

## Clinical Pharmacodynamics Principles of Drug Response and Alterations in Kidney Disease

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### Abstract

Pharmacokinetics and pharmacodynamics follow the logic of cause and consequence. Receptor-mediated and reversible effects can be distinguished from direct and irreversible effects. Reversible effects are capacity-limited and saturable whereas irreversible effects are limited only by the number of viable targets. In the case of receptor-mediated and reversible effects a threshold and a ceiling concentration can be defined. Antimicrobial drugs with concentration-dependent action are distinguished from drugs with time-dependent action. Concentration-dependent effects are associated with a high ceiling concentration and the target is the high peak. Time-dependent effects are associated with a high threshold concentration and the target is the high trough. During kidney dysfunction, alterations of drug response are usually attributed to pharmacokinetic but rarely to pharmacodynamic changes. Dose adjustment calculations, therefore, tacitly presume that pharmacodynamic parameters remain unchanged while only pharmacokinetic parameters are altered in kidney failure. Kidney dysfunction influences the pharmacokinetic parameters of at least 50% of all essential drugs. Clinicians usually consider pharmacokinetics when kidney disease is found, but pharmacodynamics is as important. Alterations of pharmacodynamic parameters are conceivable but only rarely reported in kidney failure. Sometimes surprising dosing adjustments are needed when pharmacodynamic concepts are brought into the decision process of which dose to choose. Pharmacokinetics and pharmacodynamics should both be considered when any dosing regimen is determined.

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### Background and Introduction

Similar to the fact that every patient behaves differently, individual drugs also behave in different ways compared with each other. However, in nature and thus in medicine, basic laws can be identified that apply not only to every drug but also to every patient. Pharmacokinetics and pharmacodynamics present such mathematic laws (Figure 1). Drug concentrations produce the drug effects. Pharmacokinetics are the cause and pharmacodynamics the consequence. Pharmacokinetics allow us to calculate the dose adjustment in kidney disease where sometimes dramatic alterations can be found in roughly half the drugs. Pharmacodynamics allow for a quantitative description of the individual drug response. Additionally, they aid in modeling activation, inhibition, and interaction at the target receptor side (Table 1).

Two different mechanisms can be distinguished in pharmacodynamics. The reversible effects, which are usually receptor-mediated and saturable, and the irreversible effects, which are direct and proportional to rising concentrations. The reversible effects are observed with both increasing and decreasing concentrations. The irreversible effects, however, can only be produced by increasing concentrations.

In this paper, we will describe how pharmacodynamic parameters can be extracted from published

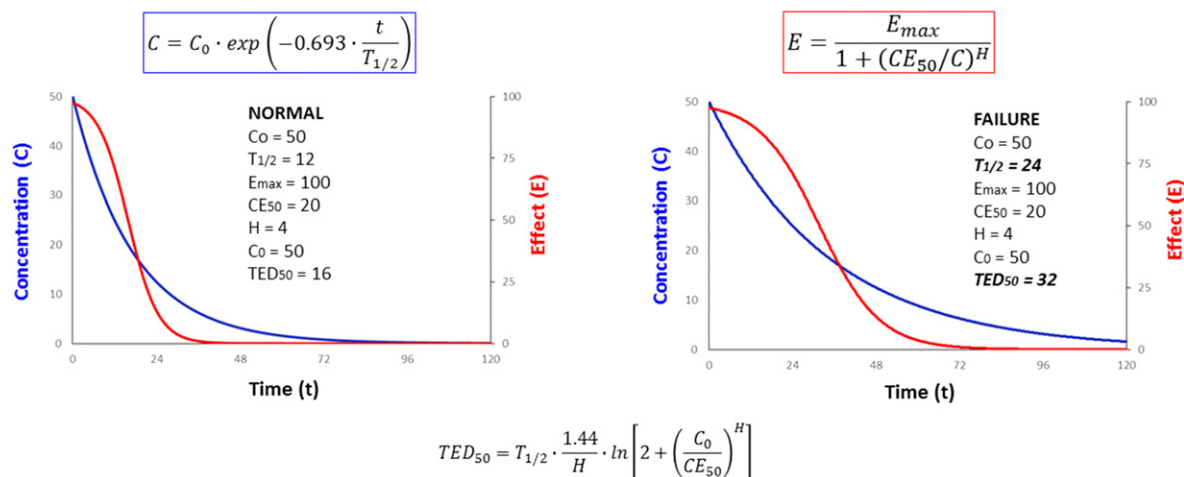
data and subsequently how these parameters can be used to modify drug dosage in the state of kidney failure. As illustrated by apixaban with a reversible effect, the effect duration will last longer and can be predicted exactly from pharmacodynamic parameters when elimination is impaired in kidney failure. As an example with an irreversible effect, we will discuss how to make pharmacodynamics instrumental for carboplatin dose adjustment to kidney dysfunction. Further drugs will be discussed in the Supplemental Material where pharmacodynamics matter for medication in kidney patients.

### Reversible Effect

Pharmacodynamics of reversible effects are capacity-limited and described by the saturable maximum effect (Emax) model (1). The effect cannot grow higher than the Emax, meaning that no more than a 100% response can be elicited due to the biologically limited number of molecular binding sites. An extension of the Emax model yields the sigmoid Hill equation (Supplemental Material). The Hill coefficient (H), sometimes referred to as the “ $\gamma$ ” coefficient, represents a purely empiric parameter that determines the sigmoidicity of the effect-concentration correlation. The higher the H, the more the effect-concentration correlation looks S-shaped (Supplemental Figure 1). The usual

## Effect-Concentration Correlation

### NORMAL Kidney Function and Kidney FAILURE



**Figure 1. | Pharmacodynamics (PD) follow pharmacokinetics (PK).** The time-dependent course of the effect can be modeled by inserting the time-dependent concentration decline (C) into the equation for the pharmacodynamic Emax model (E). In contrast to an irreversible effect, reversible effects (E) concomitantly diminish when concentrations (C) decline with time (t). The effect bisection time will rise in proportion to the  $T_{1/2}$  ( $T_{1/2} \rightarrow TED_{50}$ ). This suggests to extend the administration interval when the elimination is impaired in kidney failure ( $T_{1/2}$ : 12→24). Emax, maximum effect;  $CE_{50}$ , concentration producing half-maximum effect;  $TED_{50}$ , effect bisection time.

form of the sigmoid Emax model can be rearranged into a true hyperbolic form.

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

Dividing by a fraction is done by multiplication with the reverse fraction: When neglecting the  $1 +$  term in the denominator, one can immediately see that high concentrations (C) produce a strong effect (E). One can also see the effect of

the concentration producing the half-maximum effect ( $CE_{50}$ ). Because the  $CE_{50}$  corresponds to the  $K_d$ , a high  $CE_{50}$  is associated with only a weak effect (Supplemental Material). If the  $CE_{50}$  needed to produce 50% of Emax is low, however, the affinity to the receptor is high and this drug has a strong potency.

$$potency = \frac{1}{CE_{50}}$$

The Emax corresponds to the number of receptors or enzyme molecules. Thus, it is primarily a patient-related, not a drug-related, parameter. Emax can also explain how polypharmacy might work: in the case of synergistically acting drugs such as losartan and a thiazide, the receptor-mediated effects and thus the Emax values are additive on BP ( $E = E_{max1} + E_{max2}$ ). Antagonistic combinations such as a typical antipsychotic with a dopaminergic anti-Parkinson drug are unfavorable because the Emax is mutually minimized ( $E = E_{max1} - E_{max2}$ ).

On the other side, the  $CE_{50}$  parameter reflects the intrinsic power of the drug. It is a drug-related parameter. Alterations of the receptor affinity, however, result in  $CE_{50}$  changes and thus the individual response can be influenced by drug interaction, activation, or competition. Alterations of both Emax and  $CE_{50}$  can further occur as disease-related phenomena. In the elderly, changes in drug response often have been explained by an impaired kidney function. An increased sensitivity and a higher drug potency also can be due to a decrease in  $CE_{50}$  values in the elderly.

$$sensitivity = \frac{1}{CE_{50}}$$

An increased sensitivity has been reported for midazolam ( $CE_{50}$ : 522→223 ng/ml), nifedipine, morphine, phenytoin, and warfarin, but more resistance with a higher  $CE_{50}$

**Table 1. Pharmacodynamics of medications**

**Factors that influence the clinical pharmacologic drug response as measured by onset, intensity, and duration of effect. These factors act primarily by affecting the drug concentration at the receptor site**

- Drug dose
- Drug pharmacokinetics
- Receptor number
- Organ response to receptor activation
- Counter-regulatory (competing) influences at the receptor

**Pathologic processes (aging, acute and chronic illness, and kidney disease) can affect pharmacodynamics (clinical response)**

- Decreased receptor number (Emax) and sensitivity ( $CE_{50}$ )
- Decreased receptor binding
- Altered signal transduction

**Drugs can interact and compete for similar receptors having multiple effects**

- Synergistic effects
- Antagonistic effects
- Drug toxicity (S-shaped effect-concentration correlation and Hill coefficient)

Emax, maximum effect;  $CE_{50}$ , concentration producing half-maximum effect.

has been observed for albuterol and metoprolol (2). In the former five examples, a dose reduction might be needed due to pharmacodynamic alterations. The opposite pharmacodynamic change is seen with albuterol and metoprolol that require a higher dose or a change to an alternative drug.

### Furosemide and Canagliflozin

In contrast to tacit presumptions, a change in the  $CE_{50}$  can be predicted for furosemide and canagliflozin in CKD. Less potency and a decreased sensitivity with a higher  $CE_{50}$  will be predicted for furosemide or canagliflozin because a higher than normal dose with higher intratubular concentrations is needed to produce the diuretic effect: Although furosemide  $T_{1/2}$  rises from 2 to 10 hours, nephrologists in general experienced that the dose should not be reduced, but instead be increased from 40 to >500 mg to obtain the diuretic effect in kidney failure (3). Canagliflozin, likewise, has been shown to require a higher dose of 300 mg in patients with kidney dysfunction because 100 mg results in underdosing, irrespective of the fact that the  $T_{1/2}$  rises from 13 to 17 hours (4). The observations with furosemide and canagliflozin can be explained by pharmacodynamic not by pharmacokinetic changes in kidney failure.

The  $H$  is the exponent of a power function. A high  $H$  will result in an augmented  $CE_{50}/C$  ratio value if the ratio is >1.0 (>>1.0). In contrast, values of the  $CE_{50}/C$  ratio <1.0 will decrease dramatically (<<1.0). In the case of the special condition where the concentration,  $C$ , equals the  $CE_{50}$ , the ratio of  $CE_{50}$  over  $C$  is 1.0 with any  $H$ . Without knowing the  $H$ , therefore, the  $CE_{50}$  can be read off directly from simultaneous measurements of concentrations and corresponding effects (Figure 2).

$$1.0^{\pm H} = 1.0$$

Great progress has been made by distinguishing antimicrobial drugs with a concentration-dependent effect from drugs with a time-dependent effect. This difference can be explained by the  $H$ : Anti-infective drugs classified as concentration-dependent have a low  $H < 2.0$ , whereas anti-infective drugs with a time-dependent effect have a high  $H > 2.0$  (5). Using the sigmoid Hill equation, the threshold ( $CE_{05}$ ) and the ceiling concentration ( $CE_{95}$ ) can be derived (Supplemental Material). For a high  $H$ , the  $CE_{95}$  will be low but, simultaneously, the  $CE_{05}$  is high (Supplemental Figure 1).

$$CE_{05} = 0.053^{\frac{1}{H}} \cdot CE_{50}$$

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

Drugs with a concentration-dependent effect and a low  $H$  have a high  $CE_{95}$ , such as gentamicin, levofloxacin, linezolid, daptomycin, colistin, and voriconazole (6). In this case a higher dose results in a stronger effect (Supplemental Figure 1). Conversely, drugs with a time-dependent effect and a high  $H$  have a low  $CE_{95}$ , but the  $CE_{05}$  will be high such as with piperacillin, ceftazidime, meropenem, vancomycin, clarithromycin, doxycycline, and antiviral drugs (6): In cases with a high threshold, low trough levels might miss the therapeutic target ( $C_{trough} < CE_{05}$ ), because they presumably could fall below the microbiologically minimal inhibitory concentration (MIC).

$$CE_{05} \cong MIC$$

The dosing regimen can be adjusted to the individual condition by changing either the dose or the length of the administration interval ( $\tau$ ). The decision depends on whether the peak or the trough is the target with repetitive dosing. A high peak is aimed at for the concentration-dependent pharmacodynamics ( $C_{target} = C_{peak}$ ) and a high trough for the time-dependent pharmacodynamics ( $C_{target} = C_{trough}$ ). To increase efficiency, drugs with a concentration-dependent action require the application of a higher dose (e.g., apixaban). In contrast, drugs with a time-dependent action need a higher frequency of their dosing schedule, similar to a continuous infusion (e.g., vancomycin).

### Vancomycin, Meropenem, and Piperacillin

According to pharmacodynamically based regimens, vancomycin with a time-dependent action should be administered by continuous infusion to increase efficacy but decrease toxicity (7). The target concentration is no longer regarded as a trough level of 10 mg/L. Instead, the target is the average steady state serum concentration  $C_{ss}$  of up to 25 mg/L ( $C_{ss} \times 24 \text{ hours} = \text{area under the curve [AUC]}$ ) which is equivalent to an AUC of 400–600 hours  $\times$  mg/L (7). To meet this target a bolus loading dose of 1500 mg (20 mg/kg) with a subsequently administered continuous infusion might be needed. The subsequent infusion rate must be adjusted to the kidney function or to the RRT according to pharmacokinetic principles. Analogous to vancomycin, meropenem should also be administered as a continuous infusion with the steady state concentration as the therapeutic target ( $C_{ss}$ ) of four times the MIC and up to 32 mg/L (8). This target is in agreement with the time-dependent meropenem action because for  $H > 2.0$  the  $CE_{50}$  value roughly corresponds to four times the  $CE_{05}$  ( $4 \times CE_{05} = CE_{50}$ ) and the  $CE_{05}$  relates to the MIC ( $CE_{05} \sim MIC$ ). In agreement with these predictions, the mortality was less when  $\beta$ -lactam antibiotics were administered by prolonged infusion (>3 hours) versus short-term infusion (<60 minute); this difference was significant with meropenem and piperacillin but not with ceftazidime and not when just the  $T_{1/2}$  values are prolonged due to impaired kidney function (9).

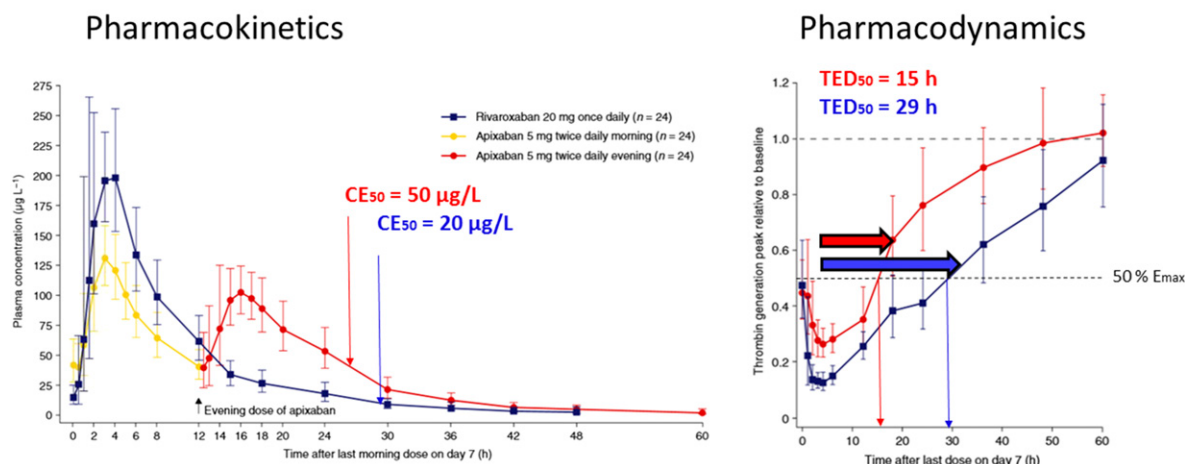
### Apixaban

Pharmacokinetics and pharmacodynamics are closely correlated (Supplemental Material). When concentrations decrease with time, the reversible, receptor-mediated effect will also decrease with time (Figure 1). Analogous to the elimination  $T_{1/2}$  in pharmacokinetics, the effect bisection time ( $TED_{50}$ ) can be stated as a measure of the effect duration in pharmacodynamics (10). The  $TED_{50}$  indicates the time needed to decrease the effect by 50% ( $E_2 = 0.50 \times E_1$ ); thus, the  $TED_{50}$  depends on the concentration ( $C_1$ ) producing the initial effect ( $E_1$ ).

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

The pharmacokinetics of apixaban and rivaroxaban are comparable regarding their normal  $T_{1/2}$  of 8 hours for both

## Apixaban and Rivaroxaban



**Figure 2.** | Pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban (12). Pharmacodynamics (right): The effect bisection time ( $TED_{50}$ ) can be read off at approximately 15 hours for apixaban (red arrow) and at 29 hours for rivaroxaban (blue arrow). The time after dosing when 50% of maximum effect ( $E_{max}$ ) is produced is 15 hours with apixaban but 29 hours with rivaroxaban. Pharmacokinetics (left): At 27 hours ( $=12+15$ ), the concentration producing 50% of  $E_{max}$  ( $CE_{50}$ ) can visually be determined with  $CE_{50}=50\text{ }\mu\text{g/L}$  for apixaban (red) but at 29 hours with  $CE_{50}=20\text{ }\mu\text{g/L}$  for rivaroxaban (blue).

direct-acting oral anticoagulants (11). However, the recommended administration interval differs with 12 hours for apixaban and 24 hours for rivaroxaban. It has been demonstrated that plasma levels after a regular dose of 5 mg apixaban reach a maximum concentration of  $139\text{ }\mu\text{g/L}$ , in comparison with 20 mg rivaroxaban reaching a higher maximum plasma concentration of  $227\text{ }\mu\text{g/L}$  (12). From the published diagram depicting the effect on thrombin generation, the  $TED_{50}$  can be read off with  $TED_{50}=15$  hours for apixaban and with  $TED_{50}=29$  hours for rivaroxaban (Figure 2). In addition, the concentration producing the  $CE_{50}$  can visually be determined with  $CE_{50}=50\text{ }\mu\text{g/L}$  for apixaban and with  $CE_{50}=20\text{ }\mu\text{g/L}$  for rivaroxaban just at the time where 50% of the maximum effect is produced (Figure 2).

Using the equation for the  $TED_{50}$  and on the basis of these pharmacokinetic and pharmacodynamic parameter values, the  $H$  can be estimated by an iterative numeric solution (Supplemental Figure 2). Thus, the still missing pharmacodynamic parameter can be derived and the estimates are quite comparable with  $H=1.4$  for apixaban and  $H=1.2$  for rivaroxaban. Accordingly, the pharmacodynamics of both apixaban and rivaroxaban can be stated to be concentration-dependent, allowing for a long administration interval. Such inferences can explain why rivaroxaban is applied with an administration interval of 24 hours, although its  $T_{1/2}$  is only 8 hours.

The insight into the pharmacodynamics might affect clinical dosing practice in kidney failure where the  $T_{1/2}$  of apixaban rises to 17 hours, whereas the rivaroxaban  $T_{1/2}$  increases to only 10 hours (11). The antithrombotic efficacy and the bleeding risk were not different for apixaban and rivaroxaban even in CKD (13). The recommended dose of apixaban is 2.5 mg twice a day in advanced kidney disease (13). With 2.5 mg apixaban twice a day the trough concentrations were measured as low as  $50\text{ }\mu\text{g/L}$  (14). Because the  $T_{1/2}$  is 17 hours, the corresponding peak concentration will be estimated with  $82\text{ }\mu\text{g/L}$ . Because

apixaban has a concentration-dependent effect, the aim should be the normal peak of  $139\text{ }\mu\text{g/L}$ .

Instead of dosing 2.5 mg every 12 hours, the pharmacodynamic dose adjustment of apixaban to kidney failure would suggest 5 mg once a day because the  $T_{1/2}$  is 17 hours and the  $TED_{50}$  will be estimated with  $TED_{50}=29$  hours. Thus, the suggested apixaban administration interval is just equal to the 24-hour interval of rivaroxaban in kidney failure not requiring dialysis. Otherwise, the trend for apixaban underdosing becomes apparent when the dose for patients receiving dialysis is recommended as 5 mg twice daily, whereas rivaroxaban could still be dosed at 15 mg once a day (13).

### Anticancer Therapy

In pharmacokinetics the drug dose results in one concentration but in pharmacodynamics one and the same concentration results in at least two effects—the beneficial and the adverse effect (Supplemental Figure 3). Conventional drugs with a beneficial effect will also have adverse effects. The adverse drug reaction can even be used for a pharmacodynamic monitoring of the therapeutic effect. The therapeutic response to the tyrosine kinase inhibitor erlotinib, likewise, can only be expected if there is a skin rash. Mild myelosuppression—not myelotoxicity, not aplasia—but still tolerable grade 3 anemia, thrombocytopenia, neutropenia, or lymphocytopenia are easy measurable drug effects that might indicate sufficiently high dosing to guarantee the therapeutic target in oncology and immunosuppression (Table 2). Therefore, a grade 3 neutropenia should not give reason to reduce the dose: Some toxicity is needed for anticancer chemotherapy to meet the therapeutic target.

### Furosemide Infusion

Ototoxicity is considered to be a serious side effect of furosemide. This side effect must be classified as

**Table 2. Adverse drug events as surrogate markers for the pharmacodynamic monitoring of therapeutic targets**

| Class             | Drug                   | Pharmacodynamic Target                                                                                             | Reference |
|-------------------|------------------------|--------------------------------------------------------------------------------------------------------------------|-----------|
| Anticancer        | Adriamycin=doxorubicin | Neutrophil count 1.5/nl                                                                                            | (27)      |
|                   | Carboplatin            | Grade 2 and 3 neutropenia 1.5–1.0/nl                                                                               | (28)      |
|                   | Cisplatin              | Neutrophil count 1.5/nl                                                                                            | (27)      |
|                   | Cyclophosphamide       | Neutrophil count 1.5/nl                                                                                            | (27)      |
|                   | Docetaxel              | Grade 3–4 neutropenia <1.0/nl                                                                                      | (29)      |
|                   | Doxorubicin            | Neutrophil count 1.5/nl                                                                                            | (27)      |
|                   | Fluorouracil (5FU)     | Neutrophil count 1.5/nl                                                                                            | (27)      |
|                   | Paclitaxel escalated   | Grade 2–3 neutropenia 1.0–1.5/nl                                                                                   | (30)      |
| Anti-infective    | Celgosivir             | Δ platelet nadir –Δ 60/nl                                                                                          | (31)      |
|                   |                        | Δ hematocrit –Δ 6%                                                                                                 |           |
| Hematology        | Valganciclovir         | White blood cell count <3/nl                                                                                       | (32)      |
|                   | Imatinib               | White blood cell count <4.0/nl                                                                                     | (33)      |
|                   | Lenalidomide           | Δ platelet –Δ 50%                                                                                                  | (34)      |
|                   | Trifluridine/tipiracil | Grade 3–4 neutropenia and thrombocytopenia<br>Neutropenia or leukopenia or anemia or<br>thrombocytopenia grade 3–4 | (35)      |
| Immunosuppression | Azathioprine           | White blood cell count <3.0/nl<br>Neutropenia <1.0/nl                                                              | (36)      |
|                   | Cyclophosphamide       | Thrombocytopenia <100/nl                                                                                           |           |
|                   |                        | Neutrophil count <4/nl,                                                                                            | (37)      |
|                   |                        | White blood cell count <4/nl,                                                                                      | (38)      |
|                   | Mycophenolate          | Lymphopenia threshold 1.0/nl                                                                                       | (39)      |
|                   |                        | Leukopenia <4/nl                                                                                                   | (40)      |
|                   | Rituximab              | CD19+ B cells <10/mm <sup>3</sup> =10/μl=0.010/nl                                                                  | (22)      |
|                   |                        | CD4+ T cells <200/μl=0.2/nl                                                                                        | (41–50)   |

Mild myelosuppression with anemia, neutropenia, lymphocytopenia, and thrombocytopenia might indicate a sufficiently high dose of anticancer, anti-infective, or hematologic and immunosuppressive drugs.

concentration-dependent because the H for the hearing loss under furosemide is reportedly low at H=1.5 (15). Accordingly, the occurrence of ototoxicity is less likely when furosemide is administered by a continuous infusion instead of bolus injection, the latter resulting in a high serum peak level. High serum peak levels and ototoxicity will be avoided by a continuous infusion. Continuous infusion also has been shown to increase the diuretic response and will be advantageous regarding the higher dosage of furosemide usually needed in kidney failure (16).

### Irreversible Effect

In contrast to the reversible effects, irreversible effects rarely have been modeled in the literature. Published examples for irreversible effects include the drugs ibrutinib (17), cisplatin (18), clopidogrel (19), and pantoprazole (20). An irreversible effect might be produced by one single drug administration. Irreversible effects persist much longer than concentrations of the drug will remain measurable in the body (Supplemental Material). Whereas reversible effects target a receptor or enzyme molecule, irreversible effects target an on-off mechanism or an active cell (bacteria, cancer cell, immune cell).

### Rituximab

The normal dose of the CD20+ B cell antibody rituximab is 375 mg/sqm weekly for 4 weeks. However, two doses of 1000 mg within 2 weeks became the preferred regimen published in the Membranous Nephropathy Trial of Rituximab on the nephrotic syndrome due to membranous GN (21). Although shorter and less frequently dosed (time

of treatment [T]=2 weeks), this protocol produces a long-lasting effect as does the standard 4 weeks regimen (21). The irreversible effect can be modeled as depending on dose (D), volume (Vd), and the time of infusion (4 hours) but also as depending on the T.

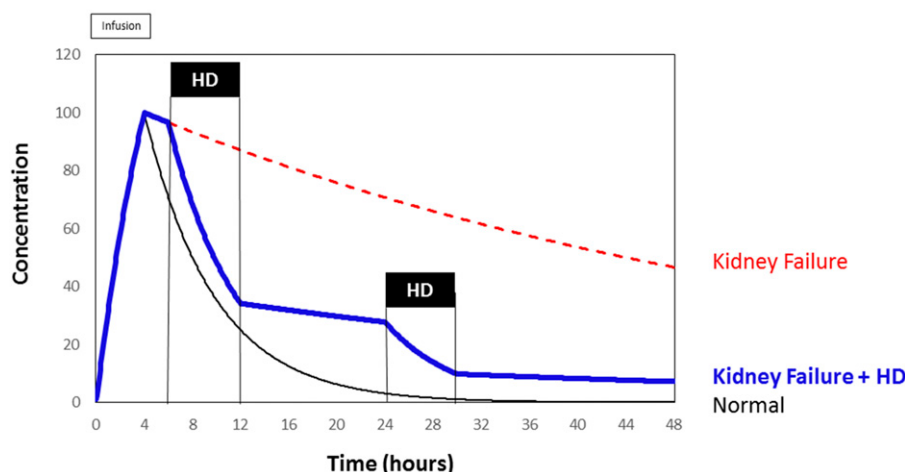
$$E_{irrev} = \frac{D}{Vd} \cdot \exp\left(-0.693 \cdot \frac{T}{T_{1/2}}\right)$$

As quantitated here for the irreversible effect, the total D (D) (2×1000 mg=2000 mg) given within a shorter time of 2 weeks (T=14 days) will induce a 2.3-fold stronger response ( $E_{irrev}$ ) than the same dose (4×500 mg=2000 mg) given within the usual 4 weeks (T=28 days). With  $T_{1/2}=11.5$  days, rituximab concentrations are negligible after 50 days but the effect on B cells will persist for 200 days or even up to 500 days (22). Thus, the effect on the initial B cell population can be stated as irreversible. The irreversible effect will persist until the bone marrow regenerates and the immune system will be able to produce a new B cell generation.

### Carboplatin

Pharmacodynamics of an irreversible effect will have considerable implications for drug dose adjustment in kidney failure. The difference between reversible and irreversible effects can be illustrated with carboplatin, where the  $T_{1/2}$  increases four-fold from 4.5 to 17 hours in kidney failure (23). With the traditional Calvert formula, the pharmacodynamics of a reversible effect are presumed and the area under the curve is kept unchanged when the kidney function changes (AUC=constant [const.]). With the target AUC of 7 minutes×mg/ml the normal dose of 1000 mg would have to

## Carboplatin



**Figure 3.** | Carboplatin and kidney failure: Near-normal elimination kinetics can be established by hemodialysis (HD) initiated 2 hours after carboplatin infusion.

be reduced to 210 mg for kidney failure with a GFR of 5 ml/min (24) when using the Calvert equation ( $210 = 7 \times [5 + 25]$ ).

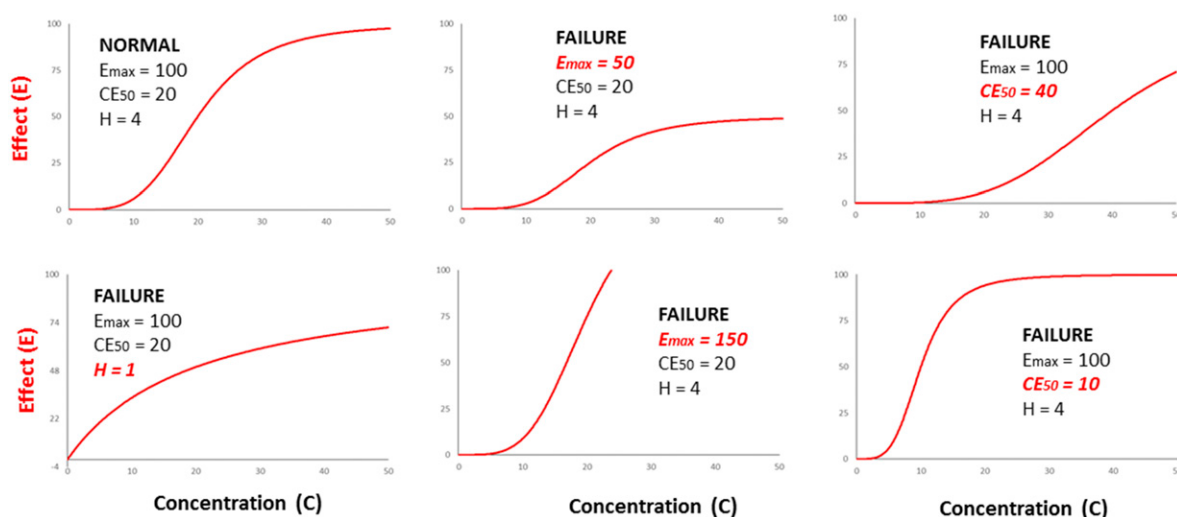
$$D = AUC \cdot [GFR + 25]$$

In the case of kidney failure, however, a less rigorous dose reduction is required than proportionate to the rise of the

$T_{1/2}$  because only the higher dose can here produce the same irreversible effect as with normal conditions ( $E_{\text{irrev}} = \text{const.}$ ): Conveniently, the recommended time of infusion is unchanged with  $T = 2$  hours (25). When keeping the infusion time const. ( $T = T_{\text{norm}} = \text{const.}$ ), the carboplatin dose must be reduced (Supplemental Material).

## Pharmacodynamics and Potential Alterations in Kidney Failure

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



**Figure 4.** | The effect (E) depends on concentrations (C) according to the sigmoid  $E_{\text{max}}$  model. Pharmacodynamic parameters as determined for normal kidney function potentially might change due to kidney failure: When the Hill coefficient decreases ( $H: \rightarrow 1.0$ ) the dose must be increased. When the maximum effect is diminished ( $E_{\text{max}}: \rightarrow 50$ ) more of the drug or another drug should be given. When the effects of two drugs are additive ( $E_{\text{max}}: \rightarrow 150$ ) the combination has advantages. When the concentration producing the half-maximum effect increases ( $CE_{50}: \rightarrow 40$ ) a higher dose will be needed. Conversely, when the sensitivity increases ( $CE_{50}: \rightarrow 10$ ) the dose must be reduced. Most frequently, but not exclusively so, the dosage should be reduced in kidney failure.

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

But the dose adjustment on the basis of the pharmacodynamics of an irreversible effect suggests that a dose of 770 mg not 210 mg will be needed to stop the cancer cells: Thus the normal standard dose will be reduced by 23% when giving the 770 mg ( $1.0 - 770/1000 = 0.23$ ) but not by 79% as when reducing to 210 mg ( $1.0 - 210/1000 = 0.79$ ). To limit the risk for severe and intolerable adverse events it will be necessary and has frequently been recommended to perform an immediate hemodialysis session just 2 hours after carboplatin administration (23,25,26). The hemodialysis can be seen as an artificial substitute of normal kidney function (Figure 3).

No dose reduction would be needed if the infusion time could be extended in parallel with the four-fold prolongation in the elimination  $T_{1/2}$ . But such a four-times-longer infusion time ( $T = 8$  hours) would be unfeasible with carboplatin in clinical practice and this regimen does not solve the problem of an increased risk for toxicity due to a rise in the AUC.

## Conclusions

Values for pharmacodynamic parameters can be extracted from the published literature using respective key words. With the keywords “EC<sub>50</sub>+pharmacodynamics” a total of 16,051 publications, with “Hill+pharmacodynamics” 2412 publications, with “E-max model+pharmacodynamics” 436 publications, and even for the keywords “CE<sub>50</sub>+pharmacodynamics” a total of 41 publications can be identified in PubMed (December 2017). In kidney failure, pharmacokinetics can dramatically change leading to alterations in drug action; but alterations in pharmacodynamic parameters have rarely been considered (Figure 4). Sometimes the values for the CE<sub>50</sub> concentration and the H can be extracted and exploited to derive dose modifications appropriate for target attainment. The target is the peak level close to the CE<sub>95</sub> for a life-saving induction therapy. The target is the trough level above the CE<sub>05</sub> with a long-term maintenance therapy. However, for irreversible effects the target should be the normal maximum concentration.

## Disclosures

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