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ANTI-EMETIC DRUG EFFECTS ON PILOT PERFORMANCE, PHASE II: SIMULATION TEST

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This report has been reviewed and is approved for publication.

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The objectives of this study were to evaluate the effects of two anti-emetic drugs, granisetron (2 mg oral dose) and ondansetron (8 mg oral dose), on flying and mission performance in an F-16 research simulator. The experimental approach, involving 9 pilots, was a placebo controlled, double blind, crossover design. Each pilot flew three defensive counter air missions. Data on eight measures of flying performance were collected via the simulator data recorder. Ratings on mission and flying performance were recorded by simulator instructor pilots. Data were also collected on symptoms and side effects, mood and vigilance. This study, carried out in the context of a simulated tactical air-to-air combat mission, produced no significant differences between the target drugs and placebo on any of the eight objective flying performance measures or on a composite measure of landing performance. There were no differences in evaluator ratings of routine misson flying or air combat performance. Pilots could not distinguish active drug from placebo and there were no differences on any of the mood scales. These results confirm our earlier findings that the drugs of interest are well tolerated and produce no cognitive, psychomotor or subjective state changes. In this study, there was no evidence of performance degradation caused by either granisetron or ondansetron when tested in a complex, military task environment.

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ABSTRACT

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PREFACE

This report documents work performed for the Armstrong Laboratory by Systems Research Laboratories (contract F41624-91-C-2003) in collaboration with co-investigators from the Sustained Operations Branch of the Armstrong Laboratory. Simulation facilities were provided by the Armstrong Laboratory, Aircew Training Research Division, Williams Gateway Airport, Mesa, AZ.

The formal requirement for this research is documented in a NATO Project Group 29 statement of work for the selection of a drug for the prevention and treatment of radiation induced nausea and vomiting. Funding for the effort was provided by the Defense Nuclear Agency (DNA), through the U. S. Army Nuclear and Chemical Agency.

Several individuals deserve recognition for their contributions: Dr. Samuel G. Schiflett of the Armstrong Laboratory for providing expertise in the area of drug effects on complex military task performance; Mr. Joe Fischer and Mr. Dan Bauer, also of the Armstrong Laboratory, for experimental design, data analysis and interpretation; Dr. Douglas R. Eddy, NTI, Inc., who provided critical review of the experimental design; Mr. Bart Raspotnik and the Aircrew Training Research Division simulator operations team; Dr. Bob Young, formerly with the DNA, and Mr. Rob Kehlet of the DNA for their confidence in this laboratory and their project recommendations.

ANTI-EMETIC DRUG EFFECTS ON PILOT PERFORMANCE
PHASE II: SIMULATION TEST

1.0 INTRODUCTION

1.1 Summary - This investigation was designed to provide scientific evidence relevant to the selection of anti-emetic drugs for safe operational use. Without studies to evaluate the side effects and safety of these compounds, aircrew and ground personnel will remain vulnerable to incapacitation from radiation induced nausea and vomiting. Alternatively, selection of a prophylactic with performance degrading side effects could threaten mission effectiveness.

This report completes our work to evaluate the operational safety of standard oral doses of the anti-emetic drugs granisetron (2 mg, supplied by SmithKline Beecham Pharmaceuticals, trade name: Kytril), and ondansetron (8 mg, supplied by Glaxo Welcome, Inc., trade name: Zofran). The simulation tests described in this report represent a follow-on to a carefully controlled laboratory investigation demonstrating that the target drugs are unusually free of undesirable side effects and do not disrupt thinking, motor performance, subjective state or complex task learning. These simulation trials provided an important opportunity to validate, in a complex task environment, the safety of new drugs with remarkably improved protective characteristics against radiation induced nausea and vomiting which can lead to significant incapacitation. Taken prophylactically, these drugs could be used to extend the ability of an individual or crew to complete a mission and return to base or reach an alternate location after exposure to radiation.

1.2 Requirement - The formal requirement for this work stems from the NATO Army Armaments Group (NAAG), involves an international consortium of four nations, and is managed by the NAAG Project Group 29 with representatives from each of the participating nations. Resources were provided by the Defense Nuclear Agency. The medical aspects and safety of this study were approved by the Armstrong Laboratory Committee on Human Experimentation

(ACHE 95-12) and the Air Force Human Use Committee, HQ AFMOA/SGPT (R95-056). Additionally, the protocol was reviewed and supported by the HQ ACC/SG, HQ ANG/SGP, HQ AFRES/SGP and the FAA/CAMI. These simulation tests represent the last in an extensive series of studies to test the safety of these compounds for use in the military task environment.

2.0 METHODS

2.1 Experimental Design - This study was based on a within-subjects, repeated measures design under partially counter-balanced order conditions. There were nine subjects in each treatment condition and 3 subjects in each of three order effects groups. The availability of subjects and simulator time precluded testing all possible orders. Moreover, in a recently completed laboratory study employing 24 subjects, there were no drug order effects that were detected by any of the measured variables (Benline, 1995). There were three treatment conditions: two anti-emetic drugs and a placebo. Both the investigators and subjects were blinded to the treatment conditions, **Table 2.1-1**.

Table 2.1-1: Experimental Design

Test Day	1		3		5
Wash-out Day		2		4	

Order Group	Drug		Drug		Drug
Grp. I	Placebo		Granisetron		Ondansetron
Grp. II	Granisetron		Ondansetron		Placebo
Grp. III	Ondansetron		Placebo		Granisetron

Drug Treatment: n = 9
Order Effects: n =3

2.2 Subjects - Nine USAF pilots volunteered to serve as subjects in the study. Eight of the nine pilots were from the Air National Guard. All were current in the General Dynamics F-16 Falcon aircraft. The remaining pilot flew the McDonnell Douglas F-15 Eagle in his previous assignment. During the period of these tests, he was assigned to the Aircrew Training Research Division of the Armstrong Laboratory, Williams Gateway Airport, AZ, as a simulator instructor

pilot. In terms of experience, this group of pilots represented an average of 2,053 h of fighter time with a range of 700 h to 4200 h. Average time in the F-16 was 1538 h with a range of 650 h to 2400 h.

Six of the nine pilots had at least 46 h of previous simulator time in the Aircrew Training Research Division's engineering research simulators, the F-16 Display for Advanced Research and Training (F-16 DART) and the F-16 Mini-DART. These six subjects were randomly assigned to the three order effects groups. The remaining three subjects were then randomly assigned across the same three treatment order groups. This quasi-random approach attempted to balance proficiency across order effects groups and to minimize the possibility of results contaminated by learning over the three mission scenarios.

Subjects ranged in age from 31-43 years with a mean age of 36 years. Individual weights were distributed between 145 and 190 lb with and average of 174 lb and heights varied between 65 and 73 in. with a mean of 69 in. All were males and officers in the rank of Captain to Lieutenant Colonel. In matters of life style, none of these pilots used tobacco, four (44%) reported using moderate amounts (an average of two drinks or less per day) of alcohol, and six (67%) used caffeine in one or more of its various forms, **Table 2.2-1**.

Table 2.2-1: Subject Demographics and Life Style

n=9	Age	Weight	Height	Male	Officer	Cauc.	Tobacco	Alcohol	Caffeine
Subjects				9	9	9	0	4	6
Percent				100%	100%	100%	0%	44%	67%
Mean	36yr	174lb	69in						
Range	31-43yr	145-190lb	65-73in						

As a condition of voluntary consent, subjects were asked to adhere to alcohol and caffeine restrictions during the study. The alcohol restriction was not more than two alcoholic beverages in any one day during the study and no alcohol within 12 h of any test session. Subjects also

agreed to refrain from consuming more than five caffeinated beverages (coffee and sodas in any combination) per day during the test period.

All subjects were medically cleared for flying duties. Subjects were screened for allergies, use of prescription medication, and any history of adverse reaction to drugs. Subjects were informed of the most frequently occurring side effects of the target drugs (i.e. headache and constipation). A drug effects questionnaire was administered before and after each simulator mission and delayed symptoms and side effects data were collected covering the 45 h period between simulator missions. Study participants were advised to consult with the onsite medical monitor on any symptoms rated moderate to severe. The stopping rule was explained so the subject could, at any time, elect to discontinue participation. A medical monitor was immediately available in the test facility on each of the test days and, in the event of an adverse reaction, could independently access the drug/subject session code. Each subject signed an informed consent document which contained the understanding they could withdraw consent and discontinue participation in the study at any time without prejudice. The original nine volunteer pilots completed all test sessions.

2.3 Target Drugs - The target drugs, granisetron and ondansetron, were selected based on their established function as competitive antagonists at 5-HT3 receptor sites. A widely supported theory of radiation sickness suggests that cellular damage and necrosis elicit the release of serotonin (5-hydroxytryptamine or 5-HT) from the enterochromaffin cells of the intestinal mucosa. This in turn activates 5-HT3 receptors along vagal afferent pathways ultimately stimulating the chemoreceptor trigger zone (CTZ) and vomiting center (VC) located in the brain stem. Radiation may also result in direct stimulation of 5-HT3 receptors in the CTZ and VC to produce vomiting. (Aapro, 1991; Andrews, 1988; Barnes, 1990; Freeman, 1992; Harding, 1988; King, 1991; Rabin, 1992; Seynaeve, 1991).

The active compounds and the placebo were administered in oral capsule form. Granisetron, trade name Kytril @ 2-mg was supplied by SmithKline Beecham Pharmaceuticals

and ondansetron, trade name Zofran @ 8-mg was supplied by Glaxo Welcome, Inc. (Granisetron, 1991; Zofran, 1993).

Ondansetron is available by prescription for administration in both oral and i.v. forms for use as an anti-emetic in treating chemotherapy patients. Oral granisetron was more recently approved for the mitigation of chemotherapy induced nausea and vomiting. For this study, both of the target drugs were granted an Investigational New Drug (IND) status by the Food and Drug Administration (FDA), IND # 44,675, dated 3/7/94, since the focus of this study was outside of the normally prescribed clinical uses for these drugs. Approvals for this study were also granted by the HQ AFMOA/SGPT Institutional Review Board, SGO # R95-056, dated 08/15/95 and the Armstrong Laboratory Committee on Human Experimentation , ACHE # 95-12, dated 08/16/95.

The target anti-emetic drugs and placebo were packaged in opaque capsules and identified as drugs a, b, and c to the investigators. The drugs (supplied by SmithKline Beecham and Glaxo pharmaceuticals) and placebo tablets (supplied by SmithKline Beecham) were cut using a pill cutter and loaded into the capsules by one of the investigators. At this point the drugs were identified by generic name, and, having been placed in individual containers, were provided to a person outside of the investigative team who served as a trusted agent for coding and blinding of test drugs.

2.3.1 Granisetron - Granisetron (trade name, Kytril, mfg. SmithKline Beecham) is a competitive serotonergic antagonist exhibiting great affinity for 5-HT3 receptor sites (Plosker, 1991). This drug has been studied extensively in animals and humans and is a well-tolerated and effective anti-emetic agent in radiotherapy-induced emesis (Hunter, 1991; Logue, 1991; Seynaeve, 1991). Granisetron is widely prescribed throughout Europe for the prevention of emesis caused by cytotoxic and radiation therapies. Granisetron, as an anti-emetic therapy for cancer patients undergoing chemotherapy, has recently been approved by the FDA. Granisetron is a potent and selective 5-HT3 receptor antagonist which has beneficial therapeutic effects in the treatment of radiation induced nausea and vomiting. Studies of granisetron in healthy volunteers have shown the drug to be well tolerated in single doses of up to 300 μg/kg i.v., a dose more than

7 times in excess of the 2 mg dose proposed for this study. With repeated dosing of granisetron for up to seven days, there was no evidence of an effect on pulse rate, blood pressure or ECG parameters (Upward, 1990). There is little evidence to suggest that Granisetron has any impact on EEG, psychometric or psychomotor performance (Leigh, 1991; Leigh, 1992). No extrapyramidal reactions have been reported (Seynaeve, 1991). The most common side effects are headache and mild constipation which normally resolve without intervention. In a study of healthy volunteers, none were able to differentiate between an infusion of the active compound and one of placebo. The only consistent complaint, which was not also noted with placebo, was constipation, first encountered at a dose of 80 μg/Kg. The incidence of headache was 15% for the granisetron group and 9% after administration of the placebo (Upward, 1990; Leigh, 1992).

2.3.2 Ondansetron - Ondansetron (trade name, Zofran. mfg. Glaxo) is also a 5-HT3 antagonist with a mechanism of action similar to granisetron, resulting in the inhibition of the nausea and vomiting reflex (Lip, 1990; Roberts, 1993; Scarantino, 1992; Tyers, 1989; Tyers, 1992). Ondansetron is available in both oral and i.v. forms for use as an anti-emetic in cancer therapy. The acceptability of this drug for the treatment of radiation induced emesis is well documented in the literature (Kidgell, 1990; Henriksson, 1992; Priestman, 1989). Ondansetron produces few side effects, no dependence liability and no end organ toxicity (Smith, 1989). This drug is well tolerated with no extrapyramidal reactions (Burnette, 1992). No major adverse events were reported after administration of ondansetron to 223 healthy volunteers or 438 psychiatric patients. Mainly, two categories of symptoms, headache and constipation, appeared related to ondansetron, occurring more frequently in repeat compared to single dose studies. The incidence of headache following a single dose administration was 17% while constipation and abdominal discomfort has been reported to occur in 1% of the subjects (Seynaeve, 1991). In a placebo controlled study of healthy subjects, administered standard oral doses of either ondansetron (8 mg, 3 x daily) or granisetron (2 mg, once daily) over 13 days, results were equivocal with regard to cognitive and psychomotor performance decrements (Wetherell, 1994).

2.4 Test Facilities - Familiarization training and testing were conducted at the Armstrong Laboratory Aircrew Training Research Division tempest facilities, located at Williams Gateway

Airport, Mesa, AZ. Alternative simulation platforms, the Air Combat Command B-1B Weapons System Trainer and the Air Education and Training Command T-1 and T-37 simulators were explored for possible use in this study. The F-16 Display for Advanced Research and Training (F-16 DART) and the F-16 Mini-DART were selected over the other potential systems for several reasons. The F-16 DART and F-16 Mini-DART are engineering research simulators owned and operated by the Armstrong Laboratory Aircrew Training Research Division. Both devices provide high quality task and image generation (terrain, weather, day-night, threat/friendly aircraft) as well as superior on-line data collection with precise clock timing of events. A two-ship formation, lead and wing, provided a more realistic air combat patrol and engagement scenario. Equally important, this investigative team had first hand experience with the F-16 DART platforms having recently completed a series of tests to explore issues related to fighter pilot fatigue.

2.4.1 DART Visual System - The DART Visual System is configured as a rear screen projected dodecahedron with nine channels of imagery surrounding the design eyepoint. The screens are flat, have a net gain of one, and are abutted with gaps of approximately one centimeter. The projectors are off-the-shelf, CRT-based, 1000-line systems. The result is wraparound real imagery, presented about 3.5 ft away with luminance levels of 10 foot-lamberts at the periphery of a screen, rising to 25 foot-lamberts at the center. The resolution is 4.25 arc minutes/pixel and the field of regard is 360 degrees horizontally by 260 degrees vertically. With eight channels on, the contrast ratio has been measured at 50:1. A Polhemus head-tracker is used to determine where imagery is not required so that six image generation channels can be channel switched to cover nine available projectors. Six channels are sufficient to minimize any distraction associated with projectors blinking on and off in the pilot's peripheral visual field. A rear mounted monochrome green projector provides an effective representation of the F-16C head-up display. Based on pilot acceptance and performance data, real imagery presented close in does not significantly affect mission performance. The DART is a unique visual system developed during prototyping for the commercial product, GE Compu-Scene IV - currently a product line of Lockheed Martin (Thomas, 1993).

2.4.2 Mini-DART Visual System - The Mini-DART is a smaller version of the DART utilizing fewer CRT projectors and image generator channels. This results in slightly decremented visual clarity and performance. The Mini-DART was developed as a lower cost image generation system that would, nevertheless, permit tactical pilots to employ the weapon system with a high degree of combat realism. The result is a rear-screen projection device using eight high definition television level, CRT projectors and four image generator channels to achieve encapsulation of imagery as viewed from the cockpit. Each projector provides the capability to synchronize to any video signal up to a noninterlaced maximum of 1280 pixels horizontally by 1024 lines vertically. All but the rear or "check six" screen are setup to be 24 in. from the design eyepoint in the cockpit. The rear screen is 20 in. from design eye. In this configuration, the CRT projectors result in central screen light levels of at least 24 foot-lamberts and contrast levels of 50:1. The resolution of the forward screen is nearly double that of the remaining screens as the angular subtend is close to 45 degrees as opposed to approximately 70 to 80 degrees presented by the other screens. The forward screen has nearly four times the brightness of the other screens in the display because of its smaller projection size. For air-to-air tasks (combat engagements, formation flying and aerial refueling), pilot acceptance for this display has been favorable (Thomas, 1993).

2.4.3 F-16 Cockpits - The cockpits used for this study were F-16 Multi-Task Trainers (MTTs). Each MTT is a high fidelity, F-16C cockpit incorporating all principle instruments, switches, flight controls, sensors, weapons and defensive countermeasures. Tactile feel and responsiveness provide a high degree of realism. MTTs are completely mission capable, supporting standard as well as instrument takeoffs, air-to-air combat, aerial refueling and instrument landings. Each MTT provides the flexibility to accept and modify weapons. Fuel loads can be accepted during aerial refueling. The operations and functional characteristics of the F-16C Inertial Navigation System (INS) are simulated. Several other operational characteristics are programmed into the MTTs, such as the Tactical Air Navigation (TACAN) system, the Instrument Landing System (ILS), automatic direction finder, landing gear warning light and tone, and in-flight refueling door. Communications equipment allows for UHF and VHF channels. MTTs use existing Air Force owned operational flight trainer code along with aircraft systems line

replaceable unit software that is converted to run on real-time multiprocessors. The use of actual aircraft code provides for high fidelity avionics and operational concurrence while the use of existing Air Force owned operational flight trainer software provides realistic cockpit simulation. One F-16 MTT was interfaced with the DART and a second F-16 MTT was stationed in the Mini-DART. For all tests, the lead pilot flew the F-16 DART while wing flew the F-16 Mini-DART.

2.5 Mission Scenario and Conduct - There were three separate missions flown on days one, three and five. Each mission was approximately 45-50 minutes in duration. For uniformity of task loading across treatment conditions, the only difference between the missions was the air-to-air engagement segment. Although the engagement was always a 2 (blue / defenders) v. 4 (red / threat), under Ground Control Intercept (GCI), the exact location and actions of the red forces varied. Because the air-to-air engagement could not be precisely controlled and because of classified aspects, instructor evaluations were used to grade this segment of the mission.

2.5.1 Scenario and Rules of Engagement - Each of the simulations centered on a defensive counter air mission to defend Chehalis Airfield, WA. Support from Ground Control Intercept (GCI) was provided. The rules of engagement were as follows: (1) all contacts except the tanker are considered bandits, (2) split flight when necessary, (3) engage and destroy threats anywhere, and (4) maximum enemy attrition.

2.5.2 Mission Conduct - Each mission involved two piloted F-16 simulators, the DART and Mini-DART, lead and wing, respectively. The same pilot flew either the DART or the Mini-DART for all tests. Except for the air-to-air engagement, each major segment in the mission (takeoff, refueling and landing) occurred sequentially (i.e. lead pilot followed by wing). The simulated takeoff was a Standard Instrument Departure (SID) with a solid cloud deck from 700 ft AGL (Above Ground Level) to Flight Level (FL) 180 (18,000 ft MSL). During the pre-takeoff phase, the pilot was instructed to wait for directions from the air traffic controller to release brakes and begin takeoff roll. These launch commands were coincident with the appearance of a computer generated Intelligent Flight Model (IFM) 100 ft above the runway, traveling at 150

KIAS (Knots Indicated Airspeed) and accelerating to 350 KIAS. The pilot's task was to launch and track on the IFM, entering the clouds at 700 ft and maintaining a radar trail separation of 1.5 nm (9,000 ft) through FL 180. At 15 nm and an altitude of 8,000 ft, the pilot was required to track the IFM through a 30° bank to a heading of 090° and maintain that heading for two minutes. The final leg of the SID required a 30° rollout to heading 360° and tracking on the IFM until it disappeared at approximately FL 180, **Figure 2.5.2-1**.

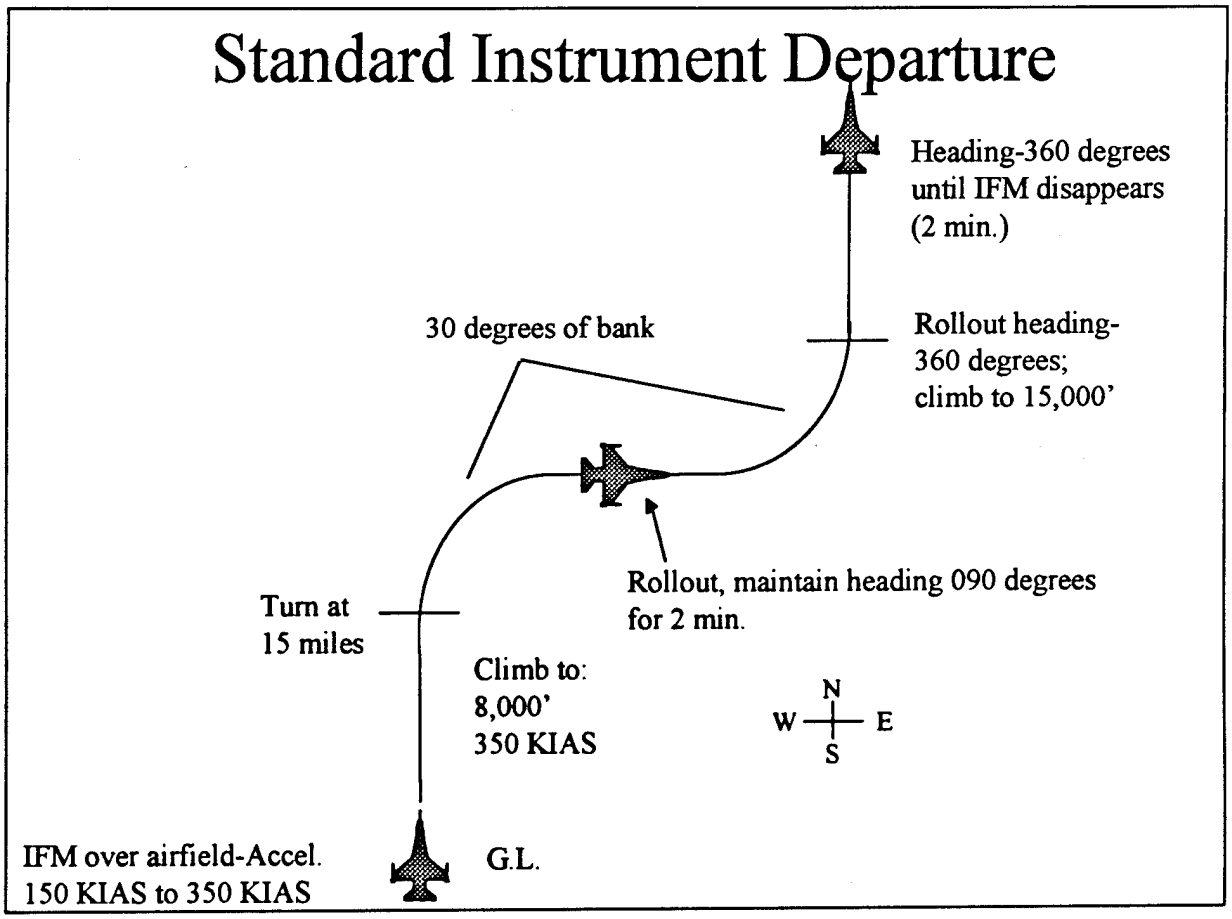


Figure 2.5.2-1: Standard Instrument Departure

Following the radar trail departures, lead and wing joined up and were vectored north in formation. Each was armed with 4 AMRAAMs, 2 AIM 9Ls and 510 rounds of 20 mm ammunition. GCI provided threat warning, bearing and range intercept with updates as dictated by the actions of the opposing (red) force. Each of the three engagements was a 2 v. 4 with

tactical variation by the red force. The engagement scenario was identical on any single day for the three treatment conditions and was graded by an expert instructor/evaluator.

At the conclusion of the air-to-air engagement, the blue force was required to rejoin and was vectored south to a waiting tanker. A KC-10 tanker was orbiting south of Chehalis Airfield at FL 200 and was flying a racetrack pattern, at 310 KIAS. The long legs of the tanker track were approximately 50 nm at headings of 090° and 270°. One pilot was required to refuel on each of the long legs of the tanker track, **Figure 2.5.2-2**.

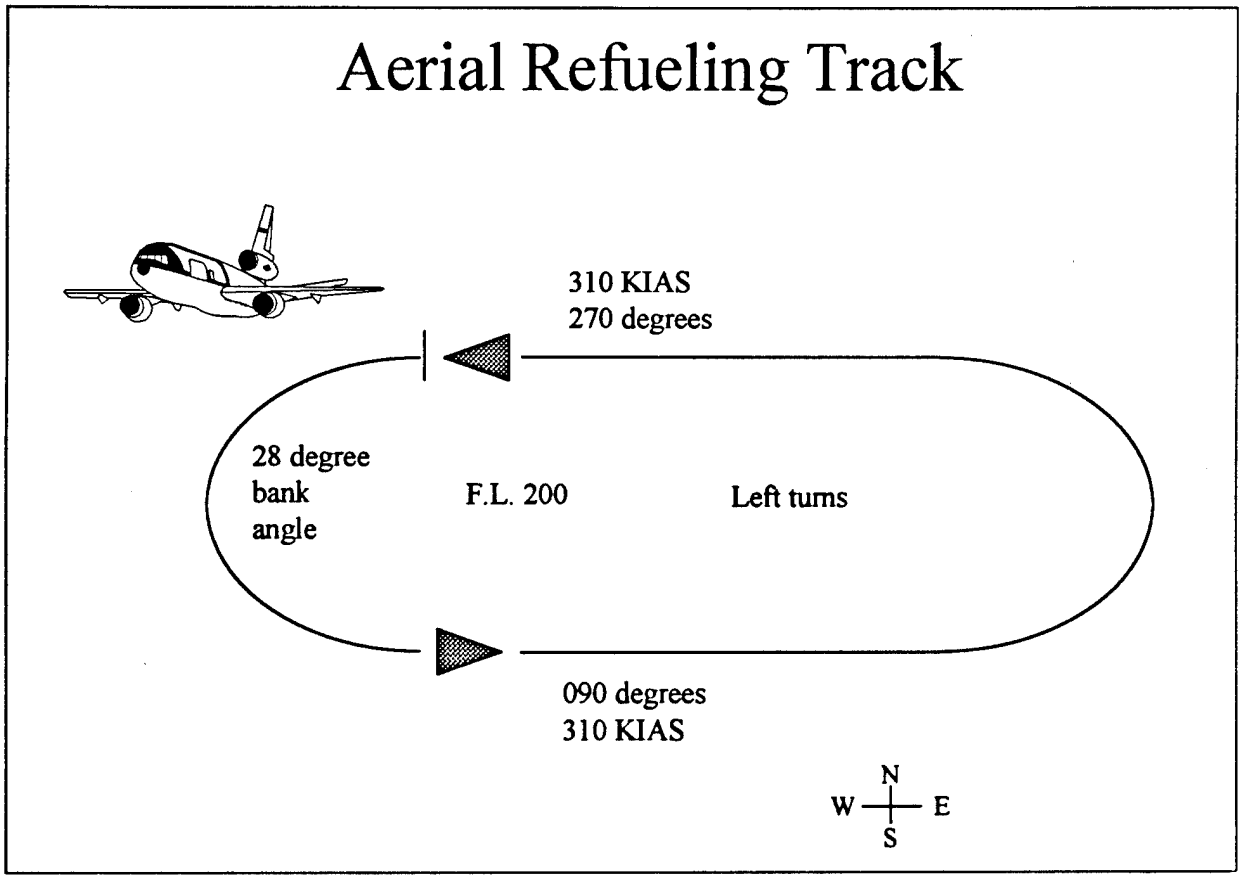


Figure 2.5.2-2: Aerial Refueling

Immediately after disconnecting from the tanker, the pilot was directed to fly to the Initial Approach Fix (IAF) (FLAEK on the approach plate) intercepting radial 117° at 300 KIAS, 14,000 ft altitude and 16 nm on the DME (Distance Measuring Equipment) from the TACAN (Tactical Air Navigation) at Chehalis Airfield. From this point, the pilot was challenged to fly a 12 DME

arc on the TACAN at 300 KIAS to an altitude of 5,100 ft, intercepting the 061° radial. From this second fix, the aircraft was to be flown to the 037° TACAN radial and an altitude of 4,000 ft. After reaching this checkpoint, airspeed was decreased to 180 KIAS together with a decent to 1,500 ft, intercepting the glideslope approximately 7.0 nm from the approach end of the runway. The ILS approach to a full stop landing required a weather penetration with the cloud ceiling at 200 ft AGL, **Figure 2.5.2-3**. See also **Appendix A**, the Chehalis Airfield Approach Plate.

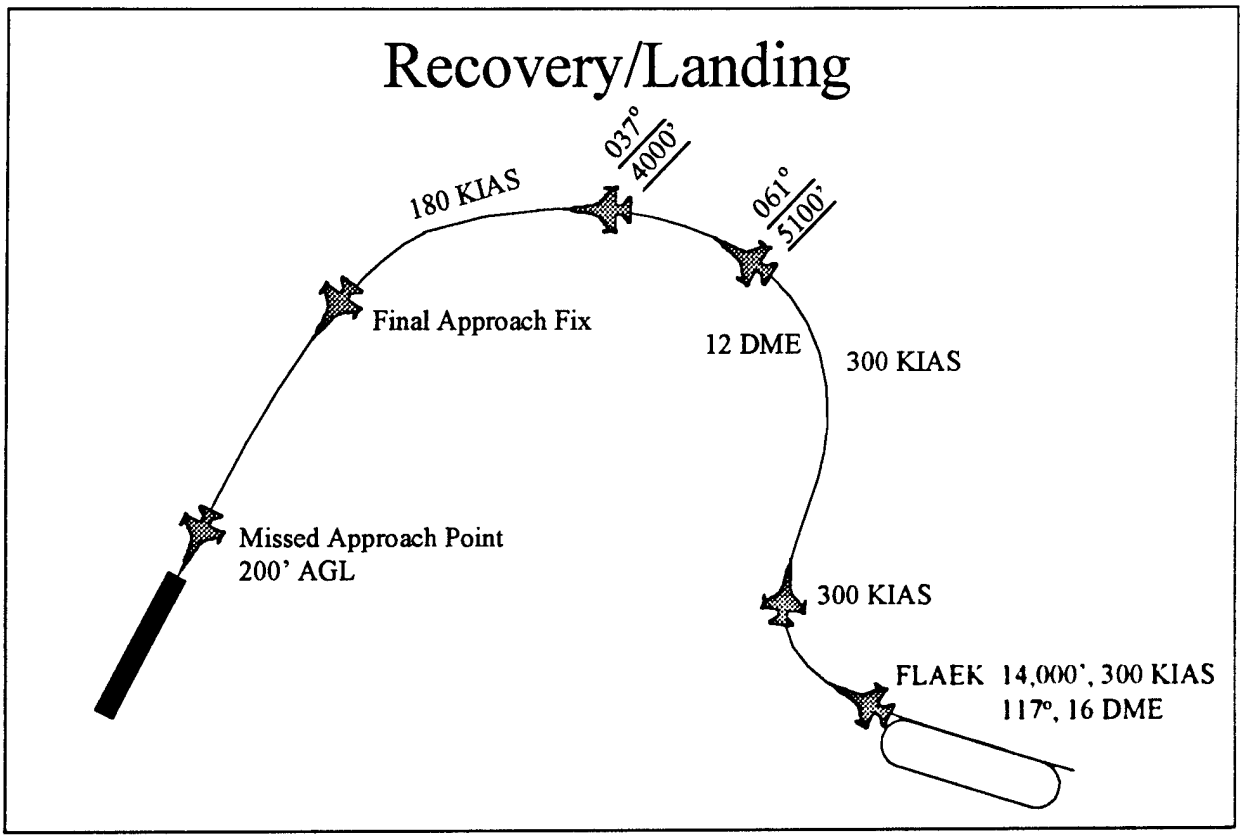


Figure 2.5.2-3: Recovery/Landing

2.6 Test Schedule and Events - Testing was conducted over a period of two consecutive weeks with 5 pilots in the first group (week 1) and 4 pilots in the second group (week 2) for total of 9 subjects. Because test conditions required pilots to fly and fight in pairs (lead and wing), the fifth pilot, tested during the first week, was paired with a simulator instructor pilot who flew the wing position. Irrespective of the test week, pilots arrived on a Sunday and were tested on Monday, Wednesday and Friday. The intervening days, Tuesday and Thursday, were designated to provide a time period for drug washout, **Table 2.6-1**.

Table 2.6-1: Test Schedule

	Day 1	Day 2	Day 3	Day 4	Day 5	
Travel Day	Simulator Flights	*Drug Washout*	Simulator Flights	*Drug Washout*	Simulator Flights	Travel Day

On first day of testing, pilots arrived at approximately 0730 h. The first 30 min were devoted to sign-in, issuance of tempest facility access badges, a research study briefing and a mission prebriefing. Immediately after the introductory briefings, a time block of about three hours was used for simulator familiarization training. Paired pilots (lead and wing) flew an orientation mission, similar to the test missions, with the opportunity for supplemental training on any tasks where performance was rated marginal or below standard by the chief simulator instructor pilot. The familiarization "ride" included a VFR (Visual Flight Rules) takeoff, a 2 v. 4 air-to-air engagement, aerial refueling and landing. The one subject who was also a simulator pilot was not required to fly a familiarization mission.

All testing under the active drug or placebo conditions occurred during the afternoon hours of test days 1, 3 and 5. Each simulator mission was approximately 45 min to 1 h in duration and there were three, two-ship missions flown on each test day during the first week, and two, two-ship missions flown on each test day during the second week of testing. The same pilots flew under each of the three treatment conditions in the same positions - lead and wing; DART and Mini-DART. Each pair of pilots arrived approximately 2 h and 15 min prior to the assigned mission block time.

Upon arrival they were asked to complete a symptoms checklist, a delayed symptoms checklist (as appropriate) and a Profile of Mood States (POMS). The drug or placebo treatment was administered 2 h prior to flying the simulator mission. This timing was based on a Phase I, laboratory study, in which blood assays confirmed peak serum-drug levels occurring between hours 2 and 3, post drug administration, for these same anti-emetics, encapsulated in an identical manner (Benline, 1995). Subjects as well as the investigators were blinded to the subject-by-drug treatment conditions.

After flying a defensive counter air simulator mission, subjects were administered a second drug symptoms questionnaire, a second POMS and each subject was asked whether they thought they had received the anti-emetic drug or a placebo, **Table 2.6-2**.

Table 2.6-2: Test Events-Days 1, 3 and 5

Time	Event	Participants
1045	Baseline Symptoms & POMS	Pilots 1 & 2
1100	Anti-Nausea Drug	Pilots 1 & 2
1145	Baseline Symptoms & POMS	*Pilots 3 & 4*
1200	Anti-Nausea Drug	*Pilots 3 & 4*
1245	Baseline Symptoms & POMS	**Pilots 5 & 6**
1300	Anti-Nausea Drug	**Pilots 5 & 6**
1300	Fly Simulator Mission	Pilots 1 & 2
1350	Postflight Symptoms & POMS	Pilots 1 & 2
1400	Fly Simulator Mission	*Pilots 3 & 4*
1450	Postflight Symptoms & POMS	*Pilots 3 & 4*
1500	Fly Simulator Mission	**Pilots 5 & 6**
1550	Postflight Symptoms POMS	**Pilots 5 & 6**

2.7 Measures - Data were collected from the flight simulator's data recorder on eight flying performance parameters (dependent measures) representing objective indicators of flying performance. These parameters were selected based on training research experience and the expert opinion of pilots and simulator instructors. Sampling rates were between 0.2 Hz and 0.5 Hz depending on pilot workload. For example, lower sampling rates were used during periods of unaccelerated, straight and level flight and higher sampling rates were used during the more dynamic phases of flight, such as approach and landing. Ratings by expert evaluators were logged on mission and flying performance and data were also collected on symptoms and side effects, mood and vigilance.

2.7.1 Objective Flying Performance - During a Standard Instrument Departure, each pilot was required to track on an Intelligent Flight Model (computer generated) and maintain a 1.5 nm trail (9,000 ft) through FL 180. This radar trail departure was in weather with a solid cloud deck from 700 ft to FL 180 and required two 90° heading changes, **Figure 2.3.2-1**.

Each mission required the pilot to perform an aerial refueling during a linear 50 nm leg of the tanker track. The total time on the boom, up to a 4 min maximum, and the number of pilot disconnects were recorded, **Figure 2.3.2-2**.

During the TACAN to ILS final approach pilots were required to fly a predefined approach pattern to Chehalis Airfield and to intercept precise checkpoints in terms of bearing, altitude and range. Altitude deviations during radial/DME intercepts were captured for: (a) the Initial Approach Fix (IAF) (FLAEK) @ 117° radial, 16 nm and 14,000 ft, (b) the 61° radial, 12 nm DME and 5100 ft and (c) the 37° radial, 12 nm DME and 4000 ft. Between the IAF and the third checkpoint, each pilot was required to fly a 12 nm TACAN arc over a distance of 20 nm, requiring approximately 4 min, **Figure 2.3.2-3**.

The landing phase required a weather penetration and ILS approach to full stop landing. Deviations from the glideslope were recorded at a sampling rate of 0.5 Hz in both the horizontal and vertical planes from just inside the Final Approach Fix (6.4 nm) down to the Missed Approach Point (1.9 nm). An index of angular deviation was computed by solving for the composite angle of deviation (theta, θ)) between the two vectors (horizontal and vertical) and the optimal approach path. The preferred approach has different horizontal and vertical boundary limits creating an elliptical approach path. Limits in the vertical plane are: +/- 0.7° (up/down) vs. +/- 3° (left/right) in the horizontal plane. Deviations are represented to the pilot as dots (up/down; left/right) on the approach display. Because the dots reflect different degrees of displacement within each range, angular deviations from the optimal flight path were normalized on a scale of 0.0 to 1.0 in order to compute a composite index of flying performance. Angle theta was computed using the following equation:

$$\theta = \arccos\left(\frac{a_1a_2 + b_1b_2 + c_1c_2}{\sqrt{a_1^2 + b_1^2 + c_1^2} * \sqrt{a_2^2 + b_2^2 + c_2^2}}\right)$$

2.7.2 Instructor Evaluations - A combination of 10 flight and mission performance tasks were graded by expert evaluators. These tasks were as follows:

1. Pre-takeoff
2. Climb Duties
3. Cruise
4. Aerial Refueling
5. Communications Procedures
6. Aircombat Effectiveness
7. Situational Awareness
8. Defensive Tactics
9. Offensive Tactics
10. Approach and Landing

Each pilot was graded on a scale of 1 (Unable to perform any of the required behaviors-made major errors and omissions that made accomplishment of the objective impossible) to 7 (Performed all required behaviors without errors or deviations and exceeded required proficiency-can or did perform the behaviors flawlessly under adverse conditions) (Storm, 1994). See **Appendix B**, Flight and Mission Performance Evaluation, for the complete set of evaluation criteria.

2.7.3 Symptoms, Mood and Drug ID - Symptoms questionnaires were administered to each pilot as follows: (a) baseline, immediately preceding drug administration at approximately 2 h 15 min prior to the flight, (b) postflight i.e. approximately 3 h post-drug administration and (c) delayed, to cover the intervening period between tests. As a part of the symptoms and side effects data collection, pilots were asked to distinguish active drug from placebo and record the results, **Appendix C**, Symptoms. Also, each pilot was administered a preflight and postflight Profile of Mood States (POMS) questionnaire (McNair, 1971). POMS is a 65 item, six dimension mood scale representing various affective states. Subjects respond to adjectives which represent the six mood states. The six dimensions are: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Confusion-Bewilderment and Fatigue-Inertia. Responses to the adjectives are based on a 5 point scale ranging from "extremely" to "not at all". A Total Mood Disturbance (TMD) score can be derived by summing scores across all six factors (weighting vigor negatively). The TMD is presumed to be reliable because of intercorrelations among the six primary POMS factors (McNair, 1971).

2.8 Data Analysis - Data collected on each of eight flying performance parameters and data from the instructor evaluations were analyzed using a three way ANOVA technique. Main effects and interaction effects were evaluated for: drugs, order of drug administration and test sessions. POMS data were analyzed using a nonparametric test developed by Connover of Texas Tech University. This technique is an extension of Friedman's Multi-Sample Test. Data were analyzed using SAS procedures. SAS is a registered product of SAS Institute, Inc. Cary, NC.

3.0 RESULTS

3.1 Objective Flying Performance - There were no significant main effects of the target drugs vs. placebo on any of the eight objective flying performance measures. Also there were no statistically significant results for order of drug administration, test sessions or their interactions. All of the above determinations to accept or reject the null hypothesis were made at $p<.05$ probability level. Graphs depicting performance during altitude intercepts reflect individual subject observations. All other graphs depict group means for each treatment condition. For error statistics, refer to **Appendix D**.

3.1.1 Radar Trail Departure - Mean separation distances (RMS error) ranged from 2444 ft to + 4011 ft with an overall average of 1298 ft. This grand mean was computed based on absolute values. This method assumes that separation distances between piloted simulator and the Intelligent Flight Model (IFM), as departure from the optimal (defined as 9,000 ft), whether positive (> 9,000 ft) or negative (<9,000 ft), would not provide additional meaningful information. In fact, for 15 takeoffs, mean separation distances were positive while for 11 takeoffs they were negative, with the loss of data due to a simulator problem on one of the instrument departures (i.e. pilot flying lead on sortie # 1, under the placebo condition). Variation among subjects was generally high as was variation across sorties. Neither of these results, as reflected by means or standard deviations, demonstrate obvious trends over the three test sessions. All results, both main effects and interaction effects, for this tracking performance parameter were nonsignificant, **Figure 3.1.1-1**.

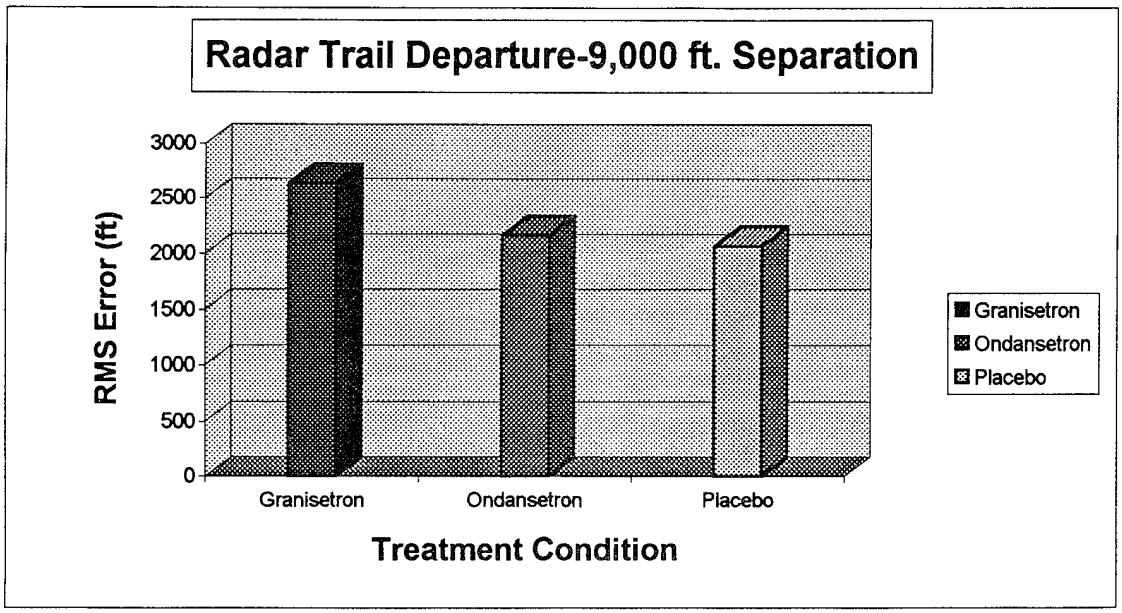


Figure 3.1.1-1: Radar Trail Departure

3.1.2 Aerial Refueling - Each pilot was challenged to accumulate 4.0 min of time connected to the refueling boom over a 50 nm leg of the tanker track. The overall mean time on the boom was 3.75 min with a range of 1.95 min to 4.0 min. On 20 of the 27 sorties, the pilots were able to achieve the refueling goal of 4.0 min on the boom. Pilot caused disconnects from the boom were recorded and the rate of disconnects per minute were later calculated. The overall mean disconnect rate was 1.8 per min with a range of 0.00 to 5.75. A pilot flying wing on sortie # 2, under the ondansetron condition, experienced a disconnect rate of 20/min which represented a highly unusual occurrence and is almost certainly an outlier. In contrast, the next worst performer had a disconnect rate of 5.75/min. The refueling data were analyzed with and without the outlier. Neither analysis produced statistically significant results. Inclusion of this trial in the data set produces a distorted graphic depiction of the effect by treatment condition which could be misleading. Accordingly, the data for this pilot have been removed from both the analysis and presentation of means data. Although this pilot performed acceptably on the other sorties, this participant was one of three pilots who had not flown the DART prior to this study. This subject was also the only pilot who failed to accumulate 4.0 min of total boom time on any of the three missions. In general, the refueling portion of the simulation was especially challenging and pilots experienced a higher number of disconnects than would be the case during an operational

refueling. These results reflect higher than normal sensitivity of the software and contact warning lights to small deviations from the optimal zone of contact with the refueling boom, **Figure 3.1.2-1**.

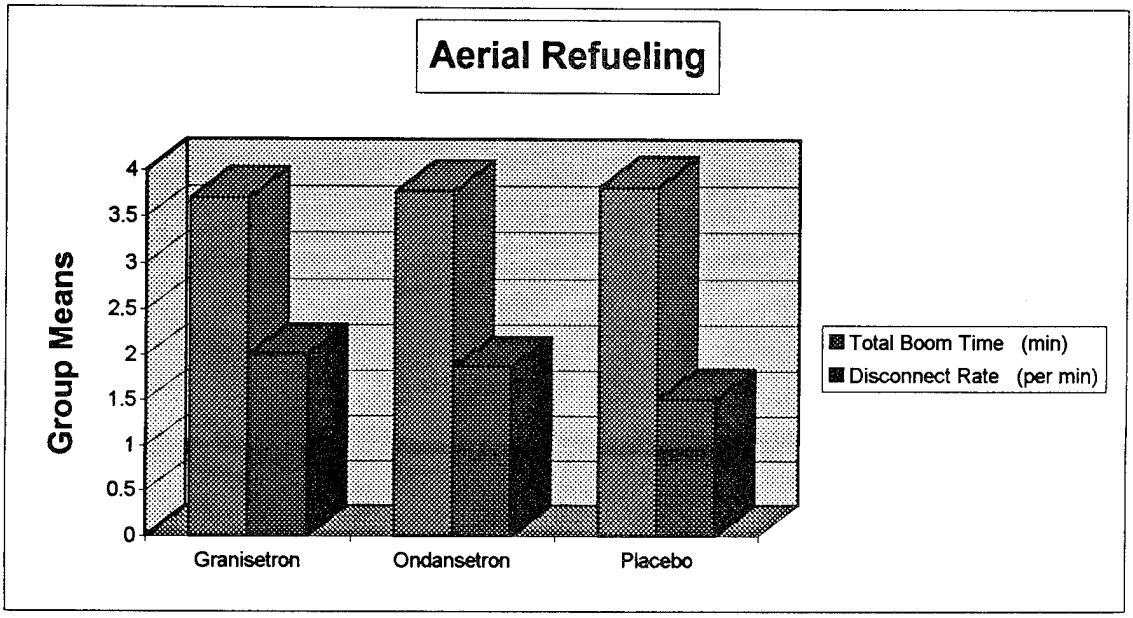


Figure 3.1.2-1: Aerial Refueling

3.1.3 TACAN to ILS Approach and Landing - The approach and landing data were analyzed with and without the pilot flying wing on sortie # 1, under the ondansetron condition. Neither analysis produced statistically significant findings. This pilot was one of three subjects who had no previous experience flying the DART. Also, his scores on 4 of 7 landing metrics were the lowest among the 27 sorties flown. Because of distortion in means data, this subject has been removed from the analysis and graphic results. Because of simulator failures, data were lost on a pilot flying wing on sortie # 3, under the placebo condition and on another pilot flying lead on sortie # 3, under the granisetron condition.

3.1.3.1 Initial Approach Fix - At the Initial Approach Fix (IAF), radial intercept 117° and 16 nm DME, departure from the assigned altitude of 14, 000 ft varied from 0.0 ft (best performance) to + 690.0 ft (poorest performance). The mean departure (in absolute values) from the assigned altitude was 106.0 ft with + or - 300.0 ft considered to be within the acceptable range of departure from the IAF altitude. In this context, two pilots were outside (arrows on

chart) of the departure standard - one under the granisetron condition and one under the placebo condition. There were no significant differences between treatment conditions, **Figure 3.1.3.1-1**.

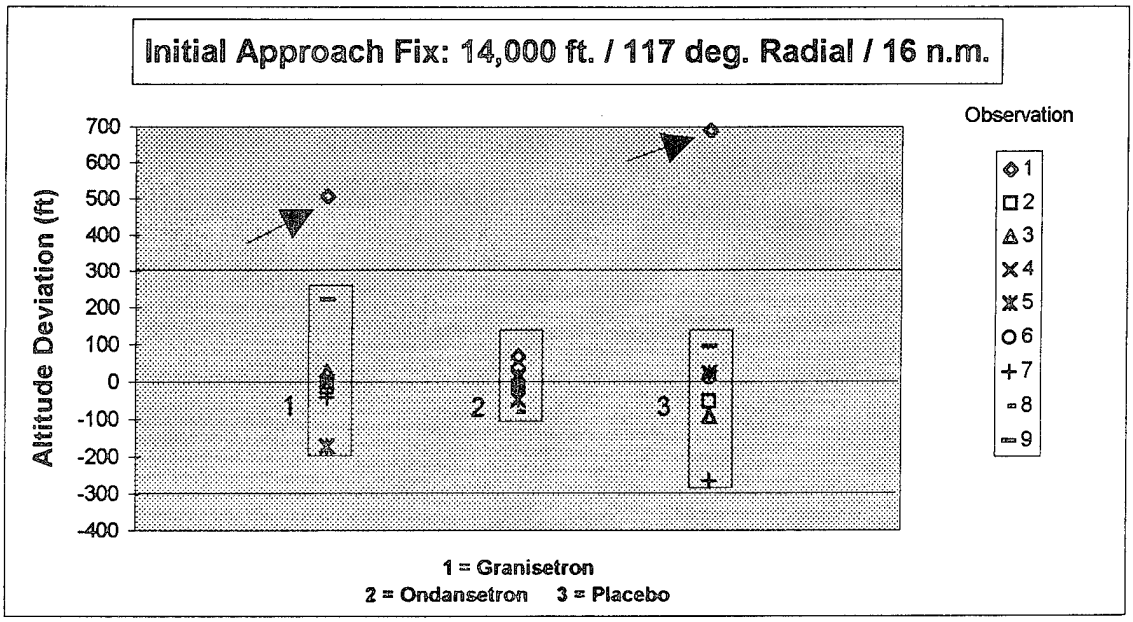


Figure 3.1.3.1-1: Initial Approach Fix

3.1.3.2 Twelve nm TACAN Arc - Mean variation by subject (expressed in RMS error units) from the 12 DME while flying a 20 nm TACAN arc ranged from 0.23 nm to 0.69 nm, exhibiting an overall mean of 0.44 nm. At the p=.05 level, there were no statistically significant differences between treatment conditions on this dependent measure of flying performance. A <2.0 nm variance was considered within the realm of acceptable performance. None of the 24 data points included in this data set were outside of the 2.0 nm standard, **Figure 3.1.3.2-1**.

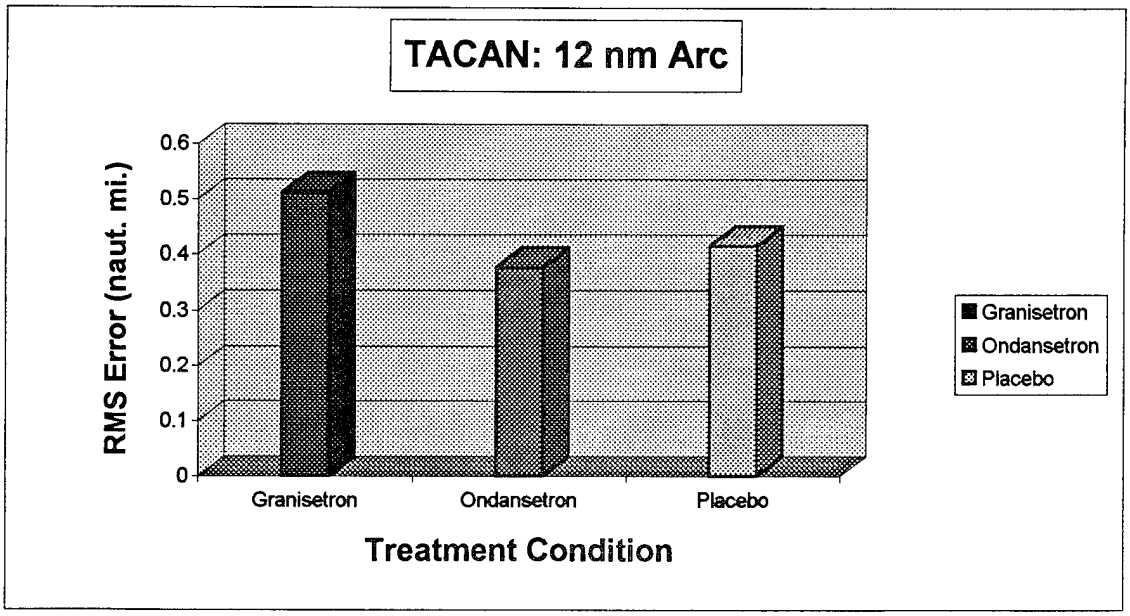


Figure 3.1.3.2-1: Twelve nm TACAN Arc

3.1.3.3 Second Radial Intercept - At the 61° radial and 12 nm DME (Distance Measuring Equipment), departure from the checkpoint altitude of 5,100 ft ranged from +2.0 ft to -487.0 ft with an overall mean of the absolute values equal to 68.0 ft. One pilot, under the placebo condition, was outside (arrow on chart) of the departure standard of + or - 300.0 ft. There were no statistical differences between the treatment conditions, **Figure 3.1.3.3-1**.

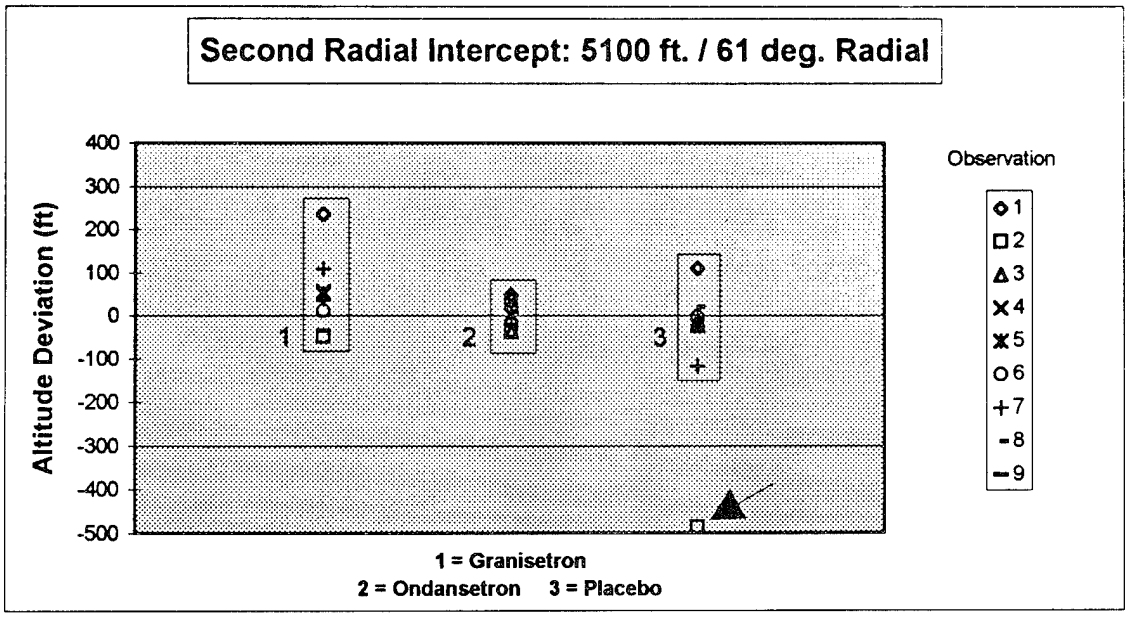


Figure 3.1.3.3-1: Second Radial Intercept

3.1.3.4 **Third Radial Intercept** - At the 37° radial and 12 nm DME, departure from the assigned altitude of 4000 ft ranged from +1.0 ft to + 249.0 ft with an average of the absolute values equal to 51.0 ft. All pilots were within the departure limits for altitude and all were in closer conformance to the approach pattern as they descended to lower altitudes in preparation for intercepting the glideslope. Again, there were no differences between treatment conditions, **Figure 3.1.3.4-1**.

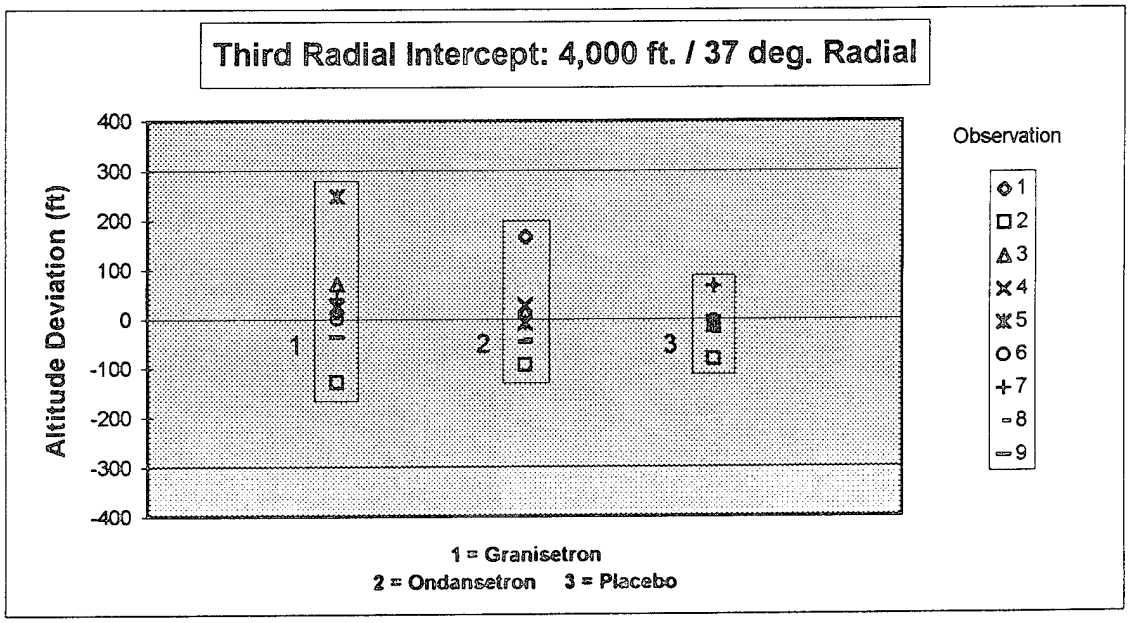


Figure 3.1.3.4-1: Third Radial Intercept

3.1.3.5 **ILS Localizer Deviation** - Horizontal deviations, during the approach, were captured in degrees of departure from the optimal flight path as measured from position of the ILS localizer antenna at the approach end of the runway. Deviations were sampled at a rate of 0.5 Hz along a 4.5 nm track from just inside of the Final Approach Fix (FAF) at 6.4 nm down to the Missed Approach Point (MAP) at 1.9 nm. RMS error scores varied from 0.07° to 0.66° with a mean of 0.24°. Again, there were no statistically significant effects, **Figure 3.1.3.5-1**.

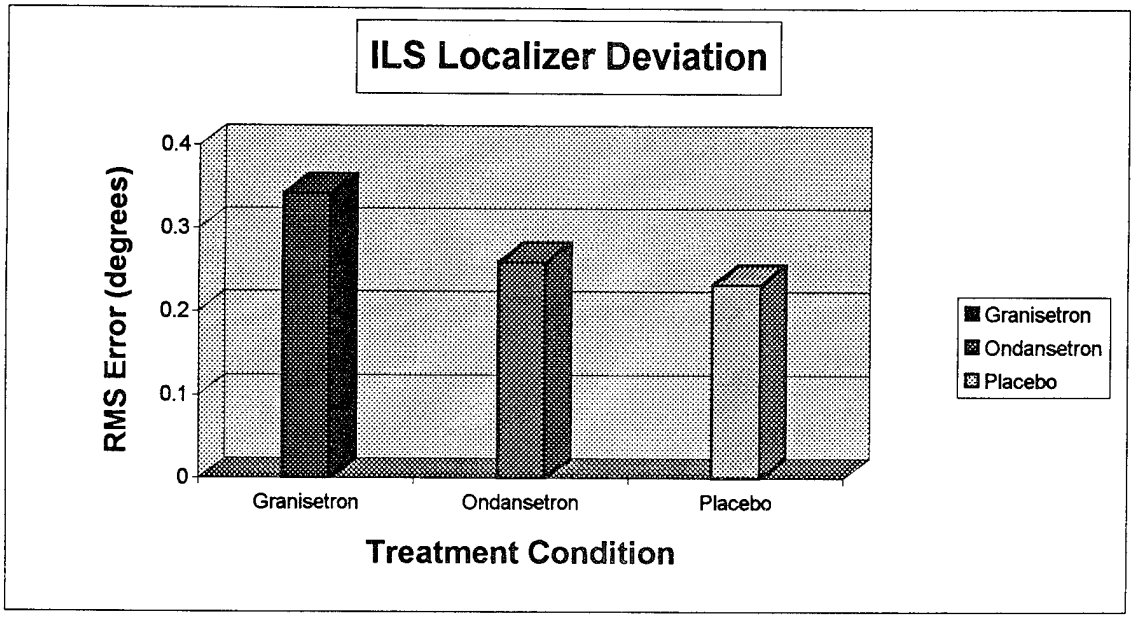


Figure 3.1.3.5-1: ILS Localizer Deviation

3.1.3.6 ILS Glideslope Deviation - Vertical deviations from the glideslope, expressed in RMS error degrees, ranged from 0.32° to 0.67° with a mean of 0.48° over 24 sorties. Mean vertical deviations are somewhat larger than would be expected during actual flight operations. This reflects an artifact of the simulator's glideslope antenna placement and is of constant magnitude across sorties and treatment conditions. All main and interaction effects were without significance, **Figure 3.1.3.6-1**.

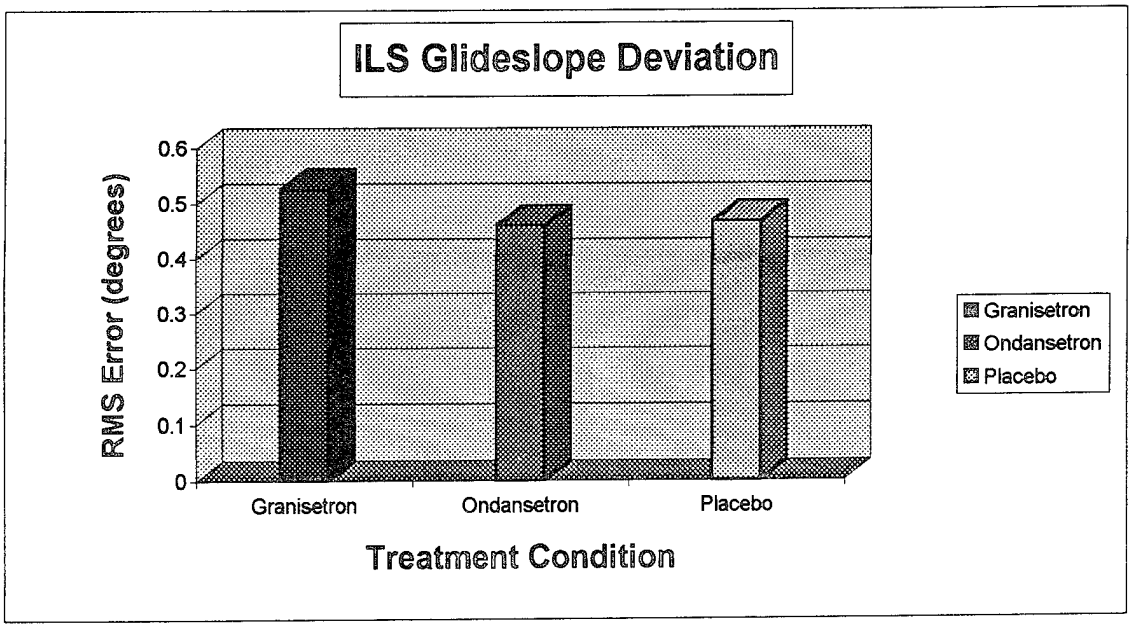


Figure 3.1.3.6-1: ILS Glideslope Deviation

3.1.3.7 **Composite Index of Angular Deviation** - This index is a transformation which simultaneously resolves deviations from an optimal ILS landing in both the horizontal and vertical planes into a single composite score (angle θ). Angle θ is then processed to compute composite RMS error. Index values ranged from 0.60 to 0.96 with a mean score of 0.69 over the 24 sorties. Differences between the treatment conditions were all nonsignificant, **Figure 3.1.3.7-1**.

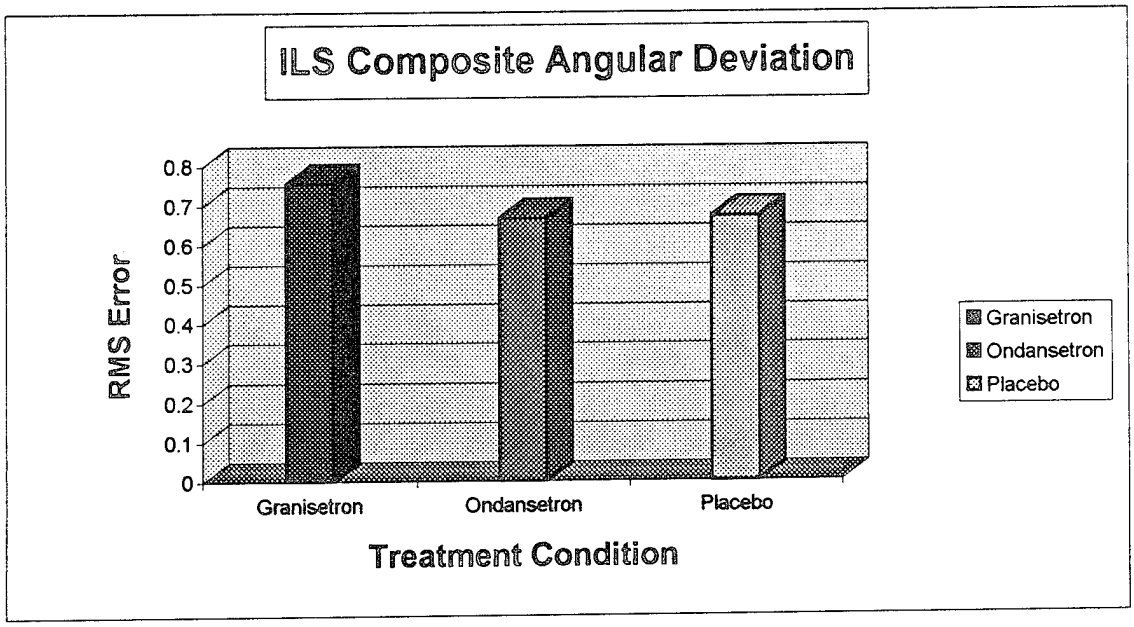


Figure 3.1.3.7-1: Composite Index of Angular Deviation

3.2 Instructor Evaluations - On a rating scale of 1 (worst) to 7 (best), raw scores varied between 2 and 7 with most ratings falling in the 5 to 7 range. Mean ratings by treatment condition on each of the 10 evaluation factors fell within a narrow band of 5.67 to 6.89. The grand mean for all ratings across the 10 performance factors was 6.41. There were no significant treatment condition effects detected on any of the performance evaluation factors. The means for the aggregate ratings by treatment condition for all ten factors are presented to summarize these findings, **Figure 3.2-1**.

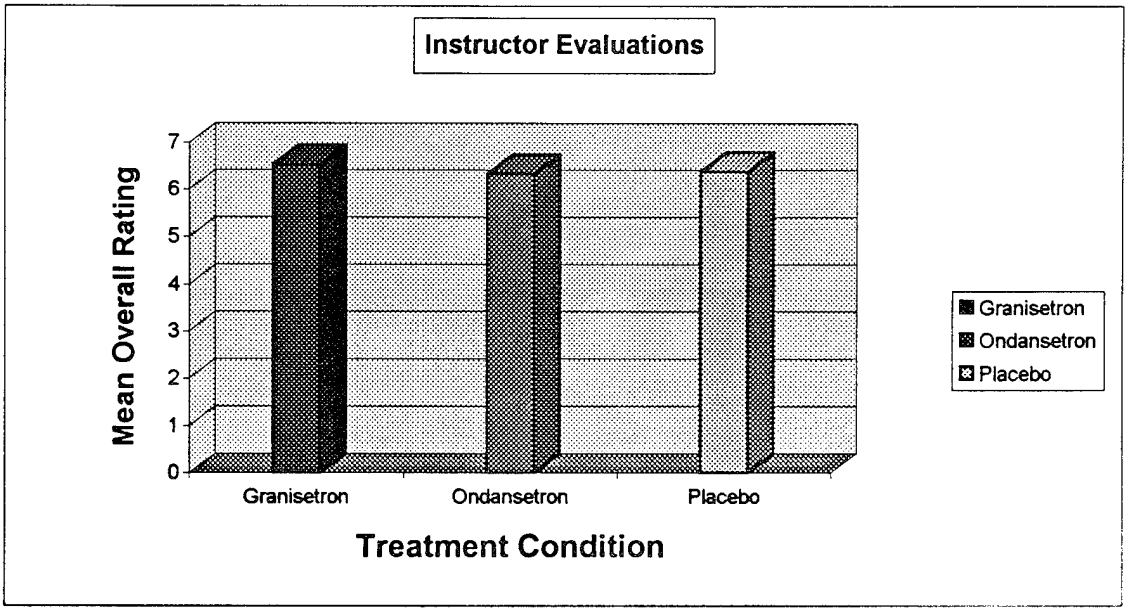


Figure 3.2-1: Instructor Evaluations

3.3 Profile of Mood States - None of the individual mood scale results were significant. There was a general trend toward mood and vigor changes in a negative direction from pre-drug to post-drug administration i.e. scores increased on the scales which measure affective state while scores on the Vigor-Activity scale declined. Overall, mean scores on the six POMS scales by three treatment conditions showed negative change 14 times, positive change 3 times and remained the same once. By treatment condition, scores were in a negative direction 5 times for the granisetron group, 5 times for the ondansetron group and four times for the placebo group, leading to speculation that these changes are not likely to be related to the treatment conditions but possibly related, in an unknown way, to the intervening simulator experience. This finding is in contrast to changes in the positive direction as follows: granisetron, 0; ondansetron, 1, and

placebo, 2. Mean scores for the granisetron group on the Anger-Hostility scale remained the same pre and post test. In order to summarize these findings, a global estimate of affective state, the Total Mood Disturbance (TMD) score, has been derived by summing the scores across all six POMS factors (negatively weighting "Vigor-Activity"), (McNair, 1971), **Figure 3.3-1**. For results on the six individual scales, See **Appendix E**, POMS Results.

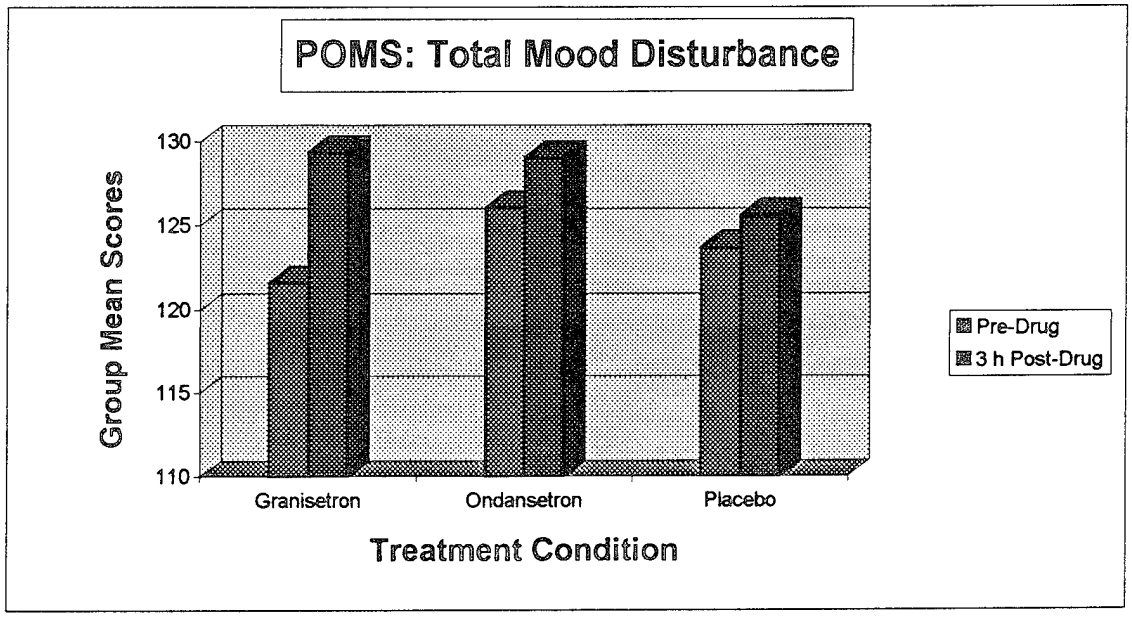


Figure 3.3-1: Profile of Mood States (TMD)

3.4 Symptoms - Symptoms questionnaires were completed by each pilot before taking the drugs and immediately after the simulator flight. The same questionnaire was used to collect symptoms and side effects data during the intervening period between simulator tests. There were a total of 13 reports of symptoms (some reported more than once) by the nine pilots over the three test sessions, **Table 3.4-1**. Nine of these occurrences (shaded entries) were present when the subject arrived at the test session and none of these increased in severity during testing. There were four reports of symptoms (1 gas, 2 sluggishness and 1 muscle weakness) which were not present prior to drug administration but were reported after the pilot took the drug and flew a sortie. Two of these occurrences were in the granisetron group and two occurred in the placebo group. Impairment was rated none to slight and in none of the four cases did the subject judge the symptom to be caused by the treatment condition. There were no reported symptoms that required medical intervention. There were three instances where the subject thought the symptom

was caused by a drug. One symptom, "relaxed", was reported under the ondansetron condition and two of symptoms, "relaxed" and "constipation", were reported under the placebo condition. The same subject reported a relaxed feeling under the ondansetron condition and under the placebo condition. The single report of constipation could have been a delayed effect since this subject had received the active compounds on test days 1 and 2.

Table 3.4-1: Symptoms Pre and Post Drug (3 h) Administration

		Pre Drug Admin		3 h Post Drug Admin		Caused x
Drug	Symptom (subj.#)	Severity	Impairment	Severity	Impairment	Drug*
Granisetron	gas (3)	none	none	1	slight	N
	headache (6)**	2	none	none	none	N
	dizziness (6)	2	none	2	none	N
	drowsiness (6)	2	none	2	none	N
	sluggishness (6)	none	none	2	none	N
Ondansetron	relaxed (2)	none	none	none	none	Y
	headache (3)	1	slight	none	none	N
	sluggishness (4)	1	none	1	none	N
Placebo	relaxed (2)	none	none	none	none	Y
	drowsiness (3)	2	none	2	slight	N
	sluggishness (3)	none	none	2	slight	N
	muscle weak (3)	none	none	1	slight	N
	constipation (6)	2	none	none	none	Y

*Reported by the subject, see para 3.1.4

**Shaded entries denote symptoms reported by the subject prior to taking the drug or placebo

3.5 Drug vs. Placebo - When subjects were asked whether they had received an anti-emetic drug (chance = 66.66%) or placebo (chance = 33.33%), 17 responses were correct and 10 were incorrect. Under forced choice conditions, chance alone would yield 18 correct and 9 incorrect.

3.6 Delayed Symptoms - There was a single report of a delayed symptom. This was a severe headache that occurred during the period following the granisetron treatment condition. The subject did not feel the headache was related to either of the anti-emetic drugs, **Table 3.6-1**.

Table 3.6-1: Delayed Symptoms

Drug	Symptom (subj.#)	Severity	Impairment	Caused x Drug*
Granisetron	headache (5)	6	none	N

* Reported by the subject

4.0 DISCUSSION

These results support our earlier laboratory findings and further demonstrate that the drugs granisetron and ondansetron do not affect cognitive or psychomotor performance and that these drugs produce few if any side effects. The current study, conducted in a simulated operational environment, provides complementary evidence regarding the safety of these compounds when taken by experienced pilots who were then tested while performing under complex task loading. This study, carried out in the context of simulated tactical air-to-air combat missions, produced no significant differences between the target drugs and placebo on any of the eight objective flying performance measures, nor on a composite measure of ILS approach performance.

In practice, a high level of task habituation (presumed to be the case for these experienced pilots) could mask the more subtle performance effects of drugs or other stressor variables. By contrast, dependent measures sensitive enough to detect subtle performance effects may have little or no operational relevance - that is, no impact on mission success or failure. In the design of these simulation tests, efforts were focused on the selection of dependent measures believed to strike an appropriate balance between sensitivity of measures and operational relevance. The simulation and metrics, developed with the assistance of experienced air combat pilots, were judged to be of sufficient fidelity to objectively demonstrate the operational safety of the anti-emetic drugs granisetron and ondansetron. Our conclusions regarding the safety of these anti-emetic drugs are further supported by a more rigorous laboratory investigation which demonstrated the sensitivity of standard performance assessment tests to a positive control drug (prochlorperazine, 10 mg oral dose) without similar performance degradation occurring under the target drug conditions (Benline, 1995). Also, in the current study, there were no differences in

evaluator ratings of routine mission segment flying (instrument departure, aerial refueling, instrument landing) or air combat performance related to the target drugs (granisetron and ondansetron) when compared to the placebo condition. Furthermore, pilots could not distinguish active drug from placebo and there were no differences on any of the POMS scales. Neither were there any obvious drug related symptoms or side effects during testing.

5.0 CONCLUSIONS

These results provide a high fidelity operational safety validation for the anti-emetic drugs granisetron and ondansetron. They strengthen conclusions reached during a Phase I laboratory performance assessment on these same drugs (Benline, 1995). There are no findings which would suggest these drugs to be different from placebo and there is no evidence to suggest that one drug is preferable to the other in terms of complex task performance. The selection of one compound over the other for use in the field should be based on factors other than cognitive/psychomotor performance, complex task performance, fatigue and circadian dyschronization, side effects and symptoms. Factors which may be more relevant to the selection of either of these anti-emetic compounds are: protection levels afforded against radiation caused nausea and vomiting, dose-response curves, interaction with other stressors such as heat and physical stress, interaction with other drugs likely to be used in the field, logistics considerations, and affordability. These investigators conclude the following: there is no evidence of performance degradation caused by the drugs granisetron or ondansetron when tested in a complex, operationally relevant, military task environment.

REFERENCES

Aapro, M.S. (1991). 5-HT3 receptor antagonists. An overview of their present status and future potential in cancer therapy-induced emesis. Drugs, 42: 551-568.

Andrews, P.L., Rapeport, W.G. and Sanger, G.J. (1988). Neuropharmacology of emesis induced by anti-cancer therapy. Trends in Pharmacological Sciences, 9: 334-341.

Benline, T.A., French, J., and Wing, J. (1995). Anti-emetic drug effects on performance. Technical Report: AL/CF-TR-1995-0146.

Barnes, J.M., Barnes, N.M., Costall, B., Naylor, I.L., Naylor, R.J. and Rudd, J.A. (1990). Topographical distribution of 5-HT3 receptor recognition sites in the ferret brain stem. Nauyn. Schmiedebergs. Arch. Pharmacol., 342: 17-21.

Burnette P.K. and Perkins, J. (1992). Parenteral ondansetron for the treatment of chemotherapy and radiation induced nausea and vomiting. Pharmacotherapy, 12: 120-131.

Freeman, A.J., Cunningham, K.T., and Tyers, M.B. (1992). Selectivity of 5-HT3 receptor antagonists and anti-emetic mechanisms of action. Anticancer Drugs, 3: 79-85.

Granisetron IV and Oral. A clinical brochure. (1991). SmithKline Beecham Pharmaceuticals.

Harding, R.K. (1988). Prodromal effects of radiation: pathways, models and protection by anti-emetics. Pharmacol. Ther., 39: 353.

Henriksson, R., Lomberg, H., Israelsson, G., Zackrisson, B., et.al. (1992). The effect of ondansetron on radiation-induced emesis and diarrhea. Acta-Oncol., 31: 767-769.

Hunter, A.E., Prentice, H.G., Pothecary, K., Coumar, A., Collis, C., Upward, J., Murdoch, R., Gandhi, L., Hamon, M., Butler, M., et al. (1991). Granisetron, a selective 5-HT3 receptor antagonist, for the prevention of radiation induced emesis during total body irradiation. Bone Marrow Transplant, 7: 439-441.

Kidgell, A.E., Butcher, M.E., Brown, G.W. (1990). Antiemetic control: 5-HT3 antagonists: review of clinical results, with particular emphasis on ondansetron. Cancer Treat. Review, 17: 311-317.

King, G.L. and Makale, M.T. (1991). Postirradiation emesis, Ch. 6. Nausea and Vomiting: Recent Research and Clinical Advances. Edited by: J. Kucharczyk, D.J. Stewart and A.D. Miller.

Leigh, T.J., Link, C.G., Fell, G.L. (1991). Effects of granisetron and Lorazepam, alone and in combination, on psychometric performance. Br. J. Clin. Pharmacol., 31: 333-336.

Leigh, T.J., Link, C.G. and Fell, G.L. (1992). Effects of granisetron and haloperidol, alone and in combination, on psychometric performance and the EEG. Br. J. Clin. Pharmacol., 34: 65-70.

Lip, H. (1990). Ondansetron, a new antiemetic therapy for oncology. An overview. Scand. J. Gastroenterol., 178: 55-61.

Logue, J.P., Magee, B., Hunter, R.D. and Murdoch, R.D. (1991). The anti-emetic effect of granisetron in lower hemibody radiotherapy. Clin. Oncol., 3: 247-249.

McNair, D. (1971). Profile of mood states. Educational and Industrial Testing Service.

Plosker, G.L. and Goa, K.L. (1992). Granisetron: a review of its pharmacological properties and therapeutic use as an anti-emetic drug. Drugs, 42: 805-824.

Priestman, T.J. (1989). Clinical studies with ondansetron in the control of radiation-induced emesis. Eur. J. Cancer Clin. Oncol., 25: S29-33.

Rabin, B.M. and King, G.L. (1992). Is all radiation-induced emesis ameliorated by 5-HT3 receptor antagonists? Mechanisms and Control of Emesis. Edited by: A. Bianchi, L. Grelot, A. Miller, and G. L. King, 223: 147-155.

Roberts, J.T., Priestman,T.J. (1993). A review of ondansetron in the management of radiotherapy-induced emesis. Oncology, 50: 173-179.

Scarantino, C.W., Ornitz, R.D., Hoffman, L.G. and Anderson, R.F. (1992). Radiation-induced emesis: effects of ondansetron. Semin. Oncol., 19: 38-43.

Seynaeve, C., Verweij, J. and de Mulder, P.H. (1991). 5-HT3 receptor antagonists, a new approach in emesis: a review of ondansetron, granisetron and tropisetron. Anticancer Drugs, 2: 343-355.

Smith, R.N. (1989). Safety of ondansetron. Eur. J. Cancer. Clin. Oncol., 25: S47-S50.

Storm, W.F., French, J., Bisson, R.U., Neville, K.J., Mitcha, J., Martinez, J., Whitmore, J. (1995). Crew performance and fatigue during sustained B-1B sorties. Technical Report: AL/CF-TR-1994-0014. (In press).

Thomas, M., Geltmacher, H. (1993). Combat simulator display development. Information Display, 9: 23-26.

Tyers, M.B. (1992). Pharmacology and preclinical antiemetic properties of ondansetron. Semin-Oncol., 19: 1-8.

Tyers, M.B., Bunce, K.T. and Humphrey, P.P. (1989). Pharmacological and anti-emetic properties of ondansetron. Eur. J. Cancer Clin. Oncol., 25: S15-19.

Upward, J.W., Arnold, B.D., Link, C., Pierce, D.M. et. al. (1990). The clinical pharmacology of granisetron (BRL 43694) , a novel specific 5-HT3 antagonist. Eur. J. Cancer, 26: S12-15.

Wetherell A. and Shattock, J.A. (1994). Cognitive and psychomotor performance during and following 13 days treatment with ondansetron and granisetron. CBDE Technical Paper 763, CBDE Porton Down.

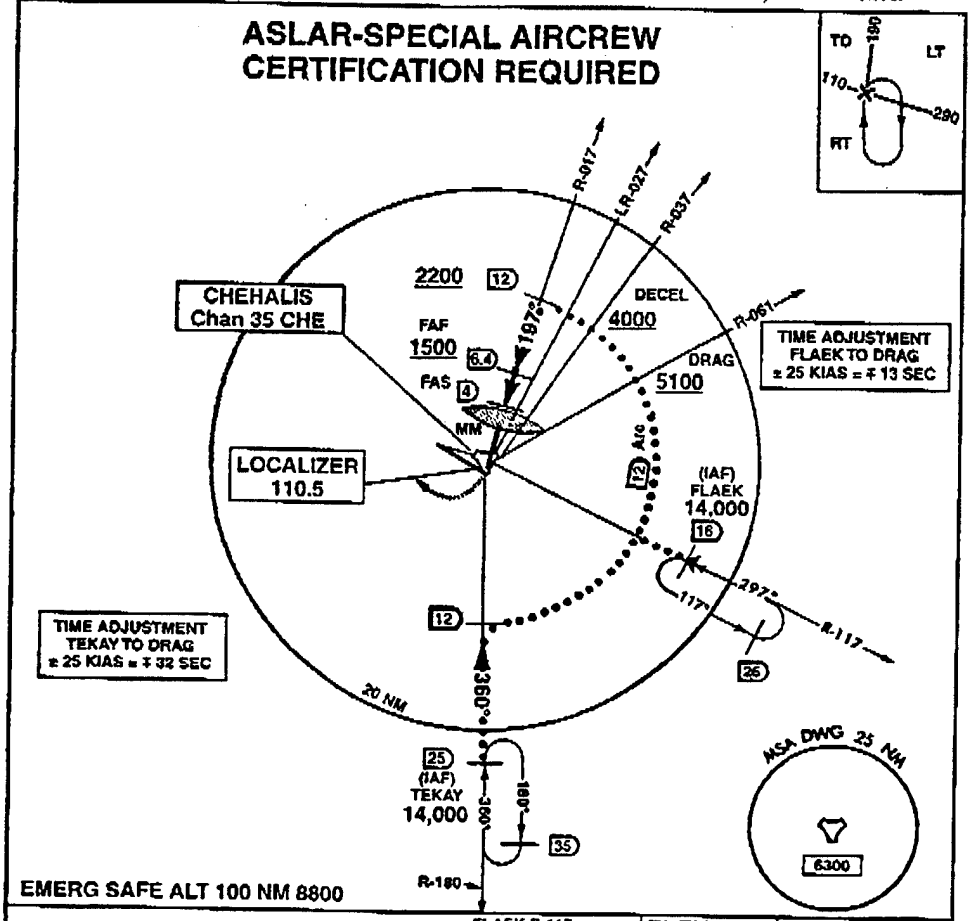
Zofran (Ondansetron HCL) Tablets. (1993). A product monograph. Cerenex Pharmaceuticals, a division of Glaxo Inc.

APPENDIX A
Airfield Approach Plate

APPENDIX A

(ASLAR) HI-TACAN/HI-ILS
4 RWY 19

CHEHALIS AFLD (KCHE)
Chehalis, Southland



CATEGORY	C	D	E
S-TAC 19*	680 (500-1)	680 (500-1 1/4)	680 (500-1 1/2)
S-ILS 19	380 (200-1/2)		

(ASLAR) HI-TACAN/ILS
4 RWY 19

APPENDIX B
Flight and Mission Performance Evaluation

APPENDIX B

Instructor Evaluation

DATE _____ / TEAM # _____ / SORTIE # _____

---

1. Unable to perform any of the required behaviors. Made major errors and omissions that made accomplishment of the objectives impossible.

2. Partially performed the behaviors. Many or serious errors resulted in non-accomplishment of the overall objective.

3. Performed some of the behaviors with marginal effectiveness. Overall objective may or may not have been met depending on the presence of ideal vs. adverse conditions.

4. Performed most of the behaviors but with some errors and deviations. Objective was met or would have been met under good conditions.

5. Performed all required behaviors with minor errors or deviations that were undetected or uncorrected. Objective was met.

6. Performed all required behaviors with no errors or only small errors that were detected and corrected. Objective was met.

7. Performed all required behaviors without errors or deviations and exceeded required proficiency. Can or did perform the behaviors flawlessly under adverse conditions.

		LEAD / DRUG _____	WING / DRUG _____
	TASKS	PILOT # _____	PILOT # _____
1.	PRE-TAKEOFF	1 2 3 4 5 6 7	1 2 3 4 5 6 7
2.	CLIMB DUTIES	1 2 3 4 5 6 7	1 2 3 4 5 6 7
3.	CRUISE	1 2 3 4 5 6 7	1 2 3 4 5 6 7
4.	AIR REFUELING	1 2 3 4 5 6 7	1 2 3 4 5 6 7
5.	COMMUNICATIONS PROCEDURES	1 2 3 4 5 6 7	1 2 3 4 5 6 7
6.	AIRCOMBAT EFFECTIVENESS	1 2 3 4 5 6 7	1 2 3 4 5 6 7
7.	SITUATIONAL AWARENESS	1 2 3 4 5 6 7	1 2 3 4 5 6 7
8.	DEFENSIVE TACTICS	1 2 3 4 5 6 7	1 2 3 4 5 6 7
9.	OFFENSIVE TACTICS	1 2 3 4 5 6 7	1 2 3 4 5 6 7
10.	APPROACH AND LANDING	1 2 3 4 5 6 7	1 2 3 4 5 6 7

APPENDIX C
Symptoms Checklist

APPENDIX C

Anti-emetic Drug Effects on Pilot Performance
TEST SESSION SYMPTOMS CHECKLIST # _____

Subject number ____ **Date _____**

Time _____

Please circle below if any of the symptoms apply to you right now. If you answer YES, circle the number which best describes the degree of the symptom.

			Slight			Moderate			Severe
1. Headache	No	Yes	1	2	3	4	5	6	7
2. Dizziness	No	Yes	1	2	3	4	5	6	7
3. Drowsiness	No	Yes	1	2	3	4	5	6	7
4. Sluggishness	No	Yes	1	2	3	4	5	6	7
5. Faintness	No	Yes	1	2	3	4	5	6	7
6. Numbness	No	Yes	1	2	3	4	5	6	7
7. Tingling	No	Yes	1	2	3	4	5	6	7
8. Hot	No	Yes	1	2	3	4	5	6	7
9. Cold	No	Yes	1	2	3	4	5	6	7
10. Sweating	No	Yes	1	2	3	4	5	6	7
11. Rash	No	Yes	1	2	3	4	5	6	7
12. Itching	No	Yes	1	2	3	4	5	6	7
13. Swelling	No	Yes	1	2	3	4	5	6	7
14. Gas	No	Yes	1	2	3	4	5	6	7
15. Indigestion	No	Yes	1	2	3	4	5	6	7
16. Nausea	No	Yes	1	2	3	4	5	6	7
17. Diarrhea	No	Yes	1	2	3	4	5	6	7
18. Constipation	No	Yes	1	2	3	4	5	6	7
19. Stomach Cramps	No	Yes	1	2	3	4	5	6	7
20. Muscle Cramps	No	Yes	1	2	3	4	5	6	7
21. Muscle Twitching	No	Yes	1	2	3	4	5	6	7
22. Muscle Weakness	No	Yes	1	2	3	4	5	6	7
23. Trembling	No	Yes	1	2	3	4	5	6	7
24. Irregular Breathing	No	Yes	1	2	3	4	5	6	7

25. Irregular Heartbeat	No	Yes	1	2	3	4	5	6	7
26. Disturbed Vision	No	Yes	1	2	3	4	5	6	7
27. Other ( )	No	Yes	1	2	3	4	5	6	7
28. Other ( )	No	Yes	1	2	3	4	5	6	7
29. Other ( )	No	Yes	1	2	3	4	5	6	7
30. Other ( )	No	Yes	1	2	3	4	5	6	7

For each symptom marked "Yes", do you think the symptom was caused by the test drug?

Symptom Name and #	Yes	No	If No, Likely Cause?

To what extent would the symptom(s) marked "yes" impair your ability to perform normally assigned military tasks to include driving to and from work?

Impairment	Symptom #___	Symptom #___	Symptom #___	Symptom #___	Symptom #___
Severe					
Major					
Moderate					
Slight					
None					

Which treatment do you think you were given?

Anti-Emetic Test Drug	
Placebo	

STOP

APPENDIX D
Error Statistics

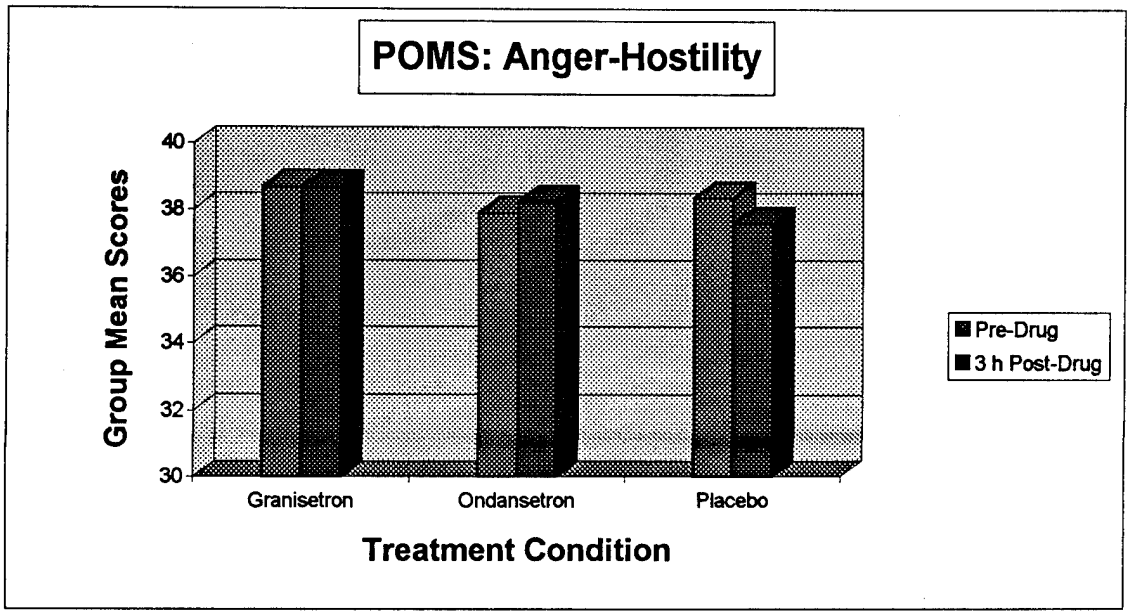
APPENDIX D

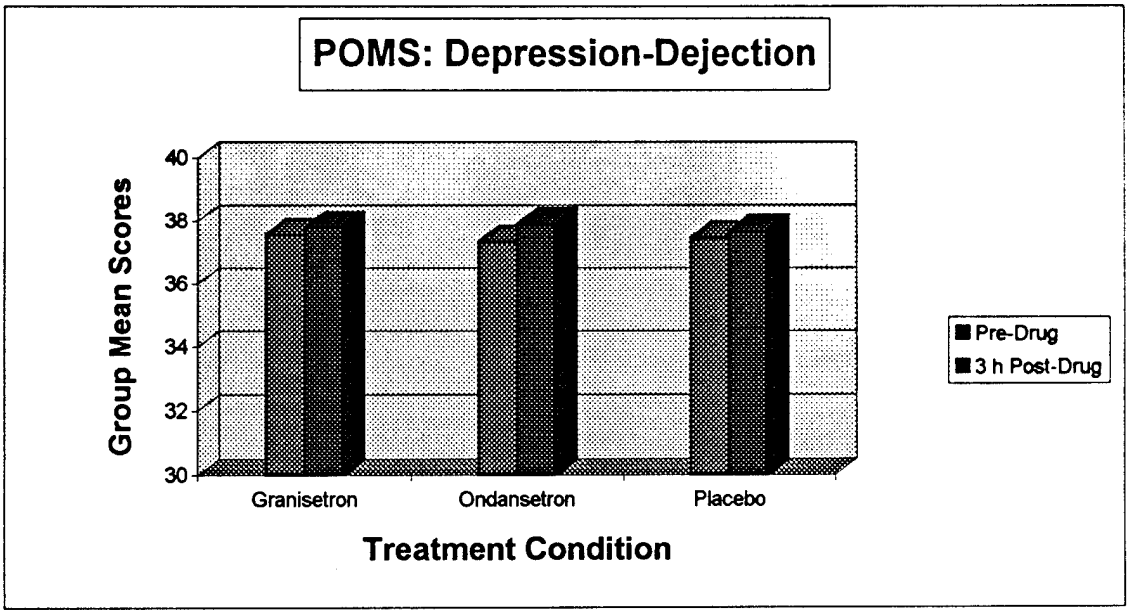
Standard Deviation (SD) and Standard Error (SEM) Ranges Across Drug Treatments (3) and Sorties (3)

	SD	SEM
Radar Trail Departure (RMS error-ft)	633 - 1912	406 - 1103
Aerial Refueling Total Boom Time (sec)	0.00 - 71.01	0.00 - 41.00
Aerial Refueling Disconnects (rate/min)	0.80 - 2.63	0.46 - 1.52
Initial Approach Fix (ft)	7.78 - 440.66	5.50 - 254.42
TACAN 12 nm Arc (RMS error-nm)	0.03 - 0.23	0.01 - 0.13
Second Radial Intercept (ft)	14.85 - 315.41	10.50 - 182.10
Third Radial Intercept (ft)	2.83 - 136.54	2.00 - 78.83
ILS Localizer Deviation (RMS error-deg)	0.00 - 0.40	0.00 - 0.29
ILS Glideslope Deviation (RMS error-deg)	0.01 - 0.16	0.01 - 0.11
ILS Composite Index (RMS error-angle theta)	0.03 - 0.23	0.02 - 0.16
Instructor Evaluations (Ratings-10 factors)	0.00 - 2.89	0.00 - 1.67

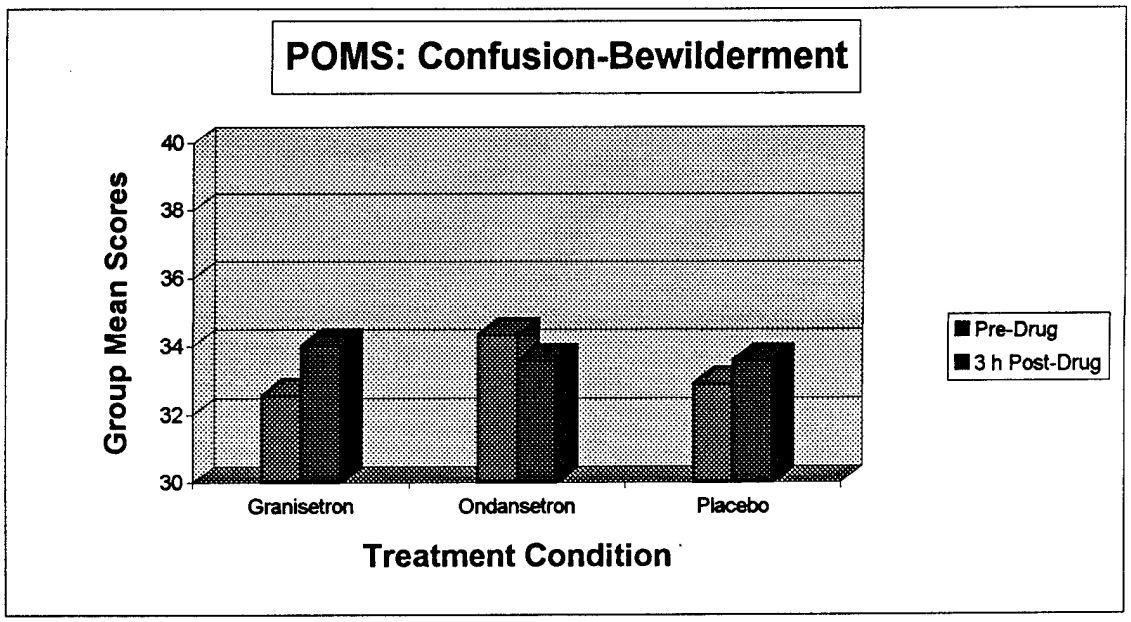
APPENDIX E
POMS Results

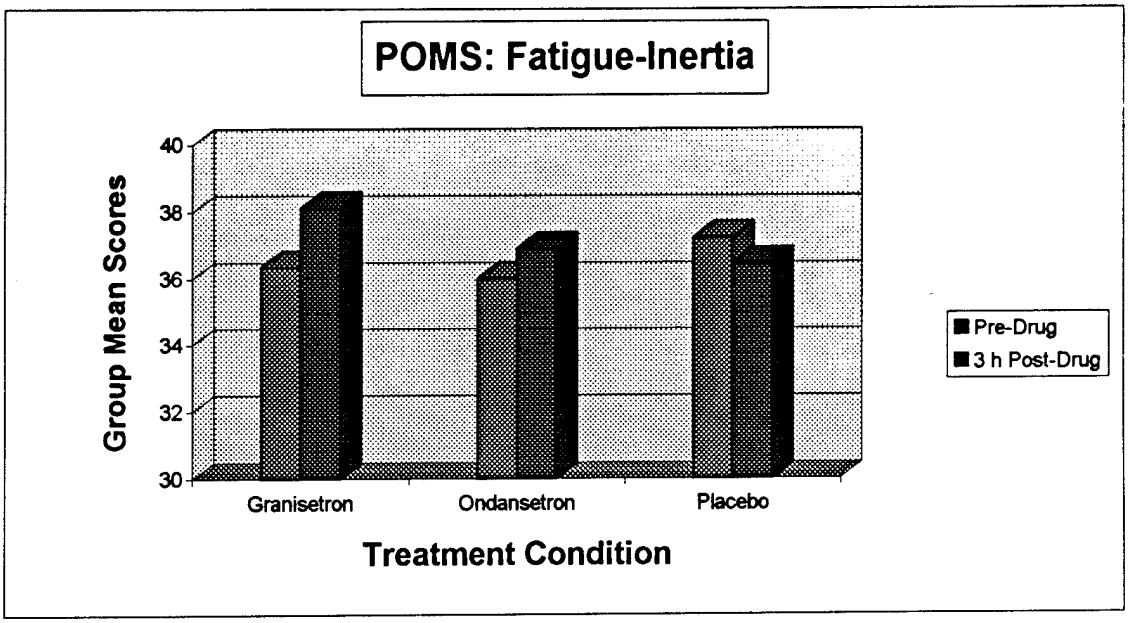
APPENDIX E


POMS: Anger-Hostility
Group Mean Scores
40
38
36
34
32
30
Granisetron
Ondansetron
Placebo
Treatment Condition
Pre-Drug
3 h Post-Drug

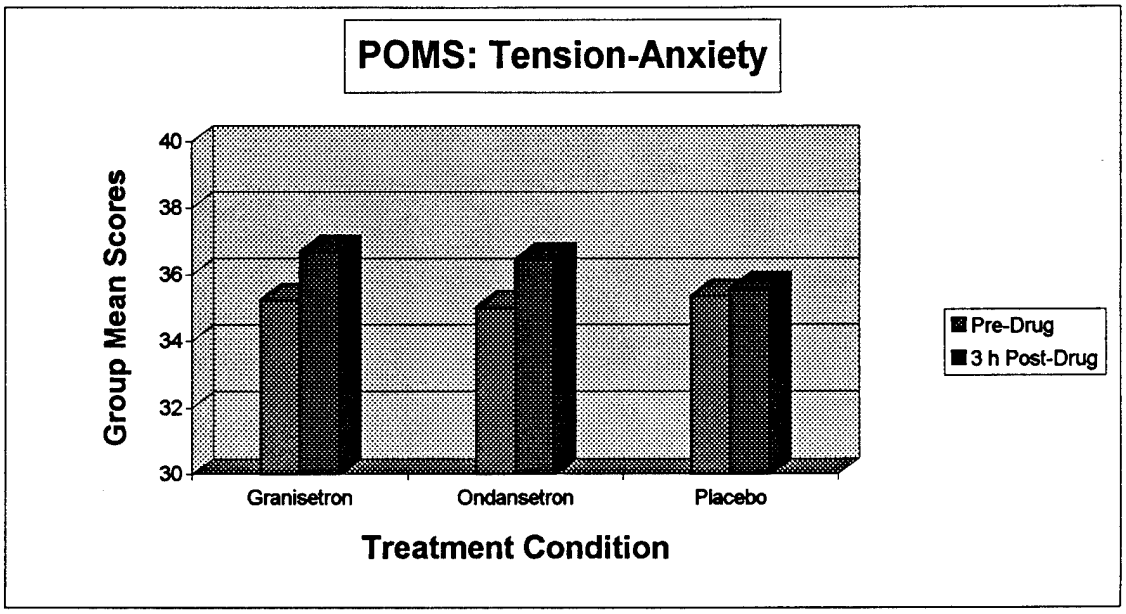

POMS: Depression-Dejection
Group Mean Scores
40
38
36
34
32
30
Granisetron
Ondansetron
Placebo
Treatment Condition
Pre-Drug
3 h Post-Drug

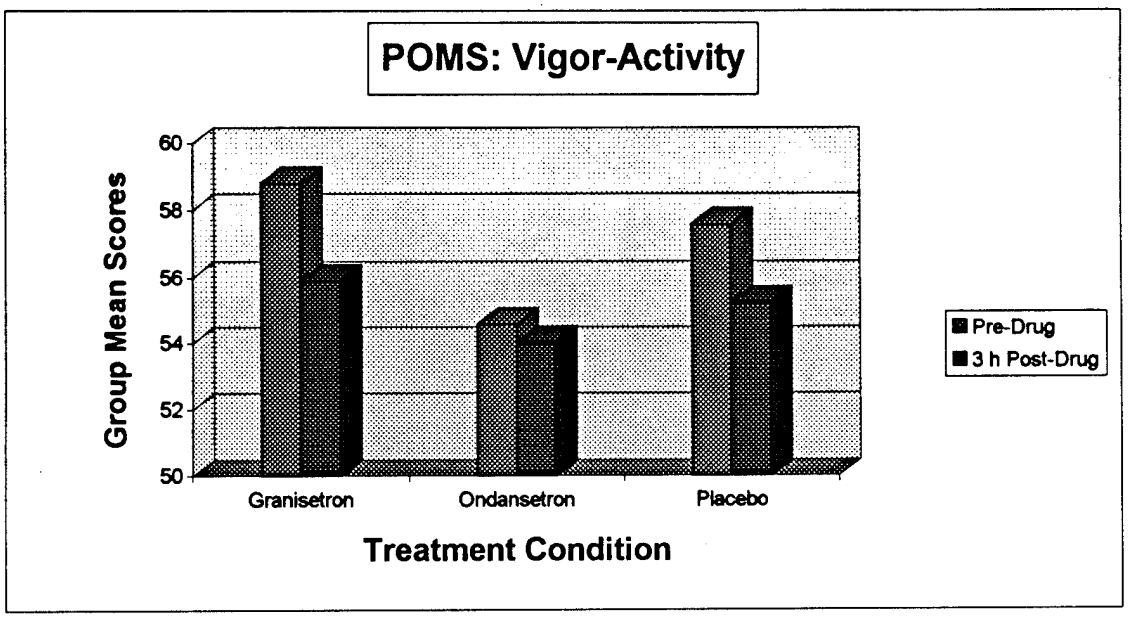
APPENDIX E


POMS: Confusion-Bewilderment
Group Mean Scores
40
38
36
34
32
30
Granisetron
Ondansetron
Placebo
Treatment Condition
Pre-Drug
3 h Post-Drug


POMS: Fatigue-Inertia
Group Mean Scores
40
38
36
34
32
30
Granisetron
Ondansetron
Placebo
Treatment Condition
Pre-Drug
3 h Post-Drug

APPENDIX E


POMS: Tension-Anxiety
Group Mean Scores
40
38
36
34
32
30
Granisetron
Ondansetron
Placebo
Treatment Condition
Pre-Drug
3 h Post-Drug


POMS: Vigor-Activity
Group Mean Scores
60
58
56
54
52
50
Granisetron
Ondansetron
Placebo
Treatment Condition
Pre-Drug
3 h Post-Drug