3D PHARM CHANGE

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WHAT IS THE RIGHT DOSE FOR PATIENTS: AN INTRODUCTION FOR LAYMEN

In my role as a consultant and in conversations with individuals who have limited experience in clinical drug development, I often find that there is some confusion between the terms "dose" and "exposure" (the plasma or local concentration of a drug). While these terms are related, they refer to distinct concepts, and understanding the difference is crucial in drug development. Determining the correct relationship between drug concentration (exposure) and its therapeutic response is a fundamental part of clinical drug development before a drug can be approved for use.

The goal of this blog is to provide an accessible introduction to these concepts, especially for those starting to become involved in clinical drug development. Though the topic is complex, I will keep the explanation high-level for ease of understanding.

The focus of this blog is on small molecules and antibodies with an exposure in plasma. These form the majority of medicines that are available. For advanced therapeutic medicinal products (ATMPs) like gene and cell therapy, the reference to exposure is to be addressed differently (and more complex), and might be subject of a future blog.

Dose versus Exposure

Overview of the Topic

When we think about taking medication, we are all familiar with the term "dose." The dosage instructions — typically found on the packaging or in the package insert — provide guidance on how much of the drug should be taken. For example, it might say "100 mg, three times daily." This is the amount of the drug the patient is instructed to take. However, the dose itself is just the quantity of the drug consumed by the patient, not the amount of the drug that actually reaches the bloodstream.

On the other hand, "exposure" refers to the concentration of the drug in the plasma or other body fluids. fter the drug is ingested, the body absorbs it, and it reaches the bloodstream.

The amount that actually circulates in the blood (the plasma concentration) is what influences the drug's therapeutic effects. If the plasma concentration is too low, the drug may not be effective; if it's too high, it could cause unwanted side effects. The challenge in clinical drug development is finding the "sweet spot" — the right exposure that will result in the desired therapeutic effect without causing harm.

While it would be ideal for a single dose to work for everyone, different patients may absorb and respond to the drug differently. The dose a person receives will not necessarily lead to the same plasma concentration in every individual. Therefore, understanding the factors that influence this variability is essential in drug development.

Variability in Exposure

When a drug is taken orally, it must be absorbed in the gastrointestinal tract, distributed throughout the body, metabolized (or not) in the liver and eventually excreted. Many factors can influence how much drug is available in the plasma at any given time. For example, absorption can be affected by the stomach's pH, that may change due to whether the patient took the drug with or without food, Once the drug enters the blood, it passes through the liver where the drug may be metabolized. This can lower plasma concentrations, but even if the drug is not metabolized, its distribution to other tissues and organs, particularly fat, will influence plasma levels. Additionally, many drugs bind to plasma proteins, and this binding can be affected by the presence of other drugs that also bind and thus compete for the same proteins. This can increase the amount of free drug in the plasma, potentially increasing the drug's effect because only free/unbound drug can exert it's action. Finally, the route of elimination (kidneys or liver) plays a role. For drugs eliminated through the kidneys, renal function is critical, and any impairment — which tends to increase with age — can significantly raise plasma concentrations. In such cases, the dose may need to be adjusted to avoid toxicity.

Luckily, more and more information is available and many of the sources of variability in plasma exposure can and are to be investigated during clinical drug development. For example, when the drug is taken with or without food can have a large impact on how much is being absorbed. So, already in the very first clinical study the "food effect" is being assessed. Another example is the impact drugs can have on the metabolism and thus the plasma exposure of other drugs taken at the same time. First in vitro assessments are conducted to investigate how the drug is being absorbed, if certain transporters are involved, to what plasma proteins it binds, how it is metabolized and how it is eliminated. This information is important to determine what mechanisms are involved, because when known, this information can be used to predict and investigate potential interactions between drugs. For example, if a drug is being metabolized by the commonly involved enzyme CYP3A4, a drug taken at the same time inhibiting CYP3A4 will result in reduced metabolism and thus higher plasma concentrations of the test drug. In parallel, it will also be investigated if the drug itself can have an impact on the plasma exposure of other drugs, for example if the test drug does inhibit CYP3A4. If so, other drugs being metabolized by CYP3A4 are likely to have increased plasma concentrations and may need to be excluded or may require a dose adjustment (lowering of the dose).

Given all these variables, two patients receiving the same dose, are likely having (very) different plasma concentrations. When the difference is large, for example 10 fold, it is easy to imagine that the patient with the high concentrations is likely to respond much stronger than the patient receiving the same dose but with a 10-fold lower concentration.

In this case, based on dose one would have expected the same response because the dose is the same but as outlined above the exposure following the dose administration is variable and driving the response. Therefore, it is critical to collect blood samples to determine plasma concentrations of the drug. In the very early studies of clinical drug development, relatively frequent samples are taken following a single or multiple dose of the drug. Based on the samples a plasma concentration profile over time can be constructed and a so-called pharmacokinetic model can be developed. When this model is available, it is possible to predict in individual patients, based on only a few samples per patient what the plasma concentration profile over time will be. Still, and very important that these few blood samples are collected because in these larger studies the variability between patients is larger and therefore, it is even more important to understand the plasma exposure in the individual patients to link it to the clinical responses in the individual patients.

Variability in Response

Even when patients have similar plasma concentrations and are treated for the same condition — say, rheumatoid arthritis — they often respond differently. Some may experience the desired clinical effects, while others may see little to no benefit.

There are several factors contributing to this variability. For example, one patient may have a flare of the disease with increased inflammation, whereas another patient may have a flare of the disease but a lower level of inflammation. When both patients receive the same dose of an anti-inflammatory drug, it is likely that the patient with the prominent inflammation will respond more clearly than the other patient.

Before potential drugs are tested in humans, researchers first need to identify and "validate" a disease target (for example showing that binding to a given receptor may influence a mechanism that is involved in the disease). Only after this has been demonstrated, candidate drugs will be further developed and tested. In non-clinical trials, drugs are evaluated in disease models in animals, and once they meet specific criteria, they move into clinical trials.

These clinical trials are often conducted in as large and as broad as possible target disease populations or indications, like “chronic neuropathic pain”. The assumption is that patients with the same diagnosis have the same mechanisms leading to their disease.

In clinical trials, we often face the disappointment of seeing that only a (small) subset of patients responds to treatment, while others show no significant effect. This discrepancy is especially common in chronic diseases, where multiple disease mechanisms can be at play, and these mechanisms may vary in activity over time. A potential explanation for this observation is that the closer the match between the drug's mechanism of action (MoA) and the patient's dominant disease mechanism (MoD), the more likely the patient will experience a clinically relevant response. To use the example of chronic neuropathic pain, the available drugs at best have (some) effect in about 30% of the patients. There are now treatment algorithms developed based on sensory testing (skin) to select the drug treatment with the best chance of success in that patient. Another example can be found in Parkinson’s disease. Patients with a GBA1-mutation are selected for studies targeting a specific underlying mechanism of disease (GSL mediated lysosomal dysfunction). In conclusion, when defining the selection criteria it is important to carefully consider the mechanism of action of the drug and what patients are likely to respond to avoid that the population is too broad resulting in a large percentage of patients with only a small or no clinically relevant response.

These are examples of mechanism based approaches to treat patients rather than treat them based on a general indication. With this in mind one might perhaps deal with negative P3-studies differently. These studies failed because the mean group effect on the primary clinical endpoint did, apparently, not differ statistically significantly from that of the mean group effect of the placebo group. Development of these drugs is often stopped. For those patients that did not respond with a clinically relevant response this makes sense. However, in most cases there is a (small) subpopulation of patients that did show a clinically relevant response not explained by a placebo response. For those patients, it would be worth investigating what factors make them respond. When these factors can be identified, from a patient’s perspective it would be relevant to have this treatment available for those patients that have these factors in common.

The Role of Clinical Pharmacology

The primary role of clinical pharmacology is to investigate the exposure–response relationship and determine what the efficacious exposure range is. This exposure range should be targeted and using modeling and simulation doses will be predicted to result in this target exposure.
It should also investigate the impact of factors (sources of variability) mentioned above that have a potential impact on the exposure and/or on the response. This information and related instructions like dose adjustment will be included in the label of the drug and in the package insert.
Important to note that in order to do this properly, adequate data needs to be collected. For exposure this includes plasma concentrations to allow for a robust assessment/prediction of individual plasma concentration versus time profiles. For response, biomarkers but also clinical endpoints need to be collected in a way that a meaningful exposure- response analysis can be conducted. Lacking information about exposure will make it impossible to determine the exposure-response relationship.

Conclusion

The primary role of clinical pharmacology is to investigate the exposure–response relationship and determine what the efficacious exposure range is. This exposure range should be targeted and using modeling and simulation doses will be predicted to result in this target exposure. It should also investigate the impact of factors (sources of variability) mentioned above that have a potential impact on the exposure and/or on the response. This information and related instructions like dose adjustment will be included in the label of the drug and in the package insert. Important to note that in order to do this properly, adequate data needs to be collected. For exposure this includes plasma concentrations to allow for a robust assessment/prediction of individual plasma concentration versus time profiles. For response, biomarkers but also clinical endpoints need to be collected in a way that a meaningful exposure- response analysis can be conducted. Lacking information about exposure will make it impossible to determine the exposure-response relationship.

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