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Interim Report

PHARMACOLOGIC COUNTER MEASURES MINIMIZING POST-SPACE FLIGHT ORTHOSTATIC INTOLERANCE

Prepared for Harold Sandler, M.D.
Chief, Biomedical Research Division
NASA-Ames Research Center
Moffett Field, California 94305

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NCC 2-232

Stanford University School of Medicine
Cardiology Division

Donald C. Harrison, M.D.
Principal Investigator

Robert Kates, Ph.D.
Coinvestigator

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Preface

The Stanford University Cardiology Division submits this interim report under NASA Cooperative Agreement NCC 2-232. The report has been requested by Technical Monitor Harold Sandler, M.D., Chief of the Biomedical Research Divison, NASA-Ames Research Center.

PHARMACOLOGIC COUNTERMEASURES FOR MINIMIZING POST-SPACE FLIGHT ORTHOSTATIC INTOLERANCE

Introduction

This interim report responds to the sponsor's request for an update on the status of the project Pharmacologic Countermeasures for Minimizing Post-Space Flight Orthostatic Intolerance. There is only limited progress to report because this project has been active for only a short time and because its formal approval by the Institutional Review Board at NASA-Ames Research Center was delayed until January 1983 by a controversial aspect of its protocol.

This project, however, is only one of many closely related projects which comprise a productive, long standing collaborative program with the Cardiovascular Research Laboratory (CVRL) at Ames. It is in the context of the overall collaborative program that the status of the current project will be reported.

Programmatic Background

For nearly two decades the Stanford University Cardiology Division has been collaborating with NASA-Ames Research Center to study the cardiovascular effects of spaceflight. The research effort has been focused in several basic areas:

1. The development, improvement, verification and calibration of physiologic instrumentation and investigative techniques to permit the minimally invasive but quantitatively meaningful measurement of cardiovascular variables in man and animals

2. Basic research to provide a better understanding of cardiovascular physiology, the altered physiology which might occur during and after space flight, and the character and mechanisms of cardiovascular responses to various types of stress

3. The development and verification of human and animal models to facilitate the conduct of ground-based cardiovascular research and to expand the ethically and logistically permissable scope of such research

4. Basic research to determine the pharmacokinetics of various substances in normal and altered cardiovascular states

5. The development and implementation of computer-based methods to automate the acquisition, storage, display and analysis of cardiovascular data

6. The development and verification of non-invasive methods for classifying individuals according to their probable susceptibility to potentially harmful cardiovascular effects of space flight

7. The development and evaluation of potential countermeasures to treat, minimize or prevent the undesireable cardiovascular effects of spaceflight

8. The accumulation of a body of data from ground-based research in experimental models to be verified in future flight experiments

The relationships among the projects which comprise this collaborative program are depicted on a time line in Figure 1, and ongoing and planned collaborative projects are listed in Table 1.

The nature of individual projects has changed with time. There has been a trend toward more specific definitions of project scope and objectives as accumulated experimental data and flight experience have focused attention on specific issues, problems and hypotheses. General physiologic investigations have been replaced by studies which focus on identifying specific mechanisms of cardiovascular deconditioning and degeneration during spaceflight and of post-flight orthostatic intolerance. In the area of instrumentation and investigative methods, efforts to develop fundamentally new technologies for measuring cardiovascular variables have been replaced in part by efforts to refine and adapt the technologies for specific, technically demanding applications such as preflight screening, chronic implantation in small animals or in-flight experiments. Another trend has been the evolution of project objectives from simply understanding flight-related cardiovascular physiology toward preventing, minimizing and treating the undesireable cardiovascular effects of space flight.

Similar trends have characterized the sequence of projects dealing specifically with the properties of drugs in normal and altered cardiovascular states. During the early 1970's, the emphasis was on studying the cardiovascular effects of drugs in research animal models or cardiovascular patients. Substances studied under a broadly scoped NASA program grant entitled Evaluation of the Cardiovascular System During Various Circulatory Stresses included dopamine, lidocaine, morphine sulfate, digitalis glycosides, and nitroprusside, among others. Interest in the latter half of the decade focused on studying the alterations in drug disposition and elimination which could be attributed to bedrest simulated weightlessness. Lidocaine, penicillin-G and indocynine green (ICG) were studied under the grant entitled The Effect of Space Flight as Simulated by Bedrest on Drug Disposition which spanned the years 1978 through 1980.

The current grant follows a period of about two years during which there was no project funding to support Cardiology Division collaboration in drug-related studies of the cardiovascular effects of space flight. Although the active grant award for this project covers a period beginning in September 1982, the award was not confirmed by NASA until February 1983. The project's formal approval was delayed by the Institutional Review Board at NASA-Ames Research Center due to controversy concerning the administration of the drug propanolol to healthy research subjects. The investigators invested substantial effort in resolving the IRB controversy and in preparing for the study in anticipation of the award. Reportable progress is limited, however, because this project has been truly active for only a short period of time.

Progress

In order to present the project in perspective, this progress report will cover a period beginning in 1980, including the two year period during which there was no funding to support collaboration in drug-related studies.

Drug disposition. Two groups of subjects were studied to determine the effect of bedrest on drug disposition and physiologic function. The first group was studied at the Stanford Clinical Research Center and consisted of twelve healthy male volunteers between the ages of 45 and 55 years. Each individual was administered an intravenous dose of lidocaine, penecillin-G and ICG during a control period and following seven days of bedrest in order to determine the effect of prolonged recumbency on drug disposition. In addition, cardiac function was evaluated before and seven days after bedrest by echocardiography.

A second group of subjects consisting of healthy, normal male volunteers between the ages of 55 and 65 years was studied at the NASA-Ames facility. Renal function was evaluated before and after several days of bedrest. Inulin, para-aminohippurate and dextran clearances were evaluated during a constant infusion protocol.

Results of the study in the first group are summarized in Tables 2 through 4. In six of the subjects, ICG clearance decreased slightly after seven days. In the other six individuals, ICG clearance was observed to be somewhat increased. It was found that the half-life, the clearance and the volume of distribution of lidocaine were not affected by seven days of bed rest The pre- and post-bed rest values for half-life, clearance and volume of distribution were 1.73 + 0.24 and 1.79 + 0.41 hours for the half-life and 4.59 + 0.67 and 4.67 + 0.69 ml/min/kg for clearance and 0.68 + 0.13 and 0.70 + 0.10 l/kg for the volume of distribution. In non-of these cases was the post-bed rest parameter statistically different from the pre-bedrest value.

Penicillin is almost totally eliminated by renal function and therefore penicillin clearance provides a good estimate of renal function. In this study it appeared that renal function did not change significantly after seven days of bed rest. As above, the half-life , clearance and volume of distribution were calculated. The half-life pre- and post-bed rest was 49.2 + 6.4 min and 51.2 + 9.1 min. The clearances were 7.0 + 1.6 and 7.4 + 1.9 ml/min/kg and the volume of distribution terms were 0.49 + 0.1 and 0.53 + 0.1 l/kg. There were no statistically significant changes pre- and post-bed rest. These results have been published (Kates RE, Harapat SR, Keefe DLD, Coldwater D, Harrison DC: Influence of prolonged recumbency on drug disposition. Clin. Pharmcol. Therap. 28:624-628, 1980)

Resting heart rate, end diastolic volume and systolic volume were all significantly changed, but cardiac output and ejection fraction were not significantly altered by bed rest.

In the second group renal function was evaluated with Inulin, para-aminohippurate and dextran. As indicated by the results summarized in Table 5, no changes were observed following seven days of bed rest.

Protocol development. Two relevant protocols were developed during this period. Funding could not be obtained for the first protocol, which had two objectives: to examine the early effects of bedrest on the disposition and elimination of propanolol and to examine the effects of menstrual cycle variability on the disposition and elimination of propanolol in females. The second protocol which was developed governs the conduct of the present project.

Studies underway. The studies which were planned for this project have been coordinated with another collaborative study which is just underway at the Veterans Administration Hospital, a part of the Stanford University Medical Center complex. Twenty normal volunteers have been recruited to undergo cardiovascular deconditiong by water immersion and six-degree head down bedrest. The coordinate protocol includes pre- and post-deconditioning analyses of renins and catecholamines, pre- and post-deconditioning echocardiographic examination and propanolol challenges at the end of the deconditioning period.

Plans

The purpose of this project is to examine a potential pharmacologic countermeasure for preventing or minimizing orthostatic intolerance following space flight and, in so doing, also to investigate the underlying mechanisms which produce this state. The working hypothesis is that beta adrenergic blockade alone or in combination with an antimuscarinic agent is an effective countermeasure for post-flight orthostatic hypotension, which has been observed frequently in previous prolonged space flights. The project addresses the following specific questions:

1. What is the relationship between dose, or plasma level, of propranolol and the change in heart rate, plasma renin activity and left ventricular function during LBNP?

2. What is the relationship between dose, plasma level, of atropine and change in heart rate and left ventricular function during LBNP?

3. Are there differences between men and women, athletes and non-athletes in regard to their dose response curves for propranolol and the combination of atropine plus propranolol?

4. What is the optimal dosage combination for preventing orthostatic intolerance in these groups of subjects?

Work will continue with the water immersion studies just beginning at Stanford and 6-degree head down bedrest studies beginning at Ames this summer. At Stanford, healthy middle-aged volunteers and volunteers with mild hypertension will undergo six hours of water immersion followed by overnight bed rest. After this exposure subjects will be given a two hour stand test during which neuroendocrine studies will be done and cardiovascular responses will be monitored by echocardiography. Control subjects will receive no medication prior to the stand test while a matched group of subjects each will receive 60 mg p.o. propanolol as a pharmalogical countermeasure for orthostatic intolerance.

During the summer at Ames, healthy men aged 35 to 50, half of whom will be endurance trained athletes, will be tested for orthostatic intolerance using three pharmacologic countermeasures. Two of the drugs, propranolol and atropine, are described in Figure 2. The third drug, phenylephrine, is a direct alpha adrenergic stimulator of vasoconstriction. It is anticipated that aerobically conditioned subjects with high levels of vagal tone will respond particularly well to atropine. This subgroup, which is especially prone to early syncope, is fairly representative of the current astronaut population.

The results from these studies will help to reveal the mechanisms which underly cardiovascular deconditioning and to foster development of safe, efficient and specific pharmacologic countermeasures tailored to the individual physiologic characteristics of each member of a flight crew.

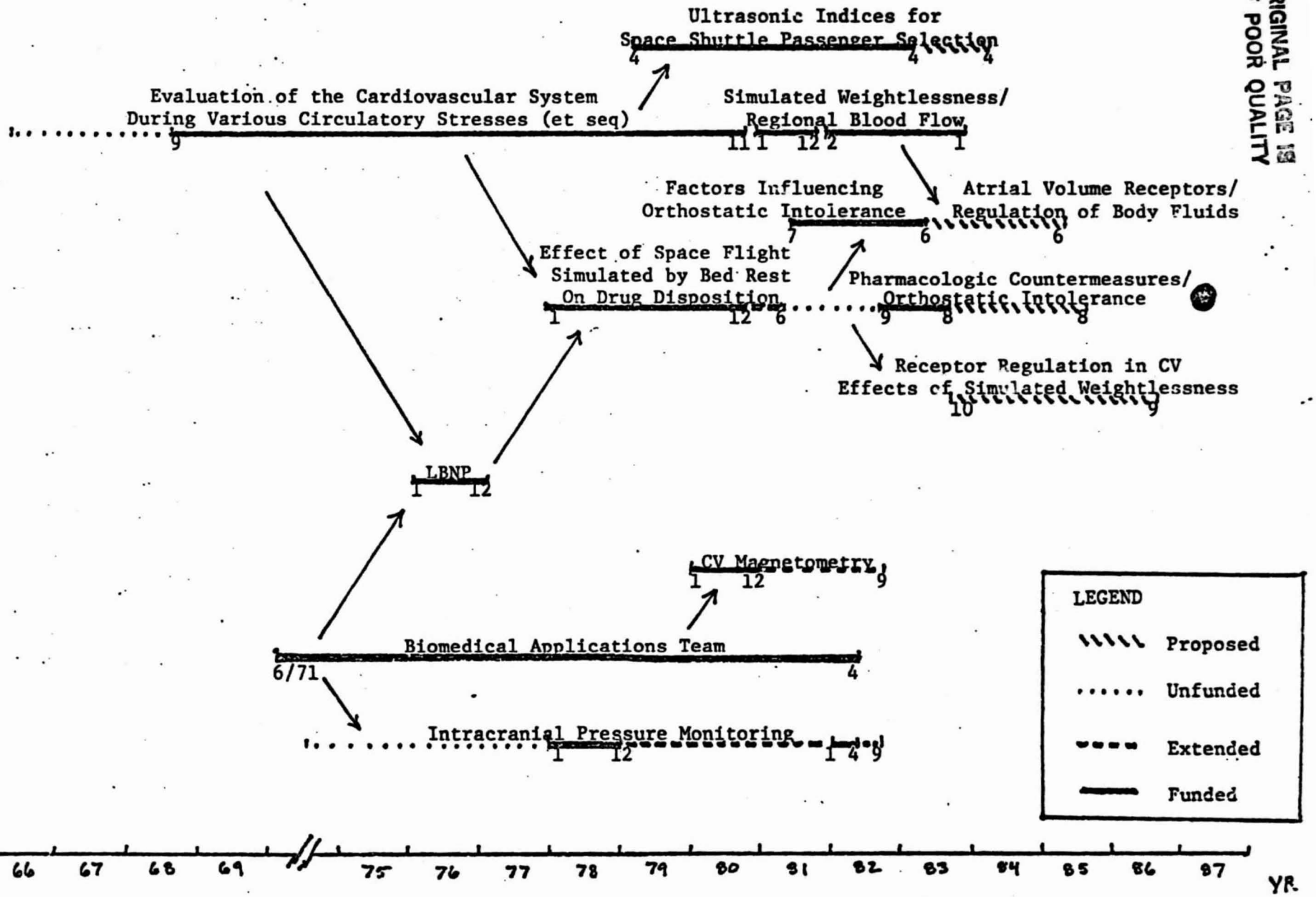


FIGURE 1: Collaborative Projects in the Cardiovascular effects of Spaceflight; (49) indicates the project for which this report is submitted.

Table 1

Ongoing and planned collaborative projects

Development of Ultrasonic Indices for Space Shuttle Passenger Selection (NCC 2-1 and proposed for continuation)

Effects of Simulated Weightlessness on Regional Bloodflow Specifically During Cardiovascular Stress (NCC 2-126)

Factors Influencing Orthostatic and Re-entry Intolerance Following Weightlessness Simulation (NCA2-OR745-108)

Pharmacologic Countermeasures for Minimizing Post-Space Flight Orthostatic Intolerance (NCC 2-232; continuation proposals planned)

The Role of Atrial Volume Receptors in the Regulation of Body Fluids in Man (Proposed)

Hyperadrenergic States and the Role of Receptor Regulation in the Cardiovascular Effects of Weightlessness (Proposal in Preparation)

Table 2

ICG Data

Subject		Date	Dose (mg/kg)	k (min^{-1})	$\bar{C}p$ (mg/ml)	$Auc]_0^\infty$ (mg/ml-min)	Clearance (ml/min/kg)	Vd ext (ml/kg)
WM	pre	9/5/79	0.5	0.2460	16.24	72.26	6.92	30.8
	post	9/15/79	0.5	0.2050	13.01	66.88	7.48	38.4
RC	pre	9/5/79	0.5	0.1290	11.60	85.73	13.31	43.1
	post	9/15/79	0.5	0.1960	16.11	84.55	5.91	31.0
FB	pre	9/19/79	0.5	0.1990	9.78	52.89	9.45	51.1
	post	9/29/79	0.5	0.2030	14.06	74.13	6.74	35.6
JH	pre	9/19/79	0.5	0.1600	10.16	64.62	7.74	49.2
	post	9/29/79	0.5	0.1870	11.36	62.61	7.99	44.0
PS	pre	10/5/79	0.5	0.1240	11.81	97.11	5.15	42.3
	post	10/15/79	0.5	0.1934	14.93	79.00	6.33	33.5
DB	pre	10/5/79	0.5	0.2120	16.03	77.17	6.48	31.2
	post	10/15/79	0.44	0.2080	13.94	72.78	6.05	31.6
EA	pre	10/19/79	0.5	0.1602	9.125	58.10	8.61	54.8
	post	10/29/79	0.5	0.1439	5.613	39.81	12.56	89.1
GP	pre	10/19/79	0.46	0.2864	9.23	32.77	14.04	49.8
	post	10/29/79	0.46	0.1700	7.61	45.99	10.00	60.4
HA	pre	12/5/79	0.5	0.3783	26.61	73.77	6.78	18.8
	post	12/14/79	0.5	0.1381	11.94	87.77	5.70	41.9
LC	pre	12/5/79	0.5	0.3036	20.58	69.38	7.21	24.3
	post	12/14/79	0.5	0.1893	17.77	96.70	5.17	28.1
Mean ± SD				NS			8.57 ± 2.94 7.39 ± 2.29	
							NS	39.5 ± 12. 43.4 ± 18.

Table 3

Lidocaine Data

Subject	Half-life (hrs) pre	post	Clearance (ml/min/kg) pre	post	Vd (l/kg) pre	post
1	1.73	1.79	3.94	4.36	0.59	0.68
2	1.92	2.69	4.21	3.79	0.70	0.88
3	1.43	1.43	5.49	5.24	0.68	0.65
4	1.65	1.48	4.99	5.26	0.71	0.67
5	1.46	1.50	4.37	5.70	0.55	0.74
6	1.64	1.80	5.10	4.00	0.72	0.62
7	1.85	1.65	3.58	4.14	0.57	0.59
8	2.16	1.95	5.07	4.85	0.95	0.82
Mean	1.73	1.79	4.59	4.67	0.68	0.70
± SD	±0.24	±0.41	±0.67	±0.69	±0.13	±0.10
	NS		NS		NS	

Table 4

Penicillin Data

	Subject	Half-life (min)		Clearance (ml/min/kg)		Vd (ℓ/kg)		Weight (kg)	
		pre	post	pre	post	pre	post	pre	post
1	B.Matolyak	52.2	48.5	5.2	7.8	0.39	0.55	85.0	83.7
2	R.Chota	43.2	56.5	7.9	8.2	0.49	0.67	95.3	93.4
3	F.Bell	51.1	44.7	9.2	10.6	0.68	0.68	64.5	64.8
4	J.Harrah	44.5	39.5	7.4	8.6	0.48	0.49	77.9	77.2
5	P.Schriewogel	40.4	46.9	9.6	8.7	0.56	0.59	85.9	84.4
6	D.Bright	37.8	42.4	6.8	7.8	0.37	0.48	99.6	97.0
7	J.Axlin[illegible]	55.1	49.1	6.9	7.6	0.55	0.54	72.6	71.2
8	G.Padden	54.0	42.5	7.0	8.9	0.55	0.55	97.6	96.0
9	R.Verbica	52.5	62.3	5.3	4.6	0.40	0.41	94.6	93.2
10	M.Kitlan	49.3	63.6	8.5	6.9	0.60	0.63	84.2	81.9
11	H.Atkinson	51.2	51.8	5.1	5.3	0.38	0.40	76.2	71.7
12	L.Cerutti	58.9	66.7	5.5	4.2	0.47	0.40	71.5	76.0
	Mean	49.2	51.2	7.0	7.4	0.49	0.53	83.7	82.5
	SD ±	6.4	9.1	1.6	1.9	0.10	0.10	11.7	10.7
	SEM ±	1.8	2.6	0.5	0.5	0.03	0.03	3.3	3.1
		NS		NS		NS		NS	

Table 5

Renal Function Studies Before and

During Bed Rest in 55 to 65 year old Male Volunteers

Subject	Glomerular Filtration Rate (ml/min)		Renal Blood flow (ml/min)		Filtration Fraction	
	Pre	Post	Pre	Post	Pre	Post
1	92.6	98.2	822.2	1064.5	0.24	0.20
2	-	-	-	-	0.21	0.20
3	121.8	82.7	754.3	782.8	0.32	0.22
4	110.3	79.0	1209.8	1036.1	0.17	0.15
5	72.3	78.8	738.3	826.9	0.20	0.19
6	68.5	89.1	754.2	850.6	0.18	0.22
7	114.0	125.2	1104.3	1321.0	0.21	0.19
8	86.5	84.4	785.1	752.7	0.23	0.23
Mean ± SD	95.1	91.0	881.2	948.5	0.22	0.20
	20.9	16.5	192.8	203.4	0.047	0.025

PHARMACOLOGIC COUNTERMEASURES FOR MINIMIZING SPACE FLIGHT-INDUCED ORTHOSTATIC AND REENTRY ACCELERATION TOLERANCE

PROPRANOLOL-B_1 AND B_2 BLOCKING AGENT COMMONLY USED:

FOR HYPERTENSION

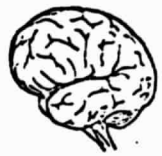
FOR ANGINA

MAY PREVENT FALLING BLOOD PRESSURE BY:

PREVENTING B_2-ADRENERGIC VASODILATION AND POOLING OF BLOOD IN LOWER BODY

FOR ARRHYTHMIAS

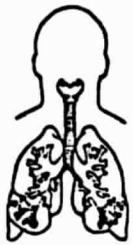
FOR MIGRAINE



INCREASING CARDIAC OUTPUT BY PROLONGING CARDIAC FILLING TIME

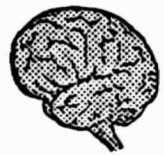
ATROPINE-ANTICHOLINERGIC, ANTIVAGAL AGENT COMMONLY USED:

FOR ARRHYTHMIAS AND SEVERE BRADYCARDIA



FOR DRYING EXCESS LUNG SECRETIONS

MAY BE USEFUL TO:



PREVENT REFLEX VASOVAGAL SYNCOPE (BLACKOUT)

AUGMENT HEARTRATE RESPONSE DURING ORTHOSTATIC STRESS

FIGURE 2: Propranolol and Atropine