Three Computational Mathematics Techniques: Comparative Determination of Area under Curve

Khalid Pervaiz Akhter [1], Mahmood Ahmad [2], * Ghulam Murtaza [2], Ishrat Shafi [1], Zafar Javed [3]

Abstract—The objective of this manuscript is to find area under the plasma concentration- time curve (AUC) for multiple doses of salbutamol sulphate sustained release tablets (Ventolin® oral tablets SR 8 mg, GSK, Pakistan) in the group of 18 healthy adults by using computational mathematics techniques. Following the administration of 4 doses of Ventolin® tablets 12 hourly to 24 healthy human subjects and bioanalysis of obtained plasma samples, plasma drug concentration-time profile was constructed. AUC, an important pharmacokinetic parameter, was measured using integrated equation of multiple oral dose regimens. The approximated AUC was also calculated by using computational mathematics techniques such as repeated rectangular, repeated trapezium and repeated Simpson's rule and compared with exact value of AUC calculated by using integrated equation of multiple oral dose regimens to find best computational mathematics method that gives AUC values closest to exact. The exact values of AUC for four consecutive doses of Ventolin® oral tablets were 150.5819473, 157.8131756, 164.4178231 and 162.78 ng.h/ml while the closest values approximated AUC values were 149.245962, 157.336171, 164.2585768 and 162.289224 ng.h/ml, respectively as found by repeated rectangular rule. The errors in the approximated values of AUC were negligible. It is concluded that all computational tools approximated values of AUC accurately but the repeated rectangular rule gives slightly better approximated values of AUC as compared to repeated trapezium and repeated Simpson's rules.

Keywords—Salbutamol sulphate, Area under curve (AUC), Repeated rectangular rule, Repeated trapezium rule, Repeated Simpson's rule.

I. INTRODUCTION

THE terms "pharmacokinetics" represents drug absorption, distribution, metabolism and excretion in the body. Plasma and urine are major biofluids used for the

Khalid Pervaiz Akhter is with Department of Mathematics, the Islamia University of Bahawalpur, Bahawalpur, Pakistan (Phone: 0092-62-9255243; fax: 0092-62-9255565; e-mail: kpakhtar@yahoo.com)

Ishrat Shafi, burhanamariam@yahoo.com

Mahmood Ahmad is with Department of Pharmacy, Faculty of Pharmacy & Alternative Medicine, the Islamia University of Bahawalpur, Bahawalpur, Pakistan (phone: 0092-62- 9255243; fax: 0092-62-925556, ma786_786@ yahoo.com).

Ghulam Murtaza, gmdogar356@gmail.com

Zafar Javed is with Department of Physics, the Islamia University of Bahawalpur, Bahawalpur, Pakistan (phone: 0092-62- 9255243; fax: 0092-62-925556, zjaved34@yahoo.com).

calculation of pharmacokinetics. However, the former is considered a good source of informations. Plasma drug concentration-time profile is used for the calculation of various pharmacokinetics parameters such as area under curve (AUC), drug absorption constant (K_a), drug elimination constant (K), volume of distribution (V_d) and others. AUC, an important pharmacokinetic parameter, provides basic informations regarding drug transit time in body because it is proportional to the drug absorbed and can be calculated by many techniques. Statistically, there are many approaches such as repeated rectangular rule, repeated trapezium rule and repeated Simpson's rule which can be employed to evaluate AUC from plasma drug concentration-time data [1].

Different numerical methods are applicable for finding AUC such as repeated rectangular rule, repeated trapezium rule and repeated Simpson's rule [2]. The repeated rectangular rule is very simple and interesting mathematical method that provides the elegant solution. It is used after dividing the curve into a large number of rectangles. The accuracy of approximate solution can be increased (decreased) by increasing (decreasing) the step size [3]. The repeated trapezium rule is another method that is used to estimate AUC in the given limits. However, the trapezium rule is used to find AUC using two points for each application. The plasma drug concentration-time curve is divided into several trapeziums. Each interval has length "h". The repeated trapezium rule is also applied. The quadratic polynomials were used to approximate the integral of a function by repeated Simpson's rules [4]. The repeated Simpson's rule can be derived by integrating a second order Lagrange interpolating polynomial interpolating the function at three equally spaced points. The repeated Simpson's method is used to compute AUC in the given limits by dividing the interval into number of trapeziums. The number of trapeziums is even [5].

This manuscript compares three methods (repeated rectangular rule, repeated trapezium rule and repeated Simpson's rule) for AUC evaluation in pharmacokinetic studies in human for 4 consecutive doses of an anti-asthmatic drug, salbutamol sulphate sustained release tablets (Ventolin® oral tablets SR 8 mg, GSK, Pakistan) and to find the comparison of exact and approximate values of AUC. These numerical rules come from numerical integration. The integration of the equation of multiple oral dose regimens gives exact values of AUC. For approximate solution, the previously generated experimental data of drug concentration-time profile for multiple oral-doses was used [6]. This data was approximated by using rational quadratic interplant. The

approximation was compared to exact AUC by using a computer program written in FORTRAN 95.0.

II. EXPERIMENTAL

A. Bioavailability Study

This manuscript is based on a previous bioavailability study for Ventolin® oral tablets carried out in 24 healthy male young non-smoker human subjects (61-85 kg mean body weight) with no clinical and biochemical abnormality [7,8]. Following the administration of 4 doses of Ventolin® oral tablets 12 hourly to 24 healthy human in a cross over study and bioanalysis of obtained plasma samples, plasma drug concentration-time profile was constructed. Various pharmacokinetic parameters such as AUC were measured using integrated equation of multiple oral dose regimens.

B. Models Considerations

The single oral-dose plasma concentration-time profile is determined by equation 1:

$$C_p = \frac{FDK_a}{V_d(K_a - K)}\left(e^{-kx} - e^{-k_ax}\right) \quad (1)$$

where, $t = x$, C_p is plasma concentration at any time t, D is the orally administered dose, F is the fraction of the dose that reaches the systemic circulation, K_a is the first-order absorption rate constant, K is the first-order elimination rate constant and V_d is the volume of distribution [9].

The plasma concentration at any time during a constant equi-interval oral multiple-dose regimen following one compartment model can be determined by following equation:

$$C_p = \frac{FK_aD_o}{V_d(K - K_a)}\left[\left(\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right)e^{-k_ax} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right)e^{-kx}\right] \quad (2)$$

Where, "τ" is the dosing interval and "n" is number of doses [10].

C. Calculation of Exact Value of AUC

The exact value AUC for single oral dose can be obtained by integrating equation 1.

$$\int_0^\infty C_p dx = \int_0^\infty \frac{FDK_a}{V_d(K_a - K)}\left(e^{-kx} - e^{-k_ax}\right)dx \quad (3)$$

After applying limits from 0→∞, the equation of C_p for single oral dose gives the equation for AUC as:

$$AUC = \frac{FDK_a}{V_d(K_a - K)}\left(\frac{1}{K} - \frac{1}{K_a}\right) \quad (4)$$

Note that the analytical integrals of the concentration functions of the models (1) exist. The exact value of the multiple oral doses can be obtained by integrating equation (2).

$$\int_o^\infty C_p dx = \int_0^\infty \frac{FK_aD_o}{V_d(K - K_a)}\left[\left(\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right)e^{-k_ax} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right)e^{-kx}\right]dx \quad (5)$$

After applying limit from 0→∞, the equation of C_p for multiple doses gives the equation for AUC as:

$$AUC = \frac{FK_aD_o}{V_d(K - K_a)}\left[\left(\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right)\frac{1}{K_a} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right)\frac{1}{K}\right] \quad (6)$$

D. Numerical Methods Used

Repeated rectangular rule, repeated trapezoidal rule and repeated Simpson's rule were used for finding approximated AUC. The range of integration $[t_0, t_k]$ was divided into N subintervals for different values of natural number N. Where, t = x:

$$\int_{x_o}^{x_N} c(x)dx = [AUC]_{x_o}^{x_N} = [AUC]_{x_o}^{x_1} + [AUC]_{x_1}^{x_2} + \cdots\cdots + [AUC]_{x_{N-1}}^{x_N} \quad (7)$$

If only two time values t_i, t_{i+1} are taken then trapezoidal rule is:

$$[AUC]_{x_0}^{x_{i+1}} = \frac{(x_{i+1} - x_i)}{2}[c(x_i) + c(x_{i+1})] \quad (8)$$

If repeated trapezium rule is applied for finding approximated AUC, we get:

$$[AUC]_{x_o}^{x_N} = \frac{h}{2}\left[c(x_o) + 2\sum_{i=1}^{N-1}c(x_i) + c(x_N = x_k)\right] \quad (9)$$

Where, $h = \frac{(x_N - x_o)}{N}$

If repeated Simpson's rule is applied for finding approximated AUC, then we get:

$$[AUC]_{x_o}^{x_N} = \frac{h}{3}\left[c(x_o) + c(x_N) + 4\sum_{i=1}^{N-1}c(x_i) + 2\sum_{i=2}^{N-2}c(x_i)\right] \quad (10)$$

Where, $h = \frac{(x_N - x_o)}{N}$

When repeated rectangular formula is applied for calculating approximated AUC then we get:

$$[AUC]_{x_o}^{x_N} = h\sum_{i=1}^{N-1}c(x_i) \quad (11)$$

Where, $h = \frac{(x_N - x_o)}{N}$

It is clear that analytic values of $[AUC]_{x_o}^{x_k}$ can be calculated by using equation 3. A monotonic piecewise rational quadratic s(t) was applied to approximate the value of concentration between the given concentration versus time data points. Then approximated concentration values were obtained at additional values of time by the values of s(t).

Let $c_i = c_{i+1} = c(x_{i+1})$, $d_i = c'(x_i)$ and $d_{i+1} = c'(x_{i+1})$. The ratio d_i and d_{i+1} may be computed from the concerned model. It is clear that d_i can be approximated as:

Let, $h_i = x_{i+1} - x_i$ for $x \in [x_i, x_{i+1}]$, $i = 0,1,2,\cdots\cdots,k-1$

$$\theta = \frac{(x - x_i)}{h},$$

$$\Delta_i = \frac{(c_{i+1} - c_i)}{h_i},$$

$$s(t) = \begin{bmatrix} p_i(\theta)/Q_i(\theta) & if\Delta_i \neq 0 \\ C_i & if\Delta_i = 0 \end{bmatrix} \quad (11a)$$

Where, $P_i(\theta) = \Delta_i C_{i+1}\theta^2 + (C_i d_{i+1} + C_{i+1} d_i) + \Delta_i C_i (1-\theta)^2$

$Q_i(\theta) = \Delta_i \theta^2 + (d_{i+1} + d_i)\theta(1-\theta) + \Delta_i(1-\theta)^2$

The central differences approximation to $C'(x)$ that is commonly used in numerical analysis, is given by:

$$C'(x_i) = \frac{C(x_i + h) - C(x_i - h)}{2h} \quad (12)$$

In this study, the spacing of the concentration data is not uniform and the central difference approximation to $C'(x)$ was calculated by using equation 8 and defined by:

$$d_i = C'(x_i) \cong \frac{C(x_i + h) - C(x_i - h)}{h_n - h_{n-1}}, i = 1,2,........k-1 \quad (13)$$

It is closer to the exact values of derivatives as compared to the values of the derivatives calculated by using forward or backward difference. So $C'(x_k)$ and $C'(x_0)$ that are initial and final values of derivatives can be found using forward and backward differences such as:

$$C'(x_o) \cong \frac{C(x_o + h_o) - C(x_o)}{h_o} \quad (14)$$

and

$$C'(x_k) \cong \frac{C(x_k) - C(x_k - x_{k-1})}{h_{k-1}} \quad (15)$$

These are backward and forward difference approximations. The drug concentration data was taken at some points separated by unequal intervals, not at all. Thus non-uniform data was obtained and converted it into equally spaced data. For this, monotonic piecewise rational quadratic interplant was used [11]. The approximate value of c(t) was calculated by using the rational quadratic interpolant. The data was generated by the approximation of s(t) at very small intervals like 0.00001. For multiple dosing data, the quadratic rational interpolant s(t) gave the approximate values at every point. The above data was used to draw curve for each dose and the area of each curve was determined. For this, different numerical methods were employed such as repeated rectangular rule, repeated trapezoidal rule and repeated Simpson's rule. The computer program of these numerical methods (Microsoft Power Station FORTRON) was produced to calculate AUC using the approximate values of s(t).

III. RESULTS AND DISCUSSION

The model of multiple doses was integrated to calculate exact values of AUC. The exact mean values of pharmacokinetic parameters such as D, F, V_d, K_a, AUC and K were calculated from plasma drug concentration versus time profiles by using integrated equation of multiple oral dose regimens and are shown in Table 1 and then calculated the approximate values of AUC. For this purpose we used data which was obtained by Ventolin® tablets.

The rational quadratic interpolant s(t) was used for calculating the approximate values of plasma drug concentration at each point. A computer program for rational quadratic interpolant was produced to calculate the values of drug concentration at each point. The approximated concentration values at additional points using s(t) taking step sizes 0.001, 0.0001 and 0.00001 were generated to find AUC by using different numerical methods such as repeated rectangular methods, repeated trapezium method and repeated Simpson's method.

The exact and approximate values of AUC were compared to check the difference. It was observed that there was a negligible difference between the exact and approximate values of AUC as calculated by above mentioned numerical rules. Approximate values of AUC for given data by repeated rectangular, repeated trapezium and repeated Simpson's rules respectively are represented in Table 1 when length of step size (h) is 0.001, 0.0001 and 0.00001 by using all of three rules. For step size 0.00001, there was best approximation of AUC and the result shows that increase in the number of trapezium gives more accuracy.

Table 2 shows approximate AUC in all cases is slightly less than the respective exact AUC. However, the approximate values of AUC are close to the respective exact values of AUC for each given length of interval. The difference between the approximate values of AUC may be significant

TABLE I EXACT MEAN VALUES OF PHARMACOKINETIC PARAMETERS FOR FOUR DOSES OF VENTOLIN® TABLETS 12 HOURLY AND APPROXIMATE VALUES OF AUC WHEN INTERVAL IS 0.00001, 0.0001 AND 0.001

		No. of Doses			
		First Dose	Second Dose	Third Dose	Fourth Dose
		Exact values of pharmacokinetic parameters			
AUC (ng.h/mL)		150.581947	157.813172	164.41782	162.787969
K_a (Hr^{-1})		3.09263	6.34173	0.65774	0.7477
F		1.12462	0.73555	1.24111	1.6800
V_d (L/Kg)		0.12622	0.18798	0.227012	0.2616
K (Hr^{-1})		0.12628	0.18795	0.227017	0.2613
		Approximate values of AUC (ng.h/ml)			
Approximate AUC values when interval = 0.00001	Repeated Rectangular Rule	149.245962	157.336171	164.25857	162.289224
	Repeated Trapezium Rule	149.244423	157.334269	164.25649	162.287349
	Repeated Simpson's Rule	149.244429	157.334274	164.25650	162.287341
Approximate AUC values when interval = 0.0001	Repeated Rectangular Rule	149.136645	157.228273	164.15197	162.181982
	Repeated Trapezium Rule	149.136492	157.228083	164.15177	162.181794
	Repeated Simpson's Rule	149.136389	157.227956	164.15163	162.181668
Approximate AUC values when interval = 0.001	Repeated Rectangular Rule	149.131635	157.222660	164.14615	162.176157
	Repeated Trapezium Rule	149.131148	157.222641	164.14613	162.176138
	Repeated Simpson's Rule	149.131138	157.222629	164.14611	162.176126

TABLE II COMPARISON OF EXACT AND APPROXIMATE VALUES OF AREA UNDER PLASMA CONCENTRATION TIME CURVE USING REPEATED RECTANGULAR RULE, REPEATED TRAPEZIUM RULE AND REPEATED SIMPSON'S RULE WHEN INTERVAL IS 0.00001

		No. of Doses			
		First Dose	Second Dose	Third Dose	Fourth Dose
Repeated Rectangular Rule	Exact area	150.581947	157.813172	164.417823	162.787969
	Approximate area	149.245962	157.336171	164.258577	162.289224
	Error	1.335986	0.477005	0.159246	0.498745
	Percentage error	0.887%	0.302%	0.097%	0.306%
Repeated Trapezium Rule	Exact area	150.581947	157.813172	164.417823	162.787969
	Approximate area	149.244423	157.334269	164.256495	162.287349
	Error	1.337524	0.478907	0.161328	0.500619
	Percentage error	0.888%	0.303%	0.098%	0.308%
Repeated Simpson's Rule	Exact area	150.581947	157.813172	164.417823	162.787969
	Approximate area	149.244429	157.334274	164.256500	162.287341
	Error	1.337519	0.478902	0.161323	0.500628
	Percentage error	0.888%	0.303%	0.098%	0.308%

from mathematical point of view but the difference is negligible from practical point of view.

It was also noted that with decreasing the value of length of subintervals, the approximate values of AUC became closer to the respective exact values. Moreover, the approximate value of AUC computed by repeated rectangular rule is closest to the exact values of AUC. This is because of shape of plasma concentration-time curve. Table 2 shows the maximum value of error percentage that is at the most one and at least 0.097%. It verifies that the approach adopted is very successful and the approximate values of AUC are almost the same as exact from the practical point of view. An advantage of this approach is that there is no need to calculate k_a, F, V_d and K using present software.

IV. CONCLUSION

All computational tools approximated values of AUC accurately but among three computational mathematics techniques such as repeated rectangular rule, repeated trapezium and repeated Simpson's rule, repeated rectangular rule gives slightly better results regarding approximation of AUC as compared to other approximation methods.

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