IJPSR (2018), Volume 9, Issue 2 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 10 May, 2017; received in revised form, 18 July, 2017; accepted, 25 July, 2017; published 01 February, 2018

THE HYPOXIC VENTILLATORY RESPONSE AND HEPATIC CYP3A4 UPREGULATION IN HUMAN AT HIGH ALTITUDE

Abhilash Thomas [*1], Sanesh P. Jose [2], K. M. Poornajith [4], K. P. Arun [2], V. Sivakumar [3] and Malay K. Samanta [1]

Department of Pharmaceutical Biotechnology [1], Department of Pharmacy Practice [2], J.S.S. College of Pharmacy, Ooty, J.S.S. University, Mysore - 643001, Tamil Nadu, India.
Department of Pharmacy Practice [3], P.S.G. College of Pharmacy, Coimbatore- 641004, Tamil Nadu, India.
Department of Psychiatry [4], Government Head Quarters Hospital, Ooty - 643001, Tamil Nadu, India.

Keywords:

CYP3A4, Pharmacokinetics, Arterial-alveolar oxygen gradient, Arterial blood gas, Hypoxic Ventillatory response (HVR)

Correspondence to Author:
Dr. Abhilash Thomas

M. Pharm, PDCR, ACCR, PhD
Assistant Professor & Head
Department of Pharmacy Practice
OXBRIDGE College of Pharmacy,
Bangalore - 91Karnataka, India.

Email: abhi0882@gmail.com

ABSTRACT: The Hypoxic Ventillatory Response (HVR) at high altitude was hypothesized to cause pharmacokinetics changes, especially metabolism of drugs due to the up regulation of CYP3A4 isoenzyme. These pharmacokinetic alteration could affect pharmacotherapy, probably lead to either sub therapeutic or supra therapeutic effects. This hypothesis was studied with a pop-PK study conducted in healthy male volunteers inhabited at geographically high altitude area. Firstly, the HVR was assessed by changes in partial pressures of blood gases, oxygen concentration in arterial blood, oxygen gradient in arterial-alveolar gas exchange and oxygen concentration of arterial blood. Secondly, the Probe drug Alprazolam 1mg oral single dose was given to find out the dysregulation of CYP3A4 and blood samples were analyzed for pharmacokinetic changes The pharmacokinetic variables such as C_{max}, T_{max}, AUC, K^{el}, MRT, t½ *etc* were significantly altered in study subjects. The C_{max} and AUC values were significantly reduced in HVR group than non HVR group (21.26 ±1.40, $p<0.05$). The elimination and clearance were significantly increased in hypoxia group ($p<0.05$) whereas the V^d was not affected. MRT and t½ was reduced the faster metabolism and elimination of drug. In conclusion, the metabolism was increased due to CYP3A4 upregulation and elimination was increased in hypoxia study subjects. Hence, this pharmacokinetic dose response pattern has to be considered for optimizing the dose of drugs metabolized by CYP3A4.

INTRODUCTION: The atmospheric pressure progressively decreases with geographical elevation due to the reduction in the density of air and thus holds low molecular concentration of oxygen. Hence those who lives in high altitude area could be found with low partial pressure of oxygen (PaO_2) in lungs and hence in blood.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(2).687-92

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(2).687-92

At geographical elevation of 2400 meter, alveolar partial pressure of oxygen (PaO_2) drops by 25%. This may possibly drop the arterial oxygen saturation (SaO_2) below 90% depending up on the degree to which the individual expose to environment [1].

The resultant subnormal oxygen concentration (Hypoxia) due to low atmospheric pressure (Hypobaria) exhibits several physiologic alterations, [2, 3, 4] which affect the effectiveness of drug; the effect may potentiate, may induce toxicity and because of alteration in rate of drug metabolism the effectiveness of therapeutic dose also shall be affected [5].

When the metabolism of lipophilic drugs is affected by hypoxia [6]; since the rate of metabolism of lipophilic drugs is the important key factor to determine its efficacy and intensity on therapeutic outcome [7], the alterations in CYP P450 produce significant effects on the therapeutic outcome. As pharmacokinetics have a close association with the therapeutic effects and adverse reactions of the drugs, the changes in the elimination rate constant (K^{el}), maximum plasma concentration (C_{max}), time taken to achieve C_{max} (T_{max}), plasma half-life (t½), clearance (Cl) and area under the curve (AUC) were thought to have a significant effect on the therapeutic and side effects of the drugs [8]. Thus, it is necessary to adjust the dose of commonly used drugs.

Alprazolam is a lipophilic drug metabolized 90% by CYP3A4 was used as study drug. Single oral doses of 1 mg Alprazolam have been well tolerated in healthy individuals [5].

It has 90% bioavailability, 90% protein-bound and C_{max} reaches in 1-2 h. The t½ of Alprazolam has been found to be 12-15 h in healthy adults [9]. Alprazolam undergoes CYP3A4 mediated oxidative metabolism in liver, producing two predominant metabolites; α-hydroxy alprazolam and 4-hydroxy alprazolam [10]. Hence, the objective of this study is to analyze the impacts of hypobaric hypoxia on the metabolizing capacity of CYP3A4 by using substrate drug alprazolam in healthy individual at an altitude of 2500m.

MATERIALS AND METHODS:

Study design and protocol: This prospective interventional population pharmacokinetic (pop-PK) study was conducted in healthy male volunteers at a study location geographically 2500m elevated in Tamil Nadu, India. The study period was in winter season (December & January) during which average atmospheric pressure of 588 mmHg (Hypobaria), average temperature of 9.7 ^{0}C (Hypothermia) were reported. In this condition, hypothetically only 75% of oxygen was available for breathing. This environmental condition called 'Hypobaric Hypoxia' was considered as hostile causative factor and its impact on CYP3A4 activity and pharmacokinetics was studied by using probe drug Alprazolam. The study protocol was approved by Institutional Review Board (Protocol id: JSSCP/DPP/IRB/008B/2013-14, Version. 2), Tamil Nadu, India and Clinical Trial Registry of India (Reg. no: CTRI/2016/11/007464), New Delhi, India.

Healthy male volunteers of age 20-60 years having normal body mass index (BMI) of 18.5-22.9 kg/m^2 and waist-hip ratio (WHR) of 0.7-0.8 were enrolled in to the study. Subjects with illness like metabolic disorders, diabetes, hypertension, cardiovascular disorders, gout, rheumatoid arthritis and known history of hepatic or renal failure were excluded. The past histories of any infection, inflammatory disorders, auditory complaints and dehydration like diarrhea for last 60 days were also excluded. Subjects taken any over the counter (OTC) drugs within past one week and did not willing to give blood samples were excluded from the study. The selected subjects were then examined by a physician and confirmed that they were healthy to participate in the study according to the criteria followed. Informed consent was obtained from the all study subjects.

After enrollment, the subjects were hosted in the clinical facility. They were instructed to cooperate with certain study conditions to be followed which includes, not consume coffee, tea, chocolate, soft drinks, fruit juices (grape and avocado) and junk foods from 48.00 h before starting of study.

In Step no: 1, the HVR was assessed by performing arterial blood gas analysis (ABG). The blood samples were collected by radial artery puncture procedure from left forearm and analyzed in the blood gas analyzer (Model: ABL800 Flex). The values of SaO_2, PaO_2, $PaCO_2$ (partial pressure of carbon dioxide), CaO_2 (oxygen content in arterial blood) and alveolar-arterial oxygen gadient (A-a Gradient) were taken. According to the changes in PaO_2, $PaCO_2$ and SaO_2, the subjects were categorized as HVR group (n-09) and non HVR group (n-15) as shown in **Table 1**.

In Step no: 2, the subjects were undergone pharmacokinetic study. The conventional tablet of 1 mg alprazolam was used as a study drug; which is metabolized 90% by CYP3A4 and 10% by CYP3A5 enzymes. Hence the pharmacokinetic data would be comparatively precise to interpret CYP3A4 activity.

After overnight fasting of nine hours, in the morning, 1 mg of Alprazolam generic conventional tablet as the single oral dose was given orally to the subjects, in sitting posture with 300 ml of drinking water of ambient temperature. The pre dose blood sample was taken prior to the administration of study drug and post dose samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours; for each timing 6 ml of blood was collected to obtain approximately 2 - 2.5 ml of plasma on centrifugation. The subjects who failed to follow-up the study conditions during the study period and who were not able to provide blood samples at all timing, were excluded. A total of 24 subjects had completed the study successfully in compliance with study conditions and preferred volume of blood samples at all time points.

The plasma was separated from whole blood samples by centrifugation at 5000rpm for 20 min and was stored at -70°C. The analysis was done by liquid chromatography mass spectrometry (LCMS-MS) and pharmacokinetic variables AUC, C_{max}, T_{max}, K^{el}, t½, V^{d}, Cl and mean residence time (MRT) were measured. The data interpretation was done by comparing the average scores and standard deviation (SD) of each parameters of pharmacokinetics between HVR and non HVR subjects. The statistical analysis was done by using 't'-test in SPSS 20 version and p-value <0.05 was considered as significant.

RESULTS: The subjects observed reduced values of PaO_2 and SaO_2 were put together and named 'HVR group' and subjects with normal values named 'non HVR' group. **Table 1** shows the oxygen transport in body represented by 1) PaO_2 (plasma saturation of oxygen) was reduced in HVR subjects (67.93±09.26 mmHg, p<0.05) as compared to non HVR subjects (87.57±2.10 mmHg) 2) SaO_2 (hemoglobin oxygen binding) was also reduced (85.44±4.88 %, p<0.05) in HVR subjects compared to non HVR subjects (97.19±1.16%). The $PaCO_2$, which is a parallel marker of HVR, was not significantly affected; seemed a compensatory mechanism to HVR might have happened. This was found by $PaCO_2$ (often used as a biomarker of compensatory mechanism) closer to lower cut-off level (37.77±4.52 mmHg) in HVR subjects. The PaO_2 and $PaCO_2$ levels were normal in non HVR subjects but the values were near to lower border (**Table 1**). This could be lead to better understanding that even though the subjects were inhabitants of same geographical region, exposed to same hostile hypobaria but some developed hypoxia due to failure in compensatory mechanisms or might due to other factors of individual physiological origin.

TABLE 1: HVR REPRESENTED BY THE PARTIAL PRESSURE OF BLOOD GASES IN NON-HYPOXIA AND HYPOXIA GROUPS. VALUES EXPRESSED AS AVERAGE (SD)

Parameters	Non-hypoxia group (n-15)	Hypoxia group (n-09)
PaO_2	87.57±2.10	67.93±09.26*
$PaCO_2$	41.45±5.17	37.77±4.52
SaO_2	97.19±1.16	85.44±4.88*

*Significance level p<0.05

The A-a gradient of oxygen was found to be lowered; expected due to failure in gas exchange between lung alveoli and the exposed hostile atmospheric air. This could be the causative factor behind the low CaO_2 (oxygen content in arteries). The age predicted values of A-a gradient was lowered in HVR subjects group because their average age was higher than non HVR subjects **(Table 2)**. Hypothetically, the inspired fraction of oxygen (FiO_2) in the current environment was considered as 0.21 (*i.e.* 21% or 100% of available oxygen) because there was still a contradiction in proving that the FiO_2 is always 0.21 in open environment [11]. Hypercapnia, the major symptom of compensatory mechanism against HVR was found in breathing pattern of all the participants (**Table 3**).

TABLE 2: HVR REPRESENTED BY THE A-a G IN NON-HYPOXIA AND HYPOXIA GROUPS. VALUES EXPRESSED AS AVERAGE (SD)

Study groups	Age predicted A-a G (mmHg)	Observed A-a G (mmHg)
Non hypoxia group(n-15)	10.09	9.12
Hypoxia group(n-9)	9.98	6.81*

*Significance level p<0.05

TABLE 3: HVR REPRESENTED BY THE BREATHING PATTERN

Pattern of breathing	Non-hypoxia group (n-15)	Hypoxia group (n-09)
Chest	06	09
Abdomen	07	04
% Abdominal Breathing	58.33	33.33

It shows abdominal breathing (diaphragmatic breathing) along with chest in both set of groups, but the numbers of subjects found changing chest breathing to abdominal breathing in non HVR were 58.33% HVR were 33.33 %. The CaO_2 values shows comparatively lower concentration of arterial volume of dissolved oxygen (14.51±1.12, $p<0.05$) in some HVR subjects compared to non HVR subjects group (19.67±2.09) as shown in **Table 4**.

TABLE 4: HVR REPRESENTED BY THE OXYGEN CONTENT OF ARTERIAL BLOOD (CaO_2) IN NON-HYPOXIA AND HYPOXIA GROUPS. THE VALUES ARE EXPRESSED AS AVERAGE (SD)

Study groups	Observed value
Non hypoxia group (n-15)	19.67±2.09
Hypoxia Group (n-9)	14.51±1.12*

*Significance level $p<0.05$

The descriptive analysis shows that pharmaco kinetic variables except V^d and T_{max} were significantly reduced in HVR subjects group compared to non HVR group **(Table 5)**. The absorption phase (C_{max} and T_{max}) of both groups showed significant lowering in concentration vs. time plot ($p<0.05$). The metabolism phase showed much remarkable sudden decline in Alprazolam concentration in HVR subjects (**Fig. 1**) after achieving C_{max}; supporting the hypothesis of CYP3A4 up regulation during hypoxemia (low oxygen content in blood) induced by hypobaric hypoxia at high geographical elevation.

TABLE 5: THE IMPACTS OF HVR ON THE PHARMA COKINETICS OF ALPRAZOLAM REPRESENTED IN NON HYPOXIA AND HYPOXIA GROUPS. VALUES ARE EXPRESSED AS AVERAGE (SD) AND STATISTICAL SIGNIFICANCE BY'T'-TEST

PK Parameters	Study groups	
	Non hypoxia group (n-15)	Hypoxia group (n-9)
C_{max} (ng/ml) *	21.26 ±1.40	20.04±1.27
T_{max} (h)	1.97±0.12	1.94±0.17
AUC 0-t (ng/ ml/h) *	186.40±27.19	143.91±17.34
AUC 0-inf. (ng/ml/h) *	255.47±47.62	181.87±27.67
t½ (h) *	13.09±1.41	9.99±1.62
Clearance (mg/ng/ml)/h *	0.00405±0.01	0.00563±0.01
K^{el} (1/h) *	0.0575±0.01	0.06977±.02
V^d (mg/ng/ml)	0.07239±0.02	0.08207±0.02
MRT (h) *	17.80±2.95	14.14±1.94

*$p<0.05$

It has already been reported that the metabolism and elimination of lipophilic drugs were reported to be faster in human exposed to hypobaric hypoxia environments [12] but there the CYP3A4 up regulation and faster metabolism studies were not performed. Hence, the elimination rate was also faster in HVR group (0.06977±.0144 h/1, $p<0.05$) than non HVR groups (0.0575±0.012 h/1). The volume of distribution was increased with exposure to hypobaric hypoxia but statistically this changes were not significant ($p>0.05$).

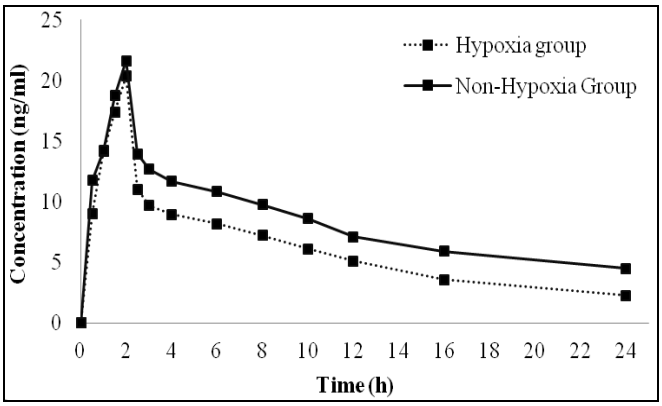

FIG. 1: THE HVR INDUCED UPREGULATION OF CYP3A4 REPRESENTED BY THE CONCENTRATION *VS* TIME OF ALPRAZOLAM IN NON-HYPOXIA AND HYPOXIA GROUPS

Due to the expected faster metabolism (**Fig. 1, Table 5**), the drug exposure in body was reduced and consequently t½ was also reduced in HVR group (13.09±1.41 h, $p<0.05$) than non-hypoxia group (14.14±1.94 h) subjects. The values of AUC (drug exposure in body) in HVR subjects group was significantly lowered ($p<0.001$) due to increased metabolism; could be vulnerable factor for treatment failure as when AUC reduces t ½ and MRT also will be reduced. Since the AUC 0-t (143.91±17.34 ng/ ml*h) and AUC 0-∞ (255.47± 47.62 ng/ ml*h) were reduced in HVR subjects ($p<0.001$) compared with non HVR subject group (186.40±27.19 ng/ ml*h, 181.87±27.67 ng/ ml*h respectively).

DISCUSSION: It has been known in several ways that exposure to high altitude hypobaric hypoxia has certain effects on hepatic CYP450 enzymes in the biotransformation of drugs. This hypobaric hypoxia was suggested to be the causative factor for increased clearance and elimination, reduced t½ and AUC in healthy human. As per the previous studies reported, healthy volunteers when exposed at high altitude for limited days, were not developed hypoxia (PaO_2 87mmHg) had observed

with decreased CYP3A4 activity but did not increase the clearance of drugs [13].

In another study healthy volunteers exposed to >14 days, observed that the drug clearance was increased by 36% suggesting that CYP1A2 activity was increased [14]. The fact of time elapsed exposure was considered in our study as the subjects were the permanent residents of study location; neither acclimated nor migrated. Hence the faster metabolism due to suspected up regulation of CYP3A4 might be the imbalance between adaptive responses and influence of environments on human body; theory of person to environment fit is being questioned.

The status of low abdominal breathing represents the failure of gas exchange called 'ventilation-perfusion defects' from environment to lungs comparatively due to lesser adaptation towards hypoxia environment which was supported by the status of decreased A-a Gradient. This could bring low oxygen concentration in arterial blood as it was shown that the CaO_2 was lowered in hypoxia subjects. The result of an *in vivo* model where animals were exposed to PaO_2 of 45 mmHg and $PaCO_2$ of 68 mmHg had found the clearance of diltiazem reduced by 20% [15, 16].

Another study where animals were exposed to low FiO_2, generating a stable PaO_2 of 50mmHg for 9.5 hours, had shown decreased clearance of theophylline ($p<0.05$); suggested that a combination of moderate hypoxemia and hypercapnia had reduced the clearance of theophylline [17]. Our study did not found hypercapnia though the $PaCO_2$ were near to upper cut-off level either overwhelmed slow chest breathing certainly might compensated hypercapnia.

Therefore, we conclude that long time exposure of hypoxia itself could produce effects on CYP3A4.The confounding factor in CYP450 probe drug studies other than disease conditions, those *in vivo* probes may be metabolized by more than one CYP450 isoenzymes [18] which could interfere with interpretation of result outcomes when we ought to demonstrate the activity of a single isoenzyme. Our study had used Alprazolam, for which hepatic CYP3A4 was the only isoenzyme involved for metabolism.

Hence, our study evidences proved that low oxygen concentration induced upregulation of hepatic CYP3A4 during hypoxia causes significant differences in liver as hepatocytes are sensitive to oxygen [19] to metabolize drugs especially oxidation (Phase I biotransformation) and any changes in oxygen gradient will affect CYP450 isoforms [5]. Since the hepatic acinar zone III (where CYP3A4 isoenzyme is located) receives least oxygenated blood, CYP3A4 responsible for phase I oxidation of drug metabolism and detoxification processes was thought to receive less oxygenated blood due to hypoxia.

Since the oxygen content in arterial blood determines the oxygen supply to hepatic acinar III the pharmacokinetic changes might be due to the lowered CaO_2. As zone III had comparatively least tolerance to hypoxia [20, 21] and it was assumed to be high levels of CYP3A4 upregulation in zone III [21, 23] and might had led to faster metabolism of Alprazolam and rapid elimination out of body.

According to the pharmacokinetic results we also speculate that CYP3A4 activity might kept normal during the initial time of exposure to hypoxia and later on increased (up regulation) on continuous exposure to due to the changes in protein expression.

Since the previous studies had observed the increased CYP3A4 in liver [23, 16, 8], the reduced oxygen concentration in blood had directly affected on serum mediators might activated signal transduction pathways and had activated transcription factors to cause upregulation of CYP3A4 [16, 8].

Since the present study was not conducted in simulated conditions as well as based on the previous evidences [23, 16, 8], the results of pharmacokinetic deviations in our study especially AUC, MRT and t½ would be probably due to the upregulation of hepatic CYP3A4 induced by hypobaric hypoxia. This decreased C_{max}, AUC, t ½, MRT and increased K^{el} and Cl in hypoxia affected subjects could probably influence the pharmacotherapy outcomes; expected to sub-therapeutic levels due to low plasma drug concentrations.

CONCLUSION: The results of our study concluded that HVR and hypoxia had influenced the pharmacokinetics of drug metabolized extremely by hepatic CYP3A4 isoenzyme in humans living in hypobaric high altitude area. Since AUC, t½ and MRT decides the extent of clinical outcome, the observed decline would affect the pharmacotherapy with drugs which are metabolized by CYP3A4. When these results extrapolated to patients undergoing treatment with multiple drugs, their dose has to be adjusted for better in fact optimum clinical outcome. Hence this pop-PK model will be useful for measuring pharmacokinetic activity of other substrate drugs of CYP3A4 including antibiotics, anti cancer drugs, anti epileptics etc. with the use of more sensitive biomarkers of hypoxia.

LIMITATIONS OF THE STUDY: The pharmaco-kinetic study could not be performed with complete sample at time points 48 h and 72 h due to the failure of maintain study conditions sampling procedure more than 24 h. The pharmacokinetic analysis with metabolites of Alprazolam could have been more authenticated to explain the activity of CYP3A4 with drug to metabolite ratio.

ACKNOWLEDGEMENT: The authors would like to thank all the participants involved in this study. They also wish to thank Microtherapeutic Research Lab, Chennai, India and Dr. Lalpathlab, New Delhi, India for sample analysis.

CONFLICTS OF INTEREST: The authors declare that they have no conflict of interest.

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How to cite this article:
Thomas A, Jose SP, Poornajith KM, Arun KP, Sivakumar V and Samanta MK: The hypoxic ventillatory response and hepatic CYP3A4 upregulation in human at high altitude. Int J Pharm Sci & Res 2018; 9(2): 687-92. doi: 10.13040/IJPSR.0975-8232.9(2).687-92.