Advances in the available non-biological pharmacotherapy prevention and treatment of acute mountain sickness and high altitude cerebral and pulmonary oedema

Joyce, K. E.; Lucas, S. J.E.; Imray, C. H.E.; Balanos, G. M.; Wright, A. D.

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Abstract:

Introduction

The physiologic responses on exposure to high altitude are relatively well known, but new discoveries are still being made, and novel prevention and treatment strategies may arise. Basic information has changed little since our previous review in this journal ten years ago, but considerable more detail on standard therapies, and promising new approaches are now available.

Areas covered

The role of pharmacological agents in preventing and treating high altitude illnesses is reviewed. The authors have drawn on their own experience and that of international experts in this field. The literature search was concluded in March 2018.

Expert opinion

Slow ascent remains the primary prevention strategy , and rapid descent for management of serious altitude illnesses . Pharmacologic agents are particularly helpful when rapid ascent cannot be avoided or when rapid descent is not possible. Acetazolamide remains the drug of choice for prophylaxis of acute mountain sickness (AMS); however, evidence indicates that reduced dosage schemes compared to the current recommendations are warranted. Calcium channel blockers and phosphodiesterase inhibitors remain the drugs of choice for management of high altitude pulmonary oedema. Dexamethasone should be reserved for the treatment of more severe cases of altitude illnesses such as cerebral oedema.

Keywords: acetazolamide, acute mountain sickness, dexamethasone, high altitude, high altitude cerebral oedema, high altitude pulmonary oedema, nifedipine

1. Introduction

The ease of accessing high altitude above 2000 m presents an opportunity to gain a greater insight into the acute responses to hypoxia [1, 2]. In this review, advances in the pharmacologic prevention and treatment of high altitude illnesses are discussed, aiming to: 1) evaluate currently used pharmacotherapies and 2) consider theoretical pharmacotherapies in light of new discoveries. The following databases were searched (inception March 1) for relevant studies focusing largely on literature produced after 2008: MEDLINE, PubMed, and Embase. Search strategies utilized a set of keywords (with synonyms and closely related words) specific to each section herein with additional studies identified by examining the reference list contained from chosen studies.

The hypobaric hypoxic conditions at altitude elicit distinct temporary and reversible physiologic responses in lowlanders who have spent a few hours to days at high altitude (generally over 3,000 m). These repsonses are predominantly attributed to hypoxemia [3, 4]. The initial physiologic acclimatisation is hyperventilation, which negates reductions in the partial pressure of oxygen (PO_2) but also results in a greater loss of carbon dioxide (CO_2) (hypocapnia) and subsequent respiratory alkalosis [5]. This respiratory alkalosis elicits a renal compensation response by which the kidneys increase bicarbonate (HCO_3^-) excretion and increase hydrogen (H^+) retention, resulting in a secondary metabolic acidosis and a mild diuretic effect [6, 7]. Hypoxia also elicits an increase in sympathetic tone, an increase in blood pressure (BP), and an

elevation in resting heart rate (HR) [8]. The magnitude of the response to hypoxia varies considerably between individuals [9].

2. Pathophysiology of High Altitude Illnesses

Three altitude illnesses and their mechanisms are reviewed: 1) acute mountain sickness (AMS), 2) high altitude cerebral oedema (HACE), and 3) high altitude pulmonary oedema (HAPE).

2.1 Acute Mountain Sickness (AMS)

The clinical presentation of AMS includes; headache, gastrointestinal distress, fatigue, and dizziness/lightheadedness [10]. The severity of AMS is determined by an overall symptom score, as an objective measure has yet to be determined. The maladaptive physiologic responses to hypoxia among those who present with AMS have been demonstrated and are different from those who remain free of AMS [11]. The pathophysiology includes: mild fluid retention, increased sympathetic drive, increased cerebral venous volume, reduced cerebrospinal fluid absorption, reduced intracranial buffering capacity, and cognitive impairment [12, 13].

Cerebral vasodilation occurs in an attempt to increase oxygenation via an increase in cerebral blood flow [12]. These elevations are normal in the acute exposure phase , returning to baseline after a few days at the same altitude [14]. In some individuals, however, these intracranial dynamics do not return to baseline and progressive increases in intracranial pressure are exhibited, particularly, if the hypoxemia stimulus is maintained in a progressive and aggressive ascent [15].

2.2 High Altitude Cerebral Oedema (HACE)

AMS and HACE probably occur along a continuum. HACE, a type of encephalopathy with neurological findings, such as, ataxia, altered mental status, and unconsciousness, is potentially fatal. [10]. The causes for the progression of AMS to HACE are unclear; however, current hypotheses attribute such progression to: 1) disruptions in the blood brain barrier (BBB); 2) intracellular oedema, and 3) venous outflow obstruction [15, 16, 17, 18].

Disruptions in the BBB are multifactorial and include: 1) over production of reactive oxygen species (ROS); 2) altered cytokine expression, and/or 3) increased vascular endothelial growth factor (VEGF) [16, 19, 20]. The intracellular oedema aspect of the progression of high altitude cerebral illness has been demonstrated on MRI scans increases in brain parenchymal volumes being associated with increasing Lake Louise Scores [21]. Reductions in venous outflow preceded by an increase in cerebral inflow in response to hypoxia are likely a cause for the progression of cerebral-related altitude illnesses [21]. Vessel deformation may occur within various levels within the brain to include the intracranial and extracranial levels; however, more recent works have demonstrated that vessel deformation at the intracerebral level may be most closely related to the development and progression of cerebral altitude illnesses [18, 21, 22, 23, 24]. The over expression of corticotropin releasing factor may also be a contributor [25].

2.3 High Altitude Pulmonary Oedema (HAPE)

Pulmonary arterial pressure (PAP) rises with exposure to altitude, being attributed to hypoxic pulmonary vasoconstriction (HPV). An exaggerated elevation in PAP contributes to the development of alveolar capillary leakage and subsequent development of HAPE [26, 27]. Potential mechanisms include: 1) inflammation, 2) altered alveolar fluid clearance, and/or 3)

uneven HPV response [26, 27, 28]. Accumulation of lung fluid in response to hypoxia has been attributed to the downregulation of epithelial sodium channels (ENaC) [29, 30]. Further, greater endothelin-1 production and reduced exhaled nitic oxide are also apparent in those who develop HAPE [31, 32, 33, 34].

3. Established Pharmacotherapies for Prevention and Treatment AMS and HACE

Pharmacologic strategies are secondary to immediate descent for the treatment of serious altitude illness (HACE and HAPE). If available, temporary supplemental O_2 to raise oxygen saturation to >90%, or immersion in a portable hyperbaric chamber, are effective treatment strategies Otherwise, the following pharmacologic approaches should be considered.

3.1 Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors (CAIs) were one of the first pharmacologic agents used to prevent AMS by promoting a preemptive and favorable acclimatization response [35]. Renal CA inhibition, vascular endothelial CA inhibition, erythrocyte CA inhibition, and CNS CA inhibition appear to be the four primary attributes that are most helpful in the prophylactic treatment of AMS [36]. Renal CA inhibition stimulates the loss of bicarbonate (HCO_3^-) and sodium (Na^+) in the urine and the subsequent retention of H^+ and chloride (Cl^-), effectively reducing serum pH and promoting a state of metabolic acidosis that ultimately stimulates ventilation to equilibrate pH [37, 38].

Vasoregulation is also altered with the administration of CAIs via the alteration of extracellular pH, as well as, the direct inhibition of CA in vascular smooth muscle [39]. It should be noted, however, that the peripheral vasculature, pulmonary vasculature, and cerebral

vasculature respond differently and/or independently in response to certain drugs [40]. For example, altitude sleep studies have demonstrated the specific influence of CAIs on cerebrovascular reactivity and the subsequent affect on cerebral blood flow [41, 42].

3.1.1 Acetazolamide

Acetazolamide (Az) is often used for prophylaxis of altitude illnesses, increasing ventilation and increasing PaO_2 [43, 44, 45, 46]. Off-target effects include: aquaporin inhibition, ROS modulation, heat shock protein-70 (HSP-70) and IL-1 receptor agonist, HIF modulation, and cAMP regulation [36]. Oral administration of Az is more advantageous than intravenous (i.v.) administration at altitude due to its easier administration, as well as, the resultant effects on periodic breathing during sleep at altitude and less reductions in CO_2 sensitivity compared with i.v. adminsitration [47, 48].

Of more recent concern has been the potential negative effect of Az on exercise performance in hypoxic conditions [49, 50, 51]. The negative effect of Az on performance is particularly apparent in the most recent study which demonstrates the magnitiude of performance decrements by qunaitifying reductions in diaphrapm contractility (18 ± 10%) and joint torques (39 ± 11%) associated with the drug [51]. It is speculated that exercise performance in older participants may be affected to a greater extent due to reduced renal clearance of Az associated with age-related declines in kidney function [49]. The mechanism by which Az impairs exercise performance is unknown, but such effects should be considered when older subjects are using Az and the maintenance of exercise performance at high altitude is a priority.

The side effects of Az for the specific treatment of altitude illnesses include: paresthesia, polyuria, rash, dysgeusia, and increased frequency of micturition [36, 52, 53]. While the side

effects are not uncommon and range in severeity, paresthesia appears to be the most common [54]. However, such side effects can become severe and appear to relate to increases in dosases in this way [55]. Therefore, it will be important to establish the most effective minimal dose that can be used in order to reduce adverse events [55].

A consensus for the time course of administration and dosage of Az has not been met, although guidelines for such applications do exist [56]. The dose of Az for AMS prophylaxis has been recommended at 125 mg – 250 mg twice daily (BID), initiating administration the day prior to altitude exposure; however, recent data suggest pre-treatment with low-dose Az (125 mg BID) should be initiated 2 days prior to exposure to altitude [52, 53, 57]. Studies concerning the effective dosage regimens of Az while at altitude provide evidence favouring reductions in dosage schemes [58, 59, 60]. Even lower dosages of 62.5 mg BID can be as effective in preventing AMS [59]. Hypoxia and, possibly, additional environmental stressors imposed by high altitude exposure may alter drug pharmacokinetics, particularly, in drugs such as Az and, thus, may reduce the clearance of such drugs [61]. Furthermore additional research is warranted to determine the individualization of Az dosing.

3.1.2 Methazolamide

Methazolamide (Mtz) may incur less side effects than Az, as it is less bound to plasma proteins and diffuses more readily into tissues [62]. Comparative studies have demonstrated that Mtz administration of 150 mg is equally effective as Az in preventing AMS with less paresthesia [63]. Additionally, Mtz may elicit less performance decrements compared to Az [51]. The differences in the pharmacodynamics of the drugs and their side effects or maybe responsible for the disparities among the magnitude of effects elicited.

Comparative studies of Az and Mtz show that when CA is fully inhibited, different effects may be a consequence of the off-target effects of the medications [64]. The magnitude of the hypoxic-ventilatory response is far less with Az than with Mtz [64]. In vitro, Mtz but not Az activates the gene transcription factor nuclear related factor 2 (Nrf-2), which is responsible for the upregulation of antioxidant proteins that serve a primary purpose of scavenging reactive oxygenated species (ROS); however, it is unclear if these effects will translate to the whole organism [65]. Early speculations of ROS involvement in the development of AMS have been supported by evidence demonstrating the importance of the balance of ROS production and ROS scavenging for the prevention of AMS [66]. Thus, it could be argued that the proper management of ROS with high altitude exposure is critical for the prevention of altitude illnesses, specifically, in those persons with a genetic profile that is indicative of hyperactive ROS production. Further, research is needed in order to evaluate the efficacy of various CAIs for the prophylactic treatment of altitude illnesses based on genetic profiles and in relation to ROS production.

3.1.3 Benzolamide

Benzolamide (Bz) has been compared with Az for prophylactic treatment of AMS [67]. Significantly lower AMS scores were obtained on Bz when compared to Az, particularly at higher elevations [68]. The effects of Bz and Az at altitude, such as, increased urinary pH and volume, as well as, increased arterial oxygenation, appear to be similar between the two drugs [68, 69]. Bz has been shown to have reduced psychomotor effects compared to Az, indicating that Bz may penetrate the central nervous system (CNS) tissue less than Az. Furthermore, due to

its more limited tissue penetrance and near isolated effects on renal CA, Bz elicits fewer CNS-related side effects [38, 68].

3.2 Corticosteroids

3.2.1 Dexamethasone (Dx)

Recent reviews have highlighted the effects of Dx in its ability to prevent altitude illnesses, which include: reductions in ROS formation, endogenous antioxidant upregulation, sympatholysis, improved O_2 saturation, alteration of aquaporin expression, and HSP-70 and adrenomedullin upregulation [36]. However, its use as a prophylactic agent could become problematic for many reasons. Unlike Az, Dx does not permit the normal acclimatization process to transpire. Additionally, if Dx is used as a prophylactic agent and is then abrubtly discontinued during ascent, acute illness may set in. For this reason, its use as a prophylactic treatment should be avoided when possible, and other drugs should be considered.

The clinical management of HACE is distinctly different. HACE is a medical emergency requiring immediate attention, and is known to occur in those whom have already developed AMS. Early treatment using Dx is the most effective [70]. An initial large dose of Dx is advised, 8 – 10 mg by intramuscular or oral administration, followed by 4 mg every 6 hours [56].

3.2.2 Inhaled Budesonide

Conflicting results have been produced concerning the efficacy of inhaled budesonide for preventing and treating altitude illnesses. Administration of inhaled budesonide for 3 days prior to ascent has been effective in preventing AMS in the first 20 hours of HA exposure [71]. However, more recent research shows no significant reductions in AMS with budesonide

administration at various dosages nor has it shown the ability of budesonide to prevent AMS to the same degree as Az [72, 73]. Budesonide is a drug that elicits isolated effects on the lung tissue as opposed to eliciting a systemic effect, thus, its efficacy for the prophylactic treatment of AMS may be limited. [74].

3.3 Diuretics

Abnormal fluid balance has been repeatedly observed in those whom present with AMS [75, 76]. While a degree of diuresis with hypoxic exposure is considered a normal response, individuals who develop AMS demonstrate significantly greater fluid retention than those who do not develop AMS [76]. Such diuresis at high altitude is also related to the ventilatory response to hypoxia, such that, a blunted ventilatory response may result in a greater degree of fluid retention and ensuing altitude illness [77, 78, 79, 80, 81]. Furthermore, such blunted responses and associated fluid retention may promote the development of HAPE. Thus, the maintenance of an appropriate fluid balance at high altitude, namely preventing a state of fluid excess, is important for the prevention of all altitude-related illnesses [76, 82]. There is limited information on the use of diuretics in preventing AMS except it has been shown that spironolactone is ineffective in preventing AMS when compared to Az [83]. It is also possible that those with AMS may be volume depleted, thus, the use of a loop diuretic in this instance could be problematic. Herein lies the rationale behind furosemide being deamed as inappropriate for the treatment of AMS which would produce excessive diuresis that may be dangerous at altitude [62]. Spironolactone has also been considered for the treatment of altitude illnesses due to the mild acidosis produced [83].

3.4 Angiotensin Converting Enzyme (ACE) Inhibitors

Angiotensin converting enzyme (ACE), found predominantly in the pulmonary and renal endothelia, plays a key role in the renin-angiotensin aldosterone system (RAAS). ACE influences the control of systemic BP via its conversion of angiotensin-I to angiotensin-II (A-II) and the subsequent downstream effects on fluid balance. The implications of ACE and performance at altitude have been evaluated but the use of ACE inhibitors was not addressed [84]. More recent discoveries surrouding genetic polymorphisms of the ACE gene and associated responses to hypoxia have resulted in the consideration of ACE inhibitors for prevention and treatment of altitude illnesses [85, 86]. As individuals with the "DD" genotype appear to be at greater risk for maladaptations at altitude, inducing physiologic response that is more consistent with a favorable II or ID genotype could be advantageous altitude [87].

The effects of ACE inhibitors during exposure to hypoxia include blunting of the hypoxic ventilatory response and reduction in PAPs [86, 88, 89]. Therefore, such drugs may reduce HAPE in a similar way to that of nifedipine [86]. However, ACE inhibitors have been shown to blunt the kidneys ability to produce eryhtoprpoetin and, thereby, producing an unwanted effect in those attempting to acclimatize [90]. While the ventilatory responses to ACE inhibitors during hypoxia have been briefly considered, further research is warranted in this area. Future research should also consider the hormonal effects of ACE inhibitors with hypoxic exposure, such as the influence on aldosterone and any subsequent relation to altitude illnesses.

3.5 Angiotensin-II Receptor Blockers (ARBs)

Intermittent hypoxia such as in sleep apnoea is accompanied by concomitant rises in BP, which may be mediated by A-II [85, 91, 92]. ARBs, such as, telmisartan have been shown to

reduce increases in BP associated with ascent to altitude up to 3400 m in healthy individuals [93, 94, 95]. Additionally, losartan appears to alleviate the oxidative stress imposed by intermittent hypoxia and may reduce ROS production [91]. Thus, ARBs may attenuate the progression of altitude illnesses by regulating fluid volume, reducing altitude associated increases in BP, and alleviating oxidative stress; however, their efficacy at extreme altitudes may be limited [91, 93]. Furthermore, ARBs and ACE inhibitors are safe to administer at altitude but comparisons between these drugs and existing pharmacologic strategies, such as Az, are warranted.

3.6 Magnesium

Magnesium is an antagonist of N-methyl-D-aspartate (NMDA). The involvement of the N-methyl-D-aspartate (NMDA) receptor in regards to hypoxic altitude convulsions has previously been implicated with a blockage of the NMDA receptor proving to have beneficial effects [62, 96, 97]. Intravenous magnesium appears to be superior over oral administration for the attenuation of AMS [62, 98, 99]. The precise connection between NMDA and AMS reamins unclear and further investigations are needed.

3.7 Ibuprofen and Paracetamol

High altitude headache (HAH) is an important symptom in the recently revised AMS scoring scheme [10]. Conflicting results have been produced regarding ibuprofen's efficacy compared. Ibuprofen has been repeatedly shown to reduce HAH due to its anti-inflammatory effects [100, 101, 102], which may also be responsible for its superiorty over paracetamol. Studies have also shown ibuprofen and paracetamol to be equivocal in preventing HAH [103, 104].

3.8 Nitrovasodilators

The involvement of endothelial nitric oxide synthase (NOS) in the development of altitude illnesses has been outlined [62] and further implicated in those studies observing lowlanders travelling to altitude exhibiting reductions in exhaled NO which have correlated with AMS scores and the presentation of HAPE [32, 33, 105, 106]. Others have argued that exhaled NO decreases with increasing altitude and may not be a contributor to HPV [105, 107]. However, recent studies concerning gene variants of the nitric oxide synthase 3 gene (NOS3), a gene encoding for eNOS, in relation to both, acclimatization and adaptation to altitude are conflicting [108, 109]. Despite, nitrates' ability to improve exercise performance at sea-level, recent findings indicate that dietary nitrate consumption exacerbates AMS symptoms and increases the sense of effort with maximal exercise in hypoxia [110].

4. Established Pharmacotherapies for Prevention & Treatment of HAPE

Despite some overlap, the development of HAPE is attributed to alternative maladaptations compared to AMS and HACE. HPV and the resultant pulmonary hypertension, stress failure of the pulmonary capillaries, and disrupted alveolar fluid clearance have all been hypothesized to contribute to the development of HAPE [4, 111, 112, 113]. While immediate descent remains the first line treatment for HAPE, drugs that act on any one of aforementioned pathways can also be helpful for prevention and treatment.

4.1 Calcium-Channel Blockers (CCBs)

4.1.1 Nifedipine

Nifedipine, a calcium channel blocker, interferes with the calcium channel blockade, inhibiting vasoconstriction and reducing PAPs. Administration of 20 mg of slow-release nifedipine every 8 hrs prevents HAPE in those persons whom are known to be susceptible [88]. For acute treatment of HAPE, an immediate dosage of 10 mg of nifedipine should be administered sublingually followed by 20 mg every 6 hrs in addition to supplemental oxygen and descent [62, 114].

4.2 Phosphodiesterase Inhibitors (PDE-5 Inhibitors)

Elevated PAPs are of concern in relation to altitude illnesses and can result in the development of HAPE and worsening hypoxemia [115]. Phosphodiesterase inhibitors (PDE-5 inhibitors) are of interest for HAPE prevention, due to their ability to attenuate rises in PAPs with ascent. Recent reviews have demonstrated the efficacy of PDE-5 inhibitors, such as tadalafil and sildenafil, for the treatment of elevated PAPs [62, 115, 116, 117]. Pre-treatment with 10 mg of tadalafil has been shown to protect against HAPE (reducing incidence by 78%) in those who are susceptible by attenuating rises in PAP [118]. Newer research is in agreement with these earlier works demonstrating reductions in the incidence of HAPE with tadalafil [119].

Although PDE-5 inhibitors are known to improve HPV and, thereby, reduce the propensity for developing HAPE, results regarding the efficacy of PDE-5 inhibitors for prevention and treatment of other altitude illnesses are less conclusive. Sildenafil may be appropriate for AMS and HACE prophylaxis based on its ability to increase cerebral oxygenation [120]. Tadalafil may have the potential to reduce cerebral specific AMS scores; however, it may also increase the potential of headache [111, 119, 121, 122]. Consequently,

more research is needed to clarify whether PDE-5 inhibitors can be used to prevent and treat AMS an HACE.

4.3 Acetazolamide.

There is evidence that acetazolamide inhibits HPV in many animal models and in humans and, therefore, could be useful in the prevention, and perhaps treatment, of HAPE [123].

4.4 Corticosteroids

4.4.1 Dexamethasone

While the treatment of HACE with Dx is recommended, its administration for the treatment of HAPE is less established. Recent guidelines provide a Recommendation Grade of 2C for Dx as a preventative strategy for HAPE due to limited evidence, and suggest that it is reserved for the clinical presentation of HAPE, known HAPE-susceptible individuals, or when alternative therapies are contraindicated [56]. It is possible that Dx could reduce HAPE by stimulating the cGMP production in response to hypoxia, increasing NOS activity and modulating sympathetic activity; however,. limited reports have documented its use in this way [118, 124, 125, 126].

4.5 Iron Supplementation

The suggestion of iron supplementation for the treatment of altitude illnesses comes from the effects that severe iron deficiency has on the pulmonary vasculature resulting in pulmonary vasoconstriction [127]. Unfortunately, however, it seems that i.v. iron supplementation has no significant protective effect against AMS [128].

5. Future Pharmacotherapies for Prevention & Treatment of Altitude Illnesses

This next section provides suggestions for the potential use of other pharmacologic agents in preventing and treating altitude illnesses.

5.1 Type A Endothelin Receptor Antagonists (ET_A Receptor Antagonist)

The effects of hypoxia in pulmonary vasculature may be detrimental and result in a greater propensity for apoptosis in the pulmonary artery smooth muscle cells [129]. Thus, susceptibility to altitude-related illnesses attributed to such effects on the pulmonary vasculature should kept in mind with the consideration of new pharmacotherapies for prevention and treatment of altitude illnesses.

Type A endothelin receptor antagonists (ET_A antagonists) elicit similar outcomes as PDE-5 inhibitors on the pulmonary vasculature, however, the mechanism of action of ET_A antagonists is inherently different. In animal models, ET_A antagonists have proven to be beneficial in reduction of PAPs in the HAPE susceptible [31, 130, 131, 132, 133]. It has also been hypothesized that additional off-target effects of ET_A antagonists may be more beneficial for the prophylactic treatment of altitude illnesses [65].

5.1.1 Sitaxentan

Research has demonstrated that the ET_A antagonist sitaxentan reduces pulmonary vascular resistance (PVR) in both, acute and chronic hypoxia with such changes in PVR being correlated with restorations in VO_{2max} [134]. Increases in PVR associated with hypoxia may be a contributing factor to the reductions in VO_{2max} observed in hypoxia. Thus, sitaxentan, may offer an alternative option to existing pharmacotherapies, especially, when exercise performance

at altitude is a priority. *In vivo* models have shown sitaxentanreduces high-altitude induced cerebral vascular leakage by 40% but its effect on altitude illnesses remains uninvestigated [65].

5.1.2 Ambrisentan

Ambrisentan is currently approved for the treatment of pulmonary arterial hypertension and having limited interactions with other medicaiotns [135]. Ambrisentan has been shown to improve exercise capacity and reduce HPV [136, 137]. When compared to sitaxentan, ambrisentan increased Nrf-2 four-fold, helping to scavenge greater amounts of ROS [65]. Additionally, *in vitro* studies have shown that ambrisentan decreased hypoxia-induced H_2O_2 production and permeability in basal media endothelial cells [65], indicating its potential use for prophylaxis of HAPE [65]. The efficacy of ambrisentan for the specific prevention and treatment of altitude illnesses is unknown.

5.1.3 Bosentan

Bosentan, also approved for treatment of PAP, has repeatedly been shown to reduce increases in PAP asscoaited with altitude exposure in animals, healthy humans and known HAPE susceptiple individuals [132, 138]. However, bosentan may have adverse effects on renal adaptation at high altitude, specifically, reducing diruresis [139]. This could present as problematic with ascent to altitude in light of the known relationship between reductions in diuresis and a greater propensity for developing altitude illnesses [140, 141].

5.14 Macitentan

Macitentan is an ET_A antagonist indicated for the treatment of PAH [142]. Macitentan improves PAP and exercise capacity, so may attenuate the development of altitude illnesses [143, 144]. Due to the effects of altitude and the associated hypobaric hypoxic conditions that elicit a disruption in the vasoregulatory processes and promote vasoconstriction, caution should be taken with drugs that may attenuate the vasoconstriction response and favorably affect PAP (see below). The vasoregulatory changes and vascular characteristic changes (reduced capillary density and diameter) induced by hypoxia appear to be attenuated with macitentan in healthy individuals in hypobaric hypoxic conditions [143]. Thus, macitentan could attenuate the development of altitude illnesses by improving capillary blood flow, and microcirculation [143], and attenuating the hypoxia-induced rise in PAPs.

5.2 IL-10 Upregulators

Gene connectivity has been used to evaluate the connections between AMS (from high altitude exposure) and genetic profiles [145]. Early research revealed that HAPE is largely attributed to a failure of the lung endothelial lining due to high intravascular pressures rather than inflammation, with this lining failure a more likely source of such vascular leak [36, 80]. These earlier studies appear not to draw attention to the potential effect of the anti-inflammatory involvement in the prevention of altitude illnesses though such an approach has been proposed recently [146, 147].

Liu et al. [145] has highlighted the genetic profiles of those with AMS compared to those without AMS during altitude exposure, revealing a contrast in the production of anti-inflammatory cytokines between AMS non-AMS groups. More specifically, Liu et al. [145] was able to isolate the change in interleukin (IL) gene expression amongst those with AMS who

presented with a downregulation of IL-2, IL-4, IL-6ST, IL-7, IL-10, IL-17B, and IL-32, as well as, an upregulation in IL-13 and IL-17F. Others have further implicated the involvement of endothelin 1 (ET-1), IL-6, and IL-17a [148]. Liu et al. [145] further analysed differential connectivity patterns among gene expressions across groups, and found that IL-10 and CCR7 were substantially downregulated and IL-17F and CCL8 were substantially upregulated in the AMS group. This could be due to an enriched DUSP1 response to oxidative stress at altitude, limiting the IL-10 production by adversely effecting p38 phosphorylation [145]. An additional mechanism [145] is the downregulation of the CCR7 protein, a protein that maintains T-cell function normal secretion of IL-10. Based on these findings there is substaintial evidence implicating the involvement of the inflammatory response (anti-inflammatory response) in the development of AMS. This evidence also supports the consideration of alternative pharmacologic agents that promote IL-10 upregulation for the prevention and treatment of altitude illnesses.

5.2.1 Gabapentin

The use of alternative drugs that influence the upregulation of IL-10 may be more appropriate as prophylactic agents. Gabapentin has been used to treat high altitude headache and is now known to upregulate IL-10; however, the use of gabapentin to treat altitude illnesses has not gained wide popularity [132, 149, 150, 151].

5.3 Rho-kinase Inhibitors

5.3.1 Fausidil

At high altitude, hypoxia-induced pulmonary hypertension is one of the physiologic factors that can result in HAPE and reduced cardiopulmonary performance [80, 152]. The rho-

kinase inhibitor fasudil reduces high-altitude pulmonary hypertension with high-altitude exposure [153]. Rho-kinase inhibitors in combination with ARBs reduce proteinuria by helping to maintain the podocyte integrity, thereby protecting the kidneys [154]. Overall, the efficacy of rho-kinase inhibitors and their use in the prophylactic treatment for high-altitude illnesses is relatively unknown.

5.4 Guanylate Cyclase Stimulators

5.4.1 Riociguat (Adempas)

A contribution of the rho-kinase signaling pathway to the development of HAPE has been suggested. Riociguat (Adempas) could b a novel treatment for HAPE, specifically in those whom are at an increased risk for developing HAPE based on their genetic profile [155]. Riociguat decreases pulmonary vascular resistance while increasing cardiac output and peripheral O_2 delivery during rest and low intensity exercise at simulated altitude (15000 ft.) [156]. Furthermore, no changes in VO_{2max} were reported with riociguat administration. This is promising in view of recent research with concern for the potential cardiovascular effects and exercise performance limitations amongst older individuals (e.g. 50+ years) [49]. The efficacy for the use of riociguat as a prophylactic agent against AMS or HAPE is unknown.

5.5 Oxyhaemoglobin Dissociation Influencers

Inducing a leftward shift in the oxyhaemoglobin dissociation curve could potentially help prevent or reduce the risk of altitude illnesses [157].

5.5.1 GBT1118 and GBT 440

GBT1118, an O_2-hemoglobin (Hb-O_2) affinity modulator via an allosteric change to haemoglobin, has been demonstrated to have favourable effects on the oxyhaemoglobin dissociation curve [158]. It reduces hypoxemia by increasing arterial oxygenation in hypoxemic animals [158]. GBT1118 also reduces leukocyte infiltration into the lungs and prevents pulmonary inflammation in hypoxemic animals [158]. GBT440 induces a favourable shift, similar to GBT440, under conditions that mimic strenuous exercise, hypoxia, and acidosis [159].

5.6 Corticotropin-releasing Factor Antagonists

Corticotropin-releasing hormone (CRH), is a peptide hormone released from the hypothalamus in response to stress resulting in the release of ACTH. CRH has been shown to contribute to the brain-endocrine-immune network and associated dysfunction in altitude illness [160]. Individuals that with AMS demonstrate enhanced plasma levels of CRH in response to hypoxia induced by rapid ascent [161]. It is possible that enhanced plasma levels of CRH, which activate the cAMP-dependent protein kinase pathway and calcium influx through L-type channels, contributes to excessive vasoconstriction in response to hypoxia, thereby, promoting AMS [161]. Over activation of the target receptor of CRH, the corticotropin releasing hormone receptor-1 (CRHR1) in response to hypoxia has also been shown to contribute to increased expression of aquaporin-4 (increasing cellular permeability), promoting cellular water influx and cerebral oedema [25]. Therefore, drugs that block or produce antagonistic effects at the CRHR1 receptor may attenuate thishypoxic response .

5.6.1 CP154,526

CP154,526 is a CRHR1 antagonist, negating the effects of CRH. CP154,526 appears to reduce the hypoxia-associated increases in pro-inflammatory markers, such as TNF-α and IL-1β, which correlate AMS [162]. It is possible that CP154,526 may reduce the stress response associated with hypoxia and reduce the incidence of AMS. Future research is warranted for the efficacy in altitude illness of CRHR1 antagonists such as antalarmin and pexacerfont in addition to CP154,526.

5.7 Nootropics

5.7.1 Oxiracetam

Oxiracetam has been reported to influence brain function at high altitude. Blood flow velocity measured by transcranial Doppler decreased in both anterior and posterior circulations following the administration of oxiracetam, attributed to vasodilation in the posterior and anterior circulation [163]. More importantly preconditioning with oxiracetam appeared to reduce the decline in cognitive function on ascent to altitude.

5.8 Glutathione S-transferase Inducers

Decreases in plasma glutathione S-transferase activity have been associated with the presentation of AMS, with specific glutathione S-transferase genes being independently associated with AMS [164, 165, 166]. Compounds that induce glutathione S-transferase activity may protect against oxidative stress and need to be investigated in the prevention of AMS [167, 168]. Interestingly, the Chinese herbal treatment *Cordyceps sinesis*, unique to the Sikkim region of the Himalayas, has been shown to increase glutathione stimulating hormone, inducing heme

oxygenase-1, and metallothionen (via activation of Nrf-2), which may increase hypoxic tolerance [169].

6. Conclusion

The evolving understanding of pathophysiologies associated with altitude has enabled for a more thorough evaluaion of existing pharmacotherapies used to prevent and treat altitude illnesses and has allowed for the consideration of alternative options. When rapid ascent is unavoidable, and immediate descent is impossible, established pharmacotherapies remain important for preventing and managing altitude-related illnesses. Additional alternative agents presented here offer a considerable expansion of existing pharmacotherapies for the future.

7. Expert opinion

The spectrum of acute altitude illnesses range from mild, self-limiting syndromes of AMS and HAH, to more severe syndromes, such as HACE and HAPE. Pathophysiologic changes that contribute to the development of AMS occur on a continuum with HACE, and thus, treatment and prevention strategies for these acute altitude illnesses also occur along this continuum. On the other hand, HAPE is attributed to an alternate pathophysiologic responses and pharmacological treatments.

Slow ascent remains the primary prevention strategy for the development of altitude illness, and rapid descent remains the primary treatment strategy for all altitude illness. Pharmacologic agents aid in both the prevention and treatment of such illnesses. Pharmacologic agents are particularly helpful when rapid ascent cannot be avoided or rapid descent is not possible. Strikingly, after decades of research, these pharmacologic prevention and treatment

strategies have not changed wildly. Acetazolamide remains the pharmacologic agent of choice for the prevention and treatment of AMS and HACE and appears to be effective in dosages as little as 62.5 mg twice daily for preventation. Consideration should be given when prescribing Az to adults over the age of 50 given the age-related reductions in kidney function and therefore lower renal clearance of Az. Calcium-channel blockers and PDE-5 inhibitors remain the pharmacologic agents of choice in the prevention and treatment of HAPE. Dexamethasone is inappropriate for prophylaxis and should be reserved for the treatment of HACE. Dexamethosone's efficacy for the treatment of HAPE remains unestablished; however, it should not be forfeited as a treatment option in thise instance entirely, particularly, when alternative treatment strategies may be contraindicated.

In light of the research advances that have been made in the last 10 years, current evidence supports the potential inclusion of alternative and newer drugs for the prevention and treatment of altitude illnesses. IL-10 upregulators may be helpful in preventing all altitude related illnesses and particularly AMS. Corticotropin-releasing factor antagonists, glutathione S-transferase inducers and nootropics may be beneficial for prophylaxis and treatment of AMS, specifically. Type A endothelin receptor antagonists, rho-kinase inhibitors, and guanylate cyclase stimulators may serve as additive or alternative agents for prophylaxis and treatment of HAPE. Agents that influence the oxyhaemoglobin dissociation curve may be beneficial in preventing and treating all altitude illnesses. Further evaluation of the efficacy of these newer treatment strategies is warranted.

Identification of those who are susceptible to altitude illnesses, as well as gaps in the existing knowledge regarding the etiology of the development of these illnesses, are challenges for the future. Ideally, an objective measure of AMS is required in addition to the Lake Louise

scoring system widely used in research studies. While the pharmacologic prevention and treatments strategies discussed herein are warranted, future research should aim to elucidate the importance of including genetic profiling prior to prescribing medication for those patients wishing to sojourn to high altitude. Genetic profiling in this instance would allow for the evaluation of gene expression and expression patterns that are consistent with (or may contribute to the development of) those who have previously been observed to develop altitude illnesses. This would allow not only for a risk evaluation and determination of susceptibility prior to sojourn, but would also allow for the appropriate prescription of pharmacologic agents .. Therefore, future pharmacologic research pertaining to the prevention and treatment of high altitude medicine should be largely focused on personalized medicine and/or combination treatments for the best outcomes.

Article highlights box

- Pathophysiology of altitude illnesses is outlined.
- Existing pharmcotherapies for prevention and treatment of AMS, HACE, and HAPE are discussed.
- Off-label pharmacotherapies for prevention and treatment AMS, HACE, and HAPE are presented.
- Updated concensus regarding pharmacologic prevention and treatment of altitude illnesses is given.
- Focus of future research for the pharmacologic prevention and treatment of altitude illnesses is suggested.

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