Journal of Natural Sciences Research www.iiste.org
ISSN 2224-3186 (Paper) ISSN 2225-0921 (Online)
Vol.4, No.2, 2014

# Eefect of Half – Life on Drug Concentration Interaction using Mathematical Methods

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**Abstract**
There are different factors that affect drug interaction. This interaction may be Pharmacokinetic or Pharmacodynamic. Either case can lead to decrease in efficacy or increase in toxicity of the drugs but, our concern in this paper is on the half-life of a drug. Here, we are looking at the half-life concentration of drugs taking anti-depressant drugs as a case study (Setraline and Tranylcypomine). In terms of half-life of a particular drug, it was shown that drugs with short half-lives are less susceptible to interaction than drugs with long half-lives. This fact is used to establish that in the administration of drugs to a patient (since patients receive at least 10 to 20 drugs at a goal), the half- life needs to be considered.
**Keywords**: Drug, Pharmacokinetics, Pharmacodynamics and Half-Life.

## 1. Introduction

The interaction of a drug can be synergistic (when the drugs effect is increased) or antagonistic (when the drugs effect is decreased) or a new effect can be produced on its own. Typically, interactions between drugs come to mind (drug-drug interactions). However, interactions may also exist between drugs and foods (drug-food interactions), as well as drug and medicinal plants or herbs (drug-plant interactions). People taking antidepressant drugs such as monoamine oxidase inhibitors should not take food containing tyramine as hypertensive crisis may occur (an example of a drug-food interaction). These interactions may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substance, [10]. To initiate a desired drug action is a qualitative choice, but when the qualitative choice is made, considerations of quantity immediately arise. When a Physician prescribes a drug and the patient takes it, their main concern is with the effect on the patient disease. To obtain the right effect at the right time, for the right duration and with minimum risk of unpleasantness or harm is what Pharmacokinetics is all about. Pharmacokinetics is the study of the time course of drug and metabolite levels in different fluids, tissue and excreta of the body and the Mathematical relationships to develop models to interpret such data. [4].
The effect of a drug depends most fundamentally on how much the drug is taken. Drugs are taken through various routes as the case may differ. Drug administration route can strongly influence the effects that drug has [7]. These routes are oral, injection, inhalation, intranasal, sublingual and transdermal.

## 2. Half-Life

The manner, in which plasma drug concentration rises or falls when dosing has begun, altered or ceased follows certain simple rules which provide a means for rational control of drug effect. [7]. Central to understanding these, is the concept of half-life denoted by $t_{\frac{1}{2}}$. This is the time in hours or in days necessary for the concentration of drug in the plasma to decrease to one half, [4].

## 3. Methodology

The stochastic Ito process representing concentration in one- compartment pharmacokinetics model with unanticipated drug interactions drug interactions can be expressed as follows:

$$\frac{dC}{C} = -Kdt + \sigma dz + (Y-1)d\pi \quad (1)$$

Where K is the elimination rate constant or the trend rate constant in the absence of drug interactions; $\sigma^2$ is the variance rate in the absence of the interaction-inducing agent; d$t$ is differential time and dz is the differential of z, the Wiener variable; and the Poisson jump variable, d$\pi$, takes a value of 1 if the jump occurs (the probability of this is characterized by $\lambda t$, where $\lambda$ is the occurrence rate of interaction events, and t is time) and a value zero if a jump does not occur. The $-Kdt$ term characterizes the Pharmaconetic trend; the $\sigma dz$ term characterizes the uncertainty caused by "usual garden-variety" variability or white noise, and $(Y-1)d\pi$ represents the increased variability caused by the sudden unanticipated arrival of the interaction. Upon the occurrence of an interaction, the elimination rate constant "jump" instantaneously by $(Y-1)$, causing the concentration to increase from C to CY. Thus, the right-hand side of eqn. 1 is a stochastically modified elimination rate constant that contains a Gaussian-distributed white-noise ($\sigma dz$) and a poisson-distributed noise term $[(Y-1)\,d\pi]$ caused by the interaction.

### 3.1. Pharmacodynamic Model

If the effect is a twice-differential function of only concentration and time, the stochastic process for effect is also similar, and can be written as follows:

$$\frac{dE}{E} = -K_E dt + \sigma_E dz + (Y_E - 1)d\pi \quad (2)$$

In eqn.( 2), the subscript E refers to effect. However, an extended version of Ito's lemma can be used to derive the values for the drift rate and variance rate in terms of the pharmacokinetic parameters and pharmacodynamic effect equation.

$$K_E = -\frac{1}{E}\left(\frac{1}{2}\sigma^2 c^2 \frac{\partial^2 E}{\partial C^2} - KC\frac{\partial E}{\partial C} + \frac{\partial E}{\partial t}\right) \quad (3)$$

$$\sigma_E = \frac{1}{E}\left(\sigma C \frac{\partial E}{\partial C}\right) \quad (4)$$

$$Y_E = E\frac{E(CY)}{E(C)} \quad (5)$$

The commonly used simple and sigmoid $E_{max}$ models are twice- differentiable functions of concentration alone, and the time partial derivative of effect with respect to time is zero, which allows the simplification of eqn.( 3) to:

$$K_E = -\frac{1}{E}\left(\frac{1}{2}\sigma^2 C^2 \frac{\partial^2 E}{\partial C^2} - KC\frac{\partial E}{\partial C}\right) \quad (6)$$

In the simple $E_{max}$ model, mean jump values in effect are likely to be more prominent with drugs that are used in the linear effect range, because $Y_E$ will be larger. At saturation, the jumps in concentration will not result in jumps in effect.

### 4. Effect of Interaction on Drug Concentration.

When the percentage change in drug concentration caused by the interaction-inducing agent is log-normally distributed, i.e., the jumps $Y_j$ are random variables drawn from a log-normal distribution with mean ($\theta$ ) and variance ($\gamma^2$), the ratio $C(t)/C_0$ also is log normally distributed. However, the variance parameter is Poisson distributed.

Additionally, because the mean $\theta$ is the expectation $\in (InY) + \frac{\gamma^2}{2} = \theta + \frac{\gamma^2}{2}$ (7)

Surprisingly, despite the discontinuous nature of the underlying stochastic processes, the distribution of concentrations is continuous. Press first provided analytical expressions for the probability density function of In C(t) but did not assume a deterministic trend. However, [2] extended the Press equation to accommodate a deterministic trend. With these assumptions, the probability density function for concentration is stationary over time and is given by:

$$\text{In}\frac{C(t)}{C_0} \Rightarrow \sum_{n=0}^{\infty}\frac{e^{-\lambda t}(\lambda t)^n}{n!}\,\text{N}(-Kt + n\theta, \sigma^2 t + n\gamma^2) \quad (8)$$

The symbol $\Rightarrow$ should be read as " is distributed as " and the $\text{N}(-Kt + n\theta, \sigma^2 t + n\gamma^2)$ is the probability density function of a normal distribution with mean , $-Kt + n\theta$ and variance $\sigma^2 t + n\gamma^2$.

The distribution in eqn. 8 is a process that consists of Poisson events superimposed on events following another independent distribution that, in this case, happens to be log-normal. With the method of characteristic functions, the various moments of this distribution can be calculated (Press, 1967). The moments can be used to demonstrate that this distribution is leptokurtic. By definition, leptokurtosis implies that the distribution has a fatter tail than a comparable normal distribution, i.e., the probability of observing outlying high-concentration events is much greater than that for a normal distribution. Additionally, the skewness of the distribution is determined by $\theta$, i.e., if $\theta$ is negative, the distribution has negative skewness; if $\theta$ is zero, the distribution is symmetric. The second moment or variance of the distribution in the presence of interactions is given by the following:

$$\text{Variance} = [\sigma^2 + \lambda(\theta^2 + \gamma^2)]t \quad (9)$$

The variance relationship (eqn.9) demonstrate that the variance in the presence of interactions is increased and that both the magnitude ($\theta$) and variability ($\sigma$)of the interaction are important.

More frequently, side effects from interaction-inducing agents are caused by drug concentrations exceeding the minimum toxic dose. To determine the probability P (In C $> In\ C_t$) of concentrations exceeding the minimum toxic dose, $C_t$, the cumulative probability distribution function has to be calculated from eqn. 8 as follows:

$$\text{P (In C} > In\ C_t) = \int_{x=InC_t}^{x=\infty}\sum_{n=0}^{\infty}\frac{e^{-\lambda t}(\lambda t)^n}{n!}\,\text{N}(-Kt + n\theta, \sigma^2 t + n\gamma^2)dx$$

However, in eqn.9 only the terms containing the normal distribution are functions of concentration and

$$\text{P (In C} > In\ C_t) = \sum_{n=0}^{\infty}\frac{e^{-\lambda t}(\lambda t)^n}{n!}\left(1 - \int_{x=InC_t}^{x=\infty}\sum_{n=0}^{\infty}\frac{e^{-\lambda t}(\lambda t)^n}{n!}\,\text{N}(-Kt + n\theta, \sigma^2 t + n\gamma^2)dx\right)$$

Or alternatively,

$$\text{P (In C} > In\ C_t) = \sum_{n=0}^{\infty}\frac{e^{-\lambda t}(\lambda t)^n}{n!}(1 - \phi)(-Kt + n\theta, \sigma^2 t + n\gamma^2) \quad (11)$$

In eqn. (11), $\phi(-Kt + n\theta, \sigma^2 t + n\gamma^2)$ is the cumulative probability distribution function of the normal distribution with mean $-Kt + n\theta$ and variance $\sigma^2 t + n\gamma^2$ evaluated at In $C_t$.
In the limit of small values of $\lambda t$, Poisson process can be approximated by a Bernoulli process[1]. The Bernoulli process is a model for interaction processes such that over a period of time, either no interaction or just one interaction occurs. The cumulative probability density function for a Bernoulli mixture of Gaussians is as follows:

$$P(\text{In } C > In\ C_t) = (1 - \lambda t)\ \phi(-Kt, \sigma^2) + \lambda t\ \phi(-Kt + \theta, \sigma^2 t + \gamma^2) \quad (12)$$

Thus, both models allow for discontinuous jumps but result in continuous distribution functions. In the following sections, eqn. (12) is used because it is reasonable to assume that drug interactions are likely to be relatively rare events with small values of $\lambda t$.

## 5. Results and Analysis

1000ml conical flask, 25ml beaker, 10ml and 1ml pipette, 12 large test tubes, water tank, drugs(sertraline-50mg/ml and tranylcypromine -75mg/ml) both drugs are anti-depressants drugs.

1. The concentration level for Sertraline can been seen in the table below:

| Tube | Mg/ml Conc. | $X10^4$ |
|---|---|---|
| A | 5 | 50,000 |
| B | 0.5 | 5,000 |
| C | 0.25 | 2,500 |
| D | 0.125 | 1,250 |
| E | 0.0625 | 625 |
| F | 0.03125 | 313 |
| G | 0.01562 | 156 |
| H | 0.0078125 | 78 |
| I | 0.0039063 | 39 |
| J | 0.0019531 | 20 |
| K | 0.0009766 | 10 |
| L | 0.0004883 | 5 |

CALCULATIONS:
Using $C_1V_1 = C_2V_2$
$1^{st}$ Dilution, $C_2 = \frac{C_1V_1}{V_2}$ = 50mg/ml ×1ml ÷ 10ml = 5mg/ml
$2^{nd}$ Dilution, 5mg/ml×1ml ÷ 10ml =0.5mg/ml

$12^{th}$ Dilution 0.0009766× 1ml ÷ 10ml = 0.0004883mg/ml
For Sertraline:

| TUBE | TIME (hr) | CONC. (Mg/ml) | CONC. (Mg/ml x $10^4$ ) | Log of conc. (Mg/ml x$10^4$ ) |
|---|---|---|---|---|
| A | 1 | 0.03125 | 312.5 | 2.49 |
| B | 2 | 0.03125 | 312.5 | 2.49 |
| C | 3 | 0.02344 | 234.4 | 2.37 |
| D | 4 | 0.01172 | 117.2 | 2.07 |
| E | 5 | 0.005859 | 58.59 | 1.77 |
| F | 6 | 0.002930 | 29.30 | 1.47 |
| G | 7 | 0.001965 | 19.65 | 1.30 |
| H | 8 | 0.001965 | 19.65 | 1.30 |
| I | 9 | 0.0009825 | 9.83 | 1.0 |
| J | 10 | 0.0009825 | 9.83 | 1.0 |
| K | 11 | 0.00049125 | 4.90 | 0.69 |
| L | 12 | 0.00049125 | 4.90 | 0.69 |

| Tube | Mg/ml Conc. | $X10^4$ |
|---|---|---|
| A | 7.5 | 75000 |
| B | 0.75 | 7500 |
| C | 0.375 | 375 |
| D | 0.1875 | 188 |
| E | 0.09375 | 469 |
| F | 0.04688 | 469 |
| G | 0.02343 | 234 |
| H | 0.01172 | 117 |
| I | 0.00586 | 59 |
| J | 0.00293 | 29 |
| K | 0.00146 | 15 |
| L | 0.00073 | 73 |

CALCULATIONS:
Using $C_1V_1 = C_2V_2$
$1^{st}$ Dilution, $C_2 = \frac{C_1V_1}{V_2}$ = 75mg/ml ×1ml ÷ 10ml = 7.5mg/ml
$2^{nd}$ Dilution, 7.5mg/ml×1ml ÷ 10ml =0.75mg/ml
.
$12^{th}$ Dilution 0.00146× 1ml ÷ 10ml = 0.00073mg/ml
For Tranylcypromine:

| Tube | Time (hr) | CONC. (Mg/ml) | CONC. (Mg/ml x$10^4$ ) | Log of conc. (Mg/ml x$10^4$ ) |
|---|---|---|---|---|
| A | 1 | 0.4688 | 4688 | 3.6 |
| B | 2 | 0.4688 | 4688 | 3.6 |
| C | 3 | 0.0352 | 352 | 2.5 |
| D | 4 | 0.0176 | 176 | 2.2 |
| E | 5 | 0.0088 | 88 | 1.9 |
| F | 6 | 0.0044 | 44 | 1.6 |
| G | 7 | 0.0022 | 22 | 1.3 |
| H | 8 | 0.0022 | 22 | 1.3 |
| I | 9 | 0.0011 | 11 | 1.0 |
| J | 10 | 0.0011 | 11 | 1.0 |
| K | 11 | 0.0001 | 1 | 0 |
| L | 12 | 0.0001 | 1 | 0 |

**5.1. Confirmatory Test**
We applied student t-test to confirm that drugs with shorter half-lives are less susceptible to interaction than drugs with longer half-lives.
$H_o$: There is no significant difference between the means of the drugs. From the table above, we evaluate $\overline{X_T}$ = 0.0842, $Var_T$ = 0.029675, $\overline{X_s}$ = 0.00944 and $Var_s$ = 0.001543219. We compared if the variances are assumed to be equal, using the variance ratio test.

$$F = \frac{Var_T}{Var_s} = \frac{0.029675}{0.001543219} = 19.229$$

At $p = 0.05$, $F = 2.82$ and since $19.229 > 2.82$, the variances are assumed to be equal and as such we can evaluate the common variance. The calculated common variance $s = 0.01541$.
Applying the student t-test as given below, we have

$$t = \frac{\overline{X_T} - \overline{X_S}}{s\sqrt{\frac{1}{n_T} + \frac{1}{n_S}}} = \frac{0.0842 - 0.00944}{0.01541\sqrt{\frac{1}{12} + \frac{1}{12}}} = 11.8$$

$t - value\ at\ p = 0.05\ from\ t\ tables\ read\ at\ 22\ degrees\ of\ freedom\ is\ 2.07.$
It implies that, there is significant difference between the means of drugs. So, we reject our$H_o$ and conclude that drugs with shorter half-lives are less susceptible to drug interaction than drugs with longer half-lives.

## 6. Recommendation

When administering drugs to a patient, it is advisable to take into cognisance the half life of the drug.

## 7. References

(1) Ball, C.A. and Torus, W.N.(1983): A simplified jump process for common stock returns Finance quant Anal 18:53 -65.
(2) Beckers, S (1981): A note on estimating the parameters of the diffusion-jump model of stock returns. Journal of finance quant Anal 16:127-140.
(3) Beers, M.H and Berkon, R (2003 and 2004): The Merck Manual of the diagnosis and therapy, 17th edition, New York.
(4) Gilbaldi, M and Perrier, D(1975): Pharmacokinetics, 2nd edition, New York.
(5) Ito, K(1951): On stochastic Differential equations, Men AM Mathematical Society vol. 4 pp 1 – 51.
(6) Lanaune, J.(1981):Handbook of Pharmacokinetics, England.
(7) Lawrence, et. Al (1997): Clinical Pharmacology, Churchill Livingstone, Edinburg London, 8th edition.
(8) Morris, C (1986): Clinical Pharmacy series, 7200.
(9) National Prescribing Service, (2009).
(10) Philip, D.H. (1995): Basic and Clinical Pharmacology, 17th edition.