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Making Sense of Biostatistics: Human Pharmacology Trials

By J. Rick Turner

Clinical trials can commence after an investigational drug has successfully completed its first set of nonclinical research studies. (A second set, involving more lengthy and considerably more expensive animal studies, is not usually started until after the drug moves into clinical trials.) Phase I clinical trials, also known as human pharmacology trials, typically involve 20 to 80 healthy adult participants. They are conducted in the clinical pharmacology units of residential or in-patient medical facilities with 24-hour supervision and extensive monitoring of the participants' health status.

From a statistical standpoint, two design features of human pharmacology studies are noteworthy. First, the number of participants in a given study is small. Second, a large number of measurements are made (and hence data collected) for each participant. These features have advantages and limitations. The primary advantage is that the extensive measurements allow the investigational drug's effects to be characterized relatively thoroughly. The primary limitation is that, since there are so few participants in the study, generalizations to the general population are more tenuous than for studies with more participants (Durham and Turner). This limitation is addressed if the drug progresses to Phase II and III trials.

Human pharmacology trials are designed to provide certain fundamental information, including:

- Evaluation and description of the safety and tolerability of the investigational drug in healthy study participants who do not have the medical condition of interest;
- Characterization of the drug's pharmacokinetic profile.

Safety and tolerability are evaluated by several means. Clinical laboratory tests include liver (hepatic) and kidney (renal) tests. Monitoring of vital signs, including heart rate, respiration rate, and blood pressure is carried out on a regular basis, typically several times a day. These measurements can be presented descriptively using means and standard deviations. Additionally, shift analyses that classify values at baseline and later time points as normal, low or high relative to a reference range can be conducted, and individual values that are considered clinically significant identified.

Although perhaps not as sensitive as other safety assessments, physical examinations can still be very helpful since a general examination may identify more pronounced responses to the drug, such as allergic reactions or edema (fluid retention). Data collected during a physical examination include the investigator's (subjective) assessment of whether a participant has normal or abnormal function for each body system examined; any determinations of abnormal function will lead to additional scrutiny. These data are typically summarized by tabulating the number and percentage of participants with each result.

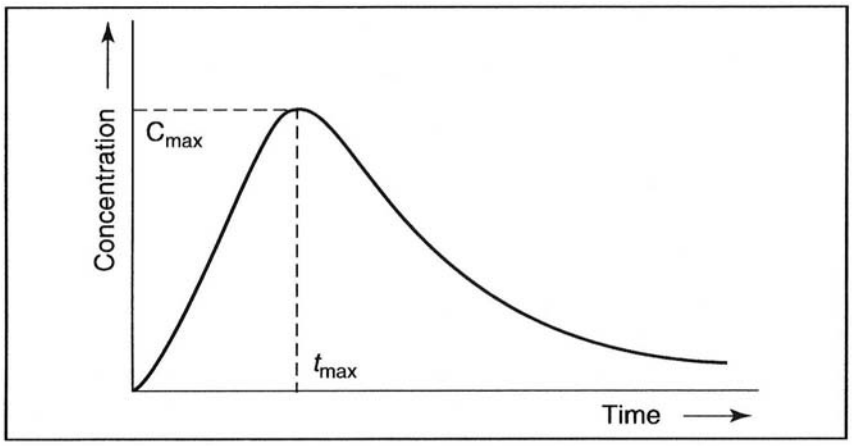
Adverse event data, both participant-reported and investigator-reported, are collected in a standardized manner using medical dictionaries such as the Medical Dictionary for Drug Regulatory Affairs (MedDRA) coding dictionary. Information collected includes the nature of the event itself, e.g., rash on left forearm, the date and time of onset, the outcome of the

event (resolved without sequelae, resolved with sequelae, ongoing), any treatments administered for the event, and whether or not the event was considered serious.

Pharmacokinetic effects are essentially "what the body does to the drug," while pharmacodynamic effects are essentially "what the drug does to the body." (Tozer and Roland provide a very good introduction to these topics.) The term pharmacodynamics is generally used to refer just to the desired effect of a drug, with the term toxicodynamics referring to undesired effects. However, strictly speaking, the term pharmacodynamics can be used for both type of effects. Human pharmacology trials have two primary interests. The first is evaluating the drug's pharmacokinetics, including a very careful evaluation of how well the drug reaches the bloodstream and how its concentration in the bloodstream changes over time. The second is evaluating undesired pharmacodynamic (toxicodynamic) effects, as reflected by adverse events and by clinical laboratory values, vital signs, and physical examination results of concern. The drug's desired pharmacodynamic effects are addressed in much more detail in Phase II and III trials, in which participants have the medical condition of concern.

The rest of this column discusses pharmacokinetics. Total systemic exposure and maximum systemic concentration are important pharmacokinetic measures that are relatively easy to obtain. They are commonly presented in study reports of human pharmacology trials. Total systemic exposure is typically measured by assessing the area under the drug concentration curve. The curve is also called the "concentration-time profile" since it makes explicit the importance of time in this evaluation. Figure 1 provides a stylistic representation of such a curve/profile. Drug concentration is shown at each time point following drug administration, defined as "time zero."

Figure 1: The drug concentration-time profile.



Using integral calculus, the area under the concentration-time profile can be estimated very accurately from time zero up to any time point. The value "area under the drug concentration curve across all time, from zero to infinity" is denoted as $AUC_{(0-\infty)}$. It is also possible to estimate the area under the curve from zero to any time point t, denoted as $AUC_{(0-t)}$. A commonly seen value in this context is the area under the curve from administration to 24 hours post-administration, represented as $AUC_{(0-24)}$. A second important measure is the maximum systemic concentration, denoted as C_{max}. This value is indicated in Figure 1. Analysis of these pharmacokinetic data is primarily descriptive. Measures like the mean and the standard deviation for $AUC_{(0-24)}$, C_{max}, and t_{max} are therefore commonly presented for each treatment group in study reports of these trials.

A range of doses and/or dosing intervals and methods of administration is typically investigated in human pharmacology trials in a sequential manner. For a given dose, and hence a given AUC and C_{max}, any degree of toxicity associated with it can be determined from the safety data collected: the less the toxicity, the safer the drug. These pharmacokinetic data are therefore used as a starting point to identify doses, dosage forms, and dosage regimens for the investigational drug that, should it progress successfully to Phase II trials, would allow a reasonable chance of evaluating the potential benefits and risks associated with its use in individuals with the medical condition of interest (Durham and Turner).

References

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Author

J. Rick Turner, PhD, PGCE, MICR, CSci is the Campbell University School of Pharmacy's Drug Safety Scholar. Contact him at 1.919.463.7869 or TurnerR@campbell.edu.