INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Assessing the Value of Nonclinical Testing to Enable Safe Entry to First in Human Clinical Trials

THE CHALLENGE

Before a new drug can be evaluated in human clinical trials, study sponsors are required to conduct animal toxicology studies to understand potential toxic effects of the drug and help establish a starting clinical dose. This testing, which is required by regulatory agencies, assumes that the animal model and toxicology studies will identify possible human hazards. However, there is active debate in the literature about the utility of animal testing in drug development and there is limited published data that scientifically addresses correlations between toxicities observed in animal models to adverse events in humans.

OBJECTIVES & APPROACH

The IQ Nonclinical to Clinical Translational Safety Working Group, which is composed of nonclinical safety subject matter experts from across IQ member companies, addressed this gap in information by collecting and analyzing how animal toxicity data predicted safety issues in humans in studies (Toxicol. Appl. Pharmacol. 2017, 334, 100-109). Using the IQ database, which allows IQ member companies to share and analyze data, the working group pooled animal toxicology and phase I clinical trial data for 182 molecules from 18 member companies. Animal toxicity data and human adverse event data were categorized by organ system and a series of statistical tests were conducted to assess how the results of toxicology studies related to clinical study results. In particular, the Working Group focused on the positive predictive value and negative predictive value (see table for definitions) to understand how well the presence or absence of toxicity in animal models predicted, respectively, the presence or absence of adverse events in humans.

RESULTS

Though its analysis, the Working Group found that an absence of toxicity in animal studies strongly predicted a similar outcome in the clinic, and that negative predictive value was generally the strongest predictive measure across test species and target organs. Positive predictive value varied by organ category and species. When data were segmented by test species, the nonhuman primate was the strongest predictor of adverse events, and the dog best predicted the absence of clinical adverse events. In cases where testing was conducted in two species, a positive finding in both species enhanced prediction of a positive human outcome.

IMPACT

This study provides a valuable contribution to the scientific knowledge base surrounding the utility and predictive power of nonclinical testing. At the time of publication, this was the only published study that combined such a large amount of animal toxicology and clinical outcome data to determine how nonclinical observations correlate with clinical observations. By demonstrating that the absence of toxicity in animal studies strongly predicts an absence of toxicity in humans, the outcome supports the current regulatory paradigm of animal testing to support safe entry of drugs into the clinic.

More broadly, this study demonstrates the critical role that pharmaceutical collaborations can play in evaluating and improving industry practices. This approach may be applied in the future to further evaluate standard safety testing paradigms. It may also provide opportunities to address translational safety gaps with newer approaches in support of the 3Rs (reduction, refinement, and replacement) of animal testing.

Key concordance parameters evaluated to determine impact of animal testing in predicting clinical outcomes	
Sensitivity (SEN)	The proportion of positive clinical findings that had positive nonclinical findings.
Specificity (SPE)	The proportion of negative clinical findings that had negative nonclinical findings.
Positive predictive value (PPV)	The proportion of positive nonclinical findings that had positive clinical findings.
Negative predictive value (NPV)	The proportion of negative nonclinical findings that had negative clinical findings.

The IQ Consortium is a not-for-profit organization of pharmaceutical and biotechnology companies with the mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader R&D community.

iqconsortium.org

Nonclinical to Clinical Translational Safety Working Group

The Nonclinical to Clinical Translational Safety Working Group created and established an IQ consortium-wide database for new molecules in drug development to determine concordance statistics and evaluate the accuracy with which animal data translates to human adverse events observed in clinical trials. This IQ Database initiative aligns with the 2011 FDA strategic plan to advance regulatory science and modernize toxicology to enhance product safety.

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