CSIR - INDIAN INSTITUTE OF TOXICOLOGY RESEARCH

COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH

Golden Jubilee Lecture

on

Use of Kinetic Data in Determining Safety Margins for First in Human Dosing (FIH)

October 19, 2015
10:30 am

Dr K. S. Rao

Senior Director
Safety Assessment Syngene International Ltd.
Bangalore

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50 Years of Service to the Nation

Dr K. S. Rao

Senior Research Director and Head of
Safety Assessment Syngene International Limited,
Bangalore, India.

Dr. K.S.Rao (B.V.Sc & A.H., M.V.Sc., Ph.D.) - a Board Certified Toxicologist with more than 40 years of global experience in safety evaluation - toxicology supporting drug discovery & development of agrochemical research and development associated with Syngene since May 2011. Dr. Rao has been with leading US pharmaceutical, agrochemical industries and CROs. Dr. Rao started his career in 1976, at G.D. Searle where he was one of six people who prepared draft GLP guidelines and presented to FDA, which became regulations around the globe. Subsequently, he joined Dow Chemical Company and Dow AgroSciences for laboratory testing, risk assessment of various chemicals and products and to provide technical support to various current and emerging issues. Later in succession he worked as Director of Jai Research Foundation in India (JRF), Quintiles before joining Advinus in July 2006 as Senior Director of Toxicology. He was Associate Vice President-Corporate Development during Jun 2009 – May 2011 and was responsible for development of Corporate Strategy for Organic and Inorganic growth in existing areas and for expanded services in Drug Development. He is Emeritus Member of the Society of Toxicology – SOT in US. The first Indian Toxicologist to be appointed for this status for being a member of the SOT for 40-years.

Dr. Rao was instrumental in getting the Diplomate of American Board of Toxicology (DABT) examination to India since 2009. In the last four years, FIFTY candidates have passed the DABT examination from India.

Dr. Rao has published research papers and made several presentions in international seminars. He is a member and actively contributed in international organizations in the field of toxicology. He is principal author of more than 200 safety evaluation study reports, of various new compounds marketed or to be marketed. These reports are submitted to various regulatory authorities of several countries, including, FDA & EPA (U.S.A), European, Japanese Health and Indian Regulatory Authorities.

Use of Kinetic Data in Determining Safety Margins for First in Human Dosing (FIH)

K.S. Rao, *M.V. Sc., Ph.D., DABT*
Senior Director
Safety Assessment Syngene International Limited
Bangalore

In the development of new drugs we rely heavily on animal studies as surrogates to humans. Often, a drug that works well in animals is ostensibly not effective in humans. One of the explanations for drug ineffectiveness is the inappropriate translation of a drug dose from animal species to humans. Selection of the starting dose in humans is a complex process, as it must fall within an optimal window. The starting dose must be low enough to be safe but high enough to avoid excessive dose escalations, which are costly and time-consuming. The most widely used method for First In Human (FIH) dose estimation is based on no observable adverse effect levels (NOAELs) in multiple species. NOAELs are determined in relevant animal studies and normalized to body surface area (in milligrams per square meter), and then extrapolated to human equivalent doses (HEDs). The HED from the most appropriate species is then divided by a safety factor to generate the maximum recommended starting dose (MRSD) in humans. However, the NOAEL-based approach relies on a somewhat arbitrary safety factor to estimate the starting dose, and the method is very conservative for FIH dose estimation. In contrast, pharmacokinetic-guided approaches provide a more mechanistic rationale and are becoming more common with many pharmaceutical companies and institutes. Human pharmacokinetic (PK) prediction methods have been developed to project the human clearance (CL) and bioavailability with reasonable accuracy, which facilitates estimation of a safe yet efficacious FIH dose. However, the FIH dose estimation is still very challenging and complex. The aim of this lecture is to present the common approaches for FIH dose estimation with an emphasis on PK-guided estimation. When predicting the first-in-human dosing, special attention is paid to the AUC after oral dosing, elimination half-life, and peak-to-trough plasma concentration ratio. This is because an estimate of exposure (AUC) is required to ensure efficacy and safety. Accurate assessment of the drug's maximum concentration (C_{max}) and trough concentration (C_{min}) is useful to avoid unwanted toxicity and maintain efficacious concentrations. Hence, early prediction of the concentration–time profiles for humans is of great importance. Currently, most PK/PD models assume only the parent drug is responsible for the pharmacological activity and/or adverse effects and the metabolites are inactive. However, this is not true in most cases. To project more accurate human dose–exposure–response–time profiles, the pharmacological activity and toxicity of the drug metabolites should be determined and integrated into the PK/PD modeling. Although PK- and PK/PD-guided approaches are gaining popularity, both mechanistic and empirical techniques should be integrated to support the FIH dose selection. Dose estimation always requires careful consideration of all of the available information. There is no universal approach that will work in every case.

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CSIR-IITR, Lucknow is the only multidisciplinary research institute in the field of toxicology in South East Asia with the motto:

Safety to Environment & Health and Service to Industry

R&D Areas

- Food, Drug & Chemical Toxicology
- Environmental Toxicology
- Regulatory Toxicology
- Nanotherapeutics & Nanomaterial Toxicology
- Systems Toxicology & Health Risk Assessment

Recognitions

- Scientific & Industrial Research Organizations (SIROs)
- UP Pollution Control Board (Water & Air)
- Indian Factories Act (Drinking Water)
- Bureau of Indian Standards (Synthetic Detergents)
- Food Safety & Standards Authority of India (FSSAI)

Services Offered

- GLP certified for pre-clinical toxicity studies
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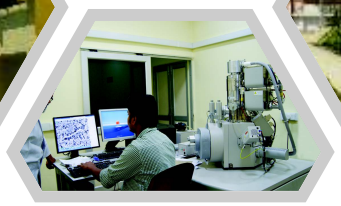
- Safety / toxicity evaluation of NCEs
- Water quality assessment and monitoring
- Analytical services
- Environmental monitoring and impact assessment
- Epidemiological studies
- Information on chemicals / products

Technologies Developed / Available

- Water Analysis Kit
- Mobile Laboratory Van for on spot water quality analysis
- Argemone Detection Kit for rapid screening of Argemone in mustard oil
- CD-Strip for detection of butter yellow, an adulterant in edible oils
- Arsenic Detection Kit



Director

CSIR-Indian Institute of Toxicology Research

विषविज्ञान भवन, 31-महात्मा गांधी मार्ग, पोस्ट बाक्स नं० 80, लखनऊ-226001, उ.प्र., भारत

VISHVIGYAN BHAWAN, 31-MAHATMA GANDHI MARG, POST BOX NO 80, LUCKNOW-226001, U.P., INDIA

Phone:+91-522-2627586, 2614118, 2628228 Fax:+91-522-2628227, 2611547

director@iitrindia.org www.iitrindia.org

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