SAFETY PHARMACOLOGY: AN OVERVIEW

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ABSTRACT

Safety pharmacology studies defined as those studies that investigate the potential undesirable pharmacodynamics effects of a substance on physiological functions. It is the discipline that seeks to predict whether a drug (in the widest sense of the word), if administered to human (or animal) populations, is likely to be found unsafe, and its professional mandate is to prevent such an occurrence. The future of safety pharmacology will depend, in part, upon the scientific and technological advances and regulatory challenges that envelop pharmaceutical development. This review is aimed to provide a brief knowledge regarding safety pharmacology.

Keywords: Pre clinical safety, Safety Pharmacology, Safety Evaluation, pharmacodynamics, regulatory challenges

INTRODUCTION

Pre-Clinical Safety Evaluation (Pharmacology)
Pharmacology studies can be divided into three categories: primary pharmacodynamic, secondary pharmacodynamic and safety pharmacology studies.1

Safety pharmacology studies defined as those studies that investigate the potential undesirable pharmacodynamics effects of a substance on physiological functions in relation to exposure in the therapeutic range and above.2

Objectives of Studies
The objectives of safety pharmacology studies are:
1) To identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety;
2) To evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies; and
3) To investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected.
Figure 1: Safety Pharmacology Overview

**General Considerations in Selection and Design of Safety Pharmacology Studies**

Pharmacological effects vary depending on the specific properties of each test substance so the studies should be selected and designed accordingly. The following factors should be considered (the list is not comprehensive):

1) Effects related to the therapeutic class of the test substance, since the mechanism of action may suggest specific adverse effects (e.g., proarrhythmia is a common feature of anti-arrhythmic agents)

2) Adverse effects associated with members of the chemical or therapeutic class, but independent of the primary pharmacodynamic effects (e.g., anti-psychotics and QT prolongation)

3) Ligand binding or enzyme assay data suggesting a potential for adverse effects;

4) Results from previous safety pharmacology studies, from secondary pharmacodynamic studies, from toxicology studies, or from human use that warrant further investigation to establish and characterize the relevance of these findings to potential adverse effects in humans.  

**HISTORY**

Safety Pharmacology is the discipline that seeks to predict whether a drug, if administered to human or animal populations, is likely to be found unsafe, and its main professional mandate is to prevent such an occurrence. Before 1990, pharmaceutical companies conducted toxicological testing of lead compounds as part of preclinical drug discovery programs. Now, it has become clear over several decades that drugs may progress as far as phase 3 clinical trials (i.e. the intended patient population) before rare and potentially lethal adverse effects
become apparent. The vigilant post-marketing surveillance efforts by regulatory authorities necessary to confirm the existence of a rare adverse event occur after approval for human use.
The creation of Safety Pharmacology has not resolved all challenges, especially with respect to detection of rare and lethal adverse effect liability. One of the most difficult problems in Safety Pharmacology is how to conduct early HTS for adverse effect liability with precision and accuracy and in a manner that the data set for a drug deemed ‘safe’ by the owner of the drug can be presented in a convincing way to regulators. This is a particular problem for rare but potentially lethal adverse drug effects. Furthermore, to interject into this discourse, we noted earlier that Safety Pharmacology (as exists today) is tasked with identifying drugs as unsafe (within the therapeutic window) so, in effect, the data set the company presents to regulators is a failure to disprove that the drug is likely to be unsafe, rather than positive indication of likely safety. We really remain years away from being able to take a drug’s range of IC50 values for different molecular targets (that is, its selectivity profile) and generate a number that reflects its risk (that is, liability to evoke TdP) that can then be balanced against a number that reflects its likely therapeutic benefit. This model applies to all and any rare, but potentially lethal, adverse effect issues.

Dose Levels or Concentrations of Test Substance

In Vivo Studies
Safety pharmacology studies should be designed to define the dose-response relationship of the adverse effect observed. The time course (e.g., onset and duration of response) of the adverse effect should be investigated, when feasible. Generally, the doses eliciting the adverse effect should be compared to the doses eliciting the primary pharmacodynamic effect in the test species or the proposed therapeutic effect in humans, if feasible. It is recognized that there are species differences in pharmacodynamic sensitivity. Therefore, doses should include and exceed the primary pharmacodynamic or therapeutic range. In the absence of an adverse effect on the safety pharmacology parameter(s) evaluated in the study, the highest tested dose should be a dose that produces moderate adverse effects in this or in other studies of similar route and duration. These adverse effects can include dose-limiting pharmacodynamic effects or other toxicity. In practice, some effects in the toxic range (e.g., tremors or fasciculation during ECG recording) may confound the interpretation of the results and may also limit dose levels. Testing of a single group at the limiting dose as described above may be sufficient in the absence of an adverse effect on safety pharmacology endpoints in the test species.

Duration of Studies
Safety pharmacology studies (SFS) are generally performed by single dose administration. When pharmacodynamic effects occur only after certain duration of treatment, or when results from repeat dose non-clinical studies or results from use in humans give rise to concerns about safety pharmacological effects, the duration of the safety pharmacology studies to address these effects should be rationally based.

Future of Safety Pharmacology
The future of safety pharmacology will depend, in part, upon the scientific and technological advances and regulatory challenges that envelop pharmaceutical development. With advances in molecular biology and biotechnology, which allows for the identification of new clinical targets, newer pharmaceutical agents are, being identified that act at these novel molecular sites in an attempt to ameliorate the disease condition. Inherent in the novelty of new targets is the risk of unwanted effects that may or may not be detected with current techniques. The scientific challenge facing safety pharmacology is to keep pace, to adapt, and to incorporate new technologies in the evaluation of new drugs in nonclinical models and
identifying the effects that pose a possible risk to human volunteers and patients. Recent examples include the safety pharmacology’s embrace of modern electrophysiological techniques to evaluate the effects of new drug(s) on the ionic components of the cardiac action potential, and telemetry techniques to permit the chronic monitoring of physiological functions in unstressed animals. Efforts continue to construct databases relating the similarities and differences between animal and human responses to pharmaceutical agents. For example, nonclinical safety studies, including safety pharmacology studies, are typically conducted in normal, healthy, young adult or adult animals. However, these tests may not appropriately detect specific responses in humans at other ages (e.g., neonates, adolescents, and geriatrics) or those with underlying chronic diseases (e.g., heart failure, renal failure, and type II diabetes), conditions which may alter the pharmacodynamics response to a drug. The main challenge is to identify nonclinical models that reflect the overall human pathophysiological condition and then to incorporate these disease models along with traditional safety models into safety pharmacology paradigms for producing integrated and more accurate assessments of possible human risk. The conundrum posed by the introduction of new techniques and technologies in formulating a risk assessment is to improve and enhance the safe progression of new drugs to the marketplace, while preventing unnecessary delays (or discontinuances), based on nonclinical findings that are not relevant or interpretable in terms of clinical response or human risk.6

Safety Pharmacology Paradigm

Figure 3: Schematic depicting the complex interaction of preclinical scientific disciplines and study models used to characterize the safety profile of a new chemical entity. A non-clinical development program includes data from drug discovery models up through Safety Pharmacology and Toxicology where an investigational new drug application (IND) is filed for a candidate drug.
In some cases information on the primary and secondary pharmacodynamics properties of the substance contributes to the safety evaluation for potential adverse effects in human and should be considered along with the finding of safety pharmacology studies.

Figure 4: Safety pharmacology study approaches. Initially, SP studies were conducted after lead candidate identification to profile safety risks in humans according to GLP compliance. In addition, more recent strategy is to initiate SP studies (non-GLP) much earlier in the drug discovery process aims to identify hazardous NCEs facilitating lead candidate selection. This ensures the reduction of risks in humans and lead candidate attrition. FiH — first in human, GLP — Good Laboratory Practice.

Safety Pharmacology Core Battery:

The purpose of the safety pharmacology core battery is to investigate the effects of the test substance on vital functions. In this regard, the cardiovascular, respiratory and central nervous systems are usually considered the vital organ systems that should be studied in the core battery. In some instances, based on scientific rationale, the core battery should be supplemented or need not be implemented.

The exclusion of certain test(s) or exploration(s) of certain organs, systems or functions should be scientifically justified.

Central Nervous System
Effects of the test substance on the central nervous system should be assessed appropriately. Motor activity, behavioral changes, coordination, sensory/motor reflex responses and body temperature should be evaluated. For example, a functional observation battery (FOB), modified Irwin’s, or other appropriate test can be used.

Cardiovascular System
Effects of the test substance on the cardiovascular system should be assessed appropriately. Blood pressure, heart rate, and the electrocardiogram should be evaluated. In vivo, in vitro and/or ex vivo evaluations, including methods for repolarization and conductance abnormalities should also be considered.
Respiratory System
Effects of the test substance on the respiratory system should be assessed appropriately. Respiratory rate and other measures of respiratory function (e.g., tidal volume or hemoglobin oxygen saturation) should be evaluated. Clinical observation of animals is generally not adequate to assess respiratory function, and thus these parameters should be quantified by using appropriate methodologies.

Follow-up Safety Pharmacology Studies
Adverse effects may be suspected based on the pharmacological properties or chemical class of the test substance. Additionally, concerns may arise from the safety pharmacology core battery, clinical trials, pharmacovigilance, experimental in vitro or in vivo studies, or from literature reports. When such potential adverse effects raise concern for human safety, these should be explored in follow-up or supplemental safety pharmacology studies, as appropriate.4

In-vivo Pharmacology Assays - Safety

GENERAL SAFETY ASSAYS

Conditioned taste aversion
In order to evaluate conditioned taste aversion causing property of NCE under evaluation, five groups of animals (Control, Positive Control Group, Three dose levels of test compound; n=8), subject to test, water and saccharin intake will be analyzed.

Visceral sickness
In order to evaluate visceral sickness causing property of NCE under evaluation, five groups of animals (Control, Positive Control Group, Three dose levels of test compound; n=10), subjected to test, kaolin consumption will be analyzed.

CNS Safety Assays

Hot Plate
In order to evaluate analgesic property of NCE under evaluation, five groups of animals (Control, Positive Control Group, Three dose levels of test compound; n=8), subject to test, the latency for hind paw or fore paw licking or jump or flutter behavior will be analyzed.

Irwin Test
In order to study the general behavior of NCE under evaluation in rats, three groups of animals (Control, Two dose levels of test compound; n=8), subject to test and parameters as per functional observation battery will be analyzed.

Maximal Electroshock
In order to evaluate anticonvulsant property of NCE under evaluation, four groups of animals (Control, Positive Control Group, Two dose levels of test compound; n=8), subject to test and time for extensor and flexor phase will be analyzed.

Open Field
In order to evaluate the CNS stimulant and depressant property of NCE under evaluation, four groups of animals (Control, Positive Control Group, Two dose levels of test compound; n=8), subject to test and distance traveled in border and center, number of rearing in the border and center, total distance traveled and total number of rearing will be analyzed.7
Core Battery:

**Core Battery Studies: An Overview**

![Diagram of core battery studies](image)

**Figure 5:** An overview of the multidisciplinary integration required to evaluate the safety profile of a new chemical entity (NCE) in Safety

The structure of a Safety Pharmacology ‘core battery’ programme is to determine the potential undesirable pharmacodynamic effects of a drug on the central nervous, cardiovascular and respiratory systems, as well as to implement supplementary tests to evaluate other organ systems. Thus, it is primarily designed to take account of regulatory requirements; scientific issues are secondary.

**CONCLUSION**

This review on safety pharmacology will become a beneficial tool for those who are seeking knowledge regarding the same. Some assays are included in this review. Researchers can take some fruitful knowledge by this review article on safety pharmacology.

**REFERENCES**
