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SOFTWARE TOOL MANAGE COMPLEX MULTIPLE DOSAGE REGIMEN CALCULATIONS

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ABSTRACT

In modern era of development health system conquer major issues linked with traditional way of calculating dose of patient. Advancement of pharmacokinetics based software ease calculation in clinical practice. A proper dosage regimen deliberately selected to acquire desired therapeutic effect with bottom prospect of side effect for drug with narrow margin of safety. For this purpose knowledge of pharmacokinetics parameters of drug should be considered because of link of pharmacokinetics parameters of drug and therapeutic effect they produced. This can be deciphering in two steps first achieving therapeutic outcome expressed in term of concentration of drug in plasma. Appropriate schedule of drug required to achieve drug level within therapeutic range. Second is relationship between dosage regimen and plasma drug concentration that effected by pharmacokinetic parameters of drug and patient factors e.g. creatinine clearance, disease state, body weight obtain plasma drug concentration various blood sample taken to check drug range within therapeutic window. Reliable software use to predict dosage regimen without time delay in clinical practice. The aim of study is to check whether multiple dosing of drug could result plasma drug concentration within therapeutic range by using software tool. Software enables fast high throughput analysis and minimize variability problem solving case study. Many decision support software developing to encounter clinical hurdles and decrease risk of intoxication and cost of therapy.

Keywords: Drug Accumulation, Dosage Regimen, Missed dose, Early and Late dose, Loading dose.

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INTRODUCTION

We unusually categorize serum drug concentration into sub therapeutic range, therapeutic range and toxic range. To flourish suitable dosage regimen drug should remain within selected therapeutic window for desire therapeutic effect. Problem emerge when drug concentration falls below breakpoint of minimum effective concentration and above breakpoints of minimum toxic concentration. When drug concentration below lower limit of range then less therapeutic and benefit effect obtained. When drug concentration cross toxic limit then more harmful effect exist and put life of patient in danger. Now a day beneficial and toxic effect increasing side by side but beneficial drug effect increase at much slower rate and patient risk that we due to toxic effect increase rapidly due to dose error calculation [1]. So to achieve desired optimal clinical effectiveness and drug concentration remain within window after multiple dose administration. Dosage regimen

depends on superposition principle that describe after multiple dose of drug administration pharmacokinetics of drug will not change. When course of therapy is given to patient, drug concentration increases in body and steady state is reached.

Steady-state concentration is the time period during which the drug remains constant in the body. There are many formulas that have been used to calculate different pharmacokinetic parameters, which ultimately help determine steady-state concentration. In a straightforward manner the average concentration is the total exposure (AUC) over one dosing interval divided by the duration of that interval [2].

After administering a single dose, we can calculate the area under the concentration-time curve from zero to infinity as an indicator of overall drug exposure. In contrast, during repeat-dose administration, we

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typically calculate the AUC during a steady-state dosing interval to assess overall drug exposure.

Two parameters are very important in developing a dosage regimen. These are size of drug dose and the second one is frequency of drug. Going into the detail greater the dose size greater the fluctuations and greater the chances of toxicity and the second is frequency of drug administration /Dose frequency. The two parameters are adjusted to have plasma concentration maintained in the therapeutic range especially for the narrow therapeutic index drugs. An appropriate balance is needed between dose size and dose frequency to have steady state conc. with minimum fluctuations. A set of equations that utilizes this information to describe first order drug elimination is available, and is useful in predicting serum drug levels [3].

Factors to be considered are Pharmacokinetic parameters (absorption, distribution, metabolism and excretion), Physiological parameters (age, weight, gender, nutritional status) [4]. Pathophysiological parameters (renal failure hepatic failure, heart disease), Lifestyle parameters (cigarette smoking, alcohol consumption) and other parameters may include drug dosage form, drug interactions etc [3].

DRUG ACCUMULATION

If dose of drug that is administered at fixed dose and fixed time interval in a body, the amount of drug in body will raise and then plateau (steady state level) to a mean plasma level higher than the peak plasma conc. obtained from initial dose.

When second dose given after time interval shorter than the time required to completely eliminating the previous dose, drug accumulation will occur in body. However, if second dose is given after time interval longer then the time required eliminating the previous dose, drug will not accumulate [5].

Therefore cautions must be taken in using single-dose pharmacokinetic parameters to calculate repeated dose regimen [6]. Drug accumulation during multiple dosage regimen results in increasing drug concentration until a steady state is achieved. At steady state the plasma concentration fluctuates between the maximum concentration C_{max} and minimum concentration C_{min} . Once a steady state is achieved C_{max} and C_{min} are constant. C_{max} is an indicator of the drug toxicity and drug accumulation. C_{max} at steady state C_{SSmax} and C_{min} at steady state is C_{SSmin} .

C_{SSmin} after IV administration are calculated as follows

$$C_{SSmax} = \frac{D}{Vd(1 - e^{-k\tau})}$$

$$C_{SSmin} = C_{SSmax} e^{-k\tau}$$

The C_{SSmax} is also a good indication of drug accumulation. If a drug produces the same C_{SSmax} at steady state, compared with the $(C_n - 1)$ max after the first dose, then there is no drug accumulation. Accumulation is affected by the elimination half-life of the drug and the dosing interval. The index for measuring drug accumulation R is

$$R = \frac{C_{SSmax}}{C_n - 1}$$

Substituting the value of C_{SSmax} and $C_n - 1$

$$R = \frac{1}{1 - e^{-k\tau}}$$

From above equation it can be concluded that drug accumulation measured with the R index depends on the elimination constant and the dosing interval. This is also concluded that the drug accumulation remains independent of the dose. Due to depend on k also depend on half-life of drug [7].

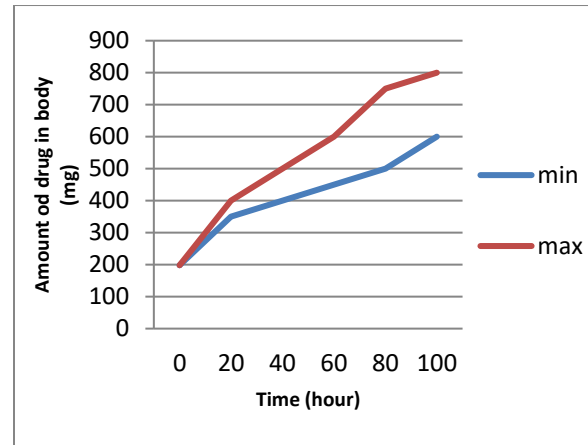


Figure 1: Minimum and maximum dose of drug.

For example, this figure shows that if dose of drug altered the time required for drug to achieve steady state is the same, but the final steady state plasma level changes proportionately.

Accumulation half-life

Equation shows relationship between accumulation half-life and half-life of drug [8].

$$\text{Accumulation half-life} = t_{1/2} (1 + 3.3 \log ka / ka - k)$$

ka is absorption rate constant and k is elimination rate constant. For IV administration, ka is very rapid (approaches ∞) k is very small in comparison to ka and can be omitted in the denominator of above Equation. Thus, the above equation reduces to Accumulation half-life = $t_{1/2} (1 + 3.3 \log ka / ka)$

$$ka / ka = 1 \text{ and } \log 1 = 0$$

$$\text{Accumulation half-life} = t_{1/2}$$

Thus, the time to reach 50% steady-state drug concentrations is dependent on the elimination $t_{1/2}$ and not on the dose or dosage interval [9].

REPETITIVE INTRAVENOUS INJECTION

Injections followed 1st order kinetics.

$$D_B = D_0 e^{-kt}$$

D_B is amount of drug in body

D_0 is initial amount of drug

$$D_B = D_0 e^{-k\tau}$$

The fraction (f) of the dose remaining in the body is related to the elimination constant (k) and the dosage interval (τ) as follows:

$$f = \frac{D_B}{D_0} = e^{-k\tau}$$

f depends on k and τ

If τ is large, f will be smaller because D_B (the amount of drug remaining in the body) is smaller.

Problem Of A Missed Dose

The equation describes the plasma drug concentration t hours after the n th dose was administered; the doses are administered τ hours apart according to a multiple-dose regimen.

$$C_p = \frac{D_0}{V_D} \left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}} \right) e^{-kt}$$

Concentration contributed by the missing dose is

$$C_p = \frac{D_0}{V_D} e^{-kt_{miss}}$$

t_{miss} = time elapsed since the scheduled dose was missed. Subtracting both equations, corrects for the missing dose as shown in following Equation.

$$C_p = \frac{D_0}{V_D} \left[\left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}} \right) e^{-kt} - e^{-kt_{miss}} \right]$$

Note: If steady state is reached (i.e. either n = large or after many doses), the equation simplifies to:

$$C_p = \frac{D_0}{V_D} \left[\left(\frac{e^{-kt}}{1 - e^{-k\tau}} \right) - e^{-kt_{miss}} \right]$$

This is useful when steady state is reached.

Generally, if the missing dose is recent, it will affect the present drug level more. If the missing dose is several half-lives later ($>5t_{1/2}$), the missing dose may be omitted because it will be very small, accounts for one missing dose, but several missing doses can be subtracted in a similar way if necessary.

Early Or Late Dose Administration During Multiple Dosing

When one of the drug doses is taken earlier or later than scheduled, the resulting plasma drug concentration can still be calculated based on the principle of superposition. The dose can be treated as missing, with the late or early dose added back to take into account the actual time of dosing, using Equation

$$C_p = \frac{D_0}{V_D} \left(\frac{1 - e^{-nkt}}{1 - e^{-kt}} e^{-kt} - e^{-kt_{miss}} + e^{-kt_{actual}} \right)$$

t_{miss} = time elapsed since the dose (late or early) is scheduled,

t_{actual} = time elapsed since the dose (late or early) is actually taken.

Loading Dose

The main objective of the loading dose is to achieve desired plasma concentrations, $C_{\infty av}$, as quickly as possible. The time required for the drug to accumulate to a steady-state plasma level is dependent mainly on its elimination half-life.

The time needed to reach 90% of $C_{\infty av}$ is approximately 3.3 half-lives, and the time required to reach 99% of $C_{\infty av}$ is equal to approximately 6.6 half-lives.

For drugs absorbed rapidly in relation to elimination ($k_a \gg k$) and are distributed rapidly, the loading dose D_L can be calculated as follows:

$$\frac{D_L}{D_0} = \frac{1}{(1 - e^{-k_a\tau})(1 - e^{-k\tau})}$$

For extremely rapid absorption, as when the product of k_a is large or in the case of IV infusion, $e^{-k_a\tau}$ becomes approximately zero and above Equation reduces to

$$\frac{D_L}{D_0} = \frac{1}{(1 - e^{-k\tau})}$$

The loading dose should approximate the amount of drug contained in the body at steady state. The dose ratio is equal to the loading dose divided by the maintenance dose.

$$\text{Dose ratio} = \frac{D_L}{D_0}$$

As a general rule of thumb, if the selected dosage interval is equal to the elimination half-life then the dose ratio calculated from the above equation should be equal to 2.0. In other word the loading dose will be equal to double the initial drug dose.

CONCLUSION

In recent years, extensive and constant increases in technology improve way of calculation and reduce risk of toxicity. Above complex calculation increase chance of toxicity and increase cost of therapy and put life of patient in danger. advancement in health system decrease burden of complex calculation by developing many software tool to ease way of calculation of dose of patient. Advancement in software Decrease cost of therapy by reducing duration of therapy, Decrease risk of intoxication, Improve drug therapy efficacy, Improve health quality life of patients by preventing improper drug use, Ease calculation without time delay.

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