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REVIEW OF MOTION SICKNESS DRUGS FROM 1954 - 1964

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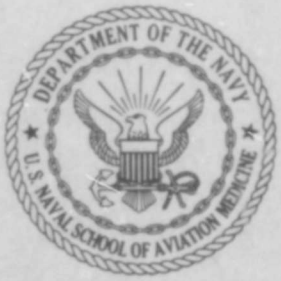

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REVIEW OF MOTION SICKNESS DRUGS FROM 1954 - 1964*

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*Opinions or conclusions contained in this report are those of the author and do not necessarily reflect the views or endorsement of the Navy Department.

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SUMMARY PAGE

THE PROBLEM

The great increase in air and sea travel has resulted in a greater need for effective antimotion sickness drugs, and the exploration of space is expected to intensify this need. Since a review of available antimotion sickness drugs has not been published since 1955, a compilation of the newer drugs and studies reported in the last ten years is presented.

FINDINGS

Hyoscine (Scopolamine) still appears to be one of our most effective antimotion sickness drugs. Its severe side effects of drowsiness, vertigo, and dry mouth limit its usefulness. Meclizine (Bonamine) and Cyclizine (Marezine) are reported to be the most effective of the antihistamines. Their side effects are milder than most other preparations, and their level of reported effectiveness approaches that of hyoscine.

Many of the newer preparations are less effective than the above-mentioned drugs and others have yet to fully prove themselves.

INTRODUCTION

The antimotion sickness drugs have been tested under a wide variety of conditions (5,29,44), and several effective new remedies have been demonstrated in the past ten years.

More recently, the great increase in air and sea travel has resulted in a greater need for effective antimotion sickness drugs, and the exploration of space is expected to intensify this need.

Motion sickness and the antimotion sickness drugs were reviewed by Chinn and Smith in 1955 (11). The present paper will concern itself with the newer drugs and studies reported since that time and will attempt to compare them with any related drugs previously in use.

For purposes of discussion these drugs are divided into four major categories as follows: the anticholinergics, the antihistamines, the tranquilizers, and a miscellaneous group.

ANTICHOLINERGICS (PARASYMPATHOLYTICS)

Various anticholinergic drugs have long been known to be effective against motion sickness and are currently considered some of our most effective remedies.

Hyoscine (Scopolamine, 90% effective) 0.6-1.0 mg. and atropine (50% effective) 1.0 mg. are two good examples of this group. According to British investigators, hyoscine has yet to be surpassed as a motion sickness preventive (22,23). They recommend 1.0 mg. before arising, 0.5 mg. mid-day, and 0.5 mg. at night for a total dose of 2.0 mg. Side effects of dry mouth, drowsiness, vertigo, and blurring of vision were frequently reported. A slightly higher dose, 0.75 mg. three times a day (for a total of 2.25 mg.) for three days, produced side effects of headache, cardiac acceleration, excitement, and in some cases hallucinations and bad dreams (9,15,26,33).

Hyoscine aminoxide (Scopodex) 2.0 mg. has long been used by several airlines as an effective remedy (54% effective) and is claimed to have few side effects. However, with prolonged administration some of the same side effects reported above with hyoscine were seen, and it was recommended that a dose of 1.0 mg. be used for repeated doses (11).

The observation that many of the drugs effective against Parkinsonism are also good antimotion sickness remedies has prompted the investigation of several of the newer synthetic belladonnas. There does not appear to be a clear correlation between these actions as many effective anti-Parkinsonism drugs are not effective against motion sickness (16).

Trihexyphenidyl (Artane) 1.0 - 5.0 mg. is one of the most effective anti-Parkinsonism drugs, and it was found to be only partially effective at the 1.0 mg. (24% effective) dosage level while the 5.0 mg. (77% effective) level was found to approach the effectiveness of hyoscine (10).

Phenglutarmide (Aturban, 74% effective) 2.5 mg. (44,46), was reported to be fairly effective in troopship studies but this was below the level found for hyoscine and the antihistamines.

Orphenadrine (Disipal) 50.0 mg. was reported to be more effective (62%) than atropine (50 %) in one large study at sea; however, conditions of the test were quite mild (44).

Benztropine (Cogentin) 1.0 mg. was effective (60%) within the same range as orphenadrine, and it was tested under more severe conditions (2).

At present hyoscine (Scopolamine) 0.6 mg. appears to be the drug of choice in this group. The other representatives have not proved to be as effective and have demonstrated side effects similar to this does of hyoscine (20,21). It is felt that the side effects of hyoscine would limit the efficiency of a person in a responsible position. Since prolonged thempy produces even more serious side effects, it would appear that this drug would be indicated for short-term use in persons who are on light duty.

Anticholinergics	Trade Name	Duration	Dose	%Effectiveness
Hyoscine	(Scopolamine)	4 hrs.	0.6-1.0 mg.	90%
Trihexyphenidyl	(Artane)	6 hrs	5.0 mg.	77%
Phenglutarmide	(Aturban)	6 hrs.	2.5 mg.	74%
Orphenadrine	(Disipal)	6 hrs.	50.0 mg.	62%
Benztropine	(Cogentin)	6 hrs.	1.0 mg.	60%
Hyoscine aminoxide	(Scopodex)	4 hrs.	2.0 mg.	54%
Atropine		4 hrs.	1.0 mg.	52%

ANTIHISTAMINES

Some of the most effective antimotion sickness drugs are to be found in this group. Their potency as an antimotion sickness remedy is not related to their effectiveness in other areas (3). This would suggest different mechanisms of action for these therapeutic uses.

Diphenylhydramine (Benadryl) 50 mg. (58% effective) (21,26,40) and dimenhydrinate (Dramamine) 50 mg. (70% effective) (8,28,34,39) have a proven effectiveness as antimotion sickness drugs and have had extensive use. Side effects such as drowsiness and vertigo are limitations on the usefulness of these preparations.

Meclizine (Bonamine) 50 mg. (85% effective) is one of our most reliable antimotion sickness drugs (1,19,34). It appears to have fewer side effects and a longer duration of action than any of the previously mentioned drugs (36).

Cyclizine (Marezine) 50 mg. (87% effective), a new drug in this group, is reported to have milder side effects and a more pronounced therapeutic effect (2,22,23,25,34). In two studies it was reported to be 100% effective (35,44). It has a shorter duration of action than meclizine which could be a disadvantage in prolonged travel.

Buclizine (Vibazine) as Bucladin with belladonna and Vitamin B_6 has a structural formula very similar to meclizine. It seems also to have similar characteristics and reported effectiveness of 50% and 90% over the placebos (2,14).

Cinnarazine (Mitronal-Cinneperine) 15 mg. X 3 or 90-120 mg. is a promising new drug. It has been used in single oral doses of 250 mg.; however, 50% of the subjects reported drowsiness as a side effect (30). This drug is also closely related to meclizine but was not found to be as effective (60%)(44). A dose of 50 mg. could possibly bring the results closer to those of meclizine.

Pyrathiazine (Pyrrolazote) 50 mg. when administered double blind reduced the incidence of vomiting in comparison to the placebo group (50.2% effective) (2). It was found to be 75% effective against air sickness by the United States Air Force but was less effective than other drugs in this group (11,43).

The chief side effects seen with higher doses of all representatives of this group are drowsiness and dizziness (18). Fewer side effects were reported with cyclizine (Marezine) than with meclizine (Bonamine); however, the longer duration of action of meclizine would appear to make it the drug of choice in this group. Buclizine and cinnarazine are two promising additions to this group.

Antihistamines	Trade Name	Duration	Dose	% Effectiveness
Cyclizine	(Marazine)	4 hrs.	50 mg.	100%
Buclizine	(Vibazine-Mixture Bucladin)	8 hrs.	50 mg.	90%
Meclizine	(Bonine, Bonamine)	12 hrs.	50 mg.	85%
Dimenhydrinate	(Dramamine)	6 hrs.	50 mg.	70%
Cinnarazine	(Mitronal Cinniperine)	6 hrs.	30-40 mg.	60%
Diphenhydramine (	(Benadryl)	6 hrs.	50 mg.	58%

(Promethazine can also be included in this group. See tranquilizers.)

TRANQUILIZERS

The use of drugs classified as tranquilizers to treat motion sickness suggests the question as to whether one is treating motion sickness or "emotion sickness." Emotional factors certainly are components in the mechanism of motion sickness, and the reported effectiveness of certain drugs in this group may be partially due to relief of anxiety. This is one of the most active areas of pharmacological research, and the many effective drugs acting on the chemoreceptor trigger zone are in this group. Only a few representatives of this group have been reported to be effective against motion sickness, but it could be anticipated that more effective antimotion sickness drugs will be found in this area.

The rauwolfias have been tried against motion sickness with no success. Alseroxylon and Reserpine both increased the incidence of vomiting over that of the controls (2).

The phenothiazine, chlorpromazine (Thorazine), was reported to be completely ineffective against motion sickness in man (2,4,13,24,26), but with good results against swing sickness in dogs (11).

Trifluprom azine (Vesprin) 25 mg. was reported to increase the incidence of vomiting over that of the control group (10).

Promethazine (Phenergan) 25-50 mg. could be included in this group or in the antihistamines. It has had extensive testing and is reported to be an effective remedy (78%), but it has a marked sedative action. Clinically, it is used as a sedative; therefore, as

would be expected, its usefulness as an antimotion sickness drug is greatly limited (2, 11, 12, 12, 23).

Prochlorperazine (Compazine) 5 mg./4 hrs. or 15 mg. spansules has been reported to give good results in from 73% to 84% of the subjects (6, 50).

In troopship studies Donaldson (17) reported 5 mg. of trifluoperazine (Stelazine) to be of therapeutic value in 67% of the cases of sea sickness. Turnbull (45) reported this drug to be up to 80% effective in therapeutic use against motion sickness on passenger ships.

Drowsiness, hypotension, and mental depression are some severe side effects seen in all representatives of this group.

Thioperazine (Vontil) is reported to be fifty times as effective as chlorpromazine on the chemoreceptor trigger zone. While it is true chlorpromazine has proven to be ineffective against motion sickness except in very high doses, destruction of the chemoreceptor trigger zone in dogs has been reported to reduce susceptibility to motion sickness (49). Therefore, Vontil should be investigated as an antimotion sickness drug.

Thiethylperazine (Torecan) 10 mg. has been reported to be a promising new drug against motion sickness. In one of the few studies on motion where this drug was used, it was reported to be 78% effective in preventing motion sickness and 37% effective as a treatment for those already motion sick (48). The structure of this drug is very close to that of chlorpromazine which was ineffective for this purpose in man and thioridazine (Mellaril) which is reported to have little if any antiemetic action. Therefore, a careful evaluation of this drug would seem to be indicated.

Promethazine appears to be the only proven antimotion sickness drug in this group. Thiethylperazine (Torecan) appears to be a very promising preparation. Prochlorperazine (Compazine) and trifluoperazine (Stelazine) have had very favorable reports.

Phenothiazines	Trade Name	Duration	Dose	% Effectiveness
Trifluoperazine	(Stelazine)	6 hrs.	5 mg.	80%
Thiethylperazine	(Torecan)	6 hrs.	10 mg.	78%
Promethazine	(Phenergan)	12 hrs.	25-50 mg.	78%
Prochlorperazine	(Compazine)	4 hrs.	5 mg.	75%
Chlorpromazine	(Thorazine)	8 hrs.	25 mg.	ineffective
Thioperazine	(Vontil)	Not tested on motion sickness		

MISCELLANEOUS DRUGS

Meprobamate (Miltown) 400 mg. was reported to be as effective as meclizine 50 mg. in recent studies at Brooks Field (19). Both drugs had an effectiveness ratio of 60% against airsickness when compared to the placebo group.

Trimethobenzamide (Tigan) 250 mg. orally or 200 mg. I.M. is a new drug with no reported side effects at the recommended dose level. No evidence of its effectiveness against motion sickness has been reported as yet although it is the antimotion sickness drug selected for the space flights. It appears to be a good antiemetic for toxicities; however, not all effective antiemetics are effective as antimotion sickness drugs. For example, chlorpromazine is an excellent antiemetic for chemically induced nausea (31) but is ineffective against motion sickness. Further research would seem to be indicated before full acceptance of trimethobenzamide as an antimotion sickness remedy.

The monamine oxidase inhibitors have been tried against motion sickness with a uniform lack of success. In fact, the incidence of vomiting appeared to be increased by these drugs. Drugs tested were phenepraz ine (Catron), phenelzine (Nandil), and nealazide (Neamid) (44).

The vitamins have been of little effect against motion sickness in spite of their reported relief of nausea in pregnancy. Pyrodoxine (B_6) and thiamine (B_1), alone or in combination, have been unsuccessful as remedies (2).

Nyledrin, a sympathomimetic substance, is sometimes used in combination with antiemetics for vertigo due to atherosclerotic conditions. It is reported to increase blood supply to the vestibular organ by producing vasodilation. Unless insufficient blood supply is a contributing factor in motion sickness, it is unlikely to be of use as an antimotion sickness drug.

Noble (38) has reported that the thiobarbiturate V_{12} is effective against motion sickness and has used it in combination with the belladonnas. While amobarbital and pentobarbital have been used in similar combinations, these barbiturates generally have been reported to be ineffective unless a pronounced level of anesthesis is attained.

Miscellaneous	Trade Name	Duration	Dose	% Effectiveness
Meprobamate	(Miltown)	4 hrs.	400 mg.	60%
D-Amphetamine	(Dexadrine)	6 hrs.	10 mg.	39%
Trimethobenzamide	(Tigan)	6 hrs.	100-250 mg.	?
Barbiturates		6 hrs.	10-100 mg.	--

COMBINATIONS

Various combinations of drugs have been tried against motion sickness. When used in combination with other drugs, usually one-half the effective dose is used. An antihistamine such as Dramamine or Benadryl is frequently used with Scopolamine and a barbiturate such as pentobarbital or butabarbital. Vitamins B_1 and B_6 may be substituted for the barbiturates. At present none of the combinations appears to be more effective than a full strength dose of their most effective component.

Perphenazine (Trilafon) 0.4 mg./Kg. in combination with meclizine (Bonamine) 5 mg. has been used to prevent swing sickness in dogs. Trilafon has no effect alone and does not significantly increase the effectiveness of Bonamine reported in other studies where Bonamine alone was used (37,47).

Amphetamine has been combined with some of the antimotion sickness drugs in an effort to counteract their depressant action. Some studies have reported that the effectiveness of the antimotion sickness drugs remains the same (3). Amphetamine alone has been reported to have antimotion sickness properties (27,32). Blackham (7) reported it to be one of the best remedies. However, a more recent report states that, when amphetamine is used, nystagmus is prolonged and more easily induced, especially in the inattentive state (41). It appears likely that amphetamine could be combined with the antimotion sickness drugs without diminishing their effectiveness.

It is as yet impossible to suggest any common mechanism of action for the divergent group of drugs used for treatment of motion sickness. A direct depression of the vomiting center is the only action that can be proposed for these drugs on the basis of our present evidence. A survey of the structural formulae presented here would indicate that it would be equally difficult to find a structural-functional relationship until our knowledge is considerably extended.

In reviewing the literature the need for maintaining standardized conditions during drug testing became apparent. Double-blind and placebo techniques for any future research are strongly recommended.

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