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SAFETY PHARMACOLOGY

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ABSTRACT

Safety pharmacology is the study of the potential undesirable pharmacodynamic effects of a substance in relation to dosage within the substance's therapeutic range and above. It is a rapidly developing discipline that uses the basic principles of pharmacology in a regulatory-driven process to generate data to inform risk/benefit assessment. The aim of Safety Pharmacology is to characterize the pharmacodynamic/pharmacokinetic relationship of a drug's adverse effects using continuously evolving methodology. It includes within its hold over a regulatory requirement to predict the risk of rare lethal events. The key issues for Safety Pharmacology are detection of an adverse effect liability, projection of the data into safety margin calculation and finally clinical safety monitoring. Integration of the newer approaches to routine Safety Pharmacology studies may significantly enhance the scope of Safety Pharmacology by refining and providing mechanistic insight to potential adverse effects associated with test compounds. The purpose of this review is to provide a combined and comprehensive overview of both current practices and newer technologies, followed by the emerging concepts in Safety pharmacology studies: risk determination assessments, Use of drugs with dependence liability integration of Safety pharmacology endpoints into regulatory toxicology studies, drug–drug interactions and future directions in Safety pharmacology.

KEYWORDS: pharmacodynamic effects, pharmacodynamic/pharmacokinetic.

INTRODUCTION

Safety pharmacology has evolved as an integrated discipline from the distinct filed of pharmacology, physiology and toxicology. The term safety pharmacology studies first appeared in ICH M3 Timing of Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals and S6 Preclinical Safety Evaluation of Biotechnology-Derived harmaceuticals as studies that should be conducted to support use of therapeutics in humans.[1,2] It is important to adopt a rational approach when selecting and conducting safety pharmacology studies. The specific studies that should be conducted and their design will vary based on the individual properties and intended uses of the pharmaceuticals. Scientifically valid methods should be used, and when there are internationally recognized methods that are applicable to pharmaceuticals, these methods are preferable. Moreover, the use of new technologies and methodologies in accordance with sound scientific principles is encouraged. Some safety pharmacology endpoints can be incorporated in the design of toxicology, kinetic, and clinical studies, while in other cases these endpoints should be evaluated in specific safety pharmacology studies. Although adverse effects of a substance may be detectable at exposures that fall within the therapeutic range in appropriately designed safety pharmacology studies, such effects may not be evident from observations and measurements used to detect toxicity in conventional animal toxicity studies.

Safety Pharmacology 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. Prior to 1990, pharmaceutical companies conducted toxicological testing of lead compounds as part of preclinical drug discovery. The Food and Drug Administration of the United States/Center for Drug Evaluation and Research uses tools such as drug experience reports, medical literature (clinical trial data) and multiple federal agency data sources (Drug Enforcement Agency (DEA); National Institute of Health (NIH); National Institute on Drug Abuse (NIDA)) in conjunction with the division of pharmacovigilance and epidemiology, which utilizes the spontaneous reporting system (SRS) to monitor adverse drug effect patterns potentially indicative of a public health concern (a potential ‘signal’).

So, how has this impacted on the unfolding (and evolving) history of Safety Pharmacology? In the absence of quantification of the predictive value of tests and programmes, industry and the regulators have attempted to accommodate one another through a series of industry- and

regulatory-led initiatives. Of the latter, the most important is the International Conference on Harmonization (ICH). The ICH is a project started in 1990 that utilizes the regulatory authorities of the United States, Europe and Japan in conjunction with experts from the pharmaceutical industry (from the three regulatory regions) to discuss scientific and technical aspects of therapeutic drug registration.[3] What has this to do with pharmacology? The answer is that Safety Pharmacology has been shaped in structure and function by this ongoing accommodation between pharmacologists and regulatory authorities.

Safety pharmacology studies were generally performed during the drug development stage on the selected candidate drug prior to FiH trials. Thus, The purpose of this review is to provide a combined and comprehensive overview of both current practices and newer technologies, followed by the emerging concepts in Safety pharmacology studies: risk determination assessments, Use of drugs with dependence liability integration of Safety pharmacology endpoints into regulatory toxicology studies, drug–drug interactions and future directions in Safety pharmacology studies in addition to assessing and mitigating risks associated with the selected candidate drug can now facilitate lead candidate selection by hazard identification and elimination of new chemical entities (NCE) with safety liabilities.[4]

Risk Determination

Integration of physiologic function data from safety pharmacology studies for purposes of risk assessment and management in humans is currently an evolving science. In a retrospective study of 88 new drugs evaluated during the period of 1987–92, Igarashi and colleagues reported 25 statistically significant correlations between specific safety pharmacology endpoints in animal studies and adverse events subsequently reported in clinical trials.[5] While the results of this landmark study were encouraging, no mechanistic basis for the specific correlations was provided and indeed some of those appeared to be obscure. In the ideal situation, where safety pharmacology provides a fully validated biomarker (e.g. where mechanistic relationships between drug, marker and adverse endpoint are fully established), a direct correlation between findings and risk in both animals and humans would be established. Prolongation of the QT interval is arguably the best known signal from safety pharmacology studies today. However, in spite of tremendous international efforts, the status of QT prolongation in vivo, or hERG channel activity and APD prolongation in vitro, as biomarkers for arrhythmia risk in humans, remains unclear. Indeed, the status of QT interval in risk assessment is illustrative of the elusive nature of a biomarker

sufficiently validated to permit decision making: arguably, an ideal candidate drug should not influence hERG, APD and QT.[6] The only evident exception to this is the class III antiarrhythmic drugs, which actually utilize blockade of hERG and/or other ion channels to normalize/prevent other cardiac arrhythmias. In the grey zone between the ideal candidate drug and the class III antiarrhythmic, the risk-benefit must be weighed carefully by assessment of the risk of TdP and the therapeutic advantage that the new drug may provide in humans. Due to species-specific differences in electrophysiological mechanisms, repolarization responses and metabolite patterns, drug effects on QT interval must be documented in early clinical studies even in the absence of a preclinical signal. 'If neither the preclinical testing nor the early clinical testing shows any electrophysiological effects related to delayed repolarization [e.g. signals], the likelihood of the new active substance showing important proarrhythmic effect during its clinical use, is considered remote'.[7] In such cases, the QT investigations in subsequent clinical trials could be confined as a standard program, including ECG measurements (PQ, QRS, QT and RR intervals) following single-dose and steady-state administrations in a suitable number of subjects and routine monitoring in later clinical trials. The challenge of validation of safety pharmacology approaches. The key question about the core battery tests (as far as the regulators are concerned) is: are they validated? In other words, does the chosen model accurately identify the safety liability of the drug candidate? Validation of Safety Pharmacology test systems for GLP compliance is achieved at each test site using positive control drugs with currently accepted models.[8] At a higher level, some initiatives such as the QT-PRODACT project have helped characterize the sensitivity of the methodologies and inter-facility variability.[9] These results have contributed to the increasing harmonization of industry practises, making it easier for regulators to make judgements based on retrospective comparison considerations (precedents).

Although test system validation for regulatory purposes appears to evolve within an accepted reference frame, does this mean that regulatory authorities will accept as 'validated' a method that has not actually been scientifically validated? From experience with regulatory audits and IND package submissions, regulatory authorities will accept models that have been demonstrated as reasonably valid in the public domain (that is, used, and the data published). Accuracy, reliability, use of standard agents as reference and security of the systems are major elements in GLP validations. True pharmacological validation remains a vexing issue in Safety pharmacology in exact mirror image of the issue of validation of disease models in drug discovery. It is important to emphasize that models and biomarkers are 'valid' only

when they detect all and only those drugs that have the same effectiveness and safety in the human. There is a major paradox inherent in this requirement, one that is not well recognized and one that is a fundamental problem for the newest most potentially revolutionary drugs. Thus, because new drugs are new by definition (FIH for an untreated condition, NCE, new mechanism of action), the disease for which the drug is intended may have no presently available treatment. Clearly without a positive control to provide a template response profile, this means there can be no validated preclinical model for discovery. Thus the models used to identify the new drug are not validated, and will not be validated until the identified drug is shown to be effective in humans. Likewise, in Safety Pharmacology, no model is validated until a range of positive and negative controls have been shown to produce the same outcome in the model as occurs in humans. This sounds simple; however, it is a huge problem for certain types of adverse effects. Thus to validate a model that is to be used for detecting a liability for a drug to evoke a very rare (but potentially) lethal event (RLE) requires precise and accurate human data on the liability of a range of drugs to evoke the RLE (the 'gold standard').

Use of drugs with dependence liability

Commonly prescribed drugs, such as anxiolytic benzodiazepines (e.g. diazepam) and opioid painkillers (e.g. morphine), are frequently abused, due to their desirable psychotropic effects.[10] Such drugs can also induce physical and psychological side effects upon treatment cessation and thus are associated with human drug dependence.[11] Hence, preclinical evaluation of drug abuse and dependence liability of lead compounds has become increasingly important in SP, with its inclusion in the regulatory guidelines by the European Medicines Authority[12] and the Food and Drug Administration.[13] Many initial in vitro and subsequent in vivo studies have been employed by pharmaceutical companies to evaluate the drug abuse and dependence liabilities of NCEs. The EMA and FDA have advocated a two-step evaluation of such studies. The initial tier relies on the comparison of lead compounds with established reference compounds of abuse, such as cocaine, using in vitro ligand binding, biogenic amine reuptake and synaptosomal dopamine release assays.[14] Positive results from these studies are indicative of the NCE's risk abuse potential, and thus, must be confirmed in the second tier of in vivo drug abuse and dependence studies.[14] Self administration, drug discrimination and drug withdrawal tests are generally carried out in rodents, however, it has been debated that non-human primate models should also be used due to species differences in receptor profiles between rodent and humans.[15] During self-

administration tests, rodents are trained to press a lever in order to self-administer an i.v. infusion of a known reference compound of abuse, such as cocaine.[14] In a reinforcement schedule, the animal must execute a fixed number of operant responses in order to receive infusion of the positive 'rewarding' substance of abuse, also known as the fixed ratio.[14] Subsequently, the reference compound is replaced with the test compound and the frequency at which the animal emits operant responses to receive the i.v. infusion of the test drug is indicative of its drug reinforcing properties and thus drug abuse potential.[14]

Drug–drug interactions

As mentioned earlier in this review, drug–drug interactions can cause adverse side effects that can lead to attrition of lead candidates or drugs. There are a number of assays available to assess the binding properties of an NCE[15] and these include the extent of cytochrome P450 inhibition[16] and P-glycoprotein interactions.[17] In vitro binding affinities should be used cautiously when extrapolating in vivo data; however, with well-designed experiments these assays can provide benefits with regard to compound design and the prediction of potential unwanted interactions. Given the low cost of these assays, it would be beneficial to include these preliminary screens and this is supported by the recent ICH draft guidance.[18]

safety pharmacology: A needful assessment

When there are a large number of drugs that have precise and known relative liabilities for producing common and frequent minor adverse effects it is a simple matter to validate preclinical models using the human template of responses to positive and negative controls. The challenge in Safety Pharmacology is dealing with rare events of a life threatening nature, especially for drugs aimed at treating non life-threatening diseases. Here follows a simple guide. It is not intended to be prescriptive and we invite the community to interrogate it, modify it and challenge it.

- ✓ Preclinical safety pharmacology models require better validation
- ✓ Validation requires a quantitative and accurate human template of liabilities of positive and negative controls with which to compare model data sets.
- ✓ Validation is not possible for models screening for liabilities that are rare or imprecise with current drugs in humans
- ✓ Validation is also not possible for methods for evaluating human-specific biologics (that are antigenic in animals)

- ✓ When validation is not possible, especially when the liability in humans is rare but life threatening, the use of surrogate biomarkers is unavoidable.
- ✓ It must be understood that interpretation of surrogate biomarker data sets is unavoidably subjective
- ✓ Preclinical safety testing in a non-validated setting must therefore be regarded as non-scientific whereby yes/no judgements will remain subjective in the absence of true validation of the models available
- ✓ Scientific validation of safety testing methods remains the goal, however, elusive this may seem
- ✓ Scientific validation requires blinded randomized testing of drugs known to have and known to not have a liability for the specific adverse effect in humans
- ✓ A rank order of liable drugs in humans (‘gold standard’) is the best template
- ✓ It must be acknowledged that a gold standard does not exist for most adverse effect liabilities. This poses a problem
- ✓ In the absence of validation it is better to live with false positives than risk the chance of false negatives.

Concluding remarks and future directions

This article has addressed the importance of analysing the predictive value of safety pharmacology models for drug discovery and development and suggests a strategy for collecting accurate data for the determination of sensitivity, specificity and predictive capacity as a starting point of evaluation. This entails the performance of a retrospective analysis on commonly used safety pharmacology models and a pro-active analysis of new models by using unbiased means. Further data are needed to enable more accurate comparisons of models e.g. PK/PD relationships and non-clinical and clinical findings for determining correspondence. In addition, whilst statistically based definitions of effects in pre-clinical models are generally available, the same is not the case for phase 1 trials. Addressing this weakness such that effects in man are defined as objectively as possible for these small, early clinical trials are an area for further investigation. This task requires the collaboration and agreement of pharmaceutical companies and regulatory bodies both with easy access to large compound databases including non-clinical and clinical data and the willingness to pool data on a large number of candidate drugs, thus increasing the power of the analysis. This exercise will serve several purposes: i) will increase the general confidence in the translational value of SP studies; ii) will serve as an objective basis for the selection of

SP models in the drug discovery process and their optimal time of execution within the development process; iii) will influence the designs of other safety studies, such as toxicological studies; iv) will have an impact in the design of Phase I studies, when clinical side effects are evaluated; and v) should drive regulators in their safety requirements for NCEs in development. Overall, this will increase the value of safety pharmacology within the drug development process and will reduce the development cost and the relatively high ratio of compound attrition observed in pharmaceutical development.

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