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PHOSPHODIESTERASE 5 INHIBITORS EFFECTS ON ADAPTATION TO HIGH ALTITUDE, HAPE PREVENTION AND TREATMENT: A LITERATURE REVIEW

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ABSTRACT

Introduction: High-altitude pulmonary edema (HAPE) is a life-threatening, non-cardiogenic form of pulmonary edema that typically occurs within 2-4 days after rapid ascent above 2,500 meters. It is characterized by hypoxia-induced pulmonary hypertension, increased capillary hydrostatic pressure, and defected alveolar-capillary barrier integrity. Current preventive strategies include gradual ascent and acclimatization, while descent and supplemental oxygen remain the mainstays of treatment. Pharmacological options, including phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil and tadalafil, appear as promising agents due to their pulmonary vasodilatory effects mediated via the nitric oxide (NO)-cGMP pathway.

Description of the state of knowledge: This review synthesizes findings from clinical trials, case series, and mechanistic studies published in the last three decades to evaluate the efficacy and safety of PDE5 inhibitors in both the prevention and treatment of HAPE. Evidence indicates that sildenafil and tadalafil effectively reduce pulmonary artery pressure, improve oxygenation, and preserve endothelial barrier function under hypoxic conditions. Their prophylactic use significantly lowers HAPE incidence in high-risk individuals, while therapeutic administration has demonstrated clinical improvement in established cases, particularly when nifedipine use is contraindicated. However, results from some high-altitude trials remain inconclusive, and individual responses may vary based on ascent profile and susceptibility.

Conclusions: Overall, PDE5 inhibitors represent a viable adjunct in HAPE management. Further large-scale, randomized studies are necessary to clarify their optimal use, dosage, and comparative efficacy alongside existing pharmacologic options.

KEYWORDS

HAPE, Sildenafil, Tadalafil, High Altitude Pulmonary Edema, PDE5 Inhibitors, Phosphodiesterase-5 Inhibitors, AMS, Acute Mountain Sickness

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Introduction and purpose:

It is estimated that more than 140 million individuals worldwide reside at elevations exceeding 2,500 meters.⁽¹⁾ Additionally, large numbers of lowland inhabitants travel to high-altitude regions each year for occupational or recreational purposes. For example, during the construction of the Qinghai-Tibet railway between 2001 and 2005, a significant proportion of the 100,000 workers operated at altitudes reaching 5,000 meters, where they were exposed to severe hypoxic conditions.⁽²⁾ HAPE most commonly develops within the first 2 to 4 days following ascent to altitudes above 2,500 meters, and may occur independently of preceding symptoms of acute mountain sickness. Its risk factors largely overlap with those associated with AMS and high-altitude cerebral edema (HACE) and include rapid ascent, sleeping at high altitude, previous history of HAPE, low-altitude residence, physical exertion. The role of dehydration remains unclear.⁽³⁾ High altitude pulmonary edema is the most common cause of death related to high altitude.⁽⁴⁾ Early symptoms include exertional dyspnea, reduced exercise tolerance, and dry cough, which can progress to breathlessness at rest, orthopnea, and productive cough with pink frothy sputum in severe cases. Further clinical signs include cyanosis, tachycardia, tachypnea, and low-grade fever, often not exceeding 38.5°C. Auscultatory findings may initially be subtle, located over the mid-lung zones, despite radiographic evidence of widespread pulmonary involvement. In advanced stages, neurological symptoms such as ataxia and altered consciousness may indicate concurrent high-altitude cerebral edema.^(5,6)

Slow ascent rate and acclimatization are the most effective ways of preventing HAPE, even in prone individuals which had documented HAPE episodes previously. Three climbers who had previously had at least two radiologically documented episodes of HAPE after rapid ascents in the Alps remained asymptomatic on subsequent high-altitude expeditions at an average altitude gain of 300–350 m/day above 2000 m above sea level. On the other hand no one is completely resistant to developing HAPE when ascent rate to high altitude is fast

enough⁽⁷⁾ Immediate improvement of oxygenation is the treatment of choice; descent remains the most effective intervention, while pharmacological therapy such as nifedipine or possibly sildenafil may be beneficial when descent is delayed or impossible⁽⁵⁾ As case series demonstrates the majority of patients with HAPE, are treated with nifedipine in addition to descent and oxygen therapy, and multiple patients received adjunctive medications such as sildenafil, dexamethasone, or acetazolamide based on severity of hypoxemia⁽⁸⁾

The aim of this study was to assess the role of Phosphodiesterase 5 inhibitors in prevention and treatment of High Altitude Pulmonary Edema. Our study material consisted of publications, which were found in PubMed, and Google Scholar databases. Combinations of key words such as: HAPE, High Altitude Pulmonary Edema, sildenafil, tadalafil, phosphodiesterase-5 inhibitors were used to find proper publications. The first step was to find proper publications from the last 30 years. The second step was to carry out an overview of the found publications.

Hape Patomechanism

Experimental findings suggests that High-altitude pulmonary edema (HAPE) is primarily characterized by an excessive rise in pulmonary artery pressure caused by hypoxic pulmonary vasoconstriction despite left atrial pressure remaining within normal range, indicating that increased pulmonary capillary hydrostatic pressure, rather than increased permeability, is the central mechanism underlying early HAPE pathogenesis.⁽⁹⁾ Increase in Pulmonary Artery pressure in susceptible individuals during high-altitude exposure, leads to mechanical stress failure of the alveolar-capillary barrier. This results in a non-inflammatory, high-permeability protein-rich and mildly hemorrhagic pulmonary edema, as evidenced by significant increases in alveolar lavage red blood cells and plasma-derived proteins, with normal levels of leukocytes, cytokines, and eicosanoids.⁽¹²⁾ Furthermore, lack of increase in exhaled NO in HAPE-susceptible individuals suggests that HAPE is not preceded by airway inflammation⁽¹³⁾ There is significant difference in pulmonary vascular response between HAPE-susceptible and HAPE-resistant individuals, where susceptible individuals present increase in pulmonary blood flow heterogeneity in response to acute hypoxia, this results in areas of under perfusion and overperfusion.⁽¹⁰⁾ These findings correspond with hypothesis of stress failure caused by high capillary transmural pressure leading to their increased permeability.⁽¹¹⁾ Some authors speculate that a defect in pulmonary NO production could be one of the factors contributing to the exaggerated hypoxia-induced pulmonary hypertension in HAPE-prone subjects.⁽¹³⁾ While acute hypoxia does not result in measurable changes in nasal nitric oxide (NO) excretion in either HAPE-susceptible individuals or healthy controls, it selectively impairs NO excretion in the lower respiratory tract of HAPE-susceptible subjects. This excretion reduction correlates with sustained rise in pulmonary artery pressure, which is significantly greater than that observed in healthy individuals under the same hypoxic conditions. These findings suggest a potential role of impaired endogenous NO signaling in the pulmonary circulation as a contributing factor to the pathogenesis of HAPE.⁽¹⁴⁾

Phosphodiesterase 5 inhibitors effects on high altitude physiological reactions:

Most studies on the effects of PDE5 inhibitors focus on preventing the increase in pressure in the pulmonary artery. Ghofrani et. al carried out randomized clinical trial, including healthy volunteers, it demonstrated that single dose of sildenafil (50 mg) significantly reduced pulmonary artery pressure both in lowland hypoxia, and at high altitude (Everest Base Camp). Participants receiving sildenafil had lower pulmonary artery pressure values at rest, higher cardiac output and better exercise tolerance than individuals receiving placebo. Moreover, in sildenafil group significantly higher blood oxygenation values were observed during exercise in hypoxia.⁽¹⁵⁾

Ricart et. all examined patients in simulated hypoxia conditions. Following administration of sildenafil (100mg), a significant reduction in pulmonary artery pressure was observed during hypoxia – to 34.9 ± 3.0 mmHg at rest ($p = 0.005$) and to 42.9 ± 2.6 mmHg after exercise ($p = 0.0005$) without affecting pulmonary pressure under normoxic condition, suggesting selective inhibition of hypoxic pulmonary vasoconstriction. Sildenafil also caused a small but statistically significant increase in SaO₂ during exercise in hypoxia – from $63.5 \pm 5.4\%$ (placebo) to $65.0 \pm 4.3\%$ ($p = 0.05$). Despite having little effect on blood oxygenation, its hemodynamic effects may be crucial in preventing HAPE⁽¹⁶⁾

In double blinded placebo-controlled study Reichenberger et al. examined 14 healthy Swiss and German members of Mount Everest expedition, focusing on hypoxia induced changes in pulmonary artery pressure and right ventricular function at rest. In conditions of normobaric and high-altitude hypoxia, sildenafil has been shown to significantly reduce the increase in systolic pulmonary artery pressure (sPAP) and improve the

global right ventricular function (TEI index). Biggest effect was observed at 5225m, where sildenafil decreased sPAP by an average of 7,1mmHG and significantly improved TEI index. ⁽¹⁷⁾

In a prospective observational study, Iwase et al. (2016) investigated the incidence of altitude-induced pulmonary hypertension (PH) and the therapeutic effects of sildenafil in 25 recreational climbers undertaking a one-day rapid ascent of Mount Fuji (3775 m). The study found a significant increase in pulmonary artery systolic pressure (PASP) from a baseline of 22.3 ± 5.3 mmHg at sea level to 29.4 ± 8.7 mmHg at high altitude. Five participants developed PASP >35 mmHg (mean 42.0 ± 3.9 mmHg), meeting the study's threshold for high-altitude PH. Following a single oral dose of sildenafil (50 mg), these individuals experienced a significant reduction in PASP to 24.5 ± 4.6 mmHg within 30 minutes. The authors concluded that while mild-to-moderate PH may occur after rapid ascent, sildenafil is effective as an acute treatment in this context ⁽¹⁸⁾

Kolluru et al. (2008) provided mechanistic insight into the protective role of nitric oxide (NO) in endothelial cells (EC) exposed to hypoxic conditions, with relevance to HAPE pathophysiology. Their in vitro study demonstrated that NO preserves endothelial barrier integrity by reducing hypoxia-induced leakiness, counteracting superoxide-mediated damage, and maintaining actin cytoskeletal organization. These effects are mediated via the NO-cGMP signaling pathway. The study further showed that sildenafil, a phosphodiesterase-5 (PDE5) inhibitor, partially restored endothelial barrier function under hypoxia, sildenafil in protecting against hypoxia-induced endothelial dysfunction. These findings support the therapeutic usage of sildenafil in HAPE by strengthening endothelial barrier integrity and suppressing vascular leak ⁽¹⁹⁾

In a study evaluating the effects of sildenafil on heart rate variability (HRV) under hypoxic conditions, no significant differences were observed between the sildenafil and placebo groups in terms of total power (TP), low-frequency (LF) and high-frequency (HF) components, or the sympathovagal balance (LF/HF ratio). Although TP decreased in the placebo group, this reduction was not significant in the sildenafil group, suggesting a possible protective effect of sildenafil on cardiac autonomic regulation during hypoxia. The authors concluded that sildenafil does not adversely affect autonomic control of heart function at high altitude and may facilitate cardiovascular adaptation by improving oxygenation and reducing pulmonary hypertension. ⁽²⁰⁾

Phosphodiesterase 5 inhibitors in HAPE prophylaxis:

George et. al in randomized double blinded placebo-controlled concept study conducted among people with a history of mild to moderate HAPE, shown tadalafil effectiveness (10mg twice a day), acetazolamide and nifedipine in HAPE prophylaxis after re-ascending to high altitude (3500 m above sea level). Tadalafil significantly lowered pulmonary artery pressure (PAP) and improved blood oxygenation comparing to placebo (PAP: $24,71 \pm 0,73$ mmHg vs. $26,57 \pm 4,25$ mmHg, $p < 0,01$; SpO₂: $89,39 \pm 1,58\%$ vs. $84,80 \pm 5,46\%$, $p < 0,0001$) None of the patients taking tadalafil developed symptoms of HAPE on the return at high altitude, while four cases of relapse were reported in the placebo group. These results supports tadalafil potential as an effective prophylactic agent for individuals prone to developing HAPE, which can be explained by its effect on reducing hypoxic pulmonary vasoconstriction and lowering PAP. ⁽²¹⁾

Maggiorinni et al. in randomized controlled trial evaluated effects of tadalafil and dexamethasone given 24h prior to ascent at 4559 m. 29 participants were included to this trial and assigned to groups receiving tadalafil (10mg), dexamethasone (8mg) and placebo. HAPE developed in 7 of 9 participants receiving placebo, 1 of 8 receiving tadalafil, and none of 10 participants treated with dexamethasone. Acute mountain sickness (AMS) was diagnosed in 8 of 9 in the placebo group, 8 of 10 receiving tadalafil, and 3 of 10 receiving dexamethasone. Median Lake Louise AMS scores were significantly lower in the dexamethasone group compared to both placebo and tadalafil groups. Tadalafil and dexamethasone both suppressed the rise in systolic pulmonary artery pressure and PaO₂.⁽²²⁾

In another randomized clinical trial conducted by Richalet et. all, 14 healthy volunteers were randomly assigned to two groups, receiving sildenafil (n=7) and placebo (n=7). Sildenafil effect on exercise tolerance, hemodynamic parameters and symptoms of acute mountain sickness were assessed. Subjects were exposed to high altitude (4350m) for 6 days. Treatment with sildenafil was well tolerated and did not result in more often adverse reactions comparing to placebo. In sildenafil group increase in pulmonary artery pressure (sPpa) was significantly lower, compared with placebo, sildenafil significantly improved arterial oxygen saturation (SaO₂), from day 2 of exposure both at rest and during exercise, and significantly reduced the altitude-induced decline in maximal oxygen uptake (VO₂max). Alveolar-arterial pressure differences (PA-PaO₂) were significantly lower in the sildenafil group at rest and during exercise. Treatment had no effect on acute mountain sickness symptoms assessed by the Lake Louise scale, although a trend towards lower values was noted in the sildenafil group. The study results suggest that sildenafil may have a beneficial effect on gas exchange parameters, and

pulmonary hemodynamics in people exposed to high-altitude hypoxia, potentially reducing the risk of developing HAPE. ⁽²³⁾

Completely different results achieved Bates et. al in double-blind, randomized, placebo-controlled trial involving 62 healthy lowland volunteers ascending to 5200 m, sildenafil group was administered 50 mg three times day of sildenafil This intervention did not significantly reduce pulmonary artery systolic pressure (PASP) at high altitude comparing to placebo group. Moreover, on day 2 at 5200 m, the median acute mountain sickness (AMS) score was significantly higher in the sildenafil group compared to placebo. These data demonstrate no statistically significant effect of sildenafil administration on Pulmonary Artery Systolic Pressure following ascent to 5200 m in healthy individuals and possible exacerbation of AMS symptoms. ⁽²⁴⁾

In case series described by Fagenzohl et al. (2007), we get an insight view into practical usage of PDE5 inhibitors in HAPE. Sildenafil was used in 7 out of 11 patients treated due to HAPE in Periche, Nepal. In five of this patients drug was added to previous treatment with nifedipine due to lack of clinical response or prolonged demand for theotherapy. In two cases sildenafil was used as first line drug due to low blood pressure (systolic <110mmhg) which limited use of nifedipine due to risk of hypotension. All patients mentioned in study tolerated sildenafil well and no adverse reactions were reported, also clinical improvement of the patients were observed measured as saturation improvement and reduction of ultrasonographic changes in lungs (comet-tail score). Despite limitations of this study, it is significant prove of efficacy and safety of sildenafil in treatment of HAPE. ⁽²⁵⁾

Conclusions

Phosphodiesterase type 5 inhibitors: sildenafil and tadalafil, demonstrate significant potential in both the prevention and treatment of high-altitude pulmonary edema. Their mechanism—based on enhancing the nitric oxide–cGMP signaling pathway—effectively suppresses hypoxia-induced pulmonary vasoconstriction, lowers pulmonary artery pressure, and supports endothelial barrier integrity under hypoxic stress.

Based on found studies we can conclude that:

- Prophylactic use of PDE5 inhibitors can reduce the incidence of HAPE in prone individuals.
- PDE5 inhibitors are effective in reducing pulmonary artery pressure at high altitude which corresponds with postulated HAPE patomechanism
- Trials shows potential clinical benefits in developed HAPE, including improved oxygenation and hemodynamic parameters, and possible use when standard agents like nifedipine are contraindicated or inaccessible.
- The safety profile of sildenafil and tadalafil appears favorable, with minimal adverse reactions reported in most studies.
- Inconsistent findings across clinical trials indicate the need for individualized patient assessment and cautious usage of PDE5 inhibitors

While PDE5 inhibitors are not a replacement for primary prevention strategies such as slow ascent and acclimatization, they are valuable pharmacological agents, particularly for individuals with prior HAPE history or in conditions where descent and oxygen therapy are not immediately available. Further, randomized, large-scale, and altitude-specific studies are needed to establish definitive guidelines for their usage in HAPE prophylaxis and management.

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