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Efficacy, nephrotoxicity and ototoxicity of aminoglycosides, mathematically modelled for modelling-supported therapeutic drug monitoring

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ABSTRACT

Therapeutic drug monitoring (TDM) of aminoglycosides has been a topic during the last thirty years. There is a tendency that – because of the once-daily regimen – TDM is considered not necessary anymore. Although once daily dosing has the potential for decreased toxicity, long-term usage can cause severe nephro- and ototoxicity. Furthermore, inadequate plasma concentrations can lead to treatment failure. This work is devoted to the development and application of the first mathematical model of aminoglycosides, which simulates in relation to the pharmacokinetics both their effects on bacteria as well as their nephrotoxicity and cochleotoxicity. Our software system is suitable for TDM.

Based on theoretical considerations, a multi-compartment mathematical model in a numerical program in Matlab is derived that incorporates the antimicrobial effects of aminoglycosides, the saturable and active uptake into kidney cells, the reversible nephrotoxicity and the irreversible cochleotoxicity.

Using fictitious person data, and an assumed pharmacokinetic and dynamic parameter set obtained from the literature, we simulated the drug concentrations, antibacterial effects, and toxicity over time in virtual patients to illustrate the benefits of optimized, efficacious dosage regimens that minimize (acceptable) nephro- and auditory ototoxicity. Our model confirms that extended-interval dosing seems the most appropriate to achieve this goal. By this manner, the present mathematical model contributes to an increase in our knowledge of how to obtain an optimized dosing strategy for individual patients.

With the developed program, we are able to demonstrate that optimal aminoglycoside dosing still needs a sophisticated system of TDM.

1. Introduction

Since most new antibiotics in advanced clinical development are predominantly anti-Gram-positive agents (Boucher et al., 2009), there is often still no alternative for aminoglycosides (AG) in life-threatening mainly Gram-negative infections. A number of factors contribute to their successful and continued use including their rapid bactericidal concentration-dependent killing, a low prevalence of bacterial resistance, a post-antibiotic effect and low cost.

Nonetheless, side-effects such as nephrotoxicity and auditory ototoxicity complicate therapy with these antibiotics. Despite ongoing efforts over the past thirty years, it is still controversial if therapeutic monitoring techniques reduce AG-induced nephrotoxicity and/or ototoxicity (Bartal et al., 2003; Black et al., 2004; Kim et al., 2004; Leehey et al., 1993; Watanabe et al., 2004; Winston and Benowitz, 2003). Evidence in both human and experimental models confirms, that high doses of AG given at extended intervals are less harmful than the same cumulative dose administered more frequently (Nicolau et al., 1995). It is believed that TDM contributes to ensure that adequate plasma peak and trough levels are obtained.

The most plausible theory, concerning toxicity, is that the drug enters the organ by active transport. Because of the saturable (Maglio et al., 2002) and concentration-dependent uptake into the kidney and cochlear cells, the extent of uptake remains "unaltered" at higher concentrations. When the drug is infused continuously, the blood concentration maintains at a constant level, causing the uptake in the cells to continue, with accumulation in the organ as a consequence.

From a meta-analysis of randomised controlled trials (Kasiakou et al., 2005) and a previously described model for the efficacy of AG, it remarkably appeared that continuous intravenous infusion tends to be the most effective according to patient's out-

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come and antimicrobial killing (Neef et al., 2002), respectively. However, in that model, the relationship with toxicity was not taken into account. In case of AG, the occurrence of renal and ototoxicity requires a pulse-wise or intermittent administration, such that the drug disappears from kidney and ear, before damage occurs. Nephrotoxicity is reversible, because proximal tubular cells are able to regenerate (Mingeot-Leclercq and Tulkens, 1999). On the other hand, destruction of auditory hair cells is irreversible, resulting in permanent hearing loss (Black et al., 2004; Rybak, 1986).

The objective of the present study was to develop a mathematical model, that can be used in therapeutic drug monitoring (TDM) to design appropriate drug regimes which combine maximal antimicrobial efficacy with minimal (acceptable) toxicity.

2. Materials and methods: model development

A mathematical program was developed in Matlab (version 6.5.0.1924 release 13, 2002, The MathWorks Inc., USA), with a user-friendly interface.

2.1. Pharmacokinetics of aminoglycosides

A pharmacokinetic–pharmacodynamic (PK–PD) model, including efficacy and toxicity, was designed, based on physiological models of kidney and inner ear (Fig. 1). The concentration of AG in blood, denoted by the central compartment $C_b(t)$, results from influx minus efflux in the central compartment. Influx depends on the administered dose, the efflux from ear fluids and renal tubular reabsorption (De Broe et al., 1989). Efflux is a combination of transfer to ear fluids and elimination. Total elimination can be separated into a renal and non-renal pathway. AG are freely filtered through the glomerulus, thus their renal clearance is linearly proportional to the creatinine clearance $CL_{CR}(t)$ (mL min^{-1}). The elimination rate constant k_e (h^{-1}) can be expressed as (Rougier et al., 2003b):

$$k_e = k_{nr} + k_s CL_{CR}(t) \quad (1)$$

where k_{nr} (h^{-1}) is the non-renal elimination rate constant, and k_s (mL min^{-1} h^{-1}) the renal clearance coefficient. Since variability in the elimination of AG due to nephrotoxicity is independent of the non-renal clearance, k_{nr} was fixed. Knowing the dominant half-life of AG, the half-life for non-renal clearance and the creatinine clearance CL_{CR0}, the AG clearance coefficient k_s is then equal to:

$$k_s = \frac{k_e - k_{nr}}{CL_{CR0}} \quad (2)$$

The rate of change of concentration in the central compartment $C_b(t)$ or in serum varies as follows, considering a simplified model of the ear:

$$\frac{dC_b(t)}{dt} = \frac{I(t)}{V_b} - (k_{nr} + k_s CL_{CR}(t) + k_{blood\text{-}ear})C_b(t) + \frac{k_{reabs}}{V_b}A_{pt}(t) + k_{blood\text{-}ear}C_{ear}(t) \quad (3)$$

where $I(t)$ (mg h^{-1}) is the infusion rate of AG, either by continuous infusion or intermittent infusion, V_b the volume of blood, $k_{blood\text{-}ear}$ (h^{-1}) the rate constant for transfer from blood to ear fluids, k_{reabs} (h^{-1}) the renal tubular reabsorption rate constant, $A_{pt}(t)$ (mg) the amount of AG in proximal tubular (PT) cells, $k_{ear\text{-}blood}$ (h^{-1}) the rate constant for transfer from ear fluids to blood, and $C_{ear}(t)$ (mg L^{-1}) the concentration of AG in ear fluids. The term $k_s CL_{CR}$ includes also the eliminated quantity of AG that is taken up by the PT cells from the tubuli (the reabsorption process).

2.2. Kidney concentration of aminoglycosides

Reabsorption of AG through PT cells starts with binding to the brush border membrane. Hereafter, AG are taken actively and saturably into the PT cells (De Broe et al., 1988, 1989; Giuliano et al., 1986b). By its presence within the PT cells, AG interfere with a number of intracellular processes. This could cause the simultaneous development of a number of otherwise unrelated metabolic

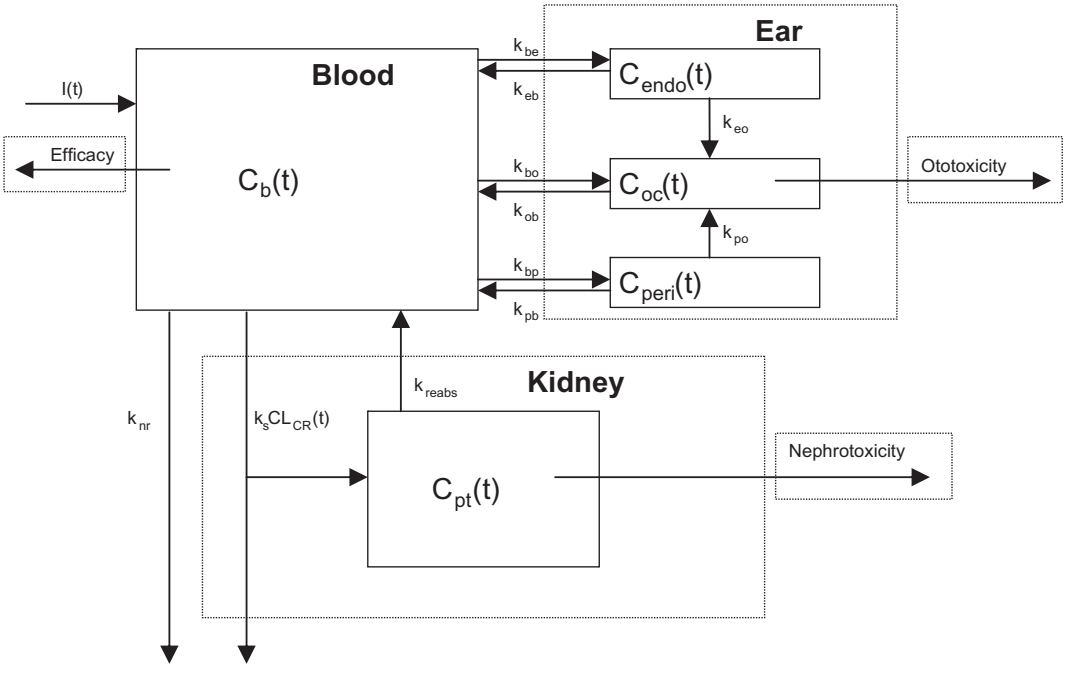

Fig. 1. Distribution scheme of aminoglycosides. Aminoglycosides are distributed from the blood compartment to the proximal tubular cells, endolymph and perilymph, and to the organ of Corti. The efficacy (defined by the decrease in number of viable bacteria) is related to the blood concentration. Nephrotoxicity is related to the concentration $C_{pt}(t)$ in the proximal tubular cells. Auditory ototoxicity is related to the concentration $C_{oc}(t)$ in the organ of Corti.

changes, many of which are capable of causing cell death (Mingeot-Leclercq and Tulkens, 1999). AG are eliminated from the PT cells to blood at a rate constant k_{reabs} which leads to the differential equation for the rate of change of concentration of AG in PT cells $C_{pt}(t)$:

$$\frac{dC_{pt}(t)}{dt} = -k_{reabs}C_{pt}(t) + V_{\max}(t)\frac{C_b(t)}{K_m + C_b(t)} - \lambda_k\left(1 - \frac{M(t)}{M_{\max}}\right)C_{pt}(t) \quad (4)$$

where $V_{\max}(t)$ (mg L^{-1} h^{-1}) is the maximum rate of uptake into kidney cells, which depends on the kidney functionality, λ_k the regeneration rate of kidney cells (h^{-1}) and K_m (mg L^{-1}) the Michealis–Menten constant. See below for terms $M(t)$ and $M_{\max}$. Extrusion of AG into the urine was assumed to be instantaneous at the moment that PT cells do not survive (De Broe et al., 1988). Note that C_b should actually be the concentration of AG in the tubuli or "primary urine compartment". For the simplicity of the model, these concentrations were considered equal.

Kidney cells are able to regenerate by tubuloglomerular feedback. Regenerating cells are less susceptible to AG, thus they induce a decrease in uptake of AG in PT cells (Mingeot-Leclercq and Tulkens, 1999). This means that $V_{\max}(t)$ in Eq. (4) is related to the toxic effect $\varepsilon(t)$:

$$V_{\max}(t) = V_0 e^{-\alpha\varepsilon(t)} \quad (5)$$

where α denotes the maximum accumulation rate decrease constant and V_0 (mg L^{-1} h^{-1}) the maximum accumulation rate at the beginning of treatment.

2.3. Nephrotoxicity

Defining the maximum number of functioning kidney cells as $M_{\max}$ and the actual number of kidney cells present as M, the fraction of death PT cells can be described as the pharmacodynamic effect $\varepsilon(t) = M_{\max} - M(t)/M_{\max}$ of AG, and is in direct relation to the concentration in PT cells (Mingeot-Leclercq and Tulkens, 1999). This relation can be represented by a Hill equation which links AG concentration in PT cells $C_{pt}(t)$ to the toxic effect (Van Boxtel et al., 1992):

$$\varepsilon(t) = \frac{\varepsilon_{\max}C_{pt}(t)^{\gamma}}{C_{50}^{\gamma} + C_{pt}(t)^{\gamma}} \quad (6)$$

where $\varepsilon_{\max}$ (dimensionless) is the maximum killing rate of kidney cells, C_{50} (mg L^{-1}) the concentration of AG in PT cells for which $\varepsilon(t)$ is equal to $\varepsilon_{\max}/2$, and γ (dimensionless) the Hill sigmoidicity coefficient.

A threshold can be incorporated in two ways (Van Boxtel et al., 1992) as demonstrated by Eq. (6) with a large value for γ and by setting the effect equal to:

$$\varepsilon(t) = \begin{cases} 0 & \text{if } C_{pt}(t) < C_{\min} \\ \dfrac{\varepsilon_{\max}(C_{pt}(t) - C_{\min})^{\gamma}}{(C_{50} - C_{\min})^{\gamma} + (C_{pt}(t) - C_{\min})^{\gamma}} & \text{if } C_{pt}(t) > C_{\min} \end{cases} \quad (7)$$

where $C_{\min}$ (mg L^{-1}) represents the threshold value.

Furthermore, the threshold can be incorporated differently (Rougier et al., 2003a):

$$\varepsilon(t) = \begin{cases} 0 & \text{if } C_{pt}(t) < C_{\min} \\ \dfrac{\varepsilon_{\max}C_{pt}(t)^{\gamma}}{C_{50}^{\gamma} + C_{pt}(t)^{\gamma}} & \text{if } C_{pt}(t) > C_{\min} \end{cases} \quad (8)$$

Now the effect is set to be zero below a certain value for the concentration of drug in the kidney cells. Above this value it is assumed that a full effect is present, instead of setting the effect proportional to the difference between the PT cellular concentration and the threshold concentration as in Eq. (7). This assumption results in a discontinuous function for toxic effects and thus for the creatinine clearance described in Eq. (9). Eq. (6) was chosen, with a large value for γ to avoid discontinuity as in Eq. (8).

2.4. Creatinine clearance

Creatinine clearance calculated by the MDRD or Cockcroft–Gault equations is often used to estimate the glomerular filtration rate (GFR). Clearance is influenced by the toxic effect by glomerulotubular feedback action, which can be represented by a Hill equation:

$$CL_{CR}(t) = CL_{CR0} - \frac{CL_{CR\max}\varepsilon(t)^{\delta}}{\varepsilon_{50}^{\delta} + \varepsilon(t)^{\delta}} + Var(t) \quad (9)$$

where CL_{CR0} (mL min^{-1}) is the creatinine clearance at initiation of treatment, $CL_{CR\max}$ (mL/min) the maximum decrease in creatinine clearance, ε_{50} (dimensionless) the fraction of dead kidney cells for which $CL_{CR}(t)$ is equal to $CL_{CR\max}/2$, δ (dimensionless) the Hill sigmoidicity coefficient, and $Var(t)$ the circadian variation (Rougier et al., 2003a). The most widespread value for this variance is 10% (Koopman et al., 1989). It was decided to neglect circadian variation. Note that two consecutive Hill equations for the relationship between clearance, C_{pt} and ε were incorporated as it has consequences for the simplicity of estimation of these parameters.

The rate of change of creatinine concentration in serum $C_{sCR}(t)$ (mg L^{-1}) varies (Rougier et al., 2003a) depending on the daily muscular production rate k_2 (mg L^{-1} h^{-1}) and renal elimination:

$$\frac{dC_{sCR}(t)}{dt} = -CL_{CR}(t)C_{sCR}(t) + k_2 \quad (10)$$

2.5. Efficacy

Efficacy was expressed as the number of viable bacteria over time and depended on the concentration in the central compartment. The bactericidal killing rate can be characterized as a function of antibiotic concentration in blood (Czock and Keller, 2007; Neef et al., 2002; Vinks et al., 1997; Zhi et al., 1986). The objective of an antibiotic regimen is to create a germ-killing effect, i.e. a 12-log$_{10}$ reduction in number of micro-organisms (Neef et al., 2002):

$$\frac{dN(t)}{dt} = \left(\lambda_b - \frac{E_{\max}C_b(t)^{\gamma_k}}{EC_{50}^{\gamma_k} + C_b(t)^{\gamma_k}}\right)N(t) \quad (11)$$

where λ_b (h^{-1}) is the bacterial growth rate constant in the absence of any antibiotic, EC_{50} (mg L^{-1}) the concentration of AG at which 50% of the maximum effect is obtained, γ_k (dimensionless) the steepness coefficient and $E_{\max}$ (h^{-1}) the maximum possible rate constant for bacterial killing.

Eq. (11) has the following solution for the number of micro-organisms:

$$N(t) = N_0 e^{\int_{t_0}^{t}(\lambda_b - F(C_b(\tau)))d\tau} \quad (12)$$

where N_0 is the initial number of micro-organisms (colony forming units (CFU) mL^{-1}) at time t_0, and τ the dosing interval. In an attempt to keep complexity of the model within limits, uncontrolled growth and development of heteroresistant subpopulations were not incorporated.

2.6. Cochlear ototoxicity

Although cochleotoxicity is mainly found in patients on prolonged exposure, its irreversibility is a major concern. The model proposed in this section must be "validated" with patient data.

AG are transported actively and saturably into inner ear fluids of the cochlea; endolymph and perilymph and the organ of Corti (Boogaard et al., 1989; De Broe et al., 1988, 1989). The rate of change of (free) concentration of AG in the perilymph, $C_{peri}(t)$, and endolymph, $C_{endo}(t)$ are related as follows:

$$\frac{dC_{endo}(t)}{dt} = \frac{k_{be}C_b(t)}{KM_{endo} + C_b(t)} - (k_{eb} + k_{eo})C_{endo}(t) \tag{13}$$

$$\frac{dC_{peri}(t)}{dt} = \frac{k_{bp}C_b(t)}{KM_{peri} + C_b(t)} - (k_{pb} + k_{po})C_{peri}(t) \tag{14}$$

where $C_b(t)$ is the blood concentration, k_{be} and k_{bp} (h^{-1}) are the maximum uptake rate constants from blood to endolymph and perilymph, KM_{endo} and KM_{peri} the concentrations at which half the maximum uptake rate is achieved, k_{eb} and k_{pb} (h^{-1}) the elimination rate constants from the endolymph and perilymph to blood and k_{eo} and k_{po} (h^{-1}) the elimination rate constants to the organ of Corti.

The rate of change of concentration of AG inside the organ of Corti $C_{oc}(t)$ is related:

$$\frac{dC_{oc}(t)}{dt} = \frac{k_{bo}C_b(t)}{KM_{oc} + C_b(t)} + k_{eo}C_{endo}(t) + k_{po}C_{peri}(t) - k_{ob}C_{oc}(t) \tag{15}$$

where k_{bo} is the maximum uptake rate from blood, KM_{oc} the concentration in the organ of Corti at which half the maximum uptake rate is reached, and k_{ob} the elimination rate to blood.

The organ of Corti is covered with approximately 15,000 outer and 3500 inner hair cells. AG inside the organ of Corti result in irreversible destruction of hair cells, causing deafness (De Broe et al., 1989). The rate of change of number of hair cells $N_{hc}(t)$ is equal to:

$$\frac{dN_{hc}(t)}{dt} = \frac{E_{hcmax}C_{oc}(t)^n}{E_{hc50}^n + C_{oc}(t)^n}N_{hc}(t) \tag{16}$$

where E_{hcmax} is the maximum killing rate for hair cells, E_{hc50} the concentration at which half the maximal killing rate is achieved (mg L^{-1}), and n (dimensionless) the Hill sigmoidicity coefficient.

Taking transfer rates to and from the ear fluid compartments and the organ of Corti into account (as shown in Table 1), Eq. (3) has to be rewritten into:

$$\begin{aligned}\frac{dC_b(t)}{dt} = {} & \frac{I(t)}{V_b} - k_{nr}C_b(t) - k_sCL_{CR}(t)C_b(t) + \frac{k_{reabs}}{V_b}A_{pt}(t) \\ & + k_{eb}(C_{endo}(t) - C_b(t)) + k_{pb}(C_{peri}(t) - C_b(t)) \\ & + k_{ob}(C_{oc}(t) - C_b(t)) - \frac{k_{be}C_b(t)}{KM_{endo} + C_b(t)} \\ & - \frac{k_{bp}C_b(t)}{KM_{peri} + C_b(t)} - \frac{k_{bo}C_b(t)}{KM_{oc} + C_b(t)}\end{aligned} \tag{17}$$

Note that the diffusion terms equal zero when $C_b(t)$ is greater than $C_{endo}(t)$, $C_{peri}(t)$ and $C_{oc}(t)$.

2.7. Optimal serum concentration for efficacy

Considering a general growth-kill model, an optimal concentration can be found in the central compartment for antimicrobial efficacy, calculated as a constant factor to a certain minimal inhibitory concentration (MIC) (Neef et al., 2002). If a one compartment model is assumed, the optimal concentration can than be determined by minimizing the function $C_b \rightarrow N_0\exp((\lambda - F(C_b))P/k_eC_b)$. Differentiating with respect to C_b, setting this derivative equal to zero and solving for concentration C_b leads to the optimal concentration C_{opt}. With the use of equation, $EC_{50} = C_{mic}((E_{max} - \lambda_b)/\lambda_b)^{1/\gamma_\kappa}$, C_{opt} becomes:

$$C_{opt} = C_{mic}\left(\frac{\lambda_b}{2}\left(E_{max}(\gamma_k - 1) + 2\lambda_b + \sqrt{E_{max}}\sqrt{\gamma_k^2E_{max} - 2\gamma_kE_{max} + 4\gamma_k\lambda_b + E_{max}}\right)\right)^{\frac{1}{\gamma_k}} \tag{18}$$

Graphically, this optimal value is reached when the line through the origin and the point $(C_b;\ F(C_b) - \lambda_b)$ is tangent to the graph of $F(C_b) - \lambda_b$ (Neef et al., 2002).

To calculate the optimal concentration for efficacy for the model incorporated kidney and ear compartments, it was assumed that no nephrotoxicity occurs, thus that $M(t) = M_{max}$ and $dM(t)/dt = 0$ (see Eq. (28) where $\varepsilon = 0$) where M is the number of living kidney cells.

In case of a constant infusion, concentration at steady state is a constant, so, Eq. (17), $dC_b(t)/dt = 0$. This also applies to concentrations in ear fluids and the organ of Corti, thus $dC_{endo}(t)/dt = dC_{peri}(t)/dt = dC_{oc}(t)/dt = 0$. Substituting this into Eq. (13)–(15) yields:

$$I(t) - (k_{nr} + k_sCL_{cr}(t))C_b(t) + k_{reabs}C_{pt}(t) = 0 \tag{19}$$

At steady state and without nephrotoxicity, it follows from Eq. (4), that:

$$C_{pt}(t) = \frac{V_{max}C_b(t)}{k_{reabs}(K_m + C_b(t))} \tag{20}$$

$$I(t) = (k_{nr} + k_sCL_{cr}(t))C_b(t) - \frac{V_{max}C_b(t)}{K_m + C_b(t)} \tag{21}$$

Writing $k_e = k_{nr} + k_sCL_{CR}$ yields:

$$C_b = \frac{I}{k_e} + \frac{V_{max}C_b(t)}{k_e(K_m + C_b(t))} \tag{22}$$

with the last term >0, which represents the portion of drugs taken up after filtration into the kidney cells.

The total amount of drug P per litre administered during total treatment time T is now equal to:

$$P = \int_0^T I(t)dt = \left(k_eC_b - \frac{V_{max}C_b}{K_m + C_b}\right)T \tag{23}$$

The number of bacteria is given by Eq. (12). At the end of treatment $N(T)$ is equal to:

$$N(T) = N_0e^{(\lambda_b - F(C_b))T} \tag{24}$$

or:

$$N(T) = N_0e^{\frac{(\lambda_b - F(C_b))P}{k_eC_b - \frac{V_{max}C_b}{K_m + C_b}}} \tag{25}$$

The optimal concentration for efficacy can be found by optimising the object function:

$$C_b \rightarrow N_0e^{\frac{(\lambda_b - F(C_b))P}{k_eC_b - \frac{V_{max}C_b}{K_m + C_b}}} \tag{26}$$

Because of the higher blood concentration than with the model as described previously (Neef et al., 2002), the killing rate $F(C_b)$ is larger than with the simple one-compartment model. Also, $k_eC_b > k_eC_b - (V_{max}C_b/(K_m + C_b))$ and thus $1/k_eC_b < 1/(k_eC_b - (V_{max}C_b/(K_m + C_b)))$.

2.8. The maximal blood concentration avoiding nephrotoxicity

A blood concentration can be determined below which no nephrotoxicity occurs. At steady state the rate of change of C_b, C_{pt} and M are equal to zero:

$$I - (k_{nr} + k_sCL_{CR})C_b + k_{reabs}C_{pt} = 0 \tag{27}$$

The change in number of living kidney cells as a function of the logistic regeneration rate and killing rate can be expressed as:

Table 1
Pharmacokinetic and pharmacodynamic parameters used for simulations.

Abbreviation	Explanation	Value	Dimension	References
w	Weight	80	kg	–
V_d	Volume of distribution	0.25	L kg^{-1}	–
$t_{½blood}$	Elimination half-life	3	h	Prins et al. (1993)
k_e	Elimination rate constant	0.231	h^{-1}	Neef et al. (2002)
$t_{½non\text{-}renal}$	Non-renal elimination half-life	100	h	Hurst et al. (1987)
k_{nr}	Non-renal elimination rate constant	0.006932	h^{-1}	Hurst et al. (1987)
CL_{CR0}	Creatinine clearance at the beginning of treatment	100	mL min^{-1}	Prins et al. (1993)
k_s	Renal clearance coefficient	0.0022	mL min^{-1} h^{-1}	Rougier et al. (2003a)
V_0	Maximum accumulation rate at the beginning of treatment	1	mg h^{-1}	Giuliano et al. (1986a) and Verpooten et al. (1986)
K_m	Michealis–Menten constant for uptake of the aminoglycoside in the kidney	15	mg L^{-1}	Giuliano et al. (1986b) and Verpooten et al. (1986)
V_{max}	Maximum accumulation rate of uptake of the aminoglycoside	1	mg L^{-1} h^{-1}	De Broe et al. (1988)
$t_{½PT\ cells}$	Half-life in PT cells	100	h	Brenner and Rector (2000) and De Broe et al. (1988)
k_{reabs}	The reabsorption rate constant from the PT cells to the blood	0.00693	h^{-1}	–
γ	Hill sigmoidicity coefficient	5	Dimensionless	Mingeot-Leclercq and Tulkens (1999)
ε_{max}	Maximum killing rate of the kidney cells	0.5	Dimensionless	–
C_{50}	Conc. in the kidney at which half the maximal killing rate is obtained	50	mg L^{-1}	Rougier et al. (2003a)
ε_{50}	Fraction of dead kidney cells at which the clearance is decreased by 50%	0.8	Dimensionless	–
δ	Hill sigmoidicity coefficient	6	Dimensionless	Rougier et al. (2003a)
k_2	Daily muscular production rate of creatinine	60	mg L^{-1} h^{-1}	Jelliffe and Jelliffe (1971) and Rougier et al. (2003a)
Vol_{CR}	Volume of distribution of creatinine	5	L	Jelliffe and Jelliffe (1971)
λ_b	Bacterial growth rate constant in the absence of an antibiotic	0.995	h^{-1}	Corvaisier et al. (1998) and Neef et al. (2002)
E_{max}	Maximum rate constant for bacterial killing	7.115	h^{-1}	Corvaisier et al. (1998) and Neef et al. (2002)
γ_k	Steepness coefficient of the curve	0.416	Dimensionless	Corvaisier et al. (1998) and Neef et al. (2002)
C_{mic}	Minimal inhibitory concentration (MIC)	1	mg L^{-1}	Neef et al. (2002)
EC_{50}	Conc. at which 50% of the maximum bacterial killing rate is achieved	78.8	mg L^{-1}	–
$t_{½ear\ fluids}$	Half-life in ear fluids	100	h	Prins (1995)
$t_{½organ\ of\ Corti}$	Half-life in the organ of Corti	100	h	Prins (1995)
k_{eb}	Elimination rate constant from the endolymph to the blood	0.00345	h^{-1}	–
k_{pb}	Elimination rate constant from the perilymph to the blood	0.00345	h^{-1}	–
k_{ob}	Elimination rate constant from the organ of Corti to the blood	0.00693	h^{-1}	–
k_{eo}	Elimination rate constant from the endolymph to the organ of Corti	0.00345	h^{-1}	–
k_{po}	Elimination rate constant from the perilymph to the organ of Corti	0.00345	h^{-1}	–
k_{be}	Maximum uptake rate constant from the blood to the endolymph	0.7	h^{-1}	–
k_{bp}	Maximum uptake rate constant from the blood to the perilymph	0.5	h^{-1}	–
k_{bo}	Maximum uptake rate constant from the blood to the organ of Corti	0.1	h^{-1}	–
KM_{endo}	Conc. at which half the maximum uptake is reached	20	mg L^{-1}	–
KM_{peri}	Conc. at which half the maximum uptake is reached	20	mg L^{-1}	–
KM_{oc}	Conc. at which ½ the maximum uptake rate is reached (organ of Corti)	20	mg L^{-1}	–
E_{hcmax}	Maximum killing rate constant for hair cells	0.1	h^{-1}	Carrière (1980)
E_{hc50}	Conc. at which half the maximum killing rate for hair cells is achieved	60	mg L^{-1}	Carrière (1980)
n	Hill sigmoidicity coefficient	8	Dimensionless	Carrière (1980)
M_{max}	Maximum number of kidney cells	2×10^6	Dimensionless	Berne and Levy (2003)
T_r	Recovery time	336	h	Brenner and Rector (2000)
λ_k	Regeneration rate constant of the kidney cells	0.00298	h^{-1}	Murray (1989)

$$\lambda_k\left(1-\frac{M}{M_{max}}\right)-\frac{\varepsilon_{max}C_{pt}^{\gamma}}{C_{50}^{\gamma}+C_{pt}^{\gamma}}=0 \tag{28}$$

and the changing concentration rate in the kidney cells:

$$-\lambda_k\left(1-\frac{M}{M_{max}}\right)C_{pt}+\frac{V_{max}C_b}{K_m+C_b}-k_{reabs}C_{pt}=0 \tag{29}$$

with $CL_{CR}=\varepsilon_{50}{}^{\delta}/(\varepsilon_{50}{}^{\delta}+\varepsilon^{\delta})$ and the fraction of death cells $\varepsilon=(M_{max}-M)/M_{max}$. From Eq. (28) the number of kidney cells at steady state is equal to:

$$M=M_{max}\left(1-\frac{\varepsilon_{max}C_{pt}^{\gamma}}{\lambda_k(C_{50}^{\gamma}+C_{pt}^{\gamma})}\right) \tag{30}$$

or the concentration C_{ptss} in the kidney cells at steady state:

$$C_{ptss}=\left(\frac{\lambda_k(M-M_{max})}{M_{max}(\lambda_k-\varepsilon_{max})-\lambda_kM}\right)^{\frac{1}{\gamma}}C_{50} \tag{31}$$

or using the definition for $\varepsilon=(M_{max}-M)/M_{max}$:

$$C_{ptss}=\left(\frac{\lambda_k\varepsilon}{\varepsilon_{max}-\varepsilon\lambda_k}\right)^{\frac{1}{\gamma}}C_{50} \tag{32}$$

Substituting this into Eq. (29) and solving for C_b, the steady state value of the blood concentration is given by:

$$C_{bss}=\frac{(\lambda_k\varepsilon)^{\frac{1}{\gamma}}C_{50}K_m(\lambda_k\varepsilon+k_{reabs})}{(\lambda_k\varepsilon)^{\frac{1}{\gamma}}C_{50}(\lambda_k\varepsilon+k_{reabs})-V_{max}(\varepsilon_{max}-\lambda_k\varepsilon)^{\frac{1}{\gamma}}} \tag{33}$$

Substituting C_{ptss} and C_{bss} in Eq. (27) gives a relation for the fraction of death kidney cells ε and the infusion rate I:

$$I=-\frac{(\varepsilon^{\delta}k_{nr}+(k_{nr}+k_s)\varepsilon_{50}^{\delta})(\lambda_k\varepsilon)^{\frac{1}{\gamma}}C_{50}(\lambda_k\varepsilon+k_{reabs})}{(\lambda_k\varepsilon)^{\frac{1}{\gamma}}C_{50}(\lambda_k\varepsilon+k_{reabs})(\varepsilon_{50}^{\delta}+\varepsilon^{\delta})-V_{max}(\varepsilon_{max}-\lambda_k\varepsilon)^{\frac{1}{\gamma}}}$$
$$-k_{reabs}\left(\frac{\lambda_k\varepsilon}{\varepsilon_{max}-\lambda_k\varepsilon}\right)^{\frac{1}{\gamma}}C_{50} \tag{34}$$

It is interesting to know whether the blood concentration, at which nephrotoxicity occurs (Eq. (33) when $\varepsilon=\varepsilon_{50}$), is higher or lower

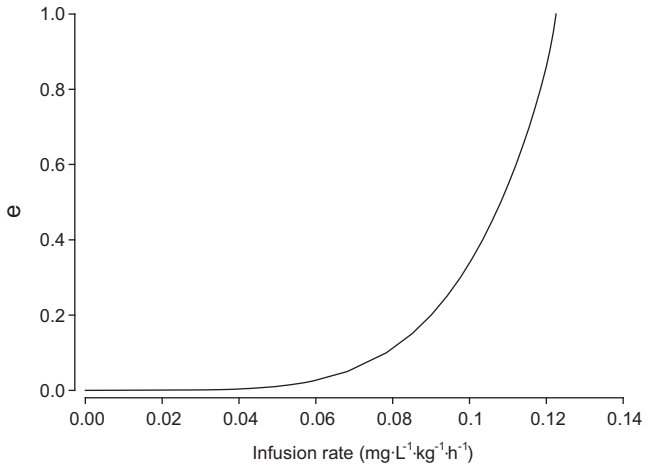

Fig. 2. The fraction of dead kidney cells ε for the parameter set of Section 2.9 as a function of aminoglycoside infusion rate in mg L^{-1} kg^{-1} h^{-1}. Nephrotoxicity occurs when ε is equal to ε_{50}. The infusion rate necessary to achieve this steady state value is 0.12 mg L^{-1} kg^{-1} h^{-1}. The toxic concentration in the kidney is 17.2 mg L^{-1} and the toxic blood concentration is 2.8 mg L^{-1}.

than the optimal concentration for efficacy (Eq. (18)). Since both concentrations are expressed in different parameters, which are independent of each other, no analytical comparison between the two can be made. The infusion rate necessary to achieve a steady state was calculated as a function of the nephrotoxic effect ε (Fig. 2).

2.9. Choice of parameters

The results obtained by the numerical program depend highly on the choice of parameter values. Most of the parameters for efficacy and nephrotoxicity can be found in literature, while model parameters for ototoxicity have to be derived from patient data. For the properties of tobramycin, a fictitious patient was chosen, with weight of 80 kg, an age of 30 years and a volume of distribution of 0.25 L kg^{-1}, corresponding to a population mean value in healthy patients (Corvaisier et al., 1998; Neef et al., 2002).

The non-renal clearance rate constant k_{nr} was chosen as 0.006932 h^{-1} to obtain a non-renal half-life of 100 h (Hurst et al., 1987). The dominant half-life of AG in blood varies between 2 and 4 h (actually this depends on the clearance rate by the kidney) and was fixed to 3 h (Prins et al., 1993). Specific values for a normal creatinine clearance are approximately 100 mL min^{-1} (Prins et al., 1993). Using $k_s = (k_e\text{-}k_{nr})/CL_{CR}$, it follows that k_s obtains the value 0.0022 mL min^{-1} h^{-1}.

The growth rate λ_b of *Pseudomonas aeruginosa* bacteria, as an example organism, was set to 0.995 h^{-1}, E_{max} to 7.115 h^{-1}, γ_k to 0.416, (Corvaisier et al., 1998; Neef et al., 2002; Vinks, 2002) and the MIC, C_{mic} to 1 mg L^{-1}. Note that higher estimates for γ_k have also been described (Czock and Keller, 2007). EC_{50} was found to have a value of 78.8 mg L^{-1}.

Parameters for uptake and elimination into and from the kidney cells were as follows. V_{max} was set equal to 1 mg L^{-1} h^{-1}. Healthy kidney PT cells eliminate AG to blood with a diffusion rate of 0.006932 h^{-1} corresponding with a half-life of 100 h (De Broe et al., 1988). Thus, k_{reabs} = 0.00693 h^{-1}. The parameter K_m for uptake of AG was drawn from rat studies (Giuliano et al., 1986b; Verpooten et al., 1986) and set equal to 15 mg L^{-1}.

To a large extent, the GFR is maintained by the renal functional reserve (RFR) to compensate for nephron loss. A comparison with liver cirrhosis can be made, where the liver can still function, with only 20% remaining unscarred cells (Berne and Levy, 2003). An estimate for the kidney is not known, but based on this argument a value of 0.8 for ε_{50} was adopted, meaning that when only 20% of the cells are functioning, the creatinine clearance is still half the baseline value. It was assumed that this process also occurs in a 'threshold' manner, so a value of 6 for δ was chosen (Rougier et al., 2003a,b; Schentag, 1988). The daily muscular creatinine production rate k_2 was set equal to 12 mg L^{-1} h^{-1} (Jelliffe and Jelliffe, 1971; Rougier et al., 2003a).

Kidney's have approximately 2×10^6 nephrons (Berne and Levy, 2003); $M_{max} = 2 \times 10^6$. Kidney's show a slow (2–5 weeks) recovery of kidney function after AG nephrotoxicity (Brenner and Rector, 2000). Therefore, a recovery time T_r of two weeks was used. The regeneration rate constant λ_k is of order O ($1\ T_r^{-1}$ (h)) (Murray, 1989). Thus, λ_k was set equal to 0.00298 h^{-1}. A value for C_{50}, 50 mg L^{-1}, was adopted from a model that shows close resemblance with the present model (Rougier et al., 2003a). The process of killing of kidney cells shows 'threshold behaviour' (Mingeot-Leclercq and Tulkens, 1999); a value of 5 was adopted for γ. In a previously evaluated once-daily administration program, it was found that after 14 days of treatment with 7 mg kg^{-1} day^{-1}, nephrotoxicity had developed in 50% of the patients (Nicolau et al., 1995). To meet this criterion a value of 0.5 for ε_{max} was set.

Uptake rates for ear fluids and the organ of Corti are unknown and were based on rat studies or patient data. The half-life's of AG in these compartments are 100 h (Prins, 1995), which corresponds to a value of 0.00693 h^{-1} for k_{ob}. For k_{eb}, k_{eo}, k_{pb} and k_{po} half

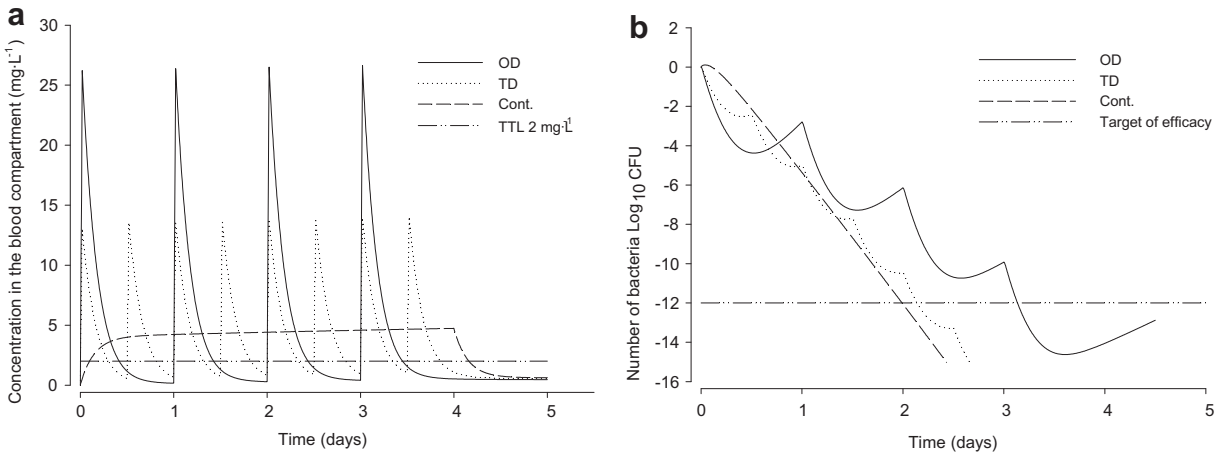

Fig. 3. (a) Blood concentrations of aminoglycosides in mg L^{-1} for OD (solid line), TD (dotted line) and continuous simulated infusions (dash-dotted line) at 7 mg kg^{-1} day^{-1} versus the time in days. Also shown is the target trough level (TTL), (2 mg L^{-1}). (b) The corresponding reductions in number of viable bacteria versus the predicted time of eradication in days. The horizontal dashed-dotted line represents the target value for efficacy.

this value was used, to obtain a half-life of 100 h for drugs inside the endolymph and perilymph. It is known that the uptake is slower than in kidney cells (Berne and Levy, 2003), thus that k_{be}, k_{bp} and k_{bo} are smaller than 1. Drug concentrations in ear fluids and the organ of Corti are lower than in kidney cells due to lower affinity and consequently KM_{endo}, KM_{peri} and KM_{oc} are higher than K_m. Furthermore, it is known that uptake in the endolymph is faster than in the perilymph, which in its turn exceeds the uptake in the organ of Corti (Berne and Levy, 2003). Therefore it was decided to chose a value of 0.7 for k_{be}, 0.5 for k_{bp} and 0.1 for k_{bo} and a value of 20 for KM_{endo}, KM_{peri} and KM_{oc}.

A patient with a complete loss of hearing function has been described in literature and was treated with gentamicin for 80 days with 302.6 mg day^{-1} (Carrière, 1980). Thus, values of 0.1 for $E_{hc\max}$, 60 for E_{hc50} and 8 for n were chosen, such that after 80 days of treatment of a twice-daily administration of 302.6 mg day^{-1}, apoptosis of all hair cells occurred.

Table 1 provides an overview of parameters used for the simulations.

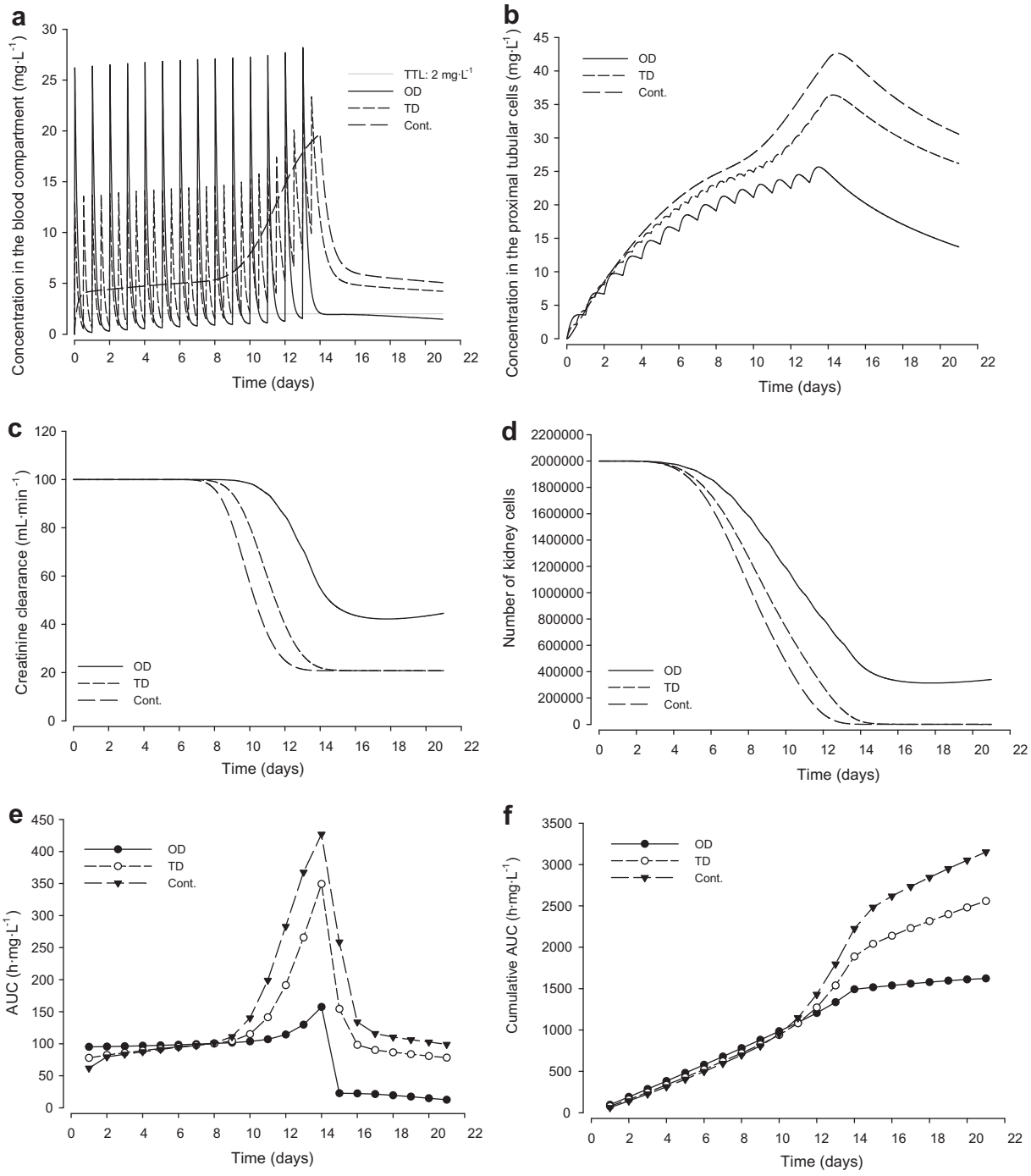

Fig. 4. Simulations of a aminoglycoside dosage regimen of 7 mg kg^{-1} day^{-1}. (a) The concentration of aminoglycosides in the blood compartment (mg L^{-1}). Also displayed is the target trough level (TTL), (2 mg L^{-1}). (b) The concentration of the aminoglycoside in the proximal tubular cells (mg L^{-1}). (c) The creatinine clearance and (d) the number of remaining kidney cells. The daily blood concentration (above the MIC) – time curve (e), AUC, for the simulated aminoglycoside dosage regimens. The cumulative AUCs are shown as well (f).

3. Results: simulations

With proper values for the parameters, the developed numerical program can calculate concentrations in individual compartments. In relation to these concentrations, it calculates the efficacy and nephro- and auditory ototoxicity as well. Consequently, insight in the behaviour of the model for different dosage schedules, i.e. once-daily (OD), twice-daily (TD) and continuous administration, can be obtained and optimal regimen can be calculated.

3.1. Once-daily, twice-daily and continuous administration

3.1.1. Concentration in the blood and efficacy

To investigate the efficacy for different dosage regimen against a homogeneous bacterial population with a MIC of 1 mg L^{-1}, treatment of four consecutive days with a dose of 7 mg kg^{-1} day^{-1} was simulated (Fig. 3a). The calculations were based on the free drug concentration. Both OD and TD administration had a trough level lower than the upper limit for trough concentrations, i.e. 2 mg L^{-1} (Rybak et al., 1999), while continuous administration surpassed this level. All regimens were effective, although OD administration reduced the number of bacteria considerably slower (Fig. 3b).

3.1.2. Nephrotoxicity

To examine the uptake of AG in PT cells for different dosage regimen, a dose of 7 mg kg^{-1} day^{-1} was administered. The fictitious patient was treated for fourteen consecutive days after which the simulation runned for six more days. A normal renal function at the start of treatment was assumed, i.e. a creatinine clearance of 100 mL min^{-1}. Nephrotoxicity was defined as a decrease of 50% or more in creatinine clearance. The trough levels of OD and TD administration were both below 2 mg L^{-1} during the first eight days (Fig. 4a). OD administration clearly caused the AG to be taken up more slowly by the PT cells than TD and continuous administration. Consequently, the killing rate of kidney cells was markedly slower with OD administration (Fig. 4d), which in its turn caused a later decrease in creatinine clearance (Fig. 4c). As a consequence of the decrease in renal elimination of AG, the concentration of the TD regimen started to exceed the target trough level. The peak concentrations were also gradually increasing for OD and TD administration. The blood concentration for continuous administration gradually increased until the ninth day, after which a remarkable increase was seen. This is a reflection of a vicious circle between AG-related nephrotoxicity and impairment of the own excretion, which could also be noticed from the (accelerated) augmentation in AUC (Fig. 4e) or the progressive increase in cumulative AUC (Fig. 4f). The sudden increase in blood concentration accelerated the uptake in PT cells (Fig. 4b). Apparently, during fourteen days of treatment, a 'steady' level in the PT cells was never reached. After the last dose, the concentration in the PT cells decayed gradually to zero for all regimen (Fig. 4b). Although exposure was ended, for all regimen the number of kidney cells still decreased thereafter (Fig. 4d), due to the concentration of AG still present in PT cells (Fig. 4b). The number of kidney cells with OD administration showed signs of recovery three days after cessation of treatment, whereas for TD and continuous administration kidney cells were not able to regenerate. Consequently, the return to baseline creatinine clearance appeared only for OD administration.

3.1.3. Uptake in organ of Corti and ototoxicity

To investigate the difference in uptake in the organ of Corti and the decrease of number of hair cells for the different dosage regimen, a treatment period of seven days with 7 mg kg^{-1} day^{-1} was simulated. The patient was monitored for 21 more days. Unfortunately, a reliable quantitative measure of (human) sensory ototoxicity which links hearing loss to the number of remaining hair cells does not exist yet. Therefore, the fractional apoptosis of hair cells is presented as a measure for ototoxicity. The release from the organ of Corti was slow, resulting in a gradual decrease of the concentration after cessation of treatment (Fig. 5a). Due to the uptake from the endolymph and perilymph into the organ of Corti, the content in the organ of Corti continued to rise after the drug was stopped. The concentration in the organ of Corti reached with continuous administration was higher than for TD administration, which surpassed OD administration. The killing of the hair cells continued after cessation of exposure, due to the uptake from the endolymph and perilymph and the slow release from the organ of Corti (Fig. 5b). This explains the findings of progressive ototoxicity in literature after cessation of treatment (Black et al., 2004; Chen et al., 2007; Rybak, 1986). The decrease in number of hair cells with OD administration was limited, compared to the other dosage regimens.

3.2. Determination of an optimal dosage regimen

As noted in Sections 2.7 and 2.8, an optimal serum concentration for antimicrobial efficacy and the maximum serum concentration to avoid nephrotoxicity, for a steady state situation, can be calculated. With the assumptions on the parameter values and assuming a constant infusion rate, an optimal peripheral protein-unbound blood concentration for microbial killing of 3.1 mg L^{-1}

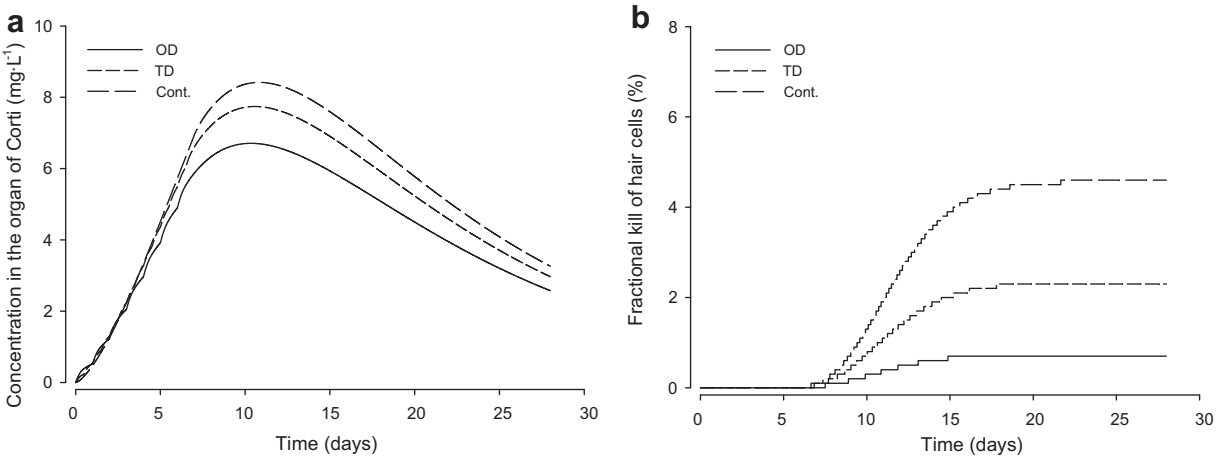

Fig. 5. (a) Concentration of aminoglycosides in the organ of Corti and (b) the number of remaining hair cells over time at a simulated dosage regimen of 7 mg kg^{-1} day^{-1}.

(considering a homogeneous bacterial population with a MIC of 1 mg L^{-1}), a nephrotoxic blood concentration of 2.8 mg L^{-1} and a nephrotoxic concentration in the kidney cells of 17.2 mg L^{-1}, were found. Thus, not surprisingly, the optimal concentration for efficacy was higher than the nephrotoxic blood concentration.

The infusion rate to be given to reach a certain steady state for the number of kidney cells is presented in Eq. (34). When nephrotoxicity occurs, these are equal to $0.2 \times M_{max}$. Using Eq. (34) a total daily dose of 56.9 mg was calculated. After ten days continuous infusion of a daily dose of 56.9 mg, the number of bacteria was found to be equal to 8.2×10^{18} CFU. This leads to the conclusion that continuous infusion did not achieve an efficient eradication. However, with a total daily dose of 56.9 mg, OD administration did not reach the nephrotoxic level for the number of kidney cells. Therefore, the total daily dose could be increased. A treatment of ten days with a total daily dose of four times 56.9 mg OD, i.e. 273.2 mg OD, was simulated and the resulting efficacy and creatinine clearance are demonstrated in Fig. 6. After 10 days of treatment the number of bacteria was reduced to 8.8×10^{-15} CFU and the creatinine clearance was unchanged. Thus, nephrotoxicity did not occur for this dosage(regimen) and treatment was effective. As shown in Fig. 5, the fractional apoptosis of hair cells is minimized by OD exposure to AG.

4. Discussion

A mathematical model for simulation of antimicrobial efficacy and cochleotoxicity of AG was developed. Each model is a simplified representation of reality, in our situation based on an understanding

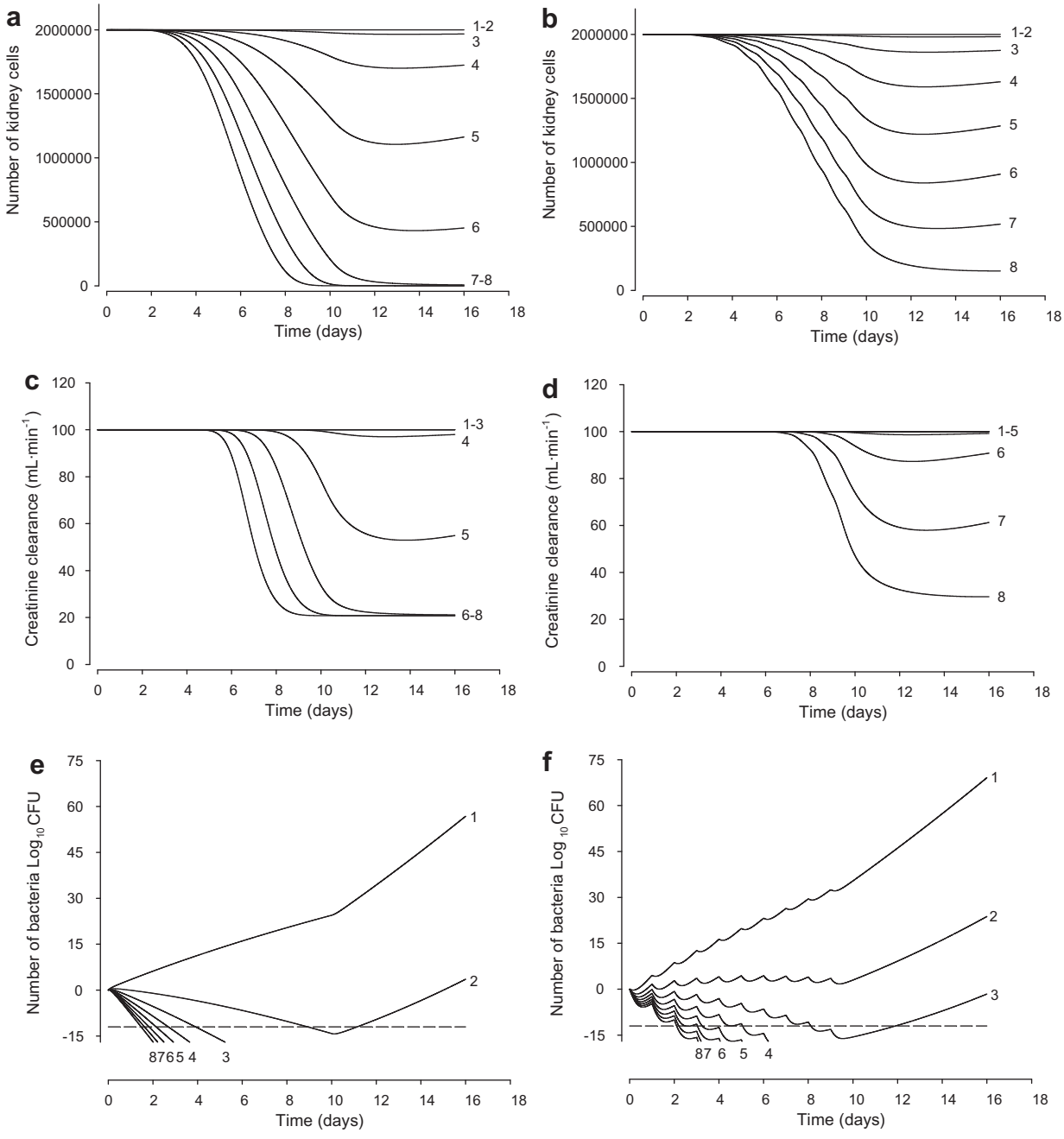

Fig. 6. Effect of aminoglycosides on the kidney function and the eradication of bacteria for continuous infusion (a, c, e) and an OD regimen (b, d, f). The horizontal dashed line corresponds to the target value for efficacy. The different simulated dosages, 56.9, 170.7, 284.5, 398.3, 512.1, 625.9, 739.7 and 853.5 mg, are represented by 1, 2, 3, 4, 5, 6, 7 and 8, respectively.

of the underlying mechanisms of action of AG. A pharmacological model is useful if it can describe, explain or predict the outcome of treatment of infections and the occurrence, the onset and severity of side effects in patients. The model is considered qualified when such predictions are confirmed by real patient data. The presented model is not qualified yet with our patient data. Nevertheless, interesting conclusions could be drawn, based on parameter values adapted from the literature.

According to what is known about AG, it was found with simulations that nephrotoxicity occurs more rapidly with continuous than with intermittent administration, and happens below the established optimal concentration. This finding is in agreement with results of a previously performed clinical study in which it was found that the daily area under the plasma concentration-time curve (AUC) for the AG was a significant predictor of nephrotoxicity (Rybak et al., 1999). Indeed, at equivalent simulated dosages of AG (7 mg kg^{-1} day^{-1}) for continuous, OD and TD administration, the onset of nephrotoxicity could be deduced from the simulated daily AUC over time. The cumulative AUC does not seem to be a proper predictor of nephrotoxicity, since an abrupt augmentation in AUC at the beginning of nephrotoxicity was not well reflected in a change in cumulative AUC. Furthermore, it is evident, from our simulations (Fig. 4b) and patient data (Rybak et al., 1999), that accumulation of AG in the PT cells is more pronounced with continuous administration, since the active uptake is more gradual over time and not immediately saturated. On the other hand, it was demonstrated with our model that bacterial killing was slower when AG were dosed intermittently. Possibly this is the reason why a meta-analysis of clinical trials paradoxically showed a tendency towards favouring continuous intravenous infusion as a manner to improve the clinical outcome of AG (Kasiakou et al., 2005). The original results were probably obtained at a relatively low MIC and/or in the absence of resistant subpopulations, and thus should be interpreted with caution (Zavascki, 2006). The optimal peripheral blood concentration (the central compartment of the model) was calculated at a certain MIC for the micro-organism, while applying a constant infusion, and mimics a concentration that would be effective in mild to severe bacteraemia. Certainly, this artificial concentration (3.1 × MIC) needs to be higher for more severe infections. As an improvement of the model, more compartments could be introduced or a more sophisticated formula to represent fluctuating growth and killing could be applied to simulate eradication of micro-organisms in tissues (deep-seated infections) (von Kleist and Huisinga, 2007) or in otherwise hard to penetrate environments, like biofilms (bacteria embedded in a self produced matrix). Therefore, a time-dependent correction factor for the EC_{50} component may need to be introduced. As an ultimate future goal, the rate of bacterial killing should also be influenced by simulating the host defence mechanism (Czock and Keller, 2007). Until now, we believe that the model applies the best to patients with a partially active immune system that can handle a limited number of resistant cells, assuming that the susceptible cells are killed quickly enough. The ultimate future improvement of the model will be solving its limitation concerning not incorporated less susceptible subpopulations.

Another extension of the model would be simulation of vestibular ototoxicity, which is probably affected by the concentration of AG in the perilymph (Rybak, 1986). In order to model auditory ototoxicity, it was required to incorporate the concentration in the perilymph. As a result of introducing the cochlear compartment, the presented model offers already the first steps towards precise cochleotoxicity modelling. Whereas cochleotoxicity is permanent, under certain circumstances patients may recover from vestibular ototoxicity (Black et al., 2004). With fictitious patient data we demonstrated that cochleotoxicity occurred on prolonged exposure, even with recommended serum trough levels achieved by intermittent dosing regimens, in consistence with what has been observed in actual patients (Black et al., 2004). So far a direct comparison between patient characteristics and outcome measurements has not been made. This would be necessary in order to discover possible inconsistencies that would provide a basis for further improvement of our model. Nevertheless, it was shown that apoptosis of cochlear hair cells continued to progress after cessation of AG exposure; another aspect of ototoxicity that is noticed as well in the clinical setting (Black et al., 2004; Chen et al., 2007). However, our model does not yet possess the ability to automatically distinguish between differences in the probability and selectivity of AG to cause cochleotoxicity and vestibular ototoxicity (Chen et al., 2007; Rybak, 1986). For this reason, drug individual E_{hc50} and n values should be determined.

5. Conclusions

Based on our simulations, OD compared to TD and continuous exposure of AG seems to have more advantages in the light of restricting nephrotoxicity and cochleotoxicity, while maintaining antimicrobial efficacy at a sufficient level.

In conclusion, it is anticipated that in the near future our constructed, but not yet "validated", model enables healthcare workers to gain insight into designing appropriate antibiotic drug regimes, which combine maximal antimicrobial efficacy with minimal (acceptable) side effects. This is of importance for AG because of their very narrow therapeutic window.

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