AD-A145 144 THE EFFECT OF NAPROXEN ON ACUTE MOUNTAIN SICKNESS AND VASCULAR RESPONSES TO HYPOXIA(U) ARMY RESEARCH INST OF ENVIRONMENTAL MEDICINE NATICK MA R T MEEHAN ET AL. 1/1

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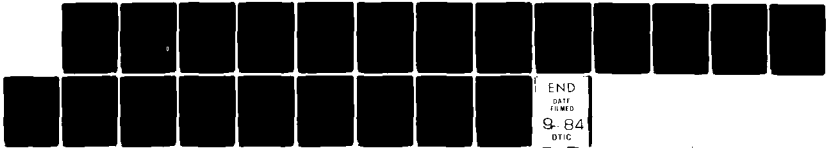

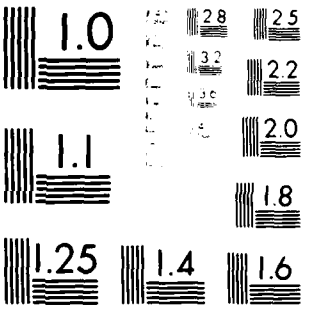

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The role of prostaglandins in the pathogenesis of acute mountain sickness and two hypoxia-induced vascular responses was evaluated using the cyclooxygenase inhibitor naproxen. Eleven males spent 24h at sea level, followed by 34h of decompression to 428 torr while receiving naproxen (N), 250 mg twice daily or placebo (P) in a double-blind crossover trial. Serum naproxen levels by high pressure liquid chromatography were not changed by hypoxia. Retinal artery diameter measured from projected fundus photographs was increased after 27h at altitude (11.4±.5mm) vs sea -

level (9.4 ± .5mm, $p < .05$) during both trials. Upright mean arterial pressure fell after 6h at altitude (79 ± 3 mmHg during N and P vs. 92 ± 3 at S.L., $p < .01$). The severity of acute mountain sickness (AMS) by the Environmental Symptoms Questionnaire scores and observer assessment were unaffected by drug treatment. Minute ventilation, and expiratory alveolar PO_2 and PCO_2 did not differ between drug trials. This study suggests vasodilating prostaglandins do not have a major role in the genesis of AMS, hypoxia-induced retinal vasodilatation, or postural blood pressure responses in man.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

THE EFFECT OF NAPROXEN ON ACUTE MOUNTAIN SICKNESS AND VASCULAR RESPONSES TO HYPOXIA

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Running head: Naproxen prophylaxis for acute mountain sickness

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ABSTRACT

The role of prostaglandins in the pathogenesis of acute mountain sickness and two hypoxia-induced vascular responses was evaluated using the cyclooxygenase inhibitor naproxen. Eleven males spent 24 hours at sea level, followed by 34 hours of decompression to 428 torr while receiving naproxen (N), 250 mg twice daily or placebo (P) in a double-blind crossover trial. Serum naproxen levels by high pressure liquid chromatography were not changed by hypoxia. Retinal artery diameter measured from projected fundus photographs was increased after 27 hours at altitude (11.4 ± .5 mm) vs. sea level (9.4 ± .5 mm, $p < .05$) during both trials. Upright mean arterial pressure fell after 6 hours at altitude (79 ± 3 mm Hg during N and P vs. 92 ± 3 at S.L., $p < .01$). The severity of acute mountain sickness (AMS) by the Environmental Symptom Questionnaire scores and observer assessment were unaffected by drug treatment. Minute ventilation, end expiratory alveolar PO_2 and PCO_2 did not differ between drug trials. This study suggests vasodilating prostaglandins do not have a major role in the genesis of AMS, hypoxia-induced retinal vasodilatation, or postural blood pressure responses in man.

INDEX TERMS:

Acute mountain sickness

Human

Prostaglandins

Retinography

Acute mountain sickness (AMS) is a symptom complex affecting susceptible individuals after 6 to 8 hours of exposure to hypobaric hypoxia. It may represent the benign end of a spectrum which includes the rare, but often fatal, high altitude cerebral edema (HACE). While the precise pathogenesis of AMS remains unknown, growing evidence suggests that exaggerated cerebral vascular responses to hypoxia may facilitate the development of symptomatic, mild cerebral edema (1-5). Acute hypoxia causes cerebral vasodilatation, pulmonary vasoconstriction, and retinal vasodilatation. Impaired capillary membrane integrity may also be involved since subclinical pulmonary edema and fluorescein leakage from retinal vessels occur during exercise at 14,000-17,500 feet (6-8).

The role of eicosanoids (prostaglandins, thromboxanes, leukotrienes) in the pathogenesis of AMS has not been evaluated, but these potent vasoactive substances are uniquely suited to selectively modulate vascular responses to hypoxia (9-12). Prostacyclin infusion in man may result in dizziness, lowered blood pressure, headache, nausea or vomiting symptoms similar to AMS (13). Experimental data for different animal species are conflicting regarding the role of prostaglandins in regulating cerebral blood flow induced by hypoxia or hypercapnia (14-16).

This study evaluated the effect of the non-steroidal anti-inflammatory drug naproxen, a known inhibitor of cyclooxygenase, upon severity of AMS and two hypoxic induced vascular responses: retinal vessel dilatation and orthostatic blood pressure. The results suggest AMS is not mediated by vasodilating prostaglandins.

METHODS

Eleven healthy male volunteers (19-24 years of age) divided randomly into 2 groups of 5 and 6 subjects participated in a double-blind, crossover study in which they received naproxen or placebo on two occasions during 34 hours at simulated altitude in a hypobaric chamber. Informed consent was secured prior to participation according to guidelines of the Human Subjects Review Committees at the University of Iowa and the U.S. Army Research Institute of Environmental Medicine.

Each group entered the altitude chamber 24 hours before ascent to allow baseline sea level (S.L.) studies. The chamber was then decompressed to 428 torr (4570 M) for 34 hours. Ambient temperature was maintained at 20°C with 35% relative humidity throughout the study. A controlled diet containing 2400 K cal, 150 mEq Na+, and 60 mEq K+ was given between 24 hours before subjects entered the chamber and continued at altitude. Distilled and demineralized water was offered ad libitum. While in the chamber, subjects were free to ambulate in the confined space and pursue sedentary activities such as playing cards or watching television.

The subjects were randomly assigned by an uninvolved investigator to receive either placebo (P) or 250 mg naproxen (N) twice daily at 6:00 a.m. (fasting) and 7:00 p.m. (two hours postprandial) beginning 24 hours prior to and continuing throughout altitude exposure. To minimize any order effect, one-half of the subjects were assigned to receive naproxen during the first exposure. Twenty-one days after the first exposure, the subjects reentered the identical protocol and received the crossover drug.

The Environmental Symptom Questionnaire (ESQ) (17) was completed by each subject daily at 7:00 a.m., 3:00 p.m. and 8:00 p.m. using a computer keyboard and cathode-ray tube display screen. Each symptom was scored 0-5 based upon severity. A composite score reflecting AMS was calculated from symptoms

scores for headache, anorexia, nausea, weakness, incoordination, visual blurring, dizziness, and feeling sick (18). The severity of AMS was also assessed on a scale of 0-3 by an observer who was unaware of treatment or ESQ responses. Grade 0 indicated no symptoms of AMS; grade 1 indicated mild headache, lethargy, anorexia or fatigue; grade 2 indicated moderately severe and persistent headache, nausea, dizziness or malaise, usually confining subjects to bed; and grade 3 indicated the subject was removed from the chamber because of severe headache, recurrent emesis and prostration.

Peripheral venous blood was obtained by venipuncture without stasis twice daily one hour after naproxen ingestion at 7:00 a.m. (fasting) and 8:00 p.m. (3 hours postprandial). Blood samples were aspirated into prechilled syringes coated with 4.5 mM EDTA and 10 µg/ml indomethacin, and plasma samples were kept at -70°C until assayed for 6 keto-PGF1α levels using a ^{3}H RIA kit (New England Nuclear, Boston, MA) (19). To determine naproxen levels, ether extracts of 0.1 ml pH adjusted (7.0) serum samples were dried and reconstituted in high pressure liquid chromatograph (HPLC) mobile phase (60/40, 0.05 M phosphate pH 7.0/methanol). The samples were chromatographed using a Beckman 334 gradient liquid chromatograph 501 auto-sampler, a 150 x 4.6 mm Regis ^{R}C-8 5 µM column with 155-40 UV detector at 262 nm, and CRIB computing integrator. Ketoprofen served as the internal standard generating a matrix corrected naproxen (1-100 µg/ml) standard curve. The least squares fit of the peak area ratio (naproxen-ketoprofen) was used for quantitative determination of test samples (20).

Retinal photographs were taken with a topcan TRE-Fe fundus camera using Kodak Panatomic-X film after the pupil was dilated with 1-2 drops of 2.5% phenylephrine HCl and 5% tropicamide. Developed negatives were projected 2.3 meters onto a screen using an Ektanar 102 mm f/2.8 lens and measurements of the superior temporal artery width at one disc diameter from the optic nerve were made using calipers.

Daily resting minute ventilation (Ve) was determined with a Hewlett-Packard 47304A flow transducer. Expiratory PO_2 and PCO_2 were analyzed by a S-3A oxygen analyzer (Applied Electrochemistry, Inc.) and LB-2 CO_2 Medical Gas Analyzer (Beckman). Blood pressure was obtained three times a day by auscultation in a supine position and 30 seconds after standing upright (21). Mean arterial pressure (MAP) was calculated as . All data were entered into a CLINFO^R computer (Bolt, Beranek and Newmon, Inc., Cambridge, MA). The Wilcoxon signed ranks test (two-tailed) was used to analyze paired data during naproxen and placebo trials at each altitude exposure. Analysis of variance was used to compare sea level to altitude values, and the Duncan's multiple range test determined where altitude exposure mean differences exist.

RESULTS

Ten of 11 subjects completed the crossover study. One subject withdrew from the study prior to the crossover for personal reasons. Four subjects (3 naproxen and 1 placebo) left the chamber after 11 hours of decompression at their own request during the first trial. One subject developed grade 3 AMS and was removed from the chamber. One subject withdrew from the study prior to the crossover for personal reasons.

Figure 1A represents ESQ scores at sea level and five times at altitude. The apparent reduction of AMS symptoms during the final 21 hours at altitude partially reflects 4 subjects who were most ill leaving the chamber. No differences were observed between placebo or naproxen trials during altitude exposure. A similar response was recorded by observer assessment (Figure 1B), and, despite higher scores at 6 and 13 hours at altitude during naproxen, those differences were not statistically significant.

Values for supine and upright MAP did not differ between placebo and naproxen trials (Figure 2A and 2B). Supine MAP was significantly increased after 34 hours of altitude exposures during both placebo and naproxen trials ($p < .01$). A significant fall in upright MAP was observed at 6 hours of altitude during both trials ($p < .05$).

Retinal artery diameter was increased compared to sea level by 27 hours at altitude during both drug trials (Fig. 3, $p < .05$), but no statistical differences were apparent after 3 hours of altitude exposure. There were no differences in retinal vessel diameter between naproxen and placebo at S.L. or altitude.

Serum naproxen concentrations (Fig. 4) after the third S.L. dose was approximately 75% of steady-state value since the half-life of naproxen elimination is 12 to 15 hours (22). The wide range in serum levels at S.L. 3 ([illegible] to 75 µg/ml) reflects individual variation normally observed during naproxen ingestion (22). Serum levels did not change significantly at altitude compared to the third S.L. value.

Peripheral venous 6-keto PGF1α levels revealed an occasional subject who had significant elevations during hypoxia, but when the aggregate data was analyzed, no differences were apparent between sea level and altitude levels.

Changes were observed as expected between sea level and altitude in Ve (9 ± 1 S.L. vs. 12 ± 1 P and 13 ± 1 N liters/min, $p < .05$), alveolar pO_2 (115 ± 3 S.L. vs. 56 ± 2 P and 56 ± 3 N mm Hg, $p < .01$) and alveolar pCO_2 (38 ± 2 S.L. vs. 30 ± 2 P and 30 ± 1 N mm Hg, $p < .01$). No differences between placebo or naproxen were observed in Ve, pO_2 or pCO_2 at any time.

DISCUSSION

The lack of significant differences between ESQ scores or observer assessments during placebo and naproxen trials indicates AMS was not reduced by

naproxen. A similar result was observed in a previous placebo-controlled study of 16 climbers during an ascent of Mount Kilimanjaro (Meehan and Baustian, unpublished data). These results support Singh's observation from an uncontrolled study that salicylates which also inhibit cyclooxygenase do not prevent AMS (23). Naproxen's lack of efficacy in this study cannot be attributed to impaired absorption during hypoxia since serum levels were similar to other studies using 500 mg of naproxen daily (22,25). We chose this dose since the efficacy of naproxen, 500 mg. daily, is comparable in controlled therapeutic trials in man to aspirin (3.6-4.0 grams/day) or indomethacin (100-150 mg/day), but adverse reactions which are similar to several AMS symptoms occur less frequently (22). It is therefore unlikely higher doses of naproxen would prove efficacious in reducing AMS.

Despite our inability to correlate 6 keto-PFG1a levels with altitude exposure or drug trials, naproxen (like aspirin and indomethacin) inhibits prostaglandin synthesis in vitro and in vivo (22,26,27).

We were also unable to demonstrate that naproxen altered postural blood pressure or retinal vsaodilatation during hypoxia. Since retinal vessels probably mimic cerebral vascular responses, our findings in man are analogous to recent studies summarized by Busija and Heistad, which report other cyclooxygenase inhibitors fail to inhibit cerebral vasodilatation during hypercapnia (24). One case of asymptomatic retinal hemorrhage occurred in a 26-year-old woman at 4,685 M on Kilimanjaro, despite receiving 500 mg naproxen (500 mg/day) for 5 days. Since this drug was also unable to prevent the extravasation of blood from retinal vessels during exercise at altitude, it is unlikely the release of prostaglandins in the retinal circulation greatly contributes to the development of high altitude retinal hemorrhage (1,6,7).

Our findings are contrasted to dexamethasone, which was reported to have prevented AMS and blocked retinal artery dilatation during hypoxia (5).

Dexamethasone may have prevented the release of 5-lipoxygenase pathway generated arachidonate metabolites such as leukotrienes (9). The leukotrienes are potent vasoactive substances which greatly facilitate edema and are implicated in the hypoxic pulmonary vasoconstrictor response and pulmonary hypertension in the neonate (9,11,28).

Until specific enzyme inhibitors of prostaglandins distal to cyclooxygenase become available, it will be difficult to delineate the precise role of endothelial-derived oxidative metabolites of arachidonic acid in regulating cerebral blood flow in man. Naproxen, 250 mg. twice daily, does not reduce the severity of AMS or alter retinal artery dilatation, supine or upright MAP, or ventilatory response to moderate hypoxemia. Therefore, this study does not suggest a major role for vasodilator prostaglandins in the pathogenesis of AMS or hypoxia-induced retinal vasodilatation, or pulmonary blood pressure responses in man.

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The results from this study do not reflect an official policy of the United States Army.

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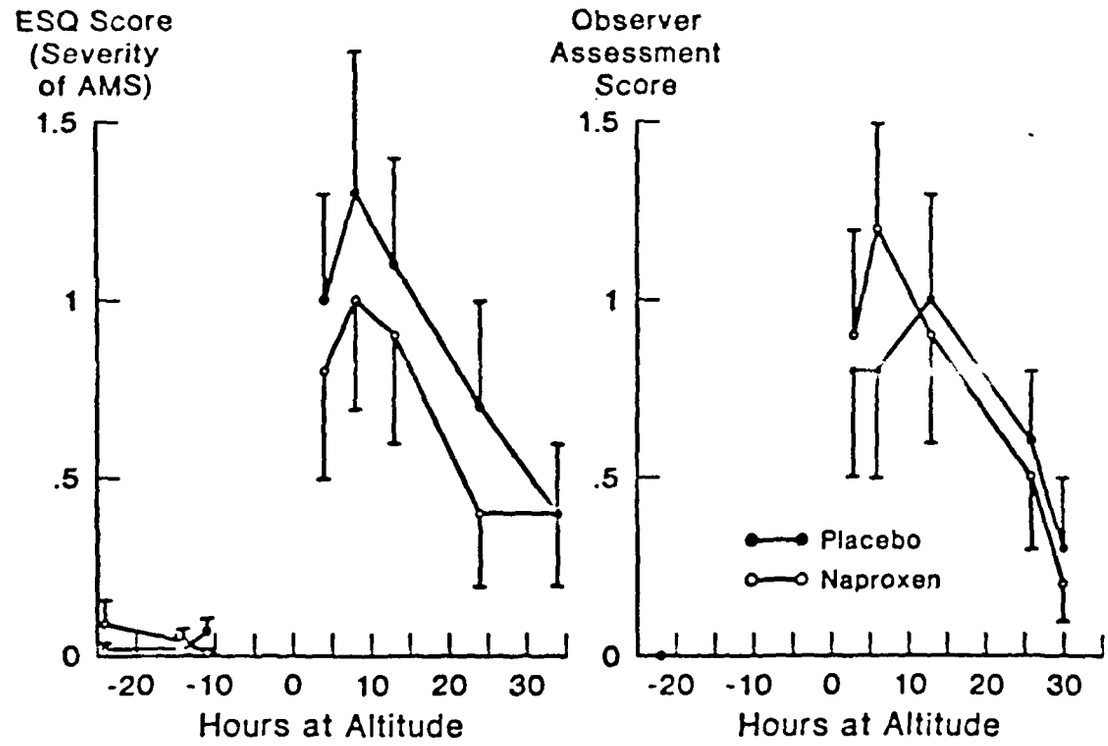
FIGURE LEGENDS

Figure 1. The severity of acute mountain sickness as assessed by Environmental Symptoms Questionnaire scores (panel A) and by independent observer (panel B). Data are expressed as means ± S.E. for 10 subjects. Hours -24 to 0 were at sea level, and hours 0-34 were at a simulated altitude of 4570 M.

Figure 2. Mean arterial blood pressures at sea level and 4570 M simulated altitude during supine (panel A) and upright (panel B). See Figure 1 for explanation of time axis and points. *$p < .05$ for comparison of sea level to altitude values.

Figure 3. The measured width of projected image of right superior temporal artery. Values represent mean ± S.E. *$p < .05$, comparison of sea level to altitude values. Hours -24 to 0 were at sea level and hours 0-34 were at a simulated altitude of 4570 M.

Figure 4. Serum naproxen levels one hour post-ingestion of 250 mg naproxen. Dose regimen was 250 mg naproxen twice daily. Values are mean ± S.E. for 11 subjects. Hours -24 to 0 were at sea level and hours 0-34 were at simulated altitude of 4570 M.


ESQ Score
(Severity
of AMS)
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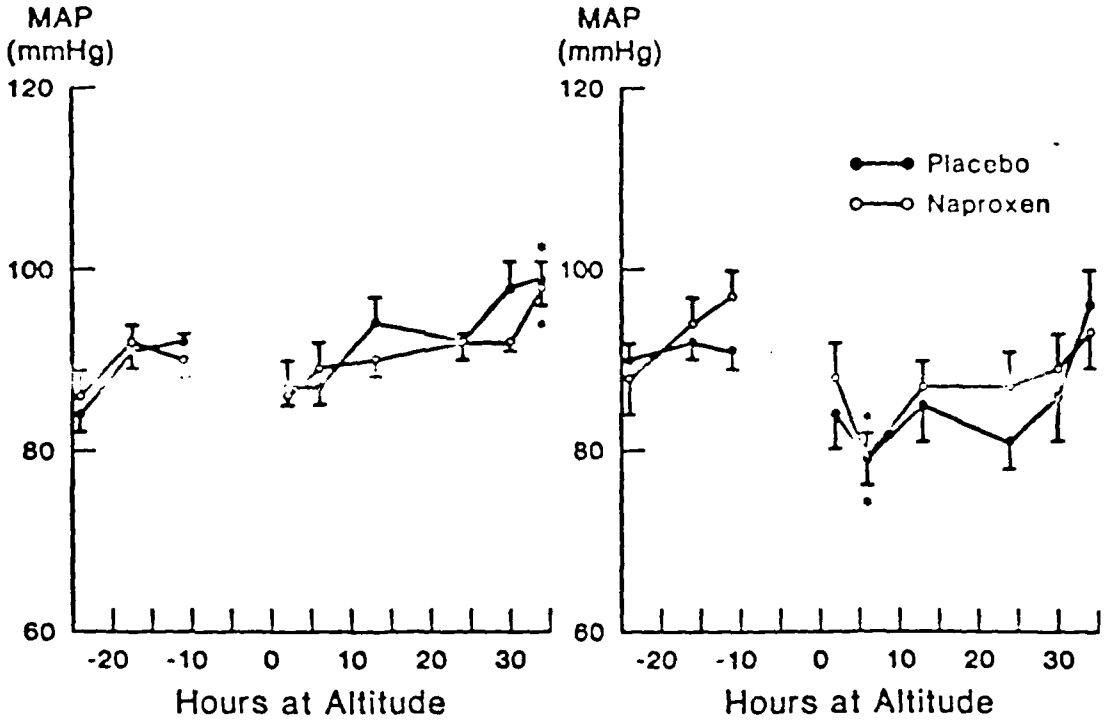
1
.5
0
-20
-10
0
10
20
30
Hours at Altitude
Observer
Assessment
Score
1.5
1
.5
0
Placebo
Naproxen
-20
-10
0
10
20
30
Hours at Altitude

Figure 1


MAP
(mmHg)
120
100
80
60
-20
-10
0
10
20
30
Hours at Altitude
MAP
(mmHg)
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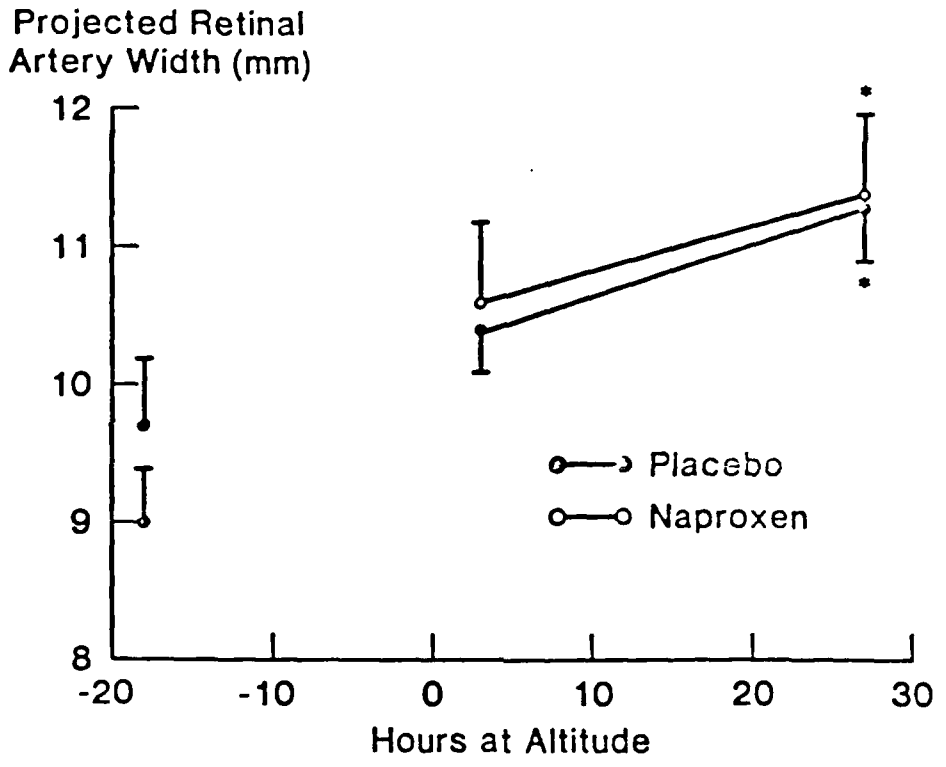
100
80
60
-20
-10
0
10
20
30
Hours at Altitude
Placebo
Naproxen

Figure 2


Projected Retinal
Artery Width (mm)
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11
10
9
8
-20
-10
0
10
20
30
Hours at Altitude
Placebo
Naproxen
*
*

Figure 3

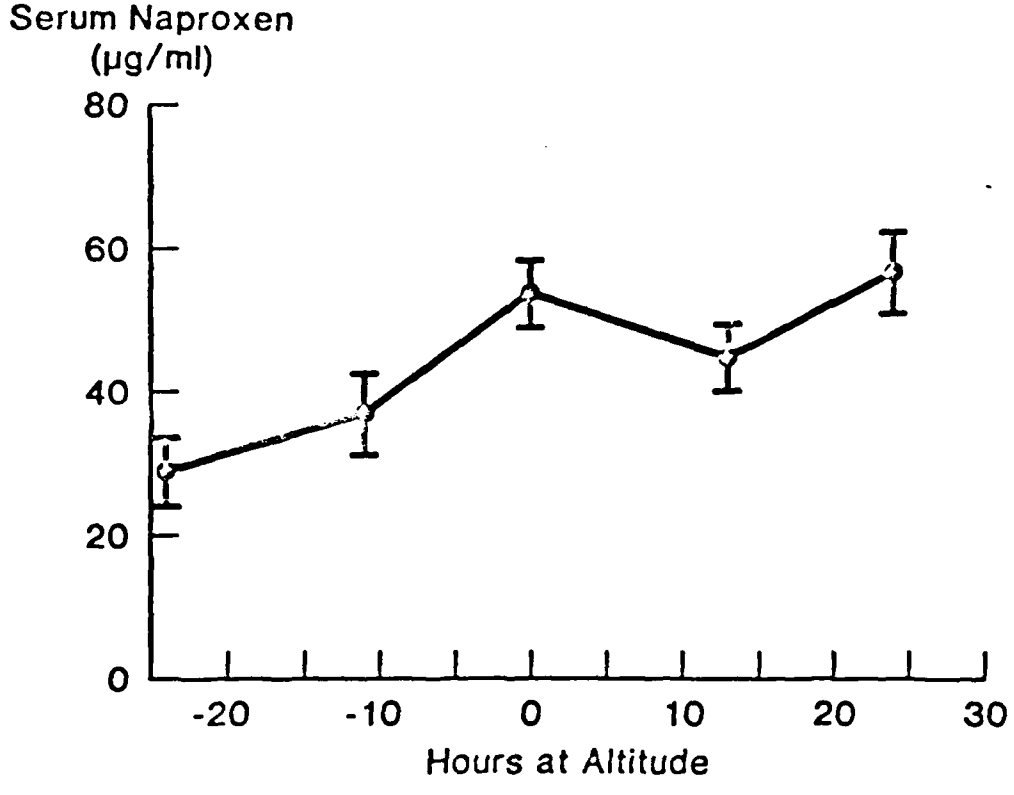
Serum Naproxen
(µg/ml)
80
60
40
20
0
-20
-10
0
10
20
30
Hours at Altitude

Figure 4