International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2013): 4.438

Two Compartmental Mathematical Analysis of the Diffusion A Therapeutic Agent in Human Tissues

E. U. Agom[1], M. S. Atureta[2]

[1]Department of Mathematics, University of Calabar, Calabar, Nigeria
[2]Mathematical Sciences Programme, Abubakar Tafawa Balewa University Bauchi, Bauchi, Nigeria

Abstract: ***In this paper, we present a unified minimal compartmental model to estimate mathematically the concentration of a Therapeutic Agent injected intravenously in a steady state into Human tissues divided into two compartments; the blood and tissues. The model takes into consideration most, if not all physiological factors of the Human system in conformity with the physical realities vis-a-vis the Therapeutic Agent concentration before uptake by the compartments. The models were a system of first order non-homogeneous ordinary differential equations. And, the result from the models gives a zero concentration in both the blood and the tissues before the advent of the Therapeutic agent.***

Keyword: Compartmental Mathematical Modelling,

1. Introduction

Several attempts at building a satisfactory model of the diffusion of foreign agents in Human system are recorded in literature. The minimal model, which is currently used in physiological research for interpretation of substances concentration, was proposed in the early eighties. In order to study the intravenous injection of Therapeutic Agents in Human, a unified model would be desirable. Therapeutic agents (TA) as they are known are meant to cure illness and or help Human beings to relaxed, but many causes a lot of tissue damages and probably death as a result of its adverse effect. Its diffusion into the human tissues occurs rapidly because of highly permeable nature of the capillary membranes. And it may accumulate in tissues in higher concentration, above the upper therapeutic range than would be expected from diffusion equilibrium as a result of binding to intracellular constituent or partitioning lipid. It can be toxic, in concentration above the therapeutic range, and can also be ineffective in concentration below the therapeutic range. Thus, for it to have the desired effect it must remain within the desired therapeutic range.

Many researchers have used mathematical compartmental analysis to study the Human biological system [2], [3], [5] and [7]. Traditionally, compartmental systems are tools used to describe the circulation of substances in models of biological processes [8] and [11]. This biological compartmental system rest on the concept of compartments sometimes called pools or domains. By compartmental models we mean the mathematical properties of the equations which arise from the description of the biological interchange between different physical system which are homogeneous and distinct in respect of chemical biological transformation of transport [9] and [12].

2. The Compartments

The blood is the transport medium of the body, it is an extremely complex substance, carrying a wide variety of cells and substances to all parts of the human body. The intercellular fluid acts as the 'middle man' in the transport exchange between the blood and the cells [1]. Transfer of TA from the blood to tissues are due to causes such as diffusion, osmosis, etc, and the rate cannot be increased any further when these processes has reached its limit

TA administered intravenously are in aqueous form and are readily soluble in blood and binding to plasma protein is superb. In particular, the flow of blood to all tissues (Fig. 1) is proportional at normal conditions.

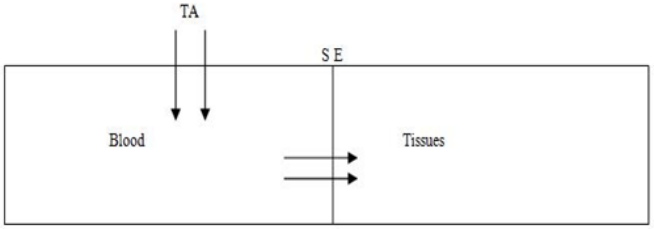

Figure 1: Human Tissues divided into two compartments

3. Formulation of the Models

TA administered intravenously does not require absorption since they immediately reach the vascular system and bioavailability is 100%. We assume the TA is administered at a constant rate into the blood and is taken up by the tissue on which it exerts its biochemical reaction.

A two compartment (blood and tissue) system will now be considered with the parameters of the blood compartment being: the total amount of the TA in the blood x gm; the volume of blood v_1; and the concentration of the TA in the blood c_1, while those of the tissues compartment are: the total amount of the TA in the tissue w; the volume of the tissue v_2; and the concentration of the TA in the tissue c_2. Finally the rate of injection is denoted by v gm/s.

We also have that

$$x = c_1 v_1 \quad (1)$$
$$w = c_2 v_2 \quad (2)$$

The rate of penetration of a $TAcm^{-2}s^{-1}$ from the blood into the tissue through the squamous epithelium (SE) will be

$$h(c_1\text{-}kc_2) \quad (3)$$

where h is the permeability of SE and k is a constant known as the partition coefficient of the TA between the blood and tissues.

If $c_1 = kc_2$, the two compartment will be in equilibrium and no flow through SE will take place. If S denote the total area of SE then the total flow from the blood to the tissue per second will be

$$Sh(c_1\text{-}kc_2) \quad (4)$$

This will be the rate of loss of the TA from the blood to the tissue. Moreover, normally when a TA is administered it undergoes decomposition in the blood. We consider for our modelling purpose that the TA decomposes at a rate proportional to its own concentration c_1. Thus we may write the rate of decomposition as

$$k_1c_1 \quad (5)$$

where k1 is a constant of proportionality. Hence the rate of disappearance of the TA from the blood due to decomposition is

$$k_1c_1v_1 \quad (6)$$

and thus the total rate of disappearance of the TA from the blood is

$$Sh(c_1\text{-}kc_2) + k_1c_1v_1 \quad (7)$$

But the total rate of change of the amount of the TA in the blood is equal to the rate of administration V less the total rate of disappearance. Hence

$$\dot{x} = V - \left[Sh\left(c_1 - kc_2\right) + k_1c_1v_1\right] \quad (8)$$

or, using equations (1) and (2)

$$\dot{x} = V - Sh\left(\frac{x}{v_2} - k\frac{w}{v_2}\right) - k_1x \quad (9)$$

We will now introduce two more parameters namely λ, μ, where

$$\lambda = \frac{kv_1}{v_2} \quad (10)$$

$$\mu = \frac{Sh}{v_1} \quad (11)$$

Substituting equations (10) and (11) in (9), we have

$$\dot{x} = V - \mu(x - \lambda w) - k_1x \quad (12)$$

The amount of drug entering the tissue is equal to the amount leaving the blood, since we consider the case where only one tissue takes up the drug. This amount is given by (4), which simplifies to

$$Sh(c_1 - kc_2) = \frac{Sh}{v_1}(c_1v_1 - kc_2v_1) = \mu(x - \lambda w) \quad (13)$$

Furthermore, in the tissue the drug is also used up and therefore is gradually destroyed.

Similar, to the above analysis we assume that destruction of the drug is proportional to the concentration c_2 in the tissue. Thus we may write the rate of destruction in the tissue using the same constant of proportionality k_1 as

$$k_1c_2 \quad (14)$$

For the whole tissue, the rate destruction is $k_1c_2v_2$ g/s which is equal to k_1w from (2). Hence the total rate of change, $\dot{W}$, of the amount of the drug in the tissue is

$$\dot{w} = \mu(x - \lambda w) - k_1w \quad (15)$$

The system of differential equation given by (12) and (15) can be readily solved by standard methods. This equation contains three constants, λ, μ and k_1, and expresses the x and w as a function of time and the three constants.

From (12) and (15)

$$\dot{x} = v - \mu(x - \lambda w) - k_1x \quad (16)$$

$$\dot{w} = \mu(x - \lambda w) - k_1w \quad (17)$$

On adding (16) and (17), we obtain

$$\frac{d}{dt}(x + w) = v - k_1(x + w) \quad (18)$$

By multiplying (17) by λ and subtracting from (16) we obtain

$$\frac{d}{dt}(x - \lambda w) = v - (k_1 + k_2)(x - \lambda w) \quad (19)$$

Where

$$k_2 = (1 + \lambda)\mu \quad (20)$$

By introducing two new variables,

$$z_1 = x + w \quad (21)$$

$$z_2 = x - \lambda w \quad (22)$$

(18) and (19) simplifies to

$$\dot{z}_1 = v - k_1z_1 \quad (23)$$

$$\dot{z}_2 = v - (k_1 + k_2)z_2 \quad (24)$$

4. Result

At the beginning of injection, t = 0, x(0) = w(0) = 0 and hence $z_1(0) = z_2(0) = 0$ at t = 0.

Solving the (23) and (24), we get

$$z_1 = \frac{v}{k_1}(1 - e^{-k_1 t}) \quad (25)$$

and

$$z_2 = \frac{v}{k_1 + k_2}(1 - e^{-(k_1+k_2)t}) \quad (26)$$

Using (21) and (22) in (25) and (26), we get

$$w = \frac{v}{1+\lambda}\left\{\frac{1}{k_1}\left(1 - e^{-k_1 t}\right) - \frac{1}{k_1+k_2}\left(1 - e^{-(k_1+k_2)t}\right)\right\} \quad (27)$$

$$x = \frac{v}{1+\lambda}\left\{\frac{\lambda}{k_1}\left(1 - e^{-k_1 t}\right) - \frac{1}{k_1+k_2}\left(1 - e^{-(k_1+k_2)t}\right)\right\} \quad (28)$$

(27) shows that for t = 0, w = 0, which is should realistically be the case, for we began with the injection at t = 0 and there was no drug in the system prior to the injection (also this was an initial condition so the result was not surprising). As t tends to ∞, w asymptotically approaches a constant value given by

$$w_\infty = \frac{v}{1+\lambda}\left\{\frac{1}{k_1} - \frac{1}{k_1+k_2}\right\} \quad (29)$$

The greater the injection rate V, the greater the asymptotic value w_∞. Since both k_1 and k_2 are positive, we have w_∞ as a positive quantity. The TA exerts observable action when its total concentration reaches or exceeds some threshold value w^* in the tissues. Let us consider that the action in question is tissue-damage. Then if $w \geq w^*$, tissue damage occur. If the quantity w_∞ given equation 68 is less than that in the critical value w^*, then no matter how long the TA is injected no lethal effect will be observed. in other that this should be the case we must have from equation (29) that

$$\frac{r}{1+\lambda}\left(\frac{1}{k_1} - \frac{1}{k + k_2}\right) \lhd w^*$$

From the mathematical models of equation (27) and (28),

r is the rate of intravenous injection, k is Partition coefficients for the penetration of the TA, v_1 is the Volume or mass of the blood, v_2 is the Volume or mass of the tissue,

$$k_2 = (1+\lambda)\mu$$

$$\lambda = \frac{kv_1}{v_2}$$

$$\mu = \frac{sh}{v_1}$$

s is the total area of the boundary between the blood and the tissue or area of the membrane. h is the permeability of the capillaries (permeability of the membrane), k_1 is the clearance rate constant of the TA (decomposition constant of the TA). And t is the time after the administration of a TA.

5. Conclusion

In this paper, we modelled the steady-state intravenous injection of a Therapeutic agent into Human tissues divided into two compartments, the blood and the tissues. We assumed that there exists a steady-state of flux of the Therapeutic agent into the initial compartment. And, all variables of the system are equal to zero when the system is at rest (until external intravenous injection of a Therapeutic agent intervenes). In the compartmental analysis, the squamous epithelium was taken as the exchange medium between the blood and the tissues. The resulting Mathematical models showed a remarkable relationship between the two compartments. This was especially obvious when t = 0. That is before the advent of the Therapeutic agent. The concentration at this point was also zero, which is expected and also in conformity with real life situation.

References

[1] R. Aldo, and S. B. James, Compartments, In R. Robert, (Ed.) Foundation of Mathematical Biology, (New York: Academic press Inc, 1972) 255-321.
[2] M. Andrea, Circulation Models of Intact-body kinetics and their Relationship with compartmental and Non-compartmental Analysis, Journal of Theoretical Biology, 160, 1993, 509 – 531.
[3] W. Geisz and M. Bourin, Identification of a Pharmacokinetic Two-compartment model Application to the case of salicylates Administered to Rabbits, Mathematical Modelling an International Journal, 7, 1986, 1245 – 1253.
[4] Goodman and Gilman, The Pharmacological Basis of Therapeutics, (McGraw – Hill, 1996).
[5] G. Istvan, Connections between Compartmental system with pipes and integro-Differential Equations, Mathematical Modelling an International Journal, 7, 1985, 1215- 1238.
[6] H. L. Loomie, Ordinary Differential Equations: An Introductory and Intermediate Courses using Matrix Method, (Addison-Wesley Publishing Company Inc, 1971)
[7] F. Ludwikow, and G. Ludwikow, A Two-compartmental model of Micronucleus Formation in Erythrocytes and Application to Mouse Bone Marrow. I. Rectangular Transient Action of Clastogen in Stationary condition. Journal of Theoretical Biology 165, 1993, 417-428.
[8] K. Marek, and A. Ovide, On Active Linear compartments, Proc of 6th International conference on Mathematical Modelling, New York, 1988, 1189-1194.

[9] J. Mazumdar, An Introduction to Mathematical Physiology and Biology, (London, Cambridge University Press, 1989).
[10] H. Nedebragt, Hierarchical Organisation of Biological systems and the structure of adaptation in Evolution and Tumorigenesis, Journal of Theoretical Biology, 184, 1997, 149-156.
[11] D. Paul, and B. S. Peter, Mathematical Modelling in the Life sciences (New York, Ellis Horwood, 1993).
[12] S. I. Rubinow, Introduction to Mathematical Biology, (New York , John Wiley and Sons, 1975)