An Introductory Walk Through R Package cpk

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Abstract

This vignette presents an introductory walk through the R package **cpk**. The package assumes blood or plasma measurements are made in units of μg/L. Here, we present an example where blood measurements are made in mg/L, and demonstrate the required unit conversions.

Keywords: clinical pharmacokinetics, pharmacokinetics, dose regimen design, dosing.

1. Introduction

This vignette presents an introductory walk through the R package **cpk** using Mehvar's example (Mehvar 1998). The **cpk** package assumes blood or plasma measurements are made in units of μg/L. Here, we present an example where blood measurements are made in mg/L, and demonstrate the required unit conversions. A glossary of symbols is tabulated in Table 1.

2. Simplified Clinical Pharmacokinetic Equations

Personalizing a drug dosing regimen using R package **cpk** involves the following steps:

Step 1 Calculate or select a target therapeutic concentration (TTC) of drug for the patient based on its therapeutic range:

$$TTC = \frac{MSC - MEC}{\ln\left(\frac{MSC}{MEC}\right)}\,(\mu\text{g/L}). \tag{1}$$

Step 2 Calculate the dose rate to acheive the desired TTC:

$$D_{Rate} = \frac{TTC \times Cl}{F} \times 0.001\,(\text{mg/h}). \tag{2}$$

Step 3 Calculate or select a dosing interval, τ, then calculate the drug's maintenance dose:

$$D_M = D_{Rate} \times \tau\,(\text{mg every}\,\tau\,\text{h}). \tag{3}$$

Table 1: Glossary of Symbols

Parameter	**Units**	**Definition**
V_d	L/kg	Apparent volume of distribution
Cl	L/kg/h	Clearance rate
k_e	h^{-1}	First-order elimination rate constant
$t_{1/2}$	h	Elimination half-life
MEC	μg/L	Minimum effective concentration
MSC	μg/L	Maximum safe concentration
D_{po}	μg	Oral drug dose
D_{iv}	μg	D_{po} when $F = 1$
F	%	Bioavailability
t	h	Time
D_B	μg	Amount of drug in the body
τ	h	Dosing interval
TTC	μg/L	Target therapeutic concentration
D_{Rate}	mg/h	Dose rate
D_M	mg every τ	Maintenance dose
AR	–	Accumulation ratio
C_{ss}	μg/L	Steady-state concentration
$C_{\max}^{\text{ss}}$	μg/L	Maximum steady-state concentration (peak)
$C_{\min}^{\text{ss}}$	μg/L	Minimum steady-state concentration (trough)
$C(t)$	μg/L	Concentration at time t
$\tau_{\max}$	h	Maximum dosing time interval
$D_L^{D_M}$	mg	Loading dose based on maintenance dose
$D_L^{C_{\max}}$	mg	Loading dose based on $C_{\max}$

When medicines are administered as a multiple-dose regimen, each successive doses are administered before the preceding doses are completely eliminated, so that medicine accumulates according to its accumulation ratio (AR):

$$AR = \frac{1}{(1 - e^{-k_e \cdot \tau})} \approx \frac{\tau}{t_{1/2}}, \tag{4}$$

where $t_{1/2}$ is the medicines elimination half-life (Greenblatt 1985). Under this constraint, the steady-state blood or plasma concentration of medicine can be calculated using the following equation:

$$C_{ss} = \frac{D_{Rate} \times F}{Cl} \times AR. \tag{5}$$

The blood or plasma concentration of medicine will also fluctuate between a maximum (peak) and minimum (trough) concentration:

$$C_{\max} = \frac{F \times D_{po}}{V_d} \times AR \tag{6}$$

and

$$C_{\min} = C_{\max} \times e^{-k_e \cdot \tau}. \tag{7}$$

The concentration of medicine in the blood or plasma over time, i.e., the medicines concentration-time or clearance curve is given by:

$$C(t) = C_0 \times e^{-k_e \cdot t} \tag{8}$$

The maximum dosing time interval for a multiple dosing interval to maintain blood or plasma medicine concentrations between MSC and MEC, $t_{\max}$, is (Tothfalusi and Endrenyi 2003):

$$\tau_{\max} = \frac{\ln\left(\frac{C_{\max} \text{ or } MSC}{C_{\min} \text{ or } MEC}\right)}{k_e}. \tag{9}$$

In some cases, administration of a loading dose is necessary, particularly, if the drug has a long elimination half-life and achieving therapeutic concentrations needs to be done quickly. In such circumstances, a loading dose D_L can be calculated using either of the following two equations:

$$D_L^{D_M} = D_M \times AR$$

or

$$D_L^{C_{\max}} = C_{\max} \times V_d.$$

3. Mehvar's Example

3.1. Background

The charactersitics of the hypothetical drug are as follows: therapeutic range = 10–20 mg/L; V_d = 35 L; Cl = 3.2 L/h; and bioavailability (F) = 1.0 (100%). Assuming a linear one-compartment model with first-order elimination, the three major drug disposition parameters are the: Cl, k_e, and V_d:

$$Cl = k_e \times V_d.$$

If any two of these parameters are known, the third can be easily calculated algebraically.

In this equation, Cl and V_d are physiologically independent parameters, while the $t_{1/2}$ and k_e (Table 1) are hybrid parameters dependent on both Cl and V_d (Tozer and Rowland 2006). V_d, a measure of the extent of drug distribution, is independent of Cl, but depends on tissue perfusion and membrane permeability, and the content of binding proteins in blood and tissues. In contrast, the $t_{1/2}$ and k_e depend on both Cl and V_d (Mehvar 2006). Thus, an increase in Cl (elimination efficiency) leads to a reduction in $t_{1/2}$ (or an increase in k_e). Intuitively, this means that more efficient elimination mechanisms would result in a faster decline of plasma drug concentrations. However, an increase in V_d results in prolongation of the $t_{1/2}$ (or decrease in k_e). This is because drug distributes more extensively into the tissues, where it is initially protected from elimination. But, because drug distribution is reversible, as the drug is eliminated from plasma and its concentrations decline, the drug in the tissue returns to plasma, resulting in a more sustained plasma drug concentration (increased $t_{1/2}$ and decreased k_e). These relationships can be expressed algebraically as follows:

$$t_{1/2} = \frac{0.693 \times V_d}{Cl}$$

and

$$k_e = \frac{Cl}{V_d}.$$

Thus, $t_{1/2}$ is dependent on both Cl and V_d. So, if the V_d changes, the $t_{1/2}$ (or k_e) changes proportionately while Cl remains constant.

3.2. Solution: Intravenous Bolus Dosing

Step 1: Load the R package **cpk**, initialize variables, and calculate the TTC:

```
library(cpk)

#####################################
# Patient weight (kg)
#####################################
wtkg = 1;  # because parameters are not given as weight-based.
```

```
#####################################
# Hypothetical Drug (Mehvar 1998)
#####################################
vd    = 35;             # L
cl    = 3.2;            # L/h
ke    = cl/vd;          # h^-1
thalf = (0.693 *vd)/cl  # h
f     = 1;              # bioavailability 100%

# therapeutic range
msc = 20;
mec = 10; # mg/L

# target therapeutic concentration (avg; C^inf_ave)
ttc <- ttc.fn(msc,mec) # mg/L

[1] "The value of ttc (ug/L) is 14.43" # mg/L
```

The # comments indicate that both the `ttc` input and output values are in mg/L.

Step 2: Calculate the dose rate to acheive the desired TTC using the `dr.fn()` function and assign result to variable `dr` :

```
dr  <- dr.fn (ttc, cl, wtkg, f)

[1] "The value of dr (mg/h) is 0.046"
```

When blood or plasma measurements are made in mg/L, the value returned by `dr.fn()` needs to be multiplied by 1000 to convert to mg/h; despite, the output indicating that the value is in mg/h.

```
dr  <- dr.fn (ttc, cl, wtkg, f) * 1000
dr

[1] 46
```

Step 3: Calculate the dosing interval and dose:

```
di.fn(msc, mec, ke)

[1] "The value of di (h) is 7.6"
```

The `di` (or $\tau_{\max}$) value of 7.6 h means that this is the longest inter-dose interval that can be chosen for this patient. However, because drug administration every 7.6 h is not practical, a τ should be selected from one of the following practical values: 4, 6, 8, 12, or 24 hr. Therefore, since the selected τ cannot be longer than $\tau_{\max}$, in this case, a τ of 6 h is the best choice (Mehvar 1998):

```
di = 6; # h
```

```
dpo <- dpo.fn (dr, di) # mg
dpo
```

```
[1] "The value of dpo (ug) is 276"
```

The `#` comment indicates that the output value units is mg/L; despite it indicating μg.

The `dm.fn()`, or maintenance dose function, requires and adjustment to convert its return value to mg:

```
dm <- dm.fn(dr, di)
dm
```

```
[1] "The value of dm (mg every di h) is 276000"
```

Thus, when measurements are made in mg/L, computing the maintenance dose using `dm.fn()` is as follows:

```
dm <- dm.fn(dr,di)/1000 # mg
dm
```

```
[1] 276
```

Steady-State Fluctuations

Steady-state fluctuations about the steady-state, C_{ss}, peak ($C_{\text{max}}^{\text{ss}}$) and trough ($C_{\text{min}}^{\text{ss}}$) levels are calculaed as follows:

```
# compute accumulation ratio
ar  <- ar.fn (ke, di)
```

```
[1] "The value of ar is 2.4"
```

```
# calculate peak
cmax <- cmax.fn (f, dpo, vd, ar, wtkg) # mg/L
```

```
[1] "The value of cmax (ug/L) is 19.2"
```

The `#` comment indicates that the output value units is mg/L; despite it indicating μg/L.

```
# calculate trough
cmin <- cmin.fn (cmax, ke, di) # mg/L
```

```
[1] "The value of cmin (ug/L) is 11.09"
```

The `#` comment indicates that the output value units is mg/L; despite it indicating μg/L.

Loading Dose

When administration of a loading dose is necessary, particularly, when the drug has a long elimination half-life and achieving therapeutic concentrations needs to be done quickly, a loading dose D_L can be calculated using either of the following methods:

```
dlar <- dlar.fn(dm, ar)
```

```
[1] "The value of dlar (mg) is 672"
```

```
dlcmax <- dlcmax.fn(cmax, vd)
```

```
[1] "The value of dlcmax (mg) is 672"
```

3.3. Solution: Extravascular Dosing

Dose calculation after extravascular dosing (e.g., oral administration) is more complicated than intravenous bolus dosing because the rate and extent (F) of a drug's availability—the portion of the administered drug that reaches the circulation—is an important factor, in addition to other kinetic parameters.

One important case for extravascular dosing is when drug absorption is so fast that it can be assumed as instantaneous for practical purposes. This case is similar to intravenous bolus dosing with $F = 1$. In practice, the abosrption of most immediate release formulations is assumed to be instantaneous. Therefore, the equations used for IV bolus dosing can also be used for design of extravascular dosage regimens with reasonable accuracy (Mehvar 1998).

3.4. Solution: Constant Intravenous Infusion

Another important case is that after adminstration of controlled release products (e.g., zero-order absorption). This results in almost constant concentrations at steady state with minimal fluctuation, a situation similar to constant intravenous infusion. In these cases, the constant infusion equations can be used for the prediction of dosage regimens.

Constant intravenous infusion is the simplest case because only the infusion rate, and not τ, needs to be calculated.

Step 1: Estimate R_0 based on the desired steady state concentration (C_{ss}) and the drug Cl:

$$R_0 = C_{ss} \times Cl$$

C_{ss} is a concentration within the MEC and MSF (therapeutic range). Using the example drug and assuming a desired C_{ss} of 14.4 mg/L, R_0 is calculated as:

```
css = ttc;
R0 <- R0.fn(css, cl) # mg/h
```

```
[1] "The value of R0 (ug/hr) is 46.18"
```

The `#` comment indicates that the output value units is mg/L; despite it indicating μg/L.

Step 1: Estimate a loading dose based on the C_{ss} and the drug V_d of the drug:

```
cmax = css;
dlcmax.fn(cmax, vd)
```

```
[1] "The value of dlcmax (mg) is 505.05"
```

Administration of $D_L^{C_{\max}}$ should produce a cocentration of 14 mg/L which is maintained by silmultaneously starting an infusion of the drug at a rate of 46 mg/L.

4. Conclusion

Over 1 million patients are injured in hospitals each year in the United States, and approximately 180,000 die annually as a result of these injuries (Bates, Cullen, Laird, Petersen, Small, Servi, Laffel, Sweitzer, Shea, Hallisey, Vliet, Nemeskal, and Leape 1995). A leading cause of medical injury is the dose-related use of medicines (Edwards and Aronson 2000), which can give rise to either undertreatment or overtreatment of disease.

The R package **cpk** may be used to design dosing regimens for individual patients and predict achievable theoretical values of therapeutic plasma concentrations of drugs; based, on the particular dose regimen design. The requirement for formulating dose regimen designs is *a priori* knowledge of a drug's basic disposition parameters and its therapeutic range. This drug information is typically provided by pharmaceutical companies in the drug's package insert and/or the *Physicians Desk Reference* (PDR). It is also available in the research literature.

The R package **cpk** may also be used to modify dosage regimens when the pharmacokinetics of a drug are altered by a drug interaction and/or disease. In some cases, it may be necessary to verify the theoretical plasma drug response in the patient (achievement of desired plasma drug concetrations), by obtaining plasma samples (therapeutic drug monitoring) at appropriate times (e.g., peaks and troughs at steady state) and if necessary, adjusting the dosage regimen (Regenthal, Krueger, Koeppel, and Preiss 1999; Kang and Lee 2009). For example, the pharmacokinetics estimated from the collected plasma samples may be different from those obtained from population data, which were used for the initial design of the dosage regimen. This can result in a plasma concentration-time profile different than the predicted one. In this case, the current pharmacokinetic parameter estimates should be used and a new dosage regimen re-calculated.

The R package **cpk** is a new tool, which may help prevent dose-related medical injury, assist clinicians with dosing decision-making at the point-of-care, and be of assistance as a first step towards personalized medicine.

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