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Review

Pre-clinical toxicology considerations for vaccine development

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ABSTRACT

Vaccine development requires pre-clinical toxicology studies, following good laboratory practice (GLP), before first in human (phase I) use. Many factors are critical in the final outcome of any pre-clinical toxicology study. The study design is one of these critical factors and should be carefully planned to avoid any false negative and/or false positive results. Preparation is another most critical factor in a successful study. Major changes in any procedure during the course of study should be avoided by all means. For example, if the protocol specified the tail as the site of blood collection and this procedure was used for the control group at the day of necropsy, this collection site should never be replaced by another site (e.g. foot, eye, or heart) in all other treatment groups. Food restrictions and acute restraint stress affect clinical pathology data and should be avoided in rodents. Institutional Animal Care and Use Committee (IACUC) guidelines for frequent blood collections (weekly, monthly, or at necropsy) in any animal species should be strictly followed. Clinical pathology data will be profoundly affected by any diversion from the recommended volumes. If CO_2 is specified in the protocol for anesthesia and/or euthanasia, ensuring enough quantity to use for all groups at necropsy is a very important factor. Using two different anesthetics in any study (e.g. CO_2 vs. pentobarbital) may result in false positive or false negative results in clinical chemistry parameters. Quality assurance elements (SOPs, instrument validation, lab certification etc.) affect the data interpretation and the final outcome of any toxicology study. SOPs should be up to date and written clearly. All lab instruments should be validated and all laboratories should be certified.

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1. Introduction

Vaccines are developed as biological preparations to stimulate the recipient's immune system to recognize targeted aspects of infectious organisms as foreign and generate host mechanisms to control or eliminate them. Toxicology studies are performed to support the establishment of nonclinical safety of vaccines prior to their use in clinical investigations. Careful consideration should be given to the collection of precise information from properly designed toxicology studies. Assessment of safety relies on various endpoints including, but are not limited to: measurement of inflammatory cells at the site of injection, decreased food consumption, loss of body weight, and changes in body temperature.

Multiple factors play an important role in the final outcome of any toxicology study. Among these factors are site of blood collection, food intake, stress, and age-related changes. Sampling sites (tail, foot, eye, and heart) affects the values for murine white blood cell counts and other hematological parameters [1,2]. Moderate to severe food restriction causes decreases in reticulocyte, neutrophil, lymphocyte, and platelet levels in rats [3]. Acute restraint stress decreases monocyte and lymphocyte levels and increases neutrophil levels in rats [4–6].

Blood volumes that are drawn on a weekly or monthly basis from each animal should not affect the clinical pathology results. For example, on a weekly basis, blood collected from mouse, rat, dogs, monkeys, and rabbits should not exceed 0.075, 1, 50, 10, and 10 mL respectively [7]. Increases in blood volume collection above this specified volume for each animal species may significantly alter hematology and clinical chemistry parameters levels. Anaesthesia is another example of a factor that may alter the outcome of toxicology studies. Choosing the type of anesthesia (e.g. CO_2, isoflurane, pentobarbital, and ketamine/xylazine) is an important factor which may influence the results of clinical pathology. When compared to CO_2, isoflurane, pentobarbital, and ketamine/xylazine cause an increase in aspartate aminotransferase (AST) and decrease in total protein, albumin and triglyceride levels [8]. Additionally, validating sample collection time points for specific protein should be performed. Other factors like the quality assurance elements (SOPs, instrument validation, laboratory certification etc.) should also be prepared.

2. Assessment of safety

In human clinical studies, common side effects of vaccines include inflammation and pain at the site of injection, malaise, fatigue, and slight febrile. In animals, measurement of inflammatory cells at the site of injection, decreased food consumption, loss of body weight, and changes in body temperature could be counterparts for these side effects. Olson et al., (2000) [9] reported a concordance rate of 71% between true positive human toxicity (HT) and rodent and non-rodent species. The rate for non-rodents alone being predictive was 63% of HTs and rodents alone was 43% of HTs. They also reported that the highest incidence of overall concordance was in hematological, gastrointestinal, and cardiovascular HTs, and the least was for cutaneous HT. In studies of 1 month or less in duration, in one or more animal models, concordant HT of 94% was first reported. These data support the value of *in vivo* toxicology studies for prediction of many significant HTs associated with pharmaceuticals. However, it should be noted that Olson et al., (2000) [9] studied pharmacologically active (chemical based) drugs with no mention of biologicals (vaccines) which may be different with respect to interspecies concordance.

In any *in vivo* pre-clinical toxicology study for vaccines, proper design and techniques (e.g., sampling sites, type of anesthesia etc.) are very important. In this paper, site of blood collection, food intake, handling stress (cage movement and restraint), and fasting effects on the final outcome of the study results will be discussed.

3. Effects of blood collection site

The effect of site of blood collection on clinical pathology was reported by both Doeing et al. (2003) and Nemzek et al. (2001). Nemzek et al. (2001) reported that white blood cell (WBC) counts (total WBCs, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) were higher when obtained from Balb/c mice's tail blood when compared to heart or eye blood samples (Fig. 1). Total WBC counts in the heart or eye samples were significantly lower than the tail blood samples. Differences were also clear in neutrophils, monocytes, eosinophils, and basophils levels. Lowest levels of WBC counts (due to the differences in the lymphocyte counts) were reported in the heart. Effect of collection site on WBC counts was pronounced in rodents. This variability in measured parameters across blood collection sites might affect the ability to detect the true hematologic effects of test articles on WBC counts.

3.1. Effects of blood sample volume

The decision to draw blood sample volumes from animals weekly, monthly, or at necropsy depends on the animal species and size. It is very important that the blood drawn not to exceed recommended volumes. The recommended volumes might be slightly different from one institute to another but they all are close to the volumes reported by Loeb and Quimby [7]. Exceeding the recommended volumes will have a significant effect on the clinical chemistry and hematology data.

3.2. Comparing the effects of some common anesthetics

Various anesthetics, analgesia, and euthanasia techniques might modulate clinical pathology parameters and inflammatory

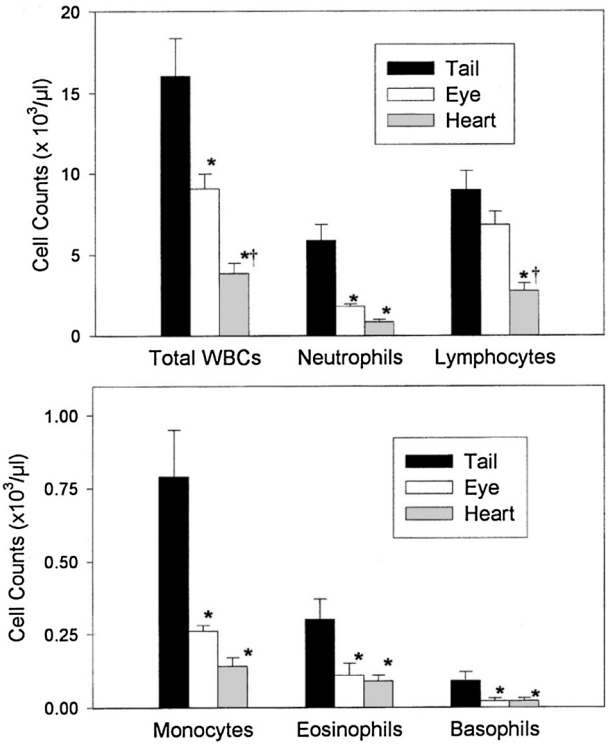

Fig. 1. Effect of sample site (blood) collection on WBC counts in BALB/c mice [2]. Reproduced with permission from "Nemzek JA, Bolgos GL, Williams BA, Remick DG. Differences in normal values for murine white blood cell counts and other hematological parameters based on sampling site. *Inflamm Res* 2001,**50**:523–527".

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