Using Differential equations to Model Drug Concentrations within the Field of Pharmacokinetics/pharmacodyanamics

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Abstract:

The Food and Drug Administration discovered that individuals taking over-the counter pain medications containing acetaminophen were at risk of unintentional overdose because these patients would supplement the painkillers with other medications containing acetaminophen.

In this paper using the Ordinary differential equations to the drug model concentrations within the field of pharmacokinetics. In this we also describes pharmacokinetics explains how the body affects a specific chemical after administration through the mechanisms of absorptions and distributions. Models have been developed to simply conceptualization of the many processes that take place in the interaction between an organism and a chemical substance.

Key words*: pharmacodyanamics, pharmacokinetics, Ordinary differential equations, Drug absorptions, acetaminophen.*

I Introduction:

To begin, we must first understand the basic principles of pharmacokinetics. According to the *2011 Nurse's Drug Handbook*, *pharmacokinetics* is a branch of Pharmacology. It is currently defined as the study of a drug's actions as it passes through the body during absorption, distribution, metabolism, and excretion . These four parts all play a significant role in the movement of drugs in the human system. Absorption implies the

medication is able to be biologically passed through a bi-lipid cell membrane either actively or passively. The drug can enter via three methods of administration, with enthral (oral), parenteral (intravenous), ortranscutaneous (topical) drugs. Distribution is the process of the drug being transferred to other regions of the body, or action sites, by bodily fluids such as one's plasma. The conversion of the drug into useful molecules and compounds is known as metabolism and occurs mainly in the liver, or hepatic system. Finally, excretion is the elimination of the drug from the body, usually taking place in the kidneys, or renal system.

This resulted in an increase in liver failures and death over the years. To combat this problem, the FDA decided to lower the dosage from 1000 mg to 650 mg every four hours, thus reducing this risk (U.S. Food and Drug Administration). The measures taken in this example demonstrate the concepts behind the field of Pharmacology. Pharmacology is known as the study of the uses, effects, and mode of action of drugs ("Definition of Pharmacology").Knowledge of drug concentrations is of extreme importance when determining the dosage and frequency in which patients are administered medication. By ascertaining how much time is required to eliminate a drug, pharmacists are able to decide when the next dosage should be administered. By diving into this field, we are able to answer questions such as "how much intravenous fluid should be administered to each individual patient?" or "Why should Tylenol only be taken every 4 hours?". Specifically, the concepts within pharmacokinetics and pharmacodynamics aim to explain these answers using specific mathematical systems.

I.A General Overview of pharmacokinetics

Pharmacokinetics is the study of how organism affects a drug, whereas pharmacodyanamics is the study of how the drug affects the organism. Both together influence dosing benefit, and adverse effects, as seen in pharmacokinetics/ pharmacodyanamics models. clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient (Spruill et al. 1). Though it is not possible to directly access the sites where the drug becomes effective, such as in human organs, we are able to successfully measure the concentration of a drug at any given time via the blood, saliva, or urine. Concentration is defined as the amount of the drug divided by the volume where the drug is distributed (Spruill et al. 10). This is very useful when determining how a drug is distributed throughout a person's plasma. A large volume of distribution indicates the drug dosage has been distributed fully into the body fluids (Spruill et al. 11). The volume of distribution varies considerably between patients given the fact that genetic differences as well as illnesses can affect the plasma concentration within that body. Thus, patients with a lower plasma concentration amount would require a lower dosage of a drug to achieve a full distribution throughout the body; something important to note when servicing patients hemorrhaging while receiving medication. The concentration used to calculate the volume distribution is constantly changing as well due to excretion (Spruill et al. 11). Therefore, concentration of the drug in the bloodstream is directly proportional to the concentration in the tissue; higher doses of the drug implies a higher dose in the bloodstream and therefore higher dose diffused into the tissue.

II The ADME Model

A complicated process is initiated as soon as a drug enters the body. This process can be divided into four phases, absorption, distribution, metabolism and elimination and hence the acronym ADME. The absorption phase describes how the drug enters the body, or more precisely how the drug enters the bloodstream. When using intravenous (iv) administration, no absorption phase is present since the drug is injected directly into the bloodstream. The

whole dose can be given in one rapid injection, calle a bolus dose, or by using a constant rate infusion over a certain period of time. All other dosing methods, that is when the drug is not injected directly into the bloodstream, are called extra vascular dosing. Examples of such methods are injections into a muscle or fat tissue and oral dosing. Those methods have one thing in common, they require an absorption phase since the drug needs to cross some boundaries in the body before it reaches the bloodstream. As an example when administrating a pill (oral dosing), the pill needs to dissolve and cross the gut wall before it reaches the blood stream. The distribution phase describes how the drug spreads through the body, into its fluids and tissues, after it has reached the bloodstream. It is in the distribution phase the drug is brought to the place of action trough the blood-stream. The time it takes for the drug to get to the place of action is very dependent on if it is easily accessible by the bloodstream. The heart is, as an example, easily accessible by the bloodstream while the bone marrow is not. The third phase, metabolism, describes a process where the initial (parent)compound is broken into another compounds, called metabolites. The metabolites can either be inactive, therefore reducing the drugs effect on the body, or they can be active, sometimes more active than the parent compound. The liver plays a leading role in metabolism since it produces many of the enzymes used by metabolism.The last phase, the elimination phase, describes how the compounds and their metabolites are removed from the body via excretion. Most drugs are eliminated via the kidneys with urine.

The **four** phases of the **ADME** model can be summarized as:

- Absorption Drug entering the body .
- Distribution Drug is spreading to different areas of the body.
- Metabolism Drug is being changed to new chemical compounds.
- Elimination Drug is removed from the body.

III Pharmacodynamics

Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects (*2011 Nurse's Drug Handbook* 5). There are a few variables that influence the relationship. Time course is one of the variables defined as the length of time a drug stays at the receptor site which in turn determines the length of its effect. Another is tolerance, which states an increased concentration over time at a receptor site can actually cause the drug's effectiveness to decrease. As demonstrated in the graph to the left, when the number of doses increases, the drug concentration must also increase to get the same desired effect because the human body develops a resistance to the drug (Spruill et al. 3). Human bodies increase its metabolism so a drug is excreted from the body quicker and its time in the body decreases. Conversely, bacteria have internal survival responses that allow the bacteria to create protective barriers that provide a resistance to certain drugs the more it is exposed. This is why the long term use of non-steroidal anti-inflammatory drugs, such as ibeprophen, and repeated use of antibiotics may actually be detrimental to the human body.

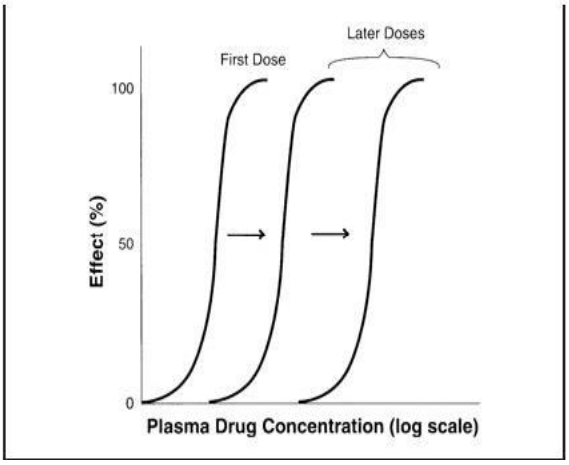
Example:

One compartment equation

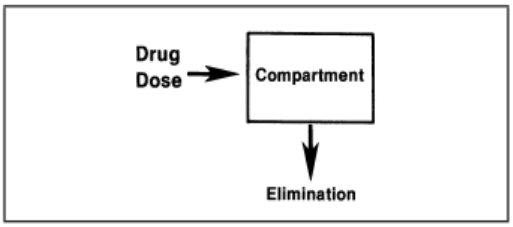
For example, a medication that aids in lowering blood pressure will target the autorhythmic cells in the human heart to block the release of calcium, thereby slowing contractions in the heart and lowering mean arterial pressure. But an antibiotic like penicillin,

that targets foreign bacteria in the body, will attach to the bacterial cell, preventing the cell from forming a protective cell wall and causing it to die.

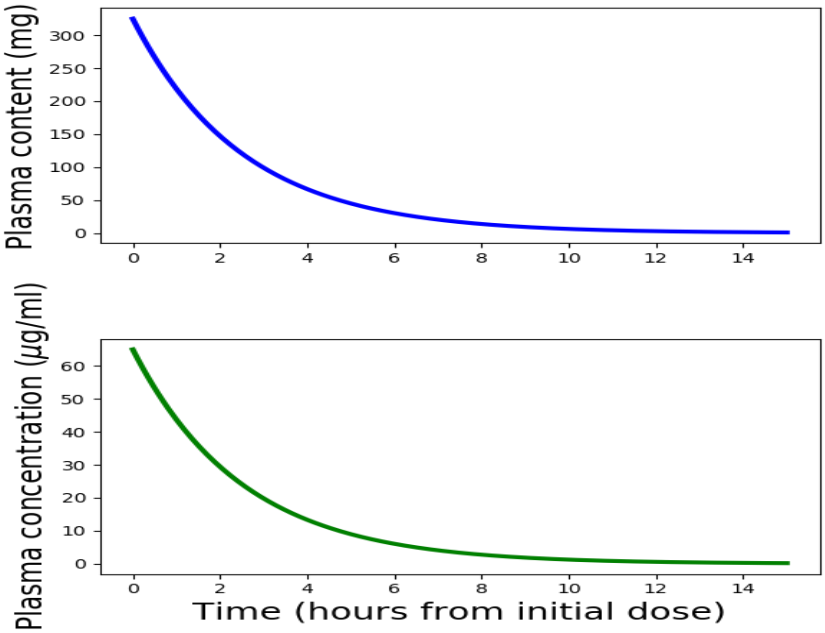
The ways in which drugs are received by the body differ by the type of drug and the drug's mode of action. Each drug has different mechanisms because receptor sites vary (Spruill et al. 2). As a result, the concentration at the receptor site must vary accordingly, proving the importance of understanding these biological processes.

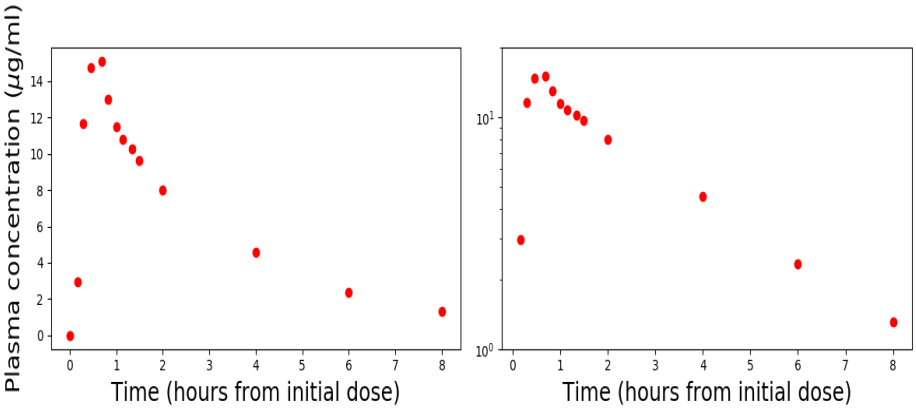


Given this knowledge of pharmacokinetics and pharmacodynamics, we can now look into some mathematical systems. We will soon be able to predict the amount of drugs in the bloodstream, and therefore tissue, at any given time and determine the rate at which it is leaving. This is achieved through compartment models (Spruill et al. 8). The compartments in a given model represent the locations where the drug travels throughout the body, for instance, the blood stream, and organ tissues, or urine. The simplest form is the one-compartment model and is in fact a first order model.



Simple compartmental model





In this instance, the drug is administered into the body, enters the plasma, and is excreted from the compartment. This can also be looked at in mathematical terms. There is the initial amount of the dosage, the compartment, which is the concentration of the drug in the body, and the movement out is the rate at which the drug is leaving, or the rate of change. Since this rate is decreasing exponentially, we can utilize the exponential decay function to determine the amount of the drug at any given time. The rate of change in theconcentration is proportional to the current concentration so we start off with the equation

$$dP/dt=Pk$$

where k is the growth rate, P is the current amount, and dP/dt is the rate of change. This equation is separable so 1/PdP=kdt

- $\int \frac{1}{P} dP = \int k dt$
- $\ln|P| = kt + C$
- $P = e^{kt+C} = e^{kt}e^{c}$

- $P = P_0 e^{kt}$

According to Calculus: Single Variable, "Every solution to the equation dP/dt = kP can be written in the form $P = P_0 e^{kt}$, where Po is the value of P at t = 0, and k>0 represents growth, whereas k <0 represents decay"(Gleason, Hughes-Hallett, McCallum 13). By utilizing this equation, we can solve real life applications. For instance, "The rate at which a drug leaves the blood stream and passes into the urine is proportional to the quantity of the drug in the blood at that time. If an initial dose of Qo is injected directly into the blood, 20% is left in the blood after 3 hours. Write an equation and solve for the quantity Q of the drug in the blood after thours" (Gleason, Hughes-Hallett, McCallum 618). Since 20% is left, we know Qo = 1 and (3) = 0.2 so we can use our decay function $Q = Q_0 e^{kt}$ and solve for k. Additionally if we plug in a time value and initial dosage amount, we can determine how much of a drug is in a patient's body at that time.

- $0.2 = e^{k3}$
- $\ln|0.2| = k3$
- $k = -0.536479$
- $Q = Q_0 e^{-0.536479t}$

For example consider the two different medicines which was impact on the human body in one compartment level and two compartment level:

Restoril & Paracetamol: Restoril (Temazepam) is a benzodiazepine with hypnotic properties. Benzodiazepines act as depressants of the central nervous system (CNS). It is believed that benzodiazepines enhance or facilitate the effects of the inhibitory neurotransmitter gamma- aminobutyric acid (GABA).

Benzodiazepines act as agonists at the benzodiazepine receptors sites. The benzodiazepine-GABA receptor-chloride ionophore complex functions mainly in the gating of the chloride channel. Benzodiazepines are thought to produce their pharmacological effects by facilitating GABA-mediated transmission in the CNS, which reportedly increase the frequency of the chloride channel opening.

In sleep laboratory studies, the effect of Temazepam 15 mg and 30 mg, was compared to placebo over a two week period. There was a linear dose-response improvement in total sleep time and sleep latency with significant drug-placebo differences occurring for total sleep time at both doses, and for sleep latency at the higher dose. REM sleep was essentially unchanged and slow wave sleep was decreased. Rebound Insomnia- A transient syndrome, known as "rebound insomnia", whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of hypnotic treatment. In the sleep laboratory studies, no measurable effects on daytime alertness or performance occurred following Restoril treatment or during the withdrawal period, even though a transient sleep disturbance in some sleep parameters was observed following the withdrawal of the higher doses.

The duration of hypnotic effect and the profile of unwanted effects may be influenced by the alpha (distribution) and beta (elimination) half-lives of the administered drug and any active metabolites formed. When half-lives are long, the drug or metabolite may accumulate during periods of nightly administration and be associated with impairments of cognitive and motor performance during waking hours. If half-lives are short, the drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to sedation or CNS depression should be minimal or absent. However, during nightly use and for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a very short elimination half-life, it is possible that a relative deficiency (i.e., in relation to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics: 1) increased wakefulness during the last third of the night and the appearance of increased day-time anxiety (see WARNINGS). Pharmacokinetics Orally administered temazepam is well absorbed in man. In a single and multiple dose absorption, distribution, metabolism and excretion (ADME) study, using 3H labelled drug, Restoril was found to have minimal (8%) first-pass metabolism. There were no active metabolites formed and the only Significant metabolite present in blood was the O-conjugate. Oral administration of 15 to 45 mg Temazepam in man resulted in rapid absorption with significant blood levels achieved in 30 minutes and peak levels at 2-3 hours. Drug levels in blood declined in a biphasic manner with a short half-life ranging from 0.4 to 0.6 hours and a terminal half-life from 3.5 to 18 hours (mean 9 hours). The inactive O-conjugate metabolite was formed with a half-life of 10 hours and excreted with a half-life of approximately 2 hours. Thus, O-conjugation is the rate limiting step in the biodisposition. In a multiple dose study, steady-state was approximated after the second daily dose with no evidence of accumulation after 5 consecutive daily doses of 30 mg temazepam. Steady-state plasma levels at 2.5hours were 382 " 192 ng/mL.

Approximately 96% of unchanged drug is bound to plasma protein.

Twenty-four hours after a single oral dose of temazepam approximately 80% - 90% of the drug was recovered in urine, primarily as the O-conjugate. Total recovery from feces and urine in single- and multiple-dose studies was approximately 95%, with only 3-13% of the radioactivity detectable in feces. Less than 1% of the dose was excreted as unchanged drug or N-desmethyl temazepam. A dose-proportional relationship has been established for the area under the plasma concentration/time curve over the 15-30 mg dose range.At the dose of 30 mg once a day for 8 weeks, no evidence of enzyme induction was found in man.

Oral administration of 15 to 45 mg of temazepam in humans resulted in rapid absorption with significant blood levels achieved in fewer than 30 minutes and peak levels at two to three hours. In a single- and multiple-dose absorption, distribution, metabolism, and excretion (ADME) study, using tritium-labelled drug, temazepam was well absorbed and found to have minimal (8%) first-pass drug metabolism. No active metabolites were

formed and the only significant metabolite present in blood was the O-conjugate. The unchanged drug was 96% bound to plasma proteins. The blood-level decline of the parent drug was biphasic, with the short half-life ranging from 0.4-0.6 hours and the terminal half-life from 3.5–18.4 hours (mean 8.8 hours), depending on the study population and method of determination.

Temazepam has very good bioavailability, with almost 100% being absorbed from the gut. The drug is metabolized through conjugation and demethylation prior to excretion. Most of the drug is excreted in the urine, with about 20% appearing in the faeces. The major metabolite was the O-conjugate of temazepam (90%); the O-conjugate of N-desmethyl temazepam was a minor metabolite (7%).

I compartment:

Formula:- $Q = Q_0 e^{kt}$

Q_0=30, t=12hours, Q(12)=40%=0.4

$Q = Q_0 e^{kt}$

$0.4=30\,e^{k12}$

$\frac{0.4}{30} = e^{12k}$

Ln(0.013)=12(k)

-4.3428=k(12)

K=-0.3618

$Q = Q_0 e^{kt} = Q_0 e^{-0.3618t}$

PARACETAMOL: In therapeutic doses paracetamol is a safe analgesic, but in overdosage it can cause severe hepatic necrosis. Following oral administration it is rapidly absorbed from the gastrointestinal tract, its systemic bioavailability being dose-dependent and ranging from 70 to 90%. Its rate of oral absorption is predominantly dependent on the rate of gastric emptying, being delayed by food, propantheline, pethidine and diamorphine and enhanced by metoclopramide. Paracetamol is also well absorbed from the rectum. It distributes rapidly and evenly throughout most tissues and fluids and has a volume of distribution of approximately 0.9L/kg. 10 to 20% of the drug is bound to red blood cells. Paracetamol is extensively metabolised (predominantly in the liver), the major metabolites being the sulphate and glucuronide conjugates. A minor fraction of drug is converted to a highly reactive alkylating metabolite which is inactivated with reduced glutathione and excreted in the urine as cysteine and mercapturic acid conjugates. Large doses of paracetamol (overdoses) cause acute hepatic

necrosis as a result of depletion of glutathione and of binding of the excess reactive metabolite to vital cell constituents. This damage can be prevented by the early administration of sulfhydryl compounds such as methionine and N-acetylcysteine. In healthy subjects 85 to 95% of a therapeutic dose is excreted in the urine within 24 hours with about 4, 55, 30, 4 and 4% appearing as unchanged paracetamol and its glucuronide, sulphate, mercapturic acid and cysteine conjugates, respectively. The plasma half-life in such subjects ranges from 1.9 to 2.5 hours and the total body clearance from 4.5 to 5.5 ml/kg/min. Age has little effect on the plasma half-life, which is shortened in patients taking anticonvulsants. The plasma half-life is usually normal in patients with mild chronic liver disease, but its prolonged in those with decompensated liver disease.

Adult dose

325 to 650mg

Route of elimination

Approximately 80% of acetaminophen is excreted in the urine after conjugation and about 3% is excreted unchanged.

Half life

1 to 4 hours

I compartment:

Formula:- $Q = Q_0 e^{kt}$

Q_0 =650, t=7hours, Q(7)=80%=0.8

$0.8=650\,e^{k7}$

$\frac{0.8}{650} = e^{7k}$

Ln(0.0012)=7(k)

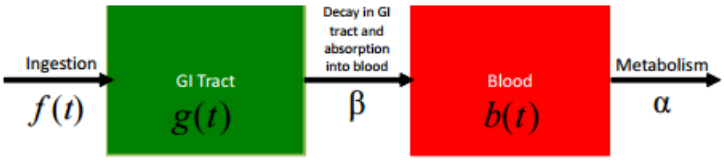
-6.725=k(7)

K=-0.9607

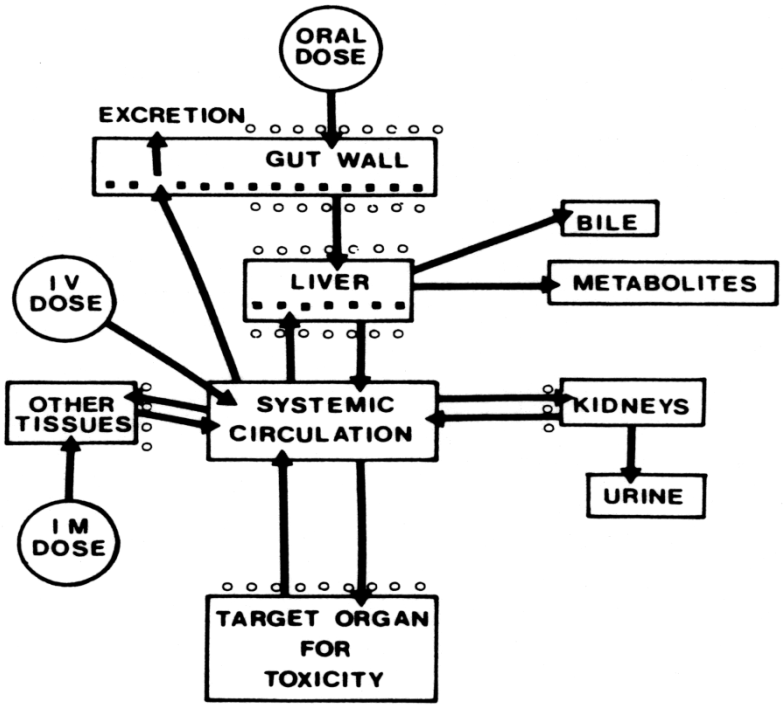
$Q = Q_0 e^{kt} = Q_0 e^{-0.9607t}$

Two compartment equation

After being introduced to the concept of one compartment models, we can now dive into two compartment models. This is a situation in which the drug passes through two separate locations within the body including the blood, organs and tissues, or urine. This effects the amount of the drug in the body because now it is being metabolized in two places at different rates. The right hand picture demonstrates this process and gives us the following system of equations to model it accordingly (Koch-Noble 237).



A Representation of a two compartment pharmacokinetics model.



$$\frac{dg}{dt} = f(t) - \beta g(t)$$

$$\frac{db}{dt} = \beta g(t) - \alpha b(t)$$

In this instance,
(t)= initial dosage of ingestion at time 0
(t)= amount of drug in the bloodstream at time t
(t)= amount of drug in the gastrointestinal tract (GI tract) at time t
α, β= the metabolism of the drug in the bloodstream and GI tract, respectively.

This is a non-homogeneous equation because (t) does not play a direct role on the other
functions. So to solve, we want to turn the system into a second order linear equation.

Generally, a second order linear equation is written in the form of $Ay''+By'+Cy=0$. To
solve, let $y=e^{rt}$ and insert into the general formula.

$$\Longrightarrow r^2e^{rt}+re^{rt}+e^{rt}=0$$
$$\Longrightarrow r^2+r+1=0$$

This last equation is the characteristic equation which we will utilize later. When the quadratic is solved, if we get distinct real roots for r, the general solution for a homogeneous equation is

$$y_h=c_1e^{-r_1t}+c_2e^{-r_2t}$$

Furthermore, the solution to a non-homogeneous equation is $y_h+y_p=y$ where p is the particular solution. We can use this to solve our system modeling the two compartments. Westart with the system,

$$\frac{dg}{dt}=f(t)-\beta g(t)$$
$$\frac{db}{dt}=\beta g(t)-\alpha b(t)$$

We rewrite these equations to factor out $g(t)$

$$[D+\beta][g(t)]=1$$
$$-\beta[g(t)]+[D+\alpha][b(t)]=0$$

(Note D represents derivative in terms of t and (t) = 1)
We want $g(t)$ terms to have the same "coefficients" to solve by elimination so we multiply the top equation by $D+\beta$ and the bottom equation by β,

$$\beta[D+\beta][g(t)]=\beta$$
$$[D+\beta](-\beta[g(t)]+[D+\alpha][b(t)])=0$$

Adding the two equations will eliminate the $g(t)$ terms and give us,

$$\Rightarrow[D+\beta][D+\alpha][b(t)]=\beta$$

When we foil, we get

$$\Rightarrow b''+(\beta+\alpha)b'+\beta\alpha b=\beta$$

Now we use the characteristic equation discussed earlier,

$$\Rightarrow r^2+(\beta+\alpha)r+\beta\alpha=0$$
$$\Longrightarrow (r+\beta)(r+\alpha)=0 \quad \text{so, } r=-\beta \text{ and } -\alpha$$

The homogeneous solution is then,

$$b_h=Ae^{-\alpha t}+Bc_1e^{-\beta t}$$

We must also consider the particular solution since this system is non-homogeneous. To do so,we let the particular solution be represented by a variable,

$$b''+(\beta+\alpha)b'+\beta\alpha b=\beta$$

$Let\ bp = K$
We plug this in and get,

$$\beta\alpha K = \beta$$

$$\Longrightarrow K = \frac{1}{\alpha}$$

So our complete equation is,

$$b(t) = Ae^{-\alpha t} + Be^{-\beta t} + \frac{1}{\alpha}$$

Here (t) is the amount of drugs in the bloodstream in terms of time, t. A and B are the drug amounts of the first and second compartment, respectively. α and β are the decay rateconstants for each compartment(Spruill et al. 78). Using this model, we can determine theamount of the drug in the blood at any given time when the drug passes into two compartments.

Example in the two compartment level for restoril &paracetamol:

II compartment:-

Formula:- $b(t) = Ae^{-\alpha t} + Be^{-\beta t} + \frac{1}{\alpha}$

A=15, B=45, t= 3hours

$\alpha = 90\% = 0.9,\ \ \beta = 7\% = 0.09$

$$b(3) = 15e^{-0.9(3)} + 45e^{-0.07(3)} + \frac{1}{0.9}$$

$$= 15e^{-2.7} + 45e^{-0.21} + \frac{1}{0.9}$$

$$= 15(0.0672) + 45(0.8105) + \frac{1}{0.9}$$

= 1.008+36.472+1.11

= 38.5905.

II compartment for paracetamol:

Formula:- $b(t) = Ae^{-\alpha t} + Be^{-\beta t} + \frac{1}{\alpha}$

A=325, B=650, t=5hours

$\alpha = 20\% = 0.2, \quad \beta = 70\% = 0.7$

$$b(5) = 325e^{-0.2(5)} + 650e^{-0.7(5)} + \frac{1}{02}$$

$$= 325e^{-1} + 650e^{-3.5} + \frac{1}{0.2}$$

$$= 325(0.3678) + 650(0.03019) + 5$$

$$= 119.5+19.62+5$$

$$= 144.12$$

IV.CONCLUSION

we have looked at just a few of the models that aid in modeling drug injection types within the field of pharmacokinetics. While the complexity of each formula varies, the result is the same; we are able to determine the amount of a drug within the body at any given time. However, it is important to note there are multiple other factors that play a role in this amount. One's ability to metabolize a single drug fluctuates between patients. Interactions between two or more medications may also influence the rate of decay. With an insight into the workings of pharmacodynamics, these factors can be considered and may be adjusted for in our mathematical interpretations. By generating these models, we can develop a deeper understanding of how drugs operate in order to further the effectiveness of their administration, thus accomplishing the ultimate goal of improving the patient's well-being.

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