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Pharmacokinetics of lithium in healthy volunteers after exposure to high altitude

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Abstract. Introduction: Exposure of the human body to high altitude causes a number of physiological changes. In previous studies, we observed that these changes may alter the pharmacokinetics of drugs. The number of erythrocytes/mm^3 increases both, after acute exposure to high altitude (HA), i.e. within 12 – 24 h after reaching high altitude (H), as well as in chronic exposure (HC) (≥ 10 months) to H. Also binding of drugs to biologic material may change with exposure to HA and/or HC. Objective: Since lithium is transported into and out of erythrocytes and binds strongly to erythrocytes, but is not plasma protein-bound, we selected this drug as candidate for the present study. Subjects, material and methods: Lithium carbonate 300 mg were administered orally to young healthy volunteers. One group residing at low altitude (Santiago, Chile, 600 m, group L), these same volunteers after 15 hours of exposure to high altitude (4,360 m, group HA), and volunteers living at high altitude for at least 10 months (group HC). Results: We found a significant increase of both hematocrit and red blood cell count (RBC) after exposure to H, both, acute or chronic. Elimination half-life increased 64.1% in group HA and 111.4% in group HC in comparison to group L. We also found an increase in volume of distribution: + 18.9% in group HA, and + 35.8% in group HC when measured in plasma, and + 16.9% in group HA and + 18.8% in group HC when measured in whole blood. Lithium uptake by the erythrocytes increases: the value of 36.7 ± 22.7% in Group L rose to 54.8 ± 21.1% and to 54.6 ± 24.2% in groups HA and HC, respectively. Total clearance decreases at high altitude, though the differences were significant only in group HC (37%). Conclusion: Results indicate that exposure to H produces alterations in the pharmacokinetics of lithium and that these variations may be clinically relevant.

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Introduction

Acute or chronic exposure of humans to high altitude (H) produces various physiological changes that may alter the pharmacokinetics of drugs. A number of physiological studies in (H) are available in scientific literature and some of these physiological alterations that may have an impact in the disposition of drugs are listed in Table 1. At sea level, barometric pressure is 760 torr while at 3,600 m it is 523 torr. The partial oxygen pressure in the body, PO_2, falls in response to low barometric pressure causing various states of hypoxia. People reaching H may experience clinical symptoms such as drowsiness, lassitude, headache, mental fatigue, muscle weakness, gastrointestinal disturbances, euphoria, sleep disorders, loss of appetite and others. According to present practice, the simultaneous concurrence of 2 or more of these symptoms is known as acute mountain sickness and it can develop during the first 12 – 72 hours of exposure.

In medical literature, only few pharmacological studies on H are listed and the pharmacokinetic studies are almost non-existent. One study done in Perú in 1940 with sulfathiazole [Rabinovich 1994] and another performed with caffeine and indocyanine-green (ICG) [Kamimori et al. 1995], demonstrate that in humans exposure to H may produce modifications in the pharmacokinetics of some drugs.

Recent studies with meperidine in volunteers at 4,360 m altitude performed by our group showed that several pharmacokinetic parameters were significantly different at H

Table 1. Physiological changes after exposure to high altitude that may have an impact on disposition of drugs.

System	Short-term exposure	Long-term exposure
Pulmonary [Monge et al. 1991] [Chiodi 1957]	↑ Ventilation	↑ Ventilation ↑ Pulmonary volume
Cardiovascular [Vogel et al. 1969]	↑ Heart rate ↑ Cardiac output	↑ Heart rate ↓ Cardiac output
Hematologic [Kurtz et al. 1985] [Hannon et al. 1969] [Cahan et al. 1990] [Goñez et al. 1993]	↓ Plasma volume ↑ Hematocrit ↔ Erythrocyte production	↓ Plasma volume ↑ Hematocrit ↑ Erythrocyte production ↑ Hemoglobin
Blood flow [Ramsoe et al. 1970] [Durand et al. 1969] [Sorensen et al. 1974] [Rennie et al. 1971]	↑ Hepatic blood flow ↓ Cutaneous blood flow ↑ Cerebral blood flow	↓ Cutaneous blood flow ↔ Cerebral blood flow ↓ Renal blood flow
Renal function [Rennie et al. 1971]		↓ Glomerular filtration rate
Hepatic function [Ramsoe et al. 1970] [Berendsohn 1962]	↑ Bilirubin	↑ Bilirubin ↔ Transaminases ↔ Albumin ↔ Total proteins
Body composition [Picon-Reategui et al. 1961] [Krzywicki et al. 1969] [Surks et al. 1966]	↓ Body fat	↑ Extracellular fluid ↑ Body fat

↑ = increase, ↓ = decrease, ↔ = no changes.

than those obtained at sea level and this was true for measurements made in both plasma and whole blood [Ritschel et al. 1996]. Another interesting aspect is the increased erythrocyte binding of meperidine after acute and chronic H exposure. Moreover, the extent of protein binding tended to decrease with H. In another study of the effects of exposure to H on the pharmacokinetics of acetazolamide, we also observed several interesting changes in the disposition of this drug [Ritschel et al. 1998].

Objective of the present study was to determine whether such changes are also seen at H with a drug like lithium which is not bound to plasma protein but highly bound to erythrocytes.

Subjects, materials and methods

Subjects and study design

The study was carried out in 3 groups of healthy volunteers and was approved by the Institutional Review Board of the University of Cincinnati, Ohio, the University of Chile, and the Chilean Armed Forces.

The volunteers were either recruited from the Chilean Army or were students at the University of Chile. All the volunteers were males aged 19 – 28 years. Inclusion parameters were at least 10 months residing either at low altitude or at H and completion of physi-

cal examination with urinalysis and blood chemistry. Exclusion parameters included any results outside the established normal range for urine and blood chemistry, except those tests that are expected to be altered at H, like hematocrit, any previous cardiovascular, pulmonary or kidney disease and use of any drugs 30 days prior to the study. All volunteers signed a written informed consent.

Volunteers were divided into 3 groups. Group L consisted of 7 volunteers living at low altitude in Santiago, Chile (600 m). Group HA included the same participants as in group L but after 15 hours of reaching H. The third group HC consisted of 10 volunteers living at H at least for 10 months, at the military base at Pacollo, 4,360 m in the Andes Mountains in northern Chile. Acclimatization to various pathophysiologic responses to H occurs over a period of a few days to a few weeks or even months [Houston 1992, Sutton 1992]. We assumed that a 10-month period was enough for achieving acclimatization to H. Mean (± SD) body weight and surface area were 70.8 ± 10.7 kg and 1.85 ± 0.18 m^2, respectively, in the L and HA group, and 70.9 ± 4.81 kg and 1.84 ± 0.07 m^2, respectively, in the group HC.

Treatment was the same in all 3 groups: after an overnight fast with water allowed ad libitum, a dose of 300 mg of lithium carbonate in an inmediate release tablet (Carboron, Beta, Chile) was administered orally with 250 ml of water. Participants were given a standard breakfast 2 hours after dosing. A catheter was inserted into a forearm vein and was maintained for 12 hours with a heparin lock. During the course of the day, they were also fed a standardized lunch and dinner, and minimal physical activity was allowed.

Blood samples were collected at 0, 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 36 hours after administration. Erythrocyte and hematocrit data were obtained at the beginning of the experiments.

An aliquot of each blood sample was lysed for analysis of drug in whole blood. Another aliquot was centrifuged and plasma separated. Urine samples were collected at 0 – 4-, 4 – 8-, 8 – 16-, 16 – 24-, 24 – 36- and 36 – 48-hour intervals. The samples collected at low altitude were immediately frozen after separation. At high altitude, samples were frozen and kept frozen during stay, and packed in dry ice for transportation to the laboratory for analysis.

Analytical procedure

All samples were analyzed for lithium by atomic absorption spectrophotometry [Pybus and Bowers 1970] using a GBC 902 equipment. To 1 ml of biological fluid were added 0.5 ml of trichloroacetic acid 50%, 2 ml of KCl solution (8,000 ppm of K) and bidistilled water to a final volume of 5 ml. The equipment was adjusted at 670 nm.

Pharmacokinetic analysis

The concentration-time data for lithium were analyzed by curve fitting using the RESID Computer program [Ritschel 1975]. Binding to erythrocytes was calculated according to the following equation:

$$C_E = \frac{C_B - C_p(1 - Ht)}{C_B} \times 100$$

where C_E is binding to erythrocytes, C_B and C_p are concentrations in blood and plasma, respectively, and Ht is hematocrit.

Statistical analysis

Each of the pharmacokinetic parameters was subjected to 1-way analysis of variance. A level of $p < 0.05$ was considered to be statistically significant.

Results

Both creatinine and creatinine clearance were in the normal range for all volunteers. Both hematocrit and RBC increased 12% and 10.6%, respectively, after 15 hours of exposure to H (HA group). These parameters were also higher in the group exposed chronically to the high altitude (HC) in comparison with the group living at low altitude (L): hematocrit + 11.5% and RBC + 10.5% (Table 2). In all these cases the differences were statistically significant.

Table 2. Physiologic and pharmacokinetic parameters of healthy volunteers in plasma and whole blood at low altitude (L), after short-term exposure to high altitude (HA), and after long-term exposure to high altitude (HC). The values in parenthesis are the SD.

	Plasma			Blood		
	L	HA	HC	L	HA	HC
Hematocrit (%)	NA	NA	NA	43.4 (2.6)	48.6 (2.1)	48.3 (1.83)
Erythrocytes $mm^3 \times 1{,}000$	NA	NA	NA	5,041 (350)	5,576 (242)	5,570 (169)
% Erythrocytes binding	NA	NA	NA	36.7 (22.7)	54.8 (21.1)	54.6 (24.2)
$t_{1/2}$ (h)	9.86 (2.21)	16.24 (5.64)	20.84 (3.05)	17.35 (4.48)	23.77 (4.06)	20.62 (2.99)
λz (h^{-1})	0.073 (0.015)	0.048 (0.02)	0.03 (0.01)	0.042 (0.009)	0.03 (0.005)	0.034 (0.005)
$t_{1/2}$ abs (h)	0.469 (0.189)	0.647 (0.29)	0.740 (0.363)	0.363 (0.126)	0.439 (0.227)	0.729 (0.462)
Ka (h^{-1})	1.698 (0.666)	1.429 (1.034)	1.13 (0.46)	2.267 (1.295)	1.674 (0.752)	1.53 (1.30)
Vz/F (l/kg)	0.539 (0.033)	0.641 (0.092)	0.732 (0.130)	0.745 (0.099)	0.871 (0.122)	0.885 (0.076)
Cl /F (ml/min/kg)	0.659 (0.154)	0.499 (0.16)	0.413 (0.088)	0.515 (0.107)	0.433 (0.093)	0.511 (0.103)
T_{max} (h)	1.12 (0.438)	1.51 (0.743)	1.92 (1.23)	0.929 (0.236)	0.91 (0.35)	1.56 (0.771)
MRT (h)	10.84 (2.68)	19.44 (7.3)	25.97 (5.11)	19.70 (5.22)	28.95 (5.39)	24.35 (5.16)

NA = Not applicable

Whole blood and plasma

Concentration-time profiles for lithium in plasma and whole blood are shown in Figures 1 and 2. Data were best fit by a 2-compartment open model. Pharmacokinetic parameters in whole blood and plasma are listed in Table 2.

Statistically significant differences between values at low altitude (group L) and values after exposure to H both, acute (group HA) and chronic (group HC) were found in $t_{1/2}$ (HA + 64%, HC + 111%) in plasma as well as in whole blood (HA + 37%, HC + 19.1%). For Vz/F (HA + 18.9%, HC + 35.8%) in plasma, all these differences were statistically significant. In whole blood Vz/F also increased in the groups exposed to H in comparison with the value at low altitude (HA + 17.5%, HC + 18.8%), however, the differences were significant only in case of HC.

Also the MRT measured in plasma was significantly increased after exposure to H (HA + 79.3%, HC + 139.6%). There was also an increase in the MRT in whole blood (HA + 50.8%, HC + 23.6%) which was statistically significant only between the L versus HA groups.

Urinary excretion

Urinary excretion rates of lithium versus time at the middle of the collection intervals

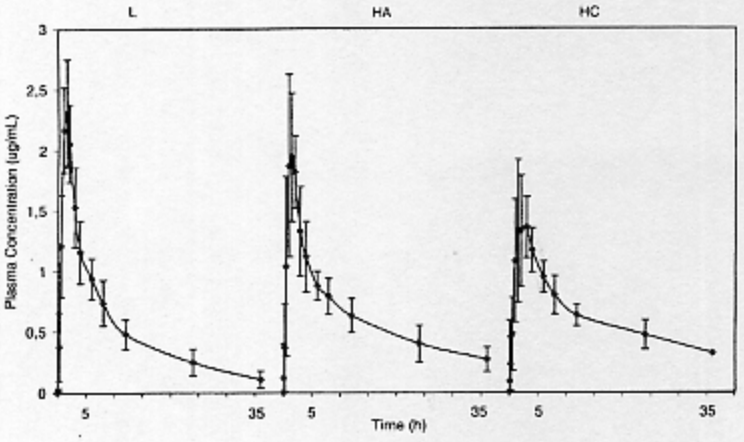

Figure 1. Mean plasma concentration-time profiles for lithium in healthy volunteers at low altitude (L), after short-term exposure to high altitude (HA) and after long-term exposure to high altitude (HC). Bars indicate standard deviations.

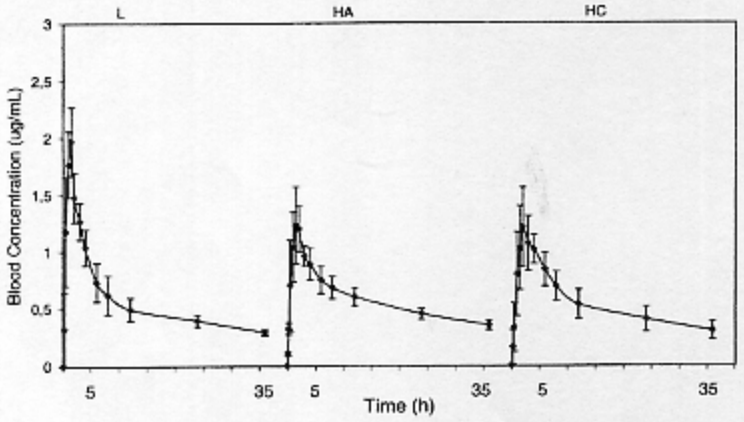

Figure 2. Mean whole blood concentration-time profiles for lithium in healthy volunteers at low altitude (L), after short-term exposure to high altitude (HA) and after long-term exposure to high altitude (HC). Bars indicate standard deviations.

profiles for the 3 situations studied (L, HA, and HC) are shown in Figure 3. Excretion rate constants and half-lives were calculated from the slopes of these graphs. The mean ± SD values of $t_{1/2}$ were 12.22 ± 2.8 h, 13.27 ± 2.4 h, and 12.87 ± 3.25 h for groups L, HA, and HC, respectively. The differences are statistically not significant.

Erythrocyte uptake

The erythrocyte uptake was significantly increased, the percent of change was 49.3% after HA and 48.8% after HC in comparison with the values at low altitude. The RBC lithium/plasma lithium ratio was 0.58, 1.21 and 1.20 at L, H, and HC, respectively.

Discussion

In our study, we found a significant increase in hematocrit of the volunteers after about 15 hours of exposure to H, the mean increase of this parameter was 12%. A parallel significant increase of 10.6% was observed in RBC. It is interesting that these variations are observed after such a short period of exposure to H. It is unlikely that this effect is due to an increase in erythrocyte production. It is more likely that it is due to a plasma volume reduction as a consequence of dehydration. Such an effect has been reported to occur shortly after exposure to the H [Hannon et al. 1969]. On the other hand, increase in both hematocrit and erythrocytes observed in the group undergoing chronic exposure to altitude of 11.3% and 10.5%, respectively, would be due to a real increase in erythrocyte production as a consequence of hypoxia due to reduced PO_2 and stimulation of erythropoietin.

In our study, we determined the concentrations of lithium, both in plasma and in whole blood. We found different values for $t_{1/2}$ in the 2 situations, 9.86 ± 2.21 h in plasma and 17.35 ± 4.48 h in whole blood. In blood, lithium is distributed in 2 compartments: the plasma and the erythrocytes. Lithium in plasma is removed more rapidly while in whole blood the drug is retained by the erythrocytes. In addition, half-life is not an absolute parameter since it depends directly on the volume of distribution and inversely on the clearance. Increase in volume of distribution and decrease in Cl would explain the rise of the value of $t_{1/2}$ in whole blood, when compared with plasma.

When one compares the half-life obtained in plasma in the 3 conditions of this study, we find that $t_{1/2}$ increases from 9.87 ± 2.21 h at low altitude to 16.2 ± 5.64 h after a short-term exposure to high altitude (+ 64.1%), and to 20.84 ± 3.05 h (+ 111.4%) after chronic expo-

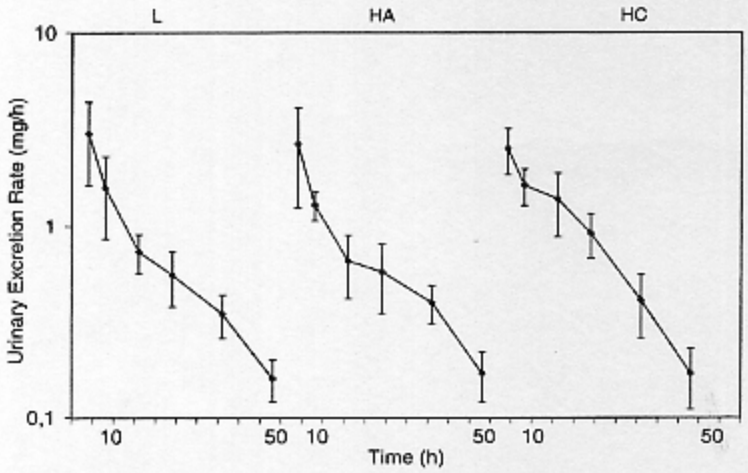

Figure 3. Mean urinary excretion rate of lithium in healthy volunteers at low altitude (L), after short-term exposure to high altitude (HA), and after long-term exposure to high altitude (HC). Bars indicate standard deviations.

sure. Half-life also increases after exposure to H when measured in whole blood, + 37% in the HA group and + 18.95% in the HC group. According to the literature, half-life of lithium fluctuates between 18 h and 27 h in subjects with normal renal function, however, a range of 5 – 79 h has been reported [Carson 1991]. Increase in half-life of lithium after exposure to H may be very important clinically since this parameter is related to the time to reach steady state concentration and is used to establish a proper dosage regimen of a drug in the individual patient. However, it is interesting to consider the differences in the value of this parameter when measured either in plasma or whole blood. Half-life in whole blood is longer, probably due to the binding to erythrocytes. We have an additional complication when we analyze the half-life obtained from urinary excretion data. In this case, values are very similar and there are no statistically significant differences in the 3 situations. These results are in accordance with other studies performed during acute altitude hypoxia in humans in which lithium renal clearance was used as an index of the delivery of sodium and water from the thin descending loop of Henle. In these studies, it was found that the altitude hypoxia did not induce significant changes in the values of lithium renal clearance [Hansen et al. 1994, Olsen et al. 1993].

We observed an increase in volume of distribution in the groups exposed to the H either when measured in plasma (+ 18.9% in group HA and + 35.8% in group HC) or in whole blood (+ 16.9% in group HA and + 18.8% in group HC). This phenomenon can be explained by the affinity of lithium for erythrocytes. It seems that there exists a relationship between erythrocytes, increase in hematocrit and rise in the volume of distribution. It also appears that clearance decreases as hematocrit increases after H.

We also found that lithium uptake by erythrocytes increases with exposure to H, the value of 36.7 ± 22.7% at low altitude rises to 54.8 ± 21.1% and to 54.6 ± 24.2% after short-term and long-term exposure, respectively, the differences being statistically significant. These results are consistent with the increase of hematocrit and RBC produced by the exposure to H. It is interesting to note that RBC lithium/plasma lithium ratio increases dramatically with exposure to high altitude. In fact, an increase of 208.6% and 206.8% in the lithium index was observed in groups HA and HC, respectively. These findings may be considered clinically relevant since lithium ratio has been reported to be associated with efficacy and neurotoxicity [Dunner et al. 1978, Smith et al. 1979]. Since free fraction of lithium, not bound to erythrocytes, is the active one, it would be of interest in a future study to monitor lithium concentrations in long-term treatment patients at H. In addition, sodium-lithium counter-transport has been reported as being important in several other diseases [Falkner et al. 1997] and also is a useful diagnostic tool [Monciotti et al. 1997]. Our study was a single-dose study, however, clinically relevant drug concentrations are those measured at steady state, because the deep compartments of distribution of lithium takes a rather long time.

Another point of interest is the volume of distribution of lithium in erythrocytes. The latter may be calculated by the following equation:

Vz erythrocytes = Vz blood – Vz plasma

The values of Vz erythrocytes in the different situations of this study, calculated from the mean values, were 0.206 l/kg, 0.230 l/kg, and 0.153 l/kg for groups L, HA, and HC, respectively. One would expect that Vz erythrocytes should decrease with the exposure to H. This happens only after chronic exposure. It is possible that other factors like the reduction in the plasma volume which occurs shortly af-

ter exposure to the high altitude may complicate the situation.

Clearance decreases after exposure to H, though the difference was significant only in the group HC, with a decrease of 37% for this parameter.

Conclusion

The results of the present study confirm our hypothesis, that the exposure to high altitude, either acute or chronic, produces alterations in the pharmacokinetics of lithium and that these variations may be of clinical relevance.

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