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The Use of Dexamethasone in Support of High-Altitude Ground Operations: Review of the Literature & Current Training of U.S. Special Operations Medical Members

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1.0 SUMMARY

Traditional altitude acclimatization is not always possible for military special forces. Therefore, pharmacologic prophylaxis is advantageous to reduce the risk of relevant high-altitude illnesses. This article reviews the effectiveness of dexamethasone on physical performance and discusses the option of using dexamethasone as prophylaxis at high altitude. We performed a literature search for 1991-2011 to identify research on dexamethasone use at high altitude. We also conducted interviews at special operations (SO) training sites for flight surgeons (FSs) and medics to assess current training in high-altitude ground operations. Past research has indicated that dexamethasone is an effective form of treatment for altitude illnesses. Also, there is U.S. Special Operations Command (USSOCOM) guidance for the use of dexamethasone as an option for prophylaxis in certain situations. Teaching in this topic is not uniform at SOFS and medics training sites, nor is formal curriculum training for all military branches uniform on dexamethasone use as a prophylaxis for high-altitude illnesses. We recommend uniform, formal Air Force, Navy, and Army curriculum training in high-altitude ground operations to include the current USSOCOM guidance in the limited use of dexamethasone as prophylaxis to prevent high-altitude illnesses be conducted during each military branch's FS and SO medics courses.

2.0 INTRODUCTION

Special forces (SF) operators are routinely exposed to a variety of environmental conditions that can alter judgment and physical performance, potentially impacting mission success. The effect of hypobaric/high-altitude hypoxia is ubiquitous. Everyone is equally susceptible to its physical and cognitive performance decrements. Therefore, the importance of preparing operators for high-altitude missions cannot be overemphasized [1]. Performing a military mission at high altitude requires specialized individual and team preparation. A well-designed physical training regimen may include several weeks of altitude exposure as well as training on the proper use of pharmacologic prophylactic therapy. Additionally, an understanding of the physical and cognitive demands that occur at various altitudes could prove useful to operators in preventing various altitude illnesses. This training will lead to a marked improvement in their physical and cognitive abilities while performing critical mission tasks [2]. Military operations may not allow enough time to accomplish acclimatization due to a rapidly changing operational environment and tempo. For example, an operator must train at an altitude of 8,000 to 10,000 feet for up to 2 weeks to acclimate, followed by 1 month of training at 11,000 feet [3]. Without proper physical training at altitude, missions performed at moderate altitude (5,000-8,000 feet), high altitude (8,000-14,000 feet), or very high altitude (14,000-18,000 feet) may be negatively impacted by illnesses including acute mountain sickness (AMS). This deleterious effect may result in irritability, physical weakness, decreased appetite, tachycardia, insomnia, dizziness, nausea, headache, and peripheral edema, where all of these symptoms may appear within the first 6 to 24 hours of arrival at high altitude [4-6]. Hence, medical planners may consider dexamethasone use to enhance the physical performance of SF operators during high-altitude ground operations.

Some of the hazardous conditions experienced when ascending to high altitude include (1) diminished partial pressure of oxygen, (2) the reduced density of air at high altitudes, and (3) the increased dryness of ambient air at altitude. Ventilation rates, cardiac output, and heart rate

increase considerably at altitude, usually appearing at 5,000 feet and above [7]. There is an estimated 1.5% to 3.5% reduction in aerobic capacity for every 984 feet of additional increase in altitude above 4,900 feet. The typical SF operator has a relatively high maximal aerobic capacity and therefore will experience the largest decrements in maximal aerobic capacity at high altitudes [8]. Additionally, the combination of low temperatures, hypoxia, strong winds, and dehydration can readily induce hypothermia and frostbite [9].

High-altitude illnesses include AMS, high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). While AMS is short lived and normally subsides within 2 to 7 days, HAPE and HACE are potentially fatal, yet are infrequent [10]. HAPE occurs in less than 10% of subjects ascending above 12,000 feet, and HACE occurs in less than 2% of subjects above 12,000 feet. In some instances, the risk of developing HACE may be increased in those who have previously experienced AMS symptoms but continue to ascend to higher altitudes [7]. Individual physiological responses to altitude and acclimatization rates vary dramatically [11]. Furthermore, not all acclimatization training strategies or medications may fully prevent the onset of AMS [11]. Nonetheless, certain forms of pharmacological therapies and acclimatization training techniques may be more helpful than others in ameliorating AMS, ultimately resulting in enhanced mission safety and mission execution.

The most prominent effects of altitude on physical performance are an increased time for task completion or the need for more frequent rest breaks. Operators are generally not afforded the opportunity to rest during critical missions and must perform key tasks in a short amount of time. Although exposures to high altitude of 1 week or more increase acclimatization, the time to complete a physical task still remains longer relative to the time to complete while at sea level. This deterioration in performance could negatively impact mission success [5,7,12,13]. In addition, operators must also contend with additional physiological stressors such as hypoxia, dehydration, and cold injury as altitude increases. These stressors further contribute to declines in physical performance [14]. For instance, performing missions below 13,000 feet may simply require the operator to use basic climbing skills, navigation, ropes, route selection, and procedures to avoid snow avalanches and landslides. Conversely, at higher altitudes more complex skills are required because material transport by helicopter is not always feasible. Therefore, troops may be required to carry heavy loads consisting of rations, kerosene oilcans, and building materials for bunkers while traveling across harsh, uneven terrain [1].

From a performance perspective, operators must also maintain proper energy balance. It is not unusual for sea level operations to require a daily caloric intake of between 3,000 to 4,000 calories. This intake could increase to 6,000 calories when missions take place at altitude. Anything less than 6,000 calories minus proper hydration could significantly reduce war fighting capabilities and further increase the operator's susceptibility to mountain-related illnesses [1].

The primary objective of this review was to learn more about the medical efficacy of dexamethasone as a pharmacological prophylaxis for the prevention and treatment of altitude illness while also discussing its applicability for improving battlefield airmen's physical performance in high-altitude environments. Furthermore, failure to implement suitable acclimatization training techniques for troops or to administer the most effective forms of pharmacological therapies both before and during rapid deployment may result in mission mishaps.

3.0 BACKGROUND

3.1 Physiological Features of High-Altitude Illnesses

SF operators will begin experiencing decrements in physical performance above 5,000 feet. The reduction in physical performance increases as activity time, altitude, and amount of muscle mass recruited to perform work also increase [7]. Physical work capacity completion time is critical during a mission at altitude. The capacity to perform heavy work for 2 minutes or more is significantly reduced at high altitude. For example, physiological responses to acute high-altitude exposure include increases in blood lactate levels, reductions in muscle glycogen, and increased ratings of perceived effort, all of which adversely affect submaximal endurance performance [4,12,15]. Although these particular physiological responses improve within 3 to 14 days after arriving at altitude, as the mission dictates, many operators may not remain at the same altitude for any period of time. Reductions in work capacity could severely limit an operator's ability to adequately sustain and to satisfactorily complete specified duties required during intense ground operations at high altitudes. The detrimental effects of ascending to high altitude are due to the diminished partial pressure of oxygen at reduced barometric pressure, resulting in tissue hypoxia [16,17]. The reduced density of air at high altitudes also affects breathing mechanics. At low barometric pressures, the ability of the respiratory muscles to exert pressure is reduced and more effort is required for effective adequate pulmonary respiration [13]. Additionally, as one ascends to altitude, the air becomes increasingly dry, resulting in greater loss of water via the respiratory tract. More importantly, the capacity of the operator to perform 2 minutes or more of heavy work is significantly diminished, with the exception of activities where air resistance plays a key role [12,13]. It is also worth noting that in 1987, the Soviet Union founded a special course to train its doctors to function effectively at high altitude. The course devotes over 100 hours to medical topics and nearly 800 hours to mountaineering lecture and practical application [18].

3.2 Nonpharmacological Acclimatization Techniques

Several key nonpharmacological acclimatization techniques exist that may facilitate in the prevention of high-altitude illnesses. One physical training technique includes the classic living and training at altitudes between 6,000 to 9,000 feet for an estimated 3 to 4 weeks [1,4]. However, for various operational reasons, operators may not have enough time to accomplish this type of training. The U.S. Army 10th Mountain Division is considered an elite mountain-trained force stationed at Fort Drum, New York. However, even these soldiers require an additional 2 to 3 weeks of acclimatization when deployed to high-altitude locations [1].

The original training concept of "live high, train low," which consisted of living an estimated 20 hours per day at 9,000 feet and training low at 3,900 feet, was modified in 2008 by the original researchers [4,19]. Their current recommendation is to live at moderate altitude (5,000-8,000 feet) and perform interval training at low altitude. Interval training consists of timed periods of high-intensity work followed by moderate-intensity relief intervals. Interval training has the following advantages: (1) allows the subject to perform more total work over a shorter period of time, (2) increases mitochondrial density, (3) improves lactate shuttle mechanisms, and (4) increased hematocrit. All of these advantages may contribute to enhanced performance at altitude [12].

Another modality to improve performance at altitude is to train in hypoxia and live in normoxia. The altitude ranges for training in hypoxia are between 6,500 to 18,000 feet. Because maximal aerobic capacity decreases at altitude, it is important that the subject trains at the same relative exercise workloads while in a hypoxic chamber or tent [4,19,20].

Dr. Stephen Muza from the U.S. Army Research Institute of Environmental Medicine recommended subjects engage in intermittent hypoxic exposures (IHEs) using the Colorado exercise tent or a similar mask device, such as the reduced oxygen breathing device, all of which may reduce AMS and provide ventilatory acclimatization. Both systems provide a normobaric, hypoxic environment by replacing oxygen with nitrogen in the inspired air [5,14,21]. For example, the Colorado exercise tent simulates altitudes of up to 15,000 feet. A 3-hour IHE for 6 to 7 days reduces AMS by an estimated 20% and increases oxygen saturation levels by 1% to 3%. Several IHE protocols exist, but none have been formally developed or researched for the Special Operations (SO) community, nor have any been studied outside of the lab.

Although IHE protocols exist, these particular protocols are not realistic for operators since they require 3 to 12 hours of IHE for 5 days. Other protocols that may enhance acclimatization and aid in athletic performance include hypoxic exposures in which the subject performs aerobic exercise inside a hypoxic tent ranging from less than 1 hour to greater than 1 hour [14]. Nonetheless, no predetermined training protocol exists for SF operators, nor do we know how long the effects from any such training exposures could be effectively sustained. Hence, pharmacologic prophylaxis treatment may need to be considered, since altitude acclimatization through physical training programs is not always possible for SF operators.

3.3 Pharmacological Acclimatization Techniques: Acclimatization with Dexamethasone

Past research, as summarized in Table 1, has indicated that dexamethasone is an effective and reliable form of treatment for AMS, HACE [11], and HAPE. Although the exact mechanisms are unknown and require further clinical investigation, there is strong evidence that dexamethasone may prevent the onset of HAPE [11].

Common dexamethasone dosages to prevent AMS for adults ascending to altitude are either 2 mg every 6 hours or 4 mg every 12 hours. However, for the ground operator who is rapidly deployed to altitudes exceeding 11,000 feet, a very high dose of 4 mg may be considered every 6 hours, but duration of use should not exceed 10 days [11]. A group of researchers [6] tested dexamethasone in eight trials with exposure above 13,000 feet and using AMS as an end point. A dosage range of 8 to 16 mg was a more efficacious prophylactic treatment for AMS than placebo and is especially worthwhile when ascent rate is high [6].

Deficits in cognitive performance are seen during the first few hours at high altitude on asymptomatic subjects, possibly due to increased leakiness of cerebral vessels, resulting in cerebral edema [2]. However, a group of investigators discovered that subjects' ability to perform certain tasks after acute exposure to high altitude improved after they were pretreated with dexamethasone [2]. This group of researchers also determined that acute exposure to high altitude in even asymptomatic subjects resulted in small cognitive deficits that could be reversed by treating with dexamethasone.

Table 1. Summary of Selected Dexamethasone High-Altitude Research Studies

Author	Subject Description	Subjects	Dexamethasone Dosage	Key Results
Ellsworth et al., 1991 [22]	Healthy climbers	Dexamethasone (n=10) Acetazolamide (n=10) Control (n=9)	4 mg every 8 h beginning 24 h prior to climb until descent	Dexamethasone decreased the occurrence of AMS and severity of symptoms ($p=0.025$)
Maggiorini et al., 2006 [23]	Adults prone to HAPE	Dexamethasone (n=10) Tadalafil (n=10) Control (n=9)	8 mg twice daily starting the day before the ascent to 4,559 m throughout the 2-day study	Dexamethasone reduced the risk of developing HAPE ($p<0.001$) and reduced the occurrence of AMS ($p=0.02$)
Fischler et al., 2009 [24]	Adults prone to HAPE	Dexamethasone (n=8) Tadalafil (n=7) Control (n=8)	8 mg twice daily starting the day before the ascent to 4,559 m throughout the 2-day study	Dexamethasone improved $\text{VO}_2\text{-max}$ ($p<0.05$) and oxygen kinetics ($p<0.05$) and reduced ventilator equivalent for CO_2 ($p<0.01$); no significant difference in peak O_2 saturation between groups
Siebenmann et al., 2011 [25]	Adults prone to HAPE	Dexamethasone (n=10) Control (n=14)	8 mg twice daily starting the day before the ascent to 4,559 m	Dexamethasone improved $\text{VO}_2\text{-max}$ ($p=0.025$); no significant difference existed in arterial O_2 saturation during maximal exercise

Dexamethasone may be useful in improving maximal aerobic capacity of special operators susceptible to HAPE. For example, Siebenmann and colleagues [25] found that dexamethasone improves maximal aerobic exercise in subjects susceptible to HAPE at 14,000 feet. Maximal aerobic capacity was evaluated on a cycle ergometer at an altitude of 1,600 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, whereas the dexamethasone group received 8 mg twice a day starting 24 hours prior to ascent. Dexamethasone prophylaxis increased maximal aerobic capacity of HAPE-susceptible subjects after the first night at 14,000 feet without affecting oxygen saturation level at maximal exercise. Additionally, if treatment with dexamethasone is started prior to hypoxic exposure, it reduces pulmonary arterial resistance and increases alveolar fluid clearance. Dexamethasone has also been found to enhance aerobic capacity even in normoxic conditions. For example, high dosages of dexamethasone are used in aerobic endurance sports to enhance physical performance. This is why the World Anti-Doping Agency prohibits the administration of any glucosteroids during competitions [25].

Fischler and colleagues [24] conducted a study on 29 mountaineers with a history of HAPE. Subjects were randomized to tadalafil 10 mg twice daily, dexamethasone 8 mg twice daily, or placebo a day before ascent 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. For example, pulse oximeter oxygen saturation at rest was significantly lower with both dexamethasone and tadalafil compared to placebo (both $p < 0.05$). However, heart rate significantly increased in all groups but was significantly lower in the dexamethasone group compared to the other groups ($p < 0.01$ vs. placebo and tadalafil). There was no statistically significant difference in AMS scores between the three groups on Day 1, but there was a statistically significant difference in the dexamethasone group on Day 2 ($p < 0.01$). Dexamethasone improved maximal aerobic capacity

and oxygen uptake kinetics and reduced hypoxia-induced pulmonary hypertension in HAPE-susceptible subjects at 14,000 feet. However, tadalafil did not significantly improve maximal aerobic exercise capacity and somewhat less-limited hypoxia-induced pulmonary hypertension [24]. The possible mechanisms contributing to improved exercise capacity in HAPE-susceptible subjects may include (1) enhanced nitric oxide availability contributing to lowered pulmonary artery pressure; (2) stimulation of alveolar sodium and water clearance, which could improve oxygen diffusion; and (3) lowered levels of an anti-inflammatory protein known as C-reactive protein. Additionally, acute hypoxia activates the sympathetic nervous system, which increases blood pressure, heart rate, and pulmonary vascular resistance. However, dexamethasone could have an inhibitory effect on the sympathetic nervous system, resulting in decreased heart rate, pulmonary vascular resistance, and ventilatory rates [24].

Ellsworth and colleagues [22] 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, 4 mg, acetazolamide 250 mg, or lactose placebo every 8 hours starting 24 hours prior to the start of each climb and continuing until descent from the highest point. For subjects in this study, the use of dexamethasone was effective in reducing the incidence of AMS during rapid ascent, and the overall rate of AMS was significantly lower in the dexamethasone group. For example, dexamethasone reduced the severity of AMS symptoms by an estimated 63%. Possible contributory mechanisms may include improvements in microcirculatory integrity and reductions in cerebral blood flow or cerebral vasoconstriction.

Maggiorini et al. [23] 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. Subjects were randomly assigned to receive prophylactic dexamethasone (8 mg), tadalafil (10 mg), 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 to mitigate the risk of developing AMS and reduce the incidence of AMS. In particular, at 14,900 feet, systolic pulmonary pressure increased less in those subjects receiving dexamethasone. Hence, dexamethasone could be considered prior to and during ascent to high altitudes by SF commanders. Dexamethasone has the ability to stimulate sodium and water reabsorption while also increasing the release of nitric oxide. These physiological responses contribute to overall pulmonary vessel dilation.

4.0 CURRENT GUIDANCE FOR DEXAMETHASONE USE IN THE U.S. MILITARY

Dexamethasone use is not without potential side effects. A minority of individuals may experience an energized feeling that may affect the ability to fall asleep and, therefore, negatively affect sleep quality. To determine which SO members are significantly affected by this, a test administration of up to three doses might be conducted prior to operational mission use. Not as relevant to short-term use in SO members, bone necrosis has been documented in a minority of patients who receive the medication on a chronic basis, usually on a continuous basis of 3 months or longer.

Guidance for the use of dexamethasone as prophylaxis during high-altitude ground operations exists in the U.S. Special Operations Command (USSOCOM): "Consider pretreatment if rapid ascent above 11,500 ft occurs (as with airlifts): A. Dexamethasone

(Decadron) 4 mg PO q [every] 6 hr within 24 hours of ascent plus acetazolamide (Diamox) 125 mg PO bid (if not allergic to sulfa)” [26].

U.S. Air Force (USAF), U.S. Navy (USN), and U.S. Army (USA) SO physician flight surgeons (FSs) and SO medics (SOMs) training sites were visited and/or contacted, including Ft. Bragg, NC (USA/USN SOM training); Kirtland Air Force Base (AFB), NM (USAF SOM training); Pensacola Naval Air Station, FL (USN FS training); Ft. Rucker, AL (USA FS training); and Wright-Patterson AFB, OH (USAF FS training). The use of dexamethasone as prophylaxis was discussed. We discovered that only three of the six groups, USA SO physician FSs, USA SOMs, and USN SOMs, had a formal curriculum in high-altitude ground operations. Furthermore, in only two of the three groups, USA SOMs and USN SOMs, the current applicable USSOCOM guidance was taught in a formal curriculum manner. Although the USAF SOMs had some instruction in high-altitude ground operations, the training was focused more on patient treatment than on SO member mission performance and prophylaxis (Table 2). Since there are many joint operation missions with members of branches overseeing members of other branches, uniformity of instruction in this area would seem to have benefits to mission performance and mission outcome, whether rescue, combat, or other missions at high altitude.

Table 2. Formal Curriculum Training of SO Physician FSs and SOMs (Sep 2012)

Medical Officer-Medic/Site	High-Altitude Ground Operations	Dexamethasone Prophylaxis
USA SO Physician FS/Ft. Rucker, AL	X	
USN SO Physician FS/Pensacola Naval Air Station, FL		
USAF SO Physician FS/Wright-Patterson AFB, OH		
USA SOM/Ft. Bragg, NC	X	X
USN SOM/Ft. Bragg, NC	X	X
USAF SOM/Kirtland AFB, NM ^a		

^aSome training, but focused more on patient care than SO member performance or prophylaxis.

5.0 CONCLUSIONS AND RECOMMENDATIONS

Current guidance regarding dexamethasone use in high-altitude ground operations is not uniform across the USA, USN, and USAF. The authors recommend the consideration of a uniform, formal USAF, USN, and USA training curriculum for all SO physician FSs and SOMs that includes USSOCOM guidance on dexamethasone use in these special circumstances.

Dexamethasone is effective in the treatment of AMS, HAPE, and HACE and can be lifesaving by effectively reversing physical symptoms that occur at high altitudes. This may allow SF operators to sustain physical and cognitive performance at altitude. The mechanisms related to improvements in performance at altitude may be due to an increase in maximal cardiac output and improved pulmonary diffusion. Both of these mechanisms may contribute to increased oxygen transport to working skeletal muscle tissues [25]. However, one must exercise caution because dexamethasone can give a false sense of security, causing one to ascend to higher altitudes to which the body has not acclimatized [27]. Otherwise healthy subjects who naturally perform well at altitude should not take dexamethasone as an “ergogenic aid” simply to go higher and/or faster. The use of dexamethasone as a prophylactic agent should be considered as an option per the USSOCOM guidance by SO forces who do not have enough time to accomplish altitude acclimatization. Studies examining the effects of prophylactic administration

of dexamethasone on physical performance at altitude are limited. Improvement by dexamethasone in maximal aerobic capacity after rapid ascent to high altitudes (10,000-14,000 feet) has been shown, especially in HAPE-susceptible subjects [24,25]. Future research examining the benefits of dexamethasone should be considered on subjects who are not HAPE susceptible to determine the precise physiological mechanisms that contribute to improved physical performance at altitude in the field.

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LIST OF ABBREVIATIONS AND ACRONYMS

AFB	Air Force Base
AMS	acute mountain sickness
FS	flight surgeon
HACE	high-altitude cerebral edema
HAPE	high-altitude pulmonary edema
IHE	intermittent hypoxic exposure
SF	special forces
SO	special operations
SOM	SO medic
USA	U.S. Army
USAF	U.S. Air Force
USN	U.S. Navy
USSOCOM	U.S. Special Operations Command