The Role of Drugs in High Altitude Disorders

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Acute mountain sickness (AMS) syndrome is a life threatening condition, which can best be managed by the descent. However, occasionally descent is impossible because of extreme weather, storms, avalanche conditions, enemy's encounter, or because the patient is too ill to move and beyond the reach of rescue services. The climber puts himself at extreme risk by choosing to ascent with symptoms clearly recognisable as those of AMS. His remarkable recovei should not seduce other high altitude sejourners into ignoring their symptoms and continuing to ascend while hoping for pharmacologic 'cure'. The pathophysiologic nature and effective pharmacologic treatment of AMS syndrome remain to be defined. Most people tend to underestimate the potential seriousness until it is too late for the person to make an easy descent. Various pharmacologic agents have been used for the treatment and prevention of AMS.

Acetazolarnide (Az) has been used for nearly 20 years to prevent or attenuate AMS. The reaction CO2 +H2OAH2CO3 is catalysed by carbonic anhydrase (CA) in red blood cells, lungs, brain and other organs. Az is a reversible and specific inhibitor of CA. There have been many studies demonstrating that Azaffects PCO2 values inblood, alveolar and brain tissue. The respiratory events include hyperventilation and a profound fall in alveolar PCO2 (PACO2), and arterial PCO_2 ($PaCO_2$2) increases slightly inin-vivo studies[1]. In a study[2]. Az not only reduced the features of AMS but also reduced the muscle and fat loss and increased exercise performance in acclimatised subjects. One clinical trial[3] on 20 subjects at 5000 m showed reduced symptoms of AMS ($P<0.02$) whilst taking Az compared with placebo and subjects improved their performance compared with a previous similar expendition ($P<0.005$). Arterial oxygenation in these subjects correlated with symptoms score and was higher whilst taking Az ($P<0.001$). Larger doses of Az have been reported[4] to increase arterial oxygen levels over a few hours leading to a reduction of AMS symptoms but data is limited and faster acting analogue such as Methazolamide may be preferable in an emergency situation. Az hastens acclimatisation and is useful inprophylaxis but is notconsideredeffective intheestablished cases of AMS.

The precise pathophysiology of AMS is unknown. The most widely accepted theory holds that the symptom complex is due to the development of high altitude cerebral oedema (HACE) that is probably vasogenic in origin. Dexamethasone (DMS). a potent synthetic gluco-corticoid with negligible mineralocorticoid activity, is effective in the management of cerebral oedema of diverse causes. The mechanism by which DMS exerts the observed beneficial effect in relieving AMS symptoms is not known. Assuring that AMS is caused by hypoxia induced cerebral ocdema, DMS may prevent symptoms by decreasing oedema formation. The drug is known to improve brain oedema, particularly of a vasogenic orinterstitial type. It may exert this beneficial effect either by improving the microcirculatory integrity or by decreasing cerebmspinal fluid formation. In a study[5], an evidence was found that DMS may alter the cerebral circulatory response to high altitude. DMS treatment resulted in a decrease in the normal vasodilation seen in retinal arteries at high altitudes. Given that, retinal circulation probably reflects cerebral circulation, DMS may have caused a reduction in cerebral blood flow. This may reduce oedema formation by decreasing filtration through the microcirculation. Alternatively, a vasoconstricting influence of DMS could improve the symptoms of brain oedema by reducing the absolute volume of blood without reduction of oedema itself. In another clinical trial[6], the reduction in symptoms in the DMS groups coincided with an increase in arterial oxygen saturation and a slight

improvement in spirornetric values. As the minute ventilation did not change the improvement in arterial oxygen saturation might have been due to a reduction in postulated interstitial pulmonary oedema. The weight loss in patients who received DMS support. might be the result of a more general mobilization of oedema fluid accumulated during the development of AMS. Recently, in a native study at 15000 feet altitude, the normality in arterial pH, PCO_2, PO_2, Na . K , Ca spirometnc variables, haematocnt, erythropoietin and other hormonal profiles was found better in the group given a combination therapy with DMS and Az than in subject placed onAz alone[7].

Some investigators[8] have studied the role of calcium channel blocker, Nifedipine, in the prevention and treatment of high altitude pulmonary oedema (HAPE) in HAPE¬susceptible subjects in ameliorating the symptoms. In a clinical trial[8], this amelioration occurred despite continued exercise at an altitude above 4000 m and without supplement oxygen. Prophylactic application of Nifedipine slow release preparation, 20 mg every 8 hours prevented HAPE in 9 out of 10 subjects with a history of radiographically documented HAPE upon rapid ascent and subsequent stay to an altitude of 4559 m. Seven of 11 comparable subjects who received placebo developed pulmonary oedema at 4559 m. As compared with the subjects who received placebo, those who received Nifedipine had a significantly lower mean systolic pulmonary artery pressure, alveolar-arterial pressure gradient of oxygen and symptom score of acute mountain sickness at 4559 m. This study suggested that Nifedipine effectively lowered hypoxic pulmonary hypertension and improved performance and gaseous exchange in mountaineers with HAPE resulting in the regression of alveolar and interstitial oedema. In a preliminary study[9] another calcium antagonist, Isradipine, has been used in the HAPE susceptible subject with no conclusive results.

Some studies[10] demonstrated a beneficial effect of vasodilators and especially short acting alpha blocker, on haemodynamics and oxygenation in persons with HAPE. These results emphasised the importance of pulmonary vasoconstnction and suggested a role for increased alpha adrenergic activity in the pathophysiology of HAPE. Hydralazine is said to interfere with sarcoplasmic calcium use in smooth muscle cells and to reduce pulmonary artery pressure (ppa) in some conditions. The fact that 02, Hydralazine and Nifedipine worked to approximately the same degree and that the effect of 02 and Nifedipine were not additive, suggest that they affected hypoxic pulmonary vasoconstriction. In a series of field trials[10] using 16 subjects with HAPE and 10 controls, pulmonary hemodynamics was measured by non-invasive Doppler echocardiography. The percent reduction in pulnionary vascular resistance and mean pulmonary artery pressure, respectively, were 46 and 33 for oxygen, 30 and 39 for Nifedipines, 29 and 25 with Hydralazine, 57 and 42 with Phentolomine, and 72 and 52 when oxygen and Phentrolainine were combined. All the vasodilators improved gas exchange, suggesting a link between oedema formation and pulmonary vasoconstriction. A number of vasodilators may be useful in the treatment of HAPE, the superiority of an alpha adrenergic blocker may implicate the sympathetic nervous system in the pathophysiology of HAPE.

The investigation of adrenergic blockers in HAPE is relatively new[10]. Phentolamine blocks both $alpha^1$ and $alpha^2$ receptors and is thought to act primarily on the arterial resistance, but venous vasodilation. especially in the lungs, may also play a role. The remarkable drop in systemic vascular resistance (SVR) than the pulmonary vascular resistance with excessive pulmonary vascular tone in HAPE, suggests that it is in part sympathetically mediated. Further studies with microneurography and no epinephrine kinetics are suggested to confirm this hypothesis.

Treatments other than descent and supplemental 02 have been discussed in this short review. Excercise gives rise to physiologic responses which may enhance AMS, HAPE and HAcE. Because of these physiologic responses to exercise, any form of treatment should always be accompa med by rest if descent is impossible. In a controlled trial[11] , it was demonstrated that mild to moderate cases of HAPE canbe treated with bed rest alone. In the setting of mountaineering. however, one should never rely on

rest as the only therapy of HAPE since the mortality of HAPE in Himalayas was estimated to be about 50% when descent is not possible and no other therapy is available[11]. The days of rest as principle form of treatment, may possibly be accompanied by analgesics or antiemetics assuring adequate fluid intake for mild to moderate AMS cases.

Two portable, fabric hyperbaric chambers are available in the market today; a) Gamow bag (maximal pressure 140 mbar, weight including pump 5.6 kg portable hyperbaric, Inc., Illion, Ny. 1335705010, USA); b) Certec bag (maximal pressure 220 mbar, weight including pump 4.2 kg, Certec, F-292 10 Sourcieux i.e., Mines, France). These devices allow a rapid descent by 1500 to 2500m depending on the altitude and the type of the bag. A rapid and considerable improvement of 02 saturation which is about equivalent to the administration of 2-3 litres of 02 per minute can be achieved and maintained as long as recompression is continued[12].

Expiratoiy positive airway pressure (EPAP) is known to improve gaseous exchange in various forms of pulmonary oedema, presumably by recruitment of microatelectatic alveoli[13]. The use of EPAP as opposed to continuous positive airway pressure reduces the probability of barotrauma and decreased venous return. Nevertheless, controlled studies comparing the long-term effects of EPAP with those of drug treatment are necessary, if EPAP is to be recommended as initial emergency treatment of HAPE. In view of the recent reports of successful treatment of HAPE with drugs, it seems unlikely, however, that this therapy will gain wide acceptance even if it should prove to be effective without significant side effects.

The mountain still remains an hostile and aggressive area. Doctors taking part in rescues must be skilled to both prehospital medical intensive care and knowledge of the mountain. Medical management must remain within the limits of diagnosis and transport therapy until arriving at the emergency section. In conclusion, low doses of Acetazolamide at high terrestrial range has proved to be a better prophylactic measure, whereas, dexamethasone invarying doses in accordance with the severity of high altitude problems is considered to be a preferable curative measure. The remaining drugs including calcium channel blockers and vasodilators are still in the experimental phase and need further exploration. The increase in the number of casualties necessitates to measure the efficacy of tight collaboration between the rescue services and medical teams.

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