BETAHISTINE

Anirban Biswas
Flat 314, Sukhsagar Apartment
252/A, Picnic Garden Road,
Calcutta-700 039

The modern equilibriometric examinations have now matured to such a stage that the neurotologist can localise with precision most lesions causing vertigo and also measure the functional activity of a specific lesion. The clinician now knows whether a lesion is central or peripheral in type, and also whether the vertiginous lession is paretic or irritative (hyperative) in nature. The management of these functional neurotological lesions can now be tailored according to the specific disturbance as identified by the equilibriometric studies. The updated clinician must be conversant with the pharmacology of the various drugs advocated for the therapy of the balance-disorder patient and must be able to make the "right choice" with precision. The choice between the wild collection of different drugs like anti-cholinergics, antihistaminics, histaminics, phenothiazines, monoaminergics, benzodiazapines, vasodialators, etc. should be based on solid pharmacotherapeutic considerations and not made at random.

One of the many drugs used in the management of the balance disorder patient is the orally active histamine agonist Betahistine. The choice of betahistine is this column is due to controversies attached to it. It is advocated by some neurotologists (and promoted by the pharmaceutical companies) as being specific for Meniere's disease which grossly limits the use of the drug in other causes of vertigo since true Meniere's disease is a rare entity (even though the diagnosis of Meniere's disease is frequently used as a convenient dumping ground for most cases of vertigo). It is known to be a histamine agonist for which many clinicians do not prescribe it apprehending gastric side effects. This seriously limits the use of this drug. There are neurotologists who have found it no better than a placebo (the short term beneficial effects being attributed to a non-specific CNS suppression) and there are numerous published reports where it has been claimed to be a wonder-drug which not only symptomatically controls the vertigo but also corrects the pathology and even facilitates vestibular compensation.

The main actions of betahistine are :

a) to induce an inhibitory effect on polysynaptic neurons within the vestibular nuclei in the brainstem. This therapeutic action of betahistine is believed to be due to its interaction with the H_1 and H_3 type of histamine receptors. The H_3 receptors are found in the presynaptic membranes of some neurons (histaminergic neurons) in the brain. The H_3 receptors control the release of histamine and other neurotransmitters in the synapse. Histamine is believed to bind to the H_3 receptors and inhibit the release of the neurotransmitters at the synapse. When betahistine is administered it stops histamine from interacting with the H_3 receptor and increases the release of neurotransmitters into the synapse. This increased level of neurotransmitters (like serotonin), inhibits the activity of the vestibular nuclei. Unemoto et. al. (1982) established the inhibitory effect of betahistine on the firing activity of the polysynaptic neurons in the lateral vestibular nuclei. This inhibitory effect prevents the occurrence of massive impulses to the polysynaptic neurons and thereby brings about the antivertiginous effect. The vestibular nuclei interpret and analyse the inputs regarding the subject's spatial orientation from the afferents received from the inner ear. The firing activity of the vestibular nuclei is influenced by the inputs received by it. When there is a derangement of this input as occurs in peripheral vestibular lesions, the firing activity of the vestibular nuclei increases. Excess firing of the vestibular nuclei leads to vertigo. Betahistine reduces this firing activity of the vestibular nuclei. This reduction of firing activity is dose dependent; hence higher

dose has more effect. The 16mg tds dose is hence a better schedule in acute conditions than the usually advocated 8mg tds dosage.

b) to induce capillary vasodilation and enhance vascular conduction in the labyrinth, i.e. increase blood supply to the inner ear. This effect of betahistine has been established by many studies viz. that of Suga & Snow (1969), Martinez (1972), and Anderson and Kubicek (1971). It has been established by Laurikainen et al. (1993) that betahistine selectively increases the inner ear blood by dilation of the microvessels in the inner ear with weak vasodilation in the other areas. Selective vasodilation of the inner ear without systemic effects is very desirable and makes the drug more user-friendly. Most other vasodialators are unselective in their action and dialate all the blood vessels in the body. This leads not only to postural hypotension, but it also may divert the blood from the microcirculatory system of the inner ear to the larger blood vessels in the other areas and thereby actually deprive the inner ear of its necessary quota. The effects of betahistine on systemic blood pressure is very minimal. This vasodilatatory effect is believed to be due partially to the stimulation of the H_1 histamine receptors in the inner ear blood vessels and partially due the liberation of histamine which in turn stimulates the H_1 receptors of the inner ear blood vessels leading to vasodilatation and increased blood flow.

In addition to these main actions of betahistine on the peripheral vestibular system described above, Claussen et al., established by means of Vestibular Evoked Potential studies that betahistine is capable of modulating central equilibrium regulating pathways.

Another effect of betahistine in balance-disorder patients is its facilitatory effect on vestibular adaptation which is very vital for speedy rehabilitation of patients who have acute peripheral vestibular failure. A study to test the efficacy of betahistine in modulating the process of vestibular compensation in experimentally induced unilateral vestibular lesion in cats was carried out by Tighilet B et al. (1995). It showed that betahistine facilitates the compensation/ adaptation process very significantly. This is in sharp contrast to the other antivertigenous drugs like sedatives, antihistaminic and also cinnarizine which are known to delay the vestibular compensatory process. It is not established whether betahistine induces the vestibular compensatory mechanism by a shut-down of the vestibular nuclei on the healthy side or by facilitating regeneration of spontaneous activity on the damaged side, neither has there been any supportive study available in humans but from the work of Tighilet et al. we can safely speculate that in humans, betahistine expectedly facilitates the vestibular compensatory mechanism or at least does not inhibit this vital process. Most other anti-vertigenous drugs are known to delay and have an inhibitory effect on vestibular adaptation/compensation mechanisms.

There are numerous clinically documented reports of controlled-study of betahistine in peripheral vestibular disorders especially in Meniere's disease. Though there has been a trend of reporting the role of betahistine in Meniere's disease mainly, yet there are quite a few well-documented reports of betahistine in non-Meniere's peripheral vestibular disorders. One such is that of Oosterveld W.J. et al. (1989) where the efficiency of betahistine in paroxysmal vertigo of any eitiology is reported in a double-blind, placebo-controlled study. This study showed that compared to placebo, betahistine significantly reduced the frequency and severity of the spells of paroxysmal vertigo. The significant alleviation of the intensity of vertigo is probably due to the inhibitory effect of betahistine on the vestibular nuclei complex, effected through the facilitation of histaminergic neurotransmission as explained above. The prophylactic effect, i.e. reduction in the frequency of the vertiginous spells is probably attributable to improved microvascular circulation in the inner ear. Aantaa (1991) had reported a study of Betahistine in acute vestibular vertigo of Meniere's disease. Though this study of Aantaa was not a double-blind cross-over study yet this clinical study did show that most cases of Meniere's diseases improved with Betahistine therapy.

This of course does not mean that Betahistine is specific for Meniere's disease. Though it has been established that distention of the endolymphatic space is the cause of Meniere's disease, it is not known with any amount of certainity what causes this distention. Of the many theories suggested as the possible cause of this endolymphatic distention, one is atrophy of the stria vascularise and reduced vascularity of the inner ear. This

however is just an hypothesis and nothing has been proved as yet. Moreover recent studies suggest that immunologic factors and altered glycoprotein metabolism are the probable causes of this pathology. Hence there is not much rationale in advocating Betahistine as a drug specific for Meniere's disease. Though there is no denying of the fact that betahistine increases inner ear blood flow, yet when we are not sure that reduced vascularity of the inner ear is the cause of endolymphatic distention, there is not much sense in accepting that Betahistine cures Meniere's disease by increasing inner ear blood flow, Reduced inner ear blood flow is a common cause of peripheral vestibular disorders and this is definitely reversed by the increase in inner ear blood flow caused by betahistine. Hence in those case (not specifically Meniere's disease only) where reduced inner ear blood flow is the cause of inner ear disturbance, Betahistine has a very big role. The beneficial effect of Betahistine in Meniere's disease is probably due to its other effects, i.e. those unrelated to increased vascularity. It has already been explained that Betahistine induces an inhibitory effect on the polysynaptic neurons in the vestibular nuclei. But this action of Betahistine occurs not only in patients of Meniere's disease but in all peripheral vestibular lesions. Hence it may be concluded that Betahistine though not specific for Meniere's, is nevertheless a very effective drug for the management of all types of peripheral vestibular disorders. It can be used in Meniere's disease for exactly the same reasons for which it is used in any other type of peripheral vestibular disorder. The added advantage of using Betahistine in cases of peripheral vestibular lesions are that it does not delay the vestibular compensatory mechanisms like the other commonly used antivertigo drugs.

Betahistine is available as 8 mg tabs and the recommended dose is 8-16mg 3 times daily. 16mg thrice daily is the preferred dosage. The drug can be used on a longterm basis since it does not have any disturbing side effects. It does not have any sedative action like the antihistamine groups of antivertigo drugs. On the contrary, H_1 agonistic effect of betahistine makes the patient more alert. Betts et al., (1991) objectively documented the effects of betahistine, prochlorperazine and placebo on driving ability and other factors related to impairment of awareness. The study showed that Betahistine did not impair driving performance and there was no impairment of awareness, whereas with prochlorperazine there was impairment of driving performance. It is apprehended by many neurotologists that betahistine being a Histamine analogue will increase gastric acid secretion and cause gastritis leading to the peptic ulcer syndrome complex. This however is not very true because betahistine has its effects mainly on H_1 and H_3 receptors and not on the H_2 receptors. Its affinity for H_2 receptors is very very feeble. In the stomach the histamine receptors are mainly the H_2 receptors-upon which Betahistine does not have a pronounced effect. Hence gastric side effects are minimal. Nevertheless to be on the safer side it is always prudent to use Betahistine immediately after meals. It has been shown that Betahistine does not nullify the action of H_2 antagonists like cimmetidine which are used for treating peptic ulcer patients.

In conclusion it may be said that Betahistine in a dose of 16mg thrice daily is a reasonably safe non-sedating antivertigo therapy which improves the inner ear blood circulation and also inhibits the vestibular nucleus. Unlike the other vestibular sedatives, betahistine does not delay or inhibit the vestibular compensatory mechanism and does not impair mental alertness. It may be used profitably in all cases of peripheral vestibular disorders irrespective of whether it is a case of Meniere's disease or any other pathology.

References

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