

Modeling and Simulation as Tools to Improve Drug Development

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ABSTRACT

Healthcare remains a national crisis. Among the associated issues are the high cost of medications and the expenses of those patients whose disease can not be managed effectively with the currently available drugs. There is a strong focus on reducing the costs of medication and reducing the time required to develop and test medications for unmet medical needs. Computer based modeling and simulation can be used to reduce drug development costs and help evaluate new therapies. Population modeling techniques are used to evaluate the time course of disease in untreated and treated conditions and to provide additional insights into the therapeutic benefit a new drug may provide. These models are then used to simulate alternative dose and treatment strategies to reduce the number of regimens tested in clinical trials. This approach provides more rapid drug development at reduced cost. Some pharmaceutical companies and regulatory agencies are strong proponents of population modeling and simulation. There are many cases where such models have been used to improve the safety and efficacy of new drugs, and to reduce development times. However the application of modeling and simulation to drug development is still a relatively new approach and its implementation is not consistently applied across all drug development programs.

INTRODUCTION

The cost of healthcare has become sharply higher over the years. Part of the cost associated with medical treatment is the costs of the medicines themselves. Much of the pricing for medications is linked to the expenses undertaken by the pharmaceutical companies during development and evaluation of new drugs. Drug development includes non clinical trials to evaluate the toxicity and pharmacological activity of the drug in animal models as well as clinical trials designed to evaluate the safety and efficacy of the drugs in humans. Early clinical trials are conducted in small groups of healthy subjects or patients, with the numbers of patients increasing as the drug progresses through development. In late development, a single clinical trial for demonstrating safety and efficacy can be very expensive if large numbers of patients are needed and also if the duration of the study is several years. The number of patients required and the duration of the clinical trial varies by the disease being treated but a single trial can require up to 20,000 patients and treatment durations of 2 years is not uncommon. Modeling can provide a more powerful means of determining drug effect by increasing the

signal to noise ratio in a clinical trial, potentially reducing the numbers of patients required to detect a drug effect [1].

Pharmaceutical companies often have to test many different dose regimens before finding a regimen that works. However it should be understood that these studies are usually conducted early in the development process and therefore these dose regimens are tested in small numbers of patients and may not reflect the patient population in general. A particular problem is the drug that fails late in development due to unforeseen problems. Often a dose regimen that worked well in a small and fairly healthy patient population doesn't work well in a larger population of less healthy patients. In this situation, the development funds have largely been spent but there is no return for this expenditure. Consequently drug pricing has to pay for these failed development programs as well as the successful development of the new drug itself.

Once a drug makes it through the development and approval process, and it is on the market, the problems have not ended. "One in five prescription drugs must be relabeled or removed from the market as a result of practitioners "not getting the dose right" [2]. This means that for most drugs after 2 years on the market the accumulated data indicate that the recommended dose is either ineffective, or more commonly, the dose is too high, resulting in more serious side effects. The problem with doses being too high often occurs in "special patient populations", for example those patients who are obese, the elderly, or those who have kidney or liver failure. Consequently, the recommended dosing in the drug label has to be adjusted, restricting the patient population that can receive this drug. In extreme cases the drug may be withdrawn from the market completely.

There are still many diseases for which no medical treatment is available and there is an urgent need to develop these medications. Consequently, many drugs currently on the market are used in situations that are not specifically covered in the drug label or package insert. This is referred to as "off-label use" and often occurs when infants and children are treated using drugs that were approved for adults. The proper dosage is not known in these situations and therefore the amount used may not be optimal. Other concerns frequently aired are the needs for new medications for diseases that have become resistant to current therapies, or for diseases for which an effective treatment is still not available. Once such a drug is in development, it can take many years before it reaches the market due to the time required to conduct the necessary clinical trials and file a new drug application with the regulatory authorities. Even though the development time for drugs intended to treat unmet medical needs can be shortened, the time required to completely develop and analyze clinical trials is still lengthy. For patients in urgent need of such therapy, the time spent waiting before they can use the drug is too long.

The process of clinical development and approval is intended to determine the risk to benefit of any new drug prior to marketing. It is imperative to determine the dose that maximizes benefit and minimizes the risk of a patient having side effects. Aside from the primary problems with side effects, they can result in the secondary problem of poor patient compliance – the patient fails to take the drug in order to avoid the side effects and their disease continues untreated. For treatment of diseases such as high blood pressure, a disease that has no physical symptoms, patient compliance is often poor because the patient feels fine but the treatment causes problems. Yet according to the American Heart Association, the direct and indirect cost of untreated high blood pressure in 2008 was \$69.4 billion [3]. Clearly, a means of determining more appropriate dosing recommendations before the drug is approved and marketed would be a substantial benefit, to the patients, the pharmaceutical companies, and to public health.

However, there are ways to improve the development process that makes it more cost effective and gets new drugs to the public quickly and safely. Modeling and simulation are tools that can be used to help expedite the identification of an appropriate dose for drugs, even those drugs that have a narrow range of safe and effective exposure. Population based modeling methods are particularly useful to identify trends in the data, such as finding reasons for higher exposure in special populations and simulation can be used to test out various dose adjustments on a computer, thus reducing the number of dose regimens that are tested in patients. The information obtained from any clinical trial is based on the scientific signal obtained out of random noise. “Noise” in a clinical trial is any source of unexplained variability. The “signal” is the variability that is explained and predicted by the computerized model. Population modeling is a way of reducing the noise and making the signals easier to measure.

Population modeling looks for trends in the data. Consider a hypothetical example of a new drug being developed to control blood pressure – this drug has been tested in healthy volunteers and a dose of 100 units has been tentatively identified as being useful to lower blood pressure. However when the drug is tested in patients, the range of blood pressures resulting from the dose of 100 units is very wide – some patients blood pressure drops to dangerously low levels while other patients do not appear to have any improvement. The first key to understanding this variability in response is to understand that each patient may have different pharmacokinetics for the drug and finding the reasons for these differences. The other key to solving the problem is to know that the patients exhibit different pharmacodynamics for this drug and again identifying what factors may predict these different responses.

“Pharmacokinetics” or PK is what the body does to the drug – how the drug is absorbed after being swallowed, and how the body eliminates this drug. “Pharmacodynamics” or PD is what the drug does to the body – for example, how the body responds to the presence of drug by changes in blood pressure.

PD can also include the probability of experiencing a side effect at a given dose of drug. Looking at the first component, PK, we can see that there might be many causes for differences between patients. For example, most drugs are removed from the body through the liver or kidneys – but both organs may not function as efficiently in older patients as compared to younger healthier volunteers. Therefore one might expect that at a dose of 100 units, older patients may have drug in their bodies much longer than do younger patients. Over several weeks or months of dosing, the excess drug will build up or accumulate, and with more drugs in the body, the blood pressure could drop to very low values. A lower dose might therefore be more appropriate in older patients. One also has to consider that most patients are taking more than one drug at a time, and some drugs can either increase the rate of drug loss from the body, or dramatically slow it. In the former case, patients taking 100 units of the new drug might not have enough drug in their body to have any effect at all.

With regards to PD, there may be other factors that affect how well the drug works. Considering again our hypothetical drug, let's assume it only works well when the high blood pressure was caused by genetic factors. In our hypothetical patient trial however, some of these patients may exhibit higher blood pressure because they were also smokers. In these patients, the drug would not be expected to have the same effect as in non-smokers, even if they all have the “right” amount of drug in their bodies.

Both the PK and the PD of drugs can be described using mathematical and statistical functions. In many cases, the distribution of PK and PD behavior resembles a bell curve or normal distribution – most patients are fairly consistent but some patients are going to form the “tails” of the distributions with their PK and PD behavior being substantially different (higher or lower) than the typical patient. If we envision a typical patient who is perhaps 50 years old, reasonably healthy and not taking other medications, the PK for this patient would be at the center of the distribution. The tails of the distribution would consist of patients in poor health, patients who are much younger (say 18 years old or even younger), or patients who are taking other medications. The differences in the PK of these patients from our typical patient gives us a means of determining what the dose adjustments should be to ensure all patients have the same exposure to the drug. This is the essence of population PK/PD modeling. Functions are tested to see how well they describe data collected in clinical trials and then trends are examined to determine how patient factors such as demography, disease status, progression, and co-medications, might affect patient exposure to the drug and their subsequent response. Once a model is developed it undergoes rigorous testing to ensure that the predictions made from this model are reasonable. For example, one might use this model to simulate the PK and PD of a new study and then compare the results from the actual study to the simulated results. After testing, PK and PD models can be used to simulate different dose regimens and treatment options. These models may also be altered or improved as data from larger trials become available. This is part of the “learn and confirm”

cycle where information from each phase of drug development is modeled, and the model is then used to help design the next study, making that study more informative and robust.

Modeling and simulation can also play an important role in evaluation of “placebo response”, a phenomenon where patients receiving placebo in a clinical trial improve even without taking the drug. In some cases, the improvement is substantial, making it difficult to tell if the drug had any benefit at all. Understanding and modeling this placebo response can help distinguish between drug effect and the placebo effect. In some therapeutic indications, such as Alzheimer’s disease or depression, the placebo effect can be marked but is often difficult to determine. If the study examining a new drug is not long enough, the placebo effect may interfere with the ability to see the longer lasting benefit of the new drug. Using modeling and simulation to try out various study designs is a good way of ensuring that clinical trials are able to see a drug effect if one exists.

Modeling the probability of a desirable response and the probability of experiencing side effects at a given dose helps justify the risk to benefit of a patient taking a drug. More importantly, this modeling can show the relative risks and benefits of increasing or decreasing the dose in certain patients. The overall impact is to provide a better and more rational dose for patients that improves their response and reduces the side effects. A related benefit is that patients may be more compliant – living longer and healthier lives.

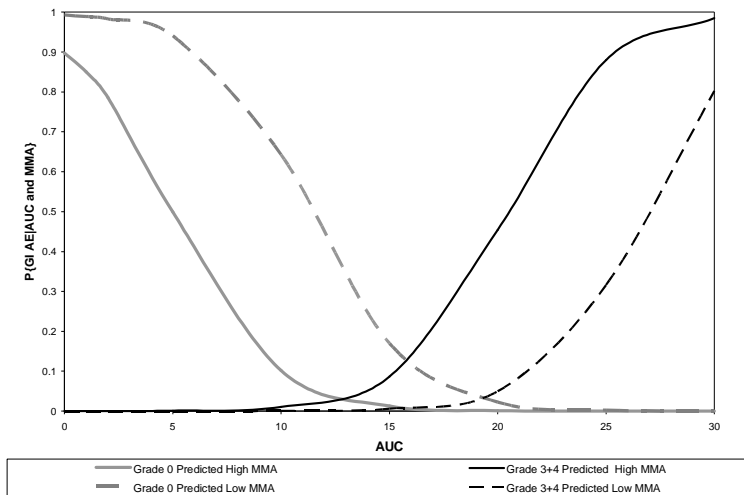
By using modeling and simulation throughout drug development, appropriate dose regimens can be identified early and dose adjustments for special populations can be inferred with fewer studies. Furthermore, fewer ineffective or toxic doses will be tested in special populations as the dose adjustments tested will be based on modeled and simulated trends in the data obtained from earlier studies rather than relying on regimens based on those used for related drugs. Population PK/PD analysis allows for more efficient use of clinical trial results for decision making in several ways: 1) it can provide better insights as to how patients tolerate and respond to a new drug; 2) it can shorten development time via the conduct of informative trials; and 3) it can help identify drug candidates that are unlikely to meet target clinical therapeutic goals early in development. The use of these methods allows more rapid identification of appropriate dose regimens so fewer clinical trials are needed. The ability to make timely and well informed development decisions translates to major cost savings.

EXAMPLES OF MODELING TO IMPROVE DOSING

An encouraging example of the benefits of modeling and simulation is the drug pralatrexate which is being developed for treatment of lymphoma [4]. Pralatrexate is an anticancer agent designed to have a higher affinity for cancer specific receptors than other drugs in its class. In the first study, the patients initially enrolled presented with an unacceptable number of episodes of GI toxicity (mucositis), and the study was temporarily halted. Preliminary

population pharmacokinetic and pharmacodynamic evaluations suggested that pralatrexate exposure could be controlled with weight or body size based dosing, and that pretreatment of patients with folic acid and vitamin B12 could reduce the incidence of GI toxicity, allowing the patients to be more effectively treated. The study was re-opened with the new dosing recommendations, and patients were successfully treated. Individualized dosing combined with vitamin pretreatment was successful in controlling gastrointestinal toxicity. Figure 1 below shows the probability curves for patients having no GI toxicity (gray lines) and patients having Grade 3 (moderate) GI toxicity (black lines). The effect of adding folic acid and vitamin B12 treatment shifts these curves so that patients receiving pralatrexate with the vitamin pretreatment have substantially lower probability of GI toxicity than patients without pretreatment at the same exposures. This finding allows patients to be dosed safely at higher doses, improving the likelihood of beneficial response and reducing toxicity.

Figure 1 Probability of Experiencing Gastrointestinal Toxicity given PDX Exposure and Vitamin B12 and Folate Status (MMA)



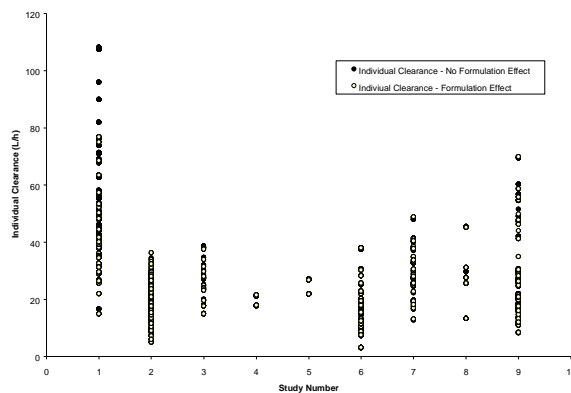
The application of model based evaluation was an important component in dose selection for this drug, and has facilitated its further development as an efficacious antineoplastic agent.

A second example of a population modeling evaluation was for topotecan (Hycamtin) [5]. This agent is administered to patients with ovarian and small cell lung cancer who have failed prior therapy but topotecan has produced Grade 4 (severe) neutropenia when used. The drug label already has dosing recommendations for body sized based dosing and makes recommendations for dose reductions for patients with moderate renal function impairment (package insert). For subjects with moderate renal impairment the dose is cut

in half. There are insufficient data to make dose recommendations for patients with severe renal impairment.

However a retrospective evaluation of the pharmacokinetics of topotecan showed that due to formulation changes, the exposure to drug in the early dose ranging studies (which identified the dose that was used in later trials and in the drug label) was lower than expected. The later studies had a more stable formulation that delivered higher exposure and thus produced more toxicity. In Figure 2, a plot of apparent clearance by study shows the clearance of topotecan appeared consistently higher than in later studies.

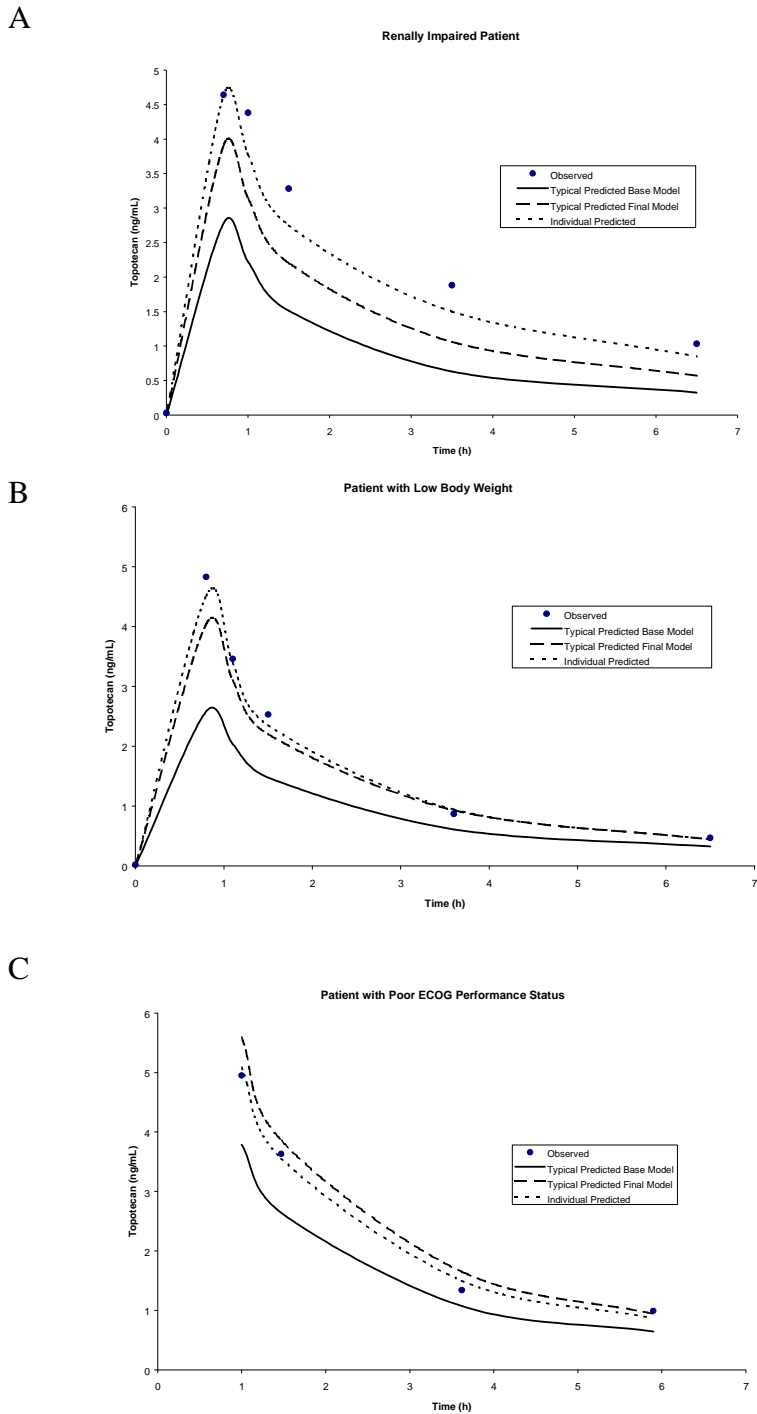
Figure 2 Effect of Study on Relative Topotecan Exposure



However part of the ability to safely administer a drug is dependent on how well a physician can estimate what the patients' exposure will be before they actually receive the drug. The physician should be able to determine a dose that will provide an exposure that is consistent with other patients. Factors such as renal impairment, age and obesity can cause the exposures to be substantially higher or lower than expected, potentially causing toxicity or loss of efficacy. In the case of topotecan, the effect of renal impairment and body size were identified previously, but renal function is not a discrete, categorical variable. Rather, it changes smoothly from good renal function (with creatinine clearance values of 80 to 100 mL/min) to mild impairment (50 to 80 mL/min) to moderate (30 to 50 mL/min) to severe (10 to 30 mL/min). Therefore accounting for the actual value for renal function greatly improves the ability to determine in advance the topotecan exposure a patient is likely to experience. In Figure 3 below; panel A shows the improvements in the agreement between this prediction when important patient factors are not accounted for (solid line), when they are accounted for (heavy dashed line), and the observed data (circles). The light dashed line is what is called an "individual prediction" and this would be based on the actual observed data. In population modeling, one goal is often the ability to help a physician determine what the exposure is likely to be before the patient receives drug. The improvement in this ability is seen as the heavy dashed line that is much

closer to the observed data when these important factors (renal function (Panel A), weight (Panel B) and performance status (Panel C)) are accounted for.

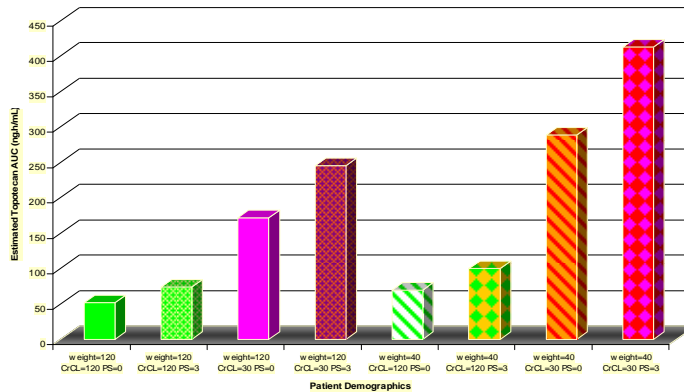
Figure 3 Ability of a Pharmacokinetic Model to Predict Individual Exposure When Patient Characteristics Are Identified and Accounted For



Given these covariates then, the range of exposures for patients receiving the same dose but having different combinations of patient factors is very large. In Figure 4, the same dose administered to a patient with good renal function,

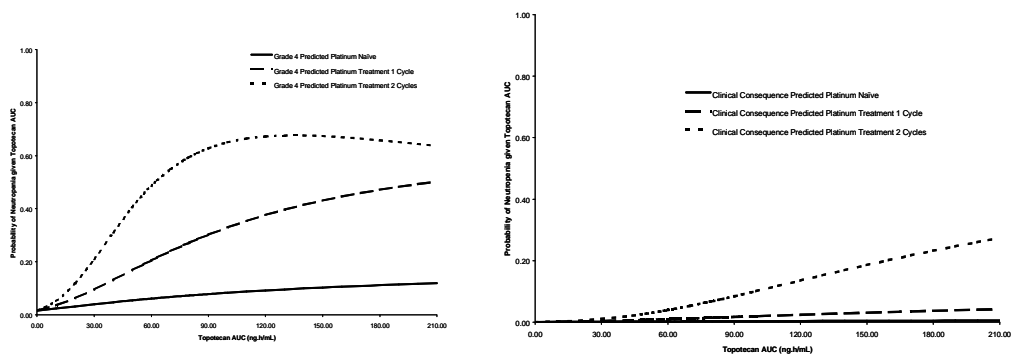
normal weight and good performance status is about 50. However the same dose given to a patient with poor renal function, low body weight and poor performance status produces an exposure of close to 400.

Figure 4 **Expected Levels of Topotecan Exposure in Patients with Different Characteristics Given the Same Dose**



So in order to maximize efficacy and minimize the probability of adverse events, the dose must be adjusted to provide a uniform exposure for each patient. When the relationship between topotecan exposure and the probability of severe neutropenia was evaluated, the curves in Figure 5 were produced. In this relationship, it became possible to see that prior exposure to platinum based chemotherapy increased the probability of neutropenia at all levels of topotecan exposure (dashed lines) as compared to naïve patients (solid lines). In order to fully understand the clinical impact of this finding, Grade 4 neutropenia that did not result in infection, hospitalization etc (left panel) was separated from Grade 4 neutropenia that did result in infection, hospitalization (right panel).

Figure 5 Probability of Severe Neutropenia Given Topotecan Exposure and Prior Treatment with Platinum Based Chemotherapeutic Agents



Developing these relationships allows physicians to gauge the risk of exposing a patient to different doses of topotecan, making it easier to treat patients effectively. In Figure 5 it's clear that platinum naïve patients can tolerate higher doses of topotecan than patients that have undergone extensive chemotherapy with platinum based agents such as cisplatin.

CONCLUSIONS

Population modeling is a useful tool that can improve the dose selection and facilitate dose adjustment at any stage of drug development. There are numerous other examples of applications of this tool, but at present not all drug development programs utilize modeling and simulation. Some regulatory agencies are strongly supportive of this application, further indicating that quantitative models allow learning from prior experience and that employing these models to plan future development is a potentially powerful solution to improve pharmaceutical company productivity [6].

DISCLOSURE

Projections Research, Inc. is a scientific consulting firm that provides expertise in clinical pharmacology to the pharmaceutical industry. The company utilizes Population PK/PD in a unique corporate structure and a team composed of highly skilled scientists from around the world. The company makes use of innovative modeling and simulation applications to advance client understanding of both new and marketed drugs and the diseases these drugs are used to treat. The Projections Research, Inc. client list includes most of the major pharmaceutical and many smaller companies.

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