# ALTERATIONS OF DRUG DISPOSITION IN HIGH ALTITUDE*

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## SUMMARY

Exposure of the human body to high altitude (H) results in significant physiologic changes and may precipitate mountain sickness, ranging from mild symptoms above 2500 m to severe symptoms above 4000 m, and coma a t even higher altitude. In a previous study in our lab s we found et vivo an increase in meperidine (M) upteke with increase i n number of erythrocytes (RBC). One of the major physiologic changes at H is a increase in hematocrit and RBC. The study was carried out in three groups of healthy volunteers (18-2' y): at sea level (L), at 4360 m the day after arrival at H (HA), and at 4360 m in subjects residing > 10 mo at H (HC), 0.75 mg/kg of M was administered I.M. between 8-9 a.m. Blood was collected for 12 h. M was measured in whole blood (WB), plasma (P) and plasma water (PW). The pharmacokinetic parameters derived from curve-fitting were analyzed by ANOVA. Significant changes were found in P and (WB) for $\lambda_z$ ↓ L vs HA (L vs HA), L vs HC; CL/F ↓ L vs HA (L vs HA), L vs HC, and MRT ↑ L vs HA (L vs HA), L vs HC. T he hematocrit significantly increased L vs HA, L vs HC end HA vs HC from 43.3 to 46.4 to 53.4%. The RBC binding significantly increase from 42.3% at L to 43.8% at HA to 50.9% at GC. The extent of protein binding shows a trend to decrease with H, however, it is not significant. Free M concentration in PW measured after 1, 2, and 4 h was significently increased after 2 and 4 h.

## INTRODUCTION

The origin of the study reportet here, was an observation of lack of clinical response to meperidine in a South American Indian at high altitude of approximately 4000 m, at Cusco, Peru. The first thought of either a pharmacogenetic different handling of meperidine as has been reported to exist (1) or due to different food did no seem to be the cause since an age and weight matched South American Indian treated at sea level had full clinical response to meperidine. Our suspicion was that changes in physiology due to high altitude may be the cause.

Following is a brief review of the cascade of pathophysiologic events on ascending to high altitude (2-6). Oxygen pressure in the body falls in dependence of barometric pressure which is 760 torr at sea level to 523 torr at 3600 m, causing hypoxia. Correspondingly the $PO_2$ of dry air at sea level which is 159 torr decrease to about 102 torr at 3600 m. At high altitude blood flow to the brain increases resulting in fluid accumulation, the pressure of which can lead to severe headache. As a result of hypoxia, fluid accumulates in the membranes of the alveoli and eventually exudating into the alveoli previnting oxygen uptake into the blood. Decrease carbon dioxide levels from increase ventilation shifts the blood pH to higher values, forcing the kidncys to remove bicarbonate to stabilize blood pH. Failure of the sodium pump at high altitude results in loss of excessive amounts of potassium, distrubing the electrolyte balance and causing edema. The hormone erythropoietin stimulates the production of red blood cells

(RBC). However, increased RBC mass may impair blood flow to tissues and cause clotting. There is an increase in plasma protein concentration during the first 48 h of reaching high altitude (7). Also during the first week at high altitude the plasma volumen is usually decreased wbich may be explained by loss of total body water, dehydration or distribution of plasma water to extracellular space (8). Acute Mountain Sickness is defined as a condition when at least three of the following symptoms are present: loss of appetite, vomiting, shortness of breath, dizziness or light headedness, unusual fatigue, sleep disturbance, and headache (6).

Recently, we studied the uptake and binding of meperidine to human blood, *ex vivo* (10). Increasing concentrations of meperidine with same RBC count did not influence % of erythrocyte uptake/binding. However, increase in RBC count from 4.1 to 9.9 million/mm3 resulted in significant increase in erythrocyte uptake of meperidine from 77.1 to 94.7%. At the same time there was an increase in protein binding. The base meperidine, is also bound to $\alpha_1$-acid glycoprotein (11). It is conceivable that the stress of exposure to high altitude may result in increase $\alpha_1$-acid glycoprotein levels and hence increase binding.

The hypothesis of the study presented here is that exposure to high altitude may alter drug disposition and consequently the pharmacodynamics. Hence, the purpose was to use meperidine as a model substance to study the effect of both long term and short term exposure to high altitude. Meperidine is both protein bound and RBC bound and is therefore relevant to be used in this study.

The pharmacokinetic parameters for meperidine are reported in the literature (9). These values represent the normal values in absence of exposure to high altitude. Meperidine has an elimination half-life ($t_{1/2}$) of 3.6 h with a range of 3.1 to 4.1 h. The volume of distribution (Vz) is 4.1 L/Kg, extent of protein binding (EPB) is 64%, fraction eliminated in urine ($F_u$) is 0.2 (ranging from 0.01 to 0.7). The time to reach maximum concentration ($t_{max}$) is 1.3 h for PO and 0.5 h for MI administration with an absolute bioavailability of 0.52 for PO and 0.80 for IM administration.

## MATERIALS AND METHODS

### Subjects and Study Design

The study was carried out in three groups of 12 healthy volunteers each and was approved by the IRB of the University of Cincinnati and the University of Santiago, Chile. The volunteers were recruited from the Chilean Army. All the volunteers were males, age 18-20 y. The beight and body weight (mean ± SD) were 170.6 ± 8.1 cm and 63.4 ± 9.0 kg for sea level and high altitude (acute), and 168.8 ± 6.4 cm and 66.2 ± 7.1 kg for high altitude (chronic), respectively. The inclusion parameters were minimum of 10 mo residence at either sea level or high altitude, complete physical exam, urinalysis and blood chemistry. Exclusion parameters were any deviations outside the established normal range for urine and blood chemistry, any previous cardiovascular, pulmonary or kidney disease, previous severe mountain sickness and use of any drug in the 30 d preceding the study. The 3 groups were: L, at sea level (military base Arica - the northernmost city of Chile); HA, acute high altitude, these were the same subjects participating in the sea level study. The ascendend 1 wk after the sea level study to high altitude

(military base Pacollo - in the Andes of North Chile, at 4360 m). They arrived in the afternoon at high altitude and the study was performed the following morning. The third group was HC, chronic high altitude, comprising of subjects residing at least 10 mo at the study site. Acclimatization to various pathophysiologic responses to high altitude exposure occurs over a period of a few days to a few weeks or even months (5). In this study, the 10 mo period is assumed to be sufficient for achieving acclimatization to high altitude.

For all groups, the treatment was same: after an overnight fast with water allowed *ad libitum*, the dose of 0,75 mg/kg meperidine was administered, between 8-9 am, I.M. into the deltoid muscle, 1 h after the subjects were given a standard breakfast. Blood samples were collected by individual needle sticks at 0, 0.083, 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 12 h. The RBC and hematocrit data was obtained from the 0 h blood samples. Blood pressure and Incentive Spirometry (Incentive Spirometer, Hudson Co., Temecula, CA) were measured at times 0 and 2 h after drug administration. Clinical assessment of loss of appetite, vomiting, shortness of breath, dizziness or light headedness, unusual fatigue, sleep disturbance or headaeh was made in the high altitude (acute) group for the periods upto 12 h and 12-24 h after arrival at high altitude, and for the high altitude (chronic) group at time 0 h. Aliquot of each blood sample was lyzed for analysis of drug in whole blood. Oxalated blood was centrifuged and plasma separated. Half of the plasma samples at 1,2 and 4 h was filtered (Micropartition System MPS-1, Amicon Division, Danvers, MA) to obtain plasma water. The samples collected at sea level were immediately frozen after separation. At high altitude, samples were frozen and kept frozen during stay and then packed in ice for transportation to sea level, then repacked in dry ice and flown out for analysis. All the samples were received in frozen condition by the laboratory.

**Analytical Procedure**

All the samples were analyzed for meperidine and normeperidine, by a gas chromatographic method using an HP 5890A Series II gas chromatographic system with NP-Detector. The column used was a 30 m, 0.32 mm. I.D., DB-5, fused silica capillary column with a film tickness of 0.25 mm. The injector was maintanined at 270°C and the detector at 280°C. Helium, carrier gas, was maintainded at constant flow mode pressure at 143 kPa. The temperature program was maintaining 120°C for 2 min, 4° C/min to 180°C held for 4 min, 10° C/min to 280°C held for 3 min.

The frozen plasma samples were thawed and subjected to a liquid-liquid extraction after which they were injected into the gas chromatograph.

**Pharmacokinetic Analysis**

The concentration-time data for meperidine were analyzed by compartment model independent analysis using AUC-RPP computer program (12) and by curve-fitting using RESID computer program (13). Both programs generate the pertinent pharmacokinetic parameters. Overall, the data from the two analyses were similar. The data reported here are those generated by the curve-fitting program. The data were best fitted by either the one -or two- compartment open model. Binding to erythrocytes was calculated according to the flllowing equation (14):

$$C_E = \frac{[C_B - C_P \cdot (1 - H)] \cdot 100}{C_B} \qquad (1)$$

where $C_E$ is binding to erythrocytes $C_B$ and $C_P$ are concentrations in blood and plasma, and H is the hematocrit.

Extent of protein binding (EPB) was determined by the following equation:

$$EPB = \frac{C_P - C_W}{C_B} \cdot 100 \qquad (2)$$

where $C_P$, $C_w$ and $C_B$ are the concentrations in plasma, plasma water and blood, respectively.

**Statistical Analysis**

Each of the pharmacokinetic parameter listed in Table I was subjected to a one-way ANOVA. Significant difference was concluded at $p < 0.05$. Similarly, all the other data on free meperine concentration, erithrocyte uptake, protein binding, ratio of meperidine to normeperidine, hematocrit and spirometry, were analyzed by one-way ANOVA. Statistical significance was conclude at $p < 0.05$.

## RESULTS

**Whole Blood and Plasma**

The concentration-time profiles for meperidine and normeperidine are shown in Fig. 1 and 2. Individual concentration-time profiles have been shown to emphasize the variability in the disposition of meperidine. In most of the cases, the data were best fit by a one-compartment model. However, in some subjects the two-compartment model better fitted the data. The pharmacokinetic parameters of the terminal disposition rate constant, $\lambda_z$; the elimination half-life, $t_{1/2}$; the rate constant for absorption, $K_a$; the clearance, uncorrected for bioavailability, CL/F; the apparent volume of distribution, uncorrected for bioavailability, Vz/F; and the Mean Residence Time, MERT; for whole blood (WB) and plasma (P) are listed in Table I, Regarding whole blood, significant differences were found only between sea level and high altitude (acute) for $\lambda_z$, a decrease in elimination rate of about 17%; for CL/F, a decrease of about 20% and for MRT, an increase of 23%. In plasma, significant differences were found for the comparisons between the groups sea level vs high altitude (acute) and sea level vs high altitude (chronic), $\lambda_z$ decreased by 22% and 17% respectively, CL/F decrease by 20% and 21% respectively, MRT was prolonged 29% and 24% respectively.

**Plasma water**

The meperidine in plasma water represents the free drug concentration. The comparisons for the 3 determination points are listed in Table II. Significant differences were observed after 2 h for sea level vs hihg altitude (acute), sea level vs high altitude (chronic) and high altitude (acute) vs high altitude (chronic) and after 4 h for sea level vs high altitude (acute) and sea level vs high altitude (chronic).

### Meperidine Binding

The binding data for meperidine are summarized in Table III. The RBC uptake significantly increased by 6% from sea level to high altitude (acute) and by 23% from sea level to high altitude (chronic). The EPB however, did not result in any statistically significant differences.

### Meperidine/Normeperidine Ratios

The ratio of meperidine: normeperidine calculated from AUC(0-12) are listed in Table IV. A significant increase in meperidine: normeperidine was found from sea level to high altitude (acute) and sea level to high altitude (chronic) in whole blood and from sea level to high altitude (chronic) in plasma.

### Hematocrit and RBC Count

The hematocrit and the RBC count are listed in Table V. The hematocrit increase significantly going from sea level to high altitude (acute) to high altitude (chronic).

### Mountain Sickness

Acute mountain sickness is defined as the presence of 3 or more of the symptoms listed in the introduction (6). In the high altitude (acute) group, oncly 1 subject had two out of seven symptoms within the first 12 hours. For the period from 12-24 h, 2 subjects had one symptom each, 5 subjects had two symptoms each, 2 subjects had three symptoms each, and 2 subjects had four or mor symptoms each. In other words, 4 our of 11 subjects were classified as having acute mountain sickness.

The purpose of measurements of blood pressure and sprirometry was clinical monitoring of the subjects, during the study. Significant reduction in spirometry was found for sea level vs high altitude (acute) and sea level vs high altitude (chronic), for both the time points. No changes in blood pressure were seen with a change in altitude.

## DISCUSSION

The increase in elimination half-life and mean residence time paired with a decrease in clearance indicates a slower elimination of meperidine upon exposure to high altitude. If one looks at the ratios of AU(0-12) of meperidine: normeperidine which increase with high altitude, it seems that metabolism is reduced. Whether this is truly altered rate or extent of metabolism or an artefact is not known at this point in time. It could well be that the diminished metabolism simply is due to higher uptake of the parent drug by erythrocytes resulting in lower free drug concentration in blood. However, the data for the free drug concentration in plasma water indicates otherwise. The mechanism responsible for the apparent changes in the disposition is not known, at this time and may also be applicable for the prolongation in elimination half-life. A complicating factor may be the protein binding. In our previously reported *ex vivo* study (10), we observed and increase in protein binding with increase hematocrit or RBC count. However, this too could be an arefact because in doubling the number of erythorcytes in the same volume, less plasma protein was present in the spiked plasma. *In vivo*, there was no significant change in plasma protein binding. Since meperidine is also bound to $\alpha_1$-acid glycoprotein, which upon exposure to stress or pathologic condition may be

greatly increase, there could be a difference *in vivo* between the binding to plasma albumin and to $\alpha_1$-acid glycoprotein, whereas the amount of $\alpha_1$-acid glycoprotein in the ex vivo study was unchanged. Since $\alpha_1$ glycoprotein is not stable and due to absence of lab facility to analyze the samples immediately after collection, it is not possible at this time to substantiate any effect which may be due to $\alpha_1$-acid glycoprotein levels.

Interesting was the observation that significant kinetic differences were observed within less than 24 h after acute arrival at high altitude. It is known that most of the acute mountain sickness symptoms occur within 24 h. It is amazing that during that periodo of time, both hermatocrit and RBC count significantly increased. In a recent study on acute mountain sickness, 25% of the subjects acutely exposed to altitude of 1900 to 2900 m suffered from acute mountain sickness (6). In our study, 36% of the subjects experienced acute mountain sickness at 4360 m and 64% experienced one or two symptoms. An analysis of the data for the high altitude (acute) group showed that there were no statistically significant differences, in the pharmacokinetic parameters, between the subjects suffering from acute mountain sickness and those who were not.

The spirometry indicated a significant reduction in breathing capacity of the subjects after acute exposure to high altitude, which seems to remain impaired even after 10 months of residence at high altitude.

This study revealed significant changes in the disposition of meperidine in healthy male volunteers, 18-20 y of age, exposed to high altitude in comparison to those residing at sea level. These changes are present in less than 24 h after arrival at high altitude, and at least in part seemed to sustain for at least 10 months. These results can have serious implications in the dosage regimen design and continuation in patients on medication who travel to tourist resorts at high altitudes, even if for a short visit.

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**Table I: Pharmacokinetic parameters (mean ± SD) of meperidine in whole blood and plasma ta sea level (L), acute (HA) and chronic (HC) high altitude**

| Parameter | Whole Blood | | | Plasma | | |
|---|---|---|---|---|---|---|
| | L | HA | HC | L | HA | HC |
| $\lambda_z$ (1/h) | 0.17 ± 0.021 | 0.14 ± 0.03 | 0.15 ± 0.04 | 0.18 ± 0.03[1,2] | 0.14 ± 0.03 | 0.15 ± 0.03 |
| $\tau_{1/2}$ (h) | 4.18 ± 0.591 | 5.11 ± 0.89 | 4.99 ± 1.49 | 3.95 ± 0.62[1,2] | 5.09 ± 1.08 | 4.80 ± 0.93 |
| $K_a$ (1/h) | 6.02 ± 5.66 | 4.25 ± 5.27 | 3.52 ± 2.92 | 5.16 ± 4.28 | 3.12 ± 1.33 | 2.95 ± 2.25 |
| CL/F (mL/min/kg) | 16.69 ± 5.04[1,2] | 13.31 ± 1.62 | 12.55 ± 2.36 | 16.19 ± 3.74[1,2] | 13.05 ± 1.74 | 12.10 ± 2.28 |
| $V_z$/F (L/kg) | 5.98 ± 1.82 | 5.85 ± 0.99 | 5.21 ± 0.94 | 5.41 ± 1.02 | 5.71 ± 1.28 | 4.93 ± 1.02 |
| MRT (h) | 6.37 ± 0.86 | 7.81 ± 1.32 | 7.64 ± 2.23 | 6.03 ± 0.92[1,2] | 7.75 ± 1.64 | 7.48 ± 1.29 |

[1] denotes statistically significant difference between L and HA at 5% level
[2] denotes statistically significant difference between L and HC at 5% level
[3] denotes statistically significant difference between HA and HC at 5% level

**Table II**

**Free meperidine concedntration (mean ± SD), in ng/mL, in plasma water, at sea level (L), acute (HA) and chronic (HC) high altitude**

| Time after dosing (h) | L | HA | HC |
|---|---|---|---|
| 1 | 36.65 ± 7.97 | 39.91 ± 8.57 | 42.75 ± 10.89 |
| 2 | 23.60 ± 6.85[1,2] | 34.99 ± 6.71[3] | 44.55 ± 10.27 |
| 4 | 19.44 ± 6.67[1,2] | 29.17 ± 6.35 | 34.20 ± 6.27 |

1 denotes statistically significant difference between L. and HA at 5% level

2 denotes statistically significant difference between L. and HC at 5% level

3 denotes statiscally significant difference between HA and HC at 5% level

**Table III**

**Eryhrocyte uptake and plasma protein binding (mean ± SD), in %, at sea level (L), acute (HA and chronic (HC) high altitude**

| Uptake/Binding | L | HA | HC |
|---|---|---|---|
| RBC uptake | 40.73 ± 10.57[1,2] | 43.85 ± 10.05 | 51.47 ± 12.83 |
| Protein Binding | 75.30 ± 19.26 | 68.40 ± 16.06 | 65.94 ± 23.48 |

1 denotes statistically significant difference between L and HA at 5% level
2 denotes statisticelly significant difference between L and HC at 5% level

**Table IV**

**Ratio (M/N) of AUC(0-12) (mean ± SD), from whole blood and plasma data, at sea level (L), acute (HA) and chronic (HC) high altitude**

| | L | HA | HC |
|---|---|---|---|
| Whole Blood | 3.15 ± 1.03[1,2] | 5.45 ± 1.98 | 4.84 ± 1.51 |
| Plasma | 4.15 ± 1.22[2] | 3.56 ± 1.08 | 6.02 ± 2.42 |

1 denotes statistically significant difference between L and HA at 5% level
2 denotes statistically significant difference between L and HC at 5% level

**TableV**

**Hematocrit and Red Blood Cell counts (mean ± SD), at sea level (L), acute (HA and chronic (HC) high altitude**

| Parameter | L | HA | HC |
|---|---|---|---|
| Hematocrit (%) | 43.33 ± 1.61[1,2] | 46.36 ± 2.01[3] | 53.42 ± 4.03 |
| RBC (mill/mm3) | 4.853 ± 0.223 | Not Available | 5.856 ± 0.385 |

1 denotes statistically significant difference between L and HA at 5% level
2 denotes statistically significant difference between L and HC at 5% level
3 denotes statistically significant difference between HA and HC at 5% level

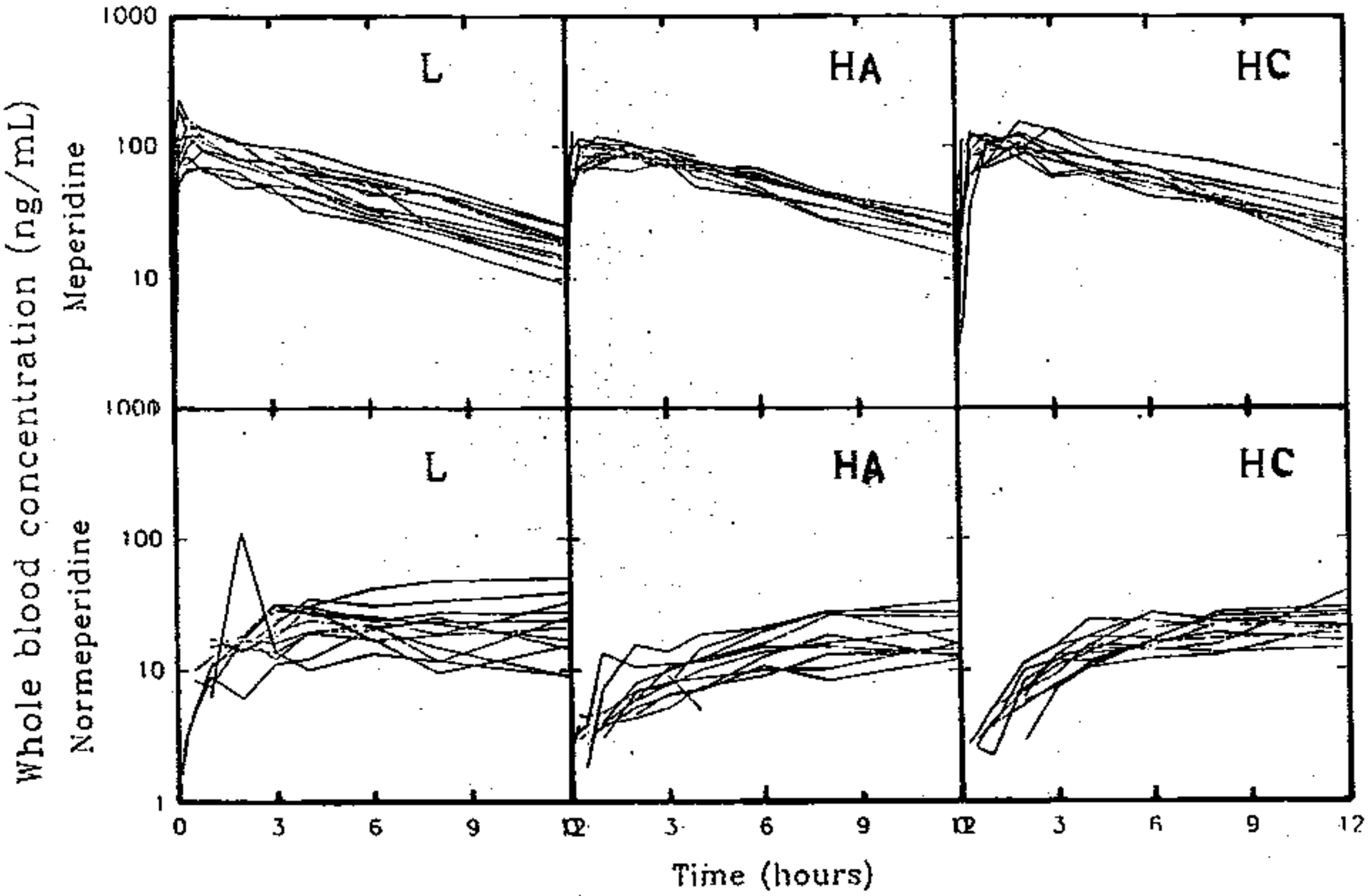


**FIG. 1.- WHOLE BLOOD CONCENTRATION-TIME PROFILES OF MERPERIDINE AND NORMEPERIDINE FOR ALL 3 GROUPS**

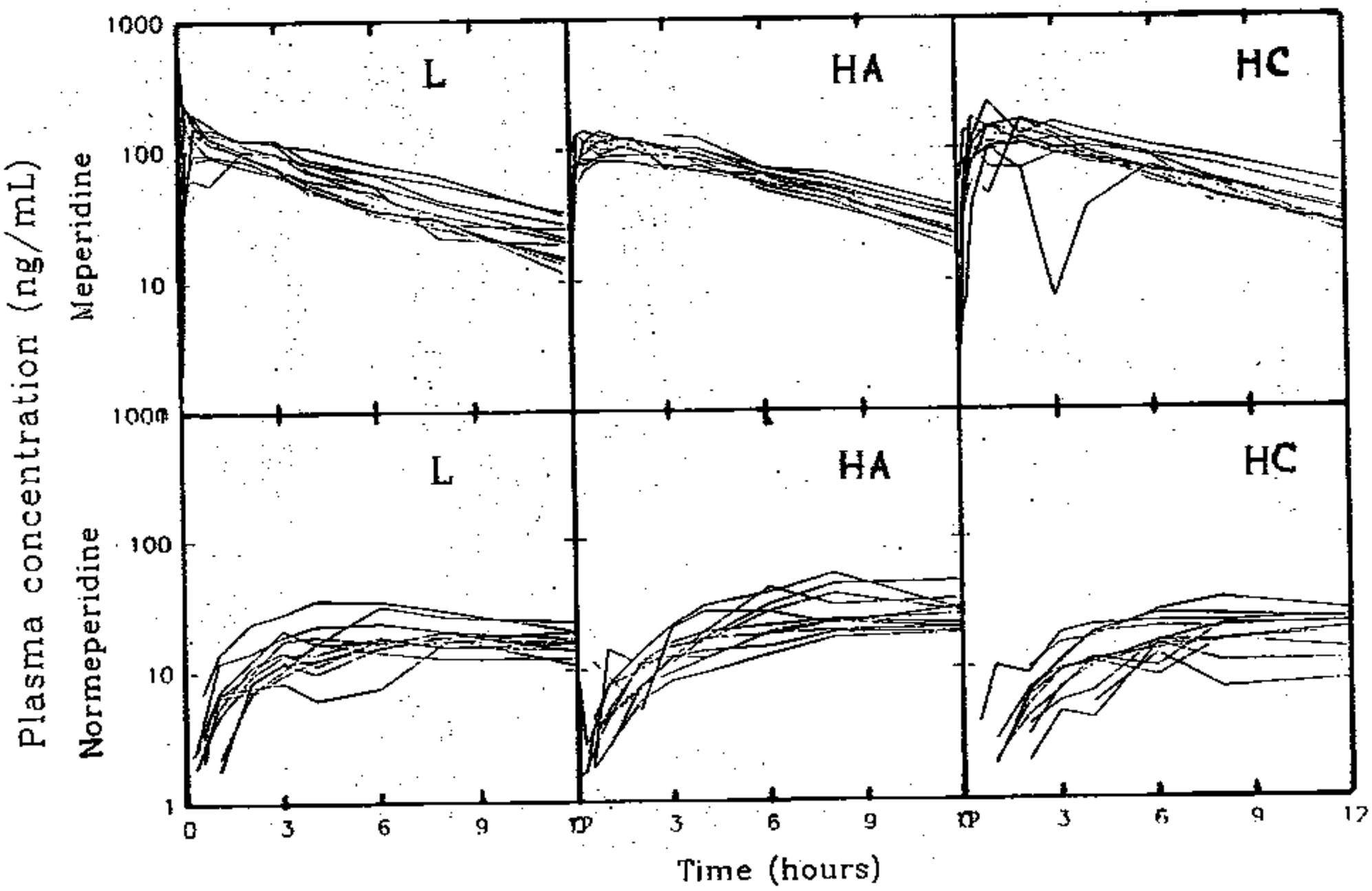


**FIG. 2.- PLASMA CONCENTRATION-TIME PROFILE OF MEPERIDINE AND NORMEPERIDINE FOR ALL 3 GROUPS**