Application of Model Animals in the Study of Drug Toxicology

Yagang Song and Mingsan Miao

Department of pharmacy, Henan University of Chinese Medicine, Zhengzhou, China
Email: songyagang1016@163.com, miaomingsan@163.com.

Abstract. Drug safety is a key factor in drug research and development. Drug toxicology test is the main method to evaluate the safety of drugs. The body condition of an animal has important implications for the results of the study. Previous toxicological studies of drugs were carried out in normal animals in the past. There is a great deviation from the clinical practice. The purpose of this study is to investigate the necessity of model animals as a substitute for normal animals for toxicological studies. It is expected to provide exact guidance for future drug safety evaluation.

1. Introduction

With the rapid development of the pharmaceutical industry, new drugs emerge in an endless stream, and the number is increasing. The safety of drugs has become the focus of drug toxicology. Previous toxicological evaluations of drugs were administered to normal animals by different administration methods. After a certain period of time, the physiological and biochemical indexes were determined by specific methods to evaluate the toxicity of the tested drugs to healthy animals. The toxicity, toxic dose and lethal dose of the tested animals were determined. To provide reference for drug entering clinical stage and extrapolate the result to human. As a result of the study of drug toxicology as a preliminary reference for drugs, we should try to simulate the clinical practice as much as possible in toxicology experiments.

It can be imagined that the object of clinical drug action is the patient, not the normal person. A large number of clinical pharmacokinetic data reflect the significant difference between the tolerance of clinical patients and the normal people [1-5]. Therefore, it is not advisable to use normal animals for toxicological assessment in toxicological experiments. At present, the clinical toxicological data are obtained from normal animals, and this result is questionable. Therefore, we believe that the use of model animals instead of normal animals for toxicological assessment in drug toxicology research can be more close to the clinical practice, and provide accurate guidance for the future clinical rational drug use.

2. There are some Problems in Using Normal Animals in the Study of Drug Toxicology

Wherever Times is specified, Times Roman or Times New Roman may be used. If neither is available on your word processor, please use the font closest in appearance to Times. Avoid using bit-mapped fonts if possible. True-Type 1 or Open Type fonts are preferred. Please embed symbol fonts, as well, for math, etc.

2.1. There are Differences in Different Physiological and Pathological States

As we all know, the health status of the body has a significant impact on the results of drug toxicology research, and there is a significant difference in the tolerance of the organism to the drug under the morbid condition. For example, atropine has a lethal dose of 80~130 mg [6] to healthy adults, and the tolerance to severe organophosphate poisoning can increase dozens of times. Patients with different
diseases in different physiological and pathological state, distribution, metabolism and elimination of meropenem body pharmacokinetic characteristics are not the same [7]. In the field of clinical Chinese medicine, the use of Aconitum and aconite is also the case. In the case of dialectical and accurate, Zheng Shiguang and others use about 20g of aconite. Compared to the normal condition the crude oral dosage of Radix Aconiti is 1.5 to 3g[8-9]. The same in the 2015 edition of the pharmacopoeia for Arisaema toxic, for external use only. According to Xu Boping reports on its clinical reuse of Arisaema treatment of malignant tumor in 82 cases, each agent is 30 to 100g, Combination Fuzhengquxie drugs, Daily 1 agent, with lesion size as a curative effect evaluation, continued to Arisaema mainly after 60 d treatment, the tumor decreased more than 50% in 4 cases, decreased in 2 cases, stable in 6 cases, there were 7 cases of increase continues to deteriorate. To observe the Arisaema for cancer treatment, its efficacy and dose, duration, if long time and decocting, taken after meals, each agent Arisaema amount not more than 100g be safe to use [10-11]. According to reports, normal people, for the prevention and treatment of diseases, blind take some rare Chinese herbal medicine, Such as Cordyceps, ginseng, pilose antler and other herbs, that lead to take Cordyceps abdominal distension discomfort reported[12]. Such as taking Ginseng appeared red hot flashes, breath shortness of breath, chest bloating unbearable, body heat, irritability, child sexual precocity [13-14]. These symptoms are rare in the corresponding clinical patients. In addition, the researchers used method of analysis technology and the combination of serum chemical chromatography, comparison of the physiological and pathological conditions of the heat syndrome in rats of cold medicine Gardenia absorption. The results show that rats in heat syndrome under the condition of water extraction of Gardenia Geniposide in incremental absorption, as well as in the serum composition shift the phenomenon [15]. Therefore; the dosage of drugs is closely related to the health status of the body. We should correct the serious problems of the normal animals in the study of drug toxicology.

2.2. The Potential Toxicity of Drugs is Easy to be Ignored in Pathological Condition
The physiological and biochemical functions of the tissues and organs are different, and the internal processes of drugs change accordingly. In the study of drug toxicology, it is ignored when normal animals are used for toxicological experiments, which leads to erroneous conclusions, resulting in serious medical accidents. For example, severe injuries occurred in twentieth Century, "thalidomide induced short limb deformities". Since its debut in 1957, the drug has led to the birth of tens of thousands of children with short limb deformities and shocked the world in just a few years. After the thalidomide event, some scholars used the animal model of pregnancy to study [16-17]. The results showed that thalidomide had obvious teratogenic effect, The reason that model animal was not used in toxicology research was thoroughly toxicological test. For example, the urgent discontinuation of Houttuynia cordata injection, because the early toxicological studies did not adopt the appropriate animal model for thorough toxicological studies, which led to serious adverse events [18]. Thus, it is easy to ignore the potential toxicity of normal animals in toxicological studies. Therefore, we advocate the study of drug toxicology, it is necessary to use model animals instead of normal animals.

2.3. There is Difference in Living Condition between Normal Body and Pathological Condition
The observation indicators of drug toxicity often include dietary status, body weight, health status, [19-21], death, hair color, activity [22-24] and other manifestations, these indicators are different before and after the administration of the animal, is it the drug itself toxic? In clinical, the patient's body state is not good, is caused by the disease itself, or after the use of drugs caused, it is worth our thinking. If model animals are used in the previous toxicological studies, the model group, the control group and the drug delivery group will be set up, and these doubts will be solved in preclinical studies, and the problems can be found in time. Although after continuous efforts of toxicology workers, the traditional drug toxicology research has made great progress in the experimental methods, but we tend to ignore some of the most simple problems, such as in the normal animal toxicology studies lead to wrong conclusion. Therefore, we advocate the use of model animals instead of normal animals in the toxicological study of drugs, and obtain more accurate experimental data, and then guide the rational use of drugs in the clinic.
3. The Importance of Model Animals in Toxicological Studies

3.1. Model Animals are Closer to Clinical Practice

Animal model of disease is an animal experimental object and material which has been established in toxicological studies with disease iconicity. The development of the disease is very complex, with itself as the experiment object to further explore the mechanism of diseases, not only in time and space limitations, and many experiments in the moral and the method is also limited. The main body of the drug is the patient, and in the toxicological test, the model animal can simulate the clinical patients and observe the toxic effect of the medicine. With the help of toxicological studies in animal models, can consciously change the impossible under natural conditions or difficult to exclude factors, to explore the existence of drugs on the toxicity of the sick, to facilitate more effective recognition of drug toxicity and the occurrence and development of research on the prevention and control measures. Therefore, the application of animal disease models in independent research is a very important experimental method and means in toxicology research.

3.2. Model Animals can Supplement the Defects in Toxicological Studies of Normal Animals

Animal model can better simulate the clinical patients pathological state, more appropriate, to investigate the drug on the pathological state of the body potential toxicity, obtain the corresponding data, to provide safe and reliable drug for clinical patients. For example, two iodine two ethyl tin and toxic encephalitis syndrome, the drug of their own development and production of a tin containing two ethyl two iodine anti infection drugs, treatment of pyogenic infection, because it did not use the animal model for toxicological research thoroughly and then led to more than 200 people were headache, vision loss and other symptoms of poisoning encephalitis. The death of more than 100 people. If the model animal be used for toxicological studies, then the drug damage could be avoided. Therefore, the disease animal model in drug toxicology research is more close to reality, to solve the problem of normal animal poisoning in drug toxicology research misleading; in addition, the animal model is helpful for us to find some other potential toxicity in the body under the pathological condition of medication.

4. Feasibility Analysis of Model Animals in Toxicological Studies

The application of model animals in toxicological research will help us to explore the toxicity of drugs to morbid organism, effectively recognize the toxicity of drugs and the law of their occurrence and development, and actively search for prevention and control measures. In toxicology study, we can set up the blank group, model group, administration group and model drug group to observe the toxicity of the medicine. Compared with blank model modeling success; model and model drug treatment group compared the drug not only, and can understand the toxic effects of drugs on animal models (the toxicity of drugs on the pathology state), helps to develop drugs on the pathological conditions of the toxic effect, The single drug group and blank group the toxic effects of drugs on normal body, model group compared to the model of drug toxicity and injury to the body compared with simple drug group, in order to better guide the clinical, it is feasible that using animal models for toxicological research, and it's also necessary.

5. Expectation

The toxicology and safety evaluation of drugs has attracted people's attention in pharmacology, provides important information safety toxicology research and development and use of these drugs, especially the study of the toxic effects of drugs. However, it is not difficult to find out that there is a significant deviation in the toxicological evaluation of normal animals in the toxicological evaluation of drugs by reviewing the previous research methods. The clinical application of the measurement problems and potential toxicity problems, if not improved, will result in clinical patients can use large doses of drugs because of its toxicity (the non toxicity model animal toxicology experiment) restrictions and difficult to play its medicine effect, ultimately hinder the normal use of drugs. In addition, the potential toxicity of drugs is not easy to be found, leading to serious clinical medical malpractice. If the animal model can be used in toxicological studies, most effective, because of toxicity limits the use of
drugs will be revitalized; clinically considered innocuous drugs, some potential toxicity may be found. We have an obligation as pharmacy workers, for the safety evaluation of drugs and other fields of research efforts to improve our innovative drug toxicology research level, to lay the foundation for the healthy development of the pharmaceutical industry, and ultimately provide a safer and more effective drugs for human.

6. Acknowledgment
Thanks for Fund of national "11th Five-Year" support program (2008BAI53B09), the national base for International Cooperation (NSC under 2016-65), the Central Plains scholars (162101510003), the national standard of Chinese medicine Chinese Medicine Administrative Bureau (2017-149-11) special fund to support this paper.

7. References
[1] Zhao Guosheng. Tolerance and pharmacokinetics of normal Human Immunoglobulin (intramuscular injection) treated with S/D. [J]. Foreign medicine. Transfusion and hematology, 2000, (03):228.
[2] Wu Chaoquan. The normal tissue irradiation tolerance effect (table [J]. foreign medical clinical radiology), 1984, (02):120-124.
[3] Zhu Nanping, Li Shuhua, et al. Beam kawlin, dynamic [J]. China drug and clinical journal, blood drug concentration and drug determination of patients with renal insufficiency of nateglinide by high performance liquid chromatography mass spectrometry (2006, 05):343-345.
[4] Wang long, Xu Xiongwei, Lin. The pharmacokinetic study of [J]. Chinese Pharmaceutical Journal, different age groups under general anesthesia of propofol in patients of Medicine 2007, (03):209-212.
[5] Zhu Zhongling, Yan Zhao, Wang Huaying, et al. Pharmacokinetics of 9- nitro camptothecin capsules in tumor patients [J]. Chinese Journal of new drugs and clinical medical, 2009, (05):346-350.
[6] Li Qiang. Clinical efficacy of different atropine administration in patients with organophosphorus poisoning. [J]. Chinese drug evaluation, 2017, (02):118-120.
[7] Zhang, Jin Lu, Ge Weihong, et al. Different physiological and pathological conditions and pharmacokinetic / pharmacodynamic difference magazine, [J]. Specific research progress China in infection and chemotherapy Luo Pei Nanyao beauty 2016, (01):92-98.
[8] Zheng time. Safe use of aconite dosage limit [A]. China Academy of traditional Chinese medicine.2011 the first international Yang Yang forum and the Fourth National Yang Yang forum [C]. Chinese Medicine Association; 2011:01.
[9] Yu Xiang. The progress of clinical application of [J]. Chinese Sichuan folk medicine, 2013, (11):136-137.
[10] Wu eastern Shandong. Guangdong Pharmaceutical University quality evaluation [D]. Schott and its processed products, 2014.
[11] Xu Boping. Large dose of Arisaema Decoction of the clinical toxicity observation of [J]. new Chinese medicine, 1997, 29 (2):25-26.
[12] Liu Lulin. Gastrointestinal emptying inhibition in 1 cases [J]. Shandong Journal of traditional Chinese medicine, Cordyceps sinensis caused 1992, 11 (5):23.
[13] Su Chunlan, Luo Zhisheng, Qin Xing Le. Ginseng abuse of 3 cases of adverse reactions caused by drug [J]. Journal of epidemiology, 2004, 13 (5):279-280.
[14] Zhang Dingqi, Ma hon, Mei Zhigang, et al. Clinical application of Chinese herbal literature analysis of adverse reactions of [J]. China Journal of traditional Chinese medicine information based on the 2015, (06):43-45.
[15] Dong Wanru, Ding Yaguang, Jing Lei, et al. Comparative study on serum medicinal chemistry of Gardenia jasminoides Ellis under pathological and physiological conditions [J]. Chinese herbal medicine, 2011, (11):2270-2274.
[16] Zhou Ying. Thalidomide induced limb deformities [J]. Adverse Drug Reactions Journal, 2010, (05):335-337.
[17] The history of [17] Zhicheng in Europe. 1956 thalidomide event [A]. Studies on toxicological history (sixth episodes) [C]; 2006:04.

[18] Quan Xi Mei, Zeng Congyan. Caused by "exigent withdrawal of Houttuynia cordata injection event" thinking of the [J]. Chinese pharmacy, 2006, (15):1124-1126.

[19] Lou Yi. Progress in research on drug toxicology based on system biology [J]. Chinese Journal of pharmacology and toxicology, 2012, (04):476-481.

[20] Liao Mingyang. Status and Prospect of drug toxicology in China [J]. Chinese Journal of pharmacology and toxicology, 2015, (05):727-728.

[21] Wang Quanjun, Wu Chunqi, Liao Mingyang. New progress in drug toxicology research [J]. Chinese Journal of new drugs, 2007, (03):177-181.

[22] Goldenthal EI. A compilation of LD50 values in newborn and adult animals [J]. Toxicol Appl Pharmacol, 1971, 18(1): 185-207.

[23] Balazs T, Arena E, Barron CN. Protection against the cardiotoxic effect of isoproterenol HCl by restricted food intake in rats [J]. Toxicol Appl Pharmacol, 1972, 21(2): 237-43.

[24] Weil CS, Wright GJ. Intra- and interlaboratory comparative evaluation of single oral test [J]. Toxicol Appl Pharmacol, 1967, 11: 378-8.