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ORIGINAL ARTICLE

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Influence of vanadium on acclimatization of humans to high altitude

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Abstract The study was conducted on human volunteers as controls as well as after administration of vanadyl sulphate on induction to high altitude (HA) at 3500 m. The plasma vanadium contents were significantly reduced in the control group on abrupt induction to HA on days 3 and 10, indicating redistribution to other organs/tissues under the stressful situation. In the vanadium salt-treated group, plasma vanadium contents were similar to those obtained at sea-level. Administration of vanadyl sulphate did not act as a diuretic. Moreover the vanadium supplemented group drank more water and also excrete less urine than the control group.

Key words High altitude · Vanadyl sulphate · Trace element

Introduction

Trace elements play an important role in the well being of higher animals and open new prospects in biochemical and medical research. Vanadium is widely distributed in very low concentration in most animals; however, limited information exists about vanadium metabolism in animals at physiological concentrations. It has been reported that vanadium is a very active pharmacological substance in vivo and in vitro (Nielsen 1985). It has been observed that vanadium deficiency significantly increases packed cell volume, which in turn may increase blood viscosity (Nielsen and Ollerich 1973). Golden and Golden (1981) have reported that administration of vanadium salt induces diuresis, which may be beneficial in the process of high altitude (HA) acclimatization where ill effects of high altitude are mainly due to fluid retention in the body. In the present communication, attempts have been made to study vanadium administration to humans during high altitude adaptation.

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Materials and methods

The studies were conducted in 16 volunteers from the Indian Army. All of the subjects were plain dwellers and had no previous experience of staying at high altitude (HA). The subjects were told in detail about the methodology and their written consent was obtained. The subjects were initially studied in Delhi (altitude of 200 m) and then divided into two groups of eight each. Before airlifting these groups to an elevation of 3500 m, the experimental group was given 5 mg of vanadyl sulphate orally filled into gelatin capsules 3 days prior to their air lift. The control group was given 5 mg of starch prepared and administered in a similar way. The total flight time was about 50 min.

After landing of the subjects of 3500 m, trace salt and placebo treatment was continued a further 3 days. Subsequently, control and experimental subjects were studied for blood pH, PO_2, PCO_2, blood viscosity, 2,3 diphosphoglycerate (DPG), and other haematological parameters. Measurement of blood gases was done by drawing mixed blood from the pulp of the left ring finger into heparinised capillaries. As well as the foregoing parameters, plasma vanadium content, fluid intake, urine volume, and plasma Na^+ and K^+ ions were also estimated. After discontinuing the vanadium treatment all the above parameters were again studied on the 10th day at high altitude. All of the parameters were also studied at sea-level (200 m) prior to air-lifting to HA.

The data were analysed using Friedman Chi-square test to compare the three separate samples of the same group. For comparing independent samples (control versus experimental) Kruskal-Wallis one-way analysis of variance was used.

Results

The data of table 1 indicate the changes in blood pH, PO_2, PCO_2 and blood viscosity at sea-level and at high altitude. On the 3rd day of induction in the control group, a significant increase in blood pH ($P<0.05$) and a significant decrease in blood PO_2 and PCO_2 ($P<0.01$) were observed. Blood viscosity also increased on the 3rd day of induction ($P<0.05$). In the same group on the 10th day of exposure, no further change was observed in these parameters except for the increase in blood viscosity ($P<0.01$). In the vanadium treated group, no further variation in these parameters was seen with the exception of increased blood viscosity but the increase was less compared with the control group (Table 2). Table 3 shows the

changes in haematological parameters and 2,3 diphosphoglycerate contents of the control group on exposure to high altitude. Significant changes in counts of red blood corpuscles, contents of haemoglobin and 2,3 diphosphoglycerate were obtained on various days of exposure. Treatment of subjects with vanadium salt did not produce any further variations in the values obtained for the control group (Table 4).

Figure 1 depicts the changes in plasma vanadium contents of human volunteers at sea-level with and without supplementation of vanadium salts and also after induction to HA in both groups on days 3 and 10. At sea-level the contents of vanadium in plasma were 27.33±2.13 ng/ml which slightly increased after oral administration of vanadium salt to 31.9±3.1 ng/ml. On the 3rd and 10th day of induction to HA, a significant decrease (P<0.001) in plasma vanadium contents was observed in the control group. On both days the vanadium contents of <5 ng/ml were significantly reduced in comparison with the value at sea-level. In the experimental group, which was fed orally for 6 days with vanadium salt, the vanadium contents rose dramatically to a level of 37.7±4.3 ng/ml on the 3rd day of HA exposure. Even after the cessation of oral vanadium feeding, the vanadium contents remained elevated and reached a value of 31.7±2.9 ng/ml.

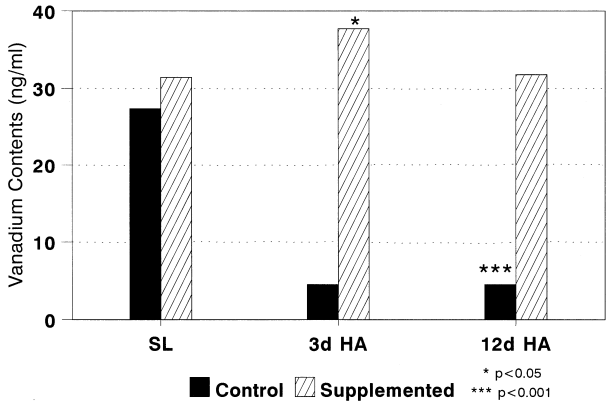

Fig. 1 Relationship between vanadium contents in plasma of control and supplemented groups at sea-level and on various days of high altitude exposure. ■ Control; ▨ suplemented. * P<0.05; *** P<0.001

Table 5 shows the liquid intake and urine output for the first 24 h of the stay at high altitude in the control

Table 3 Changes in haematological[a] parameters and 2,3 diphosphoglycerate contents of the control group on exposure to high altitude. Data are of mean±SEM (n=8)

Hypoxic stress	RBC ×10^6	Hb%	MCHC%	2,3 DPG (μmoles/ml)
Control	5.06 ±0.62	14.35 ±1.05	33.4 ±0.62	1.95 ±0.30
3rd day at HA	5.53* ±0.71	15.95* ±1.56	34.5 ±1.31	2.42* ±0.29
10th day at HA	5.76** ±0.62	15.66* ±1.26	30.0 ±1.22	2.80** ±0.31

* P<0.05; ** P<0.01

[a] *RBC* red blood corpuscles, *Hb* haemoglobin, *MCHC*% percentage mean corpuscular haemoglobin concentration, *2,3 DPG* 2,3 diphosphoglycerate

Table 4 Changes in haematological parameters[a] and 2,3 DPG contents of experimental subjects on exposure to high altitude. Data are of mean±SEM (n=8)

Supplemented group	RBC ×10^6	MCHC%	2,3 DPG (μmoles/ml)
Sea-level	4.81 ±0.84	33.4 ±0.66	2.04 ±0.30
3rd day at HA	5.46* ±0.59	32.69 ±0.77	2.41* ±0.47
10th day at HA	5.10 ±0.76	34.78 ±2.6	2.44* ±0.38

* P<0.05

[a] As defined in the footnotes to Table 3

Table 1 Changes in blood pH, viscosity and blood gases in the control group on abrupt exposure to high altitude (HA). Data are of mean±SEM (n=8)

Hypoxic stress	pH	PO_2 (mm Hg)	PCO_2 (mm Hg)	Viscosity (cP)
Control	7.38 ±0.02	75.5 ±4.8	39.2 ±3.3	4.57 ±0.29
3rd day at HA	7.40* ±0.02	54.1** ±2.8	31.5* ±1.89	5.01* ±0.57
10th day at HA	7.38 ±0.01	53.8** ±2.1	29.8** ±2.9	5.26** ±0.64

* P<0.05; ** P<0.01

Table 2 Changes in blood pH, viscosity and blood gases in vanadyl sulphate treated group after exposing to high altitude. Data are of mean±SEM (n=8)

Supplemented group	pH	PO_2 (mm Hg)	PCO_2 (mm Hg)	Viscosity (cP)
Sea-level	7.38 ±0.02	74.6 ±4.8	40.5 ±1.8	5.09 ±0.73
3rd day at HA	7.40* ±0.01	54.5** ±3.2	32.78** ±1.13	5.40 ±1.12
10th day at HA	7.39 ±0.17	55.4 ±2.44	30.15 ±2.4	5.82** ±0.99

* P<0.05; ** P<0.01

Table 5 Liquid intake and urine output in control and vanadyl sulphate treated group after exposure to high altitude. Data are of mean±SEM (n=8)

	Control group	Experimental group
Fluid intake (ml)	2291±554	2458±657
Urine output (ml)	1795±631	1339±403

Table 6 Changes in plasma sodium and potassium contents in control and experimental group on induction to high altitude (Data are of mean±SEM)

Group	Sodium (meq/l)	Potassium (meq/l)
Control		
sea-level	138.6 ±8.7	4.2 ±1.5
At 3500 m (on day 3)	143.4 ±6.7	4.1 ±0.58
Experimental		
sea-level	140.2 ±5.7	3.8 ±0.65
At 3500 m (on day 3)	139.0 ±4.8	4.12 ±0.61

and experimental groups. The experimental group consumed more liquid than the control group, compared with increased urinary output of the control group. Table 6 depicts the Na^+ and K^+ contents in the plasma on exposure to altitude of 3500 m after the administration of vanadium salt. No significant difference was noticed in the Na^+ and K^+ contents of hypoxic control and vanadium-treated hypoxic cases.

Discussion

In the present study vanadyl sulphate was given orally to human volunteers. It has been reported (Roshcin et al. 1980; Nielsen 1987) that vanadium administered by any one route (orally, subcutaneously, intramuscularly, intraperitoneally) is metabolized similarly to that administered intravenously in rats. Nechay et al. (1986) reported that the tetravalent and pentavalent states are the most important forms of vanadium in biological systems. Hence the tetravalent state was chosen for our study. Vanadium is also reported not to be toxic for humans when given orally. The toxicity of vanadium appears to be high when given intravenously and very low orally. The toxicity also varies considerably with the nature of the compound but, in general, increases as valency increases. Moreover, there has been no demonstration to date that vanadium deficiency impairs a biological function in any animal.

Table 1 indicates significant changes in blood pH, PO_2, PCO_2 and blood viscosity on induction to HA. These changes are natural physiological phenomenon at high altitude. Administration of vanadium salt did not further alter these values except blood viscosity. The decreased viscosity compared with the control may possibly be due to vanadium being chelated with imidazole and carboxylic groups in protein. Blood viscosity in general is mainly dependent on red blood cell counts and to a lesser extent on plasma proteins. Red blood cell counts were found to be significantly higher on induction to high altitude with no significant difference between the controls and the experimental group.

The role of organic phosphate is especially important in the uptake and unloading of oxygen by normal red blood cells. Various workers (Benesch and Benesch 1967; Chanutin and Curnish 1967) have demonstrated that the affinity of haemoglobin for oxygen may be decreased by the interaction of haemoglobin with organic phosphates particularly 2,3 diphosphoglycerate. On hypoxic exposure, the contents of 2,3 diphosphoglycerate increased in the control and experimental groups.

Another important parameter which is very useful for high altitude acclimatization is diuresis; intravenous vanadate has been reported to be a potent diuretic. Rats with a control urine output of 26 ml/h produced 36.2 ml/h after intravenous injection of sodium vanadate at a dose of 250 μg/kg body wt. (Balfour et al. 1978). In the presence of vanadate, extracellular potassium (at physiological concentrations) inhibits the sodium pump whereas, in the absence of vanadate, potassium is stimulatory. Our results on human volunteers, upon administration of vanadyl sulphate do not support the above findings. A possible explanation for this discrepancy is that in our study vanadyl sulphate was administered orally while vanadate was injected intravenously in the rat. The difference in valency state of vanadium may be responsible for these varied responses. Moreover, in our studies the experimental group (treated with vanadyl sulphate) drank more water with a lower amount of urine output than the control group. This indicates that vanadium in the tetravalent state may not act as a diuretic as reported in the case of pentavalent valency (i.e. sodium vanadate). The extra water is being retained by the body. Macara et al. (1980) also reported that in vivo vanadium might function as a physiological regulator of sodium pump activity. Vandate inhibits Na,K ATPase by binding to the ATP hydrolysis site but reduction of vanadate to vanadyl reverses that inhibition.

It has been confirmed from the use of radioactive vanadium (^{48}V) that vanadium was mainly present in plasma and disappeared from blood stream quickly. Hence plasma was estimated for vanadium contents and its probable retention on HA exposure. In our study the plasma vanadium contents were significantly decreased on day 3 and 10 of HA exposure. The decreased contents on hypoxic exposure may be due to redistribution of vanadium from plasma into the other organs/tissues: certain physiological changes take place in these organs on exposure to HA and hence uptake of radioactive vanadium may vary in these organs under stressful conditions. In the vanadium supplemented group, the plasma level of vanadium returned to normal. It has been reported that

radioactive vanadium (^{48}V) is taken up selectively by the various organs and for up to 96 h remains in the blood. Therefore, it is presumed that supplemented vanadium salt was responsible for the increased plasma vanadium contents, which were significantly reduced after hypoxic exposure. The contents of plasma Na and K did not alter after vanadium salt administration.

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