

The Use of Dexamethasone in Support of High-Altitude Ground Operations and Physical Performance: Review of the Literature

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ABSTRACT

Objective: Military Special Operators (SOs) are exposed environmental conditions that can alter judgment and physical performance: uneven terrain, dryness of ambient air, reduction of air density, and a diminished partial pressure of oxygen. The primary purpose of this review was to determine the medical efficacy of dexamethasone as an intervention for the prevention and treatment of high-altitude illness. The secondary purpose was to determine its ability to maintain physical performance of SOs at high altitudes. **Methods:** A search of the literature from 1970 to 2014 was performed, locating 61 relevant articles, with 43 addressing the primary and secondary purposes of this literature review. **Conclusions:** The review indicates that dexamethasone is an effective prevention and treatment intervention for high-altitude illness. Commonly used dosages of either 2mg every 6 hours or 4mg every 12 hours can prevent high-altitude illnesses in adults. Currently in USSOCOM operations, there is an option to use 4mg every 6 hours (concurrently with acetazolamide 125mg bid) if ascending rapidly to or above 11,500 ft without time for acclimatization. Researchers also determined that acute exposure to high altitude, even in asymptomatic subjects, resulted in small cognitive deficits that could be reversed with dexamethasone. Dexamethasone may also help improve cognition and maximal aerobic capacity in SOs who are susceptible to high-altitude pulmonary edema.

KEYWORDS: *high altitude, mountain, performance, strength, endurance, physical, military, Special Operations*

Introduction

Special Operators (SOs)–Special Operations Forces (SOF) members of all branches—are routinely exposed to a variety of environmental conditions that can alter judgment and physical performance, potentially affecting mission success. These situations are further exacerbated by the hazardous conditions experienced when ascending to

high altitudes such as an increase in the dryness of ambient air, reduction of air density, and a diminished partial pressure of oxygen.

Although individual physiological responses to altitude and acclimatization rates vary dramatically, the physiological effect of hypobaric high-altitude hypoxia (HHH) is ubiquitous.^{1,2} Symptoms of less severe cases of HHH, occurring within 6 to 24 hours of arrival at altitude, may include irritability, physical weakness, decreased appetite, tachycardia, insomnia, dizziness, nausea, headache, and peripheral edema.³⁻⁶ More severe cases of HHH may result in acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). Although AMS is short lived and normally subsides within 2 to 7 days, HAPE and HACE are potentially fatal if not treated immediately by trained personnel.^{1,7} Two key physiological mechanisms exist regarding the oxygen transport system and altitude acclimatization: (1) there is a reduction in the delivery of oxygen to the exercising muscles due to changes in peak blood flow and/or distribution of the amount of blood ejected from the right ventricle of the heart every minute, and (2) there is an alteration in the diffusion or utilization of oxygen by the active skeletal muscles.

A literature review was performed using the following sources: PubMed, Defense Technical Information Center, the Cochran Library, and the Franzello Aeromedical Library. Search parameters were limited to publications from 1970 to 2014 using the following keywords alone or in combination: *dexamethasone, high altitude, mountain, strength, endurance, physical, military, special operations, acute mountain sickness (AMS) treatment, high-altitude pulmonary edema (HAPE) treatment, and high-altitude cerebral edema (HACE)*. This review identified 61 articles; 43 were pertinent for further analysis. Each of these 43 studies was analyzed and included in the dexamethasone review matrix and assigned a

Strength of Recommendations Taxonomy (SORT) grade based on its individual study quality.⁸ On review, the studies were divided into four categories and given an overall SORT category grade.

The primary purpose of this literature review was to determine the medical efficacy of dexamethasone as an intervention for the prevention and treatment of high-altitude illness. The secondary purpose of this literature review was to determine the state of knowledge on the effects of dexamethasone on improving physical/cognitive performance at high altitude.

Physical Performance Decrements in SOs at High Altitude

Special Operators are an elite group, physically and mentally trained to overcome the worst possible conditions and battlefield scenarios, continuously pushing the human body to its limits. The physical prowess of SOs has been compared to elite athletes. Nonetheless, this elite group of Warfighters will begin to experience decrements in physical performance at altitudes above 5000 feet. Typically, SOs do not have adequate time to preacclimatize to altitude prior to a mission.

The increases in physical activity, altitude, and recruited muscle mass lead to an inversely proportional reduction in physical performance.⁹ Additionally, physiological responses to acute high-altitude exposure adversely affect submaximal aerobic endurance performance, potentially compromising mission success. This phenomenon is illustrated by increases in blood lactate levels and ratings of perceived exertion and decreases in stored muscle glycogen.^{3,10,11} Furthermore, environmental conditions such as low barometric pressure, low air density, and dry ambient air cause significant tissue hypoxia and loss of moisture in ventilator passageways and negatively affect normal breathing mechanics.^{12,13} Combined, these environmental variables lead to an increase in the amount of effort required to achieve effective pulmonary respiration.¹⁴ Without preacclimatization, the capacity of the operator to perform heavy work on varying terrain can significantly diminish physical work.^{10,14}

There are a number of prophylactic drugs that have been found to prevent or reduce HAPE and AMS. Currently, the most widely used and accepted of these drugs is acetazolamide, which can cause unwanted side-effects.^{15,16} Dexamethasone has been found to be equally effective as acetazolamide in reducing AMS symptoms up to 70% versus a placebo following 9 hours of hypoxia.¹⁷ Dexamethasone also proved superior to tadalafil, a phosphodiesterase-5 inhibitor that is another commonly used drug to treat AMS, in preventing AMS by 50% and in reducing the incidence of HAPE by 78%.¹⁸ Dexamethasone

was equally effective as budesonide, a glucocorticoid similar to dexamethasone.¹⁹

Pharmacological Acclimatization Techniques: Acclimatization With Dexamethasone

Dexamethasone is a potent glucocorticoid. It has a long history of treating cerebral edema derived from multiple etiologies. It is also used as a potent antiemetic for cancer chemotherapy patients. Several studies (Table 1) show that dexamethasone is an effective and reliable form of treatment for AMS, HACE, and HAPE. Although the specific mechanism of action is not fully known and under investigation, there is strong evidence that dexamethasone may prevent the onset of HAPE.^{2,19-21} Common dexamethasone dosages to prevent AMS for adults ascending to altitude are either 2mg every 6 hours or 4mg every 12 hours. For SOs who routinely deploy to altitudes exceeding 11,000 feet, a “very high” dose of 4mg taken every 6 hours may be appropriate. Nonetheless, this particular dosage should not exceed 10 consecutive days of use.^{2,5} A group of researchers, using AMS as an end point, tested dexamethasone in eight trials with exposure above 13,000 feet. The researchers reported that a dosage range of 8 to 16mg/day was a more efficacious prophylactic treatment for AMS than placebo and was especially worthwhile when ascent rate was high.⁴

Regarding the potential for side-effects, we must remember that the duration of the majority of ground operations where dexamethasone might be considered for prophylaxis will be a few days or less. There are two possible side-effects that are those most often touched on in such discussions. First, the possible side-effect of aseptic bone necrosis has usually been associated with the long-term use of dexamethasone over a period of 3 months or longer. The second is the possible side-effect of insomnia and daytime “energetic hyperness” with eventual performance decrement due to lack of sleep. Currently, that seems to occur to the point of making dexamethasone unusable in about one of every five to 10 individuals. To prevent this possible side-effect from affecting a real-world mission, unit members can have a trial of dexamethasone prior to using it on an actual Operation. Last, like all medications, there is a possibility in a minority of individuals of an allergic reaction, interactions with other medications (in this population, none are usually being taken), as well as gastrointestinal upset and others—the usual list associated with all drugs. Again, a trial of dexamethasone will reveal whether most of these side-effects are an issue in an individual Operator.

Cognitive deficits can be observed during the first few hours at high altitude for otherwise asymptomatic subjects. This is possibly a result of cerebral edema secondary to an increase in the permeability of cerebral vessels.

Table 1 Summary of Selected Dexamethasone High-Altitude Research Studies

Author	Subject Description	Subjects	Dexamethasone Dosage	Key Results
Ellsworth et al., 1991 ²³	Healthy climbers	Dexamethasone (<i>n</i> = 10) Acetazolamide (<i>n</i> = 10) Control (<i>n</i> = 9)	4mg every 8 h beginning 24 h prior to climb until descent	Dexamethasone decreased the occurrence of AMS and severity of symptoms (<i>p</i> = .025).
Maggiorini et al., 2006 ²⁰	Adults prone to HAPE	Dexamethasone (<i>n</i> = 10) Tadalafil (<i>n</i> = 10) Control (<i>n</i> = 9)	8mg twice daily starting the day before the ascent to 4559m throughout the 2-day study	Dexamethasone reduced the risk of developing HAPE (<i>p</i> < .001) and reduced the occurrence of AMS (<i>p</i> = 0.02).
Levine et al. 1989 ²⁴	Healthy adults	Dexamethasone (<i>n</i> = 5) Control (<i>n</i> = 5)	4mg every 6 h during a chamber flight to 12,100 ft	Dexamethasone decreased the occurrence of AMS and severity of symptoms (<i>p</i> = 0.005).
Fischler et al., 2009 ²⁵	Adults prone to HAPE	Dexamethasone (<i>n</i> = 8) Tadalafil (<i>n</i> = 7) Control (<i>n</i> = 8)	8mg twice daily starting the day before the ascent to 4559m throughout the 2-day study	Dexamethasone improved $\text{VO}_2\text{-max}$ (<i>p</i> < .05) and oxygen kinetics (<i>p</i> < .05) and reduced ventilator equivalent for CO_2 (<i>p</i> < .01); no significant difference in peak O_2 saturation between groups.
Siebenmann et al., 2011 ²⁶	Adults prone to HAPE	Dexamethasone (<i>n</i> = 10) Control (<i>n</i> = 14)	8mg twice daily starting the day before the ascent to 4559m	Dexamethasone improved $\text{VO}_2\text{-max}$ (<i>p</i> = .025); no significant difference existed in arterial O_2 saturation during maximal exercise.
LeFleur et al., 2003 ²²	Adults prone to HAPE	Dexamethasone (<i>n</i> = 6)	4mg given twice each prior to ascent of 4800m	Dexamethasone decreased the cognitive deficits in participants who were pretreated.

However, researchers discovered that subjects' ability to perform certain tasks after acute exposure to high altitude improved after pretreatment with dexamethasone. These researchers also determined that acute exposure to high altitude, in even asymptomatic subjects, resulted in small cognitive deficits that could be reversed with dexamethasone treatment. It is generally accepted in the scientific literature that dexamethasone can reduce the abnormal leakiness of the blood-brain barrier, thereby resulting in improved cognition.²²

Effects of Dexamethasone on Cognitive and Physical Performance at Altitude

Past studies suggest dexamethasone may be useful in improving maximal aerobic capacity of special operators susceptible to HAPE. For example, Siebenmann and colleagues²⁶ found improvements in maximal aerobic exercise in HAPE-susceptible subjects at 14,000 feet. In their study, maximal aerobic capacity was evaluated on a cycle ergometer at an altitude of 1600 feet and 24 hours after rapid ascent to 14,000 feet. Subjects were divided into a control group (*n* = 14) and a dexamethasone group (*n* = 10). The control group performed both tests without dexamethasone. The dexamethasone group received 8mg twice a day starting 24 hours prior to ascent. Researchers showed that dexamethasone prophylaxis increased maximal aerobic capacity of HAPE-susceptible subjects after the first night at 14,000 feet without affecting oxygen

saturation levels at maximal exercise. Also, treatments prior to hypoxic exposure reduced pulmonary arterial resistance and increased alveolar fluid clearance.²⁶

Fischler and colleagues²⁵ conducted a study on 29 mountaineers with a history of HAPE. Subjects were randomized to tadalafil 10mg twice daily, dexamethasone 8mg twice daily, or placebo a day before descent to 14,000 feet. Baseline maximal oxygen uptake measurements were performed at low and high altitudes (14,000 feet). Dexamethasone increased maximal aerobic capacity compared with placebo. Pulse oximeter oxygen saturation at rest was significantly lower with both dexamethasone and tadalafil compared to placebo (both *p* < .05). However, heart rate significantly increased in all groups but was substantially lower in the dexamethasone group compared to the other study groups (*p* < .01 vs. placebo and tadalafil). There were no statistically significant differences in AMS scores between the three groups on day 1. However, there was a statistically significant difference in the dexamethasone group on day 2 (*p* < .01). Dexamethasone improved maximal aerobic capacity and oxygen uptake kinetics while also reducing hypoxia-induced pulmonary hypertension in HAPE-susceptible subjects at 14,000 feet. Conversely, tadalafil did not significantly improve maximal aerobic exercise capacity. Tadalafil also showed a limited ability to reduce hypoxia-induced pulmonary hypertension. The possible mechanisms contributing to an improved exercise

capacity in the HAPE-susceptible subjects of this study may have included the following: (1) enhanced nitric oxide availability, contributing to lowered pulmonary artery pressure; (2) stimulation of alveolar sodium and water clearance, potentially improving oxygen diffusion; (3) activation of the sympathetic nervous system by acute hypoxia, leading to an increase in blood pressure, heart rate, and pulmonary vascular resistance; and (4) lowered levels of an anti-inflammatory C-reactive protein. If used appropriately, at the very minimum, dexamethasone could have an inhibitory effect on the sympathetic nervous system, resulting in a decrease in heart rate, pulmonary vascular resistance, and ventilatory rates.²⁵

Ellsworth and colleagues²³ examined the effects of acetazolamide or dexamethasone use versus placebo to prevent AMS in 18 climbers ascending to an elevation of 14,409 feet. The climbers' ascents were scheduled 2 weeks apart using a random numbers table. In this double-blind crossover study, dosage regimens consisted of either dexamethasone 4mg, acetazolamide 250mg, or lactose placebo every 8 hours starting 24 hours before the start of each climb and continuing until descent from the highest point. Dexamethasone was effective in reducing the incidence of AMS during rapid ascent for all subjects. Also, for the dexamethasone only group, the overall rate of AMS was significantly lowered and the severity of AMS symptoms was decreased by an estimated 63%. Possible contributory mechanisms to this phenomenon may include improvements in microcirculatory integrity, reductions in cerebral blood flow, or cerebral vasoconstriction.²³

Maggiorini et al.²⁰ determined whether tadalafil or dexamethasone reduced the severity of HAPE or HACE in a double-blind trial on 29 adult mountaineers with a history of HAPE. The researchers reported that dexamethasone has the ability to stimulate sodium and water reabsorption while also increasing the release of nitric oxide. These physiological responses were attributed to overall pulmonary vasodilation.²⁰ Study subjects were randomly assigned to receive prophylactic dexamethasone 8mg, tadalafil 10mg, or placebo during a 24-hour ascent and 2-day stay at 14,900 feet. Both tadalafil and dexamethasone were given 24 hours prior to the subjects' rapid ascent. This was done to mitigate the risk of developing AMS as well as to reduce its overall incidence. In particular, at 14,900 feet, there were lower levels of systolic pulmonary pressure increases in subjects receiving dexamethasone. Hence, the researchers reported that dexamethasone could be a viable prophylactic choice prior to and during ascent to high altitudes.

LaFleur and colleagues²² studied the effects of dexamethasone on improving the ability of participants to perform various computerized psychomotor and cognitive tests. Six healthy adults (four men and two women) aged 26

to 51 completed three tests previously used as part of the Automated Performance Test System to investigate the cognitive effects of exposure to high altitude. During a 4-day period, participants were acclimatized to an altitude of 12,139 feet. During the fifth day, participants ascended to 15,748 feet and predexamethasone testing was administered. None of the participants reported symptoms of frank altitude illness at 15,748 feet. To reduce acclimatization, participants descended to 12,139 feet within 4 hours. The first dose (4mg) of dexamethasone was given in the evening of day 5 and the second 4mg dose was given the following morning. Participants then ascended back to 15,748 feet, where post-testing was completed. The result was reduced susceptibility to altitude illness and improved cognition in those participants who were pretreated with dexamethasone.

In addition to the cognitive and pulmonary benefits of dexamethasone, physical performance may be improved as well. Following a double-blind placebo-controlled randomized crossover designed study, Casuso et al.²⁷ found that subjects ($n = 17$) at low altitudes who ingested 2×2 mg dexamethasone versus placebo for 5 consecutive days saw increased high-intensity one-legged kicking time to exhaustion $29 \pm 35\%$ longer and 20m shuttle run $19 \pm 23\%$ farther performances compared with a placebo. These high-intensity performance improvements would be paramount to the short-term and long-term survivability of SO forces in the field in addition to the other physiological benefits offered by dexamethasone.

Conclusions and Recommendations

Dexamethasone is effective in the prevention and treatment of AMS, HAPE, and HACE and can be lifesaving by effectively reversing physical symptoms that occur at high altitudes. This may allow SOs to sustain physical and cognitive performance while at altitude. The literature points to several different etiological mechanisms related to improvements in performance while at altitude. Maggiorini notes that dexamethasone reduces systolic pulmonary artery pressure, while others have suggested an increase in maximal cardiac output and improved pulmonary diffusion.^{20,25,26} Additionally, these mechanisms may contribute to increased oxygen transport to working skeletal muscle tissues.²⁶

For those choosing to use dexamethasone, caution is warranted. Healthy subjects who naturally perform well at altitude should not take dexamethasone as an "ergogenic aid" to go higher and/or faster. Also, overconfidence in the drug's overall performance can lead to a poor risk assessment when preplanning for high-altitude exposure.²⁸ Furthermore, the use of dexamethasone as a prophylactic agent should be considered as an option per the US Special Operations Command guidance for

SO Forces that states, “Consider pretreatment if rapid ascent above 11,500 ft. occurs (as with airlifts): A. Dexamethasone (Decadron) 4mg PO q [every] 6 hr. within 24 hours of ascent plus acetazolamide (Diamox) 125mg PO bid [twice per day] (if not allergic to sulfa).”²⁹ This would address those personnel who may not have the time to acclimate to altitude.

Studies examining the effects of prophylactic administration of dexamethasone on physical performance at altitude are limited. However, dexamethasone has been shown to improve maximal aerobic capacity after rapid ascent to high altitudes (10,000–14,000 feet), especially in HAPE-susceptible subjects.^{20,25,26} Future research should also consider non-HAPE-susceptible subjects to determine physiological mechanisms that contribute to improved physical performance while at altitude.

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