Opinion

Ethical Considerations of Preclinical Testing

Allen Goldenthal*

Faculty of Health Sciences, University of Macau, Taipa, Macau

*Corresponding Author: E-mail: aegoldenthal@umac.mo; Tel.: +853-623-75280

Abstract

The numbers of animal tests being conducted are on a sharp incline. Much of this increase is directly due to our ability to generate transgenic models and knock-outs, thereby increasing the validity of the animal model but not necessarily correlating directly with any translational medical benefits to the human counterpart. In spite of our best efforts, there still exist species differences that prevent the application directly from animal to human, and in some examples having a completely different and adverse effect from that seen in the animal model. There are several ways in which we can improve the opportunity for a positive test outcome and at the same time reduce the animal usage which is associated with our current animal testing practices. The benefit of the 3R's is that they encourage us not only to avoid wastage of life but that they require us to provide considerable foresight and extrapolated thought before directly engaging in the preclinical testing phase.

Keywords

Animal models; in vivo; regulatory; pharmaceuticals; ethics

Introduction

It has been estimated that of every 5000 new drug development projects that make it through initial computer modelling and *in-vitro* testing, only 5 will ever successfully pass preclinical tests which are mandatory before clinical testing in humans. Moreover, of those drug developments that successfully pass the preclinical testing phase, only 5 % ever make it to the market as a licensed treatment for humans. Essentially, that suggests that there is less than a 0.1 % chance of a successful drug product being developed from inception to market. Although these statistics justify why drug companies must charge accordingly to recover their cost outputs which includes all the costs of the majority of failed projects, it cannot ethically justify the number of animals that are sacrificed in order to achieve this high failure rate.

There is this vast chasm between preclinical testing in animals and the eventual successful outcome of clinical trials in humans into which the majority of these drug trials disappear. In order to compensate or reduce this failure rate, additional safeguards must be placed on which drugs do make it to the animal testing phase to at least ensure that the percentage of drugs successfully passing preclinical trials is much higher than the current 0.1 %. We cannot do much at our current level of testing and knowledge to increase the translational level of success between animals and humans, since that is still not fully understood why a drug is successful in one species and not another, but we certainly can narrow the gap

between drugs that appear to have great potential in the computer modelling and *in-vitro* stage, only to fail when they are introduced into animals.

Major Challenges

The issue with safety and toxicity testing in a preclinical trial centres on dosage. When examining the weight ratio of a mouse at 25 g versus the average human at 60 kg, then the ratio of 1:2400 would suggest that we must administer to the mouse 1/2400 of the anticipated human dose on a dose/kg basis. This would require working with extremely small quantities which may in turn be so small that they are ineffective even on an animal of such small size. That certain drugs may have a threshold level before they have any efficacy is a commonly found factor, but in terms of trying to identify what that threshold might be, often numerous pilot studies are required which not only involve time and expense on behalf of the Principal Investigator but may be exorbitant in the number of animals sacrificed in order to find that level. Even so, once established, will this threshold really correlate to the quantity that must be administered to humans? The dosages may be so high, that the equivalent dosage on a dose/kg basis may far exceed the safe levels for human administration. Sensitivity to particular drugs and treatments will vary between species, simply because we are different as even the best humanized models can confirm. But the danger in relying on the dose established in the animal model as a guideline for even administering a much lower dose in humans is a minefield as was clearly evident in the limited clinical trial of TGN 1412, using a mouse-human hybrid antibody that resulted in a cytokine storm event [1].

What that particular case brings to mind is that the animal model itself was incapable of manifesting the adverse response evident in humans and therefore left a huge gap of possible or unknown consequences that only became clear when administered into human subjects. We can extrapolate this same concept into animal models of disease such as diabetes both Type I and Type II, which although similar to their counterparts in humans, are not identical, and as we have come to appreciate, will not respond in the same manner in both species to the same drug. As can be heard in many institutions, "We have some excellent cures for diabetes in mice but unfortunately they have proven of little value in humans." As some of these models are induced, rather than having an identical genetic predisposition or aetiology as in the human subject, even though we will classify them as Type I or Type II diabetes they are in fact mimics of the disease but not the identical human disease.

Pre-test Requirements and Resolutions

As such, it is important that prior to conducting a preclinical test for a drug, we must first demonstrate that the model we will use has been proven or shown to be a reflection of the human counterpart and therefore there is a higher value to any data generated from the study. This requires that we have both *in-vitro* and computational studies to verify the evidence and increase the probability of a successful outcome. Without this initial testing, moving forward into animal testing should not be considered.

Secondly, we must have all the information at hand concerning the drug being tested, or a similar drug from the same family of compounds, especially where it concerns previous animal models tested. If similar or related class of drugs were reported in preclinical trials, having failed to move forward into human trials, or in fact failing in human trials, then it is ethically important to make the argument as to why the particular drug now being tested will have a greater chance to succeed than it did in the prior tests. If such an argument cannot be made and subsequently approved, then once again animal testing should not be considered.

In this vein, a third issue is that much of preclinical research outcomes are never published and that distorts the evidence base on which to make decisions. When we say that researchers should be interpreting preclinical outcomes in light of how similar drugs have performed in the past, it is very difficult to do that if one simply cannot consult the record of prior drugs because the results were not published as a corporate or institutional decision. We would want to see measures going forward that encourage and incentivize publication of all preclinical results, even if those results were negative, as this is vitally important to reduce redundancy of experiments with no chance of success, a situation which is frequently happening within our current framework.

Fourthly, we should perform an up-down study using a minimum amount of animals in order to establish what we believe to be the NOEL (No Observable Effects Level), LOEL (Lowest Observable Effects Level) and MTD (Maximum Tolerated Dose). By pairing animals at a particular dose then observing for effects and based on those results determining if the next pair of animals receive a higher or lower administrated dosage, then we can establish more effectively the groupings to be used for any preclinical study.

Finally, we must give consideration to intercession time points when establishing the protocol or any preclinical studies. This practice will identify key critical decision points where the study should be terminated for reasons of either severe adverse effects or no indication of any desired effects. These require that a scale be predetermined of various levels of adverse effects, as well as one on determining data to quantify that there is absolutely no beneficial outcome before the preclinical study commences.

Conclusions

It must be remembered that Preclinical studies are all operated under the umbrella of Good Laboratory Practices (GLP) and therefore any Principal Investigator conducting such studies must be familiar with the GLP and that their assistants are also equally aware of the regulatory requirements for conducting a preclinical study before they participate in the trial. Straying from the GLP not only places the study at risk but also any data generated from such a study since it may not accurately reflect the actual effects of the drug but may be unduly influenced and adversely affected by both poor husbandry and animal management.

The obtained results from animal testing must undergo several checks for reliability before presuming there will be a correlating beneficial effect in humans. Certain adverse effects of the therapy may go completely undetected because we do not have the ability to recognize subclinical or monitor low incidence effects in animals such as muscle aches, low grade fever, and even psychological manifestations that might be occurring within the animal even when being observed [2]. Hence, it is imperative that we improve our skills in animal modelling, test design, and effect recognition, if we are to attain the benefits that animal testing can provide.

References

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