World Journal of Nephrology

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DOI: 10.5527/wjn.v4.i3.330

World J Nephrol 2015 July 6; 4(3): 330-344
ISSN 2220-6124 (online)

REVIEW

Pharmacokinetic and pharmacodynamic considerations of antimicrobial drug therapy in cancer patients with kidney dysfunction

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Author contributions: Keller F contributed to the pharmacokinetics and pharmacodynamics; Schröppel B contributed to the literature context and manuscript preparation; Ludwig U contributed to the clinical relevance and practical applicability.

Conflict-of-interest statement: There is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Received: November 27, 2014
Peer-review started: November 28, 2014
First decision: December 26, 2014
Revised: January 12, 2015
Accepted: May 5, 2015
Article in press: May 6, 2015
Published online: July 6, 2015

Abstract

Patients with cancer have a high inherent risk of infectious complications. In addition, the incidence of acute and chronic kidney dysfunction rises in this population. Anti-infective drugs often require dosing modifications based on an estimate of kidney function, usually the glomerular filtration rate (GFR). However, there is still no preferential GFR formula to be used, and in acute kidney injury there is always a considerable time delay between true kidney function and estimated GFR. In most cases, the anti-infective therapy should start with an immediate and high loading dose. Pharmacokinetic as well as pharmacodynamic principles must be applied for further dose adjustment. Anti-infective drugs with time-dependent action should be given with the target of high trough concentrations (*e.g.*, beta lactam antibiotics, penems, vancomycin, antiviral drugs). Anti-infective drugs with concentration-dependent action should be given with the target of high peak concentrations (*e.g.*, aminoglycosides, daptomycin, colistin, quinolones). Our group created a pharmacokinetic database, called NEPharm, hat serves as a reference to obtain reliable dosing regimens of anti-infective drugs in kidney dysfunction as well as renal replacement therapy. To avoid the risk of either too low or too infrequent peak concentrations, we prefer the eliminated fraction rule for dose adjustment calculations.

Key words: Anti-infective drugsl; Cancer; Kidney function; Pharmacodynamics; Pharmacokinetics; Dose adjustment; NEPharm

Core tip: Cancer patients are at an increased risk for both infection and kidney dysfunction. Infections need immediate treatment; during the further course, kidney function must be taken into account. Almost any drug can be adjusted to any kidney function in every patient. Observation of the pharmacokinetic principles allows avoiding adverse events.

Observation of the pharmacodynamic principles is needed to obtain anti-infective success. The target concentration for anti-infective drugs with a concentration-dependent effect is the high peak level. The target concentration for anti-infective drugs with a time-dependent effect is the high trough level. When in doubt, the peak should be the target.

Keller F, Schröppel B, Ludwig U. Pharmacokinetic and pharmacodynamic considerations of antimicrobial drug therapy in cancer patients with kidney dysfunction. *World J Nephrol* 2015; 4(3): 330-344 Available from: URL: http://www.wjgnet.com/2220-6124/full/v4/i3/330.htm DOI: http://dx.doi.org/10.5527/wjn.v4.i3.330

INTRODUCTION

The number of patients requiring anticancer therapy is rising due to the increase in life expectancy. Presently, there is almost no malignancy without an option for either curative or palliative, adjuvant or neo-adjuvant chemotherapy. Anticancer drugs bear not only the risk of infection and "febrile neutropenia"[1] but also the risk of nephrotoxicity[2].

Acute kidney injury (AKI) of any cause is a known risk factor for and a consequence of infectious complications. AKI can also be potentiated by the nephrotoxicity of the chemotherapeutics. In cancer patients, the incidence of AKI is estimated at 15%-45% per year[3]. The prevalence of chronic kidney disease (CKD) is reported at 15%-50% in cancer patients[4,5]. This high prevalence can be due to demographic trends but in contrast to previous speculations, CKD is not a risk factor for non-renal malignancies[3].

This review addresses the pharmacokinetics and pharmacodynamics (PK-PD) of anti-infective therapies in cancer patients with impaired kidney function.

Case report

The therapeutic dilemma might be illustrated by the case of a 73-year-old female with fever and leukopenia. The diagnosis of multiple myeloma had been made 18 mo before admission. As a third-line chemotherapy, she had received 4 cycles of bendamustine and prednisolone. Now she was referred from another hospital because of acute on chronic kidney failure requiring hemodialysis (HD). After persistent fever while on piperacillin-combactam and radiological evidence of pneumonia, she received 1000 mg meropenem every 12 h as rescue therapy. Since the half-life was assumed to increase from 1.0 to 9.7 h, the administration interval was prolonged from 8 to 12 h (Table 1). The renal failure dose of 500 mg twice daily as recommended by the manufacturer was considered to be under-dosed - in agreement with recent publications[6]. She remained dialysis-dependent but could be discharged home 3 wk later.

KIDNEY FUNCTION AND DRUG DOSE ADJUSTMENT

Anti-infective treatment is given with a therapeutic or a prophylactic indication. The preemptive treatment is distinguished from the induction therapy and the empirical differs from the sequential mode of therapy. For any mode of treatment, adjustment of anti-infective drug dose to the kidney function is recommended based on estimates of glomerular filtration rate (GFR) as well as pharmacokinetic and pharmacodynamic principles.

Kidney function

The kidney function can be measured by the GFR as this quantitates the primary and principal function of the nephron. It is an anachronism to use the endogenous creatinine clearance since urine collection errors are frequent[7]. This makes such estimates unreliable, resulting in under-dosing of anti-infective and anticancer drugs. For classifying the kidney dysfunction into one of the 5 stages of CKD, the standardized chronic kidney disease epidemiology collaboration (CKD-EPI) formula is currently preferred[8]. For drug dose adjustment, the GFR estimate easiest to access is the most appropriate[9]. Both, the modification of diet in renal disease (MDRD) or CKD-EPI equations estimate the GFR (eGFR) for a standard 1.73 m^2 body surface area (BSA). To estimate the BSA, we use the Mosteller formula[10].

$$\text{GFR} = \text{eGFR} \cdot \frac{\text{BSA}}{1.73}$$

$$\text{BSA (m}^2) = \frac{\sqrt{\text{Height (cm)} \cdot \text{Weight (kg)}}}{60}$$

The eGFR value is automatically calculated in most laboratories with the standardized MDRD and the CKD-EPI equations. Weight or body surface area are important determinants of the distribution volume and thus of the dose. Since oncologists are familiar with the use of BSA, the MDRD and CKD-EPI GFR might have advantages for dose adjustment calculations.

In the Cockcroft and Gault (C and G) formula the body weight is considered; it originally estimated the creatinine clearance. Like the other creatinine-based formulas, the C and G equation can also be used as an estimate of the GFR for drug dose adjustments[11]. Luzius Dettli proposed a coefficient-free version of the C and G equation[12] that was validated recently with the new calibrated serum creatinine measurements[13].

$$\text{GFR} = \frac{150 - \text{Age (yr)}}{\text{Crea (mcmol/L)}} \cdot \text{Weight (kg)}$$

Since the GFR is the independent and the serum creatinine is the dependent variable, there can be a time lag of 1 to 2 d behind the actual true kidney function and all creatinine-based GFR estimates in acute kidney injury (AKI). An interesting extension, therefore, is the so-called kinetic GFR for increasing and decreasing kidney function in patients with AKI[14]. The published equation can be derived from the C and G equation and rearranged for readily available measurements of the initial serum creatinine ($Crea_0$) and differences (deltaX) between subsequent creatinine values ($Crea_{1,2\,...}$).

$$kinetGFR = \frac{[150 - Age\,(yr)] \cdot Weight\,(kg)}{Crea_0\,(mcmol/L)} \cdot \left[1 - \frac{Crea_2 - Crea_1}{t_2 - t_1} \cdot \frac{24\,(h)}{182(mcmol/L)}\right]$$

This approach holds for changing creatinine and is based on creatinine production. It relates the increase in serum creatinine within a specified time interval to the maximum increase in creatinine within one day. Since creatinine production and renal excretion is constant at about 1000 mg/d and the creatinine distribution volume is 42 L, the maximum 24 h increase in serum creatinine is 182 μmol/L if GFR is zero (the original publication says 133 μmol/L). If AKI is progressing and the creatinine is increasing, the above 1 - deltaX term is < 1.0 whereas the 1 - deltaX term is > 1.0 for decreasing creatinine values and restitution of AKI. The kinetic GFR estimate makes the general GFR-based dose adjustment rules (see below) also applicable to AKI and the intensive care condition with renal replacement therapy[14].

Pharmacokinetics

The main pharmacokinetic parameters are clearance, volume and half-life. Malcolm Rowland claimed the primacy for the clearance term since elimination is driven by clearance not half-life[15]. Where clearance reflects a mechanistic model, however, the half-life reflects a mathematical approach. Friedrich Hartmut Dost argued that the clearance estimate depends on bioavailability and body weight - as does the volume as well - whereas half-life does not[16].

There is a close relationship between the three parameters of clearance (Cl), volume (Vd) and half-life ($T_{1/2}$) where the half-life is inversely proportional to the elimination rate constant (Ke).

$$Cl = Ke \cdot Vd$$

$$T_{1/2} = \frac{ln\,(2)}{Ke} = \frac{0.693}{Ke} = 0.693 \cdot \frac{Vd}{Cl}$$

As discussed for antiviral drugs, the half-life is the pharmacokinetic parameter that most impacts drug action[17]. Since the half-life indicates how long an administration interval should be selected, and since the duration of drug action is correlated to the half-life, we consider the elimination half-life to be the most useful pharmacokinetic parameter for drug dosing[18]. In some cases the special half-life that represents the largest part of the area under the curve should be considered - Luzius Dettli coined it the "dominant half-life". Generally, the effect-indicative half-life at target concentrations should be used for dose calculations[18].

An increase and prolongation of the half-life was first reported by Kunin *et al*[19] for special drugs in patients with impaired kidney function. If the half-life is prolonged, drug accumulation kinetics will produce higher peak and higher trough concentrations with an increased risk for drug toxicity. According to the accumulation kinetics, the steady-state peak (C_{peak}) and the trough concentrations (C_{trough}) depend on the initial concentration after the first dose (C_0), on half-life ($T_{1/2}$) and administration interval (Tau).

$$C_{peak} = \frac{C_0}{1 - \exp(-\frac{0.693}{T_{1/2}} \cdot Tau)}$$

$$C_{trough} = \frac{C_0}{\exp(\frac{0.693}{T_{1/2}} \cdot Tau) - 1}$$

The relation between kidney function and half-life is as complex and hyperbolic as that between GFR and serum creatinine. It was a great advantage for drug dose adjustment that Luzius Dettli demonstrated the linear relationship between drug elimination and kidney function. This dependence was originally described as a linear function between the elimination rate constant and the creatinine clearance[20]. The modern approach describes this dependence as a linear function between drug clearance (Cl) and GFR.

$$Cl = a + b \cdot GFR = Cl_{nonren} + b \cdot GFR = Cl_{fail} + \frac{Cl_{norm} - Cl_{fail}}{GFR_{norm}} \cdot GFR$$

Based on this fundamental equation, the dose can be adjusted to the individual GFR in proportion to the decrease in drug clearance (Figure 1). The dose can also be adjusted in inverse proportion to the increase in half-life since in many published investigations, the inverse half-life, namely the elimination rate constant (Ke) has been related to the GFR. Based on the ideas of Luzius Dettli and for practical purposes, the fraction eliminated by the renal route (fren) has been proposed as the leading parameter for drug dose adjustment[21].

$$fren = \frac{A_{urine}}{D} = \frac{Cl_{ren}}{Cl_{tot}} = 1 - \frac{Cl_{fail}}{Cl_{norm}} = 1 - \frac{T_{1/2norm}}{T_{1/2fail}}$$

$$Cl = Cl_{norm} \cdot [1 - fren\,(1 - \frac{GFR}{GFR_{norm}})]$$

$$D = D_{norm} \cdot \frac{T_{1/2norm}}{T_{1/2}} = D_{norm} \cdot [1 - fren \cdot (1 - \frac{GFR}{GFR_{norm}})]$$

Since pharmacokinetics of anticancer drugs is rarely investigated in patients with CKD or AKI, it is an advantage that this fraction can be derived in volunteers with normal kidney function. However, kidney dysfunction also influences non-renal clearance, bioavailability and drug metabolism by the liver and intestines[22]. Therefore, the pharmacokinetics as determined in real patients with failing kidney function (CKD or AKI) should be the preferred source for drug dose adjustment calculations (*e.g.,* half-life estimates).

$$T_{1/2} = \frac{T_{1/2norm}}{1 - fren\,(1 - \frac{GFR}{GFR_{norm}})} = \frac{T_{1/2norm}}{1 - (1 - \frac{T_{1/2norm}}{T_{1/2fail}}) \cdot (1 - \frac{GFR}{GFR_{norm}})}$$

Table 1 Proposals for adjustment of an anti-infective drug dose to the estimated kidney function or to intermittent hemodialysis and continuous hemofiltration

Drug	Half life (h)		Loading dose	Normal kidney function (GFR = 100 mL/min)		Kidney impairment (GFR ≈ 30 mL/min)		Failure (GFR ≤ 5 mL/min) and hemodialysis			Hemofiltration (2 L/h) and continuous dialysis	
								Off dialysis day Dfail		$D_{HD} = D_{fail} + D_{sup}$		
	Normal	Failure	D_{start} (mg)	Maintenancedose (mg)	Dose interval (h)	Maintenancedose (mg)	Dose interval (h)	Maintenancedose (mg)	Dose interval (h)	Post dialysis D_{HD} (mg)	Maintenancedose (mg)	Dose interval (h)
Abacavir (po)	1.5	2.1	600	600	12	600	12	600	12			
Aciclovir	2.5	25	750	750	8	500	12	500	24	750	750	24
Adefovir (po)	1.6	160	10	10	24	10	48	10	168	10		
Albendazole (po)	8	8	400	400	12	400	12	400	12			
Amantadine (iv)	13	600	200	200	8	200	72	200	168	200	200	72
(po)	20	610	100	100	12	100	72	100	168	100		
Amikacin	2	40	Norm/Failure 1500/750	1500	24	500	24	250	24	750	750	24
Amoxicillin (po)	1.2	12	1000	1000	8	1000	12	500	12	1000		
Amoxicillin + Clavulanic acid	1.2 + 1.2	12 + 4.3	500 + 125	500 + 125	8	500 + 125	12	500 + 125	12	500 + 125	500 + 125	12
			875 + 125	875 + 125	8	875 + 125	12	500 + 125	12			
Amphotericin B	24 (360)	35 (360)	70	70	24	70	24	50	24	50	50	24
Amphotericin B liposomal	24/92	24/160	200	200	24	200	48	200	24	200	200	24
Ampicillin	1	13	2000	2000	8	2000	12	1000	12	2000	2000	12
+ Sulbactam	+ 1	+ 6.6	+ 1000	+ 1000	8	+ 1000	12	+ 500	12	+ 1000	+ 1000	12
Amprenavir	8	8	1200	1200	12	1200	12	1200	12			
Anidulafungin	26	26	200	100	24	100	24	100	24	100	100	24
Artesunate	0.5			180								
Atazanavir (po)	9			300	24							
Atovaquone (po)	63	63	750	750	12							
Atovaquone +	63	63	250 + 100	250 + 100	24	250 + 100	24	250 + 100	24			
Proguanil (po)	14	23										
Azidothymidine	1	1.9 (52)	200	200	8	100	8	100	8	200	200	24
Azithromycin	39	40	1000	500	24	500	24	500	24	500	-	-
Brivudin (po)	14 (144)		125	125	24 for 7 d							
Caspofungin	10	10	70	50	24	50	24	50	24	50	50	24
Cefaclor (po)	0.7	3	1000	1000	8	1000	12	1000	12	1000		
Cefazolin	2.2	34	2000	2000	8	2000	12	500	12	1500	1000	12
Cefotaxime	1.2	7 (10)	2000	2000	8	2000	12	1000	12	2000	2000	12
Cefotiam	1	8	2000	2000	8	2000	12	1000	12	2000	2000	12
Ceftaroline fosamil	2.7	6	600	600	12	600	12	600	12	600	600	12
Ceftobiprol-medocaril	3.3	11	1000	1000	8	1000	12	500	12	1000	1000	12
Ceftazidime	2.1	25	2000	2000	8	2000	12	1000	24	2000	1000	12
Ceftriaxone	8	15	2000	2000	24	2000	24	2000	24	2000	2000	24
Cefuroxime (iv)	1.1	18	1500	1500	8	1500	12	750	24	1500	750	12
(po)			500	500	8	500	12	500	24			
Chinin = Quinine	13	15	600	600	12	600	12	600	12	600	600	12
Chloramphenicol	2.5	7	1000	1000	8	1000	8	1000	12	1000	1000	12
Chloroquine	48/212	300	250 mg/8 h	150	8	75	24					
Cidofovir	3.4	45	375 mg/168 h	375	336 h = 14 d	70	336 = 14 d	35	336 = 14 d	70	140	336 = 14 d
Ciprofloxacin (iv)	4.4	10	400	400	12	400	12	400	24	400	400	12
(po)			500	500								

Clarithromycin	6.8	17	500	500	12	500	12	500	24		
Clindamycin	3	3	900	600	6 - 8	600	6 - 8	600	6 - 8	600	600	6 - 8
Colistin colistimethate Na	3 (9)	24 (11)	480 - 720	240	8	240	12	240	24	240	320	12
			= 7 Mio IE	= 3 Mio IE		= 3 Mio IE		= 3 Mio IE		= 3 Mio IE	= 4 Mio IE	
Colistin (po)	3	16	160 mg	2 Mio IE	12							
			= 2 Mio IE									
Co-trimoxazole	11/10	31/28	160/800	160/800	12	160/800	24	160/800	24	160/800	160/800	12
Dalbavancin	336		1000	500	168							
Dapsone (po)	24	31	200	200	24	200	24	200	24	200		
Daptomycin	8	33	500	500	24	500	48	500	48	500	350	24
				6-10 mg/kg		6-10 mg/kg		6-10 mg/kg		6-10 mg/kg		
Darunavir (po)	8			600	12							
Delavirdine	5.8			400	8							
Didanosine (po)	1.4	4.5	200	200	12	200	12	200	24			
Doripenem	1	8	1000	1000	8	1000	8	1000	12	1000	1000	8
Doxycycline	15	23	200	100	24	100	24	100	24	100	100	24
Efavirenz (po)	46.8	47	600	600	24	600	24	600	24			
Emtricitabine (po)	8.7	36	200	200	24	200	24	200	72			
Enfuvirtide	30			90	12							
Entecavir (po)	24 (138)	67 (384)	1.0	1.0	24	0.5	48	0.5	72	0.5		
Ertapenem	4.1	14.4	1000	1000	24	1000	24	1000	24	1000	1000	24
Erythromycin	2.3	5	1000	1000	8	1000	12	1000	12	1000	1000	8
Ethambutol	3.1	9.6	1600	1600	24	1200	24	1000	48	1600	1600	24
			20 mg/kg									
Famciclovir (po)	2.2	14	250	250	12	250	12	250	24			
Flucloxacillin	0.8	3	2000	2000	8	2000	8	2000	8	2000	2000	8
Fluconazole	25	110	800 or 400	800	24	400	24	400	48	400	800	24
Flucytosine	4	150	2500	2500	6	2500	12	2500	48	2500	1250	24
Fosamprenavir	19			700	12							
Foscarnet	4.5	100	6000	6000	12	3000	24	3000	72	4000	3000	24
				4000	8							
Fosfomycin (iv)	1.5	20	5000	5000	8	5000	24	2500	24	5000	5000	12
(po)			3000	single dose								
Ganciclovir	4.2	60	500	500	12	500	24	300	24	400	200	12
			5 mg/kg KG									
Gentamicin	2	48	Norm/Fail	240	24	120	24	40	24	120	120	24
			240/120					0	48	320 before HD		
Hydroxy-chloroquine	400			200	8							
Imipenem/	0.9/	3.3/	1000	1000	8	1000	12	500	12	1000	1000	12
+ Cilastatin	0.9	13.8										
Indinavir (po)	1.8	2.1	800	800	8	800	8	800	8			
Isoniazid	1/3.3	5/12	300	300	24	300	24	300	24	300	300	24
Itraconazole (po)	16	25	200	200	24	200	24	200	24	200		
Ketoconazole (po)	3	2	200	200	12	200	12	200	12	200		
Lamivudine (po)	6.2	21	150	150	12	150	24	100	24	150		
Levofloxacin	7.3	35	750	500	12	500	24	250	24	500	500	12
Linezolid	4.9	6.9	600	600	12	600	12	600	12	600	600	12
Lopinavir/Ritonavir	7/3.7	7/6.3	400 + 100	400 + 100	12	400 + 100	12	400 + 100	12			
Maraviroc (po)	36	36	300	300	12	300	12	300	12			

Mebendazole (po)	5		2 x 500	1000	8							
Mefloquine (po)	336	340	250	250	168	250	168	250	168			
Meropenem	1	9.7	1000	1000	8	1000	12	1000	12	1000	1000	12
Metronidazole (iv)	10	11 (34)	500	500	8	500	12	500	12	500	500	12
(po)			400	400		400		400				
Micafungin	13	14	100	100	24	100	24	100	24	100		
Miconazole	24	24	1200	1200	24	1200	24	1200	24	1200		
Moxifloxacin	12	15	400	400	24	400	24	400	24	400	400	24
Nelfinavir (po)	4.5	4	750	750	8	750	8	750	8			
Nitrofurantoin (po)	1.0	1.2	100	100	8							
Nevirapine (po)	28	22	200/24	200	12	200	12	200	12			
Oritavancin	336		1200									
Oseltamivir (po)	7	(80)	75	75	12	30	24	75	72	75		
Paromomycin	2	40		500	8	500	24	500	48			
Penicillin G =	0.5	10	10 mega	10 mega	8	10 mega	12	5 mega	12	5 mega	5 mega	8
Benzylpenicillin												
Penicillin V (po)	0.6	4.1	1 mega	1 mega	8	1 mega	8	1 mega	12			
Pentamidine (iv) (inhaled)	60	96	300	300	24	300	24	300	24			
			600	600	24							
			300	300	4 wk							
Piperacillin	1.1	4	4000	4000	8	4000	12	4000	12	4000	4000	12
+ Sulbactam	1	8	500	500	8	500	12	500	12	500	500	12
Piperacillin	1.1	4	4000	4000	8	4000	12	4000	12	4000	4000	12
+ Tazobactam	1	8	500	500	8	500	12	500	12	500	500	12
Posaconazole (po)	24	29	2 x 300	300	24	300	24	300	24			
Primaquine (po)	6.3	6.4	30	30	24	30	24	30	24			
Proguanil (po)	14	23		200	24							
Propicillin (po)	1		700 = 1 mega	700	8							
Prothionamide (po)	1.5		1000	1000	24	500	24	250	24	500	?	?
Pyrazinamide (po)	9.1	19	2000	2000	24	2000	24	2000	48	2000	-	-
Pyrimethamine	92	80	75	50	24	50	24	50	24			
Pyrvinium embonate	?	?	50	Single dosing								
Quinine	13	15	600	600	12	600	12	600	12	600	600	12
Raltegravir (po)	5.5	2.5	400	400	12	400	12	400	12			
Ribavirin aerosol	44	26	6000	6000	12	6000	12	6000	12	6000	6000	12
Ribavirin (po)	4/250	24/672	600	600	12	400	24	200	24	400	400	72
(iv)			1000	1000	8	500	12	500	48	500	500	48
Rifabutin (po)	25	37	600	600	24	600	24	300	24			
Rifabutin +	25	37	600	600	24	600	24	300	24			
Clarithromycin	6.8	17	300	300	24	300	24	300	24			
Rifampicin (iv)	4.5	4.5	600	600	24	600	24	600	24	600	600	24
(po)			450	450	12	450	12	450	12			
Rifaximin (po)	intestine	unch	400	400	12	400	12	400	12			
Ritonavir (po)	3.7	6.3	600	600	12	600	12	600	12			
Roxithromycin	12	15	300	300	24	300	24	300	24	-	-	-
Saquinavir (po)	7	13	2 x 500	1000	12	1000	12	600	12			
Stavudine (po)	1.5	6.0	40	40	12	40	12	40	12	40		
Sofosbuvir	1 (18)	(25)	400	400	24	400	24	300	24	400		
Streptomycin	2.6	100	1000	1000	24	500	48	250	72	250	500	24

Teicoplanin	52	348	3 x (800/24)	1200	24	400	24	400	48	800	400	24
Telavancin	7.3	25	750	750	24	500	24	250	24	500	750	24
Telbivudine (po)	22		600	600	24							
Tenofovir (po)	14	28	245	245	24	245	24	245	48	245		
Terbinafine (po)	16	16	250	250	24	250	24	250	24			
Tetracycline (po)	8.9	83	500	500	8							
Tigecycline	40	47	100	50	12	50	12	50	12	50	50	12
Tipranavir (iv)	2.8	2.8	500	500	12							
+ Ritonavir (po)	3.7	6.3	+ 200	+ 200								
Tobramycin	2	48	Norm/Fail 240/120	240	24	120	24	40	24	120	120	24
Trimethoprim (iv) (po)	11	31	200	150	12	150	24	150	24	-	-	-
			100	100	24	100	24					
Trimethoprim +	11	31	160	160	12	160	24	160	24	160	160	12
Sulfamethoxazole	10	28	+ 800	+ 800	12	+ 800	24	+ 800	24	+ 800	+ 800	12
Trimethoprim +	11	31	400	400	8	320	12	400	24	400	400	12
Sulfamethoxazole (Pneumocystis)	10	28	+ 2000	+ 2000	8	+ 1600	12	+ 2000	24	+ 2000	+ 2000	12
Valacyclovir (po)	2.5	25	1000	1000	8	1000	12	500	24	1000		
Valganciclovir (po)	3.0	68	900	900	12	450	24	450	72	900		
Vancomycin	6	150	1000	1000	12	1000	24	500	72	1000	1000	24
Voriconazole	8	12	2 x 400/24	200	12	200	12	200	12	200	200	12
Zalcitabine (po)	1.8	11	0.75	0.75	8	0.75	12	0.75	24			
Zanamivir	2.5	13.7	10	10	12	10	12	10	12		10	24
Zidovudine	1	1.9 (52)	200	200	8	100	8	100	8	200	200	12

Drugs are listed in alphabetical order and the parameter values for the drug (or active metabolite) are taken from our NEPharm database. If the individual GFR is not exactly 100 mL/min, or 30 mL/min, or 5 mL/min, the dose could be estimated by interpolation between the stated proposals. GFR: Glomerular filtration rate.

Dose adjustment rules

According to the proportional dose adjustment rules as proposed by Luzius Dettli, either the dose (D) should be reduced or the interval (Tau) extended (Figure 2). When the dose is reduced (Dettli 1) the peak levels are lower than in normal conditions but the trough levels are higher. When the administration interval is extended (Dettli 2) the peak and the trough concentrations are kept constant but the dosing frequency will decrease.

$$\frac{D}{Tau} = \left(\frac{D}{Tau}\right)_{norm} \cdot \frac{T_{1/2norm}}{T_{1/2fail}}$$

The dosing alternative proposed by Calvin Kunin states: The loading dose is the normal dose ($D_{start} = D_{norm}$) and the maintenance dose is one half of the loading dose where the administration interval corresponds to one half-life[23]. The Kunin rule leads to normal peak levels but higher troughs, a larger area AUC and more frequent peaks than those obtained with the Dettli rule 2.

$$\frac{D}{Tau} = \frac{(1/2) \cdot D_{start}}{T_{1/2}} = \frac{(1/2) \cdot D_{norm}}{T_{1/2}}$$

The Kunin rule can be illustrated with the example of ampicillin. In kidney failure, the ampicillin dose is decreased from 2000 mg every 8 h to 1000 mg every 12 h, since the half-life increases from 1.0 to 13 h (Table 1). For a GFR of 30 mL/min, the ampicillin half-life can be estimated at 3.8 h, giving reason to extend the administration interval from 8 to 12 h but to not change the 2000 mg dose since the half-life is shorter than the administration interval.

A general dosing rule that combines the Kunin rule with the Dettli rule 2 has been mentioned by Luzius Dettli: the eliminated fraction rule (Dettli 3). With the Dettli rule 3, the administration interval is selected according to the target trough concentration while the peak is kept constant (Figure 3).

$$D = D_{norm} \cdot \frac{1 - \exp\left(-0.693 \cdot \frac{Tau}{T_{1/2}}\right)}{1 - \exp\left(-0.693 \cdot \frac{Tau}{T_{1/2}}\right)_{norm}}$$

$$= D_{start} \cdot \left[1 - \exp\left(-0.693 \cdot \frac{Tau}{T_{1/2}}\right)\right]$$

$$= D_{start} \cdot \left[1 - \left(\frac{C_{trough}}{C_{peak}}\right)_{target}\right]$$

$$Tau = \frac{T_{1/2}}{0.693} \cdot \ln\left(\frac{C_{peak}}{C_{trough}}\right)_{target}$$

For the condition where peak as well as trough concentrations are constant and maintained as in the normal situation, the Dettli rule 3 corresponds to the Dettli rule 2 with a proportional extension of the administration interval. For the condition where the peak is constant but the trough should be no less than one half of the peak, the Dettli 3 rule corresponds to the Kunin rule.

Which rule should be applied cannot be decided by pharmacokinetic principles alone, but pharmacodynamic principles must be considered too. In addition, whenever possible, therapeutic drug monitoring should be utilized. In times where tandem mass spectrometry LC-MS/MS is possible, nearly every drug could be measured.

Therapeutic drug monitoring

Amikacin, gentamicin, tobramycin, teicoplanin and vancomycin, but recently also colistin, piperacillin, meropenem and linezolid are anti-infective drugs that routinely can be measured. When drug levels are measured for optimizing antimicrobial therapy, two important peculiarities must be observed. If impaired kidney function impacts pharmacokinetics, higher trough concentrations must be accepted to obtain efficient peak concentrations - this can be seen when the Dettli rule 1 or the Kunin rule are applied for dose adjustment (Figures 2 and 3). This was demonstrated by the use of aminoglycosides in HD patients where only troughs of at least 3 ng/mL are associated with peaks above 7 ng/mL and both peaks and troughs were significantly higher in those patients surviving than in those without anti-infective success[24,25].

In line with these statements, the target trough concentration for vancomycin has consistently been increased in the last 25 years. The area under the curve should be > 400 h x mg/L (= 24 h x Css; Css > 17 mg/L) to obtain an antimicrobial response with vancomycin[26]. The new targets are troughs of 15 ng/mL needed to guarantee peaks of 30 to 40 ng/mL[27]. The further increase in vancomycin dose and higher trough concentrations, however, might be associated with an increased risk of nephrotoxicity[28].

Counterintuitively, plasma binding does not have much impact on drug dosing since the absolute free drug concentration value (C_{free}) is unchanged when bound concentrations change[29].

$$C_{free} = C - C_{bound} = (C - \Delta C_{bound}) - (C_{bound} - \Delta C_{bound}) = const$$

If the binding decreases, only the total (C_{tot}) and the bound (C_{bound}) concentrations and not the free (C_{free}) concentration will decrease. Since the effect is supposed to depend on free concentrations, lower total concentrations do not need a change in dosage. However, plasma binding does have an effect on drug monitoring as far as total concentrations are measured ($C_{tot} = C_{initial} - \Delta C_{bound}$) and lower than normal concentrations must be the target when binding is less. This mainly applies to antibiotics with high plasma binding such as teicoplanin and ceftriaxone. And again, the decision as to which concentration should be the target can be made most rationally by considering pharmacodynamic criteria too.

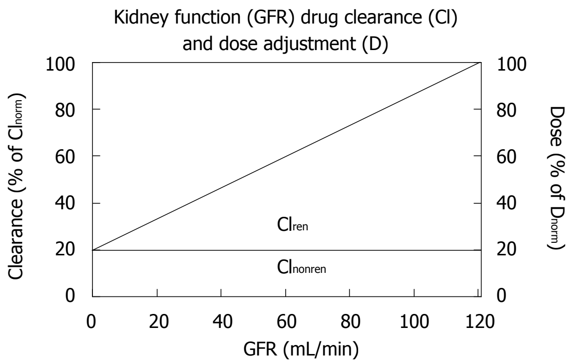

Figure 1 Linear correlation between drug clearance and the glomerular filtration rate as a measure of kidney function[20]. The dose can be adjusted in proportion to the reduced drug clearance, where $Cl = Cl_{ren} + Cl_{nonren}$. GFR: Glomerular filtration rate.

Pharmacodynamics

Pharmacokinetics is a necessary requirement for drug dose adjustment, but only the combined use of pharmacokinetics and pharmacodynamics is the sufficient condition for drug dose adjustment. Although some drug action might follow the dynamics of an irreversible effect, the most general concept of pharmacodynamics is based on the sigmoid Hill equation describing reversible effects. Even after mechanistic analysis of bacterial growth and killing dynamics, the Hill equation applies also to modeling the antimicrobial effect[30,31]. The actual effect (E) is a function of the maximum effect and of the concentration producing the half-maximum effect (CE_{50}). The Hill coefficient (H) gives a measure of the sigmoidicity of the effect concentration correlation.

$$E = \frac{E_{max}}{1 + \left(\frac{CE_{50}}{C}\right)^H}$$

From the above equation, the threshold concentration (CE_{05}) and the ceiling concentration (CE_{95}) can be derived[32]. The threshold concentration produces only 5% of the maximum effect and the ceiling concentration produces 95% of the maximum effect. The higher the Hill coefficient, the higher the threshold concentration is,

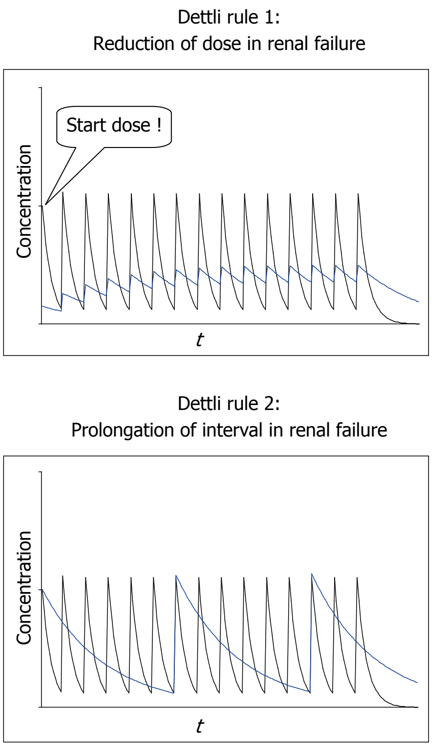

Figure 2 Dettli rules 1 and 2 for drug dose adjustment in kidney dysfunction. Dettli rule 1 leads to higher trough concentrations but lower peaks. To obtain an immediate antimicrobial effect, a loading dose must be given. With Dettli rules 1 and 2, the area under the curve AUC remains constant.

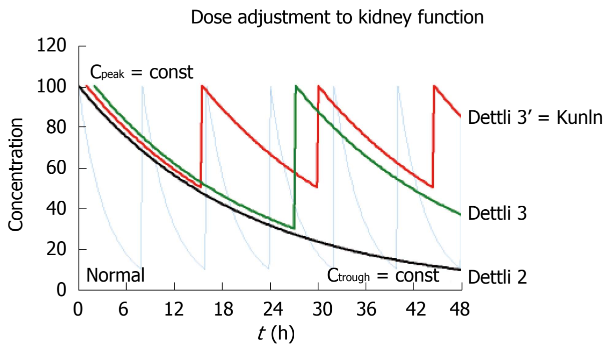

Figure 3 It is most practical to keep the peak concentration constant when the drug dose is adjusted to impaired kidney function[9]. With the eliminated fraction rule (Dettli 3), any dose and any interval can be estimated and selected. The Kunin rule is a special case of the Dettli rule 3 for the condition C_{trough} = 1/2 C_{peak}. With the Kunin rule and the Dettli rule 3, the area AUC is higher than under conditions with normal kidney function.

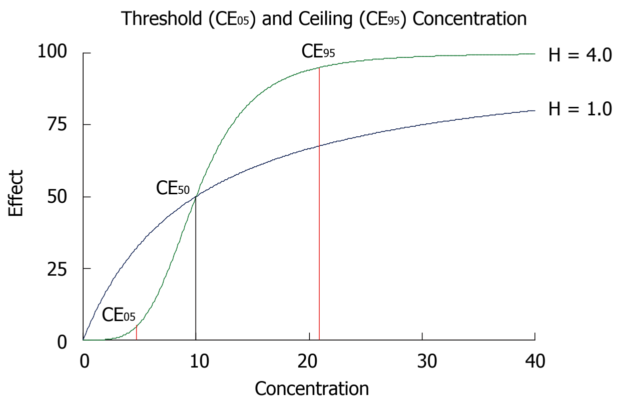

Figure 4 Pharmacodynamics. The threshold concentration CE_{05} produces 5% and the ceiling concentration CE_{95} produces 95% of the maximum effect. With a Hill coefficient of H = 1.0, the concentration is CE_{05} = 0.5 units and the CE_{95} = 190 units whereas for a higher Hill coefficient of H = 4.0, the threshold is high with CE_{05} = 6.0 units but the ceiling is low with CE_{95} = 21 units.

but the lower the ceiling concentration and the narrower the range of lower and upper target concentrations are (Figure 4).

$$CE_{05} = CE_{50} \cdot 19^{-1/H}$$

$$CE_{95} = CE_{50} \cdot 19^{1/H}$$

The ceiling concentration can be considered to be the upper limit of the target peak levels ($C_{peak} < CE_{95}$), whereas the threshold concentration marks the lower limit of effective trough levels ($C_{trough} > CE_{05}$). The distance between the ceiling and the threshold concentrations depends on H, not on CE_{50}, and the ceiling-to-threshold time $t_{ceiling\text{-}threshold}$ can be measured by multiples of the respective elimination half-life. For a drug with a short half-life and a high Hill coefficient, the therapeutic range of target concentrations can be very narrow (Figure 4).

$$CE_{05} = CE_{95} \cdot \exp\left(-\frac{\ln(2)}{T_{1/2}} \cdot t\right)$$

$$t_{ceiling\text{-}threshold} = T_{1/2} \cdot \frac{2}{H} \cdot \frac{\ln(19)}{\ln(2)} = T_{1/2} \cdot \frac{8.5}{H}$$

This conclusion might be illustrated with the beta lactam antibiotic ceftazidime where the half-life is 2.1 h and short in patients with normal kidney function (Table 1) but the Hill coefficient is 3.7 and high[33]. These values yield a short peak to trough or ceiling-to-threshold time $t_{ceiling\text{-}threshold}$ = 5 h, indicating that ceftazidime should be given at least every 6 h to maximize efficacy. In contrast, for gentamicin, the half-life is also 2 h (Table 1), but the Hill coefficient is 1.3 and low[33]. Thus, the estimated peak-to-trough time $t_{ceiling\text{-}threshold}$ is longer than 13 h: Here the administration interval could be extended to 12 h or more (Tau = $t_{ceiling\text{-}threshold}$).

The clinical progress in anti-infective dosing that has had the greatest impact has probably been achieved with the differentiation of drugs with time-dependent from drugs with concentration-dependent action[34,35]. Specific examples are the penicillins, cephalosporins, vancomycin, teicoplanin, the penems and the antiviral drugs with a time-dependent effect whereas gentamicin, amikacin, daptomycin, colistin, ciprofloxacin or levofloxacin possess a concentration-dependent activity.

It has been shown that anti-infective drugs with a time-dependent effect have a significantly higher Hill coefficient than those with concentration-dependent action[33]. This difference translates into practical consequences for the threshold and the ceiling concentration. A high Hill coefficient is associated with a relatively low ceiling concentration but simultaneously with a high threshold concentration (Figure 4). Thus, the time interval should be short between dosing of time-dependent

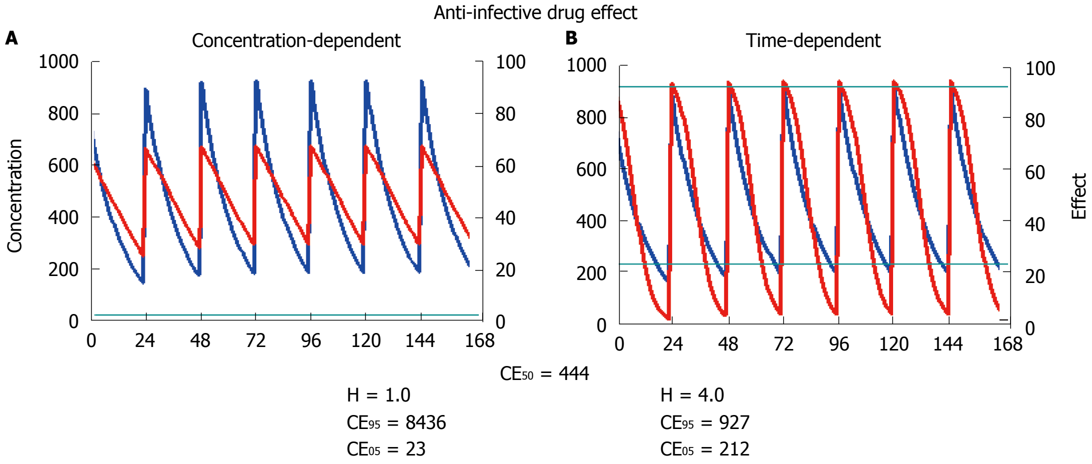

Figure 5 Pharmacodynamics of anti-infective drugs. The pharmacokinetics and the concentration curves are equal in both diagrams. Also the concentration producing the half-maximum effect is the same but the Hill coefficient is different. A: Concentration-dependent effect: With a Hill coefficient of H = 1.0, the calculated peak effect is only 60% and far from the ceiling effect CE_{95}. Thus, the concentration-dependent effect could be strengthened by increasing the dose; B: Time-dependent effect: With a Hill coefficient of H = 4.0, the calculated trough effect falls below the threshold concentration CE_{05} at the second part of the administration interval. Thus, the time-dependent effect could be strengthened by dosing more frequently.

anti-infective drugs and it makes no sense to increase the dose above the ceiling concentration. In contrast, a low Hill coefficient is associated with a high ceiling concentration and a low threshold concentration. Thus, it might increase the effect of concentration-dependent anti-infective drugs to give a single high bolus dose but it is not so critical to extend the administration interval - as proposed for aminoglycosides[36]. On a practical level, it might prove optimal to administer anti-infective drugs with time-dependent action more frequently, or even as a continuous infusion[37,38]. By contrast, anti-infective drugs with concentration-dependent action should be given with a bolus and a high maintenance dose to increase efficacy (Figure 5).

The usual measures of the antimicrobial effect such as the time over minimal inhibitory concentration MIC, or the AUC over MIC, or the peak over MIC can be unified by the following concept: A close correlation of the MIC and the concentration producing the half-maximum effect can be predicted. However, it has been shown[33] that for concentration-dependent antimicrobial action, the minimal inhibitory concentration could fall considerably below the concentration producing the half-maximum effect (MIC << CE_{50}). Consequently, it might be more reasonable to compare the bacteriological MIC with the pharmacodynamic parameter of a threshold concentration. Frequently the concentration target is stated as high as 4 times above the MIC. If this target corresponds to the CE_{50}, this translates into an average sized Hill coefficient of H = 2.1 since the following condition might hold true.

$$C_{threshold} = MIC = CE_{05} = CE_{50} \cdot 19^{-1/H}$$

In agreement with this equation, the Hill coefficient of meropenem is reported at H = 3.1 for the MIC of 1.0 mg/L and a CE_{50} at 2.6 mg/L[33].

Potency is also a significant measure of microbiology. The potency is inversely proportional to the concentration CE_{50} producing the half maximum effect. Therefore, resistance of the strain is just another word for a change in the CE_{50} and thus for reduced potency of the drug.

$$potency = 1/CE_{50}$$

To overcome resistance, a higher dose might be necessary since a high concentration CE_{50} is required to produce the half-maximum effect. This concept allows a distinction to be made between relative resistance and absolute drug resistance. A pathogen with relative resistance can be made sensitive by increasing the dose[39-41]. Thus, it has been recommended to treat severe infections with resistant strains by increasing the standard meropenem dose to 3 x 2000 mg per day[42,43] or the daptomycin dose to > 8 mg/kg per day[44] with careful monitoring of side effects.

From the concept of potency and the interpretation of the Hill coefficient, it can be considered plausible that the time-dependent action and the concentration-dependent action are only the extreme positions of a continuum. Every drug can be considered both concentration-dependent and time-dependent - more or less, either the one or the other[31]. The antimicrobial drug effect needs the presence of leukocytes, and less bacterial killing is reported in neutropenia[31]. Therefore, these patients need a 1.5 to 2 times higher than usual dose of anti-infective drugs[45]. In addition, the increasing rate of drug resistance in febrile neutropenia also strongly supports the concept of high dosing[31,46].

Dose adjustment

Anticancer drugs and anti-infective drugs should be used differently. The adjustment of anticancer drugs must not only be based on the kidney function but also on the physical condition of a patient. Tumor patients are older and anticancer drugs have a considerable potential for toxicity. Therefore, anticancer chemotherapy must be adjusted to both kidney function and to the general medical condition (in cases with Karnofsky index < 40% or ECOG > 2 performance status). In contrast to

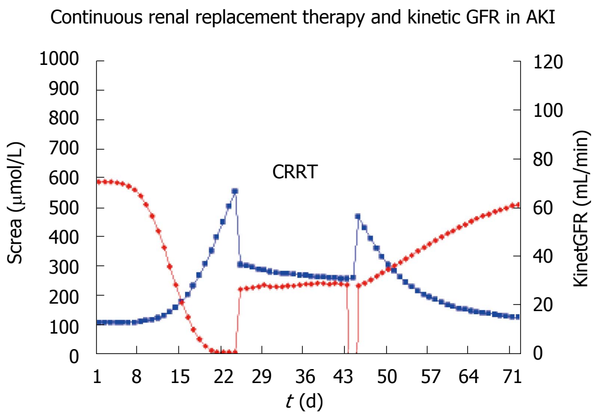

Figure 6 Serum creatinine (Screa) and estimated kinetic glomerular filtration rate in acute kidney injury. The kinetic GFR can also be estimated during continuous renal replacement therapy continuous hemofiltration (CRRT)[14]. GFR: Glomerular filtration rate; AKI: Acute kidney injury.

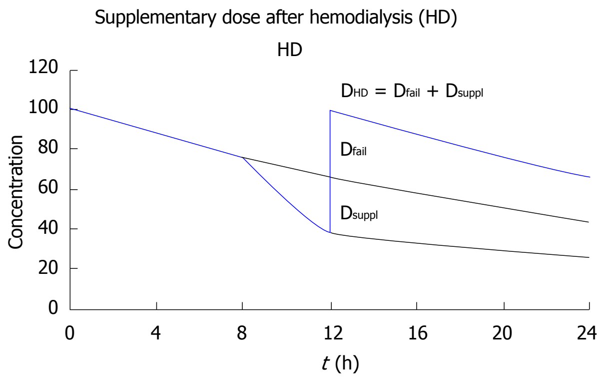

Figure 7 The dose after dialysis (D_{HD}) replaces both the dose adjusted for kidney failure (D_{fail}), and the supplementary dose (D_{suppl}) that compensates for the fraction (FR) removed during hemodialysis (HD).

anticancer drugs, however, the anti-infective therapy should be adjusted to kidney function alone, but a compromised or even poor general condition should not result in a reduced dose or selection of less active anti-infective therapy. An immediate and sufficiently high antimicrobial therapy is needed in the most vulnerable, that is, in elderly and immunocompromised cancer patients. Where the risk is low, oral dosing of anti-infective drugs is sufficient in febrile neutropenia[47]. In most cases, however, intravenous dosing might be preferable with sequential oral dosing only in responders.

Ehrlich[48] stated the principle of anti-infective therapy: "frapper vite et frapper fort" meaning "hit fast, hit hard".

For anti-infective drug therapy, the immediate and high loading dose is very important[49,50]. According to the "Tarragona strategy" the antibiotic regimen should be started fast and with a loading dose, whereas the dose adjustment follows the course and clinical condition[51]. It can be a deleterious mistake to adjust the dose to the impaired kidney function but to give no loading dose (Figure 2). The loading dose is usually the normal standard dose. However, many patients in the intensive care unit are over-hydrated and the distribution volume is much larger than under normal conditions[34]. The loading dose could well be adjusted to such volume changes by applying the BSA.

$$D_{start} = D_{norm} \cdot \frac{Vd}{Vd_{norm}} = D_{norm} \cdot \frac{Weight + V_{water}}{Weight_{norm}} = D_{norm} \cdot \frac{BSA}{1.73\ m^2}$$

Thus, the required loading dose can be higher than the normal standard dose. In patients with sepsis, the gentamicin distribution volume was 0.35 L/kg *vs* 0.29 L/kg and significantly larger compared to intensive care patients without sepsis[52]. The need for a higher dose to initiate antimicrobial therapy can be stated as the rule when the immediate and high blood level is the target as with anti-infective therapy. The immediate start of treatment and an initially high concentration are also needed to avoid selection of resistant strains. Therefore, the antimicrobial treatment starts with a normal or even higher loading dose in the intensive care patients. Afterwards, the adjustment with a reduced maintenance dose is usually not needed before day 2 or 3 of anti-infective treatment[53].

A special problem occurs in the case of aminoglycosides: It is now standard practice to administer one single bolus dose per day instead of three divided doses[36]. Such a single high bolus dose will be associated with a 20-fold increase in the AUC if renal failure is present and the half-life increases from 2 to 40 h. For aminoglycosides, we propose administering only 50% of the standard high bolus loading dose to avoid excessive exposure in kidney failure or dialysis patients (Table 1). Following the loading dose, the maintenance dose can be estimated by one of the three Dettli rules, or the Kunin rule.

In addition to the case of over-hydration with an increase in distribution volume, the so-called augmented renal clearance has been brought into debate[54]. Augmented renal clearance is estimated from serum creatinine or endogenous creatinine clearance. If a patient is overhydrated, however, the serum creatinine is diluted, making creatinine clearance and creatinine-based GFR estimates falsely high. Since the clearance can be seen as the arithmetic product of elimination rate constant and distribution volume, the higher creatinine clearance in the patients with the systemic inflammatory response syndrome and sepsis could be explained by two mechanisms, augmented renal elimination and over-hydration. The consequences are different: augmented renal elimination needs a higher maintenance dose but over-hydration requires both an increase in the loading dose and a higher maintenance dose (= weight-based dosing as in pediatrics).

Renal replacement therapy

In the intensive care unit (ICU), three modalities are used as renal replacement therapy: Continuous hemofiltration (CRRT), sustained low efficiency daily dialysis (SLEDD) and intermittent HD. The hemofiltration is applied with variable modifications either of the surface area, of the filter membrane, with predilution or post-dilution replacement fluid, and variable ultrafiltration rates that are used along with the corresponding flow rate of the substitution volume. Therefore, a global measure of the effect of hemofiltration on drug elimination will be very useful and the total creatinine clearance or the other creatinine-based measures of the GFR have been proposed for this purpose[9,55,56]. The recently introduced kinetic GFR applies also to patients with CRRT[14], and thus has clear advantages in the intensive care unit where the medical conditions can change rapidly (Figure 6).

$totalCL_{crea} = Filtration_{kedney} + Filtration_{CRRT}$

$totalCL_{crea} = eGFR = MDRD_{GFR} = CKD - EPI_{GFR} = C \text{ and } G_{GFR}$

$totalCL_{crea} = kinetGFR$

There is a trend to underestimate drug elimination by CRRT and consequently under-dose antimicrobials in the ICU[57]. By using the total creatinine clearance, the creatinine-based GFR estimates or the kinetic GFR, the dose can be adjusted according to the rules of Dettli and Kunin also for patients on CRRT. As a rule and to avoid under-dosage, the normal standard dosage should be given and not be reduced if the total creatinine clearance is above 60 mL/min.

A combination of continuous and intermittent renal replacement is the SLEDD. The frequency of under-dosage is estimated with a median value of 70% whereas the risk of over-dosage was only 5% while on SLEDD[6,58]. If this kind of treatment is applied, the daily dose at least corresponds to the post HD dose (see below) but recommendations vary widely.

$D_{SLEDD} = D_{HD} \approx D_{start}$

More complex is the drug dosing when intermittent HD is performed (Figure 7). Off dialysis, the dose must be adjusted to the failing kidney function. For intermittent HD, we argue that it is better to give the dose not at the beginning but at the end or immediately after HD. With a pre-dialysis dose, no anti-infective effect will be maintained in the interval off dialysis[59].

If the drug is given after dialysis, the post-dialysis dose should replace first the amount eliminated during the interval off dialysis, that is, the dose for failing kidney function (D_{fail}). In addition to that, the effect of HD should be compensated by a supplementary dose (D_{suppl}) replacing the fraction eliminated on dialysis (FR).

$D_{HD} = D_{fail} + D_{suppl}$

$D_{suppl} = FR \cdot (D_{start} - D_{fail})$

$FR = 1 - \exp[(-0.693/T_{1/2on}) \cdot t_{on}]$

Thus, the dose after HD is higher than the adjusted maintenance dose[9]. In many cases the dose after HD is another loading dose (D_{start}). The post-dialysis dose (D_{HD}) can again be illustrated with the example of ampicillin: The fraction eliminated by dialysis is implicitly stated in NEPharm (40%) and the dose after dialysis is 2000 mg corresponding to the size of the normal loading dose (Table 1).

$D_{HD} \approx D_{start}$

In contrast to the usual post-dialysis dosing, it might be a good option to perform HD after drug administration for removal of high-dose anticancer therapy administered before dialysis. In analogy, the dosing immediately before dialysis has been also proposed for aminoglycosides[60]. With a pre-dialysis regimen, however, aminoglycosides must be given at a higher dose (gentamicin up to 400 mg) and HD should be performed on a daily basis in order to not miss the antimicrobial effect in the interval off dialysis.

CONCLUSION

The prevalence of CKD and incidence of AKI are high in patients with malignancies. This generally makes dose adjustment necessary, usually ending in a lower dose than normal. Since 1978, we have documented pharmacokinetic parameters in the NEPharm database from extracted PubMed citations[61-63]. With the parameters recorded in NEPharm and based on the above pharmacokinetic/pharmacodynamic considerations, we have made explicit dose proposals. These recommendations are used in our institution and subjected to continuous updates (Table 1).

Anti-infective therapy should start immediately without any delay and with a high dose. Dose adjustment follows on day 2 or later in the course of treatment[53]. A loading dose that takes into account the real volume especially in volume-expanded patients should be given. When in doubt, we propose that the peak level should be the target and the standard dose should be given with an extended administration interval when kidney function is impaired[9].

The anti-infective therapy should be optimized by therapeutic drug monitoring whenever possible (gentamicin, tobramycin, amikacin, vancomycin, teicoplanin, colistin, piperacillin, meropenem, linezolid). However, the adequate practical consequences should be drawn from the measured concentrations. In patients with impaired kidney function, higher trough concentrations result from the dose adjustment according to Dettli 1, Dettli 3 or Kunin. Only the Dettli rule 2 is associated with the same peak and trough concentrations as under normal conditions. On the other hand, the plasma binding of many drugs can decrease in kidney dysfunction. In this case, lower trough concentrations are acceptable (ceftriaxone, teicoplanin) since the absolute free concentration does not change when the bound fraction decreases but free concentrations produce the effect.

The modern distinction between time-dependent and concentration-dependent effects can be parameterized by the Hill coefficient. A high Hill coefficient (> 2.1) indicates time-dependent drug action, whereas a low Hill coefficient (< 2.1) indicates concentration-dependent action. Based on the Hill equation, the threshold concentration can be distinguished from the ceiling concentration. A high Hill coefficient determines that the ceiling concentration is low but the threshold concentration is relatively high (Figure 4). In contrast, a low Hill coefficient determines that the ceiling concentration is relatively high but the threshold concentration is low. We suggest that the minimal inhibitory concentration from microbiology be correlated to the threshold concentration. The target concentration should not be less than the threshold concentration for time-dependent effects, but the target concentration could be as high as the ceiling concentration for concentration-dependent effects.

To decide between the pharmacokinetic dosing alternatives (Dettli 1-3), pharmacodynamic considerations can give an answer to whether the dose should be reduced or the interval extended in kidney dysfunction: (1) For time-dependent anti-infective action, more frequent dosing is more effective than maintaining the single high dose[35]: The target trough levels should be kept above the threshold concentration (Figure 5). The beta lactam antibiotics oxacillin or piperacillin are considered to exhibit a time-dependent action. Accordingly, it has been shown that continuous infusion produces a better antimicrobial response than intermittent dosing of the respective daily dose[37,38]; and (2) For concentration-dependent anti-infective action, however, the extension of the interval is less disadvantageous than reducing the single dose (Figure 5). The target peak levels should be close to the ceiling concentration and kept as high as possible[35]. The quinolone ciprofloxacin exhibits concentration-dependent action. Here, the high bolus dosing produced a more rapid bactericidal effect than the more frequent application of a lower dose[33,64]. Also for aminoglycosides, a high peak concentration is superior to more frequent dosing to induce bacterial killing[36,65].

For drugs with a high Hill coefficient, the area under the effect time curve may fall disproportionally less and result insufficient with a lower dose[61]. Therefore, we discourage proportional dose reduction, especially Dettli 1, if the Hill coefficient is unknown. The risk of selecting resistant strains is also less when the initial dose is high[31].

The time above MIC reflects effect duration. A pharmacodynamic measure for the duration of drug effect, the time of effect duration (TED), can be derived from the elimination half-life[18]. The intuitively most evident effect duration time is the effect bisection time (TED_{50}) that is correlated to the elimination half-life ($T_{1/2}$), the peak concentration (C_{peak}) and the Hill coefficient (H) along with the concentration (CE_{50}) producing the half-maximum effect[18].

$$TED_{50} = T_{1/2} \cdot \left(\frac{1.44}{H}\right) \cdot \ln\left[2 + \left(\frac{C_{peak}}{CE_{50}}\right)^{H}\right]$$

The longer the half-life and the higher the peak concentration - but the less the CE_{50} - the longer lasting the effect is. The half-life is 1.0 h (Table 1) and the Hill coefficient is stated at H = 3.1 for meropenem[33]. If the MIC of 6 mg/l[44] is equated to the threshold concentration (CE_{05} = MIC), the CE_{50} can be estimated at 37 mg/L. With a dose of 500 mg every 8 h and a peak concentration of 50 mg/L[44], the effect bisection time will be estimated at TED_{50} = 0.71 h. Doubling the dose, however, will more than double the effect bisection time TED_{50} to 1.5 h, thus extending the drug action while the pharmacokinetic half-life of 1.0 h is the same. However, the standard dose administered more frequently would not increase the effect bisection time.

The dose in patients with continuous renal replacement therapy can be derived from the creatinine-based GFR estimates or in case of changing kidney function, from the "kinetic GFR" (Figure 6). If this GFR estimate is above 60 mL/min, no dose adjustment is required. For intermittent HD a supplementary dose should be given after dialysis (Figure 7). The supplementary dose adds with the dose adjusted to renal failure to the post-HD dose that can be as high as the loading dose. This practice might be prudent also in cases where the drug fraction eliminated during HD is not known.

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P- Reviewer: Bellomo G, Friedman EA, Mahmoud KM, Yong D
S- Editor: Tian YL **L- Editor**: A **E- Editor**: Yan JL