complete vertigo control (63.5%) in an uncontrolled trial[52.] In a pilot study, two groups (n = 8 per group) were treated orally with either diphenidol (25 mg/d) plus acetazolamide (250 mg/48 h) (control group), or the same treatment plus prednisone (0.35 mg/kg) daily for 18 weeks (prednisone group). The frequency and duration of vertigo episodes were reduced by 50% and 30%, respectively Prednisone-treated patients manifested a significant reduction in tinnitus[53].

In another prospective randomized study with methylprednisolone a marked reduction in

vertiginous episodes was reported. The electronystagmogram returned to normal within 1 month in all 16 patients taking methylprednisolone[54]. An alternative approach for use of glucocorticoids is to inject them intratymapanically.

The exact mechanism of action of steroids remains to be known and multiple mechanisms are likely to operate. The modulation of central vestibular pathways by neuroactive steroids may involve effects on γ-aminobutyric acid-ergic and glutaminergic pathways. Conversely, a direct stimulation of MVN may be there. Experimental investigation of the effects of a glucocorticoid, dexamethasone, on vestibular disorder following unilateral labyrinthectomy in rabbits revealed that systemic injection of dexamethasone decreased the frequency of nystagmus and head deviation dose-dependently following hemilabyrinthectomy, and the rate of decrease was faster than that obtained by saline. In contrast, RU38486 (a glucocorticoid receptor antagonist) delayed the reduction of nystagmus and head deviation. These results suggest that dexamethasone directly activates the MVN neurons, thereby accelerating vestibular compensation[55].

The vestibular nuclei also express enzymes that are important in the synthesis of steroids and the steroids may modulate their activity. Steroids mediate both facilitatory and deleterious effects of stress on vestibular compensation[56].

Steroids are reported to affect the cationic transport function in semicircular canal epithelium. The measurements of short-circuit current (I_{sc}) demonstrated stimulation (7–24 h) by the glucocorticoids - hydrocortisone (EC_{50} 13 nM), corticosterone (33 nM), prednisolone (70 nM), and dexamethasone (13 nM) over physiologically and therapeutically relevant concentrations and its block by amiloride (IC_{50} 470 nM) and benzamil (57 nM), inhibitors of the epithelial sodium channel (ENaC). I_{sc} was also partially inhibited by basolateral ouabain and Ba^{2+}, indicating the participation of Na^+-K^+-ATPase and a K^+ channel in Na^+ transport. By contrast, aldosterone stimulated I_{sc} only at high concentrations (EC_{50} 102 nM). The action of all steroids was blocked by mifepristone (RU-486; K_d ~0.3 nM) but not by spironolactone (K_d~0.7 μM). Expression of mRNA for the α-, β-, and γ-subunits of ENaC was demonstrated in the presence and absence of glucocorticoids[57].

9. Diuretics : Diuretics such as *acetazolamide, bendroflurazide, chlorthalidone, Hydrochlorothiazide* and *triamterene* have shown to improve vertigo but not hearing in meniere's disease[58] The diuretics are not found to be effective in other forms of vertigo.

10. Drugs with uncertain efficacy

Methotrexate: It showed improvement in bilateral meniere's disease [59].

Acetyl leucine: It is used mostly in France and is reported to have prompt antivertigo effect when given intravenously[60]. At present it is not available in India.

Trimetazidine : It is anti-ischemic agent used in management of angina pectoris. In a French double blind trial with 60 mg trimetazidine v/s 24 mg betahistine given for 3 months in vertigo due to various causes, showed a better response with trimetazidine particularly in a subset of cases with meniere's disease. All patients in trimetazidine group recovered as against only 4 of 10 patients receiving betahistine recovered fully [61].

Gingko biloba extract : Ginseng and valerion are tried with variable results. Valerion is a product from Garden heliotrope plant and is touted to have antivertigo efficacy. Its use is associated with liver damage.

Gingko biloba extract has uncertain utility in management of vertigo and meniere's disease although it is used in a dose of 40 mg thrice a day. It is also used as cerebral activator in disorders associated with cerebral impairment. No beneficial effects are reported with ginseng in metanalysis of several trials[62]. A major problem with its use is potential for adverse drug interactions due to its antiplatelet and anticoagulant activity as it has platelet activating Factor (PAF) antagonistic effect. It should be

stopped 36 hours before surgery. Gingko also increases toxicity of phenytoin, calcium channels blockers and trazodone.

Ginger root extract (Zingibar officinale) is used in nausea, vomiting and prevention of motion sickness but carefully controlled trials do not support its efficacy. It however suppresses tinnitus in some cases. Ginseng has not shown significant antivertigo effects in metanalysis of some trials[63]. It needs to be evaluated by rigorous controlled methods.

Others: Vasopressin hypersensitivity of the endolymphatic sac may be implicated in the pathogenesis of Meniere's disease. Specific *vasopressin antagonists* will help define the role of vasopressin in Meniere's disease.

A number of drugs are known to cause vertigo or dizziness. These drugs include aminoglycosides (streptomycin, gentamicin), anticonvulsants, sedatives and hypnotics, cisplatin, vincristine, vancomycin, α blockers, and diuretics (ethacrynic acid, frusemide). Obviously these drugs should be stopped if vertiginous episodes are attributed to their use.

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