Acute Mountain Sickness Score and Hypoxemia
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Abstract

Background: Hypoxemia is the immediate consequence of hyobaric hypoxia, which is the crucial starting mechanism of acute mountain sickness (AMS). The AMS is generally a benign and self-limiting condition which can be prevented by gradual ascent. However, ascent rates recommended for prophylaxis of AMS are far slower than those attempted during military operations and by climbers.

Objective: The current study was carried out to quantify the relationship between AMS and hypoxemia along with evaluating the benefits of acetazolamide-dexamethasone chemoprophylaxis during acute ascent.

Subjects and Methods: Twenty-four lowlander male adults (age mean ± SE 27.8 ± 1.24 years) were selected. They were grouped in a double-blind fashion into four groups and each group (n=6) received placebo (multivitamin) or acetazolamide (250 mg) or dexamethasone (4 mg) or a combined regimen of the two drugs twice daily for 5 days, commencing 24 hours before ascent. The volunteers reached the altitude of 4578 meters within a span of one day. Their AMS symptoms were recorded on modified environmental symptoms questionnaire (ESQ), after 24 and 72 hours of ascent. Arterial PO2, SO2 and PCO2 were measured by GEMSTAT blood-gas analyzer (Mallincrodt-USA).

Results: The ESQ, AMS-C (cerebral) and AMS-R (respiratory) scores of combined therapy group were significantly lower as compared to the other groups on the symptom rating scale. The significant finding amongst the volunteers taking acetazolamide was mild to moderate diuresis whereas severity of headache was markedly less in dexamethasone group. The commonest feature of combined therapy was that none of the volunteers complained of headache, dyspnea, irritability and more than mild disturbance of sleep. The ESQ scores of volunteers were inversely correlated to PaO2 and SaO2 after 24 hours of ascent to 4578 meters.

Conclusion: The study concludes that severity of AMS is closely related to hypoxemia and combination therapy of acetazolamide-dexamethasone may be effective in preventing AMS (JPMA 51:1 73;2001).

Introduction

Acute mountain sickness (AMS) is a clinical syndrome consisting of headache, nausea, breathlessness, lassitude and insomnia. It is the most often experienced sickness by every mountaineer during rapid ascent to altitude greater than 3000m above sea\(^1\). AMS is rare at elevations below 2000m. The incidence and severity of AMS is directly related to the rate of ascent, the altitude achieved, the duration of stay at the altitude and the degree of acclimatisation\(^2\). Susceptibility to AMS varies among individuals. Some people never experience any problem, whereas others develop severe symptoms. The incidence of AMS is the highest in group aged 1 to 20 years, with severity of symptoms decreasing with increasing age. Furthermore, both men and women are at risk, although women are perhaps more ready to admit to symptoms than men\(^3\).

The precise pathophysiology of AMS is not known, however the primary insult delivered by the high altitude environment is ‘hypoxia’ which results in diminished alveolar oxygen tension and hypoxemia\(^4\). The hypoxia is the crucial starting mechanism for AMS but it is not the direct cause of symptoms. The PaO2 falls throughout the body within a few minutes of exposure to high altitude but the symptoms of AMS are delayed for 6-24 hours. This suggests that hypoxia initiates some process which requires a
time course of 6-24 hours before it causes symptoms. AMS is generally a benign and self-limiting condition but it may be a life threatening disorder and can be effectively prevented by gradual ascent in stages. The ascent rates recommended for prophylaxis are far slower than those attempted during military operations and by climbers. Therefore efforts were made to find the effective chemoprophylaxis for AMS. It is worth noting that acetazolamide and dexamethasone have been studied extensively for prevention of AMS and its ominous complications. High altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE). Acetazolamide promotes the excretion of bicarbonates by kidneys and corrects the respiratory alkalosis induced by hyperventilation. There is increased ventilation and arterial oxygenation in acetazolamide treated subjects at high altitude alongside marked reduction in the classical symptoms of AMS i.e., headache, insomnia and nausea. The other beneficial effects attributed to acetazolamide are better quality of sleep, diuresis, reduced CSF formation, increased brain blood flow and better exercise performance.

Dexamethasone is a synthetic corticosteroid which possesses potent glucocorticoid and negligible mineralocorticoid activity, it is effective in the management of cerebral edema of diverse causes and benefits acute mountain sickness. In a randomized, double blind, placebo controlled trial, acetazolamide and dexamethasone were compared as prophylaxis in 18 climbers who ascended Mount Rainier (elevation 4390 m). The study concluded, that dexamethasone appears to be effective for prophylaxis of symptoms associated with AMS during rapid ascent. Furthermore, dexamethasone may be given to persons who are intolerant to acetazolamide or for whom acetazolamide is ineffective.

In Karakorum mountains of Pakistan, there had been deployment of large number of troops during the last decade. Many of them suffered mild to severe effects of hypobaric hypoxia and other disasters peculiar to high mountains. In the retrospective analysis of unpublished native medical data it has been found that 797 soldiers suffered from AMS out of which 273 developed HAPE and 83 got afflicted by HACE from January 1985 to December 1994. Despite that Pakistan has very high mountains, not much work has so far been carried out in the field of high altitude physiology and chemoprophylaxis of AMS. Therefore, the present study was designed to quantify the relationship between AMS-score and Oxygen saturation of hemoglobin and to investigate the role of acetazolamide and dexamethasone chemoprophylaxis in ameliorating the symptoms of AMS.

Subjects and Methods

Volunteers
Twenty four male, low altitude residents of less than 500 meters participated in the study. The volunteers were randomly selected after medical examination. They were all in good health and not suffering from any acute or chronic systemic illness or psychiatric disease. Their ages ranged from 25 to 35 years and body mass index of less than 30. Standing height without shoes was measured in meters and weight with light clothes was taken in Kg. The body mass index was calculated as; weight in Kg divided, by height in meters square. The subjects had the first ever experience to visit high mountains as volunteers for present study. A formal written consent was obtained from every volunteer before recruiting him for the study. The objective of the study was explained to the volunteers. The volunteers travelled by road from Rawalpindi (515m)to an altitude of 4578m in Karakorum range. They reached the destination altitude within a span of 24 hours. It also included an active ascent on foot for 3 hours from 3800 meters altitude to the base camp (4578m) without any extra load with them since no vehicle could reach there.

Medication
The study was placebo controlled and the subjects were randomized in double blind fashion into four
study groups; that is, six subjects in each group (n6). The medication started 24 hours before ascent to the high altitude (4578 m) and continued for five days as follows: Group A: Placebo (multivitamin) tablet, 12 hourly.
Group B: Acetazolamide (Diamox, Lederle) 250 mg tablet, 12 hourly.
Group C: Dexamethasone (Merck Sharp & Dhome) 4 mg tablet 12 hourly.
Group D: Acetazolamide (250 mg) and Dexamethasone (4 mg) tablets, together 12 hourly.
The concomitant use of additional medication was restricted and regular intake of chemoprophylaxis was strictly supervised. The purpose and mode of data collection (including collection of blood samples) were fully explained to the volunteers. However, the details of medication were concealed from all the subjects until the treatment was withdrawn.

**Assessment of Acute Mountain Sickness (AMS)**
AMS symptoms were recorded on modified Environmental Symptoms Questionnaire (ESQ) after 24 and 72 hours exposure of non-acclimatised volunteers to altitude (4578 m) to quantitate the severity of acute mountain sickness (AMS). Eighteen symptoms were rated on a 0 to 5 point Likert scale (0, not at all; 1, slight; 2, somewhat; 3, moderate; 4, quite a bit and 5, extreme) to determine the modified ESQ score for the measurement of altitude symptoms or AMS. The following criteria for the classification of magnitude of AMS was observed:

<table>
<thead>
<tr>
<th>Category</th>
<th>ESQ Score</th>
</tr>
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<tbody>
<tr>
<td>a. Not at all (No AMS)</td>
<td>0-5</td>
</tr>
<tr>
<td>b. Mild AMS</td>
<td>6-15</td>
</tr>
<tr>
<td>c. Moderate AMS</td>
<td>16-30</td>
</tr>
<tr>
<td>d. Severe AMS</td>
<td>Above 30</td>
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</table>

Weighted averages of cerebral (AMS-C) and respiratory (AMS-R) symptom scores were calculated from the severity of two groups of symptoms. The symptoms like headache, nausea, vomiting and insomnia contributed to the AMS-C score while symptoms of breathlessness, periodic breathing, palpitation and discomfort in chest attributed to the AMS-R score. The severity of each symptom was rated from zero to 5. The average value of the severity of each symptom in the group was used to calculate the mean score of cerebral (AMS-C) and respiratory (AMS-R) symptoms. The scores greater than 0.7 for AMS-C and 0.6 for AMS-R were used to indicate the presence of AMS.12

**Collection of Blood Sample**
One ml of arterial blood was taken from radial artery in a heparinized, sterile disposable plastic syringe after adequate antiseptic measures. Lithium heparin, 25 USP units, was used as an anticoagulant for 2 ml of blood. Three arterial blood samples; one at Rawalpindi (515 m) before ascent and two during the study after 24 and 72 hours of stay at altitude (4578 m) were taken from each volunteer of non-acclimatised group in lying position.

**Blood Analysis**
The arterial sample was immediately analysed after its collection in GEMSTAT blood gas-electrolyte analyser (Mallincrodt Sensor System, USA). No extraneous equipment or reagent was required for calibration, since all the electrodes and calibrating solutions were contained within the disposable STATPAK cartridge. The protocol for the blood gas analysis was followed in accordance with the instructions given in operation manual of the equipment. After the intake of blood sample (05 ml whole blood) PaO2 PaCO2 and SaO2 were automatically measured. The response time for complete analysis of blood was 110 seconds after sample introduction. The results were displayed on the LC display and print out was retrieved for record.

The capability of the instrument to measure the range limits of various gas levels was
\[
P_0 : 0-400 \text{ mmHg, } PO_2 : 5-99 \text{ mmHg, } SO_2 : 30-99\%.
\]

**Results**
Twenty four healthy, male army personnel participated in the study. They were residents of low-altitude areas of Punjab province of Pakistan (altitude less than 500 meters). Their physical characteristics and some details of the high mountainous area of study are summarised in Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-acclimatized low-landers (at Rawalpindi)</th>
<th>(at Base Camp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Age (Mean ±SE)</td>
<td>27.8 ± 1.24 years</td>
<td>-</td>
</tr>
<tr>
<td>Height (Mean ±SE)</td>
<td>1.697 ± 0.06 meters</td>
<td>-</td>
</tr>
<tr>
<td>Weight (Mean ±SE)</td>
<td>63.4 ± 2.64 Kg</td>
<td>62.41 ± 3.757 Kg</td>
</tr>
<tr>
<td>Heart Rate (Mean ±SE)</td>
<td>67.5 ± 5.1 per minute</td>
<td>85.8 ± 5.6 mm per minute</td>
</tr>
<tr>
<td>Blood Pressure (Mean ±SE)</td>
<td>108/69 ±7.7/7.6 mmHg</td>
<td>116/68 ± 8.5/7.4 mmHg</td>
</tr>
<tr>
<td>Altitude*</td>
<td>515 meters</td>
<td>4578 meters</td>
</tr>
<tr>
<td>Barometric Pressure*</td>
<td>714 mmHg</td>
<td>437 mmHg</td>
</tr>
<tr>
<td>Ambient temperature*</td>
<td>36°C (day time at 1000 hours in June)</td>
<td>7°C (day time, at 1000 hours in June)</td>
</tr>
</tbody>
</table>

* Measured by Altiplus NI Pretel altimeter, France.

SBP = Systolic blood pressure
DBP = Diastolic blood pressure
One group comprised twenty-four volunteers, all were selected randomly for non-acclimatised group. Their age ranged between 25-35 years (Mean ± SE 27.8 ± 1.24 years). After 24 hours of arrival in the base camp and exposure to the altitude hypoxia (hypobaric hypoxia), the volunteers were interviewed for acute mountain sickness (AMS). The modified environmental symptom questionnaire was completed twice in the base camp, that is, after 24 and 72 hours of exposure to the altitude hypoxia. The comparison of modified ESQ, AMS-C and AMS-R scores of different groups has been presented in Table 2.

The analysis of modified ESQ scores revealed that placebo, acetazolamide and dexamethasone groups developed mild AMS whereas combined therapy group did not suffer AMS at all. The ESQ scores of combined therapy group were significantly lower than all other groups in 24 and 72 hours recordings. The comparison of ESQ scores of acetazolamide and dexamethasone groups to the placebo revealed no statistical difference. However, analysis of the altitude symptoms of volunteers in acetazolamide and dexamethasone groups disclosed the reason for high ESQ scores of the two groups. In acetazolamide group, 2 subjects had high ESQ scores (26 and 27 each) because of moderate to severe symptoms of loss of appetite, irritability, sleep disturbance and dyspnoea. The mean ESQ score of the other 4 subjects (10.05 ± 0.09) was lower than the placebo (11.83 ± 1.58). In dexamethasone group, one person had ESQ score of 29 because of the symptoms like dyspnoea, tachycardia, gastrointestinal disturbance and irritability. The other five subjects of the group had lower mean ESQ scores (9.00 ± 1.06) than the placebo (11.83 ± 1.58) and mean ESQ score of combined therapy group (5.33 to 1.26) (Figure 1).
The analysis of averaged AMS-C and AMS-R scores of different groups (Table-2) revealed that scores were minimum in combined therapy group, whereas scores of acetazolamide and dexamethasone groups were almost similar to the placebo. The significant finding of subjects taking acetazolamide alone or with dexamethasone, was mild to moderate diuresis. Whereas, severity of headache was markedly less in dexamethasone group. The commonest feature of combined therapy group was that none of the volunteer complained of headache, dyspnoea, irritability and more than mild disturbance of sleep.

The arterial PaO2 SaO2 and PaCO2 of nonacclimatised subjects measured 24 and 72 hours of ascent have been presented in Table-3.
No significant difference in mean values of SaO2 were observed when drug-treated groups were compared to the placebo after 24 hours. However, PaO2 in acetazolamide (P<0.003) and combined regimen groups were higher (P<0.001) than the placebo when both the values were compared 24 and 72 hours after ascent. Furthermore, it was found that PaO2 and SaO2 significantly increased (P<0.05) in acetazolamide group after 72 hours when PaO2 and SaO2 were compared with the 24 hours measurements in the base camp.

The comparison of arterial PaCO2 in various groups of non-acclimatised volunteers after 24 and 72 hours of their arrival in the base camp reveals that PaCO2 in acetazolamide, dexamethasone and combined therapy groups were less (P<0.001) than the PaCO2 obtained in placebo group. (Figure 2).
The arterial PO2, SO2 and PCO2 along with ESQ scores of each group have been presented in figures 1 and 2. ESQ scores of all the groups decreased with increase in duration of exposure, increase in PaO2 and SaO2 and decrease in P2CO2 of the volunteers at high altitude.

**Discussion**

Most often, the sample size had been small in high altitude studies\(^9\,^{10}\) due to the unpleasant hypoxic
environment. It is worth mentioning that only four to six volunteers successfully participated in famous Operations Everest: I and II. Financial constraints, logistic problems, fear enemy's encounter superadded by landslides, avalanches and health hazards, make the conditions frightening at high altitude. Therefore, it was difficult to attract more volunteers in the current study. The present study was conducted to explore the efficacy of two chemoprophylactic agents acetazolamide and dexamethasone to mitigate AMS symptoms in healthy Pakistani low-lander male adults during acute ascent to 4587m altitude.

The attempts have been made to define magnitude of AMS and to ponder relationship of AMS to changes in blood gas concentrations. The procedure of interview or self-assessment by recording major symptoms on the simple check list, has been used for clinical assessment of AMS. The symptoms are recorded by using the graduated rating scale according to their severity that is, no symptoms, mild, moderate or severe symptoms. The AMS score is derived by summing the individual scores for anorexia, nausea, vomiting, headache and unwellness. A better approach is to score individual symptoms and reach an overall score for AMS which reflects the continuum of severity. The most sophisticated system is the Environmental Symptom Questionnaire, consisting of 67 questions, many of which are overlapping and of uncertain relevance to AMS. Therefore, most workers have used a modified Environmental Symptoms Questionnaire containing 18 symptoms which can either be recorded by an observer or self-assessed. The same questionnaire has been used in the current study. The volunteers of combined therapy group remained relatively comfortable and symptom free on arrival at altitude. Their altitude symptom scores (ESQ), AMS-C and AMS-R were minimum on the symptom rating scale along with higher respiratory rate, PaO2 and SaO2 on the first day of arrival at high altitude. It appears that improved oxygenation protected the volunteers against hypoxia which probably is the only certain factor for the causation of acute mountain sickness (AMS) by unknown mechanism. The possible reasons could be the prevention of incipient cerebral edema by dexamethasone and hyperventilation by acetazolamide on arrival at high altitude. The beneficial effect of acetazolamide and dexamethasone, when given together, has suggested that combined therapy may be more effective in preventing the development of AMS.

The volunteers taking acetazolamide reported less difficulty in sleeping at altitude. Acetazolamide probably eliminates the periodic breathing during sleep, which is a common cause of frequent awakening at altitude. Furthermore, its mild to moderate diuretic effect causing decreased production of CSF may be responsible to prevent the cerebral edema and AMS. Acetazolamide pretreatment has been documented to ameliorate the symptoms of AMS on acute ascent. However, acetazolamide alone did not effectively prevent AMS symptoms of two subjects in current study in contrary to other studies. The adverse effects reported with the use of acetazolamide include, paraesthesia, polyuria, nausea, vomiting and lethargy. Nausea and vomiting is commonly seen in clinical practice and this side-effect overlaps significantly with the symptoms of AMS. Therefore, one must be cautious in advising prophylactic therapy with acetazolamide. The relatively high ESQ and AMS-R scores of acetazolamide group obscured the prophylactic effect of the drug in current study which may be due to the small sample size. However, after excluding the scores of the two symptomatic subjects, the prophylactic efficacy of acetazolamide was worthwhile when compared to the placebo for both cerebral and pulmonary AMS symptoms.

The identical AMS-C scores of placebo, acetazolamide and dexamethasone, after 24 hours of arrival at the altitude, may be due to the fact, that beneficial effects of these drugs take a longer time to establish themselves. However, dexamethasone proved more effective in reducing the cerebral symptoms than acetazolamide. The mechanism of the beneficial effect of dexamethasone is not known. Assuming that AMS is caused by hypoxic induced cerebral edema, the suggested mechanisms include a reduction in cerebral blood flow or cerebral vasoconstriction and improved microcirculatory integrity which may
reduce edema by decreasing filtration through microcirculation\textsuperscript{23}. The fall in AMS-C and AMS-R scores, with increase in duration of exposure, in all the groups of study with or without premedication, reveals that acclimatisation is a continuous process, which brings gradual adjustments in different physiologic processes of the body\textsuperscript{24}. After ascent to 4578 m altitude (barometric pressure 437 mmHg) the alveolar PO\textsubscript{2} decreased due to hypobaric hypoxia which led to the reduction in arterial PO\textsubscript{2} and oxygen saturation of haemoglobin SaO\textsubscript{2}. The acetazolamide exerted a beneficial effect on arterial P0 of volunteers taking acetazolamide with or without dexamethasone. The relatively higher PaO\textsubscript{2} of these groups may be associated with profound increase in their respiratory rate mind\textsuperscript{9,23}. The effect of acetazolamide and dexamethasone on SaO\textsubscript{2} was also beneficial as compared to the placebo which was manifested by the less reduction in SaO2 of drug treated subjects after 24 hours of acute ascent to 4578 m. The cause of less reduction of SaO2 in dexamethasone group was unclear. However, it had been suggested that dexamethasone improved the oxygen saturation of haemoglobin (SaO2) at high altitude by some unknown mechanism\textsuperscript{10} probably by reducing the postulated interstitial pulmonary edema and better diffusion of oxygen in the lung. The data of current study revealed considerable decrease in arterial PaCO\textsubscript{2} in all drug treated groups after 24 and 72 hours of ascent as compared to placebo. But reduction of PaCO\textsubscript{2} was greater in acetazolamide taking volunteers which may be attributed to drug induced hyperventilation and renal excretion of HCO\textsubscript{3}\textsuperscript{-}\textsuperscript{25,26}. The current data revealed that on going to high altitude, the subjects experienced not only hypoxia but also developed hypocapnia, therefore, both hypoxia and hypocapnia may be the factors in genesis of AMS. The linear regression analysis of PaO\textsubscript{2} S\textsubscript{a}O\textsubscript{2} and PaCO\textsubscript{2} measured after 24 hours of ascent and AMS scores, revealed that severity of AMS symptoms concided well with reduction in arterial oxygenation. AMS scores were inversely correlated ($r$=-0.5202, $P<0.05$) to PaO\textsubscript{2}\textsuperscript{27} and positively correlated ($r$=+0.6768,$P<0.05$) to PaCO\textsubscript{2}\textsuperscript{28}. Furthermore, severity of AMS has also been associated with lower oxygen saturation ($r$ = -0.4998, $P<0.05$) which is consonant to the findings of a recent study at 4243 meters in the Everest region\textsuperscript{29}. The mechanism connecting PaCO\textsubscript{2} arid AMS is believed to be the effect of CO\textsubscript{2} for increasing the cerebral blood flow which may result in cerebral edema\textsuperscript{30}. Vis-à-vis arterial hypoxemia may also dilate cerebral vessels and cause an increase in cerebral blood flow especially when PaO2 is below 60 mmHg to produce cerebral edema and symptoms of AMS\textsuperscript{31}. However, hypoxic induced hyperventilation blows out CO\textsubscript{2} and produces hypocapnia which may negate the vasodilator effect of hypoxenia. It may result in cerebral vasoconstriction to prevent cerebral edema and symptoms of AMS. The best method to prevent AMS effectively is by an adequately slow ascent N, but for those who have limited time to ascend there exist several drug therapies\textsuperscript{32} that may provide a relatively good protection. Acetazolamide (250 mg twice daily or 500 mg slow release once daily) taken before and during ascent is probably the treatment of choice. It improves the gas exchange and exercise performance and reduces the symptoms of AMS in almost individuals. Dexamethasone (4 mg, four times daily) is of more value for short term treatment or prevention. However, it should not be used for more than 2-3 days. Compared with placebo, combined therapy with acetazolamide and dexamethasone appears to be an effective prophylaxis for symptoms associated with AMS during rapid ascent. However, the use of dexamethasone for AMS prophylaxis is not without risk. The sustained use of glucocorticoids has shown to accentuate anoxic brain damage in animals\textsuperscript{17}. Therefore, more work would be needed to clearly define the role of dexamethasone. Nevertheless, many authors agree\textsuperscript{17,23,24,27} for using dexamethasone in AMS prophylaxis for those persons who are intolerant to
acetazolamide or in whom acetazolamide is ineffective or who undergo forced rapid ascent to high altitude. Thus benefit of chemoprophylaxis is not guaranteed for all subjects and likelihood of side-effects must be kept in mind before advising the drugs to climbers during ascent. The study concludes that severity of AMS is inversely correlated to PaO2 and lower oxygen saturation of haemoglobin. It appears that combination therapy by acetazolamide-dexamethasone may be more effective in preventing AMS symptoms.

References
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