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Modified release of drug: a way to its quantification

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Summary

Modified release of drug from a delivery system may be quantified by determining the area deviation of an experimental curve from a standard curve; the latter being the transformation of the individual experimental plasma concentration–time profile to a rectangle of equal area (internal standard) or the plasma concentration–time curve required for adequate effect (external standard). The advantage of this method is the precise characterization of the plasma drug profile over any required time interval. Taking an injectable controlled release drug formulation with bromocriptine (= 2-bromo-α-ergokryptine) as an example, it has been shown how controlled release from such delivery system can be quantified satisfactorily.

Introduction

Drug formulations which maintain constant plasma levels for limited time intervals are gaining increasing attention (Langer and Peppas, 1981; Buckles, 1983; Heller et al., 1983; Siegel and Langer, 1984). The methods employed for quantifying the release of drug by such formulations in vivo are not satisfactory. Rather than area under the curve (AUC) and rate of absorption, the shape of the plasma profile is indicative for modified release of drug (Meier et al., 1974; Gresser et al., 1978; Stricker, 1978; Theeuwes and Bayne, 1977).

For some time we have been using the method of area deviation (AD) of an experimental curve from a standard curve to describe quantitatively the release of drug. The standard curve was derived by transformation of the individual plasma concentration–time profile to yield the release kinetics by means of a single numerical index. The AD method has recently been used in a variant form for the comparison of oral sustained-release formulations of theophylline (Boxenbaum, 1984).

In the present paper we show as an example the release of bromocriptine from an injectable depot formulation. It is intended for single administration in human to prevent and suppress puerperal lactation.

Theoretical

We consider the method of area deviation (Boxenbaum, 1984) a very potent way to quantify plasma level data of modified release drug formulations. However, a simpler methodology would get a wider acceptance. Thus, we attempted to develop that concept further and to use it to quantify the plasma concentration–time profile of modified release drug formulations.

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In a considerable number of cases, there is lack of knowledge about the plasma concentration needed for adequate effect. Usually, the plasma concentration–time curve is the only means to judge the performance of the release characteristics of a drug formulation. One aims generally at a drug release which yields constant plasma levels. To obtain the theoretical constant plasma level–time profile (= internal standard) from the experimental plasma level–time curve the AUC_{exp} (experimental AUC) is transformed to a rectangle of equal area dividing AUC_{exp} by the time interval for modified release t_r (Fig. 1). The height of the rectangle ($= c_{p,ideal}$) represents the average experimental plasma level for t_r. Deviations of the experimental plasma level from $c_{p,ideal}$ can be quantified by positive (AUC_{Di^+}) and negative (AUC_{Di^-}) area deviations which are equal.

$$AUC_{Di^+} = |AUC_{Di^-}| = AUC_{Di} \qquad (1)$$

The average experimental plasma level is calculated for each individual separately.

Based on the internal standard the relative area deviation is used to quantify the absolute retard effect $R_{i,abs}$ (%) (Fig. 1).

$$R_{i,abs}(\%) = 100\left(1 - \frac{AUC_{Di}}{AUC_{exp}}\right) \qquad (2)$$

From Eqn. 2 it follows $R_{i,abs} \to 0$ when $AUC_{Di} \to AUC_{exp}$ and $R_{i,abs} = 100$ when $AUC_{Di} = 0$. For comparison with a reference form the relative retard effect $R_{i,rel}(\%)$ is determined as follows.

$$R_{i,rel}(\%) = 100\left(1 - \frac{AUC_{Di} \cdot AUC_{exp,ref}}{AUC_{Di,ref} \cdot AUC_{exp}}\right) \qquad (3)$$

$AUC_{Di,ref}$ = area deviation of the reference form from $c_{p,ideal,ref}$. From Eqn. 3 it follows that $R_{i,rel} = 0$ when

$$\frac{AUC_{Di}}{AUC_{exp}} = \frac{AUC_{Di,ref}}{AUC_{exp,ref}} \text{ and,}$$

that $R_{i,rel} = 100$ when $AUC_{Di} = 0$.

Two drug formulations can only be compared if the same t_r is used for calculation of AUC_{Di} and $AUC_{Di,ref}$.

Drug burst can be quantified using the ratio of the positive area deviation AUC_B (Fig. 1) for peak concentration to the total AUC_{exp}.

$$B(\%) = 100\frac{AUC_B}{AUC_{exp}} \qquad (4)$$

However, unlike in earlier work (Boxenbaum, 1984) we use absolute values of either the positive or negative area deviations for calculation of $R_{i,abs}$ and $R_{i,rel}$. For examination of a retard formulation a minimum value $R_{i,min}$ is used as the criterion of acceptance of $R_{i,abs}$.

We propose the following arbitrary criteria for a modified release drug formulation to be acceptable.

$$R_{i,abs} \geqq R_{i,abs,min} \triangleq 75\% \qquad (5)$$

For testing the significance ($\alpha = 0.05$) of the retard effect t-statistics (Winer, 1971) (one-sided test) was used to prove the following hypothesis (under the premises of normal distribution).

H_1: $R_{i,abs} \leqq R_{i,abs,min}$ ($\triangleq 75\%$)

H_2: $R_{i,abs} > R_{i,abs,min}$ ($\triangleq 75\%$)

$$t = \frac{(\overline{R_{i,abs}} - 75) \cdot \sqrt{n}}{S.D.}$$

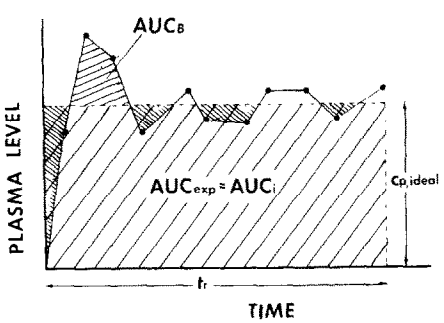

Fig. 1. Arbitrary diagram for demonstration of the method of area deviation to calculate the retard effect by means of the internal standard. AUC_{exp} and AUC_i = area under the experimental and the ideal plasma level time curve, respectively. AUC_B = area deviation based on drug burst; $c_{p,ideal}$ = ideal plasma level; t_r = time interval for modified release of drug.

where $\overline{R_{i,abs}}$ = mean of retard effect; S.D. = standard deviation; n = sample size; d_f = degrees of freedom (n − 1).

For a more rapid but less rigorous estimation the 75/75 decision rule (Rotenberg, 1981) may be acceptable, i.e. when 75% and more of the sample size of $R_{i,abs} \geqq 75\%$.

The known relationship between the plasma concentration–time curve and the time profile of the effect of drug can include the following cases.

(i) The plasma concentration of drug needed for adequate effect, i.e. $c_{p,ther}$ is known. Then, $c_{p,ideal}$ can be compared to $c_{p,ther}$ in the same way as shown for $R_{i,abs}$.

H_1: $c_{p,ideal} \leqq c_{p,ther}$

H_2: $c_{p,ideal} > c_{p,ther}$

$$t = \frac{\left(\overline{c_{p,ideal}} - c_{p,ther}\right) \cdot \sqrt{n}}{S.D.}$$

(ii) Assume the therapeutic range is known, one can construct two standard plasma concentration–time curves whose area difference will correspond to the area of the therapeutic range (AUC_{ther}). The absolute and the relative retard effects can be quantified calculating the ratio of the sum of the positive and negative area deviations to the area difference AUC_{ther}. Some authors (Vallner et al., 1983) proposed to use the area within the therapeutic range to compare drug release from a normal dosage form with that of a modified release drug formulation.

(iii) The relationship between the plasma concentration - time curve and the time profile of drug effect is known: one then uses the plasma concentration–time curve as an external standard. The total area difference between the plasma concentration–time profile of the experimental formulation and the external standard is calculated to determine the absolute retard effect $R_{e,abs}$ (see Eqn. 2).

The method of area deviation is applicable where an experimental curve is to be compared with a reference curve of any kind, e.g. to quantify a steady-state plasma level, bioequivalence or dissolution rate.

Materials and Methods

Application of drug and sampling of blood

In the experiments with man an injectable depot formulation was tested. It had a drug content of 20% (w/w). For intramuscular injection a suspension was prepared with hydrophilic vehicle.

The suspension (2 ml) containing bromocriptine was administered to 10 healthy male volunteers according to the standard deep gluteal technique. The volunteers were fully informed on the aim of the study and gave their written consent to participate. Blood (5 ml) was taken into heparinized tubes by venepuncture from the forearm at 0, 0.5, 1, 1.8, 3, 4, 6, 8, 12 and 24 h and then one single sample during the morning of the following days 2, 3, 4, 5, 6, 7, 10, 14, 17, 21, 24, 28 and 35. Whole blood was centrifuged at 4°C not later than 30 min after sampling and the plasma was deep-frozen at −20°C.

Measurement of plasma concentration by radioimmunoassay

Duplicate aliquots of 0.4 ml blood plasma were analyzed using the radioimmunoassay for the detection of parent drug (Rosenthaler et al., 1983). The lower limit of detection was 0.17 ng/ml blood plasma. The specimens were analyzed following completion of the experiments. Bromocriptine was found to be stable in blood plasma more than 4 months when kept at −20°C.

Results

The AUC's from the experimental plasma levels (Fig. 2) were calculated for each human subject using the trapezoidal rule. The ideal plasma level $c_{p,ideal}$ was calculated by transformation of the experimental plasma concentration–time curve to a rectangle of equal area and $R_{i,abs}$ was calculated by Eqn. 2. As shown (Eqn. 5), $R_{i,abs} \triangleq 75\%$ was considered the lower limit of an acceptable retard effect. An average $c_{p,ideal}$-value of active compound in human was calculated, i.e. 0.7 ng/ml blood plasma (Table 1).

For estimation of $c_{p,ther}$, i.e. the plasma concentration of active compound in human for sup-

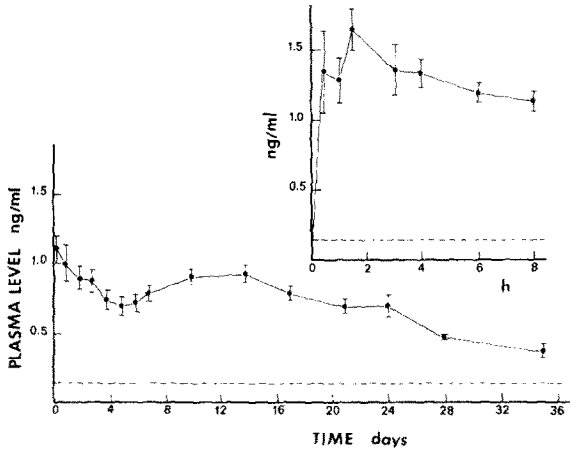

Fig. 2. Plasma concentration–time curve for unchanged drug (2-bromo-α-ergokryptine) after deep intragluteal injection in 10 healthy human volunteers. Inset shows drug release within the first day (hours) after administration. Bars denote standard error of the mean and dotted line indicates the limit of detection of active compound using radioimmunoassay.

pression of lactation we used earlier unpublished observations from a clinical study. There, it was found that 0.58 ng drug/ml blood plasma was sufficient to suppress prolactin in healthy volunteers to a mean level of 2.0 ± 0.7 (S.E.) ng/ml blood plasma. The mean prolactin level of these healthy male (n = 6) and female (n = 4) volunteers in the premedication plasma samples was 11.9 ± 3.1 ng/ml (S.E.) (range: 4.0–38.3).

TABLE 1

INTRAMUSCULAR ADMINISTRATION OF A DEPOT FORMULATION CONTAINING 50 mg 2-BROMO-α-ERGOKRYPTINE BY DEEP INTRAGLUTEAL INJECTION IN VOLUNTEERS

Experimental values were used to calculate the area under the curve AUC_{exp}, the ideal plasma level $c_{p,ideal}$ and the absolute retard effect $R_{i,abs}$ (t_r = 35 days).

Subject code	AUC_{exp} (ng/ml·day)	$c_{p,ideal}$ (ng/ml)	$R_{i,abs}$ (%)
1	25.3	0.72	81
2	29.0	0.83	90
3	32.9	0.94	83
4	20.1	0.57	91
5	21.6	0.62	83
6	26.7	0.76	87
7	20.9	0.60	96
8	20.8	0.59	90
9	22.0	0.63	89
10	26.5	0.76	80
Mean	24.6	0.70	87
S.D.	4.2	0.12	5
C.V.	17.2	17.2	6
S.E.	1.3	0.04	2

$R_{i,abs}$ and $c_{p,ideal}$ (Table 1) were tested using *t*-statistics and it was found that $\overline{R_{i,abs}} > R_{i,abs,min}$ ($P < 0.001$, $1 - \beta > 0.99$) and $\overline{c_{p,ideal}} > c_{p,ther}$ ($P < 0.01$, $1 - \beta = 0.90$).

With the 75/75 decision rule the result was as follows. All values (n = 10) for $R_{i,abs} > 75\%$, and 90% of the $c_{p,ideal}$-values > 0.58 ng/ml. Therefore, the criteria for a modified release formulation were fulfilled.

Discussion

For evaluation of modified release formulations from plasma level or urinary excretion data there is a need to quantify the concentration–time profile. Limited sections of this curve give no conclusive results on controlled release. To obtain the necessary information it was attempted to characterize modified release formulations using four parameters (Stricker, 1978). Indeed, the AUC is an integral measure for concentration over a time interval. The peak plasma concentration characterizes the curve only by means of one single point. However, the plasma level–time profile from onset until termination of the effect will yield the proper information for evaluation of modified release formulations.

An earlier reported method (Meier et al., 1974), on the one hand, employs the half-value duration of a drug. It seems suitable for preliminary characterization of curves with a single peak. For curves with several peaks, there is no way of identifying the peak pertinent to the half-value duration. Any drug burst and all subsequent fluctuations in plasma level are not accounted for by this method. On the other hand, the gravity duration or mean residence time (Meier et al., 1974) does not adequately characterize the plasma level–time profile; for example, the centres of gravity of a rectangle and a triangle of equal area are characterized by the same mean residence

time. Characterization of the plasma level–time curve by statistical moment analysis is based upon probability density functions. It characterizes the residence time frequency distribution of the drug molecules in the blood compartment which appear to be distributed according to such a function. The last data points of the plasma level–time curve should be close to zero since truncating the curve would cause considerable error. This is true for the AUC but it worsens very much for the higher-order moments (Langenbucher and Möller, 1983). A further method (Theeuwes and Bayne, 1977) employs the dosage form index (ratio of peak-to-trough level) for the quantitative description of modified release drug delivery systems over a time interval. A disadvantage of the dosage form index is that the plasma level–time profile over the whole period is characterized by only two points. Thus an unfavourably high dosage form index may result from a drug burst which is relatively insignificant when compared to the total AUC. Fluctuations between $c_{p,max}$ and $c_{p,min}$ which may be outside the therapeutic range, are not shown up by the dosage form index.

A similar approach as we described here, i.e. method of area deviation for estimation of the retard effect of a modified release formulation was described earlier (Boxenbaum, 1984). Plasma level data were used spanning 12 h and multiplied by an appropriate factor thus transforming the new plasma level–time profile to a rectangle with the same area as that from the experimental curve. The average plasma concentration obtained therefore, was the same for all dosage forms and it cannot be compared to $c_{p,ther}$. The advantage of our AD method is that it provides a quantitative measure of any type of plasma level–time curve in a single parameter, i.e. the retard effect, which takes into account both the duration of release and the shape of the curve.

When two different drug formulations, e.g. a standard tablet vs a retard formulation are being compared, the timing to terminate either drug release profile must be identical for both, but the endpoint can be chosen arbitrarily. It is for this reason, i.e. comparing various formulations that the interval for blood sampling (t_r) has to always be the same irrespective of the plasma concentration of drug at that time. The final choice between modified release formulations will depend on whether the $c_{p,ideal}$ is within the therapeutic range.

By analogy to the IND/NDA Guidelines to Bioavailability Submission (Rotenberg, 1981), we have chosen an arbitrary value of 75% being the minimal acceptable retard effect. To judge the absolute value of the retard effect, the experimental retard effect is compared to this arbitrary unit. In our experience the value of 75% seems satisfactory to set a lower limit for discrimination of modified release drug formulations.

Since the present paper is rather conceptual, the practical applications need to be tested in future experiments especially with regard to oral modified release formulations. It should be investigated if the proposed limit ($\geqq$ 75%) and deviations for the retard effect are generally applicable in practice considering inter- and intra-subject variability.

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