Effect of sildenafil and acclimatization on cerebral oxygenation at altitude

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ABSTRACT

Phosphodiesterase-5 inhibitors decrease hypoxic pulmonary vasoconstriction under hypobaric hypoxia, but are not known to affect cerebral blood flow or oxygenation. The present study was designed to evaluate the effect of sildenafil on cerebral haemodynamics during acute exposure to altitude and after acclimatization. Ten subjects were studied 1 and 3 days after rapid ascent to 3480 m before and for two consecutive hours after taking sildenafil (50 mg). Before acclimatization, HR (heart rate) rose at 1 h (76.3 $\pm$ 1.0 beats/min compared with 72.5 $\pm$ 1.5 beats/min at baseline; $P < 0.05$) and had returned to baseline at 2 h (71.3 $\pm$ 1.1 beats/min; $P > 0.05$). Mean BP (blood pressure) fell from 96.0 $\pm$ 2.0 mmHg at baseline to 91.7 $\pm$ 2.5 ($P < 0.001$) at 1 h and 89.8 $\pm$ 1.8 mmHg ($P < 0.0001$) at 2 h, whereas Sa_{O_2} (arterial oxygen saturation) increased from 83.9 $\pm$ 0.5% at baseline to 85.3 $\pm$ 0.4% ($P < 0.0001$) at 1 h and 85.0 $\pm$ 0.5% ($P < 0.01$) at 2 h. MCAV [MCA (middle cerebral artery) velocity] and P_{ETCO_2} (end-tidal partial pressure of CO_2) were unchanged, but rSo_2 (regional cerebral oxygen saturation) rose progressively at 1 h (62.7 $\pm$ 0.8%; $P < 0.05$) and 2 h (65.3 $\pm$ 0.9%; $P < 0.0001$) compared with baseline (59.3 $\pm$ 1.3%). After 3 days of acclimatization, resting rSo_2 and R_{MCA} (MCA resistance) increased and oxygen delivery fell. Changes in HR and mean BP after sildenafil were similar to day 1, but Sa_{O_2} did not change. However, rSo_2 increased [61.7 $\pm$ 0.9% at baseline to 65.0 $\pm$ 1.0% ($P < 0.0001$) at 1 h and 64.0 $\pm$ 0.9% ($P < 0.001$) at 2h], despite a reduction in MCAV [65.3 $\pm$ 1.8 cm/s at baseline to 61.3 $\pm$ 1.5 cm/s ($P < 0.01$) at 1 h and 60.9 $\pm$ 1.7 cm/s ($P < 0.0001$) at 2 h] and P_{ETCO_2} [4.1 $\pm$ 0.05 kPa at baseline to 4.0 $\pm$ 0.04 kPa at 2 h ($P < 0.01$)]. These observations suggest that sildenafil improves cerebral oxygenation at altitude. Whereas the early changes before acclimatization may be largely pulmonary in origin, the later observations may be a direct cerebral effect which warrants further study.

INTRODUCTION

Increasing numbers of people travel to or work at altitude and risk development of AMS (acute mountain sickness) [1]. The brain is sensitive to relatively minor fluctuations in cerebral oxygenation and is normally protected by cerebral autoregulatory responses which provide stable Do_2 (oxygen delivery), particularly by increasing cerebral blood flow.

Acute hypobaric hypoxia also affects the pulmonary circulation resulting in pulmonary hypertension and this may be associated with high-altitude pulmonary oedema.

Key words: acclimatization, altitude, cerebral regional oxygen saturation, hypoxia, middle cerebral artery velocity, phosphodiesterase-5, sildenafil (Viagra®).

Abbreviations: AMS, acute mountain sickness; BP, blood pressure; Do_2, oxygen delivery; HR, heart rate; MCA, middle cerebral artery; MCAV, MCA velocity; NIRS, near-IR spectroscopy; NO, nitric oxide; eNOS, endothelial NO synthase; PDE5, phosphodiesterase-5; P_{ETCO_2}, end-tidal partial pressure of CO_2; R_{MCA}, MCA resistance; rSo_2, regional cerebral oxygen saturation; Sa_{O_2}, arterial oxygen saturation.

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There has been recent interest in the use of sildenafil, a selective PDE5 (phosphodiesterase-5) inhibitor, which has been shown to be effective in reducing pulmonary hypertension. Sildenafil has variable vasodilating effects on different vascular beds attributable to the differential expression of PDE5 in the endothelium of blood vessels throughout the body. The presence of other synergistic factors is postulated to play a role as well, e.g. the presence of NO (nitric oxide) released from non-cholinergic non-adrenergic penile nerve endings, which has been utilized in the treatment of erectile dysfunction. The profound effect of sildenafil in abolishing the rise in pulmonary artery pressure during acute hypoxia-induced pulmonary hypertension in human and eNOS (endothelial NO synthase)-deficient mice experiments has raised the potential therapeutic value of sildenafil and its analogues [2]. Furthermore, it has been suggested that sildenafil might prove to be of therapeutic benefit to travellers and indigenous populations not well adapted to altitude in the prevention of pulmonary hypertension and oedema [3].

It has been assumed that PDE5 is distributed widely throughout the vasculature, including the cerebral vascular bed. Thus sildenafil induces headache and aggravates migraine at sea level, suggesting a vasodilatory effect despite no demonstrable change having been shown in MCA (middle cerebral artery) diameter [4,5]. Immunolocalization studies have demonstrated PDE5 within neuronal tissue in rat Purkinje fibres [6], but the enzyme has not been specifically identified within cerebral blood vessels. To date, sildenafil has not been shown to affect cerebral perfusion. Given its potential value in reducing altitude related pulmonary hypertension, we sought to evaluate the effect of sildenafil on cerebral blood flow and oxygenation on acute ascent to high altitude and after acclimatization.

MATERIALS AND METHODS

Two studies were performed. The first was a pilot experiment undertaken to assess the cerebrovascular changes at 150 m (Birmingham, United Kingdom) produced by sildenafil on six healthy male subjects (age 34–60 years). The aim of the main study was to evaluate the time dependency and acclimatization response to sildenafil and was carried out in ten healthy subjects (seven male and three female; age 30–65 years) at 1 and 3 days after acute ascent by cable car to 3480 m (Refugio Guide del Cervino, Aosta, Italy). Barometric pressures were 99.1 kPa in Birmingham, and 66.2 kPa and 66.4 kPa on days 1 and 3 respectively, at 3480 m. Five subjects were common to both studies.

Study protocol

Subjects were rested in the supine position for 5 min prior to any measurements. Sildenafil (50 mg; Viagra®, Pfizer) was administered orally following baseline measurements and repeat measurements made after 1 h at 150 m and at 1 and 2 h at 3480 m. HR (heart rate), BP (blood pressure), Sa_{O_2} (arterial oxygen saturation), P_{ETCO_2} (end-tidal partial pressure of CO_2), rSo_2 (regional cerebral oxygen saturation) and MCAV (MCA velocity) were recorded with five measurements made at each time point. Subjects were not taking nitrates or any other cardiovascular drugs. The side-effect profile was evaluated by direct questioning of subjects upon completion of the experiment at 3480 m. The presence of AMS was scored using the Lake Louise self-completed questionnaire [7].

The Research and Ethics Committee of the South Birmingham Health Authority granted approval for the studies, and subjects gave written informed consent.

Cerebral NIRS (near-IR spectroscopy)

In the pilot study, continuous non-invasive cerebral NIRS was performed at 150 m using a Critikon 2020 cerebral redox spectroscope (Johnson and Johnson Medical Ltd). The dual detector sensor position was standardized to a point over the right fronto-parietal region with sensor margins 3 cm from the midline and 3 cm above the supraorbital crest taking care to avoid the sagittal sinus. A Blueline Tubifast bandage (Seton Healthcare Group) was used to keep the sensor in place, and maintained a standard probe pressure. $rSo_2$was derived from the equation:

$$rSo_2 = (\text{oxygenated haemoglobin/total haemoglobin}) \times 100$$

In the main study at 3480 m, an Invos Adult Cerebral Oximeter (Somanetics; Somanetic Corporation) was used to measure cerebral oxygenation. Bilateral frontal probes were positioned and kept in place using Blue-line Tubifast bandage as before.

Transcranial Doppler

Continuous transcranial Doppler assessment of MCAV was measured by one of two experienced operators using a 2 MHz pulsed-wave, range-gated Doppler ultrasound (MultiDop T1; DWL Elektronische Systeme). The right MCA was identified by recognition of the characteristic waveform and typical flow velocity profile, and was insonated at 45–60 mm through the temporal bone window. The MCA time-averaged mean velocity (MCAV; cm/s) was recorded.

Measurement of Sa_{O_2}, P_{ETCO_2}, HR and BP

Sa_{O_2} and HR were monitored using an Ohmeda Biox 3740 Pulse Oximeter. Mean BP and P_{ETCO_2} were measured using a Datex-Ohmeda S/5 portable critical care monitor. Data were logged either manually (BP, P_{ETCO_2}, HR and Sa_{O_2}) or input via a multichannel I/O port to the hard drive of the transcranial Doppler for subsequent offline analysis.

Table 1 Time course effect of sildenafil on systemic parameters and cerebral haemodynamics on days 1 and 3 after arrival at 3480 m

Results are means ± S.E.M., $n = 10$. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ and ****$P < 0.0001$ compared with the pre-sildenafil value, as determined by a paired Student t-test. ††$P < 0.01$ and ††††$P < 0.0001$ between the 1 and 2 h time points, as determined by a paired Student t-test. ‡‡‡‡$P < 0.0001$ compared with the pre-sildenafil values on day 1, as determined by an unpaired Student t-test.

	Day 1			Day 3		
	Pre-sildenafil	1 h	2 h	Pre-sildenafil	1 h	2 h
HR (beats/min)	72.5 ± 1.5	76.3 ± 1.0*	71.3 ± 1.1††††	61.6 ± 1.2‡‡‡‡	67.4 ± 1.2***	61.0 ± 0.9††††
Mean BP (mmHg)	96.0 ± 2.0	91.7 ± 2.5***	89.8 ± 1.8****††	102.0 ± 2.7	92.0 ± 2.6***	93.8 ± 2.7**
Sa_{O_2} (%)	83.9 ± 0.5	85.3 ± 0.4****	85.0 ± 0.5**	87.4 ± 0.6‡‡‡‡	86.7 ± 0.4	88.4 ± 0.5††††
P_{ETCO_2} (kPa)	4.2 ± 0.05	4.2 ± 0.05	4.1 ± 0.05	4.1 ± 0.05	4.0 ± 0.05	4.0 ± 0.04**
MCAV (cm/s)	67.5 ± 1.4	65.0 ± 1.7	66.2 ± 1.4	65.3 ± 1.8	61.3 ± 1.5**	60.9 ± 1.7****
rSo_2 (%)	59.3 ± 1.3	62.7 ± 0.8*	65.3 ± 0.9****††	61.7 ± 0.9	65.0 ± 1.0****	64.0 ± 0.9***

Estimated cerebral Do_2 and R_{MCA} (MCA resistance)

Do_2 to the brain is proportional to the product of arterial oxygen content and brain blood flow. Since the haemoglobin concentration is unlikely to have altered within 3 days and the barometric pressure remained virtually unchanged, an estimate of the cerebral Do_2 was made using the formula:

$$Do_2 = SaO_2 \times \text{MCAV}$$

R_{MCA} was calculated as follows:

R_{MCA} (resistance units) = mean arterial BP/MCAV.

The Do_2 and R_{MCA} were calculated for individual subjects at each time point.

Statistics

Statistical and graphical analyses were performed using StatView 5.01 (SAS Institute Inc.) and Deltagraph 5 (SPSS Inc. and Red Rock Software) by unpaired and paired Student's t tests based on the parametric distribution of data. Results are expressed as mean values with data spread represented by ±1 S.D. P values < 0.05 were considered significant.

RESULTS

In the pilot study, there were no changes in HR (72 ± 9.6 and 69.2 ± 6.5 beats/min), BP (97.5 ± 11.8 and 95.5 ± 13.5 mmHg), Sa_{O_2} (96.5 ± 1.6 and 95.0 ± 1.5 %), MCAV (53.1 ± 13.2 and 49.5 ± 6.5 cm/s) or cerebral rSo_2 (69.4 ± 1.8 and 68.8 ± 1.4 %) before and 1 h after sildenafil administration respectively.

On the first day of the main study, there was one subject who had a Lake Louise symptom score of 3. There was no recorded AMS on day 3. The responses to sildenafil on days 1 and 3 are shown in Table 1. On day 1, there was a rise in the mean HR at 1 h, which then returned to the baseline level at 2 h. Mean BP was reduced at 1 h and continued to fall at 2 h. Sa_{O_2} increased at 1 h and remained so during the second hour. P_{ETCO_2} remained unchanged. MCAV did not change significantly after sildenafil on day 1 (Figure 1B), but cerebral oxygenation improved at 1 h and continued to rise at 2 h (Figure 1A). The calculated Do_2 (Figure 1C) and R_{MCA} (Figure 1D) did not change.

On day 3, HR rose at 1 h and then returned to the baseline level at 2 h. Mean BP fell at 1 h and remained so at 2 h. Although Sa_{O_2} did not alter at 1 or 2 h compared with pre-sildenafil values, there was a small fall in P_{ETCO_2} at 2 h. The mean MCAV fell and cerebral oxygenation increased. The calculated Do_2 at all time points on day 3 was reduced compared with day 1 ($P < 0.01$; Figure 1C). Following sildenafil, Do_2 fell at 2 h on day 3 (35.5 ± 1.5 to 33.1 ± 1.2 units; $P < 0.05$). The baseline R_{MCA} was higher on day 3 compared with day 1 (1.7 ± 0.1 compared with 1.4 ± 0.1 units respectively; $P < 0.05$), but this difference was abolished with sildenafil at 1 and 2 h (Figure 1D).

The main side-effect noted was facial flushing in seven subjects of whom five felt that this was mild and the remaining two considered this moderately severe. Headache was noted in three subjects (two subjects had mild symptoms and one moderately severe but not incapacitating). Three subjects experienced mild nasal congestion and two subjects noticed bloodshot eyes although none experienced photophobia. One subject had mild indigestion and one other had mild transient postural hypotension.

DISCUSSION

Sildenafil is a cGMP-specific phosphodiesterase inhibitor that causes selective vasodilatation through a reduction of intracellular calcium in vascular smooth muscle. This is effected by inhibiting PDE5, which prevents the breakdown of pre-existing cGMP, the second messenger in the NO pathway. The presence of raised levels of NO is a prerequisite for PDE5 inhibitors such as sildenafil to work, as demonstrated by the prolongation of erectile

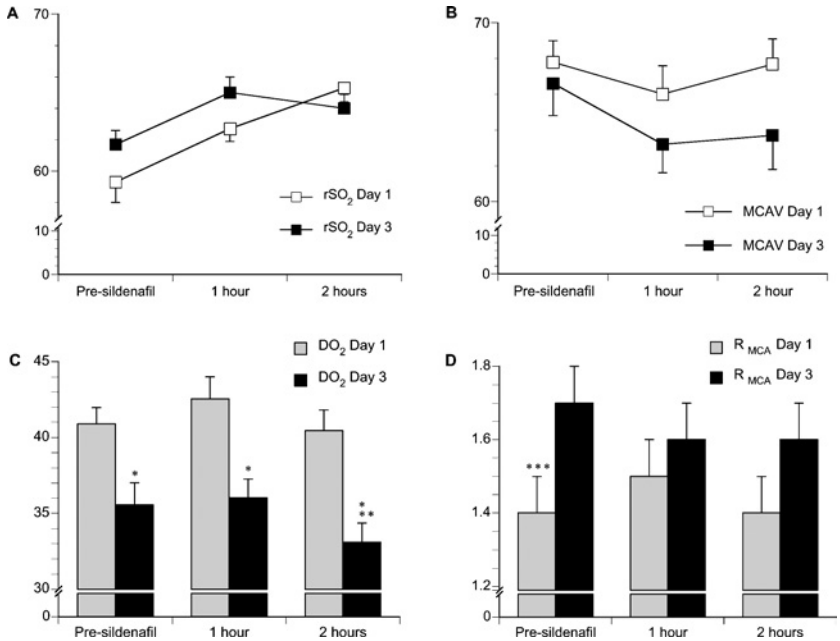

Figure 1 Effect of acclimatization and sildenafil on rSo_2 (A), MCAV (B), Do_2 (C) and R_{MCA} (D)

Results are means ± S.E.M. (single-ended error bars); $n = 10$. $^{*}P < 0.01$ comparing values at day 1 and day 3 at specified time points; $^{**}P < 0.05$ comparing pre-sildenafil with the 2 h time point on day 3; and $^{***}P < 0.05$ comparing the pre-sildenafil time point on day 1 with that at day 3. Statistical analyses on rSo_2 and MCAV are shown in Table 1.

function when non-cholinergic non-adrenergic (nitroxidergic) penile nerves are stimulated [8].

Although the reduction in systemic BP due to the vasodilatory effect of sildenafil is modest [9], there is a significant reduction in pulmonary arterial pressure in cases of pulmonary hypertension [10], presumably due to the background increase in NO in the pulmonary vasculature secondary to chronic hypoxia. Thus far, sildenafil has not been demonstrated to have an effect on cerebral blood flow by transcranial Doppler nor are there any data on the effect of sildenafil on cerebral oxygenation as measured by NIRS. The effect of sildenafil on the cerebral vasculature has been postulated but not demonstrated previously [11]. The present study describes the effect of sildenafil on cerebral blood flow and oxygenation at sea level and 3480 m. The absence of any change in cerebral oxygenation and blood flow at sea level is consistent with data reported previously [4].

Transcranial Doppler insonation of the MCA is accurate and reliable in the measurement of cerebral blood flow [12] and has been shown to be robust in assessing cerebral haemodynamics under high-altitude conditions [13]. MCAV as measured by transcranial Doppler has a linear relationship with cerebral blood flow within a wide range of flow values as measured by the ^{133}Xe clearance technique [12]. Furthermore, MCAV measurements under conditions of acute hypobaric hypoxia have been validated against sea-level measurements and are an accurate indicator of cerebral blood flow and Do_2 [14]. We have used previously cerebral NIRS under hypobaric conditions for cerebral hypoxia and have found this measure to be sensitive and reproducible as well as robust [15–17].

A comparison between the rSo_2 and MCAV curves in response to sildenafil for 1 day (unacclimatized) and 3 days (acclimatized) is shown in Figure 1. On day one, sildenafil caused a progressive improvement in cerebral oxygenation at 1 and 2 h. There is a similar rise at 1 h on day 3, but this effect appears to plateau at 2 h. This improvement, however, does not appear to be dependent on cerebral blood flow as there is no change in MCAV on day 1 and, paradoxically, a reduction in MCAV on day 3. The calculated Do_2 (Figure 1C) demonstrates the effect of acclimatization. Do_2 is proportionate to the MCAV and the Do_2 profile follows the changes in MCAV with sildenafil. The reduction in MCAV on day 3 is likely to be secondary to the overall improvement in Sao_2 and possibly a decrease in P_{ETCO_2} with acclimatization. At high altitude, the cerebral circulation is exposed to various competing influences: arterial hypoxaemia is a potent cerebral vasodilator, whereas arterial hypocapnia is a potent vasoconstrictor [18]. Both these effects are reflected in R_{MCA} (Figure 1D) and are modulated by acclimatization. In the present study there was an increase in R_{MCA} and a decrease in Do_2 with acclimatization that was overcome by sildenafil. On acute exposure to high altitude, hypoxia-induced cerebral vasodilatation appears to override the vasoconstrictor effects of hypocapnia but, by day 3, improved peripheral oxygenation with acclimatization increased R_{MCA}. In the present field study,

an indirect measure of Do_2 has been made by calculating the product of Sao_2 and MCAV which are both non-invasive measurements. Calculated Do_2 did not take into account any changes in plasma volume that may have occurred at altitude, thus changes in Do_2 after sildenafil largely reflected changes in MCAV.

The different profiles in the time-course experiment suggest that there may be multiple mechanisms at work and the observed effects of sildenafil when acclimatized may be intracranial rather than systemic. It may be postulated that the improvement in cerebral oxygenation with sildenafil on day 1 may be due, in part, to an increase in Sao_2. Despite the improvement in Sao_2 due to acclimatization, the response to sildenafil on day 3 is not correlated with any change in Sao_2. This suggests that the improvement in cerebral oxygenation is predominantly intracranial. NIRS provides a measure of the proportion of oxygenated blood in the cerebral capillaries. It does not distinguish how much is in the arterial or venous part of the capillary bed. The proportion of total blood in the cerebral capillaries has been estimated at 28% arterial and 72% venous [19,20]. It is possible that changes in these proportions could occur both at altitude with acclimatization and with sildenafil. The observed large changes in cerebral NIRS with more modest changes in MCAV would tend to support this model. A further possibility is differential vasodilatation with sildenafil (i.e. mid-sized arteries versus smaller downstream arterioles) which may potentiate the observed differences in cerebral oxygenation.

The presence of PDE5 in the cerebral arteries or microvasculature has thus far not been demonstrated, and our present findings of a change in MCAV with PDE5 inhibition suggest indirectly that this enzyme may in fact be present under hypobaric hypoxia. The absence of a discernible change in MCAV at sea level implies that a hypoxic drive is a precondition to cerebrovascular sensitivity to sildenafil. This is the first time that PDE5 inhibition has been demonstrated to affect cerebral oxygenation (both unacclimatized and acclimatized subjects) and cerebral blood flow (acclimatized subjects). Possible explanations for the unmasking of this cerebral response at altitude may be the priming effect of increased levels of local NO within the cerebral vascular bed consequent upon hypobaric hypoxia, or perhaps hypoxic up-regulation of hitherto indiscernible PDE5 at altitude. The role of NO priming has yet to be explored with respect to PDE5 inhibition, but experimental evidence showing loss of protection by ischaemic preconditioning when eNOS and nNOS (neuronal NOS) knockout mice are exposed to focal cerebral ischaemia suggests an important role for NO in the cerebrovascular response to sildenafil [21].

Although the potential role of PDE5 inhibition in the treatment of pulmonary hypertension has been highlighted previously, the present study demonstrates the wider influence of sildenafil on the cerebral vasculature. Under conditions of high-altitude hypoxia, sildenafil has a positive influence on cerebral oxygenation and an attenuation of cerebral blood flow. However, our present study was not designed to establish any therapeutic benefit from improved cerebral oxygenation. The mechanism by which these effects take place is not currently known and will need to be investigated further. These findings may influence our knowledge of PDE5 localization and direct further studies towards a potentially therapeutic role for PDE5 inhibitors in the management of cerebral hypoxia.

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