Dynamic Preclinical and Clinical Trials

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A close relative is dying. You are desperate to get to their side and they are 100 miles away. You race to your car and drive 100 miles north. Nope, that isn't the right destination. So you race back to the beginning and go 100 miles east….

You fly to Hong Kong and select expensive fabrics for a dozen suits. The tailor says he doesn't need to see you, he'll just make them up in the average adult male size….

You want to know the median lethal dose in mice. You dose 100 mice with 1 mg, 100 with 5 mg, 100 with 10 mg…and return the next day to count the bodies.

You are doing a first-time-in-man study. You write the entire protocol for 24 subjects. The first four get 1 mg then, before you know the analytical results, you give the next four subjects each 5 mg….

Wow! We have smart bombs and cruise missiles that follow a terrain map, adjusting to unexpected obstacles to home in on a target. Why not smart trials? Would you play the lottery if after each bet they told you the winning number was higher or lower than your last choice? Could you devise an optimal betting strategy?

Before the first human we usually know the kinetics and dynamics of the drug in mice, rats and a higher animal, often a primate. We've studied the pharmacology and toxicology of similar chemicals. We've examined *in vitro* metabolism of the molecule by human microsomal enzymes and association of it with human blood elements. Our experts in pharmacology, toxicology, kinetics and clinical trials can wisely develop a probability distribution around the maximum safe target concentration in plasma water, the maximum safe area under the curve of concentrations in plasma water, and a safe starting concentration target.

Of course you could use standard formulas to extrapolate from animal doses directly to the initial human dose, but this neglects all the kinetic data you have accumulated and is a crude shot in the dark.

To achieve your targets, the kinetic models you fit to animal data can be used to predict human kinetics. For each kinetic variable, examining the range of values for that variable in animals and human kinetics of related molecules, experts can estimate a probability distribution for that variable in humans. Then it is easy to relate the maximum concentration or area under the curve (AUC) to the dose.

The probability distributions on the variables represent your experts' best estimates of human kinetics. They are effective if only 10% of the time the actual value lies outside the tenth percentile on the distribution, or 10% of the time outside the 90th percentile.

To estimate the starting dose in the first human, it is easy to estimate the probability distribution of dose that would be expected to achieve the target concentration or AUC. The most standard technique is to use random numbers to select values from your probability distributions and examine the estimate from each such random selection. This technique is called Monte Carlo in homage to the French gamblers who began statistical thinking. There are many simple programs that automatically analyze a model and present a probability distribution of doses predicted to achieve the target concentration or AUC. Microsoft® Excel can do this easily with a tiny macro, as it has a good random number generator and can do all the calculations, storage of results and statistical analysis of them.

Now you have a probability distribution of the first human dose. Should you choose one millimole if that is the 10th percentile, or two mmol if that is the 50th, or four mmol if that is the 90th? The molecule, its toxicity, the subject, your limit of analytical sensitivity and other factors will determine your level of conservatism.

Could you get there just by inspecting animal no-effect doses? Sure, and you can drive north first. But if you believe your human will have different rates of metabolism and excretion or different blood element association, will you just adjust by a heuristic rule-of-thumb? Do all your scientists have the same thumb?

Now you have a model of human kinetics with probability distributions on each variable. You dose the first human. When should you sample the bodily fluids? Your kinetic model can be used to estimate optimal sampling points. They surely are not hourly. Each sample is expensive. Why not place them in time to maximally reduce the error in parameter estimation? That is simple mathematics. Kinetic models of drugs in humans have only a few variables, and mathematicians and engineers have been used to dynamic adjustment of rocket flight using dozens of variables sampled every millisecond! They can fly a rocket for thousands of miles to an impact within a few feet of the target! Tracing one injection in one subject seems like kindergarten to them.

The model also tells you which samples are the most critical to analyze first. During the day after the first dose you don't need to analyze every sample, just enough to have a rough idea of the model variables and if that model adequately describes the kinetics. Three or five properly-timed samples may be sufficient. These should be analyzed immediately, just as you are making frequent concurrent observations of dynamics.

In the U.S. and Europe many molecules are regarded as safe to give one-day's dosing to humans based on only acute toxicology—one dose toxicology—in two species. This would require a minimum amount of material. If the molecule is eliminated by routes that would apply in humans, chronic dosing is irrelevant. One dose in humans will not accumulate. So the critical animal questions are: How is the molecule eliminated, does it or a toxic metabolite concentrate in any critical tissue, and what are the kinetics and dynamics after the single dose? The best way to answer these questions is with a labeled dose.

It is also helpful to make the first human dose deuterated, as it improves the sensitivity and specificity of your assays and only a small amount need be synthesized. If from a few samples after one dose in one human you detect no unexpected metabolites and your presumptive kinetic model is reasonably accurate, then you can

proceed with your testing plan.

"One day's dosing" of the first human means the initial dose at 0 hour can be followed by a second dose, perhaps at the 23rd hour. A few blood samples after the first dose can be analyzed to estimate the kinetics. The model you have developed can be tweaked to calculate a second safe, larger dose.

What routes would you use for dosing? I believe the first dose should be given intravenously by a slow infusion. If there is a problem, you know exactly where the molecules are and you don't have an unknown reservoir in the gut. There are no "bioavailability" problems. There is no presystemic metabolism. If a clinical reaction begins to develop, you can immediately stop introduction of molecules. I would much rather have that first dose given over one hour intravenously than swallow a jigger of oral drug solution.

Never try to give the first small dose as a solid dosage form. Bioavailability is a major concern with tiny doses. Stability is an issue. Excipients are a problem. Avoid all the hassle by freeze-drying the material, thaw it at patientside, and give it intravenously or, if oral, down a small naso-gastric "feeding" tube. You can pass a small soft, flexible plastic catheter through the nose and have the patient cough out the end. Then attach a small mercury-filled finger cot and have the patient drink while you pull the tube partly out of the nose until the weight reaches the posterior pharynx and is washed into the esophagus. From there it is a rapid straight shot to the stomach. You can then inject drug or placebo down the tube without revealing its taste or timing of the administration. I've used longer versions of such tubes, reaching to the cecum, to locate small bowel bleeding and patients have tolerated them for many days, so a few hours is not a concern.

If the first dose is given intravenously, why not give the second larger dose orally (or intragastrically)? That would allow calculation of absolute bioavailability (from the liquid formulation). It would be safe, as the second larger dose would be based on the kinetics observed from the smaller first intravenous dose.

The data from this first human can be used to fine-tune your kinetic model. From the broad probability distributions on each variable you can now examine the actual values from one human and narrow the distributions considerably. From the dynamics observed in this first human, usually no effect, you can revise your target maximal plasma water concentrations and AUC. Using the tweaked kinetic model and your new targets, you can choose a conservative safe dose for the second human. The kinetics and dynamics observed in the second human can be used to calculate the dosing of the third human.

This strategy will more safely dose the first humans and will more efficiently explore the kinetics and dynamics than dosing by rote: "one potato, two potato, three potato, four…." It is more complex. You actually have to think about kinetics. You must develop a model. You need experts from several disciplines to cooperate in estimating probability distributions. Of course you would do that after the "live phase" when the data are all in. Why not do it before and make your expensive and risky human experiments safer and more efficient?

This does not require new math or new experts or new assays or new machines. It just requires an adjustment of attitude. Rather than saying, "Throw the data over the wall when it is perfect and has the Good Housekeeping seal attached and I'll get around to looking at it sometime," it is, "Let's work together to get it perfect the first time."

The protocol is sophisticated. Rather than "one potato…" it provides the estimated kinetic model and the probability distribution on the variables and the resultant calculation of the safe initial dose(s). It describes how the second dose in the first human will be calculated, to tweak the model with the observed values and target a given concentration and AUC. It describes how the second human will be dosed from the data derived from the first.

This strategy does require that analytical methods be applied in physical proximity to the patients and that the analyses be contemporary. It is like ECG monitoring. Would you rather have the ECG displayed patientside in the ICU, or wait a few days for the report to arrive from the heart station? Yes, it is easier to batch process all the samples at a remote site, but think of what we are trying to accomplish. Imagine how you will feel if all the doses you give throughout the first humans are too small or the first human's samples identify an unexpected toxic metabolite.

Thoughtful prediction and dynamic course correction from contemporaneous observations are powerful tools that are the hallmark of good care of the critically-ill patient, sailing and process control in manufacturing. Why not apply these routine quality control techniques to the first humans you dose with a new molecule?