Supplemental Material

Supplement 1: Pharmacodynamics of Reversible Effects

Pharmacokinetics describe the correlation between dose and concentration whereas pharmacodynamics describe the correlation between concentration and effect (Figure 1). Reversible and receptor-mediated effects can be derived from the law of mass action and be quantitated by the Emax model [1]. The drug is reversibly bound to a receptor where the free receptor (R) must be distinguished from the receptor-ligand complex (RC) that corresponds to the receptor binding sites occupied by the ligand drug. This receptor-ligand complex induces the effect (RC => E). The unbound drug is measured as the concentration in blood, plasma or serum (C). The constant K represents the dissociation force; the lower the K value, the stronger is the association and the higher is the affinity of the receptor-ligand complex: thus, the stronger is the effect.

$$C + R \overset{K}{\Leftrightarrow} RC$$

$$RC = E$$

$$C \cdot R = K \cdot E$$

The receptor will be saturated as indicated by the maximum effect (RCmax = Emax). The Emax corresponds to the number of target receptor or enzyme molecules.

$$R + E = RC_{max} = E_{max}$$

$$R = E_{max} - E$$

$$C \cdot (E_{max} - E) = K \cdot E$$

$$E = \frac{E_{max} \cdot C}{K + C}$$

For the condition where the concentration is equal to the dissociation constant (C = K) the effect is half maximal (E = Emax / 2). Consequently, for C = K holds that E = 0.5 x Emax, indicating that the dissociation constant can be expressed in terms of a special concentration (CE50 = K). This concentration producing 50 % of Emax can be stated as the CE50 in vivo but it corresponds to the frequently cited EC50 or IC50 in vitro.

$$E = \frac{E_{max} \cdot C}{CE_{50} + C}$$

The saturable Emax model can be applied to sigmoid dynamics by introducing the Hill coefficient (H).

$$E = \frac{E_{max} \cdot C^H}{CE_{50}{}^H + C^H}$$

The following hyperbolic form makes the Hill equation more practical and comprehensible to handle.

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

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

Thus, important applications can be derived: With the above equation two arbitrary but clinically plausible limits are given (Figure S1): The threshold concentration (CE05) defines the condition where the effect is marginal and only 5 % of Emax (E05 = 0.05 x Emax). Such concentration thresholds are known from environmental medicine with the limits of toxicity for cadmium, lead, mercury and other pollutes. In contrast, the ceiling concentration corresponds to the concentration (CE95) where the effect is near to the maximum at 95 % of Emax (E95 = 0.95 x Emax). The values of the threshold and the ceiling concentration depend on the Hill coefficient [42].

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

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

Darbepoetin

For darbepoetin, the Hill coefficient was reported high with H = 3.0 and the CE50 as 0.41 ng/mL [43]. Accordingly, the effect on erythropoiesis should be regarded as time-dependent. Therefore the application of an intravenous bolus dosage is less efficient than the subcutaneous administration with a long-lasting effect where the threshold is high with CE05 = 0.15 ng/mL, which is 1/3 of CE50. In agreement with the time-dependent effect, the

splitting of the darbepoetin dose to administer smaller dosages once per week or even more often is more dose-efficient than single applications every 2 weeks [45].

The CE50 is symmetric to the threshold and to the ceiling concentration; it can be estimated as the geometric mean from both values.

$$CE_{50} = \sqrt{CE_{06} \cdot CE_{95}}$$

The distance between the threshold and the ceiling concentration depends on the Hill coefficient where (2 x ln(19) = 5.89). Accordingly, the Hill coefficient can be estimated from threshold and ceiling concentrations without knowing the CE50.

$$H = \frac{5.89}{ln\left(\frac{CE_{95}}{CE_{05}}\right)}$$

The distance between the ceiling and the threshold concentrations marks the limit for the maximal extension of the administration interval (Tau).

$$CE_{05} = CE_{95} \cdot exp\left(-0.693 \cdot \frac{t_{ceiling\ -threshold}}{T_{1/2}}\right)$$

$$t_{ceiling\ -threshold} = T_{1/2} \cdot \frac{8.5}{H}$$

$$Tau < T_{ceiling\ -threshold}$$

Tacrolimus

The time between the ceiling and the threshold concentration determines the maximum administration interval (Tau <Tceiling-threshold). The higher the Hill coefficient and the shorter the half-life, the shorter is the optimum administration interval.

$$T_{ceiling\ -threshold} = T_{1/2} \cdot \frac{8.5}{H}$$

For example the immunosuppressive effect of tacrolimus on NFAT activated T cells can be correlated to the observed peak and trough concentrations of tacrolimus [44]. The derived pharmacodynamic parameters are a Hill coefficient H at 1.5 and a CE50 at 6.7 ng/mL. The estimated ceiling to threshold time (T ceiling-threshold) is very long with 68 hours at a half-

life of 15 hours. As indicated by these parameters, the daily tacrolimus dose might be given as one single dose with a prolonged administration interval of 24 hours instead of the usual interval of 12 hours. This is even more true when the modified or extended release preparations are given to avoid high peaks.

If the Hill coefficient is less than zero (H < 0.0), the effect will decrease not increase with rising concentrations as can be seen with apixaban and rivaroxaban (Figure 2).

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

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

Elaborated pharmacokinetics can be transferred into pharmacodynamics [46]. The 2-compartment kinetics has been utilized to explain some counterintuitive phenomena in pharmacodynamics when the peripheral compartment is identified with the effect compartment. For an indirect effect, a delay between the peak concentration and the peak effect will be observed depending on the transfer rated constant (k1e). The high peak concentration in the central compartment (Co = A + B) precedes the cropped peak in the peripheral effect compartment.

$$C_{central\ \ comp} = A \cdot exp(-\alpha \cdot t) + B \cdot exp(-\beta \cdot t)$$

$$C_{effect\ \ comp} = k_{1e} \cdot \frac{A + B}{\alpha - \beta} \cdot [exp(-\beta \cdot t) - exp(-\alpha \cdot t)]$$

This, at first sight perplexing delay has been described by the so called hysteresis loop. In addition, the high peak in the central compartment does produce a much flattened curve in the peripheral compartment. In the post distributive phase, however, the curve in the peripheral effect compartment runs in parallel to the curve in the central compartment. Thus, the concentration in the central compartment CE50 that is determined at the half-maximum effect also corresponds to a definite concentration in the peripheral effect compartment be it higher or lower (CE50 central => CE50 peripheral).

Mycophenolate

In case of mycophenolate the peak concentration after mycophenolic acid is much higher than the peak concentration after mycophenolate mofetil (13 vs 6 µg/mL). However, the mycophenolate effect on IMPDH inhibition and the low Hill coefficient with H = 1.42 as well as the low CE50 with 5.5 µg/mL were not different when determined after mycophenolate mofetil or mycophenolic acid application [47]. This discrepancy between kinetics and dynamics might be explained by the delayed action in the intracellular effect compartment. The amplitude of the concentration fluctuation is smaller in the peripheral effect compartment than in the central plasma compartment, resulting in an equivalent intracellular effect of both preparations.

A measure for the effect duration has long been sought [1]. The time of effect duration (TED) can be derived from the time needed for any reversible and receptor-mediated effect to decrease to a definite fraction (fr = E2 / E1) of the initial effect [48].

$$TED_{fr} = T_{1/2} \cdot \frac{1.44}{H} \cdot ln\left[\frac{1}{fr} + \left(\frac{1}{fr} - 1\right) \cdot \left(\frac{C_1}{CE_{50}}\right)^H\right]$$

As a special derivative, the effect bisection time TED50 indicates the decline of the effect to one half (fr = 0.50). The effect bisection time is proportionate to the half-life (T1/2) but a complex function of the Hill coefficient (H), of the concentration at half-maximum effect (CE50) and of the peak concentration (Cpeak). The effect bisection time can be determined from published diagrams (Figure 2) and be used to numerically estimate missing pharmacodynamic parameters as demonstrated for apixaban and rivaroxaban (Figure S2).

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

The TED50 equation has some peculiarities: If the peak is very high (Cpeak>> CE50), the TED50 is longer than the half-life. Conversely, if the peak is low (Cpeak< CE50) and the Hill coefficient is low (H < 2.0), the TED50 runs in parallel to the half-life (TED50 = T1/2). If, however, the peak is low, the CE50 is high and the Hill coefficient is high (H > 2.0), the effect bisection time can even fall shorter than the half-life value (TED50 < T1/2).

Sitagliptin

For the oral antidiabetic sitagliptin the Hill coefficient is stated with H = 1.0 and the CE50 with 26 nmol/L, much less than peak levels of 750 nmol/L [48]. Thus, the effect at peak levels is 97 % of Emax, and the steady-state peak concentration is over-ceiling (Cpeak> CE95 = 494 nmol/L).

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

The 24 h administration interval of this DDP4 inhibitor corresponds to the time of 90 % effect duration (TED90). In kidney failure, the sitagliptin half-life will increase from 10 to 28 hours and the TED90 rises from 24 to 51 hours [48]. Theoretically, the dose reduction from normal 100 mg once daily to 50 mg every 48 hours would be more efficacious than the pharmacokinetic equivalent dose of 25 mg every 24 hours. However, this pharmacodynamic advice, admittedly, will be less practical than the recommended dose of 25 mg daily; but the recommended regimen is under-ceiling (Cpeak = 421 nmol/L < CE95).

Valganciclovir

There is no therapy without toxicity (Figure S3). As with all conventional antiviral drugs [6], the beneficial effect of valganciclovir must be classified as time-dependent (H > 2.0). But the noxious effect might be concentration-dependent and the misfortune could happen that no therapeutic effect but only adverse events will result from concentrations below the threshold (Figure S5). This might happen due to a reduced dose of antiviral drugs in kidney failure. A low dose valganciclovir could result in sub-therapeutic trough concentrations [49]. No cure and no prophylaxis will be achieved. Instead viral resistance will emerge.

Supplement 2: Pharmacodynamics of Irreversible Effects

An irreversible effect occurs, if the rise in concentrations will prevent the number of target cells from further growth. The irreversible effect can be modelled as rising drug concentrations above the growth of target cells (cancer, lymphocytes, bacteria).

$$\frac{dC}{dt} > \frac{dN}{dt}$$

The effect will be irreversible if the target cells no longer grow and their change will be zero (dN / dt = 0). The rise in the irreversible effect corresponds the rise in the concentrations.

$$\frac{dE}{dt} = \frac{dC}{dt}$$

The analogue view would apply also for a circuit brake with a sudden on-off phenomenon (dX / dt = 0).

Opioids

The opioids and mainly the immediate release formulations or intravenous preparations could be seen as examples for an irreversible effect. When injecting opioids or heroin, the rapid rise of concentrations in the brain induces a flush and highly euphoric experience associated with the potential for drug addiction [50]. The achievement of this shooting flush might be the reason for abusive intravenous opioid injection. Euphoria occurs mainly with rising concentrations just as presumed for an irreversible effect. The target is a cerebral switch mechanism. Slow release preparations reversibly target only the opioid receptors with no overshoot in analgesia and an allegedly lesser addiction potential.

Practically, the drug cannot be administered as an instant bolus but only as a continuous infusion over seconds, minutes or hours – or by the oral route, respectively. The irreversible effect follows as a function of the dose (D), the volume (Vd), the resulting concentration (C) and of the time of administration (T).

$$E = \int_{t=0}^{t=T} \frac{dC}{dt}$$

$$E = \int_{t=0}^{t=T} \left(\frac{D\ /\ T}{Vd} - Ke \cdot C \right) \cdot dt$$

The integrated solution for this function can be obtained from the internet (www.integralrechner.de).

$$E_t = \left(\frac{D\ /\ T}{Vd} - \frac{D\ /\ T}{Vd} \cdot [1 - exp(-Ke \cdot t)] \right) \cdot t$$

The irreversible effect will be the stronger, the longer the elimination half-life comes out (T1/2 = 0.693 / Ke) because less of the dose will be eliminated during the necessary time of infusion (t => T).

$$E = \frac{D}{Vd} \cdot exp\left(-0.693 \cdot \frac{T}{T_{1/2}} \right)$$

If the dose could be administered as an immediate bolus, the time of infusion is zero (T = 0) and the irreversible effect corresponds to the initial concentration (D/Vd = Cmax). The effect corresponds to more than 95 % of the effect at Cmax if the infusion time is short and less than 7.5 % of the half-life value (T < 0.075 x T1/2).

$$E = C_{max}$$

If kidney function is impaired, the dose must also be adjusted when targeting the same irreversible effect (E = const.).

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

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

To obtain the same irreversibel effect, however, a higher dose (Dfail) must be given than the usually recommended dose that would be reduced just in reverse proportion to the increase in half-life (or in proportion to decrease in clearance). If the infusion time (T) is extended in proportion to the half-life, the adjusted dose corresponds to the normal dose.

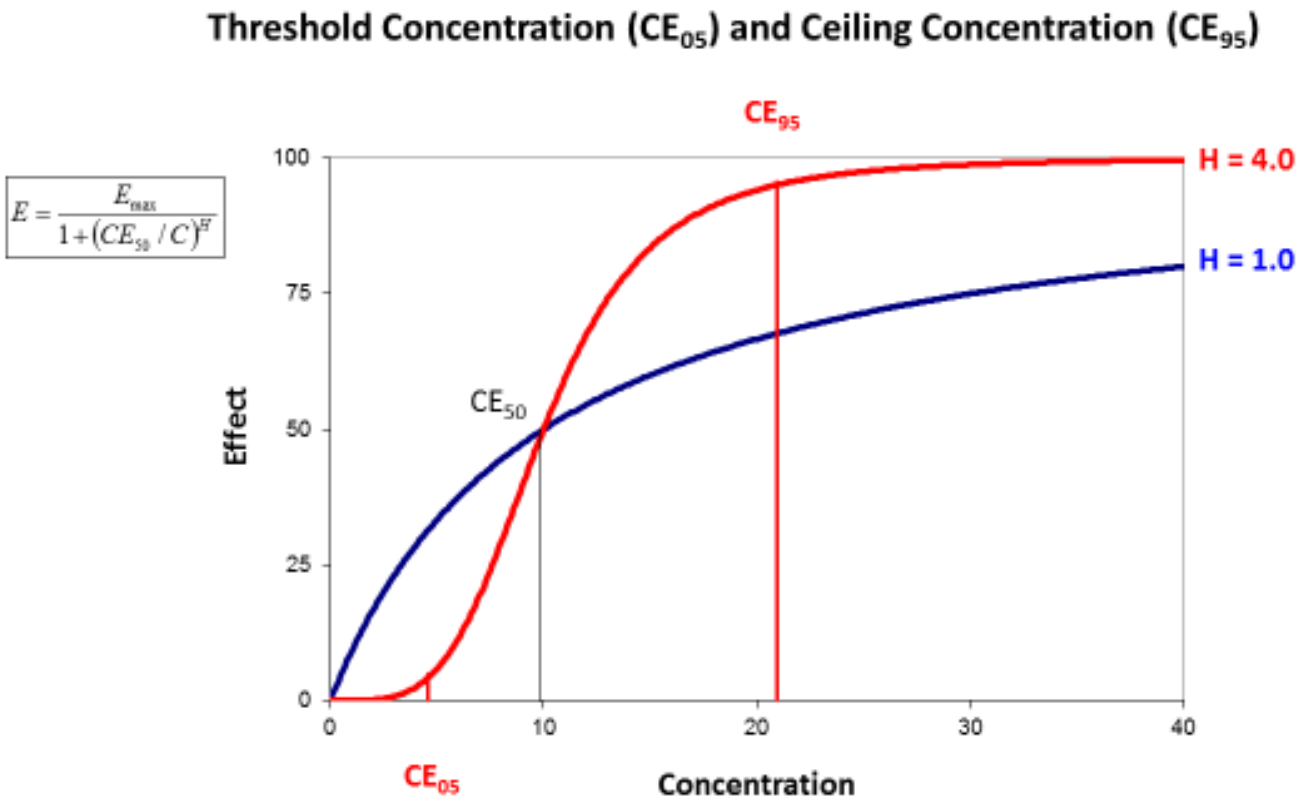

Fig. S1 For a high Hill coefficient of H = 4, the threshold concentration (CE05) comes close to one half of the CE50 concentration but the ceiling concentration (CE95) will already be reached at twice the CE50 value [42].

	Apixaban	Rivaroxaban		
T1/2	8	8	hours	[11]
Cmax	139	227	mcg/L	[11]
CE50	50	20	mcg/L	observed [12]
TED50	15	29	hours	observed [12]
Hill coeff H	**1.4**	**1.2**	hours	**estimated**
H = 0	TED50 = T1/2 * (1,44 / H) * ln(2 + (Cmax / CE50)^H)			
0,1	131	137		
0,15	89	95		
0,2	67	74		
0,25	55	62		
0,3	47	54		
0,35	41	48		
0,4	36	44		
0,45	33	41		
0,5	30	39		
0,55	28	37		
0,6	26	35		
0,65	24	34		
0,7	23	33		
0,75	22	32		
0,8	21	32		
0,85	20	31		
0,9	19	31		
0,95	19	30		
1	18	30		
1,05	17	30		
1,1	17	29		
1,15	17	29		
1,2	16	29		
1,25	16	29		
1,3	16	29		
1,35	15	29		
1,4	15	29		
1,45	15	28		
1,5	15	28		

Fig. S2 Numerical iteration to find a solution for the Hill coefficient (H) of apixaban and rivaroxaban. The values for T1/2 and Cmax are extracted from the cited reference [12]. The CE50 and TED50 values have been visually determined (Figure 2). These values can be set into the equation for the effect bisection time (TED50) to find a solution for the previously unknown Hill coefficient (H).

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

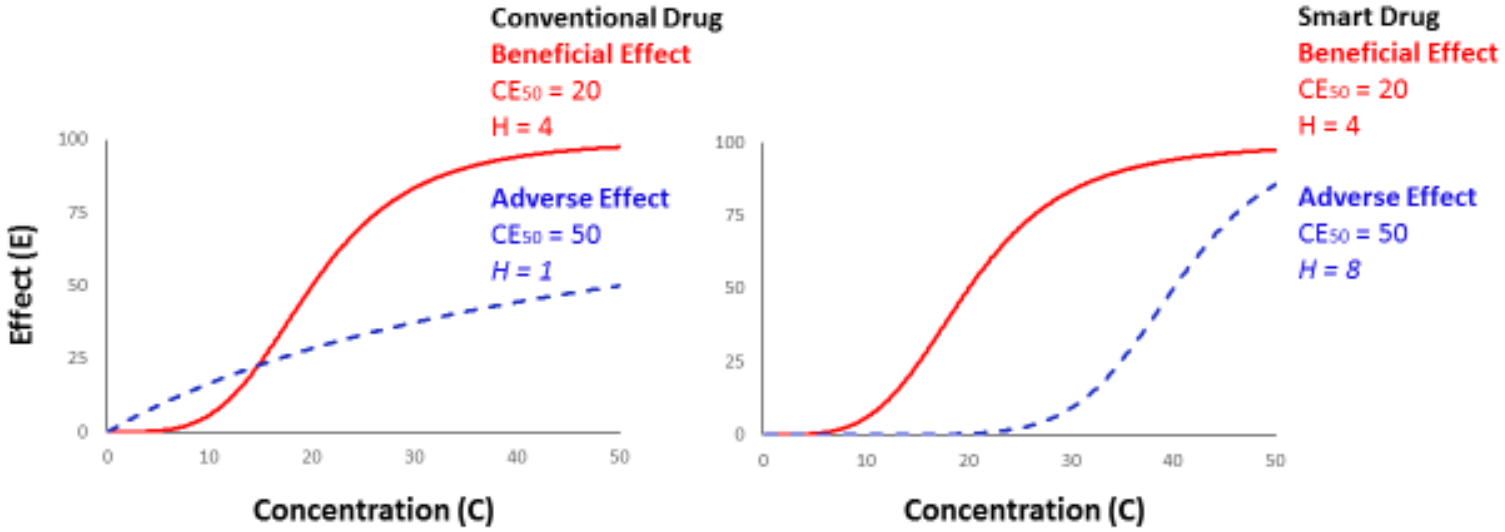

Fig. S3 Left: Conventional Drug with small Hill coefficient for adverse effects (H = 1). At low levels of 5 concentration units, already 10 % of the noxious effects can occur but without any beneficial effect. Right: Smart Drug with a wide therapeutic window. No adverse events will occur below 30 concentration units due to a high Hill coefficient for adverse events (H = 8).