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Present situation of rational drug use in plateau area

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Abstract

Plateau is characterized by low oxygen, low pressure, strong radiation, cold and dryness, among which low oxygen is the main factor that affects the normal life activities of human body. Altitude hypoxia leads to significant changes in the metabolic characteristics of drugs *in vivo*, which in turn affects the efficacy and adverse actions of drugs. This paper summarizes the present situation of rational drug use in plateau area and pinpoints the existing problems. Meanwhile, we posit the strategies and measures for realizing rational and precise pharmacotherapy of plateau residents. First, we need to acquire a panoramic view of differential and relative pharmacokinetics and pharmacodynamics in between plateau area and plain area by carrying out comparative studies on drug metabolisms and on comprehensive drug efficacies and mechanisms. Second, we must apply the findings from basic research to clinical practice and formulate guidelines and recommendations of drug use for plateau habitants. Finally, we should eventually achieve precise and individualized drug use for plateau habitants based on their characteristic etiology and pathogenesis.

Keywords

plateau; hypoxia; rational drug use; pharmacokinetics

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1 Plateau environment

The plateau has certain special environmental characteristics, such as low oxygen, low air pressure, low temperature, dryness, large temperature difference between day and night, strong ultraviolet rays, *etc.* Among them, low oxygen has the most significant impact on humans, which not only affects 140 million residents who live over 2 500 m above sea level, but also has a certain impact on people who are travelling, doing business, receiving sports training, undertaking national defense and building infrastructure in the plateau. According to altitude, altitude hypoxia can be divided into mild hypoxia (1 500-2 500 m), moderate hypoxia (2 500-4 500 m) and severe hypoxia (4 500-5 500 m). The higher the altitude is, the lower the atmospheric pressure and the oxygen partial pressure[1].

2 Clinical rational drug use at high altitude

In recent years, many scholars began to pay attention to the changes of drug metabolism in the body under high altitude hypoxia[2-4]. Under hypoxic condition, the body produces a series of complex pathophysiological changes which can affect the absorption, distribution, metabolism and excretion of drugs in the body, leading to significant changes in the metabolic characteristics of drugs thereby compromising the curative effects and deriving adverse effects, of drugs[5-6]. With growing number of people living in the plateau, it is increasingly desirable to work out a feasible plan on rational drug use in local medical institutions. To date, the majority of medical institutions in plateau areas have not taken rational-drug-use seriously. Except for some experienced physicians, others are still following the dosage of drug administration recommended for plain areas, which poses certain risks to people residing in plateau areas. In high altitude hypoxia environment, the pharmacokinetic parameters of drugs can be drastically changed, rendering the drug concentration being either lower than the therapeutic level with failure of disease control or higher than the minimum toxic level creating serious adverse reactions. In order to achieve rational use of medicines in high altitude hypoxia environment, we need first to improve our understanding of the impact, as well as of the underlying mechanisms, of high altitude hypoxia on drug metabolism in the human body[7-8]. Therefore, the topics of plateau pharmacology and drug metabolism have become a subject of increasing interest aiming to lay the groundwork and form the theoretical basis for safe and rational drug use in high-altitude populations.

3 Research of Pharmacokinetics under hypoxia at high altitude

Under high altitude hypoxia, the pharmacokinetic parameters of drugs can change significantly relative to those in plain (Table1, 2)[9-10], which can be ascribed to the changes in the activities and expression of drug-metabolizing enzymes and transporters[11-13]. It is known that the metabolism of all clinically used drugs with only few exceptions slows down in high altitude hypoxia environment, as evidenced primarily by the increase in the area under the drug-time curve (AUC), prolongation of the residence time (MRT) and half-life ($t_{1/2}$), and decreases in the elimination rate constant (K_e) and elimination rate (CL) (Table 3). The mechanisms underlying these changes are primarily attributed to the alterations of phase I drug metabolism enzymes CYP450 and ABC drug transporters. For example, the activity and expression of metabolic enzymes CYP1A1, CYP1A2, CYP2E1 and CYP3A4 are decreased, whereas those of CYP3A6 and CYP2D6 are increased (Table 4). The expression of transporters such as MRP2, PEPT1, OATP1B1, OAT1 and OCT1 in liver and intestinal tissues is significantly upregulated (Table 5). These facts prompted us to proipose that the pharmacokinetics of drugs should be reevaluated and the dosage should be properly adjusted for residents in plateau areas. Specific consideration should be given to patients at different altitudes, different durations of hypoxia, and different ethnic groups. Accordingly, it is recommended, as a principle, that the dose and the dosing interval for most medicines should be reduced when applied to high-altitude habitants below those for the patients in plain areas.

At present, the research on pharmacokinetics of drugs under high altitude hypoxia is conducted mainly in rats, rabbits and other animals, and most of them adopt acute hypoxia models or low-pressure oxygen chamber to simulate hypoxia. These models could hardly reproduce the plateau characteristics, such as low temperature, strong ultraviolet rays and dryness and reflect the real environment of the plateau. Once entering the plateau area, an organism gets into a natural anoxic environment and will thereafter undergo continuous changes in its entire physiological processes. However, experimental animals often need to be disposed of by using low-pressure oxygen chamber and other methods to simulate the plateau environment. Even in a large-scale simulating cabin for human studies, the simulated altitude of the feeding cabin has to be reduced to a level that does not affect human activities, and such a maneuver could hardly guarantee that the subject is maintained at a stable altitude during the entire experiment procedure, but could result in intermittent hypoxia thereby large variations of experimental results. The hypoxic model does not allow for adaptation process; therefore, we should take the actual plateau environment as the experimental

Table 1 Comparison of pharmacokinetics parameters of furosemide in healthy volunteers in plain, fast-moving plateau and long-staying plateau[9]

Parameters	Whole blood			Blood plasma		
	Plain	Fast-moving plateau	Long-staying plateau	Plain	Fast-moving plateau	Long-staying plateau
K (h^{-1})	0.76 ± 0.24	0.70 ± 0.20	0.61 ± 0.17	0.82 ± 0.26	0.71 ± 0.27	0.57 ± 0.16
$t_{1/2}$ (h)	0.97 ± 0.22	1.07 ± 0.29	1.24 ± 0.45	0.90 ± 0.20	1.13 ± 0.47	1.32 ± 0.52
V_d (L/kg)	10.44 ± 3.70	9.28 ± 1.87	10.50 ± 5.18	5.05 ± 1.89	4.60 ± 1.01	5.18 ± 2.27
CL (L/[h·kg])	0.39 ± 0.09	0.41 ± 0.08	0.42 ± 0.30	0.18 ± 0.04	0.20 ± 0.05	0.19 ± 0.11
AUC (μg/[h·mL])	5.22 ± 1.26	4.96 ± 0.99	5.56 ± 2.35	10.18 ± 2.39	9.23 ± 1.91	11.22 ± 4.52
C_{max}(μg/mL^{-1})	2.29 ± 0.91	1.89 ± 0.72	1.89 ± 0.92	3.93 ± 1.39	3.54 ± 1.35	3.70 ± 1.82
t_{max} (h)	1.54 ± 0.66	1.38 ± 0.57	1.58 ± 0.79	1.58 ± 0.64	1.38 ± 0.57	1.58 ± 0.79
MRT (h)	9.47 ± 4.12	8.61 ± 4.16	12.97 ± 12.00	10.65 ± 4.44	9.62 ± 4.08	13.89 ± 10.37

Table 2 Comparison of pharmacokinetics parameters of acetazolamide in healthy volunteers in plain, fast-moving plateau and long-staying plateau[10]

Parameters	Whole blood			Blood plasma		
	Plain	Fast-moving plateau	Long-staying plateau	Plain	Fast-moving plateau	Long-staying plateau
K (h^{-1})	0.06 ± 0.02	0.07 ± 0.02	0.08 ± 0.06	0.12 ± 0.02	0.16 ± 0.03	0.13 ± 0.02
$t_{1/2}$ (h)	12.0 ± 3.0	10.2 ± 2.2	8.8 ± 5.9	6.0 ± 0.9	4.4 ± 0.8	5.3 ± 0.9
V_d (L/kg)	0.30 ± 0.12	0.24 ± 0.03	0.26 ± 0.08	0.39 ± 0.06	0.32 ± 0.08	0.44 ± 0.05
CL [L/(h·kg)]	0.29 ± 0.13	0.27 ± 0.07	0.31 ± 0.16	0.74 ± 0.09	0.82 ± 0.15	0.96 ± 0.18
AUC [μg/(h·mL)]	270.9 ± 107.0	264.2 ± 57.3	263.1 ± 147.3	94.1 ± 12.4	85.7 ± 10.2	70.9 ± 12.5
MRT (h)	19.6 ± 4.4	16.5 ± 3.2	18.5 ± 8.1	9.8 ± 1.1	7.7 ± 1.3	9.1 ± 1.4

Table 3 Changes of Pharmacokinetic Parameters of Drugs under Hypoxia

Drugs	Species	MRT	C_{max}	$t_{1/2}$	K_e	AUC	V_d	*CL*	References
Ibuprofen	Rat	↑	—	↑	—	—	↑	↓	[14]
Diazepam	Rat	↑	↑	—	—	↑	—	—	[15]
Propranolol	Rat	↑	↑	↑	—	↑	↓	↓	[16]
Norfloxacin	Rat	↑	↓	↓	—	↓	↑	↑	[17]
Acetylsalicylic acid	Rabbit	↑	—	↑	↓	—	↓	↓	[18]
Gentamicin	Rabbit	↑	—	↑	↓	—	↑	↓	[18]
Phenobarbital	Rabbit	↑	—	↑	↓	—	↓	↓	[18]
Phenytoin	Rabbit	—	—	—	—	↑	—	↓	[19]
Theophylline	Rabbit	—	—	—	—	—	—	↓	[20]
Salbutamol	Rabbit	—	—	↑	—	—	↑	—	[21]
Diltiazem	Dog	—	—	—	—	—	↓	↓	[22]
Caffeine	Human	—	—	↓	↑	↓	—	↑	[23]
Indocyanine green	Human	—	—	—	—	↓	↑	↑	[23]
Acetazolamide	Human	↓	—	—	—	↓	↓	↑	[24]
Meperidine	Human	↑	—	↑	—	—	—	↓	[25]
Neurolithium	Human	↑	—	↑	—	—	↑	↓	[26]
Furosemide	Human	—	↓	—	—	↓	↓	↓	[27]
Prednisolone	Human	—	↑	—	—	↑	↓	↓	[28]
Sulfamethoxazole	Human	—	—	↑	—	↑	—	↓	[29]
Lidocaine	Human	↑	—	↑	—	—	↑	↓	[30]

Table 4 Changes of expression and activity of drug metabolizing enzymes under hypoxia

Enzyme	Species	mRNA levels	Protein expression	Activity	References
CYP1A1	Rabbit	↓	↓	↓	[31]
CYP1A2	Rat	↓	↓	↓	[32]
CYP2B4	Rabbit	↓	↓	↓	[33]
CYP2C5	Rabbit	↓	↓	↓	[33]
CYP2C9	Rat	↓	↓	↑	[32]
CYP2C16	Rabbit	↓	↓	↓	[33]
CYP2C19	Rat	↓	↓	↑	[32]
CYP2D6	Rat	↑	↑	↑	[32]
CYP2E1	Rat	↓	↓	↓	[34]
CYP3A1	Rat	↓	↓	↓	[34]
CYP3A4	Human	↓	↓	↓	[35]
CYP3A6	Rabbit	↑	↑	↑	[31]
NAT2	Rat	↓	↓	↓	[32]

Table 5 Changes of expression and activity of drug transporters under hypoxia

Object	Drug transporter	mRNA levels	Protein expression	Activity	References
Liver	MDR1	↑	↑	↑	[36]
	MRP2	↑	↑	↑	[37]
	PEPT1	↑	↑	↑	[38]
	OATP1B1	↑	↑	↑	[38]
	OAT1	↑	↑	↑	[38]
	OCT1	↑	↑	↑	[38]
	OATP2	—	—	—	[39]
	BCRP	—	—	—	[39]
Intestine	MRP2	↑	↑	↑	[37]
	PEPT1	↑	↑	↑	[38]
	OATP1B1	↑	↑	↑	[38]
	OAT1	↑	↑	↑	[38]
	OCT1	↑	↑	↑	[38]
	MDR1	↓	↓	↓	[40]
Kidney	MDR1	↑	↑	↑	[37]
	PEPT1	↑	↑	↑	[37]
	OAT1	↑	↑	↑	[38]
	OCT1	↑	↑	↑	[38]
	MRP2	↓	↓	↓	[37]
	OATP1B1	—	—	—	[38]
Heart	MDR1	↓	↓	↓	[36]

place to avoid the limitations of simulated environment and to enable investigations of the changes of drug metabolism in the special plateau environment by integrating various factors such as hypoxia, low pressure, strong radiation and cold. Chronic hypoxia in an organism can only be formed after entering the plateau and continuing to live for a long period of time. Limited by the experimental conditions, the hypoxia model is suitable

for simulating acute hypoxia, but it is difficult to simulate chronic hypoxia. Because of the differences in drug metabolism between human and other animals, we should conduct research in human subjects whenever possible to investigate the effects and mechanisms of acute and chronic hypoxia on pharmacodynamics and pharmacokinetics at high altitude.

As we all know, drugs are used to treat diseases, and patients are the consumers of drugs. Therefore, it is more meaningful and clinically relevant to study the pharmacokinetic parameters in pathological state than in normal state. However, at present, it is difficult to reflect the real situation of the pathological state of the body by using normal animals as research subjects and observing the changes of pharmacokinetic parameters in high altitude hypoxia environment.

4 Summary and prospect

Approximately 38 million people are residing in chronic hypoxia environments in high altitude areas around the world. Relative to people with short a stay in high altitude, rational and effective drug use for long-term residents at high altitude will still be a hot research topic in the future. In addition, many ethnic minorities are living in plateau areas. Due to differences in genetic factors and lifestyles, the differences in drug metabolism among different ethnic groups should be seriously considered. In the future studies, we need to give more weight to the relative drug metabolisms between plateau and plain areas to establish a more proper pharmacokinetic model for plateau population, get insight into the mechanisms for drug actions, apply the results of basic research to clinical practice to foster clinical research and trials, and formulate proper guidelines/recommendations for clinical drug use in plateau areas. In this way, we will be able to provide technical support for rational drug use and achieve accurate and individualized drug use, to benefit tens of millions of plateau residents and sojourners in plateau areas worldwide.

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Author contributions

Chu Y B prepared and wrote the manuscript. Wang R revised the manuscript and approved it for publishing. All authors discussed the results and contributed to the final manuscript.

Conflict of interest

The article was subject to the journal's standard procedures, with peer review handled independently of this member and his research groups. The authors declare that they have no other competing interests.

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