cpk: R Package for Point-of-Care Application of Clinical Pharmacokinetics

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Abstract

This paper describes the R package **cpk**, which supplies functions for point-of-care application of clinical pharmacokinetics. 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. A leading cause of medical injury is the dose-related use of medicines, which can give rise to either undertreatment or overtreatment of disease. Clnical pharmacokinetics aims to provide safe and effective dose regimen design and modification. Our R package **cpk** provides 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.

Keywords: clinical pharmacokinetics, pharmacokinetics, dosing, drugs, medicine, adverse drug event, medical injury.

1. Introduction

R is a free software programming language and environment for data analysis, statistical computing and graphics Ihaka and Gentleman (1996); R Core Team (2013). It is rapidly becoming the software of choice for users in biology, medicine, and bioinformatics Gentleman (2009); Lewis (2010). R is also used in drug development in the pharmaceutical industry Millard and Krause (2001). However, R has not been applied for point-of-care dose regimen design and modification, or personalized medicine Thomson (2003); Hamburg and Collins (2010).

Over 1 million patients are injured in hospitals each year in the Unted 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.

Clnical pharmacokinetics aims to provide safe and effective dose regimen design and modification at the point-of-care Greenblatt and Koch-Weser (1975a,b); Gibaldi and Levy (1976a,b); Linares and Linares (2011). Despite, for most prescribers, point-of-care application of clinical pharmacokinetics is difficult Rolfe and Harper (1995); Rowe, Koren, and Koren (1998); moreover, the calculations can be time consuming and error prone, especially for nonspecialists Baldwin (1995); McDonald (1976). In the past, pencil-and-paper techniques Perlin, Taylor, and Peck (1985, 1986), programmable hand-held calculators Niazi (1977), and com-

puters Walton, Dovey, Harvey, and Freemantle (1999) have been used to perform point-of-care clinical pharmacokinetic calculations. However, these once-utilized 20th-century technologies, including software, are no longer available, obsolete, or hard to get.

Today, powerful hand-held or pocket computers are available with powerful processors, large solid-state drives, and gigabytes of memory. In addition, R Ihaka and Gentleman (1996); R Core Team (2013) is now mature, wise, and easy to get. Furthermore, because R is written in C, it operates efficiently on coat-pocket microcomputers. Though 21st-century software technology advances are now readily available Boston, Stefanovski, Moate, Linares, and Greif (2003), software for point-of-care computational clinical pharmacokinetics utilizing them is not.

This paper describes application of the R package **cpk** for point-of-care dose regimen design and modification. Four case studies are presented to highlight the package and describe its use. A major aim of our work has been to make this software technology widely available through The Comprehensive R Archive Network (CRAN: http://cran.r-project.org/web/packages/). The software is readily obtained by calling `install.packages("cpk")` from within R.

2. Basic Concepts

Pharmacokinetics refers to the study of the time-course of drugs and their metabolites in the body; it is based upon the concept of drug disposition: the fate of a drug in the body with regard to its absorption, distribution, metabolism, and elimination (ADME). These processes are described by a number of parameters; for point-of-care clinical pharmacokinetics, they are tabulated in the Glossary of Symbols (Table 1).

Pharmacokinetics is linked to drug effect by the drug-receptor complex theory Burgen (1966). This theory holds that the intensity of drug effect is related, in part, to the concentration of drug gaining access to drug receptors. The time-course of drug concentration at the receptor, therefore, strongly influences the time-course of drug action. Unfortunately, most clinically-important drug receptors reside at clinically-inaccessible tissue sites. However, drug concentrations in clinically-accessible fluids such as blood or plasma correlate with drug concentrations at the receptor so that they can effectively substitute for receptor-level drug concentration measurements. Thus, for most patients, the concept of a *Minimum Effective Concentration* (MEC) and a *Maximum Safe Concentration* (MSC) defines a *therapeutic range* Peck, Conner, and Murphy (1991).

Two aspects of *therapeutic range* are important to emphasize Tozer and Rowland (2006). First, such ranges are established from studies in groups of patients; therefore, the MEC and MSC are average values only. Occasionally, a patient may show a beneficial response at a drug level below the average MEC or may not benefit until levels exceed the average MEC. Likewise, a patient may exhibit drug toxicity at drug levels below the average MSC or, in contrast, may not exhibit toxicity at levels above the average MSC. Hence, the therapeutic range should be viewed only as an initial guide to therapy. Drug levels are best interpreted in probability terms in relation to the MEC and MSC; that is, levels below the MEC are less likely to result in the expected benefit than those above, whereas high levels confer increasing probability of toxicity, as the MSC is approached or exceeded. Second, drug efficacy and drug toxicity can only be determined from direct clinical assessment of a patient's drug response. Thus, drug levels cannot be used as sole criterion for drug effectiveness or toxicity; they are

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
$C_{\max}$	μg/L	Maximum concentration (peak)
$C_{\min}$	μg/L	Minimum concentration (trough)
$C(t)$	μg/L	Concentration-time
$\tau_{\max}$	h	Maximum dosing time interval

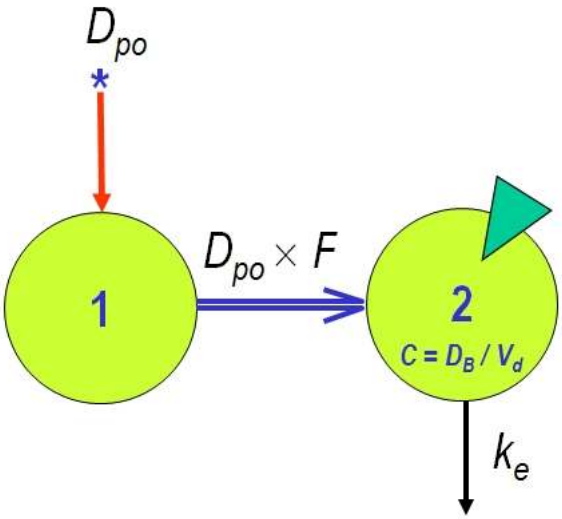

Figure 1: Dosing model.

best used in conjunction with clinical observations to investigate the contribution of drug effect to the patient's clinical state.

2.1. Dosing Model

Figure 1 shows a simplified diagram of a drug's path through a patient's body Linares and Linares (2011); Linares, Daly, Stefanovski, and Boston (2013). The patient takes a pill (D_{po}), which enters the gastrointestinal tract (compartment 1) and is absorbed ($D_{po} \times F$) into the body (compartment 2). F represents the drug's bioavailability, i.e., the portion of the oral dose that enters the bloodstream. The triangle cuts into the compartment, which is accessible for sampling (compartment 2). The pill ends up partly metabolized by the liver and partly eliminated into the urine. k_e represents the total rate at which liver and kidneys eliminate the drug from the body. The model assumes that the amount eliminated from the gastrointestinal tract into the feces is negligible. It also assumes the patient takes multiple doses and blood or plasma levels have reached steady state.

The amount of drug at time t (constant) in the accessible compartment (compartment 2, Figure 1) is given by the following linear constant coefficient differential equation:

$$\frac{dD_B}{dt} = -k_e D_B(t) + D_{po} \times F \tag{1}$$

where D_B represents the amount of drug in the body: $D_{po} \times F = D_B$; also $D_B = C \times V_d$.

Integration of Equation 2.1 gives Linares, Zech, Jacquez, Rosen, Sanfield, Morrow, Supiano, and Halter (1988),

$$D_B(t) = e^{k_e t} D_B(0) + \int_0^t e^{k_e (t-\tau)} \left(D_{po} \times F\right)(\tau)\, d\tau \tag{2}$$

where $D_B(0)$ is the initial amount of drug present in compartment 2 (accessible compartment).

2.2. Drug Disposition Parameters

Apparent Volume of Distribution: V_d is a proportionality constant, or scale factor, relating the amount of drug in the body to its measured concentration in blood or plasma. The estimate represents the volume throughout the body, which the amount of drug would have to be distributed in, to produce the measured blood or plasma concentration. In other words, it is the volume required to account for all the drug in the body if it were present throughout the body at the same concentration as in the measured sample.

Clearance rate: Cl is the volume of blood or plasma completely cleared of drug per unit time (e.g., L/h). A drug's Cl measures how well the body can eliminate or metabolize the drug. Drug Cl is used to calculate a maintenance dose of drug or to forecast steady-state drug concentrations in blood or plasma. The Cl is a composite measure that represents drug elimination from the body by all routes.

First-order elimination rate constant: k_e represents the total fractional rate of loss of drug from the body or the fraction of the V_d that is cleared of drug during an interval of time.

Elimination half-life: $t_{1/2}$ is defined as the time required for any given blood or plasma drug concentration to decrease by one-half of its original value. The $t_{1/2}$ is a good indicator for predicting when steady-state is achieved during a multiple fixed-dose regimen. Clinically, a drug can be considered to have achieved steady-state after 5 half-lives.

2.3. Simplified Clinical Pharmacokinetic Equations

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

Step 1 Determine a target therapeutic concentration (TTC) of drug for the patient based on the drug's therapeutic range, or its average:

$$TTC = \frac{MSC - MEC}{\ln\left(\frac{MSC}{MEC}\right)}\,(\mu\text{g/L}). \tag{3}$$

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

$$D_{Rate} = \frac{TTC \times Cl}{F} \times 0.001\,(\text{mg/h}). \tag{4}$$

Step 3 Select a dosing interval, τ, and calculate the drug's maintenance dose:

$$D_M = D_{Rate} \times \tau\,(\text{mg every}\,\tau\,\text{h}). \tag{5}$$

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):

$$AR = \frac{1}{(1 - e^{-k_e \cdot \tau})} \approx \frac{\tau}{t_{1/2}}, \tag{6}$$

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:

$$C_{ss} = \frac{D_{Rate} \times F}{Cl} \times AR. \tag{7}$$

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

$$C_{\max} = \frac{F \times D_{po}}{V_d} \times AR \tag{8}$$

and

$$C_{\min} = C_{\max} \times e^{-k_e \cdot \tau}. \tag{9}$$

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

$$C(t) = C_0 \times e^{-k_e \cdot t} \tag{10}$$

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):

$$\tau_{\max} = \frac{\ln\left(\frac{C_{\max} \text{ or } MSC}{C_{\min} \text{ or } MEC}\right)}{k_e}. \tag{11}$$

3. Case Studies

3.1. Case Study 1

Using pencil and paper technique, a clinician treats an 86 kg man with medicine X for stomach pain (The NHANES 1999-2002 mean weight for men in the United States is 86.1±0.4 [standard error of mean] kg). How does clinical pharmacokinetics allow the clinician to determine a more appropriate personalized dose?

Step 1: The clinician determines a target therapeutic concentration (TTC) for medicine X based on its therapeutic range of 50 to 20 μg/L:

$$TTC = \frac{50 - 20}{\ln\left(\frac{50}{20}\right)} = 33\,(\mu\text{g/L}).$$

Step 2: The clinician looks up the medicine's Cl and F (bioavailability) in the physician's desk reference (PDR), and finds that they equal 0.51 L/kg/h and 0.74, respectively:

$$D_{Rate} = \frac{33\mu\text{g/L} \times 0.51\,\text{L/h/kg} \times 86\,\text{kg}}{0.74} \times 0.001\,\text{mg/h} = 2.0\,\text{mg/h}.$$

Step 3: The clinician seeks to determine a suitable dosing interval to keep the plasma medicine X concentration between 50 (MSC) and 20 (MEC). Since,

$$\frac{MSC}{MEC} = \frac{1}{e^{-k_e \cdot \tau_{\max}}},$$

$$e^{-k_e \cdot \tau_{\max}} = \frac{MEC}{MSC} = \frac{20}{50} = 0.40.$$

Taking the natural logarithm of both sides gives

$$-k_e \cdot \tau_{\max} = -0.9163.$$

The V_d of medicine X from the PDR is 2.8 L/kg. So,

$$k_e = Cl/V_d = (0.51\,\text{L/kg/h} \times 86\,\text{kg}) \div 2.8\,\text{L/kg} = -0.1824.$$

Hence,

$$-0.1824 \cdot \tau_{\max} = -0.9163.$$

Finally, solving for $t_{\max}$ gives

$$\tau_{\max} = \frac{-0.9163}{-0.1824} = 5.0\,\text{h}.$$

The $t_{\max}$ of 5 h means that the longest dosing interval that can be selected for this patient is 5 h. But, because administration of medicine X every 5 h is not practical, a dosing interval (τ) should be selected from one of the following practical values: 4, 6, 8, 12, or 24 h Mehvar (1998). In this case, a τ of 4 h is the best choice. Now, the maintenance dose for medicine X is calculated to be

$$D_M = 2.0\,\text{mg/h} \times 4\,\text{h} = 8\,\text{mg every}\,4\,\text{h}.$$

Back calculation Gullberg and Jones (1994) can be performed to check that the administered dose predicts a plasma concentration for medicine X that falls within the desired target therapeutic concentration (TTC), or within its therapeutic range:

$$TTC_{\text{predicted}} = \frac{D_{Rate} \times F}{Cl} = \frac{2000\,\mu\text{g/h} \times 0.74}{0.51\,\text{L/h/kg} \times 86\,\text{kg}} = 33.7\mu\text{g}.$$

3.2. Case Study 2

A 46-year-old African-American man who is 6'4" (193 cm) tall, weighs 398 lb (181 kg) is 1 day postoperative from strangulated right inguinal hernia repair Linares (2010). He complains of severe 8/10 pain. Examination reveals a clean surgical scar with no signs of infection. The patient recieves morphine 5 mg intravenously every 6 h postoperatively. This dose is based on a standard morphine dosing protocol.

Morphine's disposition parameters are Baselt and Cravey (2006); Linares and Linares (2011): $t_{1/2} = 4\,\text{h}$; $k_e = 0.3180\text{h}^{-1}$; $V_d = 4.5\,\text{L/kg}$; $Cl = 1.43\,\text{L/kg/h}$. Morphine's oral F ranges from 15 to 64% and averages 38%. But, for intravenous administration, F is 100% ($F = 1$). Morphine's therapeutic range is 80 to 10 μg/L, MSC and MEC, respectively, in surgical patients, and its evidence-based analgesic plasma levels in cancer patients are $> 20\,\mu$g/L Gourlay, Willis, and Lamberty (1986); Sawe, Dahlstrom, Paalzow, and Rane (1981).

A personalized morphine dose regimen is designed for the patient using R package **cpk**.

Step 1: The clinician loads the R package **cpk** and initializes appropriate variables. Then, the clinician sets a target therapeutic concentration (TTC) of 25 μg/L based on morphine's known analgesic plasma levels ($> 20\,\mu$g/L):

```
library(cpk)

#####################################
# Patient weight (kg)
#####################################
wtkg = 181;  # kg

#####################################
# Morphine Disposition Parameters
#####################################
thalf = 4;        # h
ke    = 0.3180;   # h^-1
vd    = 4.5;      # L/kg
cl    = 1.43;     # L/h/kg
f     = 1.00;     # dpo range: 15-64% (avg 38%), IV f = 1.

#### TTC
ttc = 25;  # ug/L
```

Step 2: The clinician calculates the morphine dose rate to acheive the desired TTC using the `dr.fn()` function and assigns the result to the `dr` variable:

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

[1] "The value of dr (mg/h) is 6.47"
```

Step 3: The clinician sets the dosing interval to $\tau = 4\,$h based on morphine's $t_{1/2}$ and calculates the dose:

```
#### Set dosing interval based on thalf
di = 4;    # h

#### Calculate dose (if f = 1, dose IV)
dpo <- dpo.fn (dr, di)
dpo/1000 # convert to mg

[1] "The value of dpo (ug) is 25880"
[1] 25.88
```

Analysis: Back calculation is performed to check that the calculated morphine dose predicts a plasma concentration for morphine that falls within the desired target therapeutic concentration (TTC):

```
#### Back calculation
bc.ttc <- bc.ttc.fn (dr, f, cl, wtkg)
```

```
[1] "The value of bc.ttc (ug/L) is 25"
```

Check R package **cpk** suggested personalized dosing regimen:

```
#### Check R cpk suggested dosing regimen
#### predict avg steady-state concentration
#### predict fluctuations about steady-state
# accumulation ratio
ar  <- ar.fn (ke, di)

# concentration steady-state
css <- css.fn (f, dpo, di, cl, wtkg)
css * ar  # ug/L

# Fluctuation about steady-state (ug/L)
cmax <- cmax.fn (f, dpo, vd, ar, wtkg)
cmin <- cmin.fn (cmax, ke, di)
```

```
[1] "The value of ar is 1.4"

[1] "The value of css (ug/L) is 25"
[1] 35

[1] "The value of cmax (ug/L) is 44.48"
[1] "The value of cmin (ug/L) is 12.47"
```

To determine why the patient's morphine dosing regimen was not effectively controlling his postoperative pain, we use the R package **cpk** to analyze the postoperative morphine dosing regimen based on standard dosing:

```
#### Check postoperative dosing regimen
#### predict avg steady-state concentration
dpo = 5000;  # ug
di  = 6;     # h

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

# concentration steady-state
css <- css.fn (f, dpo, di, cl, wtkg)
css * ar  # ug/L
```

```
[1] "The value of ar is 1.2"

[1] "The value of css (ug/L) is 3.22"
[1] 3.864
```

```
# Fluctuation about steady-state (ug/L)
cmax <- cmax.fn (f, dpo, vd, ar, wtkg)
cmin <- cmin.fn (cmax, ke, di)

[1] "The value of cmax (ug/L) is 7.37"
[1] "The value of cmin (ug/L) is 1.09"
```

Findings: Clinical pharmacokinetic analysis using R package **cpk** shows that undertreatment caused the patient's lack of postoperative pain control. As shown in Figure 2 (Panel A), morphine plasma levels were below its minimum effective concentration throughout dosing periods. However, as shown in Figure 2 (Panel B), and below, the R package **cpk** multiple-dose morphine regimen design improved upon the standard dosing protocol. The dose regimen design maintained therapeutic morphine levels for over 2 hrs.

```
#### Check R cpk dosing regimen design
# concentration-time curve (ug/L)
ct <- ct.fn(cmax,  time=2.0)
ct <- ct.fn(cmax,  time=2.5)
ct <- ct.fn(cmax,  time=2.75)
ct <- ct.fn(cmax,  time=3.0)

[1] "The value of ct (ug/L) at time h is 23.55"
[1] "The value of ct (ug/L) at time h is 20.09"
[1] "The value of ct (ug/L) at time h is 18.55"
[1] "The value of ct (ug/L) at time h is 17.13"
```

3.3. Case Study 3

A 55-year-old Caucasian man is diagnosed with cancer of the prostate with spread to the spine Linares and Linares (2011). He is hospitalized complaining of severe 10/10 pain. The clinician choses intravenous morphine for pain control.

Step 1: The clinician loads the R package **cpk** and initializes appropriate variables; then, uses online help (`??ttc`) to determine an average target therapeutic concentration (TTC) for pain control in this patient:

```
#####################################
# Patient weight (kg)
#####################################
wtkg = 100;  # kg

#####################################
# Morphine Disposition Parameters
#####################################
thalf = 4;        # h
ke    = 0.3180;   # h^-1
```

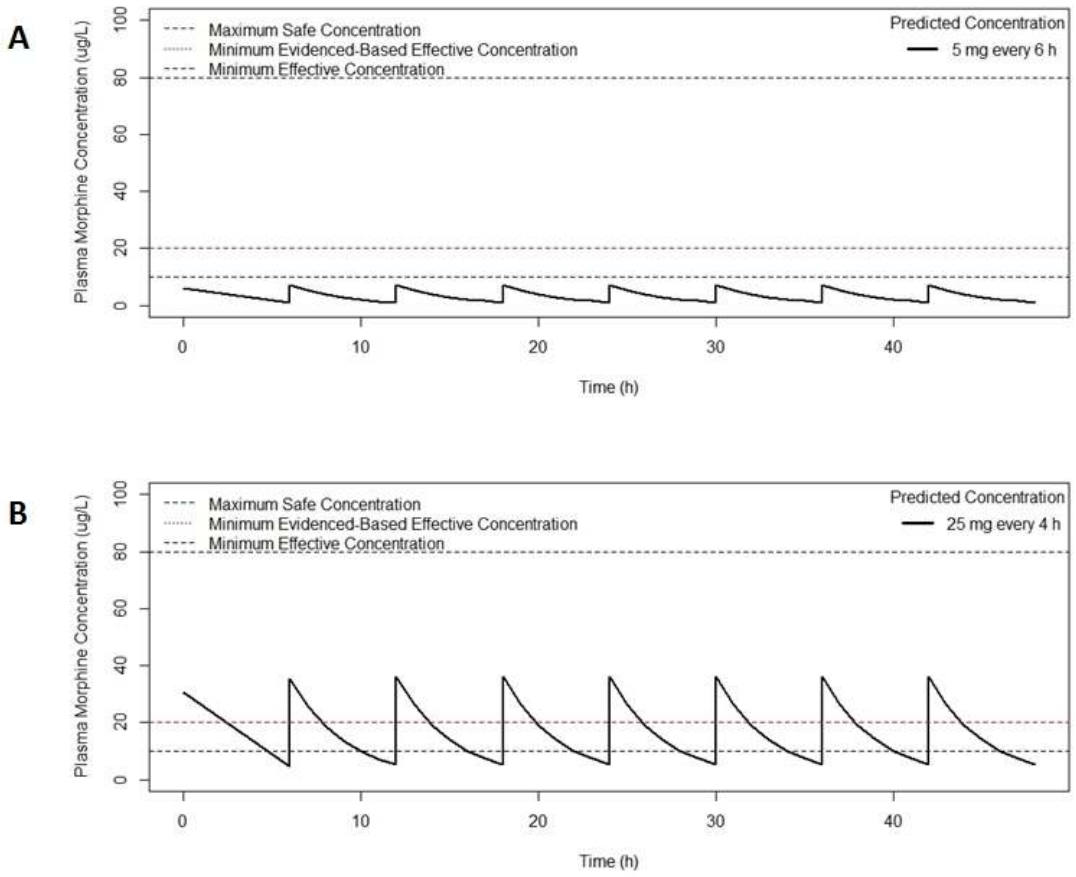

Figure 2: (A) Postoperative multiple-dose morphine regimen based on standard dosing. (B) R **cpk** package multiple-dose morphine regimen design.

```
vd    = 4.5;      # L/kg
cl    = 1.43;     # L/h/kg
f     = 1.00;     # dpo range: 15-64\% (avg 38\%), IV f = 1.

#####################################
# Morphine Therapeutic Range
#####################################
# NOTE Morphine MEC = 10; MSC = 80;
msc = 80;
mec = 10;


#### Calculate TTC
ttc <- ttc.fn(msc, mec)

[1] "The value of ttc (ug/L) is 33.66"
```

Step 2: The clinician determines the morphine dose rate to acheive the desired TTC using the `dr.fn()` function and assigns the result to the `dr` variable:

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

```
[1] "The value of dr (mg/h) is 4.86" (rounded to 5)
```

Step 3: The clinician calculates the dosing interval using the `di.fn()` function and assigns the result to the `di` variable; then, calculates the dose:

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

```
[1] "The value of di (h) is 6.5" (rounded to 6)
```

```
#### Calculate dose (if f = 1, dose IV)
dr = 5; di = 6;
dpo <- dpo.fn (dr, di)
dpo/1000 # convert to mg
```

```
[1] "The value of dpo (ug) is 30000"
[1] 30
```

Analysis: Back calculation is performed to check that the calculated morphine dose predicts a plasma concentration for morphine that falls within the desired target therapeutic concentration (TTC):

```
#### Back calculation
bc.ttc <- bc.ttc.fn (dr, f, cl, wtkg)
```

```
[1] "The value of bc.ttc (ug/L) is 35"
```

Check R package **cpk** suggested personalized dosing regimen steady-state and fluctuations in plasma morphine levels:

```
#### Check R cpk suggested dosing regimen
#### predict avg steady-state concentration
#### predict fluctuations about steady-state
# accumulation ratio
ar  <- ar.fn (ke, di)

# concentration steady-state
css <- css.fn (f, dpo, di, cl, wtkg)
css * ar  # ug/L

# Fluctuation about steady-state (ug/L)
cmax <- cmax.fn (f, dpo, vd, ar, wtkg)
cmin <- cmin.fn (cmax, ke, di)
```

```
[1] "The value of ar is 1.2"

[1] "The value of css (ug/L) is 34.97"
[1] 41.964

[1] "The value of cmax (ug/L) is 80"
[1] "The value of cmin (ug/L) is 11.87"

#### Check R cpk dosing regimen design
# concentration-time curve (ug/L)
ct <- ct.fn(cmax,  time=0)
ct <- ct.fn(cmax,  time=4.0)
ct <- ct.fn(cmax,  time=4.25)
ct <- ct.fn(cmax,  time=4.5)
ct <- ct.fn(cmax,  time=4.75)
ct <- ct.fn(cmax,  time=5.0)
ct <- ct.fn(cmax,  time=6.0)

[1] "The value of ct (ug/L) at time h is 80"
[1] "The value of ct (ug/L) at time h is 22.42"
[1] "The value of ct (ug/L) at time h is 20.71"
[1] "The value of ct (ug/L) at time h is 19.13"
[1] "The value of ct (ug/L) at time h is 17.66"
[1] "The value of ct (ug/L) at time h is 16.31"
[1] "The value of ct (ug/L) at time h is 11.87"
```

Findings: Clinical pharmacokinetic analysis using R package **cpk** shows that using the `ct.fn()` function, the dosing design predicts plasma morphine concetrations between the time of dose administration and the trough, which are within the therapeutic range (Figure 3).

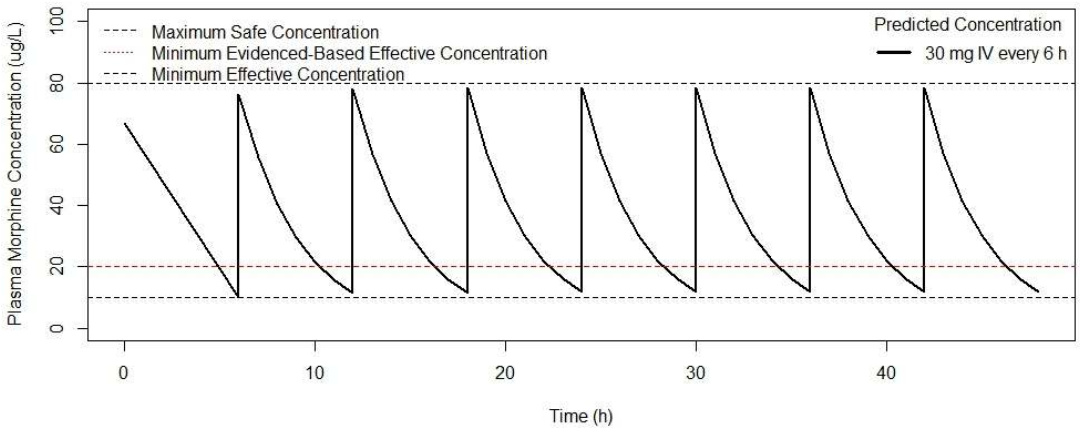

Figure 3: Cancer pain multiple-dose morphine regimen design.

3.4. Case Study 4

A 38-year-old athletic African-American woman who is 6'0" (183 cm) tall, weighs 191 lb (87 kg) is postoperative outpatient hysterectomy without oopherectomy. During 12 hours in recovery, she received a total of 150 mg of morphine intravenously. She is being discharged home on orally administered morphine pills. The average bioavailability, (`f`), of morphine is 38% and must be taken into account. The clinician choses R package **cpk** to design an outpatient postoperative pain control regimen for the patient:

Step 1: The clinician loads the R package **cpk** and initializes appropriate variables. Specifically, the `wtkg` variable is appropriately initialized and `f` is initialized to account for morphines `f` of 38%:

```
#####################################
# Patient weight (kg)
#####################################
wtkg = 87;  # kg

#####################################
# Morphine Disposition Parameters
#####################################
thalf = 4;        # h
ke    = 0.3180;   # h^-1
vd    = 4.5;      # L/kg
cl    = 1.43;     # L/h/kg
f     = 0.38;     # dpo range: 15-64\% (avg 38\%), IV f = 1.

#####################################
# Morphine Therapeutic Range
#####################################
# NOTE Morphine MEC = 10; MSC = 80;
msc = 80;
mec = 10;

#### Calculate TTC
ttc <- ttc.fn(msc, mec)

[1] "The value of ttc (ug/L) is 33.66"
```

Step 2: The clinician determines the morphine dose rate to acheive the desired TTC using the `dr.fn()` function and assigns the result to the `dr` variable:

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

[1] "The value of dr (mg/h) is 11.13" (rounded to 10)
```

Step 3: The clinician calculates the dosing interval using the `di.fn()` function and assigns the result to the `di` variable; then, calculates the dose:

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

[1] "The value of di (h) is 6.5" (rounded to 6)

#### Calculate dose
dr = 10; di = 6;
dpo <- dpo.fn (dr, di)
dpo/1000 # convert to mg

[1] "The value of dpo (ug) is 60000"
[1] 60
```

Analysis: Back calculation is performed to check that the calculated morphine dose predicts a plasma concentration for morphine that falls within the desired target therapeutic concentration (TTC):

```
#### Back calculation
bc.ttc <- bc.ttc.fn (dr, f, cl, wtkg)

[1] "The value of bc.ttc (ug/L) is 30.5"

#### Check R cpk suggested dosing regimen
#### predict avg steady-state concentration
#### predict fluctuations about steady-state
# accumulation ratio
ar  <- ar.fn (ke, di)

# concentration steady-state
css <- css.fn (f, dpo, di, cl, wtkg)
css * ar  # ug/L

# Fluctuation about steady-state (ug/L)
cmax <- cmax.fn (f, dpo, vd, ar, wtkg)
cmin <- cmin.fn (cmax, ke, di)

[1] "The value of ar is 1.2"

[1] "The value of css (ug/L) is 30.54"
[1] 36.648

[1] "The value of cmax (ug/L) is 69.89"
[1] "The value of cmin (ug/L) is 10.37"
```

Findings: Clinical pharmacokinetic analysis using R package **cpk** shows that the predicted postoperative pain control regimen maintains plasma morphine levels within its therapeutic range (Figure 4).

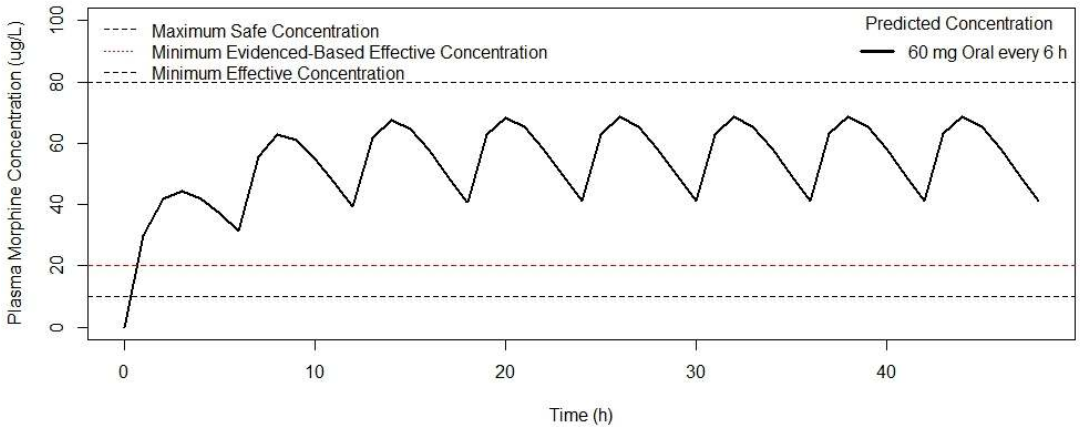

Figure 4: Predicted postoperative oral morphine dose regimen design.

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 *et al.* (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.

Drug dosing guidelines and "package inserts" provide ranges of doses thought to be safe and effective for most patients. Prescribers individualize therapy by intuitively increasing or decreasing doses based on these guidelines and package-insert instructions, as well as on their interpretation of a patient's clinical response to therapy. While the intuitive approach to drug dosing apparently works well for a number of drugs, therapy for certain drugs, e.g., cancer drugs and pain medicines, can be improved. Moreover, the intuitive approach to drug dosing has its risks and may trigger adverse drug events at the point-of-care Ghandi, Weingart, Borus, Seger, Peterson, Burdick, Seger, Shu, Federico, Leape, and Bates (2003). Because, a leading cause of medical injury is the either the over- or under-dosing of medicines Edwards and Aronson (2000), point-of-care application of clinical pharmacokinetics Greenblatt and Koch-Weser (1975a,b); Gibaldi and Levy (1976a,b) using R package **cpk** provides 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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