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GRANISETRON SHOWS NO PRO-ARRHYTHMIC EFFECT IN NORMAL SUBJECTS DURING OR AFTER EXERICSE IN A HOT ENVIRONMENT

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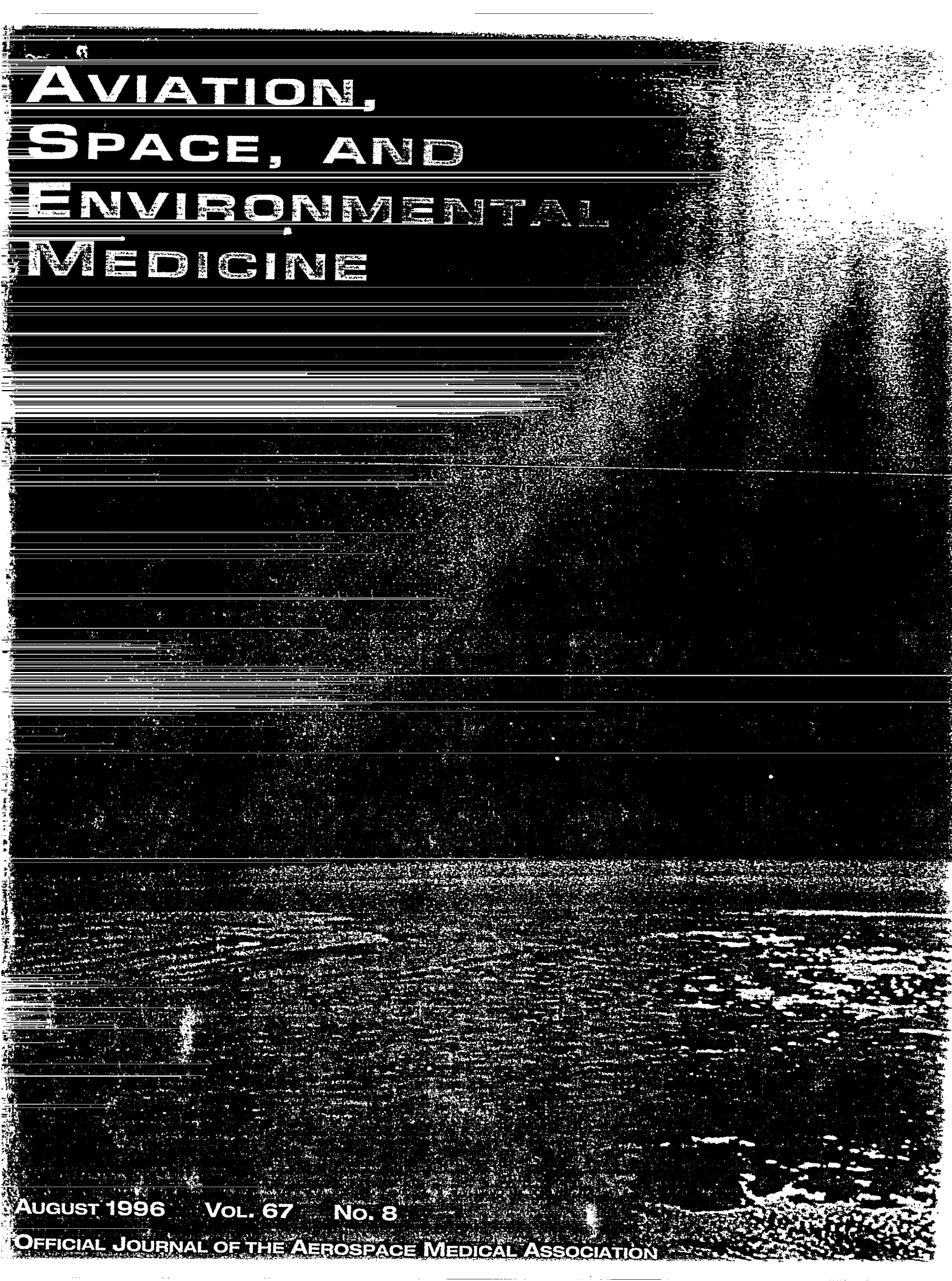

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ORIGINAL RESEARCH

Granisetron Shows No Pro-Arrhythmic Effect in Normal Subjects During or After Exercise in a Hot Environment

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GRAY GW, MCLELLAN TM, DUCHARME MB. *Granisetron shows no pro-arrhythmic effect in normal subjects during or after exercise in a hot environment.* Aviat Space Environ Med 1996; 67:759-61.

Background: 5-HT3 receptor antagonists are being evaluated as possible agents to prevent nausea and vomiting associated with radiation exposure in a non-clinical military setting. Because of concern about potential cardiovascular toxicity and the observation that certain developmental 5-HT3 antagonists produced undesirable effects, all drugs in this class are being carefully scrutinized for possible adverse cardiac effects. ***Method:*** In this study, nine subjects underwent ambulatory ECG monitoring for an average of 21.6 h after a 2-mg oral dose of granisetron or placebo in a double-blind crossover protocol. Monitoring included a 3-h period of submaximal exercise in a 40°C environment. ***Results:*** Although isolated ventricular and supraventricular ectopic activity, sinus bradycardia, and pauses were found, there were no sustained arrhythmias observed in either the placebo or granisetron conditions. ***Conclusion:*** Although the generalizability of this study is limited by the small number of subjects, these observations add to the body of evidence confirming the lack of cardiovascular toxicity of granisetron.

CANADA AND OTHER NATO nations have been interested in identifying an effective anti-emetic drug to prevent nausea and vomiting in a chemical or radiation warfare environment. Two selective serotonin type-3 (5-HT3) antagonist drugs, ondansetron and granisetron, have been identified as possible agents. Both drugs have shown good efficacy in preventing nausea and vomiting related to anti-cancer therapy in a clinical setting (1,2,7,12).

During the initial development and evaluation of this class of drugs, there were some reports of adverse cardiovascular effects (1,3,8). One candidate drug, batanopride, was dropped from further development for this reason. In preclinical and clinical trials neither granisetron nor ondansetron showed conclusive evidence of cardiovascular side-effects, and both have been approved for clinical use by regulatory agencies in Europe and North America.

Because the intended use is not in a clinical setting, but in healthy military personnel in a hostile environment, further evaluation of both drugs has been undertaken by NATO Army Armaments Group Project Group 29. This study reports the results of 24-h ambulatory ECG monitoring performed on nine healthy subjects who participated in a study to assess the effect of granisetron on the thermoregulatory and cardiorespiratory response to exercise in heat (10).

METHODS

This analysis was dovetailed into another study (10). Following approval from the institute's human ethics committee, nine male subjects participated in a double-blind crossover protocol to assess the effects of a single 2-mg oral dose of granisetron on the thermoregulatory and cardiovascular response of up to 3 h of exercise in a 40°C/30% humidity environment. Subjects were removed from the environmental chamber earlier if their rectal temperature reached 39.3°C, if their heart rate remained at 95% of the individuals predetermined maximum for more than 3 min, if nausea or dizziness precluded further exercise or if the subjects asked to be removed from the chamber.

Subjects were connected to 24-h ambulatory 2-channel ECG recorders (Cardionostics Duralite) between 0800-0900 h. Standard ambulatory 5-electrode limb lead positions were used. Subjects took either granisetron 2 mg orally or an identical placebo capsule at 0800 h and participated in the exercise-in-the heat experiment from at 0900-1200 h. The ambulatory ECG was removed while the subjects took a shower, and was then reapplied and recording continued until the following morning. Average recording time was 21.6 h (excluding the shower break). Each subject performed a drug and placebo trial in a double-blind random order with the two trials separated by a minimum of 5 d.

Ambulatory ECG's were processed by a full-disclosure analysis system (Cardionostics). The tapes were also reviewed in their entirety for arrhythmias by an internist who assessed arrhythmias, counted premature com-

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TABLE I. HEART RATE AND ARRHYTHMIAS IN SUBJECTS MONITORED ON GRANISETRON (GRAN) AND PLACEBO (PLAC).

Subject/ Condition	Max HR	Min HR	Av HR	TOT PVC	Max PVC/m	Max PVC/h	COU	PSVC	Pause >1.5 s	Comments
A plac	133	48	79	40	1	11	0	0	0	Sinus arrhythmia
A gran	150	48	82	50	1	6	0	5	0	Sinus arrhythmia
B plac	184	49	84	1	1	1	0	1	0	Sinus acceleration in sleep
B gran	178	44	74	1	1	1	0	2	0	Sinus acceleration in sleep
C plac	167	55	85	2	1	1	0	1	0	Sinus acceleration in sleep
C gran	161	53	88	1	1	1	0	1	0	
D plac	185	60	93	0	0	0	0	2	0	
D gran	163	47	83	3	1	1	0	1	0	Sinus arrhythmia during sleep
E plac	181	53	91	0	0	0	0	1	1	
E gran	174	51	90	0	0	0	0	2	1	Sinus arrhythmia
F plac	143	40	77	0	0	0	0	4	0	3 dropped beats sinus exit block
F gran	149	41	72	0	0	0	0	3	0	Sinus arrhythmia
G plac	178	52	87	6	1	2	0	1	0	Sinus arrhythmia
G gran	170	50	77	1	1	1	0	0	4	Transient AV block I PR 240--250 msec
H plac	153	44	75	82	2	12	1	19	1	
H gran	134	41	63	71	1	1	0	6	0	
I plac	190	59	85	0	0	0	0	1	24	Pauses at night; Max 2280 ms Non-conducted P's
I gran	193	58	94	2	2	2	1	1	27	Pauses all at night; Max 2200 ms Non-conducted P's

PVC = premature ventricular complex; COU = couplets; PSVC = premature supraventricular complex.

plexes and catalogued them as ventricular or supraventricular, and pauses. The internist was not aware of the condition (placebo vs drug) during the review.

Statistical analysis was done with a two-tailed paired *t*-test.

RESULTS

There were no significant arrhythmias detected. The maximum (max HR), minimum (min HR) and average heart rates (av HR), amount of ventricular and supraventricular ectopic activity, and pauses for each subject are shown in **Table I.** There was considerable variation in the amount of ectopic activity/pauses between subjects, but the amount of ectopy in individual subjects was remarkably similar during the two monitoring periods and was not affected by the single 2-mg dose of granisetron. There were only two ventricular couplets noted in two subjects, one on granisetron and the other placebo. There were no triplets or more sustained ventricular or supraventricular arrhythmias. Ventricular premature complexes in any one subject were generally monomorphic and in particular there was no complex ectopy (multiformity or frequency).

There was no difference between drug and placebo conditions in the maximum or minimum heart rate recorded, in the average heart rate over the monitoring period, or in the average number of premature ventricular complexes (PVC's) or premature supraventricular complexes (PSVC's) (**Table II**). Maximum heart rates occurred towards the end of the period of thermal/exercise stress. Minimum heart rates occurred during sleep and tended to be lower with granisetron but the difference did not reach statistical significance in this small subject pool ($p = 0.06$). Ectopic activity disappeared in all subjects during exercise, and no exercise-induced arrhythmias were noted.

DISCUSSION

Ondansetron and granisetron are 5-HT3 (serotonin type 3) receptor antagonists that are effective in reducing the nausea and vomiting associated with radiation and chemotherapy in cancer patients (2,12). Both drugs are promising candidates as prophylactic agents for radiation-induced nausea and vomiting in a non-clinical setting.

There have been some concerns raised about possible cardiovascular side-effects of 5-HT3 antagonists (1,4). Clinical case reports have implicated ondansetron with the occurrence of chest pain (3) and with thrombosis and thrombocytopenia (6,8) although the validity of the latter observation was challenged (5). In the FDA review of granisetron (9), Holter monitoring reported in normal human volunteer studies showed no arrhythmogenic effect. In a group of patients receiving anti-neoplastic therapy and granisetron, ambulatory ECG monitoring showed ventricular ectopy including nonsustained ventricular tachycardia, pauses, transient asystole, second

TABLE II. MAXIMUM, MINIMUM AND AVERAGE HEART RATES (HR) AND NUMBER OF PREMATURE VENTRICULAR COMPLEXES (PVC's), AND PREMATURE SUPRAVENTRICULAR COMPLEXES (PSVC's) DURING MONITORING PERIOD.

	Max HR	Min HR	Av HR	PVC	PSVC
Granisetron	164	48	80	14.5	3.3
Placebo	168	51	84	14.3	2.3
p	0.28	0.06	0.18	0.91	0.56

and third degree heart block, and an episode of atrial fibrillation. These observations were collected in a group of patients receiving concomitant anti-neoplastic therapy and were considered by the FDA cardiologist as being within the range of expected findings in such a patient population, and granisetron was approved for clinical use by the FDA.

Most of the human use information on 5-HT3 antagonists has come from a patient population. There is little or no information on the possible adverse cardiac effects in otherwise healthy persons or interaction with adverse environmental conditions. In this study, the combination of granisetron in a stressful thermal/exercise environment induced no arrhythmias in this group of healthy subjects, adding evidence to support the cardiovascular safety of granisetron. However, the small number of subjects in this study limits the generalizability of the observation.

Although there were no significant arrhythmias noted in this group of subjects either in the placebo or granisetron condition, minor degrees of ectopic supraventricular and ventricular activity were noted in all 18 recordings. This confirms previous similar observations that minor degrees of arrhythmia occur commonly in healthy individuals (11).

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