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The Effect of Hyperbaric Hyperoxia on the Pharmacokinetics of Caffeine in Healthy Male Volunteers

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=국문초록=

건강 자원자에서 카페인 약동학에 미치는 고압산소치료의 영향

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연구배경: 고압산소치료는 호흡기와 순환기계를 포함하여 여러가지 생리학적 변화와 연관되어 있다. 이러한 변화가 caffeine의 약동학에 미치는 영향을 4명의 건강자원자에서 평가하였다.
방법: 커피를 이용하여 경구로 카페인을 투여하였으며 7일간의 휴약기간을 두고 정상기압때와 고압산소치료때 카페인의 약동학을 교차실험하였다. 고압산소치료표는 국내에서 가장 흔히 사용되는 것을 사용하였다. 혈중 카페인농도는 고성능액체크로마토그래피를 이용하여 측정하였으며 얻어진 약동학적 경수는 비모수적 방법으로 평가하였다.
결과: 평균 농도곡선하면적과 최고농도는 정상기압시 34.27±10.1 μg·hr/ml, 4.43±0.64 μg/ml였으며 고압산소치료시 45.65±9.89 μg·hr/ml, 5.72±0.61 μg/ml였다. 평균 청소율 및 소실반감기는 정상기압시 120.09 ± 37.56 ml/hr, 3.75 ± 0.84 h였으며 고압산소치료시 85.36 ± 17.83 ml/hr, 4.03 ± 1.13 h로 나타났다. 그러나, 통계적으로 유의한 차이는 없었다 ($p > 0.05$).
결론: 일반적인 고압산소치료는 카페인의 약동학에 유의한 영향을 미치지 않았으나 명확한 상호작용의 규명을 위하여 추가적인 연구가 필요할 것으로 사료된다.

주제어: Caffeine, Hyperbaric hyperoxia, Pharmacokinetics, Drug interaction.

INTRODUCTION

Hyperbaric oxygen (HBO) therapy is defined as follows. The patient breathes 100% oxygen intermittently while the pressure of the treatment chamber is increased to greater than one atmosphere absolute (ATA). Current information indicates that pressurization should be at least 1.4 ATA. This may occur in a single person chamber (monoplace) or multiplace chamber (may hold 2 or more people). Breathing 100% oxygen at 1 atm abs or exposing isolated parts of the body to 100% oxygen does not constitute HBO therapy.[1)]

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HBO therapy has been applied to the patients with life-threatening state such as air or gas embolism, carbon monoxide poisoning, gas gangrene, necrotizing soft tissue injury, decompression sickness, thermal burns and compromised skin grafts.[2)]

HBO therapy is associated with physiological changes involving the respiratory and cardiovascular system. Bradycardia was observed in hyperbaric chamber without immersion.[3,4)] If global hemodynamic parameters remain unchanged, as sometimes observed in hyperbaric chambers, cardiac output distribution is altered under hyperbaric or hyperoxic condition.[5,6)]

The myocardial blood flow is increased, possibly as a result of contractility enhancement under hyperbaric condition. Renal blood flow may be reduced. Similarly, splanchnic blood flow and hepatic perfusion may be altered. Such hemodynamic changes may influence the disposition of drugs. A change of renal and hepatic blood flow may influence the elimination of drugs whose clearance is dependent on perfusion.[7)] In addition, drug metabolizing enzyme activity can be influenced by increase in O_2 partial pressure.

Even in normobaric conditions, many physiological changes involving the respiratory and cardiovascular system are occurred in diving or facial immersion. Breath holding and/or facial immersion alone causes bradycardia, an increase in mean arterial pressure, and a decrease of forearm blood flow.[8)] This phenomenon triggered by breath-hold diving is referred to as the "diving reflex" and is more prominent in diving mammalians than human beings. Furthermore, immersion and loss of gravity influence the hemodynamics. Blood volume is displaced from the lower limbs and central blood volume is increased when the human immerges.[9)] Stretching of the atrial wall causes an increase of atrial natriuretic factor release and a decrease of antidiuretic hormone secretion by reflex mechanisms. Increased urinary output, which is referred to as diving diuresis can cause dehydration during immerged state such as diving or swimming. Stretching of the right heart wall and the pulmonary trunk may enhance vagal tone to the heart and cause bradycardia.

Only a few studies on the influence of hyperbaric hyperoxia on the disposition of drugs have been conducted, especially in a Korean population. Several in vitro study demonstrated that demethylation of aminopyrine was reduced under hyperoxic condition in microsomal preparation from rat liver.[10)] Kramer et al[11,12,13)] showed that pharmacokinetics of theophylline, pentobarbital or mepenidine were not significantly changed at 2.8 ATA breathing 100% O_2 or 6 ATA breathing air in dogs. But, the clearance of salicylic acid was significantly increased at 2.8 ATA and 100% O_2 in dogs.[14)] It was demonstrated that pharmacokinetics of gentamycin which is eliminated by kidney was not significantly changed under hyperbaric hyperoxic condition in healthy volunteers.[15)] Because of the limited exposure times, in vivo human studies on the pharmacokinetics of drugs under hyperbaric conditions have many ethical and economical problems.

Caffeine is xanthine compound and is widely consumed throughout population via various

forms of beverages or foods. Pharmacologic actions of caffeine include increased cardiac output, diuresis, CNS stimulation and vasoconstriction in peripheral tissue.

HBO therapy should be regarded as a drug, which can cause drug interaction and is associated with physiological changes involving the respiratory and cardiovascular system.

The effect of hyperbaric hyperoxia on the pharmacokinetics of caffeine was investigated in 4 healthy male volunteers.

MATERIALS AND METHOS

Study designs and subjects

This study was open-label, two-period crossover study separated by one-week washout period. The protocol was reviewed and approved by Institutional Review Board of Soonchunhyang University, Cheonan Hospital. All subjects provided informed, written consent before participating in this study.

Pretrial screening was performed within two weeks from the first study period. Exclusion criteria included various listed conditions, such as renal, cardiac, respiratory, hepatic, metabolic, neurologic and psychiatric disorder. The subjects were not allowed to take any medications or to have food and beverage known to contain xanthine or alcohol from one week before the study to end of study periods. Four healthy male subjects (age, 27.5 ± 3 years; weight, 69.6 ± 7.6 kg; height, 174 ± 7.0 cm) were enrolled in the present study. The study phases were separated by one-week washout period, and were constitute of normobaric period and hyperbaric hyperoxic (HBO) therapy period.

Caffeine administration and sample collection

We prepared a filtered coffee over 3 Liters in the same method on each study period. An aliquot of the beverage was saved to determine the precise amount of caffeine ingested. 500 ml of filtered coffee were ingested at one time. Since, 600 ml of soluble coffee were ingested at one time in other caffeine pharmacokinetic study[19] which is performed in Germany, we decided 500 ml would be safe and appropriate for administering caffeine.

Blood samples(5 ml) were serially taken for 24 h (0.00, 0.16, 0.33, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 7.0, 10, 12, 24 h) following coffee intake, were centrifuged and the plasma was frozen at -60℃ until analysis.

Diving profile

After normobaric period, the volunteers entered a hyperbaric chamber 2.5 h after coffee

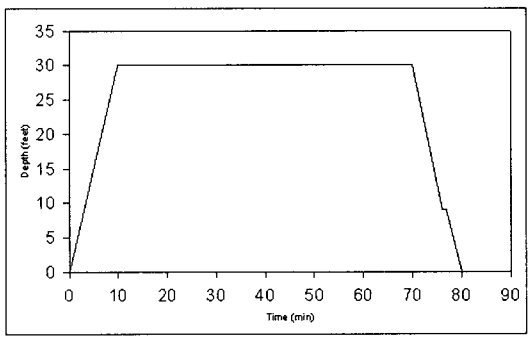

Fig. 1. Diving profile

ingestion for a total period of 80 min. The chamber was pressurized to 30 fsw(feet sea water) for 10 min and maintained for 60 min and then surfaced during 10 min. Safety stop was carried out for 1 min in the middle of surfacing. (Fig. 1)

Analytical methods

Caffeine analysis was performed by modified method of Park et al[16] using high performance liquid chromatography(HPLC). All chemicals were of analytical grade. Plasma samples were thawed at room temperature and were acidifies with same volume of 1 M trichloracetic acid for protein precipitation. After 2 min mixing and 10 min centrifugation, 50 $\mu\ell$ of supernatant was directly injected for chromatography. To measure the caffeine concentration in the coffee beverage, an aliquot was diluted in water(V:V = 1:100) and directly further processed. Caffeine was measured by reverse-phase HPLC(Gilson, Villiers Le Bel, France) system using C18 column(5μm, 3.9 × 200 mm, Waters Corporation, Milford, MA, USA) at 35℃. Mobile phase was methanol/water (V:V = 20/80, pH 7.5) and flow rate was 0.5 ml/min. Caffeine was detected by an ultraviolet wave-length detector that was set at 270 nm.

Data analysis

Pharmacokinetic parameters were calculated by non-compartmental method. Area under the plasma concentration-time curve(AUC) was determined by trapezoidal rule. The maximum caffeine concentration(C_{max}) and time to maximum caffeine concentration(T_{max}) were determined by the inspection of the individual drug plasma concentration-time profile. The elimination rate constant was obtained from the least-square fitted terminal log-linear portion of the plasma caffeine concentration-time profile. The elimination half-life($T_{1/2}$) was calculated as 0.693/elinmination rate constant. Bioavailability was assumed to be 100% based on the reports that oral bioavailability of caffeine was 90 - 100 %.[17,18] Pharmacokinetic parameters were analyzed by the non-parametric Wilcoxon signed-rank test. A p-value of less than 0.05 was considered statistically significant. All the data were analyzed using SPSS for Windows (version 12.0K; SPSS Inc, Chicago, IL, USA). Data were reported as mean ± SD.

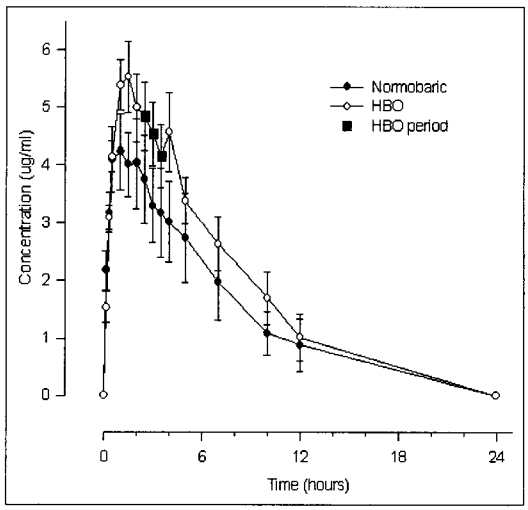

Fig. 2 Mean plasma caffeine concentration-time curve after oral administration of coffee in normobaric O2 condition and hyperbaric hyperoxic condition (Each bar represents standard deviation at each point)

Table 1. Pharmacokinetic comparison of caffeine in normobaric and hyperbaric hyperoxic condition.

Condition	Normobaric O_2	HBO therapy	p-value
Pharmacokinetic parameters	Mean ± SD	Mean ± SD	
AUC_t ($\mu g \cdot hr/ml$)	34.27 ± 10.1	45.65 ± 9.89	0.068
C_{max} ($\mu g/ml$)	4.43 ± 0.64	5.72 ± 0.61	0.068
T_{max} (hr)	1.27 ± 0.32	1.62 ± 0.35	0.414
Cl (ml/hr)	120.09 ± 37.56	85.36 ± 17.83	0.068
Vd (ml)	495.77 ± 45.00	422.94 ± 16.57	0.144
$T_{1/2}$ (hr)	3.75 ± 0.84	4.03 ± 1.13	0.715

AUC_t: Total area under the plasma caffeine concentration curve from time zero to time of the last quantifiable concentration; C_{max}: Maximal plasma caffeine concentraion; T_{max}: Time to maximal plasma caffeine concentration; Cl: Oral clearance; Vd: Volume of distribution; $T_{1/2}$: Elimination half life

RESULTS

Caffeine analysis was performed with well-validated method. With the HPLC method, no interferences of caffeine with other constituents of the sample were observed. The quantification limit for caffeine in human plasma was 0.05 μg /ml, based on a signal-to-noise ratio of 10.0. The intra- and inter-day coefficients of variation were less than 8.36 % and 7.28 %, respectively, for the concentration range from 1 to 20 μg/ml.

We carried out the study without any adverse event or any significant change of laboratory test throughout the whole study period. Even in the HBO therapy period, there was no adverse event regarding caffeine or oxygen toxicity including prodromal symptoms.

Amount of caffeine administered in normobaric period and HBO therapy period were 3.10 mg and 3.40 mg, respectively. The mean plasma caffeine concentration-time curves are shown in Figure 2. Pharmacokinetic parameters including AUC_t, C_{max}, T_{max}, $T_{1/2}$, Vd and Cl were shown in Table 1. In normobaric period, AUC_t was 34.27 ± 10.1 $\mu g \cdot hr/ml$ and C_{max} was 4.43 $\mu g/ml$. AUC_t and C_{max} was increased during HBO therapy period to 45.65 ± 9.89 $\mu g \cdot hr/ml$ and 5.72 $\mu g/ml$, respectively. In the present study, AUC_t and C_{max} were increased in HBO therapy period. It seemed that it is because of the caffeine amount administered in HBO therapy period was 3.40 mg compare to 3.10 mg in normobaric period. In order to compensate these differences, we divided caffeine amount administered by AUC_t and calculated the oral clearance. It was still lower in HBO therapy period(85.36 ± 17.83 ml/hr) than normobaric period (120.09 ± 37.56 ml/hr). But, there was no statistically significant difference in all pharmacokinetic parameters between normobaric and HBO therapy period ($p > 0.05$).

DISCUSSION

There were several studies investigating the influence of hyperbaric conditions on drug disposition. To reduce intraindividual variability, Merritt and Slade[15] choose a cross over design to

investigate alteration of gentamycin-disposition under hyperbaric and normobaric conditions in healthy volunteers. Prolonged hyperoxic exposures may nevertheless be associated with toxic effects, resulting from high O_2 pressure, time consuming decompression periods, as well as concomitant ethical and economical problems. Rump et al[19] investigate the influence of hyperbaric condition on caffeine disposition in 2 healthy volunteers without cross over design. Their data showed no clinically significant influence of HBO therapy on caffeine dispositions. In the present study, we used HBO therapy regimen, which is most widely used in Korea or internationally. But, the depth and duration of regimen seemed not sufficient to evaluate the influence on caffeine which has a relatively long elimination half-life.

Caffeine is a xanthine compound that has similar chemical structure with theophylline and aminophylline. These drugs are metabolized by hepatic N-acetyltransferase, which showed genetic polymorphisms. It was reported that the frequency of slow acetylator is 11 to 19 % in Korean and 49 to 70 % in Caucasian. It is more reasonable that influence of HBO therapy on caffeine disposition is investigated in same genotypic group.

The possibility of oxygen toxicity in hyperbaric condition is increased by caffeine because of its CNS stimulation effect. It is difficult to find safety range of caffeine concentration in hyperbaric hyperoxic condition because oxygen toxicity has a large interindividual variation and very subjective symptoms. Compared to the therapeutic range when administering caffeine to newborns for the prevention of bradycardia and apneic episodes (5 - 15 $\mu g/ml$)[18], plasma concentrations observed in the present study seem rather low. Toxic symptoms regarding to oxygen toxicity or caffeine did not occur in volunteers.

The findings of the present study do not give any evidence for effects of hyperbaric hyperoxia (30 fsw, 80 min) on the disposition of caffeine. The pharmacokinetic parameters that we determined are similar to established literature data on caffeine under normobaric conditions.[18] Caffeine absorption from the intestine is fast but shows a high variability (T_{max}: 0.3 - 3 h). The rate of absorption depends on the volume and composition of the pharmaceutical formulation. In the present study, maximal caffeine concentration were reached after 1.27 ± 0.32 h and 1.62 ± 0.35 h in normobaric and HBO therapy condition, respectively.

Caffeine causes vasoconstriction in peripheral tissues. This effect decreases the O_2 partial pressure in peripheral blood.[20] This effect may lower therapeutic efficacy in HBO therapy, which can be applied to diabetes mellitus foot, skin graft and burn treatment.

In conclusion, the pharmacokinetics of caffeine do not seem to be influenced in a clinically relevant way in humans during a stay for 80 min at 30 fsw, 100% O_2 in four normal subjects and our results do not exclude effect of a more prolonged stay at a higher depth, or repetitive dives on the disposition of caffeine. Further evaluation regarding not only pharmacokinetic but also pharmacodynamic influence of HBO therapy on the disposition of various drug

including caffeine seems mandatory.

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