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Effects of acetazolamide on overnight oxygenation and acute mountain sickness in patients with asthma

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ABSTRACT: The aim of the study was to assess effects of acetazolamide in prevention of acute mountain sickness (AMS) and on overnight oxygenation, in patients with asthma treated at the altitude of 3,200 m.

Sixteen patients with asthma, 6 males and 10 females, mean age 32 yrs, were first investigated at low altitude (760 m). They presented with mild airways obstruction, normal arterial blood gases, and normal oxygenation at night studied by pulse oximetry. After initial investigations, patients were divided by random number into the treated (T) and control (C) groups of eight patients each. T group patients received acetazolamide, 750 mg daily for 2 days, before the ascent and on the first day at altitude (3,200 m).

Symptoms of AMS developed in seven patients from group C and in three from group T. The overnight pulse oximetry, performed on the first night at altitude, revealed that group T patients had statistically higher ($p<0.05$) initial, 91 *vs* 87%, mean, 90 *vs* 86%, and minimum, 84 *vs* 75%, arterial oxygen saturation than group C patients. Overnight pulse oximetry was repeated on the 5th, 10th and 17th day at altitude, and showed that in group C patients, from the 5th day onwards, oxygenation improved to the level observed in group T patients on the first night.

We conclude that pretreatment with acetazolamide before the ascent prevented patients with asthma from developing symptoms of AMS, and alleviated acute changes in arterial oxygen saturation brought about by the high altitude hypoxia.
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The climatic treatment of asthma by sojourn in the mountains has been prescribed for many years. Its rationale is based on several facts. Firstly, house dust mites, a common allergen in asthma, cannot survive at an altitude of more than 1,500 m above sea level [1, 2]; secondly, there is a lack of environmental industrial pollution; and finally, the mountain climate has immunostimulating features [3]. Development of potent antiasthmatic drugs to control the disease has made this type of treatment much less frequently prescribed.

The majority of mountain medical centres devoted to climatic treatment of asthma are situated at middle altitude, ranging from 1,000–2,000 m. Presumably, the highest is the Tuja-Ashu Sanatorium, situated at 3,200 m above sea level, in the Northern Tien-Shan mountains (Kyrgyzstan).

Positive effects of the treatment of asthma at the Tuya-Ashu Sanatorium, evidenced by improvement of spirometric indices and reduction of medication in more than 1,000 patients treated there, have been reported previously [4–6].

The barometric pressure at the level of 3,200 m decreases to approximately 512 mmHg [7]. The oxygen pressure in the inspired air is reduced to about 107 mmHg (dry), and 98 mmHg (fully saturated in water vapour at 37°C), resulting in chronic hypoxaemia in all transients at that altitude.

Newcomers to high altitude frequently develop acute mountain sickness (AMS), characterized by headache, fatigue, dizziness, palpitations, loss of appetite, nausea and insomnia. AMS is common at altitudes above 4,000 m [8] but may also develop at the altitude of 3,000 m [9, 10]. Several authors have reported that AMS may be prevented or treated with the ventilatory stimulant, acetazolamide [11, 12].

Symptoms of AMS of varying severity were also observed in the majority of asthmatics, treated at Tuja-Ashu in the past, during the first days after arrival at altitude. Although symptoms were self-limiting, and disappeared within 3–5 days, they negatively influenced the emotional status of patients and, sometimes, affected the efficacy of high-altitude treatment [6].

High altitude alveolar hypoxia and hypoxaemia may be aggravated at night by alveolar hypoventilation during

non-rapid eye movement (nREM) sleep, and disordered breathing during REM sleep [13]. Increased airway resistance during sleep in asthmatics may additionally affect pulmonary gas exchange [14].

The aim of this study was: 1) to investigate the severity of nocturnal hypoxaemia in asthmatic patients after the ascent to 3,200 m; 2) to estimate effects of pretreatment with acetazolamide on frequency and severity of AMS and of nocturnal hypoxaemia; 3) to assess acclimatization to altitude by repeated overnight oximetry.

Patients and methods

Sixteen patients with bronchial asthma (6 males, 10 females), aged 22–49 yrs, were studied. The diagnosis was based on the typical history, physical examination, lung function tests, eosinophilia in the blood and sputum, and positive results of skin prick tests. The duration of disease ranged from 2–20 yrs. Almost all patients had daily bouts of breathlessness, which were relieved by inhaled beta$_2$-agonist. Five patients were treated with small doses of prednisolone (mean 4.2±2.1 mg·day^{-1}).

The initial investigations were performed in Bishkek (760 m above sea level) at the Pulmonary Division of the Kyrghyz Institute of Cardiology. Clinical examination, spirometry (Eton-01 spirometer), blood gas measurements (OP-215 blood gas analyser), and overnight pulse oximetry (Minolta Pulsox-7 oximeter) were performed. Transcutaneous oxygen saturation ($S_{tc}O_2$) was continuously monitored between 11 pm and 7 am. Recordings were then evaluated by means of an IBM PC computer program, calculating initial, minimum and mean $S_{tc}O_2$. Initial $S_{tc}O_2$ was the average $S_{tc}O_2$ of the first 30 min of the recording, resting awake. Minimum $S_{tc}O_2$ was the mean of the lowest $S_{tc}O_2$ recorded during each of the desaturation episodes. Levels and duration of episodes of desaturation greater than 4% below the initial level were calculated. After the initial investigations, patients were randomly divided (single-blind) into two groups. The control group (C; 8 patients) continued anti-asthmatic treatment. The treated group (T; 8 patients), additionally received acetazolamide, 250 mg *t.i.d.*, for 2 days preceding the ascent and during the first day at altitude.

The patients were driven to the sanatorium at Tuya-Ashu Pass by car. The journey lasted about 4 h. After arrival, patients were advised to restrict their physical activities, and to spend more time in bed. From the 3rd day onwards they were allowed to increase their physical activities.

The diagnosis of AMS was based on the presence of typical symptoms, such as headache, dizziness, sleep disturbance, fatigue, nausea and palpitations. The severity of symptoms was scored on a 4 point scale: 0=no symptom; 1=moderate; 2=marked; 3=severe. Overnight oximetry was repeated on the 1st, 5th, 10th and 17th night after the ascent. Blood gases were measured on the 10th day after the ascent. Spirometry was repeated on the 20th day after the ascent. Statistical analysis comprised Student's t-test for paired and unpaired parametric data.

Table 1. – Anthropometric, spirometric and blood gas variables in acetazolamide treated (T) and control (C) groups

	Group T n=8	Group C n=8	p
Age yrs	34±3	32±3	NS
Sex F/M	6/2	4/4	NS
Height cm	165±8.9	163±7.4	NS
Weight kg	66±11.7	59±5.5	NS
VC *l*	3.42±0.3	3.84±0.3	NS
VC % pred	88±4	93±4	NS
FEV_1 *l*	2.09±0.3	2.38±0.31	NS
FEV_1 % pred	65±8	68±6	NS
FEV_1 %VC	61±11	62±15	NS
Pao_2 kPa	9.78±0.3	10.6±0.4	NS
$Paco_2$ kPa	4.14±0.07	4.33±0.09	NS
pH	7.42±0.01	7.43±0.01	NS
HCO_3^- meq·*l*$^{-1}$	19.9±1.1	20.4±1.7	NS

Data are presented as mean±SD. VC: vital capacity; FEV_1: forced expiratory volume in one second; Pao_2: arterial oxygen tension; $Paco_2$: arterial carbon dioxide tension; NS: nonsignificant.

Results

Both groups studied were well-matched with regard to age, sex, height, weight, blood gas and spirometric values (table 1). Two patients in group T, and three patients in group C, were receiving oral steroids. Severity of asthma symptoms were similar in both groups. Arterial blood gas measurements revealed mild hyperventilation, and spirometry showed mild to moderate airway obstruction.

Overnight oximetry was technically faulty in one patient from group T and one from group C. Those patients were excluded from oximetric analysis. In the remaining 14 subjects, overnight mean $S_{tc}O_2$ was normal. Patients from both groups spent less than 3% of the total recording time with hypoxaemia greater than 4% below the initial level.

On the 1st or the 2nd day after ascent, some patients developed signs of AMS. The incidence and severity of symptoms of AMS were markedly different in the study groups (table 2). Subjects from the control group more often had headache and palpitations than patients from the treated group (7 and 4 subjects, respectively).

Table 2. – Incidence and severity of acute mountain sickness (AMS) after arrival at high altitude

Symptoms	Group C n=8		Group T n=8	
	Incidence Subjects n	Severity points	Incidence Subjects n	Severity points
Headache	7	1.75±0.37	3	0.75±0.37
Dizziness	1	0.13±0.12	2	0.25±0.16
Palpitation	4	1.25±0.49	3	0.38±0.18
Fatigue	3	0.50±0.27	-	-
Nausea	2	0.50±0.27	-	-
Insomnia	1	0.50±0.27	-	-
Somnolence	1	0.13±0.12	-	-
Epistaxis	1	0.13±0.12	-	-

Results are mean±SD.

The severity of these symptoms was also more pronounced in the controls. Three patients from this group complained of fatigue, two had nausea, two reported insomnia or somnolence. One patient developed epistaxis. None of the patients receiving acetazolamide reported the last five symptoms. The signs of AMS resolved by the 3rd–4th day after ascent. The ascent to altitude did not provoke any worsening in asthma symptoms in any of the patients studied.

On ascent from 760 m to 3,200 m, a fall in $S_{tc}O_2$ was observed (fig. 1). It was significantly more pronounced in the control group than in the treated group, averaging 86.9±2.5 *vs* 91.0±2.0% in groups C and T, respectively, ($p<0.01$) on the first day at high altitude. The mean nocturnal $S_{tc}O_2$ was also significantly lower in group C ($p<0.01$) (fig. 2).

Values of overnight oximetry in treated patients remained relatively stable from the 1st to the 17th day. In the control group, initial, mean and minimum $S_{tc}O_2$ increased by the 5th day to reach the level observed in group T. Further recordings of $S_{tc}O_2$ revealed no significant differences between study groups (figs 1–3).

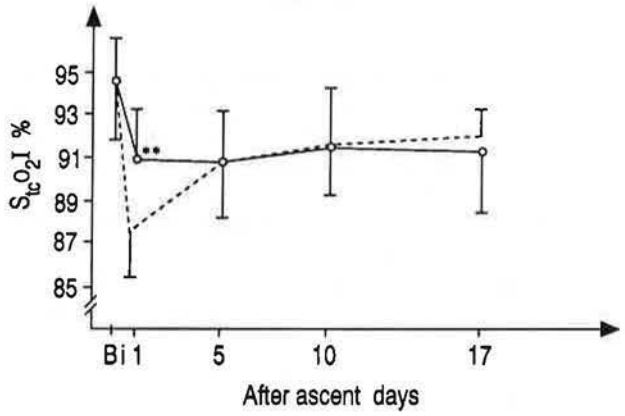

Fig. 1. – Initial (awake) saturation of arterial blood in acetazolamide treated (T) and control (C) groups, recorded at low altitude in Bishkek (Bi), and serially at altitude. Data are presented as mean, bars indicate SD. $S_{tc}O_2I$: initial awake transcutaneous oxygen saturation. o——o : treated; ------- : control; **: difference between groups significant ($p<0.01$).

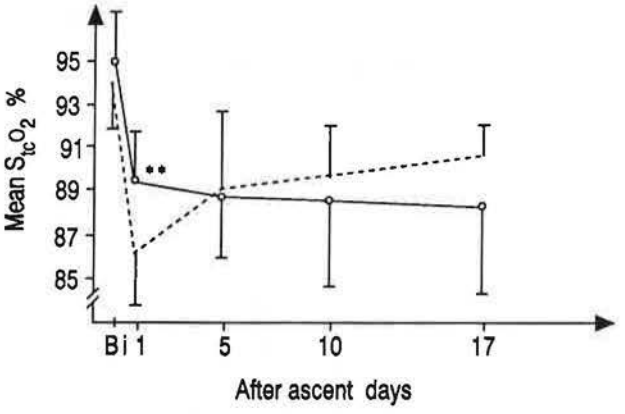

Fig. 2. – Mean overnight saturation of arterial blood. Data are presented as mean, bars indicate SD. Bi: recorded at low altitude in Bishkek. o——o : treated; -------: control. $S_{tc}O_2$: transcutaneous oxygen saturation. **: difference between groups significant ($p<0.01$).

Patients in both groups were moderately hypoxaemic when awake. Blood gases, studied on the 10th day at altitude, showed hypoxaemia and mild respiratory alkalosis (table 3). During sleep, arterial oxygen saturation fell, with transient drops below 60%. The number of desaturations averaged more than 100 episodes per night (fig. 3). Time spent in desaturations averaged 15–35% of total recording time (fig. 4).

The meteorological conditions at Tuya-Ashu were variable. Cloudy or rainy weather prevailed, with a few days of sunshine or snow. Outdoor temperature ranged from -1 to +5°C in the early morning, and from 0 to +10°C at midday. Outdoor humidity ranged from 58–100%. Indoor humidity ranged from 44–62%. Indoor temperature was relatively stable, ranging from 16–22°C. The atmospheric pressure ranged from 682.3–688.9 kPa.

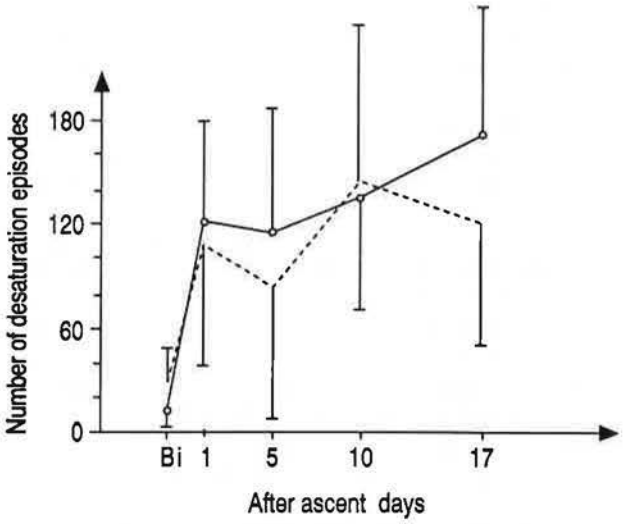

Fig. 3. – Number of overnight desaturation episodes greater than 4% below initial level. Data are presented as mean, bars indicate SD. Bi: recorded at low altitude in Bishkek: o——o : treated; -------: control.

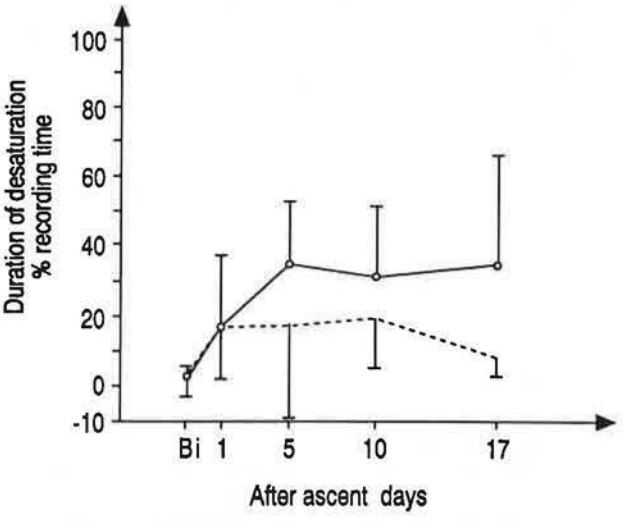

Fig. 4. – Duration of desaturation in % of total recording time. Data are presented as mean, bars indicate SD. Bi: recorded at low altitude in Bishkek. o——o : treated; -------: control.

Table 3. – Arterial blood gas analysis in acetazolamide treated (T) and control (C) groups on the 10th day after the ascent

	Group T	Group C
Pa_{O_2} kPa	7.58±0.2	7.86±0.2
Pa_{CO_2} kPa	4.04±0.1	4.18±0.1
pH	7.46±0.01	7.45±0.01
HCO_3^- mM	21.8±0.7	20.8±0.7

Data are presented as mean±SD. For abbreviations see legend to table 1.

After the first three days at altitude, patients spent most of the time walking, playing volleyball, or exercising (callisthenics). By the end of the 25th day, the number of asthmatic attacks had diminished and the dose of drugs in individual patients was reduced.

Spirometry was repeated at the 20th day at altitude. Vital capacity and forced expiratory volume in the first second (FEV_1) had significantly increased in both groups (table 4).

Discussion

The purpose of this study was to investigate oxygenation during sleep, in patients with asthma at high altitude. We also determined the effect of pretreatment with acetazolamide on the development of acute mountain sickness.

Randomization of the study group resulted in well-matched subgroups. When studied at low altitude, all patients presented with mild to moderate airways obstruction and normal blood gas values. Overnight pulse oximetry revealed normal oxygenation, with a few episodes of desaturation. Our results are similar to those observed in a group of asthmatics submitted to a polysomnographic study in Edinburgh [15], although minimum $S_{tc}O_2$ was lower in our study.

Table 4. – Spirometry in control (C), and acetazolamide treated (T) groups at low altitude (A), and on the 20th day at high altitude (B)

Variable	Group	A	B
VC % pred	C	93±4	105±3**
	T	88±4	103±6**
FEV_1 % pred	C	68±6	92±3**
	T	65±8	87±9**
MEF_{25} % pred	C	63±10	74±7
	T	49±9	71±13
MEF_{50} % pred	C	54±9	58±6
	T	42±9	51±10

Data are presented as mean±SD. **: $p<0.01$. MEF_{25}: maximal expiratory flow at 25% of the expired volume; MEF_{50}: maximal expiratory flow at 50% of the expired volume. For further abbreviations see legend to table 1.

Pretreatment with acetazolamide prevented symptoms of acute mountain sickness, which were significantly less frequent and less severe in treated than in non-treated patients. No effects of acetazolamide on symptoms of asthma, either at low or high altitude, were observed. The protective effect of acetazolamide against symptoms of AMS was probably related to the better oxygenation of patients receiving the drug. Acetazolamide produces chronic hyperventilation in normal subjects [16, 17], by increasing the blood hydrogen ion concentration, which acts at both peripheral and medullary chemoreceptor sites [18]. H^+ increase is attributed to renal loss of HCO_3^-, caused by inhibition of renal tubular carbonic anhydrase. Carbonic anhydrase inhibitors also influence HCO_3^-/H^+ reactions within lungs, by affecting carbonic anhydrase activity in the pulmonary endothelium [19]. One recent study suggested that acetazolamide also inhibits peripheral chemoreceptors [20].

Acetazolamide induced hyperventilation also alleviated acute change in arterial oxygen saturation resulting from a rapid ascent to high altitude. Ascent to altitude in patients receiving acetazolamide caused a fall in $S_{tc}O_2$ from 95 to 91%. In non-treated patients, $S_{tc}O_2$ fell during a few hours from 95 to 87%. Such a drop may have resulted in a marked reduction in oxygen transport. Similar effects of acetazolamide on arterial oxygen saturation were observed by HACKETT *et al.* [21] in healthy subjects at high altitude.

We did not obtain data on the effects of acetazolamide on the acid-base balance in patients with bronchial asthma. LANE *et al.* [22] studied arterial and cerebrospinal fluid, respiratory gases, and hydrogen ion concentration in 23 patients with chronic diffuse obstructive disease. Some of them, not numbered, were diagnosed as having "allergic airways disease". Thirteen were restudied after receiving carbonic anhydrase inhibitor. Metabolic acidosis developed in all subjects studied. We assume that the ventilatory effects of acetazolamide in patients with asthma are no different from those observed in normals, or in patients with chronic obstructive lung disease.

The non-treated patients acclimatized more slowly to high altitude than treated subjects. There were no differences in the initial, mean and minimum $S_{tc}O_2$ between treated and non-treated group from the 5 day onwards. Arterial blood gases, investigated at the 10th day at altitude, revealed mild respiratory alkalosis and hypoxaemia, equal in both groups.

The number of desaturation episodes and time spent in desaturation at night were much higher at altitude, with marked individual differences. There are two possible mechanisms that may be responsible for this phenomenon. One is a marked difference in the arterial oxygen tension (Pa_{O_2}) at low and high altitude. At low altitude a physiological drop in Pa_{O_2} of 1.33 kPa (10 mmHg), during REM sleep in a normoxaemic patient, results in a fall in $S_{tc}O_2$ of some 2%. In subjects having a Pa_{O_2} of 7.7 kPa (58 mmHg) (the mean Pa_{O_2} of our studied groups at high altitude) the similar drop in Pa_{O_2} of 1.3 kPa (10 mmHg) results in a fall in $S_{tc}O_2$ of 9% [23].

Multiple oxygen desaturation episodes may also have

resulted from periodic breathing in the patients studied. Although periodic breathing becomes common at an altitude of 5,000 m, WAGGENER *et al.* [24] reported that it occupied 24% of sleep time in subjects studied at an altitude of 2,440 m. The differentiation between those two mechanisms needs to be investigated with more sophisticated equipment than we had at our disposal. The severity of the desaturation episodes at night depended upon the arterial oxygen saturation when awake whatever the mechanism involved.

Our patients had no symptoms of nocturnal asthma whilst at altitude. We may assume that there was no substantial increase in airways resistance that might be responsible for the desaturation episodes [25].

The improvement in spirometric variables may be explained by the increase in airways calibre, resulting from the remission of the disease. However, effects of decreased density of the inspired air should also be taken into account. GUENARD and DE BISHOP [26] demonstrated an increase in maximal expiratory flow at 50 and 75% of forced vital capacity, in healthy subjects in the early phase of a sojourn at an altitude of 3,700 m.

Despite exposure to chronic hypoxia, aggravated at night, all patients completed the high altitude cure and symptoms of asthma improved, as evidenced by the increase in spirometric indices and reduction of medication. Pretreatment with acetazolamide before ascent to altitude was helpful in reducing symptoms of AMS and in alleviating acute change in blood oxygenation.

References

1. Vervloet D, Penaud A, Razzouk H, *et al.* – Altitude and house dust mites. *J Allergy Clin Immunol* 1982; 69: 290–296.
2. Charpin D, Leisbauer J-P, Lanteaume BS, *et al.* – Asthma and allergy to house-dust mites in populations living in high altitudes. *Chest* 1988; 93: 758–761.
3. Meehan R, Duncan U, Neale L, *et al.* – Operation Everest II: alterations in the immune system at high altitudes. *J Clin Immunol* 1988; 8: 397–406.
4. Mirrakhimov MM, Shogentsukova EA. – Treatment of bronchial asthma by mountain climate. Nalchic, Elbrus Publishing House, 1975.
5. Mirrakhimov MM, Uspenskaya EP, Fedoseev GB. – Bronchial asthma and its treatment by hypobaric hypoxia. Leningrad, Medisina Publishing House, 1983.
6. Brimkulov NN. – High-altitude climatotherapy of patients with bronchial asthma: mechanisms of its effect and some ways of increasing its efficacy. Synopsis of the thesis for the degree of Doctor of Sciences in medicine. Moscow, 1990.
7. International civil aviation organization. Manual of the ICAO standard atmosphere. 2nd edn, Montreal, Quebec, International Civil Aviation Organization, 1964.
8. Hackett PH, Rennie D. – Rales, peripheral edema, retinal hemorrhage and acute mountain sickness. *Am J Med* 1979; 67: 214–218.
9. Kobayashi T, Koyama S, Kubo K, Fukushima M, Kusama S. – Clinical features of patients with high-altitude pulmonary edema in Japan. *Chest* 1987; 92: 814–821.
10. Fujimoto K, Matsuzawa Y, Hirai K, *et al.* – Irregular nocturnal breathing patterns at high altitude in subjects susceptible to high-altitude pulmonary edema (HAPE): preliminary study. *Aviat Space Environ Med* 1989; 60: 786–791.
11. Forwand SA, Landowne M, Follansbee JN, Hansen JE. – Effect of acetazolamide on acute mountain sickness. *N Engl J Med* 1968; 279: 839–845.
12. Birmingham Medical Research Expeditionary Society. Mountain Sickness Study Group. – Acetazolamide in control of acute mountain sickness. *Lancet* 1981; i: 180–183.
13. Krieger J. – Breathing during sleep in normal subjects. *In*: Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine. Philadelphia, W.B. Saunders Co. 1989; pp. 257–269.
14. Fitzpatrick MF, Mackay T, Driver H, Douglas NJ. – Salmeterol in nocturnal asthma: a double-blind, placebo-controlled trial of a long-acting inhaled β_2-agonist. *Br Med J* 1990; 301: 1365–1368.
15. Catterall JR, Douglas NJ, Calverley PMA, *et al.* – Irregular breathing and hypoxaemia during sleep in chronic stable asthma. *Lancet* 1982; i: 301–304.
16. Galdstone M. – Respiratory and renal effects of carbonic anhydrase inhibitor (Diamox) on acid-base balance in normal man and in patients with respiratory acidosis. *Am J Med* 1955; 19: 516–532.
17. Larsen EB, Roach RC, Schoene RB, Hornbein TF. – Acute mountain sickness and acetazolamide. Clinical efficacy and effect on ventilation. *J Am Med Assoc* 1982; 248: 328–332.
18. Chiesa A, Stretton TB, Massoud AAE, Howell JBL. – The effects of inhibition of carbonic anhydrase with dichlorphenamide on ventilatory control at rest and on exercise in normal subjects. *Clin Sci* 1979; 37: 689–706.
19. Takahashi E, Phillipson EA. – Effect of changing venoarterial pH difference on *in vivo* arterial pH. *J Appl Physiol* 1991; 70: 1586–1592.
20. Bashir Y, Kann M, Stradling JR. – The effect of acetazolamide on hypercapnic and eucapnic/poikilocapnic hypoxic ventilatory responses in normal subjects. *Pulm Pharmacol* 1990; 3: 151–154.
21. Hackett PH, Roach RC, Harrison GL, Schoene RB, Mills WJ. – Respiratory stimulants and sleep periodic breathing at high altitude. Almitrine *versus* acetazolamide. *Am Rev Respir Dis* 1987; 135: 896–898.
22. Lane DJ, Howell JBL, Stretton TB. – The effects of dichlorphenamide on blood and cerebrospinal fluid acid-base state in chronic ventilatory failure. *Clin Sci* 1977; 39: 391–406.
23. Douglas NJ, Calverley PMA, Leggett RJE, *et al.* – Transient hypoxaemia during sleep in chronic bronchitis and emphysema. *Lancet* 1979; i: 1–4.
24. Waggener TB, Brusil PJ, Koronauer RE, Gabel RA, Inbar GF. – Strength and cycle time of high-altitude ventilatory patterns in unacclimatized humans. *J Appl Physiol: Respirat Environ Exercise Physiol* 1984; 56: 579–581.
25. Montplaisir J, Walsh J, Malo JL. – Nocturnal asthma features of attacks, sleep and breathing patterns. *Am Rev Respir Dis* 1982; 125: 18–22.
26. Guenard H, de Bishop C. – Debits ventilatoires maximaux en altitude. *Science of Sports* 1989; 4: 137–143.