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How Good are PK Models?

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Are you trying to figure out how to take advantage of Computer PK Models in drug development?

No one doubts the utility of computers for simple things like aerospace engineering and weather prediction, but pharmacokinetics is not rocket science. It's far more complex. Computers are indispensible for analyzing PK data, but how well can they do at actually predicting drug delivery and disposition?

Some people are in love with computer models, and you can't blame them. There is an undeniable appeal to setting up a complex series of interactions in microscopic bits of doped silicon, inputting a set of values and having an answer appear on a computer screen. But is the answer correct? Is it even reliable enough to be useful? This is where the controversy lies between model enthusiasts and skeptics.

First, to state the obvious: the computer is not the limitation. Computers can do pretty much anything you want them to, and in this day and age, they can do it quite quickly. But they do need to be told what to do, and that is where the limitation lies.
Figuring out where a rocket is going is largely an exercise in Newtonian physics. Many different masses and energies and gravitational fields need to be taken into account, but all of these are rather clearly defined. Biological processes such as absorption, distribution, metabolism and excretion are extraordinarily complex in comparison.

Factors affecting absorption from the GI tract may include stomach acid secretion, food and drink intake, gastric emptying rate, timing and level of pancreatic secretions, bile secretions, mucous thickness and viscosity, intestinal motility, pH, efflux pump expression, cellular damage, drug particle size, intrinsic dissolution, etc. Unlike the orientation of the sun, moon, and planets, each of these factors is highly variable not only from patient to patient but also from one minute to the next. A complete microscopic description of the system with all of its interdependent variables may or may not be too complex for a supercomputer, but it is certainly too complex for a human programmer.

By necessity, PK modeling software packages address these processes on a macroscopic, rather than a microscopic scale. Disintegration, dissolution, and transcellular diffusion are input as constants based on in vitro data and any in vivo feedback available. Biological systems are simplified and broken down into compartments, essentially

mathematical boxes among which differential equations can be expressed. It is not perfect, but it is the best we can reasonably do.

So, is it good enough?

The obvious answer is another question: good enough for what? A computer model might allow you to generate a plasma concentration curve from a chemical structure, but don't count on its being accurate. At the other extreme, data from a large scale PK study can be used to generate an accurate model, but it might not tell you anything the study results haven't already.

Where I have found PK modeling to be extremely useful is in identifying underlying mechanisms and using that understanding to focus experimental efforts. For example, we were recently working on a bioavailability enhancement project with a weak base drug that had a rather odd biphasic absorption profile in early clinical studies. After running through the standard list of PK parameters and still not matching the experimental profile, we tried altering the rate at which the drug precipitated from solution in the model and found that by optimizing this value we could match the shape of the PK profile quite exactly. Understanding that bioavailability of the drug was limited by its re-precipitation as it transited to higher pH regions of the GI tract and being able to estimate the rate at which this was occurring allowed us to design dosage forms to minimize this problem.

In many cases, we have utilized the complex PK models in such programs as Gastroplus® to assess whether formulation changes are likely to have a substantial impact on a desired outcome parameter, such as bioavailability. In other cases, we have been able to combine physicochemical characterization data with data from liver microsome, CaCo2, and animal pharmacokinetic studies to generate detailed models that allow for exceptionally accurate allometric scaling. Other programs I have found useful, independently or in conjunction with one another, are the industry standard WinNonlin® and a dissolution predictor I built in a standard spreadsheet program.

Those who would have supercomputers replace laboratories altogether will certainly need to wait, but for those of us with more limited expectations, computer modeling is an incredibly powerful tool to focus efforts, minimize risks and allow better informed decisions along the development pathway.

Are all *in silico* models accurate? The answer is a resounding no. But, all models are helpful if you know how to apply what you learn from them.

About PharmaDirections

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