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Neurokinin-1 receptor antagonist therapy for post-stroke vomiting: A case report

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Abstract

Post-stroke vomiting is a common but often challenging complication of cerebellar and brainstem strokes, which may be refractory to standard antiemetic therapy. We present a case of a 61-year-old male with recurrent ischemic strokes who suffered bilateral cerebellar infarcts and subsequently developed persistent vomiting during his inpatient rehabilitation stay. Despite empirical treatment with multiple classes of antiemetics, his symptoms remained unresolved. An off-label trial of aprepitant, a neurokinin-1 (NK-1) receptor antagonist typically used for chemotherapy-induced nausea and vomiting and post-operative nausea and vomiting, was initiated. The 3 day course of oral aprepitant, with a starting dose of 125mg once daily, followed by 80mg once daily for another 2 days, successfully resolved his vomiting. This case highlights the potential utility of NK-1 receptor antagonists in the management of refractory post-stroke vomiting. Cautious patient selection is paramount given their potential interactions with liver cytochrome enzymes, affecting the metabolism of anticoagulants such vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC). Further studies are warranted to ascertain the efficacy and adverse effects of this novel class of antiemetics in the post stroke population.

Keywords: Stroke, vomiting, antiemetics, neurokinin-1 receptor antagonists

INTRODUCTION

Post-stroke vomiting is a common sequelae of stroke especially if the cerebellum or brainstem is involved. Cerebellar ischemic infarctions account for 2%-3% of all ischemic strokes and cerebellar hemorrhages account for approximately 9%-10% of all intracranial hemorrhages.[1] Initial symptoms of cerebellar strokes include headache, dizziness, nausea, vomiting, and vertigo. At least 50% of cerebellar strokes present with nausea and vomiting, and approximately 75% of them present with dizziness.[2] Management of persistent post-stroke vomiting largely involves the empirical use of different classes of antiemetic medications which include serotonin receptor antagonists, dopamine receptor antagonists and antihistamines.[3,4] The use of aprepitant, a NK-1 receptor antagonist, in the context of post-stroke nausea and vomiting has yet to be reported in the medical literature.

CASE REPORT

A 61 year old Chinese male with a past medical history of gout, hypertension, hyperlipidaemia, chronic kidney disease and recurrent ischaemic strokes, was admitted to the hospital for a 5 day history of sudden onset intermittent vertiginous giddiness, vomiting, dysarthria and unsteady gait. On further history, he also reported being adherent to his chronic medications which included the antiplatelets, aspirin and dipyridamole.

On physical examination, motor power was full in his bilateral upper and lower limbs, and there was no loss of sensation. He had positive cerebellar signs which included dysarthria, bilateral upper limb dysmetria and intention tremors and positive heel-to-shin tests. A Magnetic Resonance Imaging (MRI) scan (Figure 1.) of his brain was done and revealed acute infarcts in bilateral inferior cerebellar hemispheres and vermis, with a small focus of

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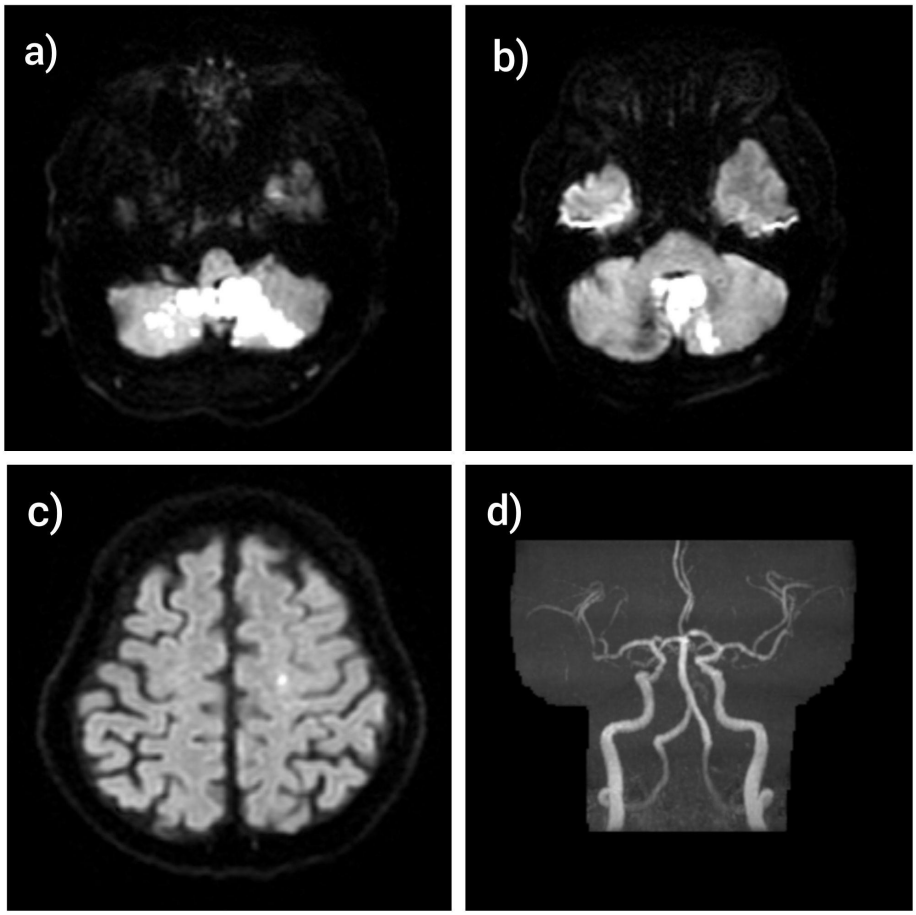

Figure 1. Magnetic Resonance Imaging (MRI) scan of the brain showed a) Bilateral inferior cerebellar hemispheres infarcts with lack of involvement of the dorsomedial surface of the brainstem b) Cerebellar vermis infarct. c) Tiny acute infarct in the left centrum semiovale. d) No large vessel occlusion detected on Magnetic Resonance Angiography (MRA)

petechial haemorrhage in the vermian infarct and a tiny acute infarct in the left centrum semiovale. He was diagnosed with multi-territorial embolic stroke of undetermined source (ESUS) and restarted back on his previous antiplatelet medications, aspirin and dipyridamole. He was subsequently transferred to the rehabilitation centre 10 days after his stroke for further inpatient rehabilitation.

Unfortunately, his rehabilitation stay was interrupted with recurrent episodes of vomiting of between 1 to 4 times each day. On further probing, these episodes of vomiting began since the day of admission and diagnosis of his current new strokes. These episodes of non bilious vomiting would occur at random throughout the day with no identified triggers. These episodes of vomiting occurred with no relation with his meals, episodes of vertigo or therapy sessions. He denied any appetite loss, abdominal pain, precordial pain, bloatedness, gastroesophageal reflux symptoms or nausea prior to these episodes of vomiting. Abdominal X-rays and a Computed Tomography (CT) Scan of the abdomen and pelvis did not reveal any abnormalities. He was referred to the Department of Gastroenterology which deemed it unsafe for a gastroscopy due to the recent stroke. Upon further review of his MRI scans of the brain, the differential diagnosis of area posterema syndrome was ruled out given the lack of involvement of the dorsomedial surface of the medulla. He was then started on regular laxatives to prevent constipation and he opened his bowels regularly. Despite the use of several multiple antiemetic agents such as serotonin receptor antagonists, dopamine

receptor antagonists and antipsychotics since the first day of admission, there was no reduction in the number of episodes of vomiting. (Figure 2.) Antiemetics received initially included metoclopramide 10mg TDS for 6 days followed by a combination of ondansetron 4mg TDS and domperidone 10mg TDS for 10 days, domperidone 10mg TDS for 7 days, olanzapine 2.5mg OM for 8 days and, finally ondansetron 8mg TDS for 4 days.

He was diagnosed with refractory post-stroke vomiting and an off-label use of a neurokinin-1 (NK-1) receptor antagonist was discussed with the patient, who was agreeable to proceed while still on ondansetron 8mg TDS. He was started on a 3 day course of oral aprepitant, a NK-1-receptor antagonist, with a starting dose of 125mg once daily, followed by 80mg once daily for another 2 days, which is the usual protocol used for prevention of chemotherapy associated vomiting. There was immediate cessation of vomiting after aprepitant was started, with no further episodes of vomiting in the days that followed. His serum hemoglobin and electrolytes were monitored during the 3 day course of aprepitant and returned within normal limits. As he was only on antiplatelet therapy for secondary stroke prevention, his serum International Normalized Ratios (INR) and anti-Xa levels were not monitored during the 3 day course of aprepitant. He was then able to tolerate his rehabilitative therapy sessions and subsequently completed his inpatient rehabilitation stay uneventfully. He was discharged with a reduced dose of ondansetron 4mg TDS PRN and given a follow up clinic appointment to review his function and post-stroke vomiting.

He was later re-admitted to the hospital for another episode of acute stroke in the weeks following his discharge from the rehabilitation centre. However, on review of his medical charts, it was noted that his vomiting episodes had not recurred during the initial days of that hospital admission.

DISCUSSION

NK-1 receptor antagonists are a novel class of antiemetics that possess antidepressant, anxiolytic and antiemetic properties. As of the

Medications	PO Metoclopramide 10mg TDS					
Day	1	2	3	4	5	6
Episodes of vomiting	1	4	3	1	2	3

Medications	PO Domperidone 10mg TDS PO Ondansetron 4mg TDS									
Day	7	8	9	10	11	12	13	14	15	16
Episodes of vomiting	3	2	1	2	1	2	1	3	1	2

Medications	PO Domperidone 10mg TDS						
Day	17	18	19	20	21	22	23
Episodes of vomiting	1	4	3	1	2	3	2

Medications	PO Olanzapine 2.5mg OM							
Day	24	25	26	27	28	29	30	31
Episodes of vomiting	1	0	1	2	1	0	1	2

Medications	PO Ondansetron 8mg TDS			
Day	32	33	34	35
Episodes of vomiting	2	2	1	2

Medications	PO Ondansetron 8mg TDS		
	PO Aprepitant 125mg OM	PO Aprepitant 80mg OM	PO Aprepitant 80mg OM
Day	36	37	38
Episodes of vomiting	0	0	0

Medications	PO Ondansetron 8mg TDS			
Day	39	40	41	42
Episodes of vomiting	0	0	0	0

Figure 2. Antiemetics and vomit chart depicting cessation of vomiting with a 3 day course of aprepitant.

time of writing, the clinical application of NK-1 receptor antagonists is mainly directed towards the prevention of chemotherapy-induced nausea and vomiting alongside post-operative nausea and vomiting, where they have demonstrated significant efficacy compared to traditional antiemetics.[5,6] Examples of these agents that are currently available include, aprepitant, rolapitant, casopitant, netupitant, maropitant, and fosaprepitant.[7]

NK-1 receptors are G-protein coupled receptors that mediate most of the central and peripheral effects of the neuropeptide, substance P, in the body. Substance P is a member of the tachykinin family and involved in pain transmission, inflammation, and vomiting. It also has excitatory properties and a high affinity for NK-1 receptors.[8] Stimulation of these NK-1 receptors, which are found in high concentrations in the vomiting centres of the brain, results in the potentiation of the vomiting reflex which leads to nausea and vomiting.[7] NK-1 receptor antagonists act centrally by blocking these NK-1 receptors located in the area postrema, nucleus tractus solitarius and afferent nerves leading up to the brain, dampening the vomiting reflex and therefore reducing the frequency of vomiting. It has also been reported that the effect of serotonin receptor antagonists e.g. ondansetron and corticosteroids e.g. dexamethasone can also be augmented with the concurrent administration of NK-1 receptor antagonists in the case of chemotherapy induced nausea and vomiting.[9]

The presence of NK-1 receptors in the cerebellum has been reported in the literature, albeit at a relatively much lower density when compared to other areas of the brain.[10] So much so that the cerebellum is used as a reference point for measuring NK-1 receptor expression in other locations of the brain.[11] There are also studies that have also reported neural pathways that project signals from the fastigial nucleus and caudal vermis of the cerebellum to the nucleus tractus solitarius via the vestibular nuclei within the brainstem.[12,13] Thus, we hypothesize that the anti-emetic effect of NK-1 receptor antagonists was not a result of direct NK-1 receptor blockade in the cerebellum, but instead from the blockade of these NK-1 receptors within the nucleus tractus solitarius.

There are a few considerations for the potential use of NK-1 receptor antagonists, such as aprepitant in our case, in the management of post-stroke vomiting. NK-1 receptor antagonists are extensively metabolized through the liver and moderately inhibits CYP3A4 and induces CYP2C9. These pharmacokinetic properties have several implications on the management of post-stroke patients, as many commonly prescribed medications for stroke are metabolized via these enzymatic pathways. The non-exhaustive list of these medications include anti-epileptics, anticoagulants, antihypertensives, and antipsychotics. Among the direct oral anticoagulants (DOAC) used in the prevention of stroke, there exists a theoretical interaction between NK-1 receptor antagonists and rivaroxaban or apixaban, leading to increased risk of bleeding when administered together. Of particular concern would be the concomitant use of NK-1 receptor antagonists with the vitamin K antagonist (VKA), warfarin. Reduced INR levels have been reported in the literature, potentially resulting in an increased risk of subtherapeutic anticoagulation and increased risk of recurrent strokes.[14] Thus, when deciding on the off-label use of NK-1 antagonists in post-stroke vomiting, these factors necessitate cautious patient selection, comprehensive drug reconciliation, and closer monitoring. Closer monitoring would entail the need for more frequent blood tests (e.g INR, anti-Xa levels) and neurological examinations for any new focal neurological deficits Authors have also suggested monitoring serum INR for at least 2 weeks after the first dose of aprepitant, in cancer patients on warfarin.[15] Although the use of NK-1 receptor antagonists may potentially alleviate symptoms and enhance a patient's quality of life, the therapeutic advantages must be balanced against the possibility of clinically significant drug-drug interactions and discussed extensively with patients.

In conclusion, we report a case of refractory post-stroke vomiting successfully treated with a short course of aprepitant. Vomiting can be a distressing symptom faced by stroke patients and can negatively impact quality of life. This case highlights the potential use of NK-1 receptor antagonists as a treatment option for post-stroke vomiting. Clinicians need to be cognizant of the potential drug-drug interactions of NK-1 receptor antagonists with common medications used for secondary stroke prevention. This includes the risk of reduced INR with VKAs and the increased risk of bleeding with DOACs. Further studies are warranted to ascertain the efficacy and adverse effects of this novel class of antiemetics agents in the post stroke population.

DISCLOSURE

Ethics: Formal, written permission was secured from the patient before publication.

Data Availability statement: Data sharing not applicable to this article as no datasets were generated or analysed during the current study

Financial support: None.

Conflict of Interest: None.

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