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Individualization of Dosage Regimen-an Approach Towards Improved Clinical Outcomes

Abstract

Dosage regimen plays the most important role in obtaining the desired therapeutic outcomes. The focus perpetually is on the design of doses, their intervals and duration to acquire the optimum response. Many factors like age, gender, weight, body surface area, pathological state play a role in formulating these regimens and each factor is given importance in deciding regimen that gives the optimum response. The experiments gradually reveal the correct regimens after repeatedly being worked upon. Different parameters such as Cmax, Tmax, are calculated and estimated in order to decide by which dose and its interval the therapeutic level is maintained in the blood. Therapeutic drug monitoring is one of the most important aspects in dosage regimen where the narrow therapeutic index drugs are given and designed in such a way as to get the therapeutic response with minimized toxicity.

Key Words: Dosage Regimen, Therapeutic Drug Monitoring, Multiple Dosage Regimen

Introduction

The scope of designing the dose regimen has increased over time with the application in therapeutic drug monitoring of many drugs such as antibiotics. This is surely done to achieve maximum therapeutic efficacy. The dosage regimen design guided by therapeutic drug monitoring gives improved clinical outcomes. For dosage regimens the pharmacokinetic parameters show the relationship between dose, plasma concentration and other clinical factors. So, by considering the pharmacokinetic factors precise dose prediction can be done. (j.cmi.). A truly individualized dose relies in the therapeutic window where the beneficial and toxic outcomes are considered and quantitative effect along with the quantitative degree of clinical significance is given importance. The dosage regimens appear to be not too low or too high but in such combination of dose, interval, and duration that it helps achieve the goal of the treatment that is maximum therapeutic outcome. Deciding a regimen is basically a targeted and coordinated strategy in which the therapeutic goal is selected, and dosage regimen is designed according to it (B978-).

Dosage Regimen

The dosage regimen is the timetable of portions of a medication, including the time between dosages, the term of treatment and the add up to be taken each time. Dose regimens additionally incorporate how a medication is to be taken, and in what plan (Jelliffe, Neely, & Bayard, 2020).

Choice of medication administration regarding formulation, route of administration, drug portion, dosing span and treatment length.

Clinical implications

For most of the drugs, a preapproved dosage regimen proposed by manufacturer and approved by registration bodies is used. The regimen must meet average patient's requirements. As an innovation and considered important, dosage regimen individualization is considered fruitful, leading toe effective treatment of patients and limited cases to

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apply selected dosing decision to improve the treatment of patient and ultimately patients' health. For example, the standard regimen should be adapted to the individual characteristics on behalf of patients (e.g., weight and age) and to the presence of comorbidity that affects the pharmacokinetics of the drugs (e.g., renal failure, liver disease).

After the therapy is initiated, individualization of the dosage regimen, considering the response, may be important to better adapt the treatment to the condition of patients.

Importance

1. Dose regimens makes us design the dose and frequency of particular drug for a particular treatment.
2. MEC &MTC can be determined by using dose regimens.
3. It helps to establish of doses of narrow therapeutic index drugs.
4. Therapeutic drug monitoring analyzes the therapeutic effects of such drugs which require proper monitoring to provide beneficial therapeutic effects.
5. For drugs to have prolonged therapeutic activity multiple dosing regimens are given.

Objectives

1. By using multiple dosage regimens, we can keep the plasma concentration of the drug within the narrow limits of the therapeutic index hence chronic diseases can be treated for example, Drug concentration in the plasma above the MEC and below the MTC.
2. Usually, dosage regimen is maintained in such a way so that exact plasma level of the drug should be maintained without the accumulation or variation of drug outside the therapeutic window.
3. We can achieve the required MEC for some specific medications like anti-microbials.
4. Medicines having a very narrow therapeutic index for example digoxin, needs MEC and MTC to be defined properly.
5. In optimizing a dosage regimen for multiple administration, main target plasma concentration of the drug substance must be in between the therapeutic window to produce the response that is desired.

Factors Affecting Dose Regimen

Age

Babies (pediatric) are unusually delicate to specific medications on account of the youthful condition of their hepatic and renal capacity by which medications are inactivated and eliminated from the body. Inability to detoxify and eliminate drugs brings about their amassing in the tissues to a poisonous level. - The decrease in renal and hepatic capacity in the older (geriatric) may slow drug clearance and expands the chance of medication amassing in the body and ensuing toxicity.

Body Weight

The official doses for drugs are viewed as appropriate for 70 kg (150 pounds) people. - The proportion between the measure of medication administered and the size of the body impacts the medication concentration at the site of activity. Thusly, drug dosage may require change from the standard adult dose for strangely lean or fat patients.

Body Surface Area

A close relation exists between a large number of physiological processes and body surface area (BSA).

Sex

Ladies are more defenseless with the impacts of specific medications than are men. Pregnant ladies and nursing moms should utilize drugs just with the advice and under the directions by physicians. Instances of medications that are transported from the maternal to the fetal circulation for example liquor, sedative gases, barbiturates, anticoagulants, and so on. Due to the lacking medication detoxification and discharge mechanisms present in the baby, concentrations of medications may arrive at a more significant level in the embryo than in the maternal circulation.

The exchange of medications from the mother to the nursing baby through human milk may happen with
different medications with the medication impacts getting show in the newborn child.

Pathological State

The impacts of specific medications might be altered by the pathological state of the patient and should be considered in deciding the dose. Cautioning and precautionary measures are utilized in the medication

labelling to make the doctor aware of specific limitations in the utilization of a specific medication.

Precaution

Is utilized to inform the prescriber regarding some potential issues specialist with the utilization of the medication. It is less prohibitive than notice. for example The utilization of antibiotic medication anti-toxin may bring about excess of growths of fungi. In such a case, the doctor may recommend a substitute medication.

Warning

It is utilized when the potential for damage is more noteworthy than in cases in which the safeguard is utilized. For example, On the off chance that tetracycline is utilized within the sight of renal disability, it might prompt amassing of the medication and conceivable liver toxicity. So lower than common doses are indicated. On the off chance that treatment is delayed, blood serum levels of the medication ought to be taken and the patient checked at ordinary spans to guarantee the support of non-harmful levels of the medication.

Contraindication

A term that used to indicate an absolute prohibition to the use of a drug in the presence of certain stated conditions. It is the most restrictive of the warnings which limits the use of drugs.

Tolerance

The capacity to persevere through the impact of a medication, especially when obtained by a proceeded with utilization of the substance. Tolerance happens ordinarily in such medications e.g. anti-histaminic, opiate analgesics. Normal sensitivity might be recovered by suspending the medication administration for a while. The development of tolerance can be minimized by:

- Initiating therapy with the lowest effective dose.
- Avoiding prolonged administration.

Drug-Drug Interactions

The impacts of a medication might be adjusted by the simultaneous administration of another medication. These medication drug interactions are because of: A- chemical or physical interaction between drugs. B- alteration of the absorption, distribution, metabolism or excretion patterns of one of the medications.

Designing of Dosage Regimen and Superposition

In designing a dosage regimen, all pharmacokinetic parameters of the drug remain constant during therapy once the dosage regimen is established. The calculations are based on one- compartment model which can also applied for two- compartment model (Sime, Roberts, & Roberts, 2015).

Design of Dosage Regimen from Plasma Concentration

In the event that the Vd and half-life of a medication is known, at that point the dosage regimen can be planned to maintain the medication concentration in therapeutic range. Maximum dosage interval which preferably relies on the therapeutic index and the elimination half-life of the medication.

Parameter

Two main parameters that can be adjusted in developing a dosage regiment are as follows.

1. Dose size
2. Dosing frequency

Dose Size

It is characterized as, the measure of medication given to the patient at every patient straight forwardly identified with the size of therapeutic and toxic impacts. It manages Amount of medication retained after admission of each dose is thought of while figuring the dose size. Dose size is proportional to fluctuations among Cmax and Cmin in during each dosing interval. Subsequently, with more dose, danger of medication toxicity is more. Expanded danger of results for drugs with small therapeutic window.

Larger Dose Size

Larger fluctuations, greater risk of toxicity apart from therapeutic response.

Optimum Dose Size

Good Therapeutic response.

Smaller Dose Size

Smaller fluctuations, poor therapeutic response.

Dose Frequency

It is characterized as the time interval between the dose for example guarantee of dosing frequency is dosing interval. Dosing interval is assessed from half - life of the medication. At the point when dosage

interval is expanded with no adjustment in dose size then Cmin and Cmax diminished however when the dosing span is decline, at that point the medication accumulation in the body and cause toxicity. In the event that the increased and dose is unaltered, Cmax, Cmin, Cav decline yet the proportion Cmax/Cmin increase.

Higher dosing frequency (< T1/2)

- Lesser fluctuation
- shows therapeutic response
- but greater risk of toxicity

Optimum dosing frequency (=T1/2)

- Good therapeutic response

Lower dosing frequency (>T1/2)

- Larger fluctuations
- But poor therapeutic response

A legitimate equilibrium ought to be acquired between dose frequency and size to accomplish steady state concentration. And with least fluctuations to guarantee therapeutic efficacy and safety.

For drugs with wide therapeutic index, for example, Penicillin's larger doses might be managed at larger intervals (the greater half-life of medications) with no toxicity impacts. For drugs with limited therapeutic index like Digoxin, little doses with frequent interval (not exactly half-life of medication) are smarter to acquire a profile with least fluctuations which is more modest to that saw with controlled drug release system.

Therapeutic Drug Monitoring

Introduction

TDM includes the estimation of medication concentrations in biological fluid and the understanding of those
concentrations. TDM is the clinical evaluation of a medication's pharmacokinetic properties. Interpretation

requires information on the pharmacokinetics, sampling time, drug history and the patient's clinical condition.

Why We Perform Therapeutic Drug Monitoring

- Individualizing therapy (assessment of MD)
- Toxicity–diagnosing toxicity when the manifestation of toxicity and disease state are similar (theophylline) –avoiding toxicity(aminoglycosides)
- Changing patient's clinical state
- Monitoring and detecting drug interactions
- Narrow therapeutic index (NTI) drugs
- Significant pharmacokinetic variability drugs
- A reasonable relationship between plasma conc. and clinical effects
- Availability of cost-effective drug assay.

Interpretation of TDM Through Graph

In most cases when steady state is reached earlier if toxicity is suspected. At the appropriate time in relation to the last dose generally measured in the elimination phase gives a more reliable guide to drug dosing like some antibiotics (aminoglycosides).

Interpretation Through Sample Concentration

Individualization of Dose Through TDM

Following parameters should be considered before making the dosage regimen

- Sample should be taken at the time after the last dose was given
- Steady or plateau state has been achieved or not.
- Whether the patient follows the dosage regimen
- There is drug-drug interaction or not
- Whether kidney or liver dysfunction is there or not.
- Drug is obeying the linear kinetics or not assessed by the clinical pharmacokinetic principles.

Plasma Drug Concentration after Multi Dose

Repeated Administration

"Drug administration of a fixed dose at a regular time interval, through a given route" In repeated administration, accumulation happens when the medication is administered before the past dose is totally wiped out. The measure of medication in the body will at that point continuously rise. In the most well-known instance of first-order kinetics, the pace of medication disposal will increment relatively. At the point when the pace of medication end remunerates the pace of medication administration, the normal medication fixation arrives at steady state or plateau. At steady state, the measure of medication lost in every interval rises to the sum acquired, that is the dose increased by the bioavailability. Hence, the plasma concentration fluctuates between dosages

likewise starting with one dosing interval then onto the next.

Factors that affect the average steady state concentration are:

1. Dose administration rate (unit dose divided by dosing interval), affecting the steady state plasma concentration proportionally.
2. Bioavailability, which manages rate of dose administration.
3. Clearance, being inversely related to steady state concentration.

During the dosing interval, the factors affecting the fluctuation of plasma concentration around the average concentration are:

1. Frequency of drug administration: For a similar dosing rate, relative frequency of administration is inversely proportional to plasma fluctuation.
2. Elimination half-life: half-life and plasma fluctuation showing inverse proportionality.
3. Rate of absorption: slower rate of absorption ultimately leading to a decline in plasma fluctuation.

Drug's half-life determines the time required to reach steady state, as is the time it takes to reach a new plateau after a change in regimen.

Assessment

We can assess the plateau state concentration using the following equation

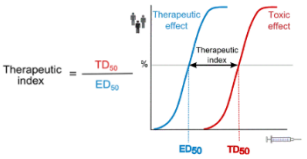
$$C_{ssav} = \frac{F * Dose}{CL * \tau}$$

Where τ indicates the dosing interval in hours, F indicates the Bioavailability of the drug and CL indicates the clearance of the drug.

We can calculate the accumulation index by using the given equation

$$RAC = \frac{1}{1 - e^{-\lambda * \tau}}$$

Where λ is equal to the elimination rate constant which is equal to the clearance/Volume of distribution



Now the accumulation index can be used to assess the steady or plateau state concentration:

$$C_{ssav} \simeq RAC * C_{single\ dose}$$

Accumulation Rate to Steady State Concentration

The concentration of the drug rises in the body upon the multiple dosing regimen just like the constant IV infusion rate. In this way, the steady state concentration of the drug will be dependent upon the elimination half-life of the medication. Phenobarbital, an antiepileptic drug will be reenacted. This drug's half-life for elimination is 100 hours i.e. 4 days and 100mg single dose is given daily.

Some chronic diseases are treated using more than one doses using multiple dosage regimen for example joint pain and high blood pressure because single drug leads to the decline of the drug concentration below the MEC after a certain interval of time. Therefore, the multiple dosage regimen is useful to treat the persistent diseases that keeps up the plasma concentration of the drug within the narrow range limits of therapeutic index to achieve the required clinical outcomes. Cardiotonic, anti-hypertensives and anti-convulsant are examples of such medications. Setting up a dosage regimen which maintains the plasma concentration level within the range without any fluctuation or accumulation is an ideal case. To calculate the dosage regimen individualized to a patient the plasma concentration

vs time curve prepared by single dose study is used to attain the PK boundaries. Using these PK parameters and the data on the dosing interval and dose size of the drug, we can predict the Plasma concentration vs time curve at any time after the dosage regimen is started.

To get an estimation of the multiple dosage regimen we need to select such subsequent dosage of the medicine in order to avoid or have an effect on the previously given dose. Superposition rule predicts that the medication's early doses will not have an impact on the pharmacokinetic parameters of the progressive doses. Therefore, following the 2nd, 3rd, and nth dose of the drug the blood concentration will superimpose the level of the drug that is attained after the n-1 portion. Moreover, the area under the curve for the principally administered dose must be equal to the plateau state area between the two regular doses.

Conclusion

The understanding of such concept is of utmost importance as the main focus has always been on the correct combination of dose, interval and its duration which helps treat the condition efficiently. The maximum therapeutic response with least toxicity is the main goal and deciding a regimen providing this is an achievement. As it is obvious, many factors which vary from individual to individual greatly effect these regimens and for such patients the regimens are to be designed according to them. The individualization of dose has helped a lot in effectively treating the condition avoiding unnecessary administration of doses. So, in calculating the multiple dosage regimen desired plasma concentration must be related to the therapeutic response that is the concentration must remain in the therapeutic window. The strategy followed is to focus the therapeutic goals and then assessing the pharmacokinetic parameters along with quantitative effects and the clinical response. So therapeutic drug monitoring helps in the dose adjustment and individualizing the regimen based on various factors to gain maximum therapeutic response.

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