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THE ONE-POINT METHOD AS CLINICAL TOOL TO CALCULATE AND/OR ADJUST DOSAGE REGIMEN

W. A. Ritschel

University of Cincinnati Medical Center

College of Pharmacy, Cincinnati, Ohio 45267

ABSTRACT

The one-point method is presented as clinical tool to calculate the dosage regimen for patients where differences in steady state blood levels are expected due to change in volume of distribution (edema, obesity, myocardial or coronary infarction, hypoalbuminemia, displacement from protein binding, etc). The one-point method is based on the c'_{min}- and superposition methods using a single blood sample upon administration of a test dose during the first dosing interval.

This method is indicated when assessment of the dosage regimen is complicated by a change in either the volume of distribution, V_d, or the elimination rate constant, k_{el}, or when the distribution coefficient, Δ', is not known. There are various clinical situations in which V_d is altered, such as in patients with edema, obesity, recent coronary or myocardial infarction, hepatic failure, hypoalbuminemia, displacement from protein binding due to other concomitantly given drugs, etc.

In these cases a test dose D_{test} is given which should be smaller than a "normal" maintenance dose size D.

The one-point method is based on the open one-compartment model by determination of a single drug concentration in blood, plasma or serum towards the end of the first dosing interval (1,2) and the c'_{min}-method (3).

After administration of D_{test} a blood sample is taken towards the end of the dosing interval. The time for sampling should be as late in the dosing interval as possible to ensure that the drug concentration is in the monoexponential elimination phase, yet allowing enough time to analyse the sample before the end of the first dosing interval. The dosing interval is chosen as normally used. This permits to already adjust the dosage regimen during the first dosing interval. The elimination rate constant, k_{el}, or terminal disposition rate constant, β, of the drug is not individually determined but retrieved as average parameter from the literature or taken from a compilation of biological half-lives (4) using equation 1:

$$k_{el} = \frac{0.693}{t_{1/2}} \qquad \text{Eq. 1.}$$

From the one blood sample taken also serum creatinine is determined. In case of abnormal serum creatinine values (>1.4) the corresponding creatinine clearance, $Cl_{creat.obs.}$ is determined either by use of the nomogram by Siersbaek-Nielsen et al. (5) or by using equation 2 by Cockcroft and Gault (6):

$$Cl_{creat.obs.} = \frac{(140-A)\cdot BW}{72-Cr_{ser}} \qquad \text{Eq. 2.}$$

In the case $Cl_{creat.obs.}$ is less than approximately 80 ml/min/1.73 m^2 correction for the retrieved k_{el} is made according to equation 3:

$$k_{el\ pred.} = k_{el} \cdot \left\{ \left[\left(\frac{Cl_{creat.obs.}}{120-S} - 1 \right) \cdot F_{el} \right] + 1 \right\} \quad \text{Eq.3.}$$

From the drug concentration, c_{px}, of the sample taken at time t_x, the minimal drug concentration at steady, $c'_{min\ test\ dose}$, is calculated as would result if one would continue to administer D_{test}:

$$c'_{min\ test\ dose} = \frac{\frac{c_{px}}{e^{-k_{el\ pred.} \cdot t_x}} \cdot e^{-k_{el\ pred.} \cdot \tau}}{1 - e^{-k_{el\ pred.} \cdot \tau}} \quad \text{Eq.4.}$$

The value obtained is treated by use of the "superposition"-method by Westlake (7) and Boxer (8) in order to calculate the "desired" dose size, $D_{desired}$:

$$D_{desired} = \frac{c'_{min\ desired}}{c'_{min\ test\ dose}} \cdot D_{test\ dose} \quad \text{Eq. 5.}$$

As $c'_{min\ desired}$ the minimum effective, MEC, or minimum inhibitory, MIC, or desired drug concentration is used.

Since the test dose, D_{test}, is usually smaller than required, and a loading dose size D* is recommended in order to obtain steady state as soon as possible, the desired loading dose, $D^*_{desired}$, is calculated. In this calculation the drug concentration persisting from

the test dose at the end of the first dosing interval has to be considered as given in equation 6:

$$D^*_{desired} = \frac{D_{desired}}{1-e^{-k_{el\ pred.} \cdot \tau}} - D_{test} \cdot e^{-k_{el\ pred.} \cdot \tau} \qquad \text{Eq. 6.}$$

The one-point method presented here is applicable for the open one-compartment or higher compartment models as long as the blood sample taken is representative for the monoexponential terminal slope and the analysis of the drug is reliable. The procedure is shown in FIG.1.

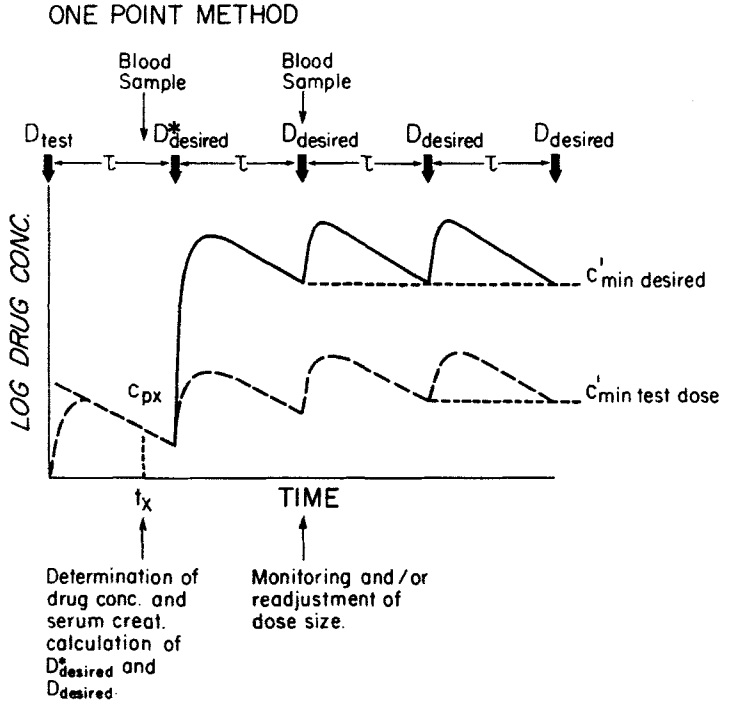

FIGURE 1

Once the desired dosage regimen is calculated the loading dose, $D^*_{desired}$, is given at the end of the first dosing interval followed by the desired maintenance doses, $D_{desired}$, in regular dosing intervals. Blood samples taken at the end of any dosing interval are used for monitoring. Readjustment if necessary can simply be made using equation 7:

$$D_{readjusted} = \frac{c'_{min\ desired}}{c'_{p\tau}} \cdot D_{desired} \qquad \text{Eq. 7.}$$

This equation can also be used in any existing dosage regimen if steady state has been reached. A readjustment might be necessary if the V_d or k_{el} change during the course of therapy.

For practical use of the one-point method one has to be aware of the assumptions and limitations implied.

The approach is based on the assumption that $k_a >> k_{el}$, particularly that no flip-flop model is involved, and that the dosing interval τ is such to ensure consecutive doses to be given when the blood level of the previous dose is in the monoexponential elimination phase.

Although equation 3 for calculating $k_{el\ pred.}$ does not allow correction in hepatic failure the one-point method can be used with the following modification: the drug concentration, c_{px}, after the test dose must be determined not at time t_x but at the end of the first dosing interval τ. In this case $c'_{min\ test\ dose}$ will result in a useful approximation. An alternative in case of hepatic failure would be to use equation 7.

A limitation of the one-point method is a change in protein binding of drugs largely bound to plasma proteins resulting in increase of free drug in plasma unless the free and not the total drug concentration is determined.

SYMBOLS:

1. A = age in years
2. BW = body weight of patient in kg
3. $Cl_{creat.obs.}$ = creatinine clearance of patient
4. $C'_{min\ desired}$ = desired minimum drug concentration at steady state = MIC = MEC in µg/ml
5. $C'_{min\ test\ dose}$ = theoretical minimum drug concentration at steady state if dosing would continue with D_{test} in µg/ml
6. $c'_{p\tau}$ = drug concentration found at the end of any dosing interval once steady state is reached
7. Cr_{ser} = serum creatinine of patient in mg/100 ml
8. $D_{readjusted}$ = readjusted maintenance dose size once steady state is reached, in mg
9. $D_{desired}$ = desired adjusted maintenance dose size for individual patient in mg
10. $D^*_{desired}$ = desired adjusted loading dose size for individual patient in mg
11. D_{test} = test dose in mg
12. k_{el} = elimination rate constant of drug in hr^{-1}
13. $k_{el\ pred.}$ = predicted elimination rate constant adjusted for patient's individual creatinine clearance in hr^{-1}
14. F_{el} = fraction of drug eliminated via kidney
15. MEC = minimum effective concentration is µg/ml
16. MIC = minimum inhibitory concentration in µg/ml
17. S = sex: for males: S=0
    for females: S=12
18. τ = dosing interval in hrs

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