REVIEW ARTICLES

Some aspects of biomedical preclinical research involving laboratory animals

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Abstract

Background: Animal research has enormous utility as understanding the complex interactions of molecular mechanisms, biochemical and physiological study ultimately depends on intact organisms *in vivo*. The use of animals for biomedical research was the subject of much debate and continues to be today. The main question of this debate is whether or not correct, morally speaking, to conduct animal research. Scientists who use animals for these purposes mean that experiments should be done as humanely as possible. They agree that animals should not be used as long as there are testing methods producing similar results. Internationally these principles are reflected in the rules developed by the Organization for Economic Cooperation and Development for Good Laboratory Practice. However, the implementation of this legislation in our country aims at purchasing proper equipment of scientific laboratories for preclinical research, monitoring biomedical ethics and ensures quality results. The experimental ethics is a prerequisite for ensuring good scientific practice.

Conclusion: The existence of a regulatory body to provide advice and evaluation of experimental design becomes mandatory enforcement of the concept of ethics in laboratory animal experiments.

Key words: animals, ethics, preclinical research.

Introduction

Scientific value and integrity of biomedical research is closely related to responsible and humanitarian treatment of animals. Animal research is enormously useful because understanding the complex interactions of molecular, biochemical and physiological mechanisms ultimately depends on the study of the intact organisms in vivo. To be carried out, such researches involve genetic and environmental factors that are difficult, if not impossible to control by studies on humans – though such experiences are valuable only if these controls are maintained with care. In addition, an experimental design that produces major pain or suffering declines subjects, if not eliminates the scientific value of the experiment. Finally, irresponsible or inhuman treatment of animals diminishes the reputation of scientific institutions, jeopardizing funding and threatens the public image of science.

Animal experiments had a remarkable contribution to the discovery of treatments for various diseases. It is enough to remember Paulescu's researches, and especially the success of the Canadian student Charles Herbert and his tutors, Dr. Banting and Prof. MacLeod (last two Nobel laureates) who, experimenting on dogs, discovered insulin hormone drug that saved in the last hundred yeas millions of lives. Animal experiments are necessary, as the experiments held on sick or healthy volunteers are necessary, even though there is no immediate benefit.

In the Helsinki Declaration, adopted in 1964 by the World Medical Association (WMA), which is a guide with recommendations for physicians involved in biomedical research on human subjects is mentioned that research on human subjects must be based on accepted scientific principles and evidence obtained through laboratory experiments on animals [1].

Animal protection legislation exists over 80 years (in the UK from 1911) and is functional in many European countries. Subsequently, many countries have adopted codes of practice to protect animals used in research. Each Ethics Committee monitors compliance with codes of practice and codes of ethics regarding animal experiments [2].

Since the twentieth century, the use of animals for experimental purposes extends beyond the fields of pharmacology and physiology, being used in fields such as psychology, cosmetics testing, testing different medicinal products and other consumer products.

It is impossible to do research using laboratory animals and not to create a minimum of discomfort to them. The need to reduce animal suffering probably arose with the need to use them, but today this is of major importance. As we move into an accelerated pace of scientific investigations, new problems for the care and use of laboratory animals continue to occur. The main question that gives rise to these debates is that whether it is correct or not correct, morally speaking, to conduct animal research. Scientists who use animals for such purposes know the problem and understand that experiments should be done as humanely as possible and that we should not use animals as long as the testing methods produce similar results.

There are two positions in animal experiments: in favor of animal experiments, only under the following conditions:

if their suffering is very small and if the human benefits derived from experiments could not be detected by other methods; against animal testing: if the experiments cause suffering, if human benefits are not proven and if you can make these experiments by other methods [3].

The use of animals in research is essential for the development and production of new drugs. Animal experiments are provided by the laws of all countries, because it is not allowed that any potential drug substance to be tested directly on humans. In order to reduce the number of animals, the "rule of three R" (replacement, reduction, refinement) is applied [4]. Russell and Burch (1959) proposed three specific strategies to minimize animal pain and stress research:

- Replacement: the researcher has to ensure that the objectives of the study cannot be achieved by alternative methods. Where possible, conscious animals should be replaced by unconscious animals or by insensitive material and higher-ranking animals should be replaced by lower-ranking ones.
- Reduction: if the number of animals involved in the experiment is higher, there is more suffering and more costs. Experiments that have a good design can be performed with a smaller number of animals without reducing scientific expectations. If the significance or accuracy of a study is not compromised, fewer animals should be used.
- Refinement: change of accommodation and experimental procedures so as to minimize the pain and stress and to promote the welfare of animals used in research, from birth until their death.

Strategies for reducing, replacing and refining not only have ethical bases, but also practical advantages. If the experiments can be made, for example, using the mice instead of the dogs, with less or no animals, the cost of these trials will be lower.

Successful implementation of the 3Rs principle strictly depends on the education and training of personnel involved in animal testing [5].

Continuous training is necessary for minimizing animal pain and the distress caused to animals, accumulation of theoretical and practical knowledge for the safety of the personnel, all leading to satisfactory scientific expectations. Increasing scientific quality is achieved only when the unit activities are preceded, the staff is trained, equipped with responsibility and strict records exist [6].

Another critical step in performing the experiment is given by the extraction, processing and dissemination. Results must be reliable, reproducible and provide repetition. Dissemination is mandatory regardless of the conclusions. Regardless of the form of dissemination, disseminating material must contain the following data about animals (species, line, strain, source, type, number, age, sex, weight and clinical status), the design of the experimental protocol (procedures used, time periods, equipment used) and analytical methods (including statistical methods). Even though a study had an appropriate design, it is useless if the results were not processed fairly and were not disseminated [7].

Organization for Economic Cooperation and Development (OECD) – a unique forum where the governments of 33 democracies work together to respond to the economic, social, those related to globalization and exploitation of globalized opportunities has developed and approved in 1981, the principles of good laboratory Practice (GLP) [OECD. Principles of Good Laboratory Practice (GLP)] use organizational and scientific methods, and experiences of various national and international sources, the specific objectives are mentioned related to the growth and maintenance of laboratory animals. The increased interest in recent years to medical experiments on animals is caused by a new scientific understanding; sustainable, humanistic and integrative view characterizing the millennium. The use of animals for research is under control in some EU countries under the provisions of the "European Convention for the protection of vertebrate animals used for experimental and other scientific purposes" [8].

In the Republic of Moldova, Law on the protection of animals nr.265 used for experimental and other scientific purposes was adopted by Parliament in July 2006 [9].

At the same time implementation of the recommendations of ISO/IEC 17025, 15190 in biomedical research centers of the country has as a goal the proper management of clinical and laboratory facilities needed to ensure their objects of study. In the researches conducted on animals, it would be ideal that the animal preserve stability in physiological status such as the response to variability of interest not to be interfered with unwanted influence. If animal welfare is compromised, consequences may include: high variability in results, the need to increase the number of animals, incomplete data, data that cannot be analyzed with low credibility, results that cannot be applied in other situations and the impossibility of publishing. Maintaining the animal welfare, identifying, controlling and eliminating factors that cause physiological and behavioral disturbances show good scientific practice. Under this context the Scientific Center of Drug Research team has set as a goal and is working on the implementation of standards GLP (Good Laboratory Practice) in preclinical study in practical science activities of Nicolae Testemitsanu State University of Medicine and Pharmacy. An important role in this direction is the work of the Ethics Committee of the university research.

In EU countries there is a tendency of standardizing the functionality of Ethics Committees, the European Federation of Associations of Laboratory Animal Science (FELASA) has published "Principles of ethical review practice for animal experiments in Europe" [10]. Regardless of the name, a control organization to assess animal research is required to ensure implementation of the concept of ethics in animal experiments and should be structured in several categories of people (doctors, researchers, neutral staff, staff from the animal protection associations, lawyers, philosophers, priests, etc.) to be neutral to the institutions initiating animal studies.

Conclusions

1. Human attitude towards animals is a relevant marker of ethical posture and level of civilization.

2. Experimental Ethics is prerequisite for ensuring good scientific practice. The existence of a regulatory body to provide advice and evaluation of experimental design becomes mandatory enforcement of the concept of ethics in animal experiments.

3. In order not to eliminate the scientific value of animal experiments in our country, it is necessary to implement Good Laboratory Practice standards.

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