Palliative Care Rounds

Ondansetron in Multiple Sclerosis

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Abstract
Two young women with chronic nausea and vertigo caused by multiple sclerosis responded to the introduction and maintenance of the 5HT3 receptor antagonist, ondansetron. Palliative care is a neglected aspect of management of degenerative neurological diseases and these cases highlight the approaches that may be used to manage difficult symptoms in the population with multiple sclerosis. J Pain Symptom Manage 2000;20:388–391. © U.S. Cancer Pain Relief Committee, 2000.

Key Words
Nausea, vertigo, multiple sclerosis, ondansetron

Introduction
Chronic and persistent nausea may be demoralizing, obnoxious and demeaning. Only rarely in nonmalignant disease is nausea an enduring symptom. Chronic and persistent nausea of central origin may be a symptom of multiple sclerosis. It is more commonly described as a paroxysmal symptom, a symptom of the inflammatory response in the brainstem rather than that of gliosis. Palliation of chronic nausea can greatly improve quality of life. 5HT3 receptor antagonists may have role in the management of nausea in nonmalignant disease. Voltz suggested that the palliative care of degenerative neurological disorders has been a rather neglected component of the ongoing management of these diseases and that palliative medicine as a specialty has much to offer neurology and neuropsychiatry.

Case 1
A 43-year-old nurse had initially presented 10 years earlier with a two-month history of a painful eye, intermittent diplopia and tingling sensation over her right face. These symptoms fully resolved spontaneously within one month. Investigations at that time included examination of the cerebrospinal fluid and CT scan of the head, both of which were normal.

Similar symptoms recurred two years later, with the additional features of mild gait ataxia and hesitant upper limb motor coordination. Pale optic discs, normal eye movements, a drift of the outstretched left arm, clumsiness with rapid alternating movements and tasks of coordination on the left, mild spasticity in the left leg, brisk left lower limb reflexes and a left-sided Babinski response were the clinical findings. Oligoclonal banding of CSF IgG, abnormal visual evoked potentials and multiple hyperintense foci in the white matter of both cerebral hemispheres and brainstem on the MRI supported the clinical diagnosis of multiple sclerosis. The ataxia and incoordination promptly resolved following a five day course of parenteral corticosteroids. Associated clinical features at this time included a major depressive episodes which necessitated the introduction of an anti-
depressant regimen, (the reversible inhibitor of monamine oxidase, moclobemide), which was well tolerated and resulted in considerable improvement of mood.

Within a few months of presentation, she complained of persistent nausea, without vomiting. The nausea was aggravated by positional factors, occurring most commonly while standing, and intensified by the onset of fleeting and erratic episodes of vertigo, during which the patient had the perception that her lower limbs were completely outside her voluntary control. The nausea was constant, more oppressive if fatigued. It was not induced by food but there was associated anorexia. Bilateral optic atrophy was apparent on clinical examination, as well as a sensory loss to light touch over the right side of the face and both feet extending up the calves to the knees, proprioceptive errors in the left big toe, increasing bilateral pyramidal weakness in the legs and a broad-based deliberate gait. These findings indicated a progression of the disease. Nystagmus was still not evident. The brief “spins” were considered to be a paroxysmal syndrome related to multiple sclerotic plaques. These responded very well to carbamazepine initially, at the therapeutic anticonvulsant levels. Multiple hyperintense foci were seen on the MRI scan in paraventricular and pontine locations, as well as in the hemispheres and frontal lobes. Further pulses of corticosteroids were administered in an effort to achieve symptom relief but they had no effect on the nausea. They did improve vision and motor coordination, however. Over the next year, the patient lost 28 kilograms, or about 25% of her total body weight. The nausea and vertigo became intractable. Regularly scheduled trials of prochlorperazine, metoclopramide, cyclizine, haloperidol, hyoscine and lorazepam (in various combinations) all proved ineffective. High dosage metoclopramide was intolerable and resulted in akathisia. A trial of the 5HT3 receptor antagonist ondansetron was initiated and within a day, the patient’s visual analogue scale for nausea fell from the range of 7–8 (out of 10) to 0–3.

Since 1994, this patient has remained on ondansetron 8 mg twice daily, with the resultant near total containment of her nausea. Constipation, controlled by diet, is the only significant adverse effect. Cyclizine 50 mg three times a day has been continued, as has the antidepressant. Carbamazepine has been phased out and the “spins” are now a very rare event, presumably because the vertigo is now persistent. Every 6 to 12 months, a course of corticosteroid is administered, as the multiple sclerosis continues to relapse, with only partial remissions. Interferon-beta is not as yet available in New Zealand. To date, she continues to fulfill her employment obligations and acknowledges the very considerable improvement of quality of life provided by maintenance ondansetron.

Case 2

A 35-year-old mother of two pre-school children was referred to the neurology service with a two week history of acute vertigo, nausea, ataxia, left facial weakness and clumsiness of the left upper and lower limbs. The patient described a feeling of “unsteadiness,” a sense of “drunkenness,” particularly if she looked around or moved her head precipitously. Although this aggravated the nausea, it was continual and was independent of the vertigo. Both nausea and vertigo were exacerbated if patient was tired. Clinical features included a bilateral internuclear opthalmoplegia (and vertical nystagmus), mild ataxia, and hyperesthesia to pin-prick over the left face. Attempts to induce vertigo or relieve it by positioning maneuvers were unsuccessful. The history revealed that she had experienced a one month episode of sensory change over the left face, numbness of the right upper limb, and paroxysms of dysarthria about a decade previously. At that time, these symptoms were considered to be probably of multiple sclerotic origin, although investigations at the time had been inconclusive. MRI scanning was not then available. In view of the clinical possibility of paroxysmal brainstem episodes associated with demyelination, the attending clinician had introduced a short trial of carbamazepine, with a resolution of symptomatology.

On the more recent presentation in 1996, an MRI scan suggested the diagnosis of multiple sclerosis. Note was made of a moderate size area of demyelination in the right cerebellar peduncle, as well as multiple lesions in the cerebral hemispheres. She was considered to be clinically depressed and fluoxetine was introduced. It proved tolerable and certainly re-
sulted in improvement of mood, but with no significant influence upon the nausea. Corticosteroids had no effect upon the nausea or vertigo, though there was significant improvement in gait and sensation. A transient response on this occasion to carbamazepine was achieved for her episodes of vertigo, but this had no effect on her nausea. Oral ondansetron 8 mg twice daily resulted in partial, perhaps 50% improvement of nausea, a response which has been maintained though progressive neurological debility continues to occur.

Discussion

Many of the symptoms experienced by patients with multiple sclerosis can occur paroxysmally. Paroxysmal tonic seizures, paroxysmal dysarthria with ataxia, trigeminal neuralgia and paroxysmal vertigo are the most commonly recognized of these phenomena, and low doses of carbamazepine, phenytoin or baclofen almost always result in complete control of these symptoms. These symptoms usually occur in established cases of multiple sclerosis, or perhaps those are the cases in which clinicians register such symptomatology.

An acute vestibular syndrome has been described in multiple sclerosis, and comprises severe vertigo, nausea, vomiting, and postural instability. The vertigo, the illusion of movement, in the cases presented was neither rotational nor “falling,” but more concerned with the position of the lower limbs, a less common vertiginous symptom. Previous documentation of this phenomena suggests that it is short-lived and presumably inflammatory in origin. The persistence of this symptom in these patients and the enduring MRI signs suggest that gliosis had occurred. Whether the chronic nausea was associated with the vertigo, perhaps the patients at times accommodating to the vertigo but not to the nausea, or was an indication of the damage to the chemo-receptor zone (CRZ) or the emetic center is uncertain. The nausea was not related to the introduction of antidepressant medications in either case (antidepressant medications can induce nausea, which may be 5HT3 receptor antagonist responsive). “Central” nausea proved unresponsive to assertive trials of antiemetics and combinations of antiemetics as recommended by the palliative care literature, but responsive, particularly in the first case, to ondansetron. Subsequent to commencing the first of these patients on ondansetron in 1994, Rice and Ebers published seven cases of central vertigo, five of whom had multiple sclerosis that was responsive to 5HT3 receptor antagonists. The mechanism of action of ondansetron is presumably not on ‘ephaptic conduction’ but on blockade of the vomiting center. The existence of 5HT3 receptors in the brain has been demonstrated, with high concentrations in the area postrema, presumably a site of neuronal damage in these patients. Very high dosage metoclopramide, which has 5HT3 receptor activity, proves generally to be a clinically intolerable option. Corticosteroids presumably had little impact because the condition was long-standing, and not the inflammatory nature of acute multiple sclerotic plaques. A non-medicinally prescribed cannabinoid trial in one patient proved ineffective. Both patients had coexistent major depressive disorders, and treatment resulted in the resolution of mood symptoms but little change in the intensity of the nausea.

The palliative care of degenerative neurological disease deserves attention. Young and active persons with multiple sclerosis and distressing symptoms such as nausea and vertigo require assertive interventions, prescribed with a similar philosophy to those persons with malignant diseases. Symptom relief is a desired clinical goal. There is often a pessimism attached to the clinical care of these patients; a careful mapping of their neurological decline and the expression of sympathy are but too rarely a concerted multidisciplinary approach to symptom relief. Novel immunomodulatory treatments of multiple sclerosis, such as interferons, may influence the natural history of the disease, and thereby the symptom management, and while there may be reason for cautious optimism, currently multiple sclerosis remains incurable. Multiple sclerotic vestibular syndromes are rare, particularly persisting syndromes, but cross-fertilization from palliative medicine to neurology of a therapy, admittedly with a high acquisition cost, is noteworthy.

References


