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ORIGINAL RESEARCH

Medroxyprogesterone at High Altitude. The Effects on Blood Gases, Cerebral Regional Oxygenation, and Acute Mountain Sickness

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Objective.—To study the effect of medroxyprogesterone on blood gases and cerebral regional oxygenation at high altitude, alone and in conjunction with acetazolamide, and to assess the effect on acute mountain sickness (AMS).

Design.—Two placebo-controlled trials during rapid ascent to high altitude.

Participants.—In the first trial, 20 participants, and in the second trial, 24 participants.

Setting.—During rapid ascent to 4680 m and on rapid ascent to 5200 m.

Intervention.—In the first trial, participants were randomized to receive medroxyprogesterone 30 mg or a placebo twice a day. In the second trial, participants were randomly assigned to one of 4 groups: a placebo twice daily, medroxyprogesterone 30 mg twice daily, acetazolamide 250 mg plus a placebo twice daily, or acetazolamide 250 mg plus medroxyprogesterone 30 mg twice daily.

Main Outcome Measures.—Blood gas changes and symptom scores of AMS in both trials and cerebral regional oxygen saturations in the first trial only.

Results.—Medroxyprogesterone improved peripheral oxygen saturations in both trials and improved Pa_{O_2} in combination with acetazolamide. Cerebral regional oxygen saturation was not altered by medroxyprogesterone. The reduction in symptom scores and in the extent of AMS was not significant in this limited study.

Conclusions.—Medroxyprogesterone acts as a respiratory stimulant, but the clinical benefit regarding the development of AMS was unproven at high altitude. Combined medroxyprogesterone and acetazolamide gave the best Pa_{O_2}.

Key words: acute mountain sickness, progesterone, high altitude, oxygenation, acetazolamide

Introduction

Individuals vary in their rate of acclimatization and in their susceptibility to acute mountain sickness (AMS); hence, it is difficult to set a safe rate of ascent for a group so that no one is affected by AMS.[1] Ascent profiles are also determined by transport arrangements and time constraints. As a result, prophylactic measures to prevent AMS are often required. This has led to the use of drugs such as acetazolamide, which is of proven value in the prevention of AMS[2] and has also been used in the acute treatment of AMS.[3] However, acetazolamide does not fully protect against AMS, and side effects such as paresthesias sometimes limit its application. Other drugs that have been used in the treatment of established AMS, such as nifedipine for high-altitude pulmonary edema[4] and dexamethasone for high-altitude cerebral edema,[5] have also been tried in the prevention of AMS. Nifedipine is ineffective,[6,7] and although dexamethasone is protective,[8] the potential side effects when using the recommended dose of 12 mg daily are of concern when it is used for prevention.

Acetazolamide increases ventilation at altitude, thereby increasing arterial and tissue oxygen concentrations.[2]

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This may be particularly important in persons who have poor hypoxic ventilatory responses.[9] It is possible that other respiratory stimulants would be effective, but so far, only almitrine has been reported as improving arterial oxygen saturation but also worsening periodic breathing in short-term studies at high altitude.[10] Progesterone is known to increase hypoxic ventilatory responses with an improvement in oxygen saturation and a reduction in hematocrit for persons residing at 3100 m[11] and to benefit patients with hypoventilation syndromes and sleep apnea.[12] In animals, progesterone reduces brain edema,[13] possibly by tightening the blood-brain barrier through the inhibition of Na+/K+-adenosine triphosphatase (ATPase). Progesterone has few side effects when taken in short courses. These features suggest it has potential in the prevention of AMS and would be useful in combination with acetazolamide.

The purpose of these studies was to assess the effect of medroxyprogesterone alone and in combination with acetazolamide on blood gases at altitude. We wished to assess the effect of medroxyprogesterone on cerebral regional oxygenation and in the prevention of AMS.

Methods

PILOT STUDY

An initial open pilot study was performed in Birmingham (150 m), to determine the side effects and changes in acid-base parameters of medroxyprogesterone alone, acetazolamide alone, and both drugs in combination. Five participants were given acetazolamide 500 mg daily for 7 days, followed by a 1-week washout, and then medroxyprogesterone 60 mg daily for 7 days, followed by a 1-week washout, and finally, acetazolamide 500 mg with medroxyprogesterone 60 mg daily for 7 days. Drug effects were recorded, and acid-base measurements were made on arterialized, capillary blood samples at the beginning of the study and at the end of each treatment period.

HIGH-ALTITUDE STUDY 1

Twenty healthy persons, 17 men and 3 women aged 24 to 59 years, were randomly allocated to groups on a double-blind basis that were administered an encapsulated placebo (ascorbic acid) or medroxyprogesterone 30 mg twice daily. Information on side effects was obtained prospectively each day using a structured interview. After an overnight stay at sea level (La Serena, Chile), rapid ascent in a minibus was achieved after 3 days to 2770, 3650, and 4680 m (Paso del Agua Negra).

HIGH-ALTITUDE STUDY 2

Twenty-four healthy persons, 22 men and 2 women aged 22 to 65 years, were randomly allocated to groups that were administered one of 4 treatments, with 6 persons in each group:

1. Placebo (ascorbic acid, 3 tablets of 50 mg twice daily),
2. Medroxyprogesterone (3 tablets of 10 mg twice daily),
3. Acetazolamide (250 mg twice daily) plus a placebo (3 tablets twice daily), or
4. Acetazolamide (250 mg twice daily) plus medroxyprogesterone (3 tablets of 10 mg twice daily).

The medroxyprogesterone part of the trial was double blinded and placebo controlled, while acetazolamide was an open trial. Information about drug side effects was obtained prospectively by use of a self-administered, symptoms questionnaire completed twice daily and, retrospectively, by a structured interview held on the last day of the trial. All participants flew to 1300 m (Kathmandu) and, 2 nights later, to 2800 m (Lukla). Subsequent ascent was by trekking, with overnight stops at 3440 m (Namche Bazaar), 4120 m (2 nights at Pheriche), and then 5200 m (Gorek Shep).

In both altitude studies, stratification of approximately two thirds of the participants according to previous susceptibility to AMS was performed before random allocation to treatment groups. Randomization was performed independently by the hospital pharmacy. Female participants were started on their allocated medication, medroxyprogesterone or a placebo, from the first day of their menstrual cycle prior to the drug trials and were randomly allocated to groups so that at least 1 participant was in the active medroxyprogesterone group. Compliance with assigned therapy was assessed by counting unused tablets.

Symptoms of AMS were recorded using the Lake Louise self-reporting AMS questionnaire twice daily.[14] A score of 3 or more at any one time indicated significant AMS. In study 1, the scores from 7 participants who completed questionnaires, starting from their arrival at 2770 m until the second evening at 4680 m, were used to calculate a total AMS score. In study 2, the scores from 10 participants who completed questionnaires, starting from their arrival at 3440 m until the second morning at 5200 m, were used to calculate a similar total score. In both studies, participants were interviewed each day by 2 physicians experienced in high-altitude medicine. As necessary, participants were withdrawn from the drug trial and given acetazolamide according to clinical indications. One participant in study

Table 1. Acid-base data for the pilot study (mean and SD)

Pilot study	*pH*	*$PaCO_2$, kPa*	*HCO_3, mmol/L*
Baseline (no drugs)	7.4116 (0.22)	5.32 (0.24)	24.9 (1.05)
Medroxyprogesterone	7.4314 (0.028)	4.5 (0.27)†	23.9 (1.6)
Acetazolamide	7.3596 (0.037)*	4.51 (0.15)†	20.6 (2.2)*
Medroxyprogesterone plus acetazolamide	7.3747 (0.036)*	3.89 (0.18)†‡	20.2 (1.7)*

†$P < .001$ compared with baseline.
*$P < .05$.
‡$P < .001$ compared with acetaxolamide alone.

1 required additional dexamethasone on the second day at 4680 m. Results from these participants have been included in the original randomized groups on an intention-to-treat basis.

BLOOD GASES

In study 1, blood gases were measured on arterialized capillary samples using a Medical Analyzer (model 348; Chiron Diagnostics, Emeryville, CA) at 2770 and 4680 m, and oxygen saturation in blood and heart rate were measured at 1-minute intervals at all altitudes using a digital pulse oximeter (Ohmeda 3770; BOC Group, Hatfield, UK). In study 2, blood gases were measured on arterialized capillary samples using a Corning Blood Gas Analyzer (model 238; Ciba Corning, Medford, MA) at 3440, 4120, and 5200 m.

CEREBRAL REGIONAL OXYGENATION

In study 1, cerebral regional oxygen saturations were measured using near-infrared spectroscopy (Critikon 2020; Johnson & Johnson Medical Ltd, Ascot, UK).[15] Cerebral regional oxygenation was calculated using [HbO_2 ÷ total Hb]·100.

STATISTICS

Significant differences in oxygen saturations and blood gas data were determined by repeated-measures analysis of variance. Significant differences among the 4 treatment groups in study 2 were determined by 2-way analysis of variance using repeated measures.[16] Other differences were determined by the Student's *t* test. *P*-values $<.05$ were considered significant.

Ethical approval was given by the Research Ethics Committee of the South Birmingham Health Authority, and permission to use medroxyprogesterone was given by the Department of Health Medicines Control agency. Participants gave informed consent.

Results

PILOT STUDY

All participants noted mild hyperventilation on medroxyprogesterone, particularly when combined with acetazolamide, but there were no other side effects. $PaCO_2$ was reduced to a similar extent by both acetazolamide and medroxyprogesterone, and a combination of the 2 drugs gave an additive effect (Table 1). pH was not significantly changed on medroxyprogesterone, but it decreased on acetazolamide and remained reduced when the 2 drugs were combined.

HIGH-ALTITUDE STUDY 1

All participants had some symptoms of AMS, and 7 of the 10 participants on medroxyprogesterone compared with 9 of the 10 participants on the placebo achieved a score of 3 or more on at least one questionnaire at high altitude. Total AMS scores for the 4 days at altitude were not significantly different for participants on medroxyprogesterone (mean, 16.0; SD, 9.2) compared with those on the placebo (mean, 20.7; SD, 8.8). Mean peripheral oxygen saturations were higher throughout the study for participants on medroxyprogesterone ($P = .049$), but cerebral regional oxygen saturations were not different (Figure 1). PaO_2 levels were not measured because of equipment failure. End tidal CO_2 was significantly reduced throughout the study for participants on medroxyprogesterone ($P < .001$) (Figure 2).

$PaCO_2$ was significantly reduced at 2770 m for participants on medroxyprogesterone (mean, 3.96 kPa; SD, 0.3) when compared to the placebo group (mean, 4.31 kPa; SD, 0.27; $P < .05$) but was not significantly different at 4680 m (mean, 3.58; SD, 0.37, compared with mean, 3.75; SD, 0.18, respectively). At both altitudes, arterial pH values were not different between the 2 groups (mean, 7.468; SD, 0.035, compared with mean, 7.483; SD, 0.035, respectively).

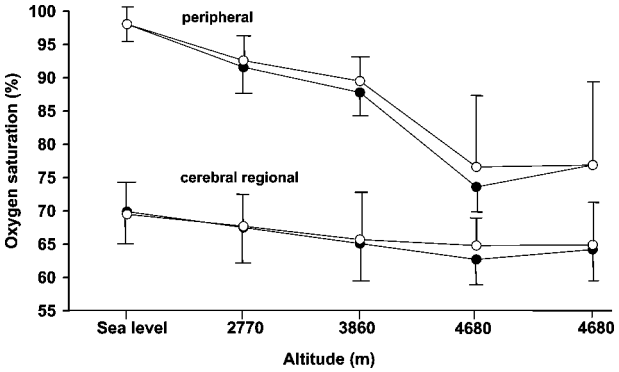

Figure 1. Peripheral oxygen saturation (top 2 lines) and cerebral regional oxygenation (bottom 2 lines) before and during ascent to high altitude. Measurements were made at daily intervals after an overnight stay at that altitude. A second measurement was made after an additional 24 hours at 4680 m. Means (SD) of 10 participants on the placebo (●) and 10 participants on medroxyprogesterone (o). Peripheral oxygen was greater for participants on medroxyprogesterone ($P = .049$). Cerebral regional oxygenation was not significantly different for participants on medroxyprogesterone.

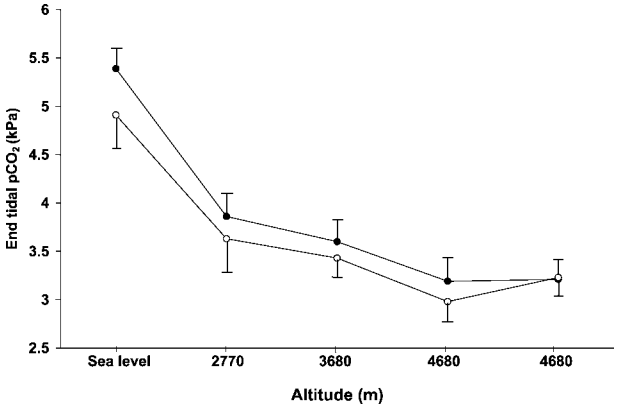

Figure 2. End tidal P_{CO_2} before and during ascent to high altitude. Measurements were made at daily intervals after an overnight stay at that altitude. A second measurement was made after an additional 24 hours at 4680 m. Means (SD) of 10 participants on the placebo (●) and 10 participants on medroxyprogesterone (o) were significantly different ($P < .001$).

HIGH-ALTITUDE STUDY 2

All participants had some symptoms of AMS. All of the participants on the placebo, 3 of the 6 participants on medroxyprogesterone, 3 of the 5 participants on acetazolamide, and 4 of the 6 participants on the combination of drugs achieved an AMS score of 3 or more on at least one questionnaire at high altitude. Total AMS scores were not significantly lower on medroxyprogesterone (16.2; SD, 16.3) or acetazolamide (26.3; SD, 16.0) or on the combination of the 2 drugs (17.0; SD, 8.0) when compared with the placebo (28.3; SD, 11.4). As clinically indicated, 4 participants were withdrawn from the drug trial at 4120 m; 1 participant taking the placebo and 2 participants taking medroxyprogesterone were started on acetazolamide and continued ascent, and 1 participant taking acetazolamide descended with an unrelated illness that has been described elsewhere.[17]

There was an overall difference in Pa_{O_2} among the 4 treatment groups ($F = 5.05$, $P < .01$) (Table 2). Pa_{O_2} was higher for participants on the combined therapy than for those on the placebo ($F = 8.48$, $P < .02$) but not for participants on medroxyprogesterone or acetazolamide alone. There was an overall difference in Pa_{CO_2} among the 4 treatment groups ($F = 10.02$, $P < .01$); both medroxyprogesterone and acetazolamide reduced Pa_{CO_2} ($F = 10.24$, $P < .01$). Pa_{CO_2} for participants on combined therapy was lower than for those on acetazolamide alone ($F = 9.43$, $P < .01$). There was an overall difference in plasma bicarbonate among the 4 treatment groups ($F = 8.79$, $P < .01$); both medroxyprogesterone and acetazolamide lowered plasma bicarbonate when compared with placebo ($F = 13.7$, $P < .01$). Plasma bicarbonate for participants on combined therapy was not different from plasma bicarbonate for those on acetazolamide alone. pH was reduced for participants on acetazolamide alone and on combined therapy ($P < .05$) but was not significantly different from pH for those on medroxyprogesterone when compared with placebo.

DRUG SIDE EFFECTS AND COMPLIANCE

In study 1, medroxyprogesterone was well tolerated, and at the end of the trial, none of the male participants was able to indicate whether he was taking the active medication. Peripheral edema was detected in the same number of participants on medroxyprogesterone and the placebo. Compliance with allocated therapy was 86% for the placebo and 93% for medroxyprogesterone.

In study 2, all participants on acetazolamide reported slight-to-moderate paresthesias; in 7 participants, it was intermittent throughout the study, and in 5 participants, it tended to ameliorate at higher altitudes. Two participants on the placebo reported paresthesias, but none of the participants on medroxyprogesterone alone reported paresthesias. The severity and pattern of paresthesias were identical to those for the participants on combined therapy when compared with those on acetazolamide alone. Four participants, 2 on medroxyprogesterone alone and 2 on combined therapy, reported the sensation of deeper breathing or hyperventilation at rest. There was no evidence that medroxyprogesterone alone or in combination was associated with any increase in periph-

Table 2. Blood gas data in high-altitude study 2 (mean and SD for each group on each of the test dates)*

	Blood gases, altitude (m)			
	Day 2, 2660	*Day 4, 3440*	*Day 6, 4120*	*Day 8, 5200*
PaO_2, kPa				
Placebo	7.27 (0.41)	6.160 (0.59)	5.63 (0.65)	4.71 (0.43)
Medroxyprogesterone	6.93 (0.43)	6.2 (0.44)	5.57 (0.36)	5.07 (0.4)
Acetazolamide	7.17 (0.51)	6.49 (0.11)	6.17 (0.76)	4.91 (0.43)
Az + Mp†	7.77 (0.52)	6.93 (0.31)	6.09 (0.4)	5.37 (0.41)
H^+ion, nmol/L				
Placebo	7.483 (0.01)	7.475 (0.019)	7.483 (0.038)	7.453 (0.044)
Medroxyprogesterone	7.478 (0.035)	7.478 (0.023)	7.477 (0.019)	7.473 (0.043)
Acetazolamide	7.428 (0.017)	7.418 (0.033)	7.427 (0.039)	7.427 (0.035)
Az + Mp	7.46 (0.018)	7.442 (0.021)	7.457 (0.018)	7.423 (0.018)
$PaCO_2$, kPa				
Placebo	4.83 (0.6)	3.67 (0.32)	3.29 (0.36)	3.16 (0.83)
Medroxyprogesterone	4.09 (0.48)	3.11 (0.29)	3.07 (0.13)	2.49 (0.2)
Acetazolamide	4.37 (0.58)	3.09 (0.25)	3.04 (0.36)	2.8 (0.53)
Az + Mp	4.04 (0.31)	2.77 (0.27)	2.53 (0.19)	2.11 (0.23)
HCO_3, mmol/L				
Placebo	28.4 (2.0)	23.3 (0.7)	22.3 (1.6)	20.3 (1.5)
Medroxyprogesterone	25.3 (1.8)	21.5 (0.7)	21.0 (1.1)	19.2 (2.1)
Acetazolamide	23.6 (2.3)	19.0 (1.4)	19.0 (1.5)	18.4 (2.9)
Az + Mp	24.2 (0.7)	18.9 (1.2)	18.8 (0.9)	16.1 (1.0)

*PaO_2 was higher in participants on combined therapy ($P < .02$); pH was reduced in participants on acetazolamide and on combined therapy ($P < .05$). $PaCO_2$ was reduced in participants on medroxyprogesterone and acetazolamide ($P < .01$) and was further reduced in participants on combined therapy ($P < .01$).

†Az + Mp indicates acetazolamide plus medroxyprogesterone.

eral edema. Loss of libido was reported by 1 participant assigned to the placebo group and by 1 participant on combined therapy. Minor breakthrough vaginal bleeding occurred in the 1 female participant on medroxyprogesterone. Compliance with allocated therapy was 99% for the placebo, 98% for medroxyprogesterone, and 98% for acetazolamide.

Discussion

Medroxyprogesterone did not prevent AMS as defined by a Lake Louise score of 3 or more in the small numbers studied. In both studies, although there was a trend toward lower AMS scores on medroxyprogesterone and more participants had no AMS (score, <3) on medroxyprogesterone than on the placebo or acetazolamide, the differences were not significant. It is possible that a more sensitive scoring system than the Lake Louise questionnaire is required,[18] as our own modified environmental system questionnaire showed greater differences among the treatment groups in study 2 (data not shown); however, this was not used in study 1. A formal combination of the results of the 2 high-altitude studies was not possible because the rate of ascent and the amount of exercise were different. Larger numbers of participants are required to overcome the variable susceptibility to AMS. Ideally, a crossover study should be performed using participants as their own controls in order to prove the efficacy of medroxyprogesterone, but acclimatization would introduce another variable.

Progesterone stimulates an estrogen-dependent receptor at hypothalamic sites and influences the respiratory center via a neural pathway.[19] Progesterone also stimulates peripheral chemoreceptors.[20] Our studies confirmed the expected effect of a reduction in $PaCO_2$ and an improvement in peripheral oxygen saturation. The failure to show an improvement in cerebral regional oxygenation may have been due to the small effects observed, but it is also possible that the effect of a fall in carbon dioxide reduced cerebral blood flow and offset any improvement in peripheral oxygen saturation. Although we assumed that the small clinical effects of medroxyprogesterone were due to increased oxygenation, it is pos-

sible that other effects such as the inhibition of Na+/K+-ATPase are important.

The side effect profile for medroxyprogesterone was acceptable and better than that for acetazolamide. Suppression of plasma gonadotrophins and testosterone was noted with these high doses of medroxyprogesterone in the pilot study but with no immediate clinical effect. The time course of these altitude studies was similar to that of the pilot study. Medroxyprogesterone in female participants, however, was difficult to use and required confirmation that the woman was not pregnant as well as the initiation of therapy at the onset of menstruation. It also risked some breakthrough uterine bleeding.

These studies used pharmacologic doses of medroxyprogesterone, which may have effects different from physiologic levels of progesterone.[21] Women have been variously described as protected,[22,23] equally susceptible,[24] or at greater risk[25] of acquiring AMS when compared with men. However, studies have not always been limited to the luteal phase of the menstrual cycle. Whether the high concentrations of progesterone occurring during pregnancy or the relatively lower doses of progesterone used in contraceptive preparations are beneficial remains unknown. The role of progesterone in the treatment of the severe forms of AMS has not been assessed, but it is unlikely to be effective as monotherapy, given the modest effects seen in our studies.

Conclusions

In conclusion, the improvement in peripheral oxygenation on medroxyprogesterone was small and was not detected in cerebral regional oxygenation. Larger numbers of participants would be required to demonstrate a reduction in AMS scores and the prevention of AMS. The practical difficulties of using this drug in female participants preclude this.

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