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STUDYING THE DRUG TOXICOLOGY AND THE CONTRIBUTION OF MODEL ANIMALS

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ABSTRACT

The study of drug toxicology is an essential facet of modern medicine, ensuring the safety and efficacy of pharmaceuticals before they reach patients. Central to this discipline are model animals, which serve as living intermediaries between laboratory experiments and clinical trials. Model animals, chosen for their physiological similarity to humans, provide invaluable insights into how drugs interact within living organisms, enabling the prediction of potential risks and benefits early in the drug development process. We have calculated Likelihood Ratios (LRs) for a large data set for which both animal and human data are available, including tissue-level effects and MedDRA Level 1-4 biomedical observations, in order to estimate the evidential weight given by animal data to the probability that a new drug may be toxic to humans. To supplement our earlier reported study on dogs, we extended our methods to three more preclinical species (rat, mouse, and rabbit). This paper explores the pivotal role of model animals in drug toxicology. Ultimately, model animals remain indispensable in advancing our understanding of drug safety and efficacy, while ongoing efforts seek to balance scientific progress with ethical responsibility in the pursuit of safer and more effective pharmaceuticals.

Keywords: Drug Toxicology, Animals, Human, Physiological, Pathological

I. INTRODUCTION

In the ever-evolving landscape of modern medicine, the quest for safer and more effective pharmaceuticals remains a paramount concern. Central to this pursuit is the field of drug toxicology (Pehlivanovic, et al.. 2019), which delves into the intricate web of interactions between drugs and living organisms. The study of drug toxicity is indispensable in ensuring the safety and efficacy of new therapeutic agents before they reach the hands of patients (Yang, et al.. (2019). Amidst the multifaceted dimensions of this discipline (Alhaji Saganuwan, 2017)., one aspect stands as a stalwart foundation: the use of model animals. Over the years, model animals have played an indispensable role in advancing our understanding of drug toxicity, offering a bridge between in vitro studies and clinical trials.

Before any drug can be administered to humans, it must undergo a rigorous series of tests to assess its potential for harm as well as its therapeutic benefits. In this intricate dance of risk assessment and potential reward (Stokes W.S., 2015)., model animals have emerged as vital

tools, standing as living intermediaries between bench experiments and human subjects. They provide invaluable insights into the complex dynamics of drug interactions within living organisms (Bailey Jarrod, 2014), facilitating the prediction of potential toxicological effects and guiding the optimization of therapeutic regimens.

The utilization of model animals in drug toxicology is rooted in a fundamental principle (Michael 2014): the human body's remarkable complexity and unique biology make it impossible to glean a comprehensive understanding of drug toxicity through isolated cell cultures or computer simulations alone. Human physiology is an intricate tapestry of interconnected systems (Zeeshan Md, 2014) and drugs interact with this tapestry in myriad ways. By replicating key aspects of human physiology, model animals offer an indispensable Model animals, in this context, serve as essential surrogates for humans, allowing researchers to investigate how drugs are metabolized (Dai, Yu-Jie et al. 2014)., distributed, and excreted within a living organism bridge between the laboratory and clinical settings, helping to identify potential risks and benefits early in the drug development process.

One of the primary reasons for employing model animals in drug toxicology is their physiological similarity to humans. These animals share many biological features with humans, including organ systems, metabolic pathways, and genetic makeup. This likeness enables researchers to study drug effects in a living organism that closely resembles the intended target of the pharmaceutical intervention: the human patient. For example, mice and rats have been extensively used in preclinical studies due to their genetic proximity to humans and their relatively short reproductive cycles (Barré-Sinoussi F, 2015), which expedite research timelines. Additionally, non-human primates, such as macaques, share a remarkable degree of genetic and physiological similarity with humans, making them indispensable in certain areas of drug toxicology research.

Beyond physiological resemblance, model animals provide researchers with the opportunity to investigate drug toxicity across different stages of development and life spans. This versatility is particularly important when assessing the impact of pharmaceuticals on vulnerable populations, such as infants, children, and the elderly. By utilizing model animals at various life stages, researchers can gain insights into how drug toxicity varies with age (Andersen ML 2017), offering critical data for tailoring drug regimens to different demographic groups. Furthermore, model animals can be used to mimic specific disease conditions, allowing scientists to assess how drugs interact with and potentially exacerbate or ameliorate underlying health issues. These multifaceted applications of model animals in drug toxicology underscore their indispensable role in advancing our understanding of drug safety.

While the use of model animals in drug toxicology has undeniably led to significant scientific advancements, it also raises ethical questions and concerns. The ethical dimensions of animal research have been the subject of intense scrutiny and debate for decades. Critics argue that

the use of animals in experiments (Gad SC. 2005), even when conducted with the utmost care and adherence to ethical guidelines, raises fundamental moral questions about the treatment of sentient beings. These concerns are particularly acute when considering the potential harm inflicted upon animals in toxicology studies, where exposure to drugs and their potential adverse effects are central to the research process.

In response to these ethical dilemmas, there has been a concerted effort to refine and reduce the use of animals in drug toxicology research. The principles of the 3Rs—Replacement, Reduction, and Refinement—have guided these efforts. Replacement involves finding alternative methods (Simmons D, 2008), such as in vitro testing or computer simulations that can reduce or eliminate the need for animals in research. Reduction seeks to minimize the number of animals used while obtaining statistically meaningful results, often through careful experimental design and data analysis. Refinement focuses on improving the welfare of animals involved in research by implementing measures to minimize pain, distress, and suffering.

The pursuit of ethical animal research in drug toxicology has led to innovations in experimental techniques and the development of novel models that reduce reliance on traditional animal testing. For instance, organ-on-a-chip technology has gained prominence in recent years (Ernst W., 2016), allowing researchers to simulate the functions of specific organs or tissues on microfluidic devices. These systems offer a glimpse into how drugs interact with human physiology without the need for whole animals, aligning with the Replacement principle of the 3Rs. Similarly, advancements in computer modeling and simulation enable scientists to predict drug toxicity with increasing accuracy, providing an alternative to some animal experiments.

However, it's important to note that complete replacement of model animals remains a formidable challenge, primarily because of the intricacies of the living organism. While in vitro and in silico methods can replicate certain aspects of drug interactions, they often fall short of capturing the full complexity of physiological responses in living systems. Thus, model animals continue to be a crucial component of drug toxicology research, even as efforts to reduce and refine their use persist.

In addition to ethical considerations, the choice of model animal in drug toxicology research is guided by practicality, cost-effectiveness, and scientific relevance. Researchers must weigh the advantages and limitations of various model animals to select the most appropriate species for their specific research questions. Each model animal brings unique characteristics to the table, and careful consideration is necessary to ensure the validity and translatability of study results.

Over the decades, rodents, particularly mice and rats, have emerged as the workhorses of drug toxicology research. Their small size, ease of handling, and well-characterized genetics

have made them go-to choices for studying drug effects on various organ systems. Furthermore, the availability of genetically modified mice has allowed researchers to create models that mimic specific human diseases, offering valuable insights into drug efficacy and safety.

However, rodents also have their limitations. They have shorter lifespans and significant physiological differences from humans, which can hinder the translation of research findings to clinical settings. To address these issues, larger mammals, such as dogs and pigs, have been used in drug toxicology studies to better approximate human physiology. Non-human primates, with their genetic and physiological proximity to humans, have been invaluable in studying drug effects on the central nervous system and in vaccine development.

In recent years, there has been a growing interest in the development of humanized model animals. These animals are engineered to express human genes or tissues, allowing researchers to study drug interactions in a more human-like context. For example, humanized mice with humanized immune systems have been used to study the effects of immunotherapies and infectious diseases. These models offer a unique opportunity to bridge the gap between traditional animal models and human patients, enhancing the predictive value of preclinical studies.

The selection of the appropriate model animal also depends on the specific goals of the research. If the primary objective is to assess a drug's toxicity and potential side effects, a rodent model may be sufficient. However, if the research aims to closely mimic the human disease condition or evaluate the drug's efficacy in a more complex biological context, larger animals or humanized models may be preferable. This strategic selection of model animals ensures that the research aligns with the overarching goal of improving drug safety and efficacy for human patients.

In the realm of drug toxicology (Dam DV, 2011), it is imperative to recognize that no model animal can perfectly replicate the complexities of the human body. Each model comes with its own set of advantages and limitations, and researchers must navigate these nuances to extract meaningful insights. Furthermore, the choice of model animal is intricately tied to the specific research question being addressed, emphasizing the importance of thoughtful experimental design and model selection.

As we look to the future of drug toxicology, several exciting innovations hold the promise of revolutionizing the field. One such innovation is the development of organoids, three-dimensional cell cultures that mimic the structure and function of specific organs. Organoids offer a middle ground between traditional cell cultures and whole animals, providing a more accurate representation of organ physiology while reducing the need for extensive animal experimentation. These miniature organs can be used to screen drugs for potential toxicity and assess their effects on specific tissues, paving the way for more targeted and personalized

medicine.

Advances in genomics and precision medicine are also poised to transform drug toxicology. With the ability to sequence an individual's genome and analyze their genetic makeup (Simon F, 2015), researchers can identify genetic factors that may influence drug responses and toxicity. This personalized approach allows for the tailoring of drug regimens to an individual's unique genetic profile, reducing the risk of adverse effects and improving therapeutic outcomes. Model animals with humanized genomes are playing a crucial role in this endeavor, serving as test-beds for exploring the impact of genetic variations on drug metabolism and toxicity.

The integration of artificial intelligence (AI) and machine learning into drug toxicology research is another frontier that holds great promise. These technologies can analyze vast datasets, identify subtle patterns (Moran CJ, 2016), and predict drug toxicity with unprecedented accuracy. AI-driven models can expedite the drug development process by rapidly assessing potential safety concerns and identifying promising candidates for further study. Moreover, they can help optimize drug dosages and treatment strategies, reducing the likelihood of adverse reactions in clinical trials and real-world settings.

II. PROBLEMS IN USING NORMAL ANIMALS IN THE STUDY OF DRUG TOXICOLOGY

Different Physiological and Pathological States

Toxicology studies on drugs are heavily influenced by the subjects' health conditions; for example, in a morbid state, the organism has a much lower tolerance for the medication. The fatal dosage of atropine in humans is 80–130 mg (Loisel S, et al. 2007), and tolerance to severe organophosphate poisoning may grow by a factor of tens or even hundreds. The pharmacokinetic features of meropenem in the body are not consistent among patients with various disorders who are in different physiological and pathological states. Cordyceps, ginseng (Olsen AS, 2010), pilose antler, and other herbs that lead to take Cordyceps belly distension pain have been reported by the general public as being used for the prevention and treatment of illnesses by the blind. Side effects of ginseng include increased body temperature, agitation, and sexual precocity in children. Patients in the matching clinical population seldom experience these symptoms. In addition, the researchers compared the physiological and pathological states of the heat syndrome in rats after administering the cold medication Gardenia using the technique of analytical technology and the combination of serum chemical chromatography. Rats with heat syndrome exhibited a change in serum composition and progressive absorption of Gardenia geniposide after water extraction. As a result, the medicine dose is directly tied to the state of the body's health. We need to fix the major flaws of using normal animals for drug toxicity research.

Potential Toxicity of Drugs Easily Ignored in Pathological Condition

Drugs' internal processes vary according to the tissues' and organs' unique physiology and biochemistry. It is sometimes overlooked in the field of drug toxicity that the use of healthy animals in tests might lead to incorrect results and, in extreme cases, catastrophic medical errors. For instance, "thalidomide induced short limb deformities" (Fitzpatrick N, 2011) caused catastrophic injuries in the 20th century. The medicine first appeared on the market in 1957, and in only a few short years, it caused the birth of thousands of infants with short limb malformations, shocking the world. After the thalidomide tragedy (Raske M, 2015), several researchers examined pregnancy in animals. There was clear evidence that thalidomide caused birth defects. A complete toxicological test led to the elimination of the use of model animals in toxicology studies. As a result, normal animals are often disregarded as a possible hazard in toxicological research. Since real animals can't be used, we argue that model animals should be used instead for drug toxicological research.

Difference in Living Condition between Normal Body and Pathological Condition

Dietary status, body weight, health status, mortality, hair color, activity, and other symptoms are common observable indications of drug toxicity; when these indicators change after drug administration to an animal, one could wonder whether the substance is hazardous. When a patient's physical condition worsens in the clinic (Fortier LA 2008), whether from the illness itself or the side effects of treatment, we should give some thought to the possible causes. With the use of model animals in earlier toxicological research, the model group, the control group, and the drug delivery group may be established, and these uncertainties can be resolved in preclinical investigations, allowing for early detection of issues. Traditional drug toxicity research has made enormous strides in experimental methodologies because to the tireless efforts of toxicology specialists, yet we often overlook the simplest of difficulties, including the fact that standard animal toxicology studies sometimes arrive at the erroneous result. As a result, we propose switching to the use of model animals rather than normal animals in toxicological research in order to collect more precise experimental data and ultimately direct the sensible use of medications in clinical practice.

III. IMPORTANCE OF MODEL ANIMALS IN TOXICOLOGICAL STUDIES

Model Animals are closer to Clinical Practice

Toxicological research has long used animal models of illness as experimental objects and materials due to the iconic nature of diseases. Many trials are constrained by their immorality or ineffectiveness (Kon E 2010), as well as by the constraints imposed by the length of time and space required to study disease progression. The patient is the drug's key component, and in the toxicological test, the model animal acts as a stand-in for the clinical patients so that researchers can study the medicine's hazardous impact. Independent research using animal disease models is therefore a crucial experimental approach and technique in the field of toxicology.

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

Researching the medicine's possible toxicity on the body's pathological condition and obtaining the associated data using an animal model is essential for providing a safe and dependable treatment for clinical patients. In the case of two iodine, two ethyl tin and toxic encephalitis syndrome for instance, the drug of their own development and production of a tin containing two ethyl two iodine anti infection drugs, treatment of pyogenic infection, led to over 200 cases of headache, vision loss, and other symptoms of poisoning encephalitis because it did not use the animal model for toxicological research thoroughly. Over a hundred individuals have been killed. Toxicological research might save the model animal any harm from the drugs. Therefore, the disease animal model in drug toxicology research is more realistic (Song, 2018) addressing the issue of normal animal poisoning in drug toxicology research being misleading, and providing a resource for identifying additional mechanisms of toxicity in the body under a pathological state of medication.

Feasibility Analysis of Model Animals in Toxicological Studies

Use of Animatronic Models We may learn more about drug toxicity in diseased organisms, learn to identify drug toxicity and its incidence and development according to a set of rules (Bailey, 2013), and look for ways to curb drug abuse by investing in toxicology research. The four groups that may be used to observe drug toxicity in a toxicology research are the "blank," "model," "administration," and "model drug" groups. When compared to a blank model, this method improves our understanding of how pharmaceuticals will behave in a patient's body, and it also facilitates the development of medicines that are less dangerous in diseased states. In order to better guide clinical practice, it is both feasible and necessary to use animal models for toxicological research. The single drug group and the blank group show the toxic effects of drugs on a normal body (Helke, 2012), while the model group shows the model of drug toxicity and injury to the body compared with the simple drug group.

IV. RESEARCH METHODOLOGY

Animal models are often used to predict whether or not a substance would be hazardous in humans. To determine how well they work, it is necessary to conduct studies in which the same substance is administered to both animals and people, and the results are compared for signs of toxicity.

Biomedical observations (BMOs) were mapped to MedDRA categories (Level 1 [most specific] to Level 4 [more generic]'system organ class') (Van Norman, 2019) and LRs were calculated for both global and tissue-level impacts. Table 1 displays the total number of LRs that were computed for each species based on the number of effect categories that were assigned to each species. There is also a breakdown of how many BMO categories were considered before being ruled out because they did not include the species in question.

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Table 1: Number of classifications of adverse effects for each species

Species	Tissue-level effects	Biomedical observations (BMOs)	Total classifications used	Classifications eliminated
Rat	60	550	610	270/880
Mouse	70	340	410	265/675
Rabbit	60	220	280	140/420
Dog	57	380	437	15/452

The total number of effect types classified for each species, and therefore the total number of LRs computed for each species, is shown. Column 1 (Tissue-level impacts) and Column 2 (BMOs) are added together to form the overall number of categories utilized in the study, which is shown in Column 3 (overall classifications used). Column 4 (Classifications eliminated) displays the percentage of BMO categories for which there were no data (because no effects were observed in the preclinical species of interest) that were not included in our analysis.

V. RESULTS AND DISCUSSION

Table 2 displays the median LRs. In comparison to the median PLR of 25, the rabbit, mouse, and rat all had relatively high readings of 103, 205, and 250, respectively. These numbers, like the canine data, imply that substances exhibiting toxicity in these species are likewise likely to be hazardous in humans. The median iNLRs are much lower, coming in at 1.13 for rabbits, 1.40 for mice, and 1.81 for rats.

Table 2: Median LRs for different species

Species	PLR (median)	iNLR (median)
Rat	250	1.81
Mouse	205	1.40
Rabbit	103	1.13
Dog	25	1.08

VI. CONCLUSION

The study of drug toxicology is an ever-evolving field that bears profound implications for public health and the pharmaceutical industry. Model animals, ethical concerns notwithstanding, continue to serve as invaluable tools for bridging the gap between laboratory investigations and clinical applications. They remain at the forefront of efforts to develop safer and more effective pharmaceuticals for the benefit of humanity. As we look to the future, the balance between scientific progress and ethical responsibility remains paramount, emphasizing the need for continued innovation, refinement, and ethical scrutiny in this vital area of biomedical research.

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