parameters were calculated using a computer program for non-linear regression analysis [6].

Results

The absorption of LP was significantly faster than that of HI. As shown in Figure 1A, maximum plasma insulin concentrations (C_{max}) were reached after 30 (LP) *vs* 51 min (HI). Peak insulin concentrations were significantly greater with LP (146 μU/ml) than with HI (88 μU/ml). Insulin concentrations returned to baseline values more quickly with LP than with HI. At 120 min after injection, plasma insulin concentrations were 37% of C_{max} (LP) *vs* 77% (HI). Data obtained by computer-assisted calculation revealed that the absorption half-life of LP was significantly shorter compared with HI (12 ± 8 *vs* 32 ± 8 min), whereas the elimination half-life and the volume of distribution of LP were not di erent from HI (43 ± 21 *vs* 40 ± 9 min; 61 ± 54 *vs* 75 ± 49 l). Blood glucose levels declined within 20 min after LP injection (Figure 1B), whereas after HI injection blood glucose even increased during the first 40 min. The nadir of blood glucose was reached 3 h after LP injection, whereas with HI glucose levels decreased further.

Discussion

In diabetic haemodialysis patients, the rapid changes in insulin and glucose metabolism require fast and short-acting insulin preparations. In these patients, the time-action profile of HI with its delayed onset and prolonged duration of action does not coincide with glycaemic excursions. In contrast, LP is absorbed more rapidly, leading to a faster onset and shorter duration of action compared with HI. The pulsatile pharmacokinetic profile of LP may not only facilitate the correction of hyperglycaemia but may also decrease the risk of late hypoglycaemic episodes which are of particular clinical relevance in haemodialysed diabetic patients. Furthermore, LP o ers the advantage of immediate pre-meal injection which is important for treatment satisfaction and may enhance the quality of life.

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Pharmacodynamic half-life and e ect–time course in renal impairment

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Background and objective

In patients with renal impairment, the elimination of drugs often is impaired, and elimination half-life increases [1]. In pharmacokinetics, the kinetic half-life ($T^{1}_{2\,kin}$) is used to describe the relation between concentration (C) and time (t). To describe the relation between e ect (E) and concentration (C) the sigmoid E_{max}-model is used with Hill coe cient (H), and concentration (CE_{50}) producing half-maximum e ect [2].

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

If the term half-life is not reserved to be used for log-linear first order kinetics, a pharmacodynamic half-life can be derived for the e ect–time course that depends on the concentration–time course. Such a parameter might be used to specify the e ect–time course in renal impairment.

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Pharmacodynamic half-life

The bisection time ($t_{2-1}=t_2-t_1$) is required to decrease the e ect by one half ($E_2=\frac{1}{2}E_1$). For the most simple case, this bisection is due to a mono-exponential decrease in concentrations according to the linear coe cient (λ).

$$C_2=C_1\exp(-\lambda\ t_{2-1})$$

The bisection time of the e ect depends on the linear coe cient (λ):

$$t_{2-1}=(\ln[C_1/C_2])/\lambda$$

Transforming the equation of the sigmoid E_{max} model, we obtain:

$$C_1^H=\frac{CE_{50}^H}{(E_{max}/E_1)-1}$$

The concentration (C_2) at e ect ($E_2=\frac{1}{2}E_1$) can also be stated.

$$C_2^H=\frac{CE_{50}^H}{(E_{max}/\frac{1}{2}E_1)-1}$$

Since ($E_1=E_{max}\ {C_1}^H/[{CE_{50}}^H+{C_1}^H]$) we can eliminate C_2 in the above equation derived for t_{2-1}.

$$t_{2-1}=(\ln\left[\frac{C_1}{CE_{50}/[2(CE_{50}^H/C_1^H)+1]^{1/H}}\right])/\lambda$$

Transformation results in:

$$t_{2-1}=(1/\lambda)\ (1/H)\ \ln[2+C_1^H/CE_{50}^H]$$

The bisection time of the e ect (t_{2-1}) depends on the linear coe cient, and thus on the kinetic half-life ($T^{\frac{1}{2}}_{kin}=\ln(2)/\lambda$).

$$t_{2-1}=[T^{\frac{1}{2}}_{kin}/\ln(2)]\ (1/H)\ \ln[2+C_1^H/CE_{50}^H]$$

The bisection time (t_{2-1}) of the pharmacodynamic e ect can be termed pharmacodynamic half-life ($T^{\frac{1}{2}}_{dyn}=t_{2-1}$). The pharmacodynamic half-life ($T^{\frac{1}{2}}_{dyn}$) is a concentration-dependent parameter and a non-linear function of the kinetic half-life ($T^{\frac{1}{2}}_{kin}$), where [$1/\ln(2)=1.44$].

$$T^{\frac{1}{2}}_{dyn}=T^{\frac{1}{2}}_{kin}\ (1.44/H)\ \ln[2+C_1^H/CE_{50}^H]$$

High drug concentrations ($C_1\gg CE_{50}$) will lead to prolonged drug action, and increased dynamic half-life [3]. A high Hill coe cient ($H>1$) results in a short dynamic half-life ($T^{\frac{1}{2}}_{dyn}<T^{\frac{1}{2}}_{kin}$).

Example and discussion

Physostigmine has a pharmacokinetic half-life of 0.27 h. The pharmacodynamic e ect on plasma butyrylcholinesterase activity decreases with a 5-times longer half-life of 1.4 h [4]. This indicates that the pharmacokinetic–pharmacodynamic relation is located in the right bent, concave and saturated part of the sigmoid E_{max}-model ($C>CE_{50}$). Since for low concentrations the e ect near-linearly increases with the concentration,

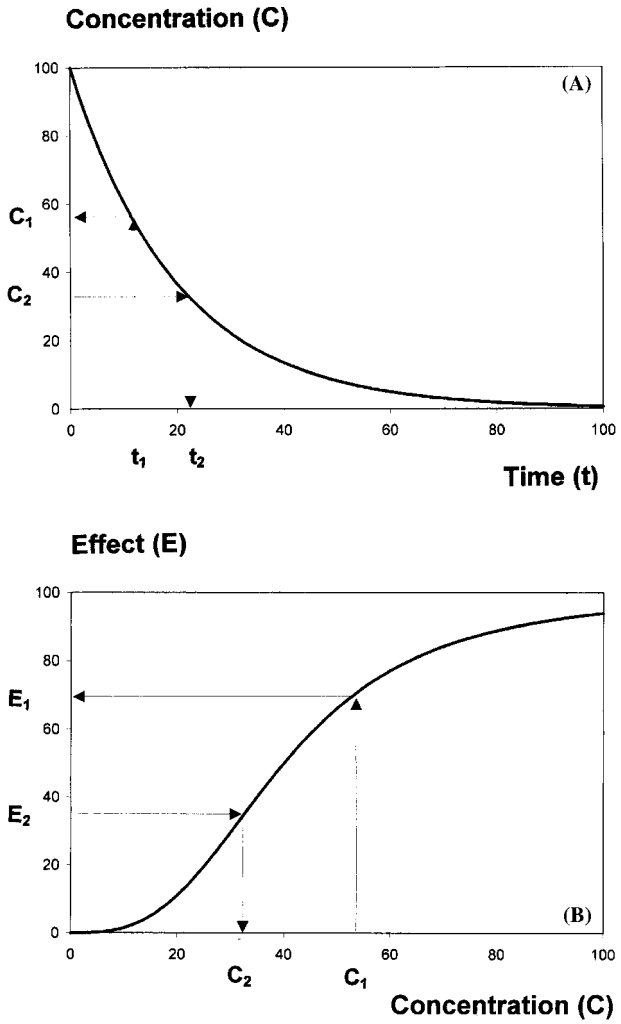

Fig. 1. Pharmacokinetic half-life and pharmacodynamic half-life. (A) At time t_1 concentration is C_1, and decreases to concentration C_2 at time t_2, where obviously ($C_2>\frac{1}{2}C_1$). The corresponding time interval is less than one pharmacokinetic half-life ($t_2-t_1<T^{\frac{1}{2}}_{kin}$). (B) Concentration C_1 produces the e ect E_1, that is bisected to one-half, or E_2 at concentration C_2, where ($E_2=\frac{1}{2}E_1$). The respective time interval (t_2-t_1) is required to make one-half of the e ect, and corresponds to the pharmacodynamic half-life ($t_2-t_1=T^{\frac{1}{2}}_{dyn}$). For this example, the pharmacokinetic half-life is shorter than the pharmacodynamic half-life ($T^{\frac{1}{2}}_{kin}<T^{\frac{1}{2}}_{dyn}$), in agreement with sigmoidicity coe cient ($H>1$).

it can be assumed that it holds ($H\approx1$). The peak level (C_{peak}) was 12.5 nM, corresponding to 3 ng/ml. According to the above equations, the unknown concentration at half-maximum e ect can be calculated ($CE_{50}=0.42$ nM), corresponding to 0.1 ng/ml. Since we do not know the E_{max}, the value would be read o 12-times higher from the published graph ($CE_{50}=$ 5 nM), corresponding to 1.2 ng/ml.

We can draw practical inferences on the usually unknown dynamic parameters if we know the kinetic and dynamic half-lives describing drug elimination and e ect duration [5]. With constant target concentration ($C_{peak}=C_1$), dynamic half-life or duration of drug e ect will increase in proportion to elimination half-life in renal failure. Even when the dose is adjusted to

identical target concentrations (C_{peak} = constant), the e ect might be longer lasting with a prolonged dynamic half-life in renal impairment.

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Cross-talk between activated tubular epithelia of human kidney and monocytes: a basis for target cell-specific pharmacotherapy?

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Changes in the tubulointerstitial compartment govern the progression and outcome in most patients su ering from renal diseases. Under pathological conditions, the influx of monocytes into the kidney and local proliferation of blood-derived macrophages releasing proinflammatory and fibrogenic cytokines contribute to structural and functional deterioration [1]. In addition, cell lesions may result directly from cooperative but maladapted cell interactions between 'activated tubular cells' which are capable of recruiting and stimulating monocytes to invade the glomeruli and/or the tubulointerstitium, thus resulting in progressive sublethal injury, necrosis and fibrosis. In the present work, we summarize our experimental and clinical data which support an engaged interaction (cross-talk) of tubular epithelia of proximal and distal origin with monocytes/macrophages in human renal diseases [2–4].

Human renal proximal and distal tubular cells.

Human renal proximal (PTC) and distal (DTC) tubule cells were isolated immunomagnetically as described earlier, applying monoclonal antibodies raised against distinct segments of the human nephron [2]. PTC were strongly positive for aminopeptidase M (CD13); however, DTC were negative for CD13 antigen. Ultrastructural analyses of PTC primary isolates revealed a highly preserved brush border, whereas DTC showed multiple basolateral invaginations and many fewer apical microvilli. Both cell types formed tight junctions and expressed cytokeratin and vimentin, whereas stains for desmin, α-actin and von Willebrand's factor were negative. A di erent response after hormonal stimulation [parathyroid hormone (PTH), calcitonin] was found where cAMP production was especially high in DTC after challenge with PTH [2,5].

Activated tubule cells

After incubation of cultured cells with a mix of 25 U/ml interleukin (IL)-1β, 10 ng/ml tumour necrosis factor-α (TNF-α) and 200 U/ml interferon-γ (IFN-γ), the production of RANTES, a chemokine for monocytes, increased dramatically in both PTC and DTC [6]. Compared with basal conditions, the release of RANTES into the supernatant was 107- to 133-fold increased up to 364 pg/48 h/10^5 cells. In parallel, expression of HLA-DR and interstitial cell adhesion molecule-1 (ICAM-1) increased significantly, as analysed by flow cytometry. Unstimulated PTC and DTC did not express HLA-DR; DTC expressed ICAM-1 constitutively in very small amounts.

E ect of anti-inflammatory drugs

Glucocorticoids such as dexamethasone (10^{-6} M) as well as cyclooxygenase II inhibitors down-regulated

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