Review Article

Current Trends in the Pharmacotherapy of Vertigo

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Abstract

Vertigo is one of the commonest disorders, affecting 20-30% of the general population. It may arise due to pathology in the inner ear, brainstem, cerebellum or due to psychological causes. Vertigo is a distressing symptom for anyone to experience and a challenging task to treat. Pharmacotherapy plays a predominant role in the management of vertigo. The classes of drugs used in vertigo include histamine analogues, vestibular suppressants, anti emetics, steroids, antibiotics, beta blockers, GABA modulators, calcium channel blockers, selective serotonin reuptake inhibitors (SSRI), potassium channel blockers, diuretics and ginkgo biloba. As each class has its own merits and demerits, the selection of drugs suitable for a particular patient depends on the physician's choice. This review attempts to highlight the characteristics of each group of drugs which would help in rational therapy of vertigo.

Key Words: Vertigo, Motion sickness, Meniere's disease, Betahistine, Vestibular suppressants.

Introduction

Vertigo is the most inconvenient, distressing symptom disorder affecting 20-30% of the general population[1]. The incidence of vertigo increases with age and is about two to three times higher in women than in men[2]. Vertigo is a sensation of motion in which the individual or the individual's surroundings seem to whirl dizzily. The word "Vertigo" is of Latin origin, meaning, 'whirling round'. It is not a disease by itself but the cardinal symptom of different diseases of varying etiology. Vertigo is classified into peripheral and central.

Peripheral vertigo, as the name indicates, is due to problems of inner ear and the most common causes are benign paroxysmal positional vertigo (BPPV), meniere's disease, vestibular neuronitis. Other less common causes include labyrinthitis, perilymph fistula, superior semicircular canal dehiscence syndrome (SSCDS). Central vertigo is due to disorders in CNS such as haemorrhage, hypoxia, tumours and lesions of VIII cranial nerve.

The treatment approaches for vertigo are:

1.Vestibular rehabilitaion therapy (including otolith repositioning maneuvres)
2.Pharmacotherapy
3.Psychotherapy
4.Surgery (only in rare situations)

The classes of drugs that have been found to be useful in vertigo are:

1.Histamine analogue
2.Vestibular suppressants
    Antihistamines
    Anticholinergics
    Benzodiazepines
3.Antiemetics
4.Steroids
5.Antimicrobials
6.Beta blockers
7.GABA modulators
8.Calcium channel blockers
9.Selective Serotonin Reuptake Inhibitors(SSRI)
10.Potassium channel blockers
11.Diuretics
12.Plant products such as Ginkgo biloba

Apart from this list of drugs several other groups of drugs such as anti epileptics, tricyclic antidepressants and aminoacid like acetyl leucine are being tried.

Histamine analogue

Betahistine dihydrochloride, a histamine analogue, is one of the most widely used drugs for vertigo. It is a partial agonist at H1 receptor and a potent antagonist at H3 receptor. Various animal and human studies have shown that betahistine increases cochlear blood flow as well as cerebral blood flow through its action on H1 receptors.

H3 receptors are located presynaptically in the brain and serve primarily as an autoreceptor controlling histamine release from neurons in brain.

Betahistine acts centrally by enhancing histamine synthesis within tuberomamillary nuclei of the posterior hypothalamus and histamine release within vestibular nuclei through antagonism of H3 autoreceptor[3].

Peripherally, Betahistine may also regulate the asymmetric function of the sensory vestibular organs. Betahistine is mainly used in the long term management of meniere's disease[4]. Dosage : 8-16mg three times daily, taken preferably with meals, for 6-8 weeks. Daily dose should not exceed 48mg[5].

Adverse effects: Headache, gastric side effects, insomnia, nausea, hypersensitivity reactions in predisposed individuals. Betahistine has to be avoided in bronchial asthma as it can increase bronchospasm and in peptic ulcer because of the possibility of increasing acid secretion.

Vestibular suppressants

Vestibular suppressant is a drug that reduces nystagmus evoked by vestibular imbalance or which reduces motion sickness.

It includes three major groups of drugs:

1.Anticholinergics

2.Antihistamines

Benzodiazepines

Anticholinergics

These are competitive muscarinic antagonists and increase the motion tolerance. They act centrally by suppressing conduction in the vestibulo cerebellar pathways. Anticholinergics that do not cross the blood brain barrier are ineffective in controlling motion sickness.

Scopolamine is available as transdermal patch, and is the most effective anticholinergic in motion sickness[6]. The patch has to be applied 4 hours before journey. Each patch contains 1.5 mg of scopolamine programmed to deliver 1mg over 3 days, when applied transdermally[7]. Patches on removal can produce withdrawal syndrome like dizziness, nausea, vomiting and abdominal cramps.

Antihistamines

Though histamine analogue betahistine is the most commonly used anti vertigo agent, paradoxically antihistamines are also found to give relief in vertigo. Dual mechanism can be attributed to its effect. 1) Because of anticholinergic effect, it can act similar to scopolamine. 2) Modulation of the emetic linkage between neural mismatch signal and the emetic centre[10].

Antihistamines prevent motion sickness and reduce the severity of symptoms, even if taken after the onset of symptoms[8].

Meclizine 25-50mg thrice daily is the preferred antihistamine, to be taken one hour before travel. Dimenhydrinate 50mg thrice daily is also found to be equally efficacious.

Sedation is the common side effect. Antihistamines with anticholinergic properties have to be avoided in men with prostatic hypertrophy due to the risk of urinary retention and glaucoma as they can increase the intraocular pressure due to angle closure.

Benzodiazepines

Benzodiazepines are GABA agonists acting on the GABA A receptor chloride channel complex. They suppress the vestibular responses, due to their CNS depressant action. Diazepam , clonazepam and lorazepam are the mainly used drugs in this group.

Low doses of diazepam (5mg once daily) or lorazepam (0.5mg twice daily) can prevent addiction. Clonazepam is also effective[6].

Antiemetics

Nausea being one of the symptoms often associated with vertigo, anti emetics essentially have a role. Oral, suppository formulation or I.V. injections may be used depending on the severity of symptoms.

The antihistamines promethazine, meclizine have significant antiemetic effect in patients with vestibular disorders. Whereas the well known antiemetics domperidone and metoclopramide have no effect on motion sickness[9]. Domperidone does not cross the blood brain barrier and metoclopromide is not effective against emetic reflexes arising from the vestibular apparatus.

Serotonin receptor (5HT3) antagonists like ondansetron and granisetron effective in preventing anti cancer therapy induced emesis, have no effect against motion induced emesis[10] as 5HT3 receptors are not reported to be involved in motion sickness.

Steroids

Methylprednisolone was found to be successful in improving the vestibular function in patients with vestibular neuronitis due to its anti inflammatory activity. The dose was 100mg once daily, stepped down by 20mg every 4th day[11]. In Acute Cogan Syndrome, initial high dose methylprednisolone (1000mg/day I.V) and dose reduction depending on course of disease has been proved to be effective[12,13]. Precipitation of peptic ulcer, predisposition of hypertension and diabetes mellitus, fixed drug eruptions and steroid induced depression are expected to occur with prolonged high doses.

Antimicrobial

Trans tympanic low dose gentamicin (10-20mg) 3-4 injections, at intervals of 8-12 weeks has been found to reduce the frequency of attacks in Meniere's disease. Gentamicin produces its effect by directly damaging the type I hair cells of the inner ear because of which it is also called ototoxic antibiotic. Minimal hearing loss is expected to occur following the therapy[13,14].

Beta blockers

Beta blockers are the drugs of choice in vestibular migraine prophylaxis. Propranolol 40-160mg/day has

to be continued for a period of 6 months. Metoprolol succinate 50-200mg/day is an effective alternative[15,16]. They decrease the central sympathetic outflow and hence the neuronal activity and excitability. Propranolol also has membrane stabilizing properties and potential to inhibit nitric oxide synthesis. Nitric oxide is a potent vasodilator. Inhibition of its synthesis leads to vasoconstriction and relief in migraine. Bradycardia is the expected side effect. Patients with bronchial asthma and diabetes mellitus need to be monitored closely as beta blockers may precipitate bronchospasm and mask the symptoms of hypoglyce mia respectively.

GABA modulator

Topiramate, an anti epileptic, that potentiates the GABA ergic transmission, is approved by FDA for the prophylaxis of vestibular migraine. Started with 25mg daily, in the first week, the dose can be escalated by 25mg every week, till a maximum of 100mg daily in 2 divided doses. It's effect is due to reduction in the genetically mediated brain hyper excitability that precipitates migraine in susceptible individuals[17]. Diarrhea, nervousness, visual and speech disturbances and weight loss are the common side effects.

Calcium channel blockers

Calcium channel blockers may be useful in vertigo. They may exert vestibular suppression by blocking the calcium channels in the vestibular hair cells. Cinnarizine, mainly an antihistamine, has calcium channel blocking property as well. Cinnarizine is found to be very effective for peripheral vertigo. The dose is 12.5mg thrice daily. Flunarizine, a fluorinated derivative of Cinnarizine is more potent and long acting. It is a powerful peripherally acting labyrinthine suppressant. The dose is 10mg/day. Headache, gastro intestinal irritation, hypersensitivity reactions and tremor are expected adverse reactions[18,19,20].

Selective serotonin reuptake inhibitors (SSRI)

SSRIs are antidepressants effective in treating vertigo in patients with major or minor depressive symptoms. Citalopram 10-20mg/day can be used in phobic vestibular vertigo. Sertraline 25-150mg/day, Fluoxetine 5-60mg/day, Paroxetine 5-40mg/day are other effective alternatives. From the reports of various clinical trials conducted, it is clear that SSRIs have better outcomes than vestibular suppressants or benzodiazepines in vertigo with psychiatric symptoms / migrainous headaches[21].

Potassium channel blockers

Potassium channel blockers can be successfully used to treat the down beat nystagmus, central positional nystagmus, episodic ataxia and gait disorders, associated with cerebellar vertigo syndromes. 4 –Aminopyridine, 10mg/day twice daily or its sustained release formulation, Fampridine, which is primarily indicated to improve walking ability in multiple sclerosis can also be used on off-label basis in treating cerebellar vertigo syndromes.

The probable mechanism of action could be by increasing the physiological inhibitory influence of vestibulo cerebellum on vestibular nuclei[22,23,24].

Diuretics

Diuretics along with low salt diet were previously used in treating meniere's disease. Recent studies have shown that diuretics reduce the volume and pressure in the endolymphatic partition of the labyrinth, abruptly lowering the blood pressure. This can lead to exaggerated vasomotor response inducing ischaemia to the inner ear leading to permanent damage. Hence the role of diuretics in meniere's is still questionable[25].

Ginkgo biloba

Ginkgo biloba is a Chinese herbal medicine, claimed to improve cognitive function. The benefial effect of *ginkgo biloba* extract in treating vertigo of vestibular and non vestibular origin has been demonstrated in preclinical and clinical studies. In a multicentric clinical trial conducted by Larysa Sokolova et al., *Ginkgo biloba* extract 120mg twice daily, for a period of 12 weeks was found to be safe and as effective as betahistine[26,27].

Conclusion

Vertigo being a symptom of varying etiology, is a challenge to offer complete cure or long term remission. Pharmacotherapy plays a key role in its management. Betahistine, the most commonly prescribed drug for vertigo, plays an essential role in meniere's disease. Vestibular suppressants are the mainstay of treatment for acute attacks. Antiemetics prevent nausea and vomiting associated with vertigo and motion sickness. Corticosteroids successfully improve the vestibular function in vestibular neuronitis. Transtympanic gentamicin reduces the frequency of attacks in meniere's disease. Beta blockers, Topiramate and Calcium channel blockers are effective drugs for prophylaxis of vestibular migraine. Selective Serotonin Reuptake Inhibitors effectively control vertigo associated with psychiatric symptoms. Potassium channel blockers are used in treating cerebellar vertigo syndromes. The benefit of Diuretics in meniere's disease is uncertain. *Ginkgo biloba*, is a potential herbal alternative. Though various groups of drugs are available for the treatment of vertigo, the selection of drugs depends on the etiology, type and associated illnesses. Betahistine still remains the main drug used in the treatment of vertigo.

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