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Editorial
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Importance of Exposure-Response Information to Optimal Dosing in Clinical Trialsa

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Editorial

Exposure-Response (E/R) generally refers to the relationship between dose and various measures of acute or integrated drug concentrations in plasma and other biological fluid (e.g., Cmax, Cmin, Css, AUC) on one hand, and direct measures of the pharmacologic effect of the drug on the other. Response includes a broad range of endpoints ranging from biomarkers to surrogate endpoints, to clinical endpoints related to either efficacy or safety.

Exposure-Response relationships have traditionally been employed to support the following applications during drug development

a) link animal and human findings

b) provide evidence that the hypothesized mechanism is affected by the drug (proof of concept)

c) provide evidence that the effect on the mechanism leads to a desired short-term clinical outcome (more proof of concept)

d) provide guidance for designing initial clinical endpoint trials that use a plausibly useful dose range

The concept of Exposure-Response took on a new role with the advent of FDAMA 1997, which stated in Section 115 that ``based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness''. This meant that instead of the conventional requirement of two adequate and well-controlled clinical trials to support a new drug application, the sponsor may rely on the results of a single adequate a well-controlled clinical trial combined with confirmatory evidence (primarily Exposure-Response data). Since the however, there have been no examples of drug applications that have seized upon this concept.

The utility of Exposure-Response has been limited for the most part to supporting evidence for approval of different doses, dosing regimens, or dosage forms, or use of a drug in different populations, when effectiveness is already well-established in other settings and the study demonstrates a pharmacokinetic-pharmacodynamic (PK/PD) relationship that is similar to, or different in an interpretable way from the established setting. The lack of examples involving the use of Exposure-Response data as confirmatory evidence may be commonly attributed to the lack of a complete understanding of the mechanism of action, which in turn undercuts the ability to rely on reasonably well-established biomarkers/surrogates in lieu of the clinical endpoint. Additionally, the design and analysis of studies intended to generate exposure-response data for use as confirmatory evidence is intricate involving randomization, modeling and simulations to account for placebo effect and a comprehensive prospective PK/PD sampling and analysis plan.

Applications of E/R Relationships

The choice of a starting dose and subsequent dose titration requires clinical judgment as to the relative importance of desirable and undesirable effects and the distance between the E/R profiles for efficacy and safety, respectively. When these curves are well separated, the selection of initial and maintenance doses becomes less critical since side effects may be less likely at an effective dose. Such characteristics are desirable for all drugs, but in particular for drugs used in diseases that require aggressive yet effective long-term interventions. For drugs whose benefit and risk profiles are in close proximity to each other (i.e., narrow therapeutic index drugs), an individual's doses and dose titration steps need to be carefully adjusted and monitored. Patient intrinsic and extrinsic factors (e.g. renal or hepatic function, drug-drug and food-drug interactions) may lead to elevated or reduced plasma concentrations and hence the need for dosing adjustment. An understanding of E/R relationship and the corresponding role of important patient factors is key to maintaining therapeutic benefit through optimal dosing.

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