ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/338335576

Compartmental and Non-Compartmental Pharmacokinetic Analysis of Extended Release Diclofenac Sodium Tablet

Article · January 2016

CITATIONS
3

READS
2,429

3 authors, including:

Khawla H. Rasheed
Ibn Sina University for Medical and Pharmaceutical Sciences
9 PUBLICATIONS **8** CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:

Drug Pharmacokinetics study View project

All content following this page was uploaded by Khawla H. Rasheed on 02 January 2020.

The user has requested enhancement of the downloaded file.

Al-Nahrain University, College of Engineering Journal (NUCEJ) Vol.19 No.1, 2016 pp.161 - 165

Compartmental and Non-Compartmental Pharmacokinetic Analysis of Extended Release Diclofenac Sodium Tablet

Uns Qusai
Medical Eng. Dep., Al-Nahrain University
Uns_alneami@yahoo.com

Asma Hameed
Medical Eng. Dep., Al-Nahrain University
Nane21972@yahoo.com

Khawla Hameed Rasheed
Medical Eng. Dep., Al-Nahrain University
greentala2002@yahoo.com

Abstract:

Compartmental modeling describes the movement of a substance from one compartment to another. it is concerned with maintaining correct chemical levels in the body and their correct fluid volumes. From another side non compartmental analysis have many benefits over compartmental analysis like it requires less experience and skill on the part of the modeler, in-vivo study made on seven healthy volunteers, plasma concentration versus time obtained then both compartmental and non compartmental analysis applied to data, the clearance, volume of distribution, half life, and area under the curve from zero to infinity were comparable to each other for tow methods, The correlation between observed and predicted plasma concentration versus time profiles using compartmental analysis was 0.95.

1. Introduction:

Pharmacokinetic models are hypothetical structures that are used to describe the fate of a drug in a biological system following its administration.

The most commonly employed approach to the pharmacokinetic characterization of a drug is to represent the body as a system of compartments, even though these compartments usually have no physiologic or anatomic reality, and to assume that the rate of transfer between compartments and the rate of drug elimination from compartments follow first-order or linear kinetics. The one-compartment model, the simplest model, depicts the body as a single, kinetically homogeneous unit. This model is particularly useful for the pharmacokinetic analysis of drugs that distribute relatively rapidly throughout the body. Almost invariably, the plasma or serum is the anatomical reference compartment for the one-compartment model, but it not assumed that the drug concentration in plasma is equal to the concentration of drug in other body fluids or in tissues, Drug elimination from the body can often occur by several pathways, including urinary and biliary excretion, excretion in expired air, and biotransformation in the liver or other fluids or tissues. [1]

There are several possible candidates for compartments in specific biological system, blood plasma can be considered as well as substance glucose within plasma zinc in bone and thyroxin in the thyroid gland can also be compartments. Thus, it should be apparent that a physical space may actually represent more than one compartment [2].

This research aims to compare between two types of studying the drug absorption mechanisms which are compartmental and non compartmental analysis

1.1 Non-compartmental or model independent approaches:

Pharmacokinetic data analysis has been increasingly utilized since this approach permits the analysis of data without the use of a specific compartment model. [3]

The pharmacokinetic parameters representing different exposure measures involve the area under the plasma or blood concentration–time curve (AUC) for total exposure, partial AUC for early exposure, maximum or peak concentration (Cmax), and time to achieve maximum concentration (tmax) for peak exposure, respectively. The measurements of these pharmacokinetic parameters can be derived either directly from the observed blood or plasma concentration–time curve, which is independent of a model, or is obtained by fitting the observed concentrations to a one- or a multicompartment pharmacokinetic model. [4]

1.2One-compartmentmodel:

Following drug administration, the body is depicted as a kinetically homogeneous unit (Figure 1). This assumes that the drug achieves instantaneous distribution throughout the body and that the drug equilibrates instantaneously between tissues. Thus the drug concentration–time profile shows a monophasic response.[5]

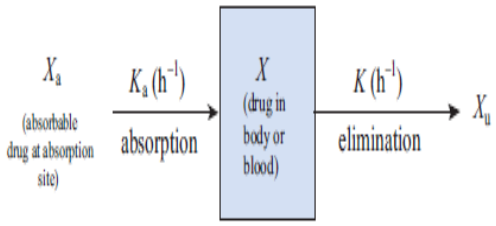

Figure 1: single compartment model.[6]

This model could be represented by the following differential equations:

Eq.1,2 represents rate of drug change in GI-tract:

$$\frac{dGI}{dt} = -k_a GI \quad \ldots\ldots (1)$$

$$GI(t) = GI_0 \exp(-k_e t) \quad \ldots\ldots (2)$$

Eq.3,4 represents rate of drug change in body:

$$\frac{dB}{dt} = k_a GI - k_e B \quad \ldots\ldots (3)$$

$$B(t) = \left(\frac{k_e GI_0}{k_e - k_a}\right)[\exp(-k_a t) - \exp(-k_e t)] \quad \ldots. (4)$$

Eq.5,6 represents rate of drug elimination:

$$\frac{dE}{dt} = k_e q_1 \quad \ldots\ldots (5)$$

$$E(t) = GI_0 - GI(t) - B(t) \quad \ldots\ldots (6)$$

$$E(t) = GI_0 \left\{1 - \left(\frac{1}{k_e - k_a}\right)[k_e \exp(-k_a t) - k_a \exp(-k_e t)]\right\} \quad \ldots\ldots (7)$$

1.3 Two –compartment model:

The simplest multi-compartment model is a two-compartment model ,Although these compartments have no physiological or anatomical meaning, Drug distribution occurs very rapidly in the tissues that make up the central compartment into which drug is administered, it comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. but the distribution of a significant amount of the drug to other tissues occurs at a noticeably slower rate.[7] A two-compartment model is a model in which the peripheral space is assumed to be homogenous, so that the drug is well mixed within it, and the exchange rates between the two compartments, as well as elimination, are constants. The peripheral space as everything else, i.e., the total body space the drug is distributed in minus the central compartment. [8]

2. Materials and method for bioavailability test:

2.1 Instrumentation:

. High performance liquid chromatography (HPLC, KNAUER); HPLC pump (KNAUER); Spectrophotometer variable detector (KNAUER); HPLC column ODS (C18) (KNAUER); Data processing modular or interface (KNAUER); UV (Ultra violet) spectrophotometer (UV 1601 Shimadzu, Japan); Membrane filters pore size) (Sartorius, Germany).

2.2 Sampling procedure:

The blood samples were drawn from the arm vein. The blood samples were collected at 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, and 12.0 hours after the oral drug administration. The blank blood samples were taken in all volunteers. The blood samples were collected in EDTA tubes then transformed to special glass centrifuge tubes. At each sampling time, 5mL of blood was drawn with the help of disposable syringe plasma was separated and stored in freezer below -20°C until used for analysis of diclofenac.

2.3 Method of HPLC assay:

An accurate High Performance Liquid Chromatographic (HPLC) method which was developed and applied. A system (KNAUER) equipped with a UV detector (series 200 UV-visible set at 283nm) and Hypersil ODS C18 (5µm) reversed phase column (250 × 4.6 mm I.D.) was used; HPLC interface (NC 1900) (KNAUER).The mobile consisted of a mixture of acetonitrile and 0.01M ammonium acetate buffer in the ratio of 60:40. The pH of mobile phase was maintained at 3.4 by glacial acetic acid. Optimum flow rate was 1.5 mL/min. Further, the method was validated by establishing standard solution (10µg/ml) diclofenac sodium.

2.4 Assay procedure:

Stock solutions (10µg/ml) of diclofenac sodium were prepared fresh daily by dissolving the drug in the mobile phase. 2mL of acetonitrile was added to 1mL of plasma samples to precipitate the proteins and vortexed for 1 minute. It was then centrifuged for 5 minutes at 3500 rpm. After centrifugation, supernatant layer was transferred to another test tube and evaporated to dryness under nitrogen flux. The residue was then dissolved in 400µl of mobile phase and 20µl injected into the injection port. Serum diclofenac concentrations were measured by reversed-phase HPLC with ultraviolet detection

3. Result and discussion:

Plasma concentration versus time profile of diclofenac sodium after an oral dose of 100 mg delayed release tablet was measured and plotted as shown in Fig.2. It's non- compartmental analysis made and statistically evaluated as shown in table (1).

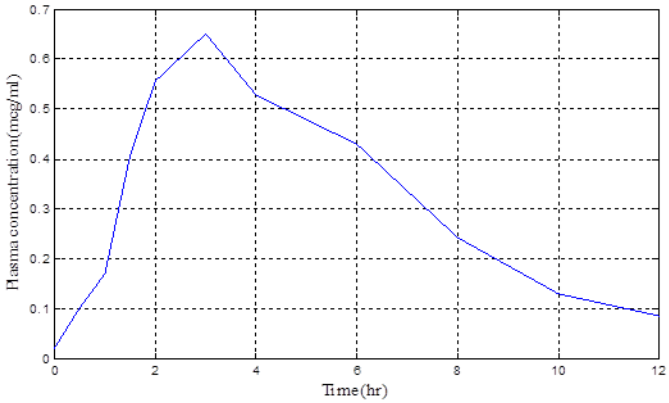

Figure 2: Mean plasma concentration in (µg /ml) of seven healthy volunteers

3.1 Non compartmental analysis:

The maximum plasma concentration (C_{max}) and the time to reach maximum concentration (T_{max}) were directly determined from the plasma concentration versus time curves. The area under the plasma concentration versus time curve from 0 to t ($AUC_{0\to t}$) was calculated by the linear trapezoidal rule. The area under the curve from (0 hour to infinity) ($AUC_{0\to\infty}$) was estimated by summing the area under the curve from 0 to t ($AUC_{0\to t}$) and t to infinity ($AUC_{t\to\infty}$), where $AUC_{t\to\infty} = C_t/k_e$, with C_t defined as the last measured plasma concentration at time t, and k_e the slope of the terminal portion of the ln (plasma concentration) versus time curve. The elimination half-life ($t_{1/2}$) was calculated using the pharmacokinetic relationship $t_{1/2}$=ln(2)/ k_e. The half-life of diclofenac sodium in plasma varies from 1-3 hours (Adeyeye & Li, 1990; \Reynold, 1993; Willis et al., 1979; Degen et al., 1988; Said & Sharaf, 1981 and Landsdorp et al., 1990). [9, 10, 11]

Table 1: pharmacokinetic parameters obtained from bioavailability test.

Parameter name	Parameter value Mean± SD
$AUC_{0\to t}$ (µg. h/ml)	3.892±0.228
$AUC_{0\to\infty}$ (µg. h/ml)	4.224±0.162
$AUMC_{0\to\infty}$ (µg. h^2/ml)	24.231±0.134
Tmax(h)	3±0.5
Cmax(µg/ml)	0.649±0.331
$t_{1/2}$(h)	2.675 ± 0.514
MRT(h	5.736±1.07
Vd/F (L)	91.405±1.48
Cl/F(L/h)	23.674±0.790

where, $AUC_{0\to t}$ is the area under the curve from time zero to t, $AUC_{0\to\infty}$ area under the curve from zero to infinity, $AUMC_{0\to\infty}$ area under the curve from zero to infinity, Tmax is the time needed to reach the maximum concentration, C_{max} the maximum plasma concentration, k_a absorption rate constant, k_e elimination rate constant, $t_{1/2}$ half life time, MRT mean residence time, Vd/F volume of distribution, Cl/F clearance.

Then the plasma concentration versus time profile fitted to single and two compartments model using method of residuals, to fit the plasma concentration profile to two compartments model the absorption phase should be composed of two exponential terms ß and α. It was found that there's no α phase and that means that there's no significant distribution phase so the plasma profile fitted to single compartment model with one time variant input and one time variant output. The data using compartmental analysis obtained as shown in table(2) and Eqs (2,4,7) plotted in Figs(3,4,5)to show the rate of change of drug amount in GI –tract ,in Body, and in elimination site.

Table 2: parameter obtained using compartmental analysis.

Parameter nam	Parameter value
$k_e(h^{-1})$	0.259
$k_a(h^{-1})$	0.699
$t_{1/2}$(h)	2.653
$AUC_{0\to t}$(µg. h/m	4.032
Vd/F(L)	94.71
Cl/F(L/h)	24.53

Where k_a is the absorption rate constant and $k_e$is the elimination rate constant other parameters as mentioned in table (1). if compare between the values of $AUC_{0\to t}$, $t_{1/2}$(h), Vd/F(L), Cl/F(L/h) obtained in compartmental and non-compartmental analysis they are approximately identical, but Non-compartmental analysis offers

several benefits over compartmental analysis. Like that fewer plasma samples may be required, the timing of the samples is not as critical as it is for multi-compartmental analysis. and The modeling process is more straight forward and requires less experience

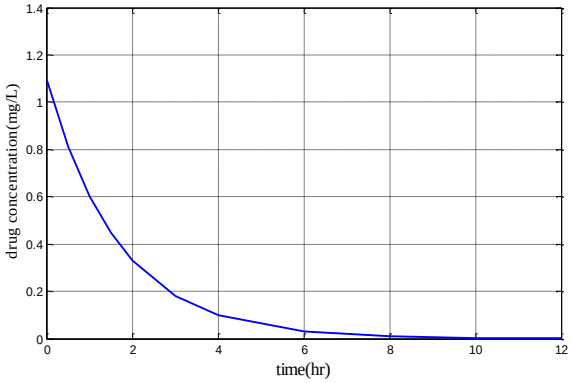

Figure3 : Rate of change drug amount in the GI-tract versus time.

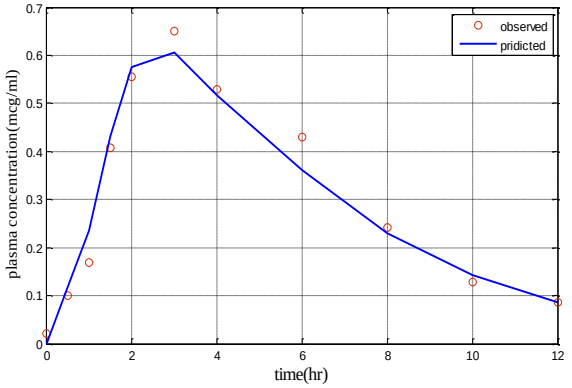

Figure 4: predicted plasma concentration versus time using single compartment model.

The data with red marker represents the observed plasma concentration and the blue line represents the predicted profile using single compartment model. The correlation between observed and predicted profiles was 0.95.

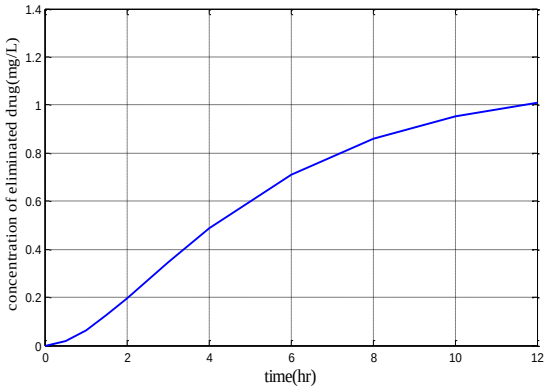

Figure 5: Amount of drug eliminated versus time.

Table 3: compartmental and non-compartmental primary pharmacokinetic parameters.

Parameter name	compartmental	Non-compartmental
Cl	24.53	24.23
Vd	94.71	91.41
$t_{1/2}$	2.92	2.46
AUC_0^∞	4.03	4.49

4. Conclusions:

- Both of compartmental and non compartmental analysis describes the pharmacokinetic parameters accurately
- The clearance, volume of distribution, half life, and area under the curve from zero to infinity were comparable to each other for two methods as shown in table (3)
- Non compartmental analysis was easier and needs less experience.
- Compartmental analysis describe the movement of drug better by the differential equations and plotting the predicted plasma concentration versus time profile.
- The correlation between observed and predicted plasma concentration versus time profiles using compartmental analysis was 0.95.

5. References:

[1] Milo Gibaldi, Donald Perrier, **"Pharmacokinetics"** 2nd edition, Informa Healthcare USA, pp.145-434, 2007.

[2] Joseph Bronzino, "**Introduction to biomedical engineering**", ACADEMIC PRESS SERIES IN BIOMEDICAL ENGINEERING, pp. 382-379, 2012.

[3] SARA ROSENBAUM, "**Basic Pharmacokinetics and Pharmacodynamics**", by John Wiley & Sons pp.91-204,2011.

[4] Shein-Chung Chow،Jen-pei Liu, **'Design and Analysis of Bioavailability and Bioequivalence Studies Third Edition'**, Taylor & Francis Group , pp.9-12, 2009.

[5] Shargel L, Wu-Pong S, **"Applied Biopharmaceutics and Pharmacokinetics".** 5th Ed. McGraw-Hill, pp. 70-77, 2005.

[6] Sunil S Jambhekar, Philip J Breen, **"Basic Pharmacokinetics"**, Pharmaceutical Press,pp 106-125, 2009.

[7] Andres Kalen,'**Computational Pharmacokinetics**', Chapman &Hall Biostatistics Series, pp. 98-102, 2007.

[8] Emami J.,Ghassami N.,Talari R. **"A rapid and sensitive HPLC method for determination of diclofenac sodium in human plasma and its application in pharmacokinetic studies".** DARU Vol. 15, No.3 . pp.132-138. 2007.

[9] Bilal Yilmaz, Ali Asci, and Saziye Sezin Palabiyik. **"HPLC Method for Determination of Diclofenac in Human Plasma and Its Application to aPharmacokinetic Study in Turkey"**. Journal of Chromatographic Science, Vol. 49,pp.422-427,2011.

[10] S.M. Farid Hasan, Tasneem Ahmed, Nasira Talib and Fouzia Hasan. "**Pharmacokinetics OF Diclofenac Sodium in Normal man**". Pakistan Journal of Pharmaceutical Sciences. 18-24. 2005.

تحليل الحرائك الدوائية مقسم وغير مقسم للوحي ديكلوفيناك الصوديوم الإصدار الموسع

انس قصي
قسم الهندسة الطبية – كلية الهندسة
جامعة النهرين

اسماء حميد
قسم الهندسة الطبية – كلية الهندسة
جامعة النهرين

خولة حميد رشيد
قسم الهندسة الطبية – كلية الهندسة
جامعة النهرين

الخلاصة:

النمذجة يغلب يصف حركة مادة من حجرة واحدة إلى آخر. فإنه يهتم بالحفاظ على مستويات المواد الكيميائية الصحيحة في الجسم وعلى حجم السوائل الصحيح. من جانب آخر تحليل غير مقسم يكون العديد من الفوائد عبر تحليل مقسم مثل أنه يتطلب أقل خبرة ومهارة من جانب صانع التماثيل، دراسة في فيفو على سبعة من متطوعي صحية، تركيز البلازما مقابل وقت الحصول عليها ثم تحليل يغلب كل مقسم وغير المطبقة للبيانات، وإزالة، وحجم التوزيع، نصف الحياة، والمنطقة تحت المنحنى من صفر إلى اللانهاية، كانت قابلة للمقارنة مع بعضها البعض لأساليب السحب ، ولاحظ العلاقة بين وكان تركيز البلازما المتوقعة مقابل ملفات تعريف الوقت باستخدام تحليل يغلب 0.95.

View publication stats