PHARMACOLOGY OF MOTION SICKNESS

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Introduction

This brief overview will attempt to be comprehensive in the inclusion of drug groups, but will use representative rather than exhaustive references. Complete reference lists are available in several reviews (2,7,31,33,47,50,51). Apologies are extended to any author who may not have been fully cited.

Motion Stimuli

Clinical trials of drugs are either operational conditions, parabolic flight, or rotation in a laboratory setting. Operational conditions include aerobatic flight, cruising small craft into ocean swells, transatlantic crossing by ship, or maritime operations. Parabolic flight describes 20 parabolas with g forces from 0 to 1.8. A common end point in such studies is vomiting. Laboratory tests include several variations on subjects seated in a chair that rotates while they make head movements in the four cardinal directions. The variations include alterations in the visual field, the use of different constant rates of rotation, or a progressive increase in the rate of rotation after each set of head movements. The end point is usually nausea.

Squirrel monkeys of the Bolivian phenotype are tested in a rotating chair similar to that used most of the drug data rotates the chair at 16 RPM and adds a 15 cm sinusoidal vertical motion at 0.5 Hz (4). Suncus murinus, an insectivore, is responsive to a reciprocating shaker. Motion is in the horizontal plane with excursions of 40 mm and a frequency of 1.0 Hz (48). Cats respond to sinusoidal vertical motion or a swing. The laboratory generating drug data uses a device similar to a Ferris wheel, differing mainly in that the subjects ride sideways rather than fore and aft (10). The cats are free to move in plexiglass boxes suspended from the ends of a 0.89 m horizontal beam. The beam rotates at the optimum frequency of 0.28 Hz (17 RPM), which is close to the human optimum of 0.2 Hz.

Drugs Used Clinically

Antimuscarinics

Scopolamine (hyosine) is the single most efficacious drug for motion sickness, but suffers from the drawback of having considerable side effects (34,50). Scopolamine is nonselective for the five types of muscarinic receptors found in vivo. The M₁ and M₅ muscarinic antagonists, zanifencacn, was as effective as scopolamine in human subjects tested on a rotating chair (44).

Scopolamine prevents motion sickness in Suncus, though the only dose reported was of 100 mg/kg (48). It is effective in the squirrel monkey with an ED₅₀ of 80 to 90 µg/kg when given intravenously (5). Scopolamine is also ef-
effective in the cat with an ED50 of 85 μg/kg when given subcutaneously, but the M1 and M2 antagonist, idaveroine, is not (26). A test of this M3 and M5 receptor antagonist in animal models remains to be done. Antimuscarinics were described as not being effective in preventing motion sickness in dogs. However, a review of the original literature reveals that doses now considered to be rather low were used, leaving uncertain the efficacy of this drug class in dogs (21).

**Antihistamines**

Though less efficacious than antimuscarinics, antihistamines are more commonly used due to higher safety, longer duration of action and, with the exception of drowsiness, fewer side effects (33,34,38,50). Interestingly, their affinity for histaminergic receptors does not correlate well with their ability to suppress motion sickness (33). Cyclizine has been displaced in the United States by the longer acting meclizine (Bonamine) (34).

Meclizine is weakly effective in *Suncus*, perhaps reflecting the relatively low efficacy of antihistamines in human subjects (48). However, histamine transmission does play a role in motion sickness in both *Suncus* and cats, as its depletion with high doses of the histamine synthesis inhibitor, alpha-fluoromethylhistidine, reduces motion sickness in both species (14,29).

Though billed as calcium channel blockers, cinnarizine and its derivative, flunarizine, are also antihistamines. Cinnarizine is not listed as available in the United States, but is effective in a variety of species, with the exception of *Suncus*. Flunarizine is effective in the rotating chair (19) as well as in the monkey at the dose of 10 mg/kg (5).

**Antimuscarinic/Antihistamines**

These drugs are frequently described as antihistamines that also have anticholinergic effects because, historically, they were discovered in a search for antihistamines. At therapeutic doses, they are highly anticholinergic. For example, promethazine (Phenergan) is more anticholinergic than diphenhydramine (Benadryl), and the latter is used for its anticholinergic action to reverse acute dystonias elicited by neuroleptics.

Like scopolamine, promethazine is effective in alleviating sickness elicited by any form of motion tested. It is also effective in the monkey at 3 mg/kg and in *Suncus* at 50 mg/kg (5,48).

Diphenhydramine is effective in human subjects during turbulent flight and in the rotating chair (6,50). It is quite effective in *Suncus* at 20 mg/kg (48), but is not effective in dogs at low doses (8) or in cats over a range of doses (29).

The form of diphenhydramine used clinically for motion sickness is the 8-chlorotheophylline salt, dimenhydrinate (Dramamine). It is slightly more effective than diphenhydramine, while 8-chlorotheophylline is only weakly effective (6). Interestingly, dimenhydrinate is not very effective in *Suncus* at 32 mg/kg, which is equimolar to the effective dose of diphenhydramine (48).

**Mechanism of Action of Antimuscarinics, Antihistamines, and Mixed Agents**

The mechanism of action of the above drugs is poorly understood. The most common assertion is that they suppress integration of sensory stimuli in the vestibular nuclei. This arises from observations such as their ability to suppress potentials in the vestibular nuclei elicited by stimulation of the vestibular apparatus (13) and to suppress nystagmus during rotation (39). If true, this would lead to the prediction that they would interfere with habituation to provocative sensory stimuli that no longer present patterns consistent with past experiences (see Oman article, this issue). Indeed, scopolamine is suspected to interfere with habituation to microgravity and has been shown to interfere with habituation in the rotating chair (52).

In contrast, promethazine does not interfere with habituation to provocative motion in human subjects (18). Further, promethazine is used to suppress vomiting elicited by a wide range of emetic stimuli, not just motion. However, these two observations could be reconciled with an action in the vestibular nuclei. The differing re-
sults on habituation could arise from differences between the studies. Notably, the promethazine study used a mental task to maintain alertness, a factor in learning/habituation paradigms. Other differences in the relative affinities of scopolamine and promethazine for the different subtypes of muscarinic receptors and the additional antihistaminergic effect of promethazine could have roles. As for the range of stimuli against which promethazine is effective, a number of drugs believed to elicit vomiting by stimulating the area postrema only elicit vomiting at higher doses when the vestibular apparatus is bilater-

5-HT$_3$ antagonists are not effective in preventing motion sickness in human subjects, cats, or Suncus (20,43,46). Dopamine antagonists are not effective in human subjects (50). The selective D$_2$ dopamine antagonist, sulpiride, is highly effective in the squirrel monkey (31), but only slightly so in cats (24). In Suncus, chlorpromazine and a D$_1$ dopamine antagonist, but not a D$_2$ dopamine antagonist, are effective (30,48). Chlorpromazine is effective in the dog (8). Naloxone slightly enhances motion sickness in both humans and cats (1,9), while sympatholytics produce no effect in either species (25,50). Also ineffective in cats are a cannabinoid, adenosine antagonists, and antagonists of CCK (unpublished observations).

Receptor Mechanisms Effective in Animal Models

Numerous 5-HT$_{1A}$ agonists are effective against both motion- and drug-induced vomiting in both cat and Suncus (22,24,37). The drug available for use in humans, buspirone, is only a partial agonist and would require roughly 200 to 300 mg for a reasonable clinical trial. Doses which lack receptor selectivity (23). A clinical trial with a suitable dose of a full agonist would provide a more definitive test of this mechanism. Stimulation of 5-HT$_3$ receptors is highly effective in Suncus (36), but only weakly effective in cats (unpublished observations). Potential hallucinogenic effects by this receptor mechanism make it unlikely that a clinical trial

Sympathomimetics

Amphetamine is quite effective in the rotating chair and in some operational conditions, such as commercial transatlantic cruises (16,50,51). However, studies using the endpoint of vomiting, including swing sickness and operational conditions such as acrobatic flight, transatlantic troopships, and small craft in heavy seas, all report no benefit (41,47). It is not clear whether these discrepancies result from differing durations of testing, severity of the stimuli, differing endpoints (nausea versus vomiting), or motivational factors. Amphetamine suppresses motion-induced vomiting in Suncus at 2 mg/kg (48) and in monkey at 0.1 mg/kg (5), but not in cat (unpublished observations).

Ephedrine is quite effective in humans in the rotating chair (50), but not in the monkey (5).

Experimental Approaches with Human Subjects

Phenytoin (Dilantin) is effective in human subjects exposed to the rotating chair, parabolic flight, and rough sea conditions. Efficacy is obtained when plasma levels have risen to at least 9 &g/mL, which is comparable to its anticonvulsant range of 10 to 20 &g/mL (3,17). Another agent, dexamethasone, is effective in the rotating chair when preloaded for 48 hr (15). The major disadvantage of either drug is the prior dosing requirement before therapeutic levels are obtained. Ginger has been reported to be effective aboard a sailing ship (12), but not in the rotating chair (42).
will be attempted. The NK-1 antagonist CP-99,994 is effective in both *Suncus* and cats (11, 49). The possibility that it may block vomiting but not nausea is discussed below. NMDA channel blockers are effective in cat (22), while blockade of AVP1 but not AVP1/AVP2 receptors is effective in the monkey (4). The NMDA antagonists or AVP1 antagonists would warrant clinical trials.

**Additional Considerations with Animal Models**

The endpoint measure varies in the different models cited. Most of the clinical drug studies in the last four decades used nausea in the rotating chair, with any follow-up studies using nausea and vomiting in sea trials or parabolic flight. The early literature predominantly used vomiting. In *Suncus*, the measure is the presence or absence of vomiting and the number of vomits in this rather productive species. The monkey studies used a nonparametric rating scale with the highest number of points awarded for retching or vomiting, moderate points for different levels of chewing, and fewer levels of points for salivation, drowsiness, or odd behaviors. In the cat, the primary measure is the presence or absence of vomiting. The responsiveness of different species to the drugs reviewed above is summarized in Table 1. While there is a good deal of concordance between all species, there are no two species with the exact same profile of responsiveness.

One immediate discrepancy between studies with human subjects and those with animal subjects is that there is nothing that can be measured in an animal as nausea. The rating scales rely on species-specific unusual behaviors that are associated with emetogenic stimuli and as such might reflect neural activity early in the final common pathway for vomiting. In the rating scale devised for the cat, points are awarded on a nonparametric scale that uses measures such as varying levels of salivation, panting, defecation, urination, and retching/vomiting (45).

Some of the drug data from the cat cited above published the symptom scale without the points for retch/vomits to provide a measure independent of vomiting. However, caution is required in using this rating scale. In cats, sympatholytics increase some symptoms, while sympathomimetics increase others. Thus, drugs that directly or indirectly alter sympathetic function could lead to a false negative conclusion with the scale. Similarly, several symptoms are reduced by peripheral blockade of the parasympathetic system without a change in the number vomiting. Drugs directly or indirectly altering parasympathetic function could thus produce false negative or false positive conclusions with the scale (25).

Another measure in the cat focuses on the motor act of vomiting. Cats respond to provocation of the motor component is the duration from the first retch to the last vomit, which is occurring in succession. A more accurate measure of the motoric component is the duration from the first retch to the last vomit, which is

### Table 1. Comparison of Drug Effectiveness against Human, *Suncus*, and Cat Models

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human</th>
<th><em>Suncus</em></th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cyclizine/meclizine</td>
<td>(+)</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Cinnarizine/flumizine</td>
<td>+</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>N-Fluoromethylhistidine</td>
<td>NT</td>
<td>(+)</td>
<td>NT</td>
</tr>
<tr>
<td>Promethazine</td>
<td>+</td>
<td>NT</td>
<td>+</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>+</td>
<td>0</td>
<td>NT</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>+</td>
<td>(+)</td>
<td>NT</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>+?</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>+</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>5-HT3 antagonists</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dopamine antagonists</td>
<td>0</td>
<td>+ (+)</td>
<td>+</td>
</tr>
<tr>
<td>5-HT1A agonists</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>5-HT2 agonists</td>
<td>NT</td>
<td>(+)</td>
<td>NT</td>
</tr>
<tr>
<td>NK-1 antagonists</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Sympatholytics</td>
<td>0</td>
<td>NT</td>
<td>0</td>
</tr>
</tbody>
</table>

**+= Effective, (+) = Weakly effective, 0 = No effect, NT = Not tested.**

### Table 2. Effects on Measures Other Than Vomiting of Drugs That Suppress Motion-induced Vomiting in Cats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Symptom</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>5-HT1A agonists</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>NMDA channel block</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>NK-1 antagonists</td>
<td>0</td>
<td>↓</td>
</tr>
</tbody>
</table>
remarkably consistent in averaging from 20 to 35 seconds and is resistant to most drugs.

For drugs that decrease the number of cats vomiting in response to provocative motion, the drug effects on duration of vomits and on symptom points after evaluating autonomic effects are summarized in Table 2. Scopolamine, which may act within the vestibular nuclei, produces a decrease in some symptoms that cannot be accounted for by peripheral muscarinic blockade and has no effect on the duration (25). The 5-HT1A agonists, which may be acting early in the final common pathway, may act on dorsal motor vagal neurons. Thus, more detailed evaluation of the available data can provide insight as to where a given drug works in the final common pathway.

REFERENCES


45. Suri KB, Crampton GH, D'Iantonio NG. Motion sickness in cats: a symptom rating scale used in laboratory and flight tests. Aviat Space Environ Med 1979;50:14-9.


