JPMA (Journal Of Pakistan Medical Association) Vol 53, No.10,Oct. 2003
Original Articles

Hypoxia and Pulmonary Acclimatisation at 4578 M Altitude: the role of Acetazolamide and Dexamethasone

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Introduction

Hyperventilation is the first physiological adjustment observed in response to sudden exposure to hypoxia. It is initiated by hypoxic stimulation of peripheral arterial chemoreceptors (carotid and aortic bodies) and central integration of chemosensory inputs in brain stem via medullary respiratory center.1 Besides hyperventilation, the lungs undergo several changes which may impair its functions. Several studies2-4 have recorded the reduction in forced vital capacity (FVC) during first week at Mount Everest base camp (5300m elevation) and an increase in forced expiratory flow (FEF 25-75%). The native study on 16 Pakistani lowlander volunteers have revealed a significant reduction in FVC, %FEV1, MVV and PEFR on the first day of arrival at 4570 m altitude.5 Despite reduction in airway resistance due to decreased air density at high altitude the ventilatory muscle endurance may be decreased by hypobaric hypoxia6 which may be a limiting factor in ventilatory function. Therefore, exacerbating hypoxemia at high altitude can impair lung functions which may be associated to the arterial blood gases. Gradual ascent in stages has been the thumb rule to achieve adaptation to high altitude and to prevent untoward effects of hypoxia. However, acetazolamide and/or dexamethasone has been tried to speed up the process of adaptation especially when acute ascent to high altitude is compelled during rescue climbing or military operations. The present study is an effort to evaluate the changes in spirometric lung volumes and flow rates alongwith changes in arterial blood gases in healthy volunteers during acute exposure to hypobaric hypoxia following ascent to 4578 m altitude. Furthermore, it has been tried to assess the role of acetazolamide and/or dexamethasone prophylaxis in ventilatory response during acute ascent to high altitude.

Subjects and Methods

Volunteers

Forty four male, low altitude residents of less than 500 meters, 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 age ranged from 25 to 35 years and body mass index was 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 the present study. A formal written consent was obtained from every volunteer before recruiting him for the study. In addition, the study was approved by the Armed Forces Research and Development Council before its execution.

Non-Acclimatised Volunteers

The volunteers travelled by road from Rawalpindi (515 m) to an altitude of 3478m 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.
The study was placebo controlled and the subjects (Army Personnel) were randomized in double blind fashion into four sub groups, that is, six subjects in each. The medication started 24 hours before ascent to the high altitude (4578m) and continued for five days as follows:-
a) Placebo (multivitamin) tablet 12 hourly.
b) Acetazolamide (Diamox, Lederle)250 mg tablet 12 hourly.
c) Dexamethasone (Merck Sharp and Dhome) 4 mg tablet 12 hourly
d) Acetazolamide (250 mg) and Dexamethasone (4mg) 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 the subjects until the treatment was withdrawn.

Acclimatised Volunteers

The second group of twenty male volunteers (Army Personnel) were randomly inducted in the study who had arrived at the same altitude (4578 m) 4 and 8 weeks earlier from the low altitude(less than 500 m). They were symptoms free and able to perform their routine duties without any problem. The similar information, data and blood samples were collected as from non-acclimatised group.

Expiratory Spirometry
Expiratory Spirometry was carried out by Compact Spirometer (Vitalograph) at Rawalpindi (515 m) before ascent and after arrival (24 and 72 hours) at 4578 m altitude, to record forced vital capacity(FVC), forced expiratory volume in first second (FEV1), percent forced expiratory volume (%FEVl), peak expiratory flow rate (PEF), forced expiratory flow rate (FEF 25-75%) and maximal voluntary ventilation (MVV) Spirometry was also carried out in acclimatised group. The precise technique for lung function test was based on instructions given in the operation manual of the instrument with special reference to the official verdict by the American Thoracic Society7 on standardization of spirometry -1987. The objective of the test was explained to each subject and procedure of spirometry was demonstrated. All queries by the subjects were answered to promote cooperation. The recordings were completed on each subject in standing position and best recording out of the three forced expiratory manoeuvers were reported at BTPS. The ambient temperature was 70 C and 100 C on two occasions when lung functions were recorded at 4578 m altitude.
Each subject when relaxed, was also connected to 'Engstrom Elisa Duo' Expiratory CO2 Analyzer in sitting posture to monitor the resting breath rate for 2 minutes after 24 and 72 hours of stay at altitude. Resting breath rate of acclimatised subjects were also recorded.

Collection of Blood Samples

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 2ml of blood. Three arterial blood samples; one at Rawalpindi (515m) before ascent and two during the study after 24 and 72 hours of stay at altitude (4587m) 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 (0.5 ml whole blood) PaO_2, $PaCO_2$, pH and SaO_2 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:
PO_2: 0-400mm Hg, PCO_2: 5-99 mmHg, SO_2: 30-99%, pH: 6.80-7.80

Results

The physical characteristics of forty four healthy male volunteers and some details of the mountainous site of study have been summarized in Table 1.
The respiratory rates of different sub groups of non-acclimatised subjects recorded after 24 and 72 hours of ascent (Table 2) revealed significant increase when compared to their pre-ascent level (Rawalpindi). The data shows that respiratory rate continued to increase significantly ($P<0.03$) even after 72 hours of ascent till 4 weeks after ascent. Later on the respiratory rate gradually decreased ($P<0.05$) but remained higher than the respiratory rate recorded after 72 hours of ascent. In addition, the respiratory rates in acetazolamide and combined therapy sub groups after 24 and 72 hours of ascent were significantly higher ($P<0.05$ to $P<0.01$) when compared to the placebo and dexamethasone sub groups. The changes in respiratory rates after acute and chronic exposure to high altitude revealed an inverse correlation ($r= -0.7828$, $P< 0.01$) to PaO_2.
PaO_2, $PaCO_2$, SaO_2 and pH changes in different sub groups of non-acclimatised volunteers after 24 and 72 hours of ascent are presented in Table 3. The arterial PO_2 and SO_2 decreased following acute ascent when compared to the pre-ascent level but PaO_2 of volunteers taking acetazolamide was found higher than the other sub groups. The arterial PCO_2 decreased significantly ($P<0.001$) in acetazolamide taking volunteers after acute ascent when compared to the placebo sub group. Furthermore, the pH decreased significantly ($P< 0.001$) in volunteers taking acetazolamide.
The comparison of pre-ascent PaO_2, $PaCO_2$, SaO_2 and pH levels of volunteers after acute (24 hours) and chronic (4 and 8 weeks) exposure to high altitude is presented in Table 4. The values of PaO_2 and SaO_2 decreased substantially ($P<0.001$) after 24 hours of ascent (hypobaric hypoxia). However, during subsequent 4-8 weeks of stay at high altitude, PaO_2 and SaO_2 levels significantly increased ($P<0.04$ to $P<0.006$).
The comparison of arterial PCO_2 and pH after 24 hours of ascent to the pre-ascent levels showed significant ($P<0.001$) reduction in acetazolamide treated subgroups . The arterial $PaCO_2$ and pH gradually decreased (though statistically non-significant) during 4-8 weeks of study at high altitude (Table 4).
The comparison of spirometric variables of non-acclimatised volunteers after acute (24 and 72 hours) and chronic (4 and 8 weeks) exposure to high altitude has been presented in tables 5 and 6. It revealed the significant decrease in FVC ($P<0.02$) and PEF ($P<0.0.3$) after 24 hours of ascent. During subsequent 48 hours of exposure to hypobaric hypoxia, there were gradual improvement in lung functions in non-acclimatised volunteers. The FVC, FEV1, %FEV1 and PEF revealed no statistical change when compared with the pre-ascent measurements at Rawalpindi except FEF 25-75% ($P<0.05$). The lung functions of acclimatised volunteers after 8 weeks of stay at high altitude, were comparable to the lung functions of non-acclimatised volunteers recorded before ascent (at Rawalpindi).

Discussion

The respiratory rate min-1 increased significantly in all the groups of current study following acute ascent to high altitude as observed by other workers.5,8,9 The changes in minute respiratory rate and arterial PO2 after 24 hours of acute ascent to 4578 m altitude (PBP 437 mm Hg) revealed an inverse correlation ($r= -0.7828$, $P<0.01$) which indicates that reduction in arterial PO2 and oxygenation of haemoglobin on exposure to hypobaric hypoxia (1) increases the minute respiratory rate. The suggested mechanism is that peripheral chemoreceptors (carotid and aortic bodies) being sensitive to decreased PO2 of arterial blood, will produce strong stimulation of peripheral chemoreceptors which ultimately stimulate respiratory center. The first contact with hypoxia causes an increase in ventilation within seconds that reaches full intensity within minutes because of an increase in carotid sinus nerve input to the brain stem.10

The data of present study indicate the greater increase in respiratory rate in acetazolamide and combined (acetazolamide and dexamethasone)therapy sub groups as compared to the placebo. The administration of acetazolamide has been documented to cause 10-20% greater increase in ventilation and 3-6% rise in arterial haemoglobin saturation at high altitude.11 The acetazolamide causes respiratory stimulation through inhibition of carbonic anhydrase which would build up CO2 at peripheral and central chemoreceptor level. Therefore stimulation of ventilation is carried out via both peripheral and central cehmoreceptors and resultant hyperventilation would lower PaCO2 and increase PaO2.11

The inverse correlation ($r= -0.6323$, $P<0.02$) between PaCO2 and respiratory rate min-1 explained that development of hypocapnia was the outcome of hyperventilation. However, after staying for days and weeks at 4578 m altitude, the PaO2 gradually increased due to hyperventilation ($r= +0.867$, $P<0.01$) which causes hypocapnia and development of respiratory alkalosis.12 Therefore, initial hypoxic stimulation of ventilation driven by peripheral chemoreceptors is blunted by respiratory alkalosis and alkalemia, acting both at peripheral chemoreceptors to reduce their hypoxic responsiveness and central chemorceptors to reduce their tonic discharge to the respiratory control centers. The renal adjustment of acute hypocapnia by reduction in HCO-3 reabsorption and acid secretion would take days to be fully realized11 which may be enhanced by acetazolamide.

The volunteers who had arrived 4 weeks earlier at 4578 m altitude revealed an increase in respiratory rate min-1 even greater than after the first 3 days at altitude. This gradual rise in respiratory rate min-1 may be the outcome of increases in peripheral chemo receptor or CNS excitability generated over days in response to hypoxia. The increase in respiratory sensitivity may be the first necessary step in altitude acclimatisation and might serve as a useful marker of this adaptation.13 Respiratory sensitivity improves during earlier days of exposure to the altitude and achieves the base line after 17 to 27 days of stay under chronic hypoxic conditions. The improvement in respiratory sensation could be a primary signal in the physiological and psychological adaptation to high altitude which was manifested by rapid respiratory rate despite hypocapnia.14

The volunteers taking acetazolamide with or without dexamethasone had relatively higher PaO2 than other sub groups that may be associated to the increase in respiratory rate min -1.15-17 It had been suggested that dexamethasone improved the oxygen saturation of haemoglobin (SaO2) at high altitude probably by reducing the postulated interstitial pulmonary edema and better diffusion of oxygen in lung.18

The decrease in arterial blood pH of acetazolamide and combined therapy sub groups, after 24 and 72 hours of ascent, was not unexpected. It may be attributed to the inhibition of cytoplasmic and brush border membrance carbonic anhydrase of proximal and distal tubules that results in decreased availability of protons (H+) for Na+ -H+ exchange and HCO-3 reabsorption in proximal tubules which can reduce H+ secretion and development of metabolic acidosis.19 In addition, the

total or near total inhibition of red cell carbonic anhydrase will lead to the retention of CO_2 in all tissues including brain. A build up of CO_2 and hypercapnia at peripheral and central chemorceptors would stimulate ventilation11 as manifested by the marked increase in respiratory rate in volunteers taking acetazolamide.

The persistent hyperventilation at high altitude may be attributed to the recovery of the sensitivity of central chemoreceptors to respond to the new lower levels of $PaCO_2$ which is an important aspect of altitude acclimatisation. Thus altitude acclimatisation involves the tolerance and responsiveness to both decrease PaO_2 and $PaCO_2$.20 The data of current study revealed the considerable decrease in $PaCO_2$ in all drug treated groups after 24 and 72 hours of ascent as compared to placebo. However, the reduction in $PaCO_2$ was greater in acetazolamide taking volunteers due to drug induced hyperventilation and possible renal excretion of HCO^-.21

The spirometric measurements in current study revealed the reduction in forced vital capacity (FVC) and peak expiratory flow rate (PEF) at 24 hours of ascent which coincides with previous studies.3,5,22-24 At high altitude the respiratory function can be affected by the presence of an increased pulmonary blood volume and/or the development of pulmonary interstitial edema.3 Selland and his colleagues in 1993, recorded23 the decrease in expiratory flow rates (FEV1 and FEF 25-75%) in susceptible subjects coinciding with the development of signs and symptoms of pulmonary edema and reduction in vital capacity. The spirometric recordings on the first day of arrival at high altitude by Pakistani5 and Indian22 workers had also recorded the reduction in FVC,FEV1, %FEV1 and PEF. The increase in FVC, FEV1, FEF 25-75% and MVV in acetazolamide group compared to placebo after 24 hours of arrival at altitude suggests that acetazolamide might affect lung mechanics and gas exchange at high altitude.25

The non-significant change in FVC, FEV1 ,% FEV1 and reduction in PEF, FEF 25-75% and MVV observed in dexamethasone group after 24 hours of their ascent could not be explained. It may be due to the improved microcirculatory integrity and reduction in pulmonary interstitial edema by decreasing filtration through microcirculation.26 The substantial rise in FVC and flow rates of combined therapy group as compared to placebo after 24 and 72 hours of arrival at the altitude (4578 m) may be due to the beneficial effect of the two drugs on pulmonary mechanics when given together.27

Although no direct relationship between the levels of PaO_2 and MVV could be established but we have recorded the reduction in both PaO_2 and MVV after 24 hours of ascent as compared to the pre-ascent level. The reduction in MVV can be associated to the decreased ventilatory muscle endurance by hypobaric hypoxia.6 After 72 hours of ascent the MVV had started improving in all the sub groups especially more significantly in volunteers taking acetazolamide who had increase in their PaO_2 and SaO_2. It indicates that hypoxia, perhaps, decreases the endurance of ventilatory muscles which may be responsible for reduction in lung functions at high altitude.

The lung functions (FVC and flow rates) of low-lander male Pakistani adults after 8 weeks of exposure to 4578 m altitude were comparable to the lung functions recorded at Rawalpindi. It suggests that pulmonary acclimatisation sets in gradually over the period of 8 weeks stay at altitude by building larger lung volumes28 and increase in PaO_2 and SaO_2 in these subjects. The data of elite climbers of the world who had reached the altitudes greater than 8500 m or above without supplementary oxygen presented higher than predicted total lung capacity, forced vital capacity and FEV1 and %FEV1.29 Therefore, it may be suggested that increase in pulmonary volumes either due to prolong duration of exposure to altitude hypoxia or by chemoprophylaxis is an adaptive response which indicates pulmonary acclimatisation.

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