Vertigo and motion sickness. Part II: Pharmacologic treatment

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Abstract
Vertigo is a sensation of movement when no movement is actually occurring. It is often accompanied by visceral autonomic symptoms including pallor, diaphoresis, nausea, and vomiting. Vertigo is similar to motion sickness in that both may be caused by vestibular stimulation that does not match an internal model of expected environmental stimuli. Indeed, a functioning vestibular system is necessary for the perception of motion sickness. For this reason, many of the same drugs are used to treat both conditions. The investigation of drugs that treat motion sickness helps to discover medications that may treat vertigo caused by disease of the vestibular system. In this article, we discuss the pharmacologic agents that are now available for the treatment of vertigo and those agents that are still under study.

Introduction
The efficacy of medications used to treat vertigo often can be inferred from their usefulness in treating motion sickness. This is especially true when the medication being evaluated is a vestibular suppressant. Additional objective data concerning a drug’s efficacy can be gained from (1) large clinical studies of patients who experience similar environmental challenges, (2) evaluation of laboratory-induced motion sickness, (3) electronystagmography, and (4) animal studies.

Clinical trials. Interest in studying treatments for motion sickness increased during World War II when large numbers of troops were being transported by sea. Transport ships provided a good setting for early studies comparing efficacy. Research continued, and in a notably large study published in 1980, Hargreaves reported the results of a double-blind, placebo-controlled evaluation of cinnarizine for the prophylaxis of seasickness.1 In that study, 335 volunteers were given either cinnarizine or placebo during voyages of 5 to 7 days. Symptoms were evaluated by questionnaire, and the results indicated a statistically significant reduction in the incidence of seasickness in the active-treatment group. Similar studies are still being performed.

Rotation testing. Probably the most widely used method of objectively evaluating an antivertiginous drug’s efficacy in the laboratory involves inducing motion sickness in a controlled fashion. Subjects are placed in a chair and rotated about a vertical axis. Subjects are then asked to perform a defined series of head motions out of the plane of motion over a set period of time. The number of head movements that can be accomplished before vomiting or severe nausea occurs or prior to the subject’s request to stop the rotation becomes an objective measure of tolerance to motion sickness-inducing stimuli. Each subject can be used as his or her own control, which allows researchers to individualize the rate of rotation. More susceptible subjects are then able to participate at a slower, more comfortable rotational velocity without compromising the integrity of the study.2

Caloric stimulation. Electronystagmography can be used to test a drug’s ability to suppress vestibular activity. In a study comparing the antihistamine dimenhydrinate with placebo, Barber et al examined changes in the frequency, duration, and velocity of the slow component of nystagmus.3 They found that measurement of the velocity of the slow component was the most useful indicator of suppressed vestibular function.

Animal models. A number of animal models for the study of motion sickness have been used over the years. Researchers once expressed some concern about the use of canine models in early studies because dogs did not respond to scopolamine, while humans experience a strong reaction; however, subsequent trials suggested that the problem with these earlier studies might have simply been inadequate dosing. Feline models are very useful because we have...
accumulated a wealth of neuroanatomic, neurochemical, and neurophysiologic information on cats. 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.

In this article, we review the different classes of drugs that are used to treat motion sickness and vertigo. We discuss the agents that are now available (table 1) and those that are still under investigation (table 2). (In part I of this article, we discussed the essential anatomy and physiology of the vestibular system and the associated vomiting reflex.)

Benzodiazepines

Diazepam. Sekitani et al first reported on the suppressant activity of diazepam in the medial vestibular nuclei of cats. They used microelectrodes to record the spontaneous firing rates of neurons in the medial vestibular nucleus. They found that diazepam 0.4 mg/kg exerted a strong suppressant activity and reduced the firing frequency by nearly 75%. They also found that a dosage as low as 0.1 mg/kg had similar suppressant activity. Both of the \( \gamma \)-aminobutyric acid (GABA) receptors—GABA A and GABA B—have been found in the vestibular nuclei, but benzodiazepines are active only at the GABA A receptors. These receptors are believed to mediate diazepam’s vestibular suppressant activity.

Diazepam has been tested specifically for the prevention of motion sickness in humans. McClure et al alternated oral administration of diazepam 5 mg, dimenhydrinate 50 mg, and placebo in a group of normal subjects; subjects were also tested after receiving no treatment. Results were determined according to the length of time that had passed between administration and exposure to motion stimuli. Motion stimuli were provided by rotation and head-tilt maneuvers, and treatment efficacy was measured by analyzing the number of maneuvers tolerated and the recordings of skin sweat sensors. The greatest effect was observed when patients took diazepam 120 minutes prior to the onset of the stimuli, which was the longest interval studied. Clinically, doses of diazepam as small as 2 mg can be effective in controlling vertigo.

Lorazepam. Intravenous lorazepam is used to treat acute vestibular vertigo in some emergency departments. Marill et al compared lorazepam 2 mg IV with dimenhydrinate 50 mg IV and found that lorazepam provided better control of symptoms.

Clonazepam. Clonazepam, which has marked antiepileptic properties, was reported to control symptoms in most patients in a study of migraine-related vertigo. Because the drug takes 4 hours to reach peak plasma levels, it is not used orally for acute vertigo.

Alprazolam. The properties of alprazolam, a short-acting benzodiazepine, are similar to those of diazepam. However, short-acting benzodiazepines carry a greater risk for abuse and withdrawal symptoms. Benzodiazepines also have generalized central nervous system effects, and they are sedating.

Care should also be taken to avoid benzodiazepine overdose, which can result in respiratory depression, especially in elderly individuals.

Antihistamines

The histamine-1 (H\(_1\)) blockers have long been used to prevent motion sickness. It has been argued that their antivertiginous efficacy is not the result of the H\(_1\) effects but rather the result of their central anticholinergic actions. Wood et al compared antihistamines to phenothiazines, anticholinergics, sympathomimetics, and various combinations. Subjects were evaluated (1) in a slow-rotation room, (2) during aerobatic maneuvers, (3) at sea, and (4) during zero-gravity parabolic flight. Results were based on the duration of stimuli that was tolerated. The authors concluded that antihistamines as a group are in the moderate range of effectiveness for the treatment of motion sickness. Most of these agents are insufficient for treating motion sickness induced by civilian travel, but antihistamines are not as useful in severe conditions or in highly sensitive patients. (Combinations of a sympathomimetic and scopoline or promethazine were most effective.)

Ethanolamines

Two of the most studied anti-motion sickness drugs are diphenhydramine and dimenhydrinate. Wood and Graybiel included these two medications in their evaluation of the relative efficacy of 16 anti-motion sickness drugs. This study involved the laboratory assessment of human subjects who performed head-tilt maneuvers during rotation about a vertical axis. Efficacy was judged by the number of head tilts that were tolerated. Dimenhydrinate 50 mg proved to be more effective than meclizine 50 mg. In addition, Muth et al found that dimenhydrinateducedincreasesingastricmotilityduring motion sickness-inducing stimuli.

Ethylenediamines and alkylamines. Ethylenediamines (e.g., tripelennamine) have \( \mathrm{H}_1 \) antagonistic effects, but they do not demonstrate strong central effects. Alkylamines (e.g., chlorpheniramine) are effective at low doses in preventing motion sickness, but they do have strong central effects and therefore produce marked drowsiness.

Piperazines. Meclizine, cyclizine, and buclizine are long-acting antihistamines. They also produce light sedation. Meclizine, the best known of these, is commonly used for prevention of nausea and vomiting.
## Table 1. Selected medications approved in the U.S. for motion sickness and vertigo

<table>
<thead>
<tr>
<th>Drug</th>
<th>MS</th>
<th>AV</th>
<th>CV</th>
<th>Action</th>
<th>Dosage</th>
<th>Precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td></td>
<td>GABA A-mediated inhibition in the vestibular nuclei</td>
<td>Oral: 2, 5, or 10 mg bid to qid; Slow IV: 5 to 10 mg q4h</td>
<td>Sedation; avoid in patients w/pulmonary insufficiency, sleep apnea, or liver or kidney disease; addiction is possible</td>
</tr>
<tr>
<td>Diazepam</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Same as diazepam</td>
<td>Oral: 1 to 2 mg tid; IM/slow IV: 2 mg</td>
<td>Same as diazepam</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Same as diazepam</td>
<td>Oral: 0.5 mg tid;</td>
<td>Same as diazepam</td>
</tr>
<tr>
<td>Antihistamines</td>
<td></td>
<td></td>
<td></td>
<td>H₁ blockade; anticholinergic effects</td>
<td>Oral: 25 to 50 mg q4h to q6h; IM/IV: 10 to 50 mg qid</td>
<td>Sedation</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Same as diphenhydramine</td>
<td>Oral: 50 mg q4h to q6h IM/IV: 25 to 50 mg q4h to q6h</td>
<td>Sedation</td>
</tr>
<tr>
<td>Meclizine</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Same as diphenhydramine</td>
<td>Oral: 25 to 50 mg qd to qid</td>
<td>Sedation</td>
</tr>
<tr>
<td>Cyclizine</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Same as diphenhydramine</td>
<td>Oral: 50 mg q4h to q6h</td>
<td>Sedation; may aggravate severe heart failure</td>
</tr>
<tr>
<td>Promethazine</td>
<td>++</td>
<td></td>
<td></td>
<td>H₁, blockade; strong anticholinergic effects</td>
<td>Oral: 25 mg q6h; suppository: 50 mg q12h IM: 25 mg q4h to q6h</td>
<td>Sedation; use w/caution in patients w/renal failure</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td></td>
<td></td>
<td></td>
<td>M₁, M₂, and M₃ blockade; M₃ blockade is likely most important</td>
<td>Oral: 0.6 mg q4h transdermal: 1.5-mg patch delivers 1.0 mg q3d</td>
<td>Sedation, dry mouth, blurred vision, acute angle glaucoma, dermatitis, possible withdrawal symptoms; rare psychosis reported</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scopolamine/ephrine*</td>
<td>++</td>
<td></td>
<td></td>
<td>Same as scopolamine alone plus adrenergic and dopaminergic effects</td>
<td>Oral: 0.6 mg/25 mg q6h</td>
<td>Hypertension, anxiety, arrhythmia; use w/caution in patients w/hyperthyroidism, diabetes, or glaucoma</td>
</tr>
<tr>
<td>Scopolamine/d-amphetamine*</td>
<td>++</td>
<td></td>
<td></td>
<td>Same as scopolamine/ephrine</td>
<td>Oral: 0.6 mg/5 to 10 mg q6h</td>
<td>Same as scopolamine/ephrine</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td></td>
<td></td>
<td></td>
<td>Antiadrenergic and antidopaminergic effects; analgesia w/fentanyl</td>
<td>IM/slow IV: droperidol 2.5 to 5 mg/fentanyl 50 μg/ml q12h</td>
<td>Hypotension, respiratory depression; use w/caution in patients w/liver or kidney disease</td>
</tr>
<tr>
<td>Droperidol/fentanyl</td>
<td>+</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Both adrenergics are effective as monotherapies.  
Key: MS = motion sickness; AV = acute vertigo; CV = chronic vertigo.
the prevention of motion sickness in civilian environments. In addition to the finding that meclizine 50 mg was less effective than dimenhydrinate 50 mg, meclizine has been found to be less effective than transdermal scopolamine. In a placebo-controlled study, Dahl et al exposed 36 subjects to a ship-motion simulator after they had received either oral meclizine 25 mg or a transdermal scopolamine patch. Meclizine was given 2 hours prior to testing and transdermal scopolamine was given 12 hours prior to testing. Subjects were graded on a 5-point nausea scale, with 0 representing no symptoms and 5 representing vomiting. Subjects who wore the scopolamine patch had significantly lower scores than either the meclizine or placebo subjects; meclizine was significantly more effective than placebo.

Table 2. Selected investigational medications and agents not approved in the U.S.

<table>
<thead>
<tr>
<th>Drug</th>
<th>MS</th>
<th>Vertigo</th>
<th>Suspected drug action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td></td>
<td></td>
<td>M&lt;sub&gt;1&lt;/sub&gt; and M&lt;sub&gt;2&lt;/sub&gt; receptor blockade</td>
</tr>
<tr>
<td>Idavirine</td>
<td>−</td>
<td></td>
<td>M&lt;sub&gt;1&lt;/sub&gt; and m&lt;sub&gt;3&lt;/sub&gt; receptor blockade</td>
</tr>
<tr>
<td>Zamifenacin</td>
<td>+</td>
<td></td>
<td>Stabilization of neuronal membranes in CNS</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td></td>
<td></td>
<td>Labyrinth suppression, possibly at the level of the vestibular hair</td>
</tr>
<tr>
<td>Phenyo tin</td>
<td>+</td>
<td></td>
<td>Same as flunarizine</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td></td>
<td>+</td>
<td>Same as flunarizine</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>+</td>
<td>+</td>
<td>Labyrinth suppression, possibly at the level of the vestibular hair</td>
</tr>
<tr>
<td>Cinnarizine</td>
<td>+</td>
<td>+</td>
<td>Same as flunarizine</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>+</td>
<td></td>
<td>Same as flunarizine; possible CNS modulation</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>+</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td></td>
<td></td>
<td>Strong H&lt;sub&gt;1&lt;/sub&gt;, antagonist, adrenergic, and anticholinergic effects; weak dopaminergic effect</td>
</tr>
<tr>
<td>Doxepin</td>
<td>+</td>
<td></td>
<td>5-HT&lt;sub&gt;1&lt;/sub&gt; agonist effects, probably in the vestibular nuclei</td>
</tr>
<tr>
<td>Serotonergics</td>
<td></td>
<td></td>
<td>5-HT&lt;sub&gt;1&lt;/sub&gt; agonist effects</td>
</tr>
<tr>
<td>8-OH-DPAT</td>
<td>++</td>
<td></td>
<td>Increase in concentration of serotonin in synapses</td>
</tr>
<tr>
<td>DOI</td>
<td></td>
<td></td>
<td>5-HT&lt;sub&gt;1&lt;/sub&gt; agonist effects</td>
</tr>
<tr>
<td>Imipramine/fluoxetine</td>
<td>+ (A)</td>
<td></td>
<td>Increase in concentration of serotonin in synapses</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>−</td>
<td></td>
<td>5-HT&lt;sub&gt;1&lt;/sub&gt; receptor blockade, likely in the area postrema (chemoreceptor trigger zone)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td>NK&lt;sub&gt;1&lt;/sub&gt; receptor blockade</td>
</tr>
<tr>
<td>GR203040</td>
<td>+</td>
<td>(AH)</td>
<td>NMDA blockade in the vestibular nuclei and the final common pathway for vomiting</td>
</tr>
<tr>
<td>LY233053</td>
<td>+</td>
<td>(A)</td>
<td>Suppression, possibly in the vestibular nuclei</td>
</tr>
</tbody>
</table>

Key: MS = motion sickness; CNS = central nervous system; 8-OH-DPAT = 8-hydroxy-2-(di-n-propylamino)tetralin; DOI = 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; A = in animals; AH = in animals and humans; NMDA = n-methyl-d-aspartate.
Cinnarizine is a piperazine that exerts calcium channel blocking effects. It has been used in Europe for many years, but there is concern regarding its central side effects. (Cinnarizine is discussed in more detail in the section on “Calcium antagonists.”)

Piperidines. The best known piperidine is terfenadine. Although it has been removed from the market, one human study by Kohl et al demonstrated that a single large (300 mg) dose of terfenadine increased to a statistically significant degree the number of head movements tolerated by subjects during rotation. Because terfenadine does not cross the blood-brain barrier, this finding raised the possibility that motion sickness might be treatable by blocking only peripheral receptors. However, structures such as the area postrema, median eminence, portions of the hypothalamus, and other circumventricular organs that lie outside the blood-brain barrier play an integral role in the vomiting reflex. Therefore the effectiveness of terfenadine may well be attributable to its central sites of action.

Astemizole, another highly selective H1 inhibitor with little central nervous system penetration, has also been reported to be effective in the treatment of chronic vertigo. In a prospective study, Jackson and Turner evaluated 38 patients with chronic vertigo who exhibited repeatable spontaneous or positional nystagmus. Patients with Ménière’s disease were excluded from the study. Patients were given 5, 10, or 20 mg/day of astemizole for 13 weeks. Patients were evaluated by electronystagmography. A positive response was defined as a 50% reduction in the number of nystagmus beats recorded during a body-positioning protocol. Patients were also evaluated by a subjective symptom questionnaire. This study revealed that although some patients showed no objective or subjective changes, 73% did improve. Responses were demonstrated after 2 to 4 weeks of therapy, and the return of symptoms was delayed by 2 weeks or more after the drug was discontinued.

In another human study, Kohl et al tested 20 subjects after they had taken oral astemizole 30 mg/day for 1 week. Although subjects were found to have therapeutic blood levels of astemizole, the drug demonstrated no effectiveness against motion sickness-inducing stimuli. These subjects also exhibited no change in their vestibulococular reflex.

Phenothiazines. The phenothiazines were first explored for their usefulness in treating psychoses. They also have antiemetic properties, but most drugs in this group are only slightly effective against motion sickness, promethazine being a notable exception.

Promethazine exerts strong antiemetic properties, and it is more effective than any antihistamine in preventing vertigo. Promethazine also has the strongest anticholinergic activity of all the phenothiazines. Wood and Graybiel reported that oral promethazine 25 mg was only slightly less effective in preventing motion sickness than scopolamine 0.6 mg. Intramuscular promethazine 25 mg was shown to increase the number of head movements tolerated by 78%, although this was less than the 91% reduction seen with scopolamine 0.2 mg. However, promethazine’s duration of action is 12 hours, versus 4 hours for scopolamine.

Promethazine hastens adaptation to motion sickness-inducing stimuli, as Lackner and Graybiel demonstrated in a controlled human head-tilt experiment. Three groups of subjects were given either placebo or promethazine 50 mg orally prior to testing sessions. The sessions were held 2 days apart to allow for habituation. Patients in one of the two promethazine groups were allowed to perform 10 head movements as possible, while those in the other promethazine group were forced to match the number of head movements performed by those in the placebo group. At the final session, all groups received placebo only. Analysis of the results revealed statistically significant increases in the number of head movements performed by all groups. However, the group given promethazine and allowed to perform as many head movements as possible showed the greatest improvement. The promethazine group in which the number of head movements was restricted did not better than the placebo group. These findings suggest that if subjects increase their exposure to motion sickness-inducing stimuli, promethazine may actually help to increase adaptation.

Promethazine does exert significant sedating properties and the 25-mg dose can impair functional performance, but the sedative effect can be circumvented by adding 10 mg of amphetamine/dextroamphetamine (d-amphetamine). Larger doses of promethazine degrade performance to such an extent that sedation cannot be prevented by adding amphetamine. (As discussed later in this article, d-amphetamine exerts antivertiginous effects of its own.)

Prochlorperazine, another phenothiazine, demonstrates H1 blockade and a high degree of anticholinergic properties. It also has a 40-fold greater antidopaminergic effect than does promethazine, and it is an effective antiemetic. Prochlorperazine does have some anti-motion sickness effects, but it ranks well below scopolamine and the antihistamines in this regard. For example, not only was prochlorperazine 5 mg shown to be less effective than meclizine in preventing motion sickness, tripling the dose actually decreased the number of head tilts tolerated.

Chlorpromazine has no anti-motion sickness efficacy, even though it is quite effective against chemically induced nausea.

Anticholinergics

Anticholinergic medications act on muscarinic receptors. (There are five known structural subtypes of muscarinic receptors, designated M1 through M5. The capitalized designations M1, M2, and M3 represent pharmacologic definitions, which are based on the actions of various drugs that bind muscarinic receptors selectively.) One study
involving bovine brain tissue found that the highest densities of muscarinic receptors were in the area postrema and the vagal nuclear complex. Intermediate densities were found in the parvicellular reticular formation, and the lowest concentration of receptors was found in the vestibular nuclei.

Scopolamine. Scopolamine is believed to bind well to all types of muscarinic receptors. In their study of 16 agents, Wood and Graybiel found that oral scopolamine was the most effective single agent in preventing vertigo. They also evaluated scopolamine in combination with two other adrenergic medications that were found to have anti-motion sickness activity of their own; scopolamine had an additive effect when combined with ephedrine and a synergistic effect when combined with amphetamine. In fact, the combination of scopolamine and amphetamine proved to be the most effective of all medications alone or in combination. Operational performance has been shown to decrease with doses of scopolamine of 0.8 mg or more. However, the addition of d-amphetamine 5 mg with scopolamine 1.0 mg prevented a decrease in performance.

Although scopolamine is effective, adaptation to new environmental stimuli can be delayed. This was demonstrated in one clinical study of 51 sailors who worked in rough seas over a period of 7 days. Upon embarking on their voyage, the subjects were given either transdermal scopolamine or transdermal placebo and instructed to wear the patch for 3 days. Initially, vomiting did occur less often in the scopolamine group. But on day 6, 3 days after removal of all patches, vomiting occurred in 23% of the scopolamine group but in none of the placebo controls.

The scopolaminetransdermaltherapeuticsystemdelivers a continuous 1-mg total dose over 3 days; thereafter, a new patch may be applied. The effectiveness of transdermal scopolamine has been proven to be similar to that of oral scopolamine. Its autonomic side effects include reduced salivation and blurred vision from reduced accommodation. The most common side effect is dry mouth, which has been reported in 30 to 50% of patients. Blurred vision commonly occurs with continued use. In a study of 12 subjects, Parrot monitored visual acuity during the placement of sequential patches. Blurred vision occurred in 1 subject upon placement of a second patch, 4 subjects experienced blurred vision with a third patch, and 6 reported blurred vision with a fourth. Central nervous system side effects include decreased alertness, impaired attention, and difficulty remembering new information. Addiction and psychosis have also been reported with use of transdermal scopolamine for 1 month or longer. Reports of addiction relate to patients’ inability to discontinue medication because of severe withdrawal symptoms, such as nausea, vomiting, headache, and disequilibrium. Transdermal scopolamine has also been documented to cause acute angle-closure glaucoma, and therefore it should not be used in patients suspected of having glaucoma.

Contact dermatitis may occur in 10% of patients after 1 month or more of use; this rate may rise to more than 30% among patients who use transdermal scopolamine for 1 year or longer. Buccal administration of 1 mg of scopolamine in a sustained-release hydroxypropylmethylcellulose vehicle was shown to reduce vomiting during parabolic flights by 50% and to reduce nausea scores by approximately 31%.

Glycopyrrolate. Glycopyrrolate is commonly used to decrease copious secretions and to prevent vertigo-induced vagal inhibitory cardiac reflexes. Storper et al tested glycopyrrolate for efficacy in treating vertigo in 37 patients with Ménière’s disease. Of this group, 22 patients were given oral glycopyrrolate 2 mg twice a day. Compared with the remaining 15 patients who had not received glycopyrrolate, the study group had a significantly greater reduction in Dizziness Handicap Inventory scores.

Idaverine. Idaverine, which is not approved in the United States, is believed to be a selective M2, and M4 antagonist with a significantly lower affinity for M1 receptors. Lucot et al investigated its efficacy in preventing motion sickness by comparing it with scopolamine in a cat model. They found that idaverine exerted no protective effects; in fact, larger doses actually induced emesis. This finding suggests that the M4 receptor may be responsible for the anti-motion sickness effects of scopolamine.

Zamifenacin. Zamifenacin is a new selective anticholinergic under investigation. This agent binds selectively to M1 and M3 receptor subtypes, and it has been shown to be as efficacious as scopolamine in preventing motion sickness. This suggests that the M1 receptor, the M3 receptor, or both may be responsible for scopolamine’s anti-motion sickness effect. Further research may or may not determine that the use of zamifenacin or other selective anticholinergics can effectively control motion sickness and vertigo with fewer side effects.

Neuroleptics

Neuroleptics are known for their antipsychotic properties. Two major groups of neuroleptics are the phenothiazines and the butyrophenones. (The phenothiazines are discussed in more detail in the earlier section on “Antihistamines.”)

The butyrophenones are essentially derivatives of haloperidol. Droperidol is used almost exclusively in anesthesia because of its strong sedating properties and antiemetic effects. Droperidol has a diadrenergic and antidopaminergic effect. It is believed that its antiemetic effects may be attributable to the blocking of dopamine receptors in the area postrema. A fixed-dose combination of droperidol 2.5 mg/ml and fentanyl 50 μg/ml is commercially available. Dowdy et al performed caloric tests prior to and 1 week after administration of a single dose of droperidol/fentanyl and observed a complete suppression of caloric nystagmus...
in 8 of 9 subjects.³⁵ Subjects who received either droperidol alone or fentanyl alone demonstrated an absence of or only a slight reduction in caloric responses.

Droperidol has been proven useful, either alone or in combination with fentanyl, in clinical studies of treatments for acute vertiginous episodes brought on by Ménière’s disease.³⁶,³⁷ Gates reported his personal experience with droperidol/fentanyl for the control of vertigo in 12 patients with Ménière’s disease.³⁶ He found that 58% of these patients achieved long-term control of their vertigo during a follow-up of 2 to 8 years. The mechanism for any proposed long-term effects of droperidol/fentanyl is not clear. Currently, droperidol/fentanyl is being used in emergency departments for the control of acute peripheral vertigo; good results have been reported by Irving et al.³⁸

Johnson et al evaluated droperidol alone for the control of peripheral vertigo.³⁷ Twelve patients with acute vertigo secondary to Ménière’s disease were given either placebo or droperidol 5 mg intramuscularly. Patients in the active-treatment group experienced a resolution of symptoms within 60 minutes, whereas the controls remained unchanged. The controls were then put on droperidol, and their vertigo resolved, as well. The usual droperidol dose for adults is 2.5 to 5 mg intramuscularly or intravenously. Monitoring of vital signs and respiratory support are necessary during administration in view of the drug’s risk for causing hypotension and respiratory depression. Benadryl 25 to 50 mg can also be given prior to droperidol administration to help prevent extrapyramidal side effects.³⁹

A highly selective dopamine-2 (D₂) receptor antagonist, l-sulpiride, is under investigation. In squirrel monkeys, l-sulpiride has been found to exert strong anti-motion sickness effects and no extrapyramidal side effects at the dosing levels studied. Miller and Brizée compared l-sulpiride with domperidone, a peripherally acting D₂ antagonist.⁴⁰ Domperidone demonstrated no ability to prevent motion sickness. Because domperidone would have been available to the area postrema (outside the blood-brain barrier), it is likely that the anti-motion sickness effects of l-sulpiride occur outside the area postrema. This conjecture supports the hypothesis that although the area postrema is part of the chemoreceptor trigger zone, it is not associated with the production and control of motion sickness.
Anticonvulsants
Phenytoin acts diffusely upon the central nervous system to stabilize neuronal membranes. It is believed to stabilize the threshold against hyperexcitability caused by excessive stimulation while leaving normal neuronal activity essentially unaffected. The neural mismatch produced by motion sickness can be viewed as a source of excessive stimulation. Chelen et al investigated the usefulness of phenytoin in preventing motion sickness in 7 healthy male volunteers using a rotation and head-tilt protocol. Subjects were treated with a loading dose of 1 to 1.4 grams of phenytoin during the 20 hours preceding the study, and their blood was tested to measure therapeutic levels. The authors discovered that phenytoin was associated with an 11-fold shorter duration of tolerance to motion sickness than placebo. This duration of tolerance was 4-fold greater than that associated with a scopolamine/d-amphetamine combination. Chelen et al made no specific recommendation to use phenytoin to prevent motion sickness, but they alluded to larger ongoing trials that they were conducting. In another study, Stern et al showed that phenytoin decreased gastric motility in response to motion sickness-inducing stimuli.

Calcium antagonists
Calcium ions are present in the endolymph. In response to movement of the endolymph, calcium ions flow into the cells of the cristal ampullaris. This triggers an action potential that is propagated centrally. It is postulated that calcium channel blockers inhibit the flow of calcium from the endolymph into the cells of the crista ampullaris. Flunarizine. Flunarizine is one calcium channel blocker that has been found to be a powerful peripherally acting labyrinth suppressant. At both 10 and 30 mg, it has been found to be more effective in reducing caloric responses than is prochlorperazine 5 mg. Additionally, flunarizine reduces vestibulocochlear reflex gain in harmonic acceleration tests, and it is clinically useful in preventing motion sickness and vertigo.

Cinnarizine. Cinnarizine is similar to flunarizine, but it is less potent. The usual dose of cinnarizine is 30 mg orally 2 hours prior to motion sickness-inducing stimuli. During prolonged exposure to stimuli, cinnarizine can be continued at 15 mg three times daily. Children aged 5 to 12 years can be treated with one-half the adult dose. In a squirrel monkey study, d-amphetamine was also effective toward reduction in peak saccadic velocity. This finding suggests the possibility that calcium antagonists exert central effects.

Flunarizine and cinnarizine have been used in Europe, but not widely elsewhere in the world. Neither drug is selective for a particular calcium channel subtype. They therefore exert their effects throughout the central nervous system. Potential side effects include weight gain, depression, sedation, and even parkinsonian symptoms. Flunarizine has a long half-life, and steady-state plasma levels are not reached for 2 months. Residual concentrations are detectable for up to 4 months after cessation of therapy.

Nimodipine. Nimodipine is a highly lipophilic agent that readily crosses the blood-perilymph barrier. It is approved in the U.S. for the reduction of cerebrovasospasm following subarachnoid hemorrhage. In a retrospective study, Lassen et al reported that nimodipine was given to 12 patients with Ménière’s disease who had failed to respond to first-line medical management with diet restrictions and a diuretic (and, on occasion, a vestibular suppressant). The authors found that vertigo had been controlled in 67% of these patients. The duration of treatment and follow-up in this study ranged from 5 to 27 months; patients who had failed treatment did so within 6 months. In addition to blocking calcium influx into vestibular hair cells, nimodipine’s antivertiginous effects might be attributable to its central modulation of signals secondary to peripheral vestibular irritation. The recommended dosage for nimodipine is 30 mg twice a day.

Nifedipine. During a double-blind study of nifedipine’s antihypertensive effects, Marley and Joy serendipitously discovered that nifedipine alleviated a single patient’s motion sickness.

Sympathomimetics
The anti-motion sickness efficacy of d-amphetamine alone was found to be equal to the midrange efficacy of the antihistaminics in the comparison study by Wood and Graybiel. In a squirrel monkey study, d-amphetamine was also effective against motion sickness when the animals were exposed to a combination of vertical oscillations and horizontal rotation. The mechanism of action of amphetamine, a noradrenaline releaser, in preventing motion sickness is unclear. Its effects were once believed to be produced by an increase in noradrenergic activity in the brainstem, but this hypothesis is now being questioned. This theory was weakened by the results of an animal study in which Takeda et al measured the turnover of catecholamines in rat brainstems during a double-rotation protocol; although methamphetamine 5 mg/kg prevented pica, no increase in brainstem catecholamines was observed.

Another theory holds that the anti-motion sickness ef-
fected amphetamine are attributable to the enhancement of selective dopaminergic stimulation. This hypothesis is supported by the fact that both methylphenidate (a nonamphetamine-like stimulant that enhances dopaminergic transmission but not norepinephrine transmission) and d-amphetamine have antino-motion sickness effects. These drugs may exert their anti-motion sickness effects via their similar enhancement of dopaminergic transmission. Additionally, the anti-motion sickness effects of the L-isomer of d-amphetamine are weaker than those of d-amphetamine; the weaker dopaminergic effects of the L-isomer might explain its lack of efficacy.

Ephedrine 25 mg in combination with scopolamine can be used to lessen the performance degradation caused by sedation. Use of this combination also takes advantage of the synergistic activity of the two medications. Ephedrine 25 mg can also be used in combination with promethazine 25 to 50 mg.

Tricyclic antidepressants
Two of the tricyclic antidepressants that have been investigated for anti-motion sickness effects are imipramine and doxepin. (Owing to its ability to inhibit serotonin uptake, imipramine is discussed later in the section on “New horizons” in the subsection on “Serotonergic agonists and antagonists.”)

Doxepin exerts strong H1 antagonistic effects, and it has adrenergic and anticholinergic effects, as well. One human study demonstrated that doxepin is as effective as the combination of scopolamine and amphetamine for the prevention of motion sickness. Subjects were exposed to rotation with head-tilt maneuvers daily for 5 consecutive days. Results were based on the number of head tilts that were tolerated. Both treatment groups demonstrated increasing tolerance to coriolis stimulation daily (no statistically significant difference), suggesting that therapy facilitated adaptation, and both regimens were significantly superior to placebo. However, doxepin does have substantial sedating properties as well as other undesirable anticholinergic side effects. Doxepin also has a strong potential for adverse interactions with other drugs.

New horizons
Serotonergic agonists and antagonists. Serotonin (5-hydroxytryptophan [5-HT]) is an indole amine found throughout the body. Its effects are mediated via 5-HT receptors. The 5-HT1A, 5-HT2, 5-HT3, and 5-HT4 receptors have been identified in vivo. Additional 5-HT1, 5-HT2, and 5-HT3 receptor subclasses have been identified and characterized, as well.

The 5-HT1A receptors are probably present in the vestibular nuclei and elsewhere in the emetic pathway. In cats, 5-HT1A receptor agonists such as 8-hydroxy-2-(di-n-propylamino)tetratin (8-OH-DPAT) have been shown to prevent vomiting elicited by both motion-induced and chemical-induced nausea. Biver et al studied the distribution of 5-HT1 receptors in human brain tissue via positron-emission tomography. A radiotracer specific for 5-HT1 receptors revealed a primarily cortical distribution; these receptors were found to a lesser extent in the basal ganglia and cerebellum. A 5-HT1 agonist—1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)—has been shown to block emesis induced by motion and cisplatin in an animal model.

The 5-HT3 receptors are present in high densities in both the central and peripheral nervous systems. They are found in the area postrema, nucleus of the tractus solitarius, cerebral cortex, spinal cord, and visceral autonomic and sensory nerves. The 5-HT3 receptor antagonists (e.g., ondansetron) are used extensively for the control of postoperative nausea and vomiting. Stott et al demonstrated that their antinausea effect does not prevent motion-induced vomiting.

Selective serotonin reuptake inhibitors (SSRIs) work by increasing synaptic concentrations of serotonin. Imipramine (a tricyclic antidepressant with strong serotonergic properties) and fluoxetine (an SSRI) have been tested in the animal model Suncus murinus. Both agents exhibited dose-dependent effectiveness in preventing motion sickness. Their usefulness in humans is not yet clear.

Neurokinin receptors. Neurokinin type 1 (NK1) receptors are naturally bound by substance P, and they are involved in a variety of processes, including smooth muscle relaxation or contraction, neuronal depolarization, and exocrine gland secretion. Substance P is a peptide neurotransmitter that is localized to many neuronal structures. Substance P is believed to play a role in the transmission of sensory information, particularly that associated with noxious stimuli, from the periphery to central structures. Some NK1 receptor antagonists have been shown to have strong antiemetic properties. One of the most selective NK1 receptor antagonists, GR203040, has demonstrated effectiveness against motion-induced emesis in animal models. It should be noted that although this drug is highly selective for NK1 receptors, it has some affinity for H1 receptors. In human studies, however, NK1 receptor antagonists alone and in combination with the 5-HT3 receptor antagonist ondansetron have proven to be no more effective than placebo in the treatment of motion-induced nausea in humans. The fact that NK1 receptor antagonists have demonstrated effectiveness in preventing chemotherapy-induced nausea but not motion sickness-induced nausea suggests that there is a different mechanism of action for motion-induced nausea.

Miscellaneous agents. N-methyl-D-aspartate (NMDA) antagonists have been evaluated in animal models in an effort to find a drug that will serve as a broad-spectrum antiemetic. The selective competitive antagonist LY233053
has been shown to act in this capacity by blocking both motion- and chemical-induced emesis in cats. The sites of action appear to be both the vestibular nuclei and later in the final common pathway for vomiting.

Animal studies have also shown that short adrenocorticotropic hormone (ACTH) fragments relieve vertigo symptoms and accelerate their disappearance. The site of action of one fragment, ORG 2766, appears to be in the vestibular nucleus complex itself.

Ineffective agents include ginger root and acetylleucine. Ginger root (Zingiber officinale) has been found to have no effect on motion sickness in rotary-chair tests and only a very mild effect on tachygastria in motion sickness. Acetylleucine, which has been used in France since 1957, has no clinical trials to support its use; neither does the Ginkgo biloba extract EGb 761.

Selecting a medication
It is possible to predict the clinical usefulness of some medications by referring to the neurophysiologic model for vertigo and motion sickness. For example, if a vestibular suppressant is effective for treating motion sickness, it will likely be useful for treating vertigo as well. It is also important to consider a medication’s onset of action. A drug with a rapid onset of action is required to treat acute vestibular vertigo or ongoing motion sickness, whereas a slow-acting medication is appropriate for chronic vertigo.

References