FORMULATION OF POPULATION PHARMACOKINETIC MODELS OF ANTI-CANCER AGENTS

by

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FORMULATION OF POPULATION PHARMACOKINETIC MODELS OF ANTI-CANCER AGENTS

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Abstract

The primary objective of the study is to assemble population pharmacokinetic models from the cancer pharmacokinetics literature for different types of anti-cancer drugs and to formulate them in ways suitable for input into cancer simulation programs.

To fulfill the objectives, a step-based approach is adopted:

1) To catalogue the types of pharmacokinetic models through general review articles and books
2) To develop a search strategy for defining a body of research literature related to cancer pharmacokinetics in clinical trials for a limited set of drugs (Taxol, Platinum compounds. Fluoropyrimidine and Topoisomerase inhibitors)
3) To collect pharmacokinetic articles according to defined search criteria
4) To gather information from the collected PK articles
5) To synthesize the information separately for each drug, using a questionnaire instrument and present them in template form for each class of antineoplastic agent.
6) To formulate population pharmacokinetic models for each anti-cancer drug, from the constituent submodels for components of the overall model.

This work will promote public health, specifically in support of the development of anti-cancer drug regimens for cancer patients, by providing standardized information about pharmacokinetics for input into simulations.

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1. INTRODUCTION

An objective of clinical studies is to assess whether a drug candidate will be effective in the treatment of disease or condition and benefit/risk assessment with pre-existing drugs for treatment. Pharmacokinetic information collected during clinical trials helps physicians and pharmacists to use the drug to the best advantage for potential patients, thereby maximizing the benefit of the drug and minimizing the risk to the patient. The benefit would be immense if we could quantitate and predict the dose-concentration-effect relationship with possible variations in the subpopulations. We have the choice of altering the dose and/or dosage intervals to enhance the chance of successful trial. Hence choosing the right dose and dosage interval is the major advantage of incorporating pharmacokinetics into the decision-making process for clinical drug development. In addition to this, the recent trend is in identifying sources of variability in pharmacokinetic parameters to determine the right dosage regimen for certain patient subpopulations or dose individualization, especially drugs with narrow therapeutic index. Thus the major contribution of pharmacokinetics is dosage regimen selection and adjustment for individual patients.

Application of pharmacokinetics from drug development perspective

Drug development relies significantly on acquiring knowledge of pharmacokinetics for a new drug entity. This is based on the hypothesis that the clinical effect takes place with a particular plasma concentration for a specific time period to reach the target site. Thus selecting the right dosage regimen takes place in stages Phase I – III.

Phase I

The purpose of phase I is to determine the safety of the drug candidate. These trials rely on preclinical information and aims at safety assessment, determination of maximum tolerated dose and whether the drug has desirable pharmacokinetic properties.

Phase II

After safety assessment and assuming the safety of the drug is established in phase I, the drug candidate will proceed to phase II.

> "Phase II studies are sometimes categorized as phase IIa or phase IIb depending on their goals:
>
> To prove the drug "works" in patients (phase IIa)
>
> To determine the best dose, dose range, titration scheme, and dose interval (phase IIb) [1]".

Phase III

Phase III studies are conducted on larger patient population compared to phase II to provide statistical power to reject the null hypothesis of no treatment effect. If treatment is proved efficacious, it is based on the assumption that randomization has removed the bias in the form of confounding factors. The results of these pivotal trials are the primary factor in proving potential drug candidate to be approved by the Food and Drug Administration (FDA) and move on to the marketing phase. The focus shifts to characterizing the remaining unknown sources of pharmacokinetic variability to identify subpopulation of patients who may have special risks or require dosage regimen adjustments. This is achieved by population pharmacokinetics or by initiation of small, focused pharmacokinetic studies in special populations.

2. BACKGROUND AND LITERATURE REVIEW

2.1. Pharmacokinetics

Pharmacokinetic processes are classified as absorption, distribution, metabolism and excretion (ADME). Each pharmacokinetic processes comprises of two components: 1. Kinetic component and 2.Extent component

Kinetic component

Kinetic component refers to the rate of movement or how fast the process occurs over time[1]. The basic pharmacokinetics issue about a drug disposition is whether it undergoes linear or nonlinear pharmacokinetics.

Linear pharmacokinetics is defined from the differential equations that express the change in the amount or concentration of drug over time[1].

$$\frac{dC}{dt} = -k_{el} \times C$$

k_{el} is the first-order rate constant for elimination out of the body. In the above equation, linear refers to the fact that the rate is directly proportional to concentration. Nonlinear applies to rate equations in which the rate is no longer linearly related to concentration. In pharmacokinetics this often applies to drugs for which metabolic pathways or plasma protein binding become saturated at concentrations usually within the therapeutic range[1].

Nonlinearity scenarios

Area under the curve (AUC) is a parameter which gives an indication of systemic exposure and if there is disproportionate increase in AUC with dose escalation is an indication of nonlinear pharmacokinetics. Nonlinearity can be found using the plot AUC

vs. dose and AUC gets affected, perhaps by decrease/increase in clearance or decrease/increase in bioavailability or both.

- Nonlinearity can occur due to one of the following reasons:
- Saturation of metabolic pathway
- Saturation of plasma binding site
- Dose dependency
- Time dependency
- Affinity to the same binding site by concomitant drugs
- Drug-drug interaction

Extent component

The extent component refers to the amount of drug or fraction of the dose that is absorbed, distributed, metabolized or excreted[1] and described by pharmacokinetic processes.

Pharmacokinetic processes

Absorption

Absorption is defined as the net transfer of drug from the site of absorption into the circulating fluids of the body[1].

Oral absorption takes place via gastrointestinal membrane and hepatoportal system into the systemic circulation. Drug may get metabolized before it reaches systemic circulation and this effect is known as first-pass effect or pre-systemic metabolism.

Bioavailability is a measure of the rate and extent of absorption. C_{max}, t_{max} and Area Under the Curve (AUC) are the primary measurements used to determine

bioavailability from oral concentration-time curves. Mathematically, it can be represented as a ratio of oral AUC and intravenous AUC which is known as absolute bioavailability and calculation of the ratio for AUC generic and AUC reference products is referred to as relative bioavailability.

Two products are said to be Bioequivalent if there is no statistical difference exist among C_{max}, t_{max} and AUC for the generic and reference products. Relative bioavailability is used in determining bioequivalence.

Distribution

Distribution is defined as the net transfer of drug from the circulating fluids of the body to various tissues and organs. The volume of distribution is a measure of physiological volume in which the drug is contained[1].

$$amount = V_d \times C$$

V_d is referred to as proportionality constant between amount and concentration. Binding properties, whether drug undergoes saturable distribution, if it undergoes saturable distribution, under what dose range does it occur, what are the covariates affecting the distribution characteristics might be few interesting questions which might help in understanding the distribution portion of the disposition of the drug.

Elimination (Metabolism+Excretion)

Clearance is defined as the milliliters of blood cleared of drug per minute[1].

$$Cl_R = \frac{\frac{\Delta X_u}{\Delta t}}{C_{tmid}}$$

$\frac{\Delta X_u}{\Delta t}$ is the change concentration of drug in urine over a specified time interval.

C_{tmid} is the concentration of drug in plasma over the same specified time interval.

$$Cl = Cl_R + Cl_M$$

Cl_R and Cl_M represent renal and all non-saturated metabolism in the body.

What covariates explain the inter-individual variability? Does the drug undergo saturable elimination? How concomitant administration of drugs does affects the clearance?

Metabolism

Metabolism is the bioconversion of drug to another chemical form or metabolite, mostly by endogeneous enzyme systems involving phase I reactions, such as oxidation (often by cytochrome P-450 system), reduction, hydrolysis or dealkylation or by phase II reactions such as acetylation, sulfation or glucurodination[1].

Possible questions in this section are What are the main metabolites of the drug and what is the enzyme involved in the metabolism, is inter-individual variability present and to what extent it affects the metabolism characteristics.

Excretion

Excretion is the removal of drug from the body primarily via urine and occasionally via faeces, bile, sweat, or exhaled air[1].

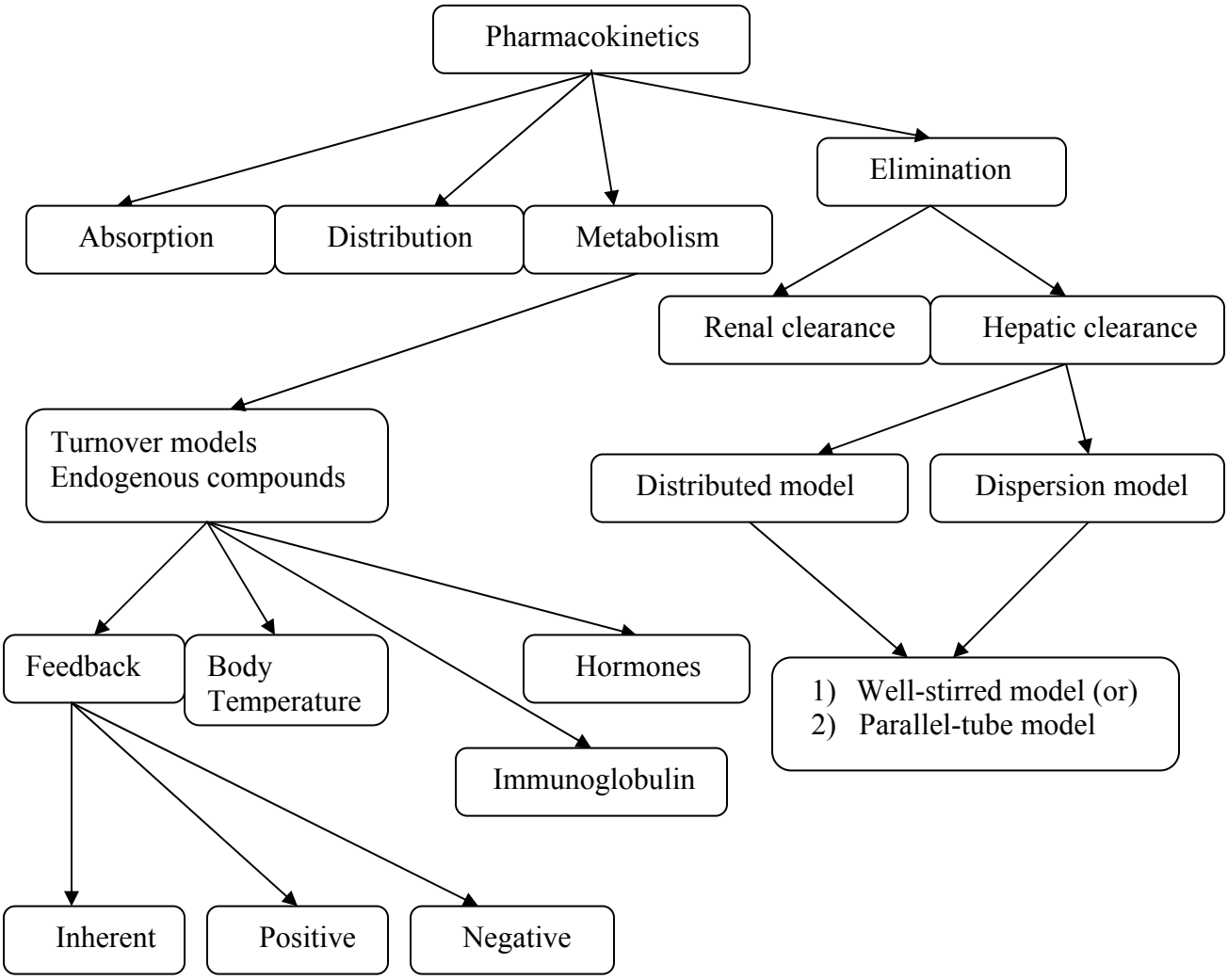

Figure 1. Classification of Pharmacokinetics

Pharmacokinetic models

Empirical based models though simple but are outdated and doesn't give resourceful pharmacokinetic information. On the other hand, physiologically based pharmacokinetic models are complex, difficult to comprehend but highly useful in

understanding the pharmacokinetic processes at tissue level. All the articles discussed in this study are related to compartmental models. These models are discussed based upon whether the pharmacokinetics undergoes one, two or three compartment model or based on a particular mechanism with the distribution and elimination characteristics of the central compartment. Drugs in circulating fluids and rapidly perfused tissues are assigned to the central compartment, whereas drugs in fluids of distribution and poorly perfused tissues are assigned to peripheral compartment. Occasionally, the kinetics of the drug may follow a three-compartment model for which the two peripheral compartments represent shallow and deep compartments connected to the central compartment. The process in which the drug is transferred from one compartment to another compartment is determined by first order or zero order rate constants.

In addition to blood flow and blood volume, partitioning and binding are also determinants of drug disposition. Partitioning, a rapid phenomenon, is responsible for drug reaching a rapid equilibrium with all tissues in a compartment. The concentration at equilibrium is in part due to hydrophilic/lipophillic properties of the structure of the drug. Drugs are also capable of binding to plasma proteins, which can reduce or slow distribution to tissues. Partitioning, tissue and plasma protein binding depend not only on tissues but also on drug properties[1].

2.2. Pharmacokinetic Models

Approaches to modeling pharmacokinetic data

There are three basic approaches in modeling pharmacokinetic data: traditional compartmental models or classical models, non-compartmental models, and

physiologically based models. Models with common features can be linear or non-linear, time-variant or time-invariant, deterministic or stochastic.

Objectives for analysis of pharmacokinetic data:

1) To summarize the kinetics of the drug
2) To quantify the kinetic processes of the drug
3) To explain the pharmacokinetics and to make reasonable pharmacokinetic predictions

Models with common features

Linear model

A model is said to be linear if the parameter values are independent of drug dose or input function.

Non-linear model

Non-linear models are dependent on drug dose or input function. These models violate the principle of superposition.

Nonlinear kinetics can be described with respect to capacity, time, flow and binding and how these variables may have an impact on clearance.

The major distinguishing features between capacity (dose) and time dependency, is that the latter involves an actual physiological or biochemical change in the organ(s) of the body associated with the drug disposition parameter in question[2].

For example, in time dependence of the auto- or heteroinduction type, the increase in drug intrinsic clearance results from an increase in amount of enzyme (e.g. in protein synthesis). However, in atypical Michaelis-Menten capacity (dose) dependency, drug clearance changes with concentration and such a system should not be considered time-

dependent simply because the values of pharmacokinetic parameters change with time. If that was a true time-dependent system, drug clearance should change with time while drug concentration is time invariant. It is still possible that capacity and time dependency exist simultaneously[2].

If nonlinearities are observed in the half-life after intravenous administration, this is caused by changes in the disposition of drug (Cl, V_c, Cl_d, V_t). If AUC is changed, this may be due to either changes in F or Cl. If the principle of superposition is violated, we have either a change in Cl, F or the distribution (V_c, V_t or Cl_d)[2].

Time-variant Vs Time-invariant

If the drug concentration-time profile following a given input is independent of the time when the input is applied, the system is said to be time-invariant. On the other hand, if the model parameters change with time the response will vary with the time of application of the input and the system is said to be time-variant.

Traditional Compartmental Models

Compartments are chosen to represent the body based partially on an empirical or a physiological basis. The number of compartments is determined from best model, which fits the data. The route of administration also determines the structure. The model must specify transfer between compartments, including the direction of transfer and the order of transfer (first order, zero order. etc.). If every compartment is connected to a central compartment, then it is referred to as a mammalian model.

Assumptions

Assumptions, and their justifications, for classical pharmacokinetic modeling includes existence of barriers between compartments, transfer of drug with certain order and certain direction from one compartment to another[1].

Compartment characteristics

Each compartment consists of group of tissues and drug is homogeneously and instantaneously distributed[1].

Drug

Elimination of the drug happens only from the central compartment. There is no irreversible tissue binding[1].

One compartmental model

The simplest compartmental model is the one-compartment model with intravenous bolus administration and first-order elimination of the drug. This model includes an apparent volume of distribution, V. This volume parameter is used to relate the amount of drug in the body with the concentration measured in plasma, serum, or blood. Volume of distribution is not a physical volume and may be many times larger than the size of the subject in cases where the drug is extensively distributed outside the blood.

$$V = \frac{X}{C}$$

X=Amount of drug in the body

C=Concentration of drug

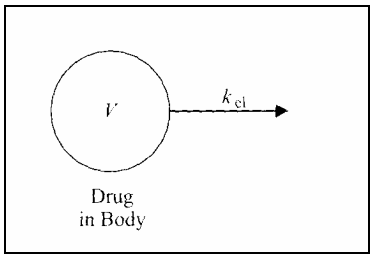

Figure 2. A one-compartment model with first-order elimination after an IV bolus [1]

When elimination follows first-order kinetics, this model can be represented by the differential equation, Equation is as follows

$\frac{dC}{dt} = -K_{el} \times C$ with the initial condition $C_0 = \frac{D}{V}$

Rate of change of concentration can be integrated to give equation as follows:

$$C = \frac{D}{V} \times \exp(-K_{el} \times t)$$

This approach can be expanded to include other routes of administration such as IV infusion and extravascular administrations such as oral, intra-muscular, subcutaneous, or topical.

Differential and Integrated equation of extravascular (Oral, GI) administration model is given by:

Differential Equation

$$\frac{dC}{dt} = \frac{K_a \times X_g}{V} - K_{el} \times C$$

Integrated Equation

$$C = \frac{F \times D \times K_a}{V \times (K_a - K_{el})} \times [\exp(-K_{el} \times t) - \exp(-K_a \times t)]$$

Multi-compartment models

Distribution and elimination are occurring throughout the concentration vs. time profile. It is the slower distribution with these drugs that requires the use of multiple-compartment models. In this case, a second compartment can be included in the scheme where X_1 and X_2 represent compartments 1 and 2,

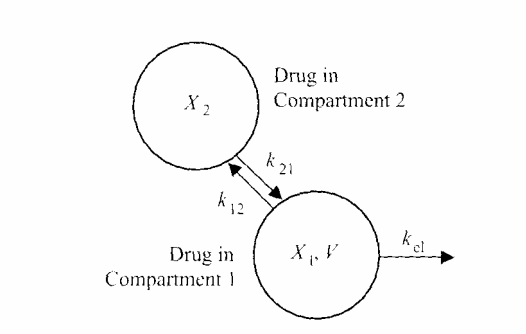

Figure 3. A two-compartment model[1]

V represents the volume of compartment 1 with k_{12} and k_{21} representing the first-order rate constants entering and leaving the respective compartments and k_{el} representing elimination out of the body.

This model can be described mathematically with the differential equation.

$$\frac{V \times dC}{dt} = -(k_{el} + k_{12}) \times X_1 + k_{21} \times X_2$$

Rate of change of concentration can be integrated to give equation as follows:

$$C = A \times \exp-(\alpha \times t) + B \times \exp-(\beta \times t)$$

where $A = \frac{D \times (\alpha - k_{21})}{V \times (\alpha - \beta)}$ and $B = \frac{D \times (k_{21} - \beta)}{V \times (\alpha - \beta)}$

Non-linear compartmental models

As discussed in previous sections, we include nonlinear processes if there exists saturable metabolism or protein binding. For example, for some drugs one or more metabolism processes may follow Michaelis-Menten kinetics.

Elimination k described in equation $\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C}$ with a nonlinear metabolism process with the parameters V_m (maximum velocity) and K_m (Michaelis constant)[1].

At high concentrations the denominator K + C approaches C and the above Equation becomes zero order with $\frac{dC}{dt} = -V_m$ [1].

Non-compartmental models

This process can also be named as non-parametric pharmacokinetics because a structure with compartments and corresponding parameters are not modeled, but instead the response is modeled. The drug is distributed through stochastic random I processes: convection and diffusion (through various membranes and tissues) [1]

There are two main assumptions inherent to this approach.

Superposition

This assumption relates the response and the inputs where simultaneous inputs should produce the response equal to when the inputs are given separately produces the sum of independent responses.

For example, if an IV dose and an oral dose were given and the response to each was known, then when both are given simultaneously, the response would be the sum of the two separate responses. This is the principle that is used to determine the response following multiple doses[1].

Time invariance

This assumption is that if a certain dose is given produces the same and a certain response regardless of the dose given at any time. However, some drugs exhibit time-dependent pharmacokinetics. Examples of these situations can be when a dose given in the morning may not produce the same result as when it is given at night and the elimination rate changes with saturable elimination.

Physiologically Based Pharmacokinetic models (PBPK)

PB/PK models should be viewed as a powerful means to represent drug disposition based on mass transport principles, and should he considered as a modeling approach when the emphasis is on understanding the pharmacokinetic properties of the drug in tissues. Physiological models are developed a priori in that independent experimental data are used to propose a model before the experimental response is available. But empirical and compartmental models are formulated after measurement of the experimental response.

Many of the same assumptions for the compartments of the traditional models apply here as well. In addition, blood flow must be known or estimated through each compartment.

Hepatic clearance models are further divided into the well-stirred and parallel tube models and they have been used to describe hepatic elimination of drugs. The amount of drug entering and leaving the compartment should be determined.

Assumptions

Each organ system forms a separate compartment and the drug is homogeneously and instantaneously distributed within that compartment

Partition coefficient can be determined from the concentration of the drug in the tissue compared to the concentration in the blood,

Rate constant is determined by the barriers between compartments in physiological systems. This transfer rate is dependent on the blood flow within an organ. Each compartment has a characteristic clearance rate and is constrained by the rate of blood flow[1].

Drug

Elimination is only from certain compartments that are specified in the model, for example the liver and kidneys with no irreversible binding of the drug to the tissue[1].

Features of PBPK models

- Mass balance approach to characterize drug disposition
- Differential equations are utilized to describe model systems
- Helps in understanding drug disposition in tissues
- Predicts drug concentrations under different physiological and pharmacological conditions
- Can be scaled from animals to humans[1]

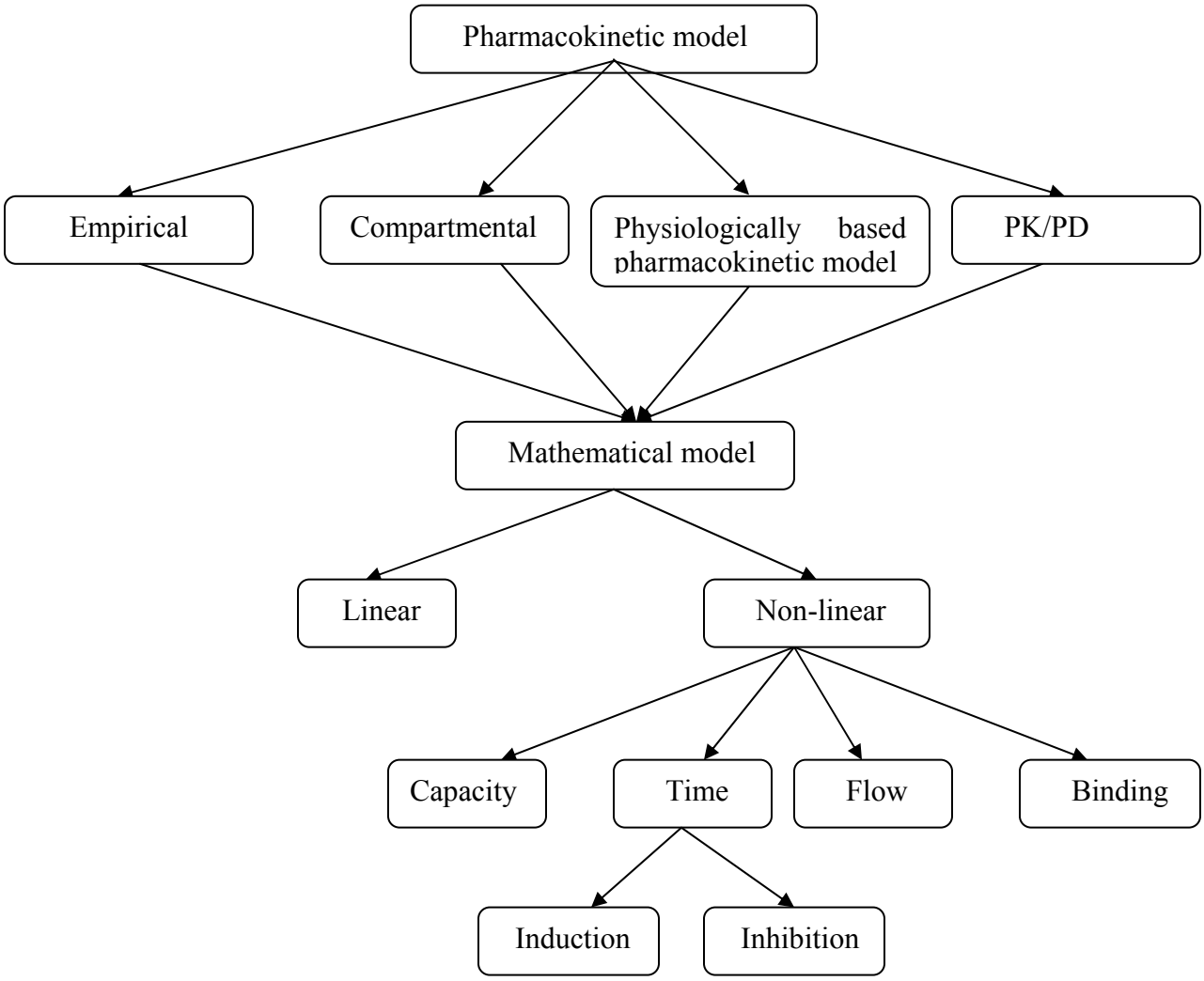

Figure 4. Classification of pharmacokinetic model

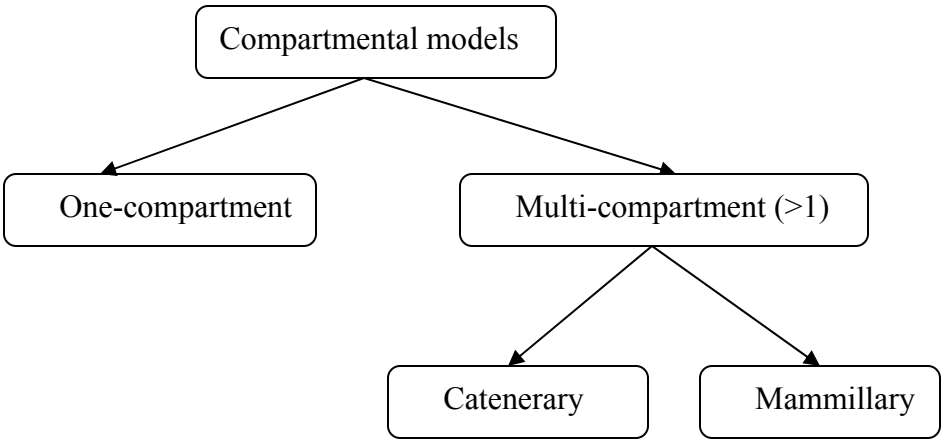

Figure 5. Classification of compartmental model

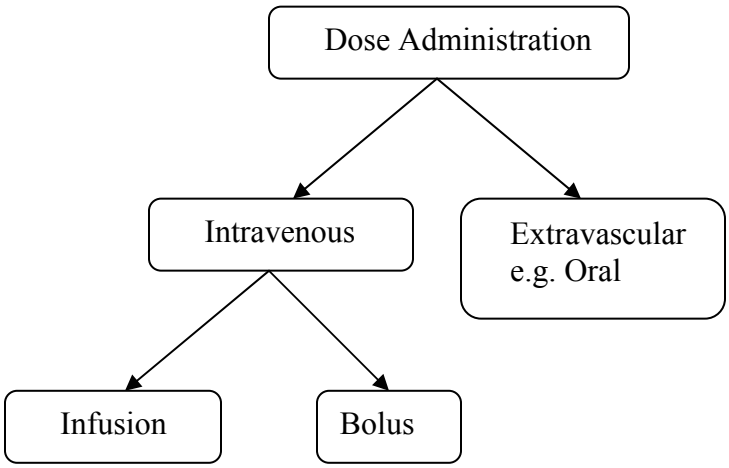

Figure 6. Classification of dose administration

Table 1. Comparison of modeling techniques

Comparison	Empirical or Non-compartmental Modeling	Compartmental Model	Physiologically based pharmacokinetic model
Complexity in mathematical modeling	Simple	Intermediate	Complex and difficult to determine many of the physiological or anatomical parameters
Structural relevance (Physiological or anatomical relevance)	Attempts to model the response rather than the structure of the process, hence little explanation why the drug exhibits a certain kinetic profile	Difficult to assign structure to the model and the resulting parameters, does little to address the specific structure of the kinetic process	Compartments as well as the model parameters that are determined, such as blood flow, elimination rate, and partitioning coefficients
Assumptions	Drug distribution generally occurs by two stochastic processes: Convection and Diffusion. Two assumptions that must be verified for this approach are superposition and time invariance.	Many of the assumptions are difficult to verify	Many parameters and assumptions cannot be verified
Data collection	Blood and urine samples	Blood and urine samples	Blood, urine, tissue concentrations and organ blood flow rates
Study objective	To summarize kinetics, quantify a pharmacokinetic process, or make pharmacokinetic predictions	To develop descriptive pharmacokinetics of a drug	Drug discovery process to identify the kinetics and action of a new compound
Disadvantage	Does not help in understanding the overall mechanism of the kinetics of the compound studied	Not meaningful to summarize in terms of structure specific parameters that do not have physiological or anatomical significance.	Complex and many parameters and assumptions cannot be verified. Massive sample collection is required and many validation experiments need to be done

PK/PD MODELS

PK/PD model relates the time course of pharmacological effects with plasma drug concentrations to predict the temporal pattern of their pharmacological effects.

Frequently used PK/PD models

Linear PK/PD model

The linear model assumes drug concentration is proportional to the observed drug effect, as shown in the following equation:

$$E = E_0 + b \times C$$

Where E_0 is the baseline effect and b is a slope.

Sigmoid E_{max} PK/PD model

Effect (E) relates to the concentration(C) as follows,

$$E = \frac{E_{max} \times C^{\gamma}}{EC_{50}{}^{\gamma} + C^{\gamma}}$$

This relationship can be theoretically described based on the interaction between γ drug molecules and one common interaction site. However, in most cases γ only serves as a shaping factor to allow for a better data fit. Therefore, γ is not necessarily an integer value. The steepness of the concentration-effect curve depends on the magnitude of γ; the larger γ, the steeper the linear phase of the log-concentration-effect curve. The Emax model can be considered as a special case of the sigmoid Emax model with γ=1[1].

2.3. Population Pharmacokinetics

Introduction

This section comprises of an overview of the purpose of population pharmacokinetics and its significance in the drug development process. We also describe different types of population approaches and their shortcomings, many of which are overcome by nonlinear mixed effects modeling. In order to understand the model building process with this approach, the mathematical concepts, algorithms, statistical models, assumptions and issues involved behind this approach is discussed in detail. Finally, we walk through the steps involved in the process of model building.

Why do we go for population pharmacokinetics?

High interindividual variability in pharmacokinetic parameters for all major anticancer drugs: three to tenfold interindividual variation in systemic exposure have been reported, even in patients without renal or liver failure or other metabolic dysfunction. A fundamental goal is to provide quantitative platform to assess if and in what manner a patient's covariates impact on the drug's pharmacokinetics.

When the pharmacokinetic model is constructed for an individual, we understand the pharmacokinetics for that particular individual which is traditional pharmacokinetics. But in the phase of drug development, participants who vary in covariates such as demographic, pathophysiological or environmental are quantified as fixed effects and also vary at random quantified as random effects (unexplained part of the variability). Both types of effects affect the pharmacokinetics of a drug. Hence we construct a mixed-effects model to quantify the fixed effects and random effects of pharmacokinetic parameters, which is the hallmark of population pharmacokinetics.

The key pharmacokinetic parameters, including volume of distribution and clearance, vary from individual to individual which are re-parameterized in terms of covariates in understanding the inter-individual variability for dose individualization. Dose individualization produces beneficial effect when drugs have narrow therapeutic index and toxicity effects.

Thus population pharmacokinetics recognizes variability as an important feature that should be identified and measured during drug development or evaluation. Also, it seeks to obtain relevant pharmacokinetic information in patients who are representative of the target population to be treated with the drug.

What is the significance of the estimates of identified variability and unexplained variability?

Background: The primary objective of dose administration is to achieve drug levels within the target range of clinical effect. Drug levels outside the target range are attributable to the uncompensated variability in the relationship of dosage to steady state drug concentration.

Discussion: The magnitude of the unexplained (random) variability is important because the efficacy and safety of a drug may decrease as unexplainable variability increases. Thereby unnecessary failure rates of trials might be avoided.

Concentrations appear to vary due to inexplicable day-to-day or week-to-week kinetic variability and due to errors in concentration measurement. Estimates of this kind of variability (residual intrasubject, interoccasion variability) are important for therapeutic drug monitoring using the empiric Bayes approach.

The knowledge of the relationship between concentrations, response, and physiology is essential to design dosing strategies for rational therapeutics that may not necessarily require therapeutic drug monitoring.

When do we perform population approach?

When the population under the investigated trial is heterogeneous, the application of population approach is more appropriate. In drug development, the population approach can help increase knowledge of the quantitative relationships between drug input patterns, patient characteristics, drug disposition, and responses. The population approach may increase the efficiency and specificity of drug development by suggesting more informative designs and analyses of experiments. The population approach can also be applied to phases 2 and 3 of drug development to gain information on drug safety (efficacy) and to gather additional information on drug pharmacokinetics (and pharmacodynamics) in special populations, such as the elderly. It is used to characterize drug disposition in large populations. It is also useful in postmarketing surveillance (phase 4) studies.

Utility of population-based pharmacokinetic model

- The clinical significance of a population pharmacokinetic model is that it may be used to prospectively individualize drug therapy to achieve a target systemic exposure. In simple terms, it aids in specific dosing guidelines sought for subpopulations and individuals.

- It helps in the development of limited sampling strategies utilized in phase II clinical studies, considerably reducing patient discomfort and labor intensity and therefore makes PK studies easier to perform and on pharmacokinetic-pharmacodynamic relationships.

Population analysis methods

Pooling sparse data from several individuals can provide valuable information about drug disposition in the population.

1. Naïve Pooled Data (NPD)

This method combines all the data as if they come from a single individual. Residual variability is overestimated and cannot estimate parameters for an individual.

2. Naïve Averaged Data (NAD)

This method obtains the average concentration across individuals at each time point. Disadvantages of this method are: not ideal for investigation of sources of variability, biased estimates of the true "mean" parameters across individuals, need experiments with identical sampling times across subjects.

3. Standard Two Stage (STS)

Step 1: Estimate an individual subjects PK and/or PD parameters from rich data using standard fitting procedures.

Step 2: Estimate the population parameters across the subjects.

Using regression analysis techniques, a covariate relationship between PK parameters across and/or within subjects and fixed effects can be investigated.

Bias: Mixed-effect modeling vs. STS

Parameters for the individuals are estimated and mean values of the parameter have little or no bias. Covariates can be included in the model. But variance-covariance of parameters across subjects is biased. Numerous blood samples at appropriate times are required to obtain accurate estimates. STS performs well when residual variability is absent and provide upwardly biased estimates of inter-individual error as residual error increases.

Mixed effect modeling results in less biased estimates when residual error is present and sparse blood sampling strategy at appropriate times is enough to obtain accurate estimates[3].

Development of population model described with an example

Assumptions about Random Error

Ordinary Least Squares OLS

Assumes a homoscedastic error structure (common or homogeneous variance regardless of response). The random error is the same for all observations.

$$\sum_{i=1}^{n}(Y_{obsi} - Y_{cali})^2$$

Weighted least squares WLS

Assumes a heteroscedastic error Structure (variance changes with the response). The random error is assumed to he some function of the observed data (i.e. if $w_i = 1 / Y$ the variance is proportional to the response).

$$\sum_{i=1}^{n}[w_i(Y_{obsi} - Y_{cali})^2]$$

Extended least squares ELS

Assumes heteroscedastic error structure. The variance is expressed as a model parameter along with the structural model parameters. ELS is designated as a maximum likelihood (as opposed to least squares) if the random effects are assumed to be normally distributed.

$$\left[\sum_{i=1}^{n}\frac{(Y_{obsi}-Y_{cali})^2}{\sigma i^2}+\ln(\sigma i^2)\right]$$

The intra-individual model is

$$C_{ij}=\frac{Dose}{V_i}\times\exp-(k_i\times t)+\varepsilon_{ij}$$

$$y_{ij}=f\left(x_{ij},P_i\right)+\varepsilon_{ij}$$

where y_{ij} the jth observation for the ith individual

x_{ij} all independent variables used to predict the jth observation for the ith individual

P_i are the structural model parameters for ith individual

$f(x_{ij,}\ P_i)$ the model prediction for y_{ij}

ε_{ij} random error associated with y_{ij}

Different types of residual random effects model

Residual random effects are the combination of intra-individual error and residual error. Residual errors (ε) are assumed to be identically, independently distributed~ N (0, σ^2).

The residual random error model can be:

1. Homoscedastic (additive, or constant variance)

$$Y=F+\varepsilon_1$$

2. Heteroscedastic (proportional or constant coefficient of variation (CV))

$$Y = F \times (1 + \varepsilon_1)$$

3. Exponential (approximates constant CV)

$$Y = F \times \exp(\varepsilon_1)$$

4. Combination additive and proportional error

$$Y = F \times (1 + \varepsilon_1) + \varepsilon_2$$

The inter-individual model

$$V_i = \theta_1 + \theta_2 \times v_1 + \eta_{Vi}$$

$$P_i = g(v_i, \theta, \eta_i)$$

where v_i the independent variables needed to predict P_i

θ the population mean parameters

η_i the random inter-individual errors for the parameters of the ith individual

$g(v_i, \theta, \eta_i)$ the model describing P_i

Different types of inter-individual random effects model

Usually assumed to be identically, independently distributed ~ N (0, ω^2)

1. Homoscedastic (additive, or constant variance)

$$V_i = \theta_1 + \theta_2 \times \text{cov}_1 + \eta_{Vi}$$

2. Heteroscedastic (proportional or constant coefficient of variation (CV))

$$V_i = (\theta_1 + \theta_2 \times \text{cov}_1)(1 + \eta_{Vi})$$

3. Exponential (approximates constant CV)

$$V_i = (\theta_1 + \theta_2 \times \text{cov}_1) \times \exp(\eta_{Vi})$$

The Population model is as follows:

$$C_{ij} = \frac{Dose}{\theta_1 + \theta_2 \times \mathrm{cov}_1 + \eta_{Vi}} \times \exp -(\theta_3 + \eta_{ki})t_{ij} + \varepsilon_{ij}$$

$$yij = f\left(xij, g(zi, \theta, \eta i)\right) + \varepsilon_{ij}$$

Methods involved in the inter-individual variability parameter estimation are first order approximation, first order conditional estimation, expectation maximization algorithm, discrete/continuous nonparametric maximum likelihood and Bayesian inference using Gibbs Sampling: Bayesian methods implementing Markov chain Monte Carlo methods.

Pharmacokinetic parameters for individuals

Bayesian estimation

The prior distribution of the parameters across a population of subjects and the actual data from an individual are used when estimating the parameters for an individual. The estimation of parameters in the individual uses the posterior probability of the parameters.

$$OBJ(\phi_i) = \left(y_{obsi} - y_{predi}\right)^T \sum_i^{-1} \left(y_{obsi} - y_{predi}\right) + \left(\phi_i - \phi_{pop}\right)^T \Omega^{-1} \left(\phi_i - \phi_{pop}\right)$$

When the number of samples for an individual is small the prior distribution of the parameters usually predominates. When the number of samples for an individual is large, the data from the individual is more important than the prior distribution of the parameters.

Advantage of this estimation is sparse sampling and disadvantages of this estimation needs estimates of the priors for the parameters and residual error variance and fit may be dependent on priors[3].

Conditional estimation procedures

POSTHOC using FO and FOCE, Laplacian conditional estimation, Hybrid estimation are some of the estimation methods to estimate ηs for each individual.

Model Development process

Step 1: Define the modeling objectives

The first step in the development of mathematical model is to define the modeling objectives. A good understanding of the modeling objectives is useful when making critical decisions during the modeling process.

Step 2: Exploratory analysis

Population PK analysis involve large amounts of response data (PK or PD) and covariate, demographic data. Distribution analysis of covariates under investigation, covariate correlation analysis, and investigation into disease process time course if necessary. An examination of the dataset can reveal errors or provide hints about unexpected relationships in the data.

Step 3: Define a preliminary structural model

The structural model is the PK model that describes the fate or the effect of the drug. A common assumption is that the model is the same for all individuals within the population.

Step 4: Define preliminary random effect models

NONMEM estimates population parameters as typical parameter values with corresponding interindividual variability. This is accomplished by allowing each individual's data to be described by subject-specific pharmacokinetic parameters P_i. This parameter is assumed to come from the distribution of parameters in the population

$P_i = P_{pop} \times \exp(\eta_i)$ where $\eta \sim N(0, \omega^2)$

For mixed effects models, the residual error corresponds to the difference between the observed concentration and the predicted concentration by individual parameters (P_i).

Step 5: Obtain initial estimates of parameters

The ability of non-linear regression model to converge successfully at a global minimum is sometimes dependent upon the initial estimates that one uses to fit the model to the data. With most nonlinear least-squares analysis, local minima exist such that a number of initial estimates must be used to ensure that a global minimum is obtained.

Step 6: Estimate the population parameters for the basic structural model

This step is accomplished by assessing the goodness of fit of the model to the data, which is evaluated by the statistical significance of minimizing the objective function value (OFV).

OFV provided by NONMEM used for comparison of models, discrimination between hierarchical models based on OFV using the log-likelihood ratio test.

Step7: Estimate individual parameters

Individual Bayesian estimates of the pharmacokinetic parameters are obtained by using the POSTHOC option in NONMEM; for each subject, individual pharmacokinetic parameters are calculated taking both the individual observations and population effects into account.

Step8: Explore relationships between covariates and structural model parameters

The relationships between the individual pharmacokinetic parameter estimates and the covariates is visually inspected and investigated using stepwise procedure.

A generalized additive modeling procedure (GAM) is applied to select explanatory variables and calculations using Xpose.

Step9: Build covariate model

Covariates that correlated significantly with the pharmacokinetic parameters, as indicated by Akaike Information Criterion (AIC) is selected for testing in NONMEM.

Step10: Perform model checking

Model checking is done by checking assumptions and models fit and determine predictive performance of the population pharmacokinetic model by internal validation: data splitting cross validation or resampling and external validation.

Advantages

The population model built using NONMEM can estimate inter-individual variability of the parameters, random residual error and parameters for individuals. Additional advantages are covariates can be included in the model, can be used with dense data or sparse data and correctly handles differing numbers of data points per patient (imbalance). Population approach also allows us to analyze data from different studies differing in dose and frequency.

3. DESIGN

3.1. Collection of pharmacokinetic articles

Literature selection

Literatures were selected to gather information on pharmacokinetic articles for different anti-cancer drugs. Since articles are related to drugs, EMBASE database was also chosen in addition to MEDLINE and ISI database. EMBASE has only 37% overlap with MEDLINE and is particularly strong in the area of drugs. We follow general search

strategy and apply search criteria for relevant article collection. We delete articles based on deletion criteria.

3.1.1. Introduction about search database

MEDLINE

The MEDLINE database is produced by the National Library of Medicine (NLM) and covers the fields of medicine, dentistry, psychiatry, public health, pharmacy, nursing and other biomedical sciences

EMBASE

The EMBASE database is produced by Elsevier Sciences and covers more than 3,500 international journals. The main focus indexes biomedical literature with emphasis on drugs & pharmacology. This database is strong on European and Japanese titles. EMBASE offers drug literature record access through chemical name, drug trade name or manufacturer nameprecise and reliable indexing using EMTREE, a hierarchically-ordered, synonym-controlled thesaurus — with almost 42,000 drug and medical indexing terms and 180,000 synonyms.

ISI

ISI covers over 8,000 international journals in the sciences, social sciences, and the arts and humanities.

3.1.2. Search criteria and search strategy

Developing the search strategy is the process of:

- Formulating the search query

Define the question relevant to what we are looking for and identify the main terms or ideas to combine the ideas with AND or OR from the search topic.

- Choosing the appropriate database
- Selecting the best Medical Subject Headings (MeSH) or terms to describe your topic
- Combining the terms or sets
- Limiting your retrieval to appropriate references or citations

After performing a search, a list of articles should appear which contain the main terms from the search strategy.

If the articles are too broad or general, then

- Add more search terms or more specific terms using combine and limit
- Search terms with common keywords used in the title of articles
- Consider related or similar terms for better results
- Focus/explode to restrict/expand main subject headings options.

There are two major steps involved in article search:

- Combine: “Combine” sets using the Boolean AND or OR

- Limit: “Limit” restricts the search to logical variables such as English language, human subjects, age groups, gender, publication types, publication years, etc.

Validation and reliability: Validation is achieved by using comparable search criteria and search strategies across different databases (e.g. Medline and Embase) and reliability by utilizing different user interfaces (PubMed and Ovid for Medline) is achieved.

Useful functions in article search

Explode: “Explode” is an option you will make about each subject heading (MeSH) during the search process. Exploding will retrieve MeSH terms that are part of the family or tree of the original term[5].

Focus: “Focus” will retrieve only those articles where the term is emphasized, a major point, or a main topic[5].

Deletion of articles:

Articles were deleted if their main focus was irrelevant to the purpose. Thus articles with main focus was CT imaging, physics, computer model, mathematical model (out of scope), molecular model, chemical and physical properties of drug, focus on renal functions, immuno-compromised and immunosuppressant drugs, toxicity analysis, pharmacogenomics, dynamics including receptor action, ligands, biologic and molecular mechanism, monoclonal antibodies or animal models were deleted.

1) Medline via PubMed

a) The search for PK articles in PubMed was done through an Endnote connection file. Keyword “pharmacokinetics” was entered in the title field to obtain set of articles. Keywords

"cancer and model" are entered in a new search field to obtain another set of articles. These sets are combined using AND operator. This resulted in 254 articles. Deleting the articles before 1995 reduced the total to 150 articles. Furthermore, articles considered irrelevant to the collection were deleted using pre-defined deletion criteria finally resulted in 104 Pk articles.

b) By using different search criteria with keywords "population", "pharmacokinetics" and particular type of anti-cancer drug limited to Title/Abstract, publication type by clinical trial, all ages, publication date from year 1995-2003, English language, Human with no subsets and gender yielded 10-20 articles on each drug[6] using PubMed. Relevant articles were chosen which resulted in 93 articles.

Certain drugs (Triptolein, Propecia, Imuran, Femara etc.) didn't produce any results with the above search criteria. This may be attributable to the usage of brand names or lack of population models for these drugs or both.

c) Another way of searching in PubMed by exploding "Antineoplastic agents" by Medical Subject Heading (MeSH) resulted in 9 subheadings and the search resulted in 497920 articles. The keyword pharmacokinetics model* was used in the search field resulting in 1817 articles. Combining the searches (497920 and 1817 articles) gave 88 articles.

2) ISI via Web of Science

Keywords "pharmacokinetics", "model" and "anti-neoplastic agents" were used in separate search fields resulted in 373 articles.

3) Medline via Ovid

Step1: The use of the keywords "pharmacokinetics model$" in the search field limited to humans and English language resulted in 688 articles.

Step 2: By exploding antineoplastic agents using MeSH produced 200837 articles. Combining steps 1 and 2 resulted in 100 articles.

4) Embase via Embase.com

Step1: Drug search is used in exploding anti-neoplastic agent published years from 1996-2004 restricted to human and English (128842 articles)

Step2: Advanced search is used for the keyword "pharmacokinetics" (37222 search results)

Step3: Again, advanced search is used for emtree keyword (similar to MeSH) model, which constituted non-biological and theoretical model (22602)

Step 4: Combining 1, 2 and 3 resulted 136 articles.

An additional search was done using these criterion "pharmacokinetic model" and "population" as keywords in the advanced search for population pharmacokinetic articles. Irrelevant articles were discarded from the 300 articles according to the deletion criteria.

Table 2. Number of articles in each Medline provider collected on anti-cancer drugs

Drugs	Ovid	ISI	Pubmed	Embase	Overlap*	Total (by Drug)
Carboplatin	4(4)	9(8)	16(8)	7(6)	8	28
Cisplatin	2(2)	15(10)	9(5)	7(6)	7	26
Topotecan	3(3)	4(5)	7(4)	5(3)	8	11
Irinotecan	2(1)	4(3)	8(4)	5(5)	5	14
Etoposide	4(4)	12(6)	8(6)	8(6)	6	26
Paclitaxel	6(6)	32(14)	21(12)	4(3)	14	29
5-Fluorouracil	6(4)	25(14)	19(10)	7(5)	18	23
Total	27	101	88	43		259(157)

*Represents duplicates over all of the databases.

The numbers in brackets represent the number of journals from which the articles were collected.

Discussion on results

Results from the sampled articles had 17 articles in common using different user interfaces (PubMed and Ovid) accessing Medline out of 100 articles. This may be attributable to the difference in indexing of keywords, MeSH and comparable search criteria. The major reason we might get different results from PubMed and Ovid are the ways in which the two databases process the search query. For example, PubMed automatically explodes MeSH terms to pick up narrower terms, while Ovid requires you to make that choice. The way each system maps your original search term to the official MeSH terms is different as well and could lead to different results. For e.g., when we use Medical Subject Heading "neoplasms", the subheadings under this topic differs in PubMed and Ovid. Also, when we search using Ovid and PubMed, the collection of articles in Ovid is 4-6 times less compared to PubMed. The reason is PubMed also retrieves the articles using the keyword search. For e.g., when we combine keywords "pharmacokinetics", "cancer" and "model" in both PubMed and Ovid, we get 3541 articles in pubMed compared to 746 articles in Ovid. This could also possibly lead to different search results. It is more likely we would collect the article, if one of the keywords used in the search criteria were indexed in the article. For e.g., this article "A sequential Bayesian algorithm for dose individualisation of carboplatin" is retrieved from ISI, EMBASE, and PubMed but not from Ovid. Another example "Altered clearance of unbound paclitaxel in elderly patients with metastatic breast cancer" found in ISI and PubMed but not retrieved in Ovid for the same reason. On the other hand, "Mechanism-based pharmacokinetic model for paclitaxel" and "Population pharmacokinetic

modelling of unbound and total plasma concentrations of paclitaxel in cancer patients" are found in both PubMed and Ovid because Ovid was able to pick one of the MeSH terms used in keyword search. Results accessed from MEDLINE and EMBASE were entirely different sets and it can be understood from the fact that EMBASE focuses on drugs and worldwide journals, especially European and Japanese journals. For e.g., This article "Population pharmacokinetic analysis of cisplatin and its metabolites in cancer patients: Possible misinterpretation of covariates for pharmacokinetic parameters calculated from the concentrations of unchanged cisplatin, ultrafiltered platinum and total platinum" is from the journal "Japanese Journal of Clinical Oncology". EMBASE.com would retrieve different results in part because there are many journals from EMBASE in that database that are not included in MEDLINE. This article "Long-term body retention and tissue distribution of platinum in cisplatin treated cancer patients" is from the journal "Journal of Radioanalytical and Nuclear Chemistry" which is not found in MEDLINE. Another e.g. was the article "Differences in metabolism of 5-fluorouracil and 5-fluorouridine and regulation by glucosamine in human colon cancer multicell tumor spheroids" from the journal "NMR in Biomedicine" which is also not found in MEDLINE.Any other difference would be attributed to the way in which the database processes queries. Though EMBASE main focus indexes biomedical literature with emphasis on drugs & pharmacology, ISI resulted in the largest set of articles (373) as compared to 134 articles from EMBASE. The possible reason is ISI includes over 8000 journals from all different disciplines while MEDLINE includes over 4000 journals from health sciences and related literatures. Also, we get more with ISI because we are doing a simple keyword search (collect articles that mention the search terms) rather than using a subject heading approach. Thus, different search results are attributable to one or combination of the following reasons. How the database handles the MeSH for the keyword

search and what are the sub-headings included in the MeSH, inclusion of variety and type of journals and comparable search criteria.

A class of drugs is selected from the results namely Paclitaxel falls under Taxol, 5-Fluorouracil (5-FU) under Fluoropyrimidine, Carboplatin and Cisplatin under Platinum and Topotecan, Irinotecan and Etoposide under Topoisomerase inhibitors. ISI had correspondingly three times the collection of articles in total compared to other databases.

3.2. Questionnaire

The following questionnaire is used for collecting basic information from the pharmacokinetic articles. Other useful or peculiar information is added from the article without the help of questionnaire.

1) What are the drugs and its metabolites involved in the study?

2) What are the drug indications?

3) What are the dose ranges, levels and types of administration?

4) Is the drug sequence dependent when concomitant drugs are used?

5) Is there a drug interaction between the administered drug and the concomitant drugs? If so, then we have the possible sub-questions:

a) How does the administered drug affect the dose-response relationship?

b) Is there a significant influence of the administered drug on the concomitant drug disposition?

c) How does drug interaction affect area under the curve and does it affect the disposition parameters?

6) Does the drug undergo linear or non-linear pharmacokinetics? Supposing the parameters show non-linear characteristics, what are the reasons attributed to this scenario?

7) How is the pharmacokinetic model described and what are the possible models used to describe the concentration-time data? Is the drug schedule dependent or dose dependent?

a) Absorption

Is the drug given orally? How is the absorption parameters affected? Does the absorption phenomenon have time-lag? What is the oral bioavailability? Does the oral administration exhibits wide inter-individual variability?

b) Distribution

Does the drug undergo saturable distribution? What is the mechanism involved in the properties of distribution? Does the distribution properties differ for subpopulation? What are the covariates explaining the variability in the volume of distribution? Does the drug binds to different types of proteins in blood cells? Is the drug found as bound and free drug? How is the bound drug e.g. any covariates affecting binding properties?

c) Elimination

Does the clearance vary in the sub-population? What are the covariates affecting the clearance? Does the drug undergo saturable elimination? What are the enzymes involved in the metabolism and is there genetic polymorphism? Is the clearance parameter time variant or time-invariant?

Is clearance dose or time or schedule dependent? Are there any rate-limiting enzymes and what are the inhibitors used to inhibit metabolism?

8) PK/PD relationship

What are the common hematological and non-hematological toxicities? What is the dose-limiting toxicity and maximum tolerated dose? What are the possible models, which describe the PK/PD relationship?

4. RESULTS

The collected information from the PK articles is compiled in a structured format. These results comprises of templates on four classes of drugs. Some articles for each class are excluded as the information does not contribute to the template or due to redundant information.

4.1. Templates on drugs

4.1.1. PACLITAXEL

Drug and metabolites involved in the study

Paclitaxel is the parent drug and 6-alpha-hydroxypaclitaxel, 3'p-hydroxypaclitaxel and 6-alpha, 3'-p-dihydroxypaclitaxel are its main metabolites[21].

Drug indication

Paclitaxel is used in the treatment of breast cancer, ovarian cancer, non-small cell lung cancer and esophageal cancer and is widely used in the treatment of advanced breast cancer. Paclitaxel alone, as well as combination of CP and 5-FU has significant clinical activity against upper aerodigestive tract cancers[22].

Dosage and administration

Drug is administered by Infusion for 3h and the dosing levels are 135mg/m^2, 175mg/m^2, and 235mg/m^2 [23]. Dose ranges from 135 mg/m^2 to 250 mg/m^2 and is administered by intravenous infusions of 1-24h duration[24]. Paclitaxel can be administered upto 250 mg/m^2 with G-CSF support [21, 22]. The recommended dosage for paclitaxel is 100 mg/m^2 when administered along with Gemcitabine 1500 mg/m^2 as it exhibits linear pharmacokinetics[25]. Weekly administration of paclitaxel has demonstrated efficacy together with a more favorable toxicity profile[26]. 3-h infusion has reduced hematological toxicity compared to 24-h infusion without compromising efficacy[22]. Paclitaxel is administered with the cremophor EL (CrEL) due to its poor solubility[6].

Drug sequence

Paclitaxel is sequence dependent when it is administered with cisplatinum agents, which can be shown with increasing toxicity[22]. Doxorubicin-paclitaxel is better compared to paclitaxel-doxorubicin sequence as the former resulted in grade 2 and 3 stomatitis[27]. C_{max} and clearance of doxorubicin was affected by paclitaxel-doxorubicin sequence[27]. There was a significant difference for the metabolite 6 alphahydroxypaclitaxel (6 OHP) AUC and higher 6 OHP is observed when carboplatin is administered before paclitaxel[28].

Drug interaction

Paclitaxel and CrEL with epirubicin inhibit production of the metabolite epirubicinol but marked increase in inhibition is found by CrEL. Paclitaxel-Epirubicin interaction is found in E_{max} model exhibiting 50% reduction in Absolute Neutrophil Count (ANC) at 7.7h compared to 11.16h with paclitaxel alone[29]. This difference may be due to the combined effects of Epirubicin and Paclitaxel and there is significant influence of paclitaxel/cremophor EL on epirubicinol and epirubicin disposition; however, both of these drugs do not interfere with Gemcitabine disposition[30].

Pharmacokinetics

Paclitaxel undergoes non-linear pharmacokinetics[6, 23,30,31]. Nonlinear pharmacokinetics is reflected by a disproportionate increase in area under the curve (AUC) in relation to increased dose. This is attributable to saturable distribution and saturable elimination and may be partly due to Cremophor EL (CrEL) binding. There is three-fold inter-individual variability in the paclitaxel disposition at any dose level. This variability can be accounted by understanding the various biological factors that may influence paclitaxel disposition and polymorphism of

paclitaxel metabolism[22]. Population studies show Body Surface Area (BSA) explained the variability in clearance and volume of distribution[33].

Pharmacokinetic model

The disposition is modeled as two-compartment model[22, 25,32,33]. In another study, three-compartment, nonlinear distribution and elimination model is fitted to the plasma concentration-time data[6, 29,31]. Two or three-compartment model can be fit to the unbound concentration-time profile[6].

Absorption

Distribution and binding properties

Paclitaxel is found as bound and unbound drug[6, 26,33]. Unbound drug displays linear pharmacokinetics. Cremophor EL (CrEL) traps this drug, thereby less available for distribution to tissues, metabolism and biliary excretion. CrEL concentration affects the binding properties: At high CrEL, paclitaxel is mainly bound to CrEL and at low concentrations, it shows linear binding to plasma proteins and blood cells. In the absence of CrEL, plasma protein binding would be 85% and it has been shown to bind to both albumin and α1-acid glycoprotein.

Bound plasma concentration is modeled by three compartments with a binding compartment directly proportional to CrEL concentrations, a linear binding and a nonlinear binding to other plasma components.

> "Mechanistic basis of paclitaxel properties of distribution has been determined with micelle trapping with Cremophor EL (CrEL), distribution to RBCs, and binding to albumin, alpha acid glycoprotein, and platelets[6]".

Elimination (Metabolism + Excretion)

Clearance of unbound and total paclitaxel is significantly different among the elderly and younger age group with negative correlation (clearance is faster in elderly than the younger age group) whereas it is reduced with concomitant administration of verapamil[26]. Clearance is unaffected when the drug is administered for 96 h compared to 3-h infusion[34]. Paclitaxel and cremophor EL are good substrates for P-gp and competition for this carrier protein may result in decreased hepatic clearance[29, 35].

Metabolism

Paclitaxel undergoes extensive metabolism and biliary excretion[6]. The three main metabolites are formed via CYP2C8 and CYP3A4 enzyme mediated pathways[35]. Cytochrome P450 (CYP450) enzyme involved in the metabolism of paclitaxel to its major metabolite 6α-hydroxyl paclitaxel[22].

6-alpha-hydroxypaclitaxel, 3'p-hydroxypaclitaxel and 6-alpha, 3'-p-dihydroxypaclitaxel are the major metabolic products of products found in human bile[21]. Higher paclitaxel and 6-alpha-hydroxypaclitaxel AUC levels are found with liver function disturbances resulting in more pronounced neuropathy[21]. There is a difference found in metabolism among patients[23].

Exposure-Toxicity/Effect relationship

In one of the studies, paclitaxel-cisplatin (paclitaxel followed by cisplatin) combination chemotherapy is found to be efficacious and feasible for an ovarian cancer patient under hemodialysis; however, Grade IV neutropenia and grade III thrombopenia are observed[36]. Dose Limiting Toxicity (DLT) is febrile neutropenia at the dose of 157.5 mg/m^2 and Maximum Tolerated Dose (MTD) of paclitaxel is 140 mg/m^2/7 days[37]. Cumulative neuropathy is the major DLT only after multiple cycles of paclitaxel followed by cisplatin[22]. Frequently encountered

side-effects are neutropenia, neuropathy, asthenia and alopecia[25, 28,29,36]. Older age and hyperglycemia are associated with greater neurotoxicity[38].

4.1.2. 5-FLUOROURACIL

Drug and metabolites involved in the study

Oral pro-drugs of 5-FU: 5-fluoro-pyrimidonone (5FP), Capecitabine, Ftorafur

5-FU metabolites: 5'-deoxy-5 fluorocytidine (5'-DFCR), 5'-deoxy-5-fluorouridine (5'-DFUR), dihydrofluorouracil, α-Fluoroβ-Alanine (FBAL) [12,13,40,42]

Drug indication

5-Fluorouracil (5-FU) is widely used in the treatment of colorectal and breast cancer. 5-FU is also used in the treatment of advanced gastrointestinal cancer, breast cancer, and variety of malignancies of epithelial origin, head and neck cancers, 5-FP in anti-tumor activity in P 388 leukemia models[8]. Greater hepatic metabolism shows that the drug is efficacious against liver metastases or primary liver cancer[8]. Capecitabine shows clinical effect for patients with taxane-refractory breast cancer and as first-line monotherapy for patients with metastatic colorectal cancer[12].

Dosage and administration

5-FU dosage is 400 mg/m^2 by loading dose and then 600 mg/m^2 by continuous infusion[7]. 5FP is administered orally once daily for 5 days every 4 weeks. Initial dose level is 23 mg/m^2/d and dose escalation by 30-35% till dose-limiting toxicity is observed[8]. In advanced colorectal cancer, continuous i.v. Infusion has resulted in a significantly higher response rate and less toxicity, compared with i.v. Bolus injections[9]. The starting dose for renal impairment is reduced to 75% of the standard starting dose[42]. Folinic acid (Leucovorin, LV) is administered with 5-FU

for biochemical modulation to increase the efficacy and the combination has proven high clinical activity in metastatic breast cancer patients[43]. UFT is administered as a combination of ftorafur (tegafur) and uracil at a molar ratio of 1:4[43].Continuous intravenous infusion of 5-FU is superior to bolus injection as increase in exposure to tumor tissues is directly related to tumor response[13, 44].

Drug sequence

Irinotecan maximum tolerated dose (MTD) is reached at 300 mg/m^2 when irinotecan followed 5-FU at 450 mg/m^2 when it preceded 5-FU[45]. Better tolerability is achieved when Irinotecan followed by 5-FU sequence is adopted[45].

Drug interaction

Oxaliplatin-Fluorouracil combination demonstrates synergistic effects with 5-fluoruracil (5-FU), even in 5-FU resistant tumors[46].

Pharmacokinetics

There is lower inter-occasion variability compared to inter-individual variability shows promising signs for dose individualization in future courses[46]. Maximum velocity (V_{max}) tends to increase with body surface area and the liver metastatic volume of involvement[10, 11]. Ideal body weight (IBW) is selected as a predictor of 5-FU volume of distribution and weight as a predictor of 5-FU clearance[46].

Pharmacokinetic model

5-Fluorouracil (5-FU) disposition is fit by one-compartment model with linear or non-linear elimination kinetics[7, 46,47,48]. Disposition of the drug is also best described by two-compartment model with nonlinear elimination[11, 49].

In one of the studies,

"A four-compartment parent-drug metabolite (5-DHFU) model with nonlinear Michaelis-Menten elimination from the central compartment of the parent drug (5-FU) is applied to describe 5-FU and DHFU pharmacokinetics[10]".

Absorption

Tegafur is completely and rapidly absorbed after oral administration [9,43,47]. Oral UFT/LV compares favorably with intravenous 5-FU/LV[50]. 5-FP (5-Fluoropyrimidonone) is administered as an oral prodrug of 5-FU and oral bioavailability of 5FP varies between 78 and 100% depending on dosage and dosing regimen[8].

Distribution

"V_{max} tends to increase with body surface area and the liver metastatic volume of involvement[11]".

Ideal body weight (IBW) is selected as a predictor of 5-FU V_d[46].

Elimination (Metabolism + Excretion)

A circadian rhythm following continuous infusion of 5-FU results in diurnal variations in clearance, which is due to dihydropyrimidine dehydrogenase activity[7]. One of the fixed variable affecting the clearance is time and modeled as a sum of two cyclic components[7]. Renal impairment causes a moderate and majority increase in the metabolites depending on the percentage being excreted in the urine[12, 42]. Clearance of 5-fluorouracil is significantly reduced by increased age and is lower in women compared with men[11]. Plasma clearance of 5-FU is schedule dependent. 5-FU clearance is significantly reduced by increased age, low PMNC-DPD, high serum alkaline phosphatase and elapsed time during infusion[51]. 5-FU undergoes rapid hepatic metabolism to give various metabolites with anti-neoplastic properties[7].

Metabolism

Ftorafur gets metabolized slowly in the liver by CYP450. Capecitabine and Ftorafur, both utilize the high activity of thymidine phosphorylase in malignant tissue, resulting in a generation of 5-FU preferentially in tumor tissue.

> "Capecitabine is first metabolized in the liver to 5'-deoxy-5 fluorocytidine (5'-DFCR) which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumor tissue. Further catalytic activation of 5'-DFUR to 5-FU then occurs preferentially in the tumor by the tumor-associated angiogenic factor thymidine phosphorylase, thereby minimizing the exposure to normal tissues to 5-FU. Subsequently, 5-FU is further metabolized to dihydrofluorouracil and then FBAL[12]".

5-FU displays nonlinear pharmacokinetics as a result of saturable metabolism located mainly in the liver[10, 11,49]. As we increase 5-FP dose, there is no corresponding increase in 5-FU, which may be due to saturable metabolism of aldehyde oxidase in converting from 5-FP to 5-FU. This can be seen from the difference in the extent component (AUC) of the prodrug 5-FP and metabolite 5-FU. Uracil acts as an inhibitor of the 5-FU catabolizing enzyme dihydropyrimidine dehydrogenase (DPD), resulting in elevated and sustained concentrations of 5-FU in the body. DPD is the rate-limiting enzyme of 5-FU and UFT, Eniluracil and S1 are some of the DPD inhibiting fluoropyrimidines.

Excretion

Renal clearance accounts for 15% of the total body clearance[13]. Patients with severe and moderate renal impairment, the AUC of 5'-DFUR is higher than in patients with normal renal function[12].

Exposure-Toxicity/Effect relationship

Toxicities observed are related to gastrointestinal and fatigue[8]. The most common dose-limiting toxicity is hand-foot syndrome and in some cases myelosuppression[8, 11]. Non-hematological toxicities in patients receiving 5-FU/leucovrin are grade 3 or 4 related adverse events diarrhea and stomatitis[9, 13,42]. Higher incidences of these events are found among patients with moderate renal impairment. The most frequently occurring toxicities in the capecitabine group are hand-foot syndrome and diarrhea and elderly patients have a higher incidence of grade 3 or 4 gastrointestinal events[42, 52]. Dose limiting toxicity is mucositis for continuous infusion and myelosuppression for the bolus injection[8, 11]. Digestive intolerance and oral mucositis are the major limiting toxicities during prolonged 5-FU infusions[44]. Decrease in DPD enzyme activity can predispose cancer patients to severe life-threatening toxicity[46].

The maximum tolerated dose is identified as 625 mg/m^2/d orally for 5 days every 28 days[8]. Capecitabine when administered in a continuous twice-daily schedule has a maximum tolerated dose (MTD) of 828 mg/m^2 twice daily[13]. Hand-foot syndrome, nausea/vomiting, diarrhea, neutropenia and abdominal pain are found to limit the capecitabine dose[13]. Capecitabine is highly active compared to 5-FU[13].

4.1.3. PLATINUM COMPOUNDS

4.1.3.1. Cisplatin

Drug

Cis-diaminodichloroplatin (CDDP) Cisplatin, Cisplatin is hydrolyzed to monoaqua complex[53].

Drug indication

Cisplatin [cis-diamminedichloroplatinum (II), CDDP] is a potent anticancer agent for treatment of testicular, bladder, head/neck (H/N), peritoneal carcinoma, ovarian (recurrent) and esophageal cancer. Paclitaxel and cisplatin combination chemotherapy is efficacious and feasible for an ovarian cancer patient under hemodialysis[54]. Cisplatin with continuous infusional 5-FU and epirubicin (ECF) regimen is used to treat gastrointestinal cancers[55].

Dosage and administration used in various studies

Cisplatin dosage is 80 mg/m^2 by infusion over 2 h, 3.5 h or 4 h[56, 57]. Cisplatin dosage escalation ranges from 100 to 400 mg/m^2 in the case of hyperthermic peritoneal perfusion to patients with peritoneal carcinomatosis[58]. Cisplatin is administered intravenously and dosage ranging from 60 to 100 mg/m^2 for 90 minutes[57, 60]. Dosing like any other anti-cancer drug is based on body surface area[59].

Time factor and sequence

Paclitaxel at a dose of 150 mg/m^2 is administered as a 3-h continuous i.v. infusion[36]. Thirty minutes after paclitaxel administration, cisplatin is administered at a dose of 30 mg/m^2 for 30 minutes[36].

Drug interaction

Cisplatin-Etoposide (PE) yielded a better response rate compared with cyclophosphamide, methotrexate, 5-fluorouracil (CMF) without prior chemotherapy because of the in vivo synergy between PE[55]. In pretreated patients with anthracycline resistant disease, the response rate is slightly higher for patients treated with higher doses of cisplatin and docetaxel[55].

Pharmacokinetic model

Disposition of Cisplatin is described by one-compartment model[56]. Concentration-time data is also described by two-compartment model with an additional peritoneal compartment in case of cisplatin peritoneal perfusion[57].

Absorption

Distribution and binding properties

The volume of distribution is considerably smaller for the monohydrated complex than for cisplatin[53]. The reason might be cisplatin has more lipophilic property compared to monohydrated complex, which mainly stays in the blood[53].

Cisplatin mainly binds to plasma proteins and 95% of cisplatin is protein bound after 24 hours[59]. Cisplatin can also bind to RNA and cellular proteins[55]. Platinum accumulations are mostly found in the liver, uterus, testes, ovary and thyroid and the lowest in the brain and blood[62].

Elimination

Clearance of unchanged Cisplatin is affected by dose schedule and body surface area[56]. Regarding dose schedule, the clearance of cisplatin is found to increase after 2-hour infusion schedule compared with clearance after longer infusions[56]. Clearance of filtered platinum is significantly related to N-acetyl-β-D-glucosaminidase (urinary enzyme) [60].

Metabolism

Excretion

Exposure-Toxicity/Effect relationship

Nephrotoxicity, which is the most serious side effect of cisplatin, can be managed using sparse data in a clinical setting[53, 55, 59, 63]. The benefit of peritoneal perfusion is gaining higher

and directy drug exposure to the patients with peritoneal carcinomatosis[58]. This is shown by higher AUC and C_{max} by peritoneal perfusion compared to conventional intravenous infusion[58]. Monohydrated complex has also been linked to nephrotoxicity besides cisplatin[53]. Cisplatin-Vinblastine combination may alter the severity of neutropenia[55].

4.1.3.2. Carboplatin

Drug indication

Carboplatin has wide anti-tumor activity with proven efficacy in ovarian cancer, germ cell tumors, non-small cell and small-cell lung cancer, head and neck cancer, soft tissue sarcoma, urinary tract tumors, breast cancer and brain tumors[86].

Dosage and administration used in various studies

Carboplatin is usually given as single doses in the range 20-500 mg/m^2 [86]. Carboplatin administerd according to body surface area in pediatric patients show large variation in area under the curve[61].

> "Carboplatin is the only cancer drug for which conventional doses are individually adjusted according to estimated clearance and target area under the curve[93]."

Pharmacokinetics

Carboplatin undergoes dose-independent pharmacokinetics. It is established that the pharmacokinetics of carboplatin are linear upto doses of 450 mg/m^2. This can be shown by dose-proportional increases in peak plasma concentration and area under the concentration-time curve values and pharmacokinetic parameters of high dose carboplatin agree with those obtained at low doses[86].

"The unbound plasma carboplatin (fu) could be predicted as a function of time, infusion rate and covariates affecting unbound carboplatin clearance, weight, nephrectomy status and serum creatinine[15]".

Pharmacokinetic model

A two-compartment model is used to describe the concentration-time data[64, 87].

Absorption

Distribution and binding properties

Weight is a significant covariate on the volume of distribution of the central compartment and reflects an increase in physiological or distributional spaces available to unbound carboplatin as weight increases[15, 86]. The rate of plasma carboplatin binding is low and not dependent on patient characteristics[89].

Elimination

Total body clearance is predicted by Cockcroft and gault formula[63]. Unbound carboplatin clearance is dependent on weight, age, nephrectomy status and serum creatinine[15, 86, 87]. The interindividual vriability in clearance decreased from 74% to 49% by taking account of weight and to 29% under the final regression formula[62]. Carboplatin clearance is significantly related to creatinine clearance and body height, explaining 73% of the interindividual variability[92].

Metabolism

Carboplatin doesn't undergo appreciative metabolism but is extensively hydrolyzed.

Excretion

Renal clearance (primarily due to glomerular filtration) is the major route of excretion with 50-75% of the urine in 24 h[86].

Exposure-Toxicity/Effect relationship

Myelosuppression, especially thrombocytopenia, is the dose-limiting toxicity of carboplatin[86]. There is a strong relationship found between the systemic exosure (AUC) of free Carboplatin and toxicity (Thrombocytopenia) [88]. Ototoxicity is strongly related to the cumulative carboplatin AUC[90]. A sigmoid-maximum effect model describing the relationship between thrombocytopenia and free platinum exposure when carboplatin is given along with paclitaxel. This shows that the patients experience less thrombocytopenia compared to carboplatin alone[91].

4.1.4. TOPOISOMERASE INHIBITORS

4.1.4.1. Topotecan

Drug indication

Topotecan shows activity in human tumor types, including ovarian cancer, non-small cell lung cancer (NSCLC), metastatic epithelian ovarian cancer, second-line therapy in patients with small cell lung cancer (SCLC) and non-lymphocytic haematologic malignancies. Since the topotecan penetrates the CSF, it is used to treat brain tumors[17, 65].

Dosage and administration

Topotecan is administered intravenous as a 21 day continuous infusion every 28 days[16]. Dosages ranged from 0.4 to 0.6 mg/m^2 per day[66]. Topotecan is administered as 5.5 or 7.5 mg/m^2 per day as a 24-h continuous infusion or 0.5-1.25 mg/m^2 per day as a 72-h continuous infusion or as 30 minute infusion daily on 5 consecutive days every 3 weeks[17].

Drug interaction

Amifostine, 300 mg/m^2 does not significantly affect the pharmacokinetics of topotecan Pharmacokinetics[67].

Pharmacokinetics

Since inter-invidual variability is large compared to inter-occasion variability (6%), there is scope for dose individualization[68]. Inter-patient variability is attributed to differences in organ function, serum aspirate aminotransferase and albumin levels and are predictive of topotecan pharmacokinetics[16].

Pharmacokinetic model

The pharmacokinetic profile of topotecan is usually characterized by a two-compartment model and is linear in the dose range of 0.5-3.5 mg/m^2 [69, 70]. A three-compartment model adequately described topotecan lactone and total concentrations in the plasma and Cerebral Spinal Fluid (CSF)[17].

Absorption

Distribution

Topotecan is a derivative of campothecin, which has been structurally modified to increase water solubility[71].

Elimination

Elimination of topotecan is independent of the dose[70]. Topotecan clearance is related to serum creatinine level and age[72].

Exposure-Toxicity/Effect relationship

The main dose-limiting toxicity (DLT) is non-cumulative myelosuppression[16].

4.1.4.2. Etoposide

Drug indication

Etoposide (VP16) is widely used in the treatment of patients with a broad variety of solid malignancies and hematologic cancers.

Dosage and administration used in various studies

Oral etoposide is given to children ranging from 25 to 75 mg/m^2/day for 21 days[72]. VP16's efficacy is dose and schedule dependent as drug is more active during the G2 and S phases of the cell cycle is usually administered over 3-5 days[18, 73].

Drug interaction

Cisplatin-Etoposide (PE) yielded a better response rate with cyclophosphamide, methotrexate, 5-fluorouracil (CMF) without prior chemotherapy raises the possibility of in vivo synergy between Cisplatin-Etoposide combination[55].

Pharmacokinetics

VP16 displays a mixed renal and hepatic clearance, a high level of protein binding and a significant biliary excretion[18]. These characteristics suggest that small inter-patient or intra-patient variations in hepatic or renal function may modify VP16 pharmacokinetics behavior and subsequent plasma drug exposure[18]. Etoposide is schedule dependent and the drug is usually administered over 3-5 days[18].

Pharmacokinetic model

Concentration-time profile is best fitted by a three-compartment model after high dose Etoposide in children[74]. A two-compartment open pharmacokinetic model with constant rate i.v. infusion, first-order elimination and first-order absorption for patients receiving oral etoposide is used to describe the pharmacokinetics of total and unbound etoposide[72, 73].

Absorption

Etoposide has good oral bioavailability but with substantial inter-individual variation[55]. Exposure to free etoposide during prolonged oral treatment is highly variable among patients[75].

This marked inter-individual variability in pharmacokinetics suggests that therapeutic drug monitoring might be necessary, especially for oral etoposide[18, 73,75].

Distribution and Binding properties

Etoposide is highly protein bound and the free etoposide concentration is highly correlated with increasing age[18, 73,74]. Concentration dependent variability among patients in binding may occur only at high etoposide levels[74].

Elimination

Majority of the elimination is associated with β-phase and only fewer percentages associated with γ-phase[74]. Dose normalized for body weight and age of the patient are found to have significant correlation with clearance[74]. A drug interaction is found during doxorubicin and cyclophosphamide co-administration affecting biliary elimination[76]. Co-administration of other cytotoxic agents is known to influence etoposide clearance significantly or renal impairment and etoposide metabolism[74]. Etoposide clearance is affected by previous administration of cisplatin, which decreases etoposide clearance by three times compared without previous administration of cisplatin[73].

Excretion

Biliary excretion is more significant than metabolism[73].

PK/PD modeling and Exposure-Toxicity relationship

The dose-limiting toxicity of etoposide is reversible myelosuppression[55]. Several schedules of administration show a correlation between pharmacokinetic parameters of etoposide and neutropenia, which represents its main toxicity[77]. Toxicities included infection, cardiotoxicity, myelosuppression, stomatitis and reversible increases in serum creatinine and bilirubin[19].

4.1.4.3. Irinotecan (CPT11)

Metabolites: 7-ethyl-10-hydroxycampothecin (SN-38), glucuronic acid conjugate SN-38G, 7-ethyl-10- [4-N- (5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin (Aminopentane carboxylic acid-APC), 7-ethyl-10-[4-amino-1-piperidino] carbonyloxycomptothecin (NPC).

Drug indication

Colorectal cancer, children with solid tumors

Dosage and administration used in various studies

Dosage and administration of Irinotecan ranges from 100 to 350 mg/m^2 and intravenous infusion (0.75 to 2.25 h) respectively[78, 79].

Time factor and sequence

The sequence of treatment with irinotecan and infusional 5-FU affects the tolerability of this combination[80]. Irinotecan MTD is reached at 300 mg/m^2 when irinotecan followed 5-FU and 450 mg/m^2 when it preceded 5-FU[80].

Pharmacokinetics

CPT-11 and SN-38 are found in two forms: lactone and carboxylate[78, 81]. The inter-conversion between the lactone and carboxylate forms of CPT-11 is relatively rapid compared to SN-38[78]. SN-38 is excreted or metabolized quickly or is distributed extensively into tissues[78]. Results show that the parent drug and its three major metabolites account for virtually all CPT-11 disposition, with fecal excretion representing the major elimination pathway[20].

Pharmacokinetic model

Plasma concentration-time data of irinotecan and its metabolites is described by use of two or three compartment models[78]. A linear four-compartment model is fit simultaneously to the IRN, SN-38 and APC lactone plasma concentrations vs. time data[81].

Distribution

The V_{ss} of irinotecan has extensive distribution into the peripheral compartments[78]. CPT-11 lactone has extensive tissue distribution compared with carboxylate form[78].

Elimination

Clearance is higher for the lactone form compared with carboxylate form[78].

Metabolism

The enzymes involved in CPT-11 metabolism is regulated by pregnane X receptor (PXR)[79]. PXR activation leads to increased biliary excretion of CPT-11 and lowering the formation of metabolite SN-38 by reduced of exposure to hepatocytes[79]. Elderly patients and patients with a performance status of 2 are found to have reduced irinotecan clearance[79]. Sex, biliary function, higher total serum bilirubin and genetic variations in the UGT1A1are some of the factors affecting SN-38 formation[79].

Excretion

SN-38G is both non-active and non-toxic and is primarily eliminated by excretion in the urine and in bile[79]. The relatively higher amount of SN-38 in feces compared with bile is presumably due to hydrolysis of SN-38G to SN-38 by enteric bacterial beta-glucoronidases[20]. Fecal excretion representing the major elimination pathway[20].

Exposure-Toxicity/Effect relationship

The major dose-limiting non-hematologic toxicity of irinotecan is diarrhea and is highly correlated with SN38G AUC[78].

4.2. Population pharmacokinetic models

4.2.1. 5-fluorouracil

Background

5-fluorouracil (5-FU) is used in the treatment of colorectal cancer. 5-FU is also used in the treatment of advanced gastrointestinal cancer, breast cancer and several other types of cancer. 5-Fluorouracil (5-FU) dosage is 400 mg/m^2 by loading dose and then 600 mg/m^2 by continuous infusion and folinic acid dosage is 200 mg/m^2 administered by intravenous infusion. A circadian rhythm following continuous infusion is reported.5-FU is rapidly metabolized by the liver to give various metabolites with anti-neoplastic properties. Renal clearance accounts for 15% of the total body clearance.There are significant intra- and inter-patient variability in pharmacokinetic parameters. Individual 5-FU dose adjustment with pharmacokinetic monitoring provided a high survival rate and percentage of responses, with good tolerance.

Structural model or covariate-free model

5-FU concentration-time data are fitted by a one-compartment model with linear elimination kinetics[8].

$$C = \frac{D}{V} \times \exp(-K_{el} \times t)$$

"Data are fitted to a circadian function defined as the sum of two cyclic components of 12- and 24-h periods respectively:

$$CL_{ss} = CL_{av} + CLA_1 \times \cos\left[\left(t - t_{z1}\right) \times \frac{2\Pi}{24}\right] + CLA_2 \times \cos\left[\left(t - t_{z2}\right) \times \frac{2\Pi}{12}\right]$$

where CL_{av} is the average clearance

CLA_1 and CLA_2 the amplitude of the first and the second periodic component, respectively

t_{z1} and t_{z2} are the acrophase (peak) times of the first and the second periodic components, respectively[8].”

Inter-individual variability model

Volume of the jth subject is described by the relationship:

$$V_j = V_{mean} \times \exp(\eta_{Vj})$$

where V_{mean} is the population mean

η_{Vj} is the difference in volume of distribution between the population mean and the jth subject and η_V is assumed to be a Gaussian random variable with mean zero and variance $\sigma^2_{\eta.}$

$$CL_j = CL_{mean} \times \exp(\eta_{CLj})$$

where CL_{mean} is the population mean and η_{CLj} is the difference in clearance between the population mean and the jth subject; η_{CL} is assumed to be a Gaussian random variable with mean zero and variance σ^2_{η}[8].

Covariate model

$$CL_{mean} = sex \times \theta_1 + \theta_2$$

where θ_1 and θ_2 are model parameters.

Intra-individual variability model

The concentration-time profile in the jth individual is assumed to be affected by an additive error described by ε_{ij}

$$C_{ij}(t) = f(p_j, D_j, t_{ij}) + \varepsilon_{ij}$$

where p_j are the pharmacokinetic parameters (clearance, Volume and first-order rate constants) of the jth subject,

t_{ij} is the time of the ith measurement

D_j is the dosing history of the jth subject, f is the pharmacokinetic model

ε_{ij} represents the residual departure of the model from the observations and contains contribution from intra-individual variability, assay error and model misspecification[8].

Population pharmacokinetic model

$$Ci_j = \frac{Dose}{V_{mean} \times \exp(\eta_{Vj})} \times \exp - \left(\frac{CL_{mean} \times \exp(\eta_{CLj})}{V_{mean} \times \exp(\eta_{Vj})} \right) + \varepsilon_{ij}$$

Population parameters

$V_{mean} = 18.4$

$\eta_{Vj} = 114$

$\theta_1 = 60.2$

$\theta_2 = 65.0$

$\eta_{CLj} = 55.7$

$\varepsilon_{ij} = 0.416$

5-Fluorouracil

Pharmacokinetics of 5-FU is parsimoniously described by a one-compartmental model with inter-individual and inter-occassional random effects on clearance only[82]. A combined additive and proportional model best described the pattern of residual error.

Population pharmacokinetic model

$$Cij = \frac{Dose}{\theta 1 \times \exp(\eta Vj)} \times \exp - \left(\frac{\theta 1 + \theta 2(age - 55) \times \exp(\eta CLj)}{\theta 3 \times \exp(\eta Vj)} \right) \times (1 + \varepsilon ij) + \varepsilon ij$$

Population parameters

$\theta 1 = 0.907$

$\theta 2 = 7.94$

ηCLj = 10

$\theta 3$ = 15.2

ηVj = Unestimated

εij = 31%

4.2.2. Etoposide (VP16)

Backgound

Etoposide is administered by intravenous infusion 40 mg/kg for 4 h. The focus of the article is to examine the pharmacokinetics of etoposide with a special focus on terminal concentration.

Low dose Vs. High dose

There is no significant difference found between the kinetics in adults and children at lower doses. However, data on the kinetics in children under high dose conditions are limited.

Data were best fitted by a three-compartment model after high dose Etoposide in children.

Significant correlation between clearance, dose normalized for body weight and age of the patient was found. Majority of elimination is associated with the β-phase and only fewer percentage of elimination is associated with the terminal γ-phase. There is a difference in clearance values for high dose etoposide in children compared to high dose etoposide in adults. Coadministration of Phenobarbital, known to induce cytochrome P-450 enzymes, may explain high CL values. There is high inter-patient and intra-patient variability in the protein binding of Etoposide with an increase in unbound drug at high etoposide concentrations.

Structural model or covariate free model

Data are best fitted by a three-compartment model after high dose etoposide in children[74].

$$C = \frac{Dose}{Vc}\left(A_1 \times \exp-(k_{10}t) + B_1 \times \exp-(k_{12}t) + C_1 \times \exp-(k_{13}t)\right)$$

Inter-individual variability model

$$Vc_j = V_{cmean} \times \exp(\eta_{Vj})$$

$$K_{10\,j} = K_{10\,mean} \times \exp(\eta_{k10\,j})$$

$$K_{12\,j} = K_{12\,mean} \times \exp(\eta_{k12\,j})$$

$$K_{13\,j} = K_{13\,mean} \times \exp(\eta_{k13\,j})$$

Intra-individual variability model

The concentration-time profile in the jth individual is assumed to be affected by an exponential error described by the relationship:

$$C_{ij}(t) = f(p_j, D_j, t_{ij}) + \varepsilon_{ij}$$

Population pharmacokinetic model

$$C_{ij} = \frac{Dose}{V_{cmean} \times \exp(\eta_{Vj})} \begin{pmatrix} A_1 \times \exp-(K_{10mean} \times \exp(\eta_{k10\,j})t) + \\ B_1 \times \exp-(K_{12mean} \times \exp(\eta_{k12\,j)}t) + \\ C_1 \times \exp-(K_{13mean} \times \exp(\eta_{k13\,j})t) \end{pmatrix} \times \exp(\varepsilon_{ij})$$

Population parameters

$V_{cmean} = 0.061$

$\eta_V = 21\%$

$K_{10mean} = 0.526$

$\eta_{k10\,j} = 8\%$

$K_{12mean} = 1.263$

$\eta_{k12\,j} = 18\%$

$K_{13mean} = 0.038$

$\eta_{k13\,j} = 25\%$

$\varepsilon_{ij} = 12\%$

4.2.3. Topotecan

Background

Topotecan is used in the treatment of ovarian cancer. The focus of the article is to explore inter- and intraindividual variabilities in topotecan clearance using a population pharmacokinetic approach. The dose-limiting toxicity of topotecan is myelosuppression, predominantly neutropenia. Total Topotecan plasma levels were analyzed according to a two-compartment model with linear elimination from the central compartment[73].

The final model with creatinine clearance (CrCl) or that with age and Scr may be useful for individual dosing of Topotecan. There is large interoccasion variability between cycle 1 and cycle 2 than between days of the same cycle.

General population pharmacokinetic model is given by

$$Yij = f(xij, pi) + \varepsilon ij$$

$$Cobs = Cpred \times (1 + \varepsilon 1) + \varepsilon 2$$

$$CLj = CLmean \times (1 + \eta CLj)$$

$$Vcj = Vcmean \times (1 + \eta Vcj)$$

$$Vpj = Vpmean \times (1 + \eta Vpj)$$

$$Cij = \frac{Div}{(\theta 3 \times weight)(1 + \eta Vcj) + \kappa ij} \left\{ \frac{k21 - \frac{CLj}{Vcj}}{\beta - \frac{CLj}{Vcj}} \times \exp - \left(\frac{CLj}{Vcj} t \right) + \frac{k21 - k12}{k12 - \beta} \times \exp - (k12 \times t) \right\} \times (1 + \varepsilon ij) + \varepsilon ij$$

$CLmean = \theta 1 \times CrCL$ for cockcroft-gault formula

$$Vcmean = \theta 3 \times Weight$$

$$Vpmean = \theta 4$$

Population Parameters

$\theta 1 = 5.47$

$\eta Vcj = 24\%$

κij = unestimated (non-significant)

$\theta 3 = 0.584$

$\eta CLj = 50\%$

$\theta 4 = 33.9$

$\eta Vpj = 53\%$

PE $\varepsilon ij = 17.1\%$

AE $\varepsilon ij = 0.45$

4.2.4. E7070

Structural model or covariate free model

Data are fit by three-compartment model with saturable transport to the peripheral compartment and both linear and saturable elimination from the central compartment[72].

$$C = A_1 \times \exp - \left(k_{10} + \frac{V_{\max}}{K_m + C} \right) t + B_1 \times \exp - \left(\frac{T_{\max}}{T_m + C} \right) t + C_1 \times \exp - \left(K_{13} \right) t$$

Inter-individual error model

$$V_{cj} = V_{cmean} \times \left(1 + \eta_{Vcj}\right)$$

$$V_{\max\, j} = V_{\max\, mean} \times \left(1 + \eta_{V\max\, j}\right)$$

$$K_m = K_{mmean} \times (1 + \eta_{kmj})$$

$$T_{\max\, j} = T_{\max\, mean} \times \left(1 + \eta_{T\max\, j}\right)$$

$$T_{mj} = T_{mmean} \times \left(1 + \eta_{Tmj}\right)$$

Covariate model

$$V_{cmean} = \theta_1(1 + \theta_2 \times [BSA - 1.76])$$

$$V_{\max mean} = \theta_3(1 + \theta_4 \times [BSA - 1.76])$$

Intraindividual error model

The concentration-time profile in the jth individual is assumed to be affected by combination (additive+exponential) error described by the relationship:

$$C_{obsij} = C_{predij}(1 + \varepsilon_1) + \varepsilon_2$$

Population pharmacokinetic model

$$Cij = \frac{Dose}{V_{cmean} \times (1 + \eta_{Vcj})} \left[\begin{array}{l} A_1 \times \exp - \left(\dfrac{k_{10mean}(1 + \eta_{k10j}) + }{\dfrac{V_{\max mean}(1 + \eta_{V\max j})}{K_{mmean}(1 + \eta_{kmj)} + C}} \right) t \\ + B_1 \times \exp - \left(\dfrac{T_{\max mean}(1 + \eta_{T\max j})}{T_{mmean}(1 + \eta_{Tmmeanj}) + C} \right) t \\ + C_1 \times \exp - \left(K_{13meanj}(1 + \eta_{k13j}) \right) t \end{array} \right] \times (1 + \varepsilon_{ij}) + \varepsilon_{ij}$$

Population Parameters

$\theta_1 = 6.51$

$\theta_2 = 0.646$

$\eta_{Vcj} = 26\%$

$\theta_3 = 2.55$

$\theta_4 = 0.528$

$\eta_{V\max j} = 46\%$

$K_{mmean} = 0.485$

η_{kmj} = unestimated

$T_{\max mean} = 23.5$

$\eta_{T\max j} = 50\%$

$T_{mmean} = 2.25$

$\eta_{Tmj} = 120\%$

$K_{13meanj} = 0.96$

$\eta_{k13j} = 28\%$

4.2.5. Cyclophosphamide

Background

Cyclophosphamide pharmacokinetics is best described by a one-compartment model[82]. Lower clearance (CL) is found in the second course compared to the first course. Both intravenous and oral cyclophosphamide given at conventional doses indicate interoccasion variability is not significant. Interindividual variability in clearance is 35% and 21% for interoccasion variability.

Intraindividual error model

$$\ln[C_{obs}] = \ln[C_{pred}] + \varepsilon_{ij}$$

Population pharmacokinetic model

$$C_{ij} = \frac{Dose}{\theta_4 \times \exp(\eta_{Vj})} \times \exp - \left(\frac{\theta_1 + \theta_2(wt - 70) + \theta_3 \times OCC_1) \times \exp(\eta_{CLj})}{\theta_4 \times \exp(\eta_{Vj})} \right) \times \exp(\varepsilon_{ij})$$

Population parameters

$\theta_1 = 70.1$

$\theta_2 = 0.907$

$\theta_3 = 13.6$

$\eta_{CLj} = 35\%$

$\theta_4 = 30.1$

$\eta_{Vj} = 14\%$

PE $\varepsilon_{ij} = 13\%$

4.2.6. Methotrexate

A two-compartmental model is fitted to the Methotrexate pharmacokinetics data with inter-individual and inter-occassional random effects on CL, V, Q, and V2 with proportional error model best described the pattern of residual error[82].

Inter-individual variability with covariate model

Pharmacokinetic model

$$C = \frac{D}{V} \times \left[\frac{(\alpha - k_{21})}{(\alpha - \beta)} \exp-(\alpha \times t) + \frac{(k_{21} - \beta)}{(\alpha - \beta)} \times \exp-(\beta \times t) \right]$$

Covariate model

$$CL_j = \left(\theta_3 \times OCC1 + \theta_4 (WT - 75)\right) \times \exp(\eta_{CLj})$$

$$Vc_j = \left(\theta_1 - (GFR - 80) \times \theta_2\right) \times \exp(\eta_{vj})$$

$$k_{12\,j} = \left(\theta_5\right) \times \exp(\eta_{k12\,j})$$

Population pharmacokinetic model

$$Ci_j = \frac{D_{iv}}{\left(\theta_1 \times OCC_1 + \theta_2 \times (WT - 75)\right] \times \exp(\eta_{Vj})} \left\{ \begin{array}{l} \dfrac{k_{21} - \dfrac{CL_j}{V_{cj}}}{\beta - \dfrac{CL_j}{V_{cj}}} \times \exp-\left(\dfrac{CL_j}{V_{cj}} t\right) \\ + \dfrac{k_{21} - k_{12}}{\dfrac{CL_j}{V_{cj}} - \beta} \times \exp-\left(k_{12} t\right) \end{array} \right\} \times \exp(\varepsilon_{ij})$$

Population parameters

$\theta_1 = 15.5$

$\theta_2 = 0.229$

η_{Vj} = 37%

θ_3 = 128

θ_4 = 1.05

η_{CLj} = 20%

$\eta_{k12\,j}$ = 28%

ηvp_j = 22%

4.2.7. Ifosfamide

Background

Ifosfamide (Holoxan) is a prodrug, which needs activation by cytochrome P450-3A4 (CYP3A4) to 4-hydroxyifosfamide. Ifosfamide metabolites are 2-, 3-dechloroethylifosfamide and 4-hydroxyifosfamide. Pharmacokinetics of 4-hydroxyifosfamide are formation rate-limited. The Focus of the article is to develop population pharmacokinetic model that describe the pharmacokinetics of ifosfamide and its metabolites. Drug indication of this drug is found in small-cell lung cancer. Dosage and administration are 2 or 3 g/m2 1-h intravenous infusion over 1 or 2 days respectively. Ifosfamide active in small cell lung cancer is also effective when added with Paclitaxel and Carboplatin as ifosfamides metabolites are able to penetrate the blood-brain barrier. Ifosfamide metabolism is subject to autoinduction, which will increase metabolism of ifosfamide with time. Considerable interindividual variability was observed in urinary recoveries. Both ifosfamide and 4-hydroxyifosfamide exhibited a steeper dose-exposure relationship than dechloroethylated metabolites.

Intra-individual error model

Ifosfamide concentration-time profiles are adequately modeled by the development of autoinduction with an ifosfamide concentration dependent increase in ifosfamide clearance[83].

$C_{obs} = C_{pred}(1 + \varepsilon_1) + \varepsilon_2$

Inter-individual variability model

Inter-individual variability of each pharmacokinetic parameter estimated using a proportional error model.

$Pi = P_{pop} \times \exp(\eta_i)$ where P_{pop} is the parameter value of a typical individual with $\eta \sim N(0,\omega 2)$.

$$\frac{dA_{ifo}}{dt} = R - \left(CL_{init} \times A_{enz} \times \frac{A_{ifo}}{V_{ifo}} \right)$$

where R- infusion rate of ifosfamide

CL_{init}-initial ifosfamide clearance

A_{enz}-relative amount of enzyme in a hypothetical enzyme compartment

V_{ifo}-volume of distribution

Autoinduction

Change in A_{enz} over time in the enzyme compartment is dependent on C_{ifo} as follows

$$\frac{dA_{enz}}{dt} = k_{enz,\,out} - k_{enz,\,out} \times A_{enz} \times \left(1 - \frac{C_{ifo}}{C_{ifo} + IC_{50}} \right)$$

where $K_{enz,\,out}$ is the first-order rate constant for enzyme degradation/inactivation.

IC50 is the ifosfamide concentration at 50% of the maximum inhibition of enzyme degradation.

The change in the amount of metabolite (A_m) over time would be described as

$$\frac{dA_m}{dt} = F_m \times CL(t) \times \frac{A_{ifo}}{V_{ifo}} - k_m \times A_m$$

where K_m is the elimination rate constant of the metabolite. F_m is the fraction of the ifosfamide metabolized to the metabolite.

Population Parameters

$CL_{init} = 2.49$

$\eta_{CLinit} = 41\%$

V_{ifo} = 46.2

$\eta vifo$ = 17%

ε_{ij} = 17.4%

F^*_{2DCE} = 0.0426

$\eta F^* 2DCE$ = 52%

K_{2DCE} = 2.22

$\eta K 2DCE$ = unestimated

ε_{ij} = 6.89

F^*_{3DCE} = 0.00771

$\eta F^* 3DCE$ = 36%

K_{3DCE} = 0.138

PE ε_{ij} = 33.1%

AE ε_{ij} = 0.366

F^*_{4OHIF} = 0.018

K_{4OHIF} = 9.9

PE ε_{ij} = 30.5%

AE ε_{ij} = 0.218

4.2.8. Nedaplatin

Background

Nedaplatin, cis-diammineglycolatoplatinum, is an anticancer agent, which is a platinum derivative like cisplatin (CDDP) and carboplatin (CBDCA). Drug indication is found in head cancer, neck cancer, nonsmall cell lung carcinoma, oesophagal cancer, testicular tumor and

cervical cancer. Nedaplatin has a short elimination half-life and the platinum clearance is predicted based on individual renal function using creatinine clearance after nedaplatin dosing. The clinical use of nedaplatin causes less nephrotoxicity, but limiting factor may be its hematological toxicity.

Structural model

Two-compartment model was fitted to the plasma platinum concentration data[84]. Significant covariates affecting pharmacokinetic parameters: Clearance-Creatinine clearance (CLcr calculated by Cockcroft-Gault formula), Vc-Body weight

Intraindividual error model

A two-compartment pharmacokinetic model with zero-order input and first order elimination is used to describe the data.

$$C_{obs} = C_{pred} \times \exp(\varepsilon_{ij})$$

Pharmacokinetic model

$$C = \frac{D}{V} \times \left[\frac{(\alpha - k_{21})}{(\alpha - \beta)} \exp-(\alpha \times t) + \frac{(k_{21} - \beta)}{(\alpha - \beta)} \times \exp-(\beta \times t) \right]$$

Interindividual variability model

$$P_{ij} = \overline{P} \times \exp(\eta_{ij})$$

$$CL_{mean} = \theta_1 + \theta_2 \times CLcr$$

$$V_{cj} = (\theta_3 + \theta_4 \times BW) \times \exp(\eta_{Vcj})$$

$$K_{12j} = \theta_5 \times \exp(\eta_{k12j})$$

$$K_{21j} = \theta_6 \times \exp(\eta_{k21j})$$

Population pharmacokinetic model

$$C_{ij} = \frac{D_{iv}}{(\theta_3 + \theta_4 \times (BW)] \times \exp(\eta_{Vcj})} \left\{ \begin{array}{l} \frac{k_{21j} - k_{12j}}{k_{12j} - \frac{CL_j}{V_{cj}}} \times \exp - \left(\frac{(\theta_1 + \theta_2 \times CLcr) \times \exp(\eta_{CLj})}{(\theta_3 + \theta_4 \times (BW)] \times \exp(\eta_{Vcj})} t \right) \\ + \frac{k_{21j} - k_{12j}}{\frac{(\theta_1 + \theta_2 \times CLcr) \times \exp(\eta_{CLj})}{(\theta_3 + \theta_4 \times (BW)] \times \exp(\eta_{Vcj})} - k_{12j}} \times \exp - (k_{12j} t) \end{array} \right\} \times \exp(\varepsilon_{ij})$$

Population parameters

$\theta_1 = 4.47$

$\theta_2 = 0.0738$

$\eta_{CLj} = 25.5\%$

$\theta_3 = 12$

$\theta_4 = 0.163$

$\eta_{Vcj} = 21.4\%$

$k_{12j} = 0.304$

$\varepsilon_{ij} = 12.6\%$

5. CONCLUSION AND DISCUSSION

We achieved the objectives through this work; let us now discuss on the implications of this work. We start with the introduction to pharmacokinetics in understanding the need for pharmacokinetics in the area of drug development. We apply this understanding to the articles on pharmacokinetics by asking relevant questions. This helps us in gathering information from the articles. The questions we ask on pharmacokinetics from trials are not objective because of the extensiveness of the research in this field. However, we briefly reflect the frequently asked questions in chapter 2, section 2. Chapter 3 describes our process of collecting relevant biomedical articles by applying a single search criterion and strategy across several National Library of Medicine (NLM) service providers. Interestingly, articles collected didn't overlap much and only 20% repeated and this might be partly due to differences in the Medical Subject Headings (MeSH). For example, models might fall under biological models in one database and mathematical models in another database. The questionnaire helps in the collection of PK information from the articles on a particular anti-cancer drug in a structured format. In the future, this part may play a pivotal role for scientific researchers and oncologists for future drug development utilizing the pre-existing research work. The pre-existing research comprises interpretations and possible explanations for pharmacokinetic observations based on biological phenomenon. This information was synthesized under sub-headings in chapter 4, section 1 and includes dosage and administration, PK processes and models and drug interaction. PK processes and models focus mainly on distribution, elimination characteristics and compartmental models respectively.

From statistician point of view, the details in chapter 4, section 2 might be useful for stochastic simulation and modeling techniques involved in the formulation of population

pharmacokinetics. The main advantage is to understand the significance of the error models and the consequence if assumptions are violated.

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