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Short Communication

Is concurrent prophylactic use of acetazolamide and dexamethasone superior to acetazolamide alone in un-acclimatized lowlanders on ascent to high altitude ?

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Abstract

This pilot study was undertaken in lowlanders, during their ascent from 2600 m to 3500 m, to evaluate the effects of Acetazolamide and Dexamethasone on Cardio-Respiratory parameters and Exercise Capacity. 40 un-acclimatised low-landers were divided into 2 groups. Subjects of Group 'A' were given Acetazolamide and Dexamethasone and those of Group 'B' were given Acetazolamide and placebo. 8 subjects matched for age, physical fitness, height and weight were randomly selected from each study group and were evaluated for their Exercise Capacities. Both study groups showed significant rise in Heart Rate, Respiratory Rate and a significant fall in Systolic Blood Pressure. There was no difference in Exercise capacities achieved by subjects of two groups at 3500 m.

Introduction

It is an established fact that physiological acclimatization does not fully compensate for the stress associated with High altitude (HA). The altered physiological processes in response to HA when imbalanced or exaggerated can be responsible for HA related illnesses like Acute Mountain Sickness (AMS), High Altitude Cerebral Edema (HACE) and High Altitude Pulmonary Edema (HAPE) in susceptible individuals. Acetazolamide and Dexamethasone are the main prophylactic and therapeutic modalities for AMS and HACE, as per the guidelines given by the expert panel convened in 2009 by Wilderness Medical Society (WMS). However, there is no substantial data supporting role of these two drugs in prevention of HAPE. Dexamethasone is shown to prevent HAPE in susceptible individuals probably by decreasing systolic pulmonary arterial pressure (1). Similarly, clinical observations suggest that Acetazolamide may prevent re-entry HAPE in children re-entering HA because it facilitates acclimatization and possibly reduces hypoxic pulmonary vasoconstriction as shown in animal models (2). The expert panel also recommends that in rare circumstances (eg, military or rescue teams who must ascend rapidly to and perform physical work at altitudes 3500 m), consideration can be given to the concurrent use of acetazolamide and dexamethasone (3).

It is also well known that Exercise Capacity decreases as PIO_2 falls on ascent to HA. The Exercise Capacity declines ~1% per 100 m altitude

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gain above 1500 m even after complete acclimatization (4). It remains to be seen whether use of Acetazolamide with Dexamethasone or with placebo brings any change in Exercise Capacity on ascent. Earlier studies have shown varied results. The effects of use of Acetazolamide alone on Exercise Capacity in hypoxic conditions have been variable with reporting of decreased (5), increased (6) and unchanged outcome (7). On the other hand, Dexamethasone, when used alone partially prevented the limitation of Exercise Capacity in adults prone to HAPE at 4559 m (8, 9). Effects of use of combination of these two drugs on Exercise Capacity at HA have been poorly explored in literature. Therefore this pilot study was planned which involved comparison of combination of these two drugs with Acetazolamide alone on cardiovascular and other physiological parameters and Exercise Capacity of low-landers when ascending from 2600 m to 3500 m.

Methods

Selection of subjects

40 healthy lowlander males (between age group of 24 to 35 years), being freshly inducted to HA by road, were considered for the study. These subjects were exposed to HA (2600m) for the first time on Day-0(D-0). Before becoming part of the study, all subjects were actively involved in regular physical exercise (as part of their professional requirement) at their previous location situated at 200 feet above msl. The study was carried out between 20 Sep and 01 Oct 2011. All subjects were explained the experimental protocol and associated risks before the start of the study and written informed consent was taken from subjects volunteering for the study. The study protocol was cleared by Institutional Ethical Committee.

Experimental protocol

Within 2 hours of reaching 2600 m on D-0, subjects were matched for age, physical fitness, height and weight and randomly divided into 02 groups (Group 'A' and 'B') consisting of 20 subjects each by lottery method (Simple random sampling). All subjects of the study group were examined for cardiovascular and respiratory parameters at an altitude of 2600 m and subsequently every 12 hours for next 3 days till they arrived at 3500 m. During these examinations, any subject found to have any concurrent illness or any symptom suggestive of any HA related illness was excluded from the study. During these 3 days subjects passed through various altitude (while travelling by road) varying from 2600 m to 4000 m. The travel times for each day were 3 hr, 7 hr and 5 hr on Day-1 (D-1), Day-2 (D-2) and day-3 (D-3) respectively. Their sleeping altitudes were 2600 m, 3300 m, 3600 m and 3500 m on D-0, D-1, D-2 and D-3 respectively.

Group 'A' (Gp'A') subjects were started with Tab Acetazolamide 125 mg BD and Tab Dexamethasone 4 mg BD; whereas subjects of Group 'B' (Gp'B') were given Tab Acetazolamide 125 mg BD and Placebo after the exercise testing at 2600 m. All medications for the study group were continued under supervision thereafter for 4 days (D-0 to D-3). Also, 8 individuals, selected by simple random sampling, from each study group were evaluated for Exercise Capacity at 2600 m and again on D-4 at 3500 m.

The resting cardio-respiratory parameters like Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Oxygen Saturation (SpO_2) and Respiratory Rate (RR) were measured using Multi-parameter Monitor (Schiller Truscope Classic). AMS was assessed by Lake Louise protocol, which consisted of self reported questionnaire and a clinical examination. All subjects were evaluated between 0530 and 0630 hrs in the morning and between 1930 and 2030 hrs in the evening in closed room having facilities of heating the room air with ambient temperature being maintained between 20° to 22°C.

The study protocol involved subjects to undertake exercise on Bicycle Ergometer (Monark Ergomedic 839E, GIH Sweden) with continuous HR monitoring by using POLAR Wear Link transmitter as part of POLAR RS 400 Heart Rate Monitor (Polar Electro Oy, Finland).

The Exercise Capacity was measured by giving the

exercise schedule consisting of warm up period of 2 minutes initially followed by initial exercise load of 100 W on the Bicycle Ergometer while maintaining 50 rpm throughout the exercise protocol. The subjects continued to exercise at this load for 06 min. HR was measured at the end of 5th min and 6th min. If the subject achieved HR of 130-170 bpm (beats per minute) at the end of 6th min and the difference in HR was not more than of 5 bpm, mean of HR of last 2 minutes was taken and the final workload was noted for calculation of Exercise Capacity. If the HR response of the subject was less than 130 bpm at 100 W, the load was increased to 150 W and the whole of the protocol was repeated with an aim of achieving difference of not more than 5 beats between the 5th and 6th minute readings. Finally the predicted Exercise Capacity was noted based on this HR using Astrand Nomogram (10).

Statistical analysis

All recorded data was expressed in Mean±S.D. Parameters of Gp'A' and Gp'B' at 3500 m were compared using unpaired 't' test whereas intra-group changes in parameters on ascent from 2600 m to 3500 m were analysed using paired 't' test. Two-way ANOVA was applied to evaluate the effects of rise in altitude and pharmacological intervention on Exercise Capacity. Statistical significance meant that 'p' value of the corresponding statistical test was ≤0.05.

Results

Our subjects tolerated exposure to HA well and only one subject from Gp'B' had Lake Louise Score of more than three on evening D-2 at sleeping altitude of 3600 m, which could have been due to prolonged travelling time in mountainous terrain (7 hours) on D-2.

Gp'A' showed significant increase in resting HR, RR and significant fall in resting SBP after induction from 2600 m to 3500 m. Similar findings of significant increase in resting HR, RR and fall in resting SBP were seen in Gp'B' (Table I).

Resting cardiopulmonary parameters of Gp'A' and Gp'B' at 3500 m, when analysed using unpaired 't' test, showed no significant difference. Also, there was no significant difference in Exercise capacities of Gp'A' and Gp'B' at 2600 m and after ascent to 3500 m (Table II).

Discussion

The purpose of the present study was to test the hypothesis that concurrent use of Acetazolamide and Dexamethasone is superior to Acetazolamide alone in lowlanders ascending from 2600 m to 3500 m in terms of cardiopulmonary parameters and exercise

TABLE I: Analysis of resting cardiopulmonary parameters of Gp'A' and Gp'B' at 2600m and 3500m with paired 't' test (n=20).

	Group 'A'		*Group 'B'*	
	At 2600 m	*At 3500 m*	*At 2600 m*	*At 3500 m*
HR(bpm)	65.2±8.77	69.05±7.63*	70.7±8.62	77±9.72##
SBP (mmHg)	128.3±7.5	123.3±6.51**	123.95±6.75	120.05±7.28$
DBP (mmHg)	75.05±7.83	73.95±6.29NS	76.7±8.75	74.55±8.01NS
MAP (mmHg)	89.65±8.92	86.95±8.5NS	89.45±8	88.6±5.63NS
SpO_2(%)	93.6±1.28	93.9±1.34NS	92.5±1.57	92.75±1.7NS
RR(per min)	18.35±3.55	19.7±4.94#	18±3.62	19.6±3.67$$
Paired 't' test	*t=2.29	**t=2.94 #t=2.33	##t=3.63	$t=2.41 $$t= 3.64
df=19, 5% significant limit is 2.09	NS = Not significant		NS = Not significant	

TABLE II: Two Way Analysis of Variance of Exercise Capacities of Gp'A' and Gp'B' at 2600 m and 3500 m.

	At 2600 m	*At 3500 m*	*At 2600 m*	*At 3500 m*
Exercise Capacity (L/min) (n=8)	2.55±0.35	2.58±0.37	2.21±0.38	2.26±0.44

F = 2.95, df = 3,28; p<0.05, No statistically significant difference observed (Computed 'F' Ratio=0.19).

capacity. We observed a significant rise in resting HR, RR and a significant fall in resting SBP in both the groups after ascent. There was no difference in Exercise Capacities achieved by two study groups at 3500 m.

Rise in resting HR seen in both the groups can be attributed to direct sympathetic activation via stimulation of peripheral chemoreceptors and vagal withdrawal mediated by afferent discharge due to rise in ventilation and increase in work of breathing (11). This rise seen in ventilation could be a combined interaction of both response to hypoxia and effect of acetazolamide mediated acidosis. In the present study, a rise of 7.36% and 8.89% was seen in resting RR in Gp'A' and Gp'B' respectively after ascent. Although Dexamethasone prophylaxis decreases pulmonary arterial resistance and enhances alveolar fluid clearance, thereby improving the oxygenation but the influence of this action on respiratory rate could not be observed in combination with acetazolamide (3, 9).

Significant fall in resting SBP in both the groups could be a manifestation of sympathetic down-regulation occurring at plains in response to sustained sympathetic activation (12, 13). The variation in observed response to hypoxia could be an inter-play of training status of the individuals and response to acetazolamide. One of the observed beneficial effects of Acetazolamide in acclimatization is improved levels of PaO_2. This could be a contributing factor resulting in varied response of SBP to hypoxia (14).

Our subjects from both the groups did not show hypoxia related decline in Exercise capacity after reaching 3500 m. According to Fulco and colleagues a fall of 9% was expected in exercise capacity of our subjects when they gained an altitude of 900 m over 4 days. On the contrary an insignificant rise in Exercise Capacity was seen in both the groups which could be attributed to pharmacological intervention (4).

Similar findings of increased exercise capacity of 6 healthy males in hypoxic conditions (FiO_2=0.118) because of higher PAO_2 and PaO_2 resulting from intake of Acetazolamide have been reported by Schoene et al (6). Other studies have reported contrary outcomes of no effect or fall in Exercise capacity on use of acetazolamide at HA. This difference in findings could be due to variable experimental conditions, training status of individuals, dose regimen, altitude of evaluation and mode of exercise (5, 7).

It remains to be seen if Dexamethasone contributes to changes in Exercise capacity of Gp'A'. Fischler et al have reported that Dexamethasone prevented the limitation of Exercise Capacity in HAPE susceptible mountaineers at 4559 m. Authors brought out that Dexamethasone resulted in improved ventilation-perfusion ratio because of enhanced availability of NO and alveolar Sodium-water clearance responsible for maintenance of Exercise capacity. But conclusions of this study might not necessarily be applicable to our subjects of Gp'A' who were not HAPE susceptible. As there was no difference observed in exercise capacities of two groups at 2600 m and 3500 m and only common factors affecting subjects of both the groups were acetazolamide and gain in altitude, it can be implied that role of Dexamethasone, as compared to acetazolamide, in preventing hypoxia related fall in exercise capacity remains obscure (8).

Our study had its own limitations like small sample size, HR based measurement of Exercise Capacity and absence of a control group. The sample size was kept smaller in view of administrative and logistic limitations like electricity/generator supply at the places of evaluation. It was imperative to do the sub-maximal exercise testing based on HR, especially when it was done in temporary exercise laboratories established in fairly remote areas away from the medical settings. Although HR based method for evaluation of exercise capacity using Astrand Nomogram has its limitations but has been proved to be valid in clinical monitoring and research purposes (15). A control group was excluded from the study for ethical considerations by institutional Ethical Committee.

In conclusion, the present study suggests that the prophylactic use of Acetazolamide could possibly result in absence of decrement in exercise capacity in healthy males between 24 to 35 years on induction from 2600 m to 3500 m. The beneficial role of Dexamethasone in combination with Acetazolamide, if any, remains obscure.

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