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REVIEW ARTICLE

Pharmacokinetics and dosage adjustment in patients with renal dysfunction

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Abstract
Introduction Chronic kidney disease is a common, progressive illness that is becoming a global public health problem. In patients with kidney dysfunction, the renal excretion of parent drug and/or its metabolites will be impaired, leading to their excessive accumulation in the body. In addition, the plasma protein binding of drugs may be significantly reduced, which in turn could influence the pharmacokinetic processes of distribution and elimination. The activity of several drug-metabolizing enzymes and drug transporters has been shown to be impaired in chronic renal failure. In patients with end-stage renal disease, dialysis techniques such as hemodialysis and continuous ambulatory peritoneal dialysis may remove drugs from the body, necessitating dosage adjustment.
Methods Inappropriate dosing in patients with renal dysfunction can cause toxicity or ineffective therapy. Therefore, the normal dosage regimen of a drug may have to be adjusted in a patient with renal dysfunction. Dosage adjustment is based on the remaining kidney function, most often estimated on the basis of the patient's glomerular filtration rate (GFR) estimated by the Cockroft–Gault formula. Net renal excretion of drug is a combination of three processes: glomerular filtration, tubular secretion and tubular reabsorption. Therefore, dosage adjustment based on GFR may not always be appropriate and a re-evaluation of markers of renal function may be required.
Discussion According to EMEA and FDA guidelines, a pharmacokinetic study should be carried out during the development phase of a new drug that is likely to be used in patients with renal dysfunction and whose pharmacokinetics are likely to be significantly altered in these patients. This study should be carried out in carefully selected subjects with varying degrees of renal dysfunction. In addition to this two-stage pharmacokinetic approach, a population PK/PD study in patients participating in phase II/phase III clinical trials can also be used to assess the impact of renal dysfunction on the drug's pharmacokinetics and pharmacodynamics.
Conclusion In conclusion, renal dysfunction affects more that just the renal handling of drugs and/or active drug metabolites. Even when the dosage adjustment recommended for patients with renal dysfunction are carefully followed, adverse drug reactions remain common.

Keywords Dosage adjustment · Non-renal drug clearance · Pharmacokinetic/pharmacodynamic processes · Renal dysfunction · Renal drug clearance

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Introduction

The two principal organs responsible for the elimination of drugs and their metabolites from the body are the liver and the kidney. In many cases, drugs are rather lipid soluble and therefore cannot efficiently be removed from the blood circulation by renal excretory mechanisms but must first undergo biotransformation to more polar metabolites. The number of drugs that are completely or almost completely eliminated from the body by renal excretion in unchanged form is rather limited. For example, of the approximately 300 drugs listed in the pharmacokinetic data table in

Appendix II of the eleventh edition of *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, only 22% are eliminated for at least 50% by renal excretion in unchanged form [1]. However, renal dysfunction not only alters the renal excretion of unchanged drug and/or their metabolites, but it can also lead to modifications in the distribution, transport, and biotransformation of drug substances. In addition, the pharmacodynamic actions of drugs can be affected by renal dysfunction. Therefore, it would be too naive to suppose that only the dosage of drugs with a relatively important contribution of the kidneys to their overall elimination should be adjusted in patients with renal dysfunction to avoid excessive accumulation of drug and/or active drug metabolites.

Renal disease and markers of renal function

Kidney disease is a common, progressive illness that is becoming a global public health problem. Indeed, the incidence of chronic kidney disease (CKD) is increasing alarmingly in most industrialized countries. For example, the prevalence of CKD among the U.S. adult population was recently estimated to be >13% (>25 million adults), and the number of patients with end-stage renal disease (ESRD) alone has risen from 209,000 in 1991 to 472,000 in 2004 [2]. Whereas glomerulonephritis was one of the leading causes of kidney disease several decades ago, hypertension and diabetes are currently the two major causes worldwide. In addition, life expectancy is increasing in the Western world, and improved longevity is another reason why the incidence of CKD is increasing [3]. Given the pathogenic progression of kidney disease, patients with CKD are at high risk for progression to ESRD, a condition requiring renal replacement therapy, i.e., dialysis or kidney transplantation, to maintain the patient's long-term survival.

Chronic kidney disease is a progressive condition marked by deteriorating kidney function. The glomerular filtration rate (GFR), which is most frequently estimated (eGFR) using equations that incorporate serum creatinine concentration along with demographic data, is the most commonly used index of overall kidney function [4, 5]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) classifies CKD into five stages [6]. The definition of stages 1 and 2 CKD is based upon manifestations of renal damage, i.e., the presence of either micro- or macro-albuminuria, erythrocyturia, or abnormalities on renal ultrasound. Determination of the eGFR in these earlier stages is required only to distinguish between stages 1 and 2 (eGFR >90 or between 60–89 mL min^{-1}per 1.73 m^{-2}, respectively). These early stages of CKD are generally asymptomatic: the kidney functions normally, but the risk for progressive disease is significant. As kidney disease worsens, kidney function begins to deteriorate (stages 3 and 4 CKD). Eventually, kidney failure (stage 5 CKD) ensues, and kidney replacement therapy is required. Stages 3, 4, and 5 are exclusively defined by GFR (eGFR 30–59, 15–29 or <15 mL min^{-1} per 1.73 m^{-2}, respectively).

The GFR gives a reasonably good estimate of overall kidney function. It is reduced before the onset of symptoms of renal impairment and is related to the severity of the structural abnormalities in chronic renal impairment. Although glomeruli control the GFR, damage to the tubulointerstitium (renal tubular function) is also an important predictor of GFR and progression towards renal failure. Renal tubules make up 95% of the renal mass, do the bulk of the metabolic work, and modify the ultrafiltrate into urine. They control a number of kidney functions, including the acid–base balance, sodium excretion, urine concentration or dilution, water balance, potassium excretion, and small molecule metabolism (such as insulin clearance). The measurement of tubular function is impractical for daily clinical use and, consequently, GFR is commonly used to assess overall renal function. The GFR can be precisely measured using the filtration markers inulin, ^{125}I-iothalamate, ^{53}Cr-ethylenediaminetetraacetic acid, ^{99m}Tc-diethylenetriaminepentaacetic acid, and iohexol [4, 5, 7]. However, because these markers are, to varying degrees, costly and cumbersome to use and may involve radioactivity, which necessitates special handling and disposal measures, these standard methods of GFR determination are not typically used in clinical practice. Calculated creatinine clearance (CL_{CR}) based on serum creatinine concentration is the most convenient method to estimate GFR as it requires only a single blood sample. As serum creatinine is so highly dependent on age, gender, and body size, a number of formulas and corrections have been developed to estimate the muscle mass and assumed creatinine production (Table 1) [8–11]. The NKF KDOQI advocates using the traditional Cockroft–Gault equation or the Modification of Diet in Renal Disease (MDRD) study equation (full or abbreviated) for routine estimation of the GFR. However, these formulas may be inaccurate at low serum creatinine concentrations, and correction factors may have to be introduced for creatinine concentrations <85 or 60 μmol/L [12, 13]. In addition to the Cockroft–Gault and MDRD equations, many other equations have been developed and proposed for routine prediction of GFR, but all of them seem to exhibit levels of error when compared with standard iohexol GFR values, which make these estimated GFR values suboptimal for the clinical treatment of patients with renal dysfunction [11]. The Cockroft–Gault equation is still most often used for estimating GFR in pharmacokinetic studies and for drug dosage adjustment, although some studies have shown the MDRD Study equations to be more accurate for estimating GFR [14].

Table 1 Equations for glomerular filtration rate (GFR) prediction[a]

Equation	Formula/correction
Cockroft–Gault[b]	$\frac{(140-age)\times weight}{72\times S_{cr}}$ (×0.85 if female)
MDRD 1[c]	$170 \times S_{cr}^{-0.999} \times age^{-0.176} \times$ (0.762 if female) × (1.180 if black) × $S_u^{-0.170} \times alb^{+0.318}$
MDRD 2[c]	$186 \times S_{cr}^{-1.154} \times age^{-0.203} \times$ (1.212 if black) × (0.742 if female)
Nankivell[d]	$(6.7/S_{cr})$ + (weight/4) — $(S_u/2)$ — $(100/height^2)$ + 35 if male (or 25 if female)
Jeliffe 1[b,e]	$\frac{98-0.8\times(age-20)}{S_{cr}}$ (×0.90 if female)
Jeliffe 2[b]	MALE: $100/S^{cr}$ — 12 FEMALE: $80/S^{cr}$ — 7
Mawer[b]	MALE: $\frac{weight\times[29.3-(0.203\times age)]\times[1-(0.03\times Scr)]}{(14.4\times Scr)\times(70/weight)}$ FEMALE: $\frac{weight\times[25.3-(0.175\times age)]\times[1-(0.03\times Scr)]}{(14.4\times Scr)\times(70/weight)}$
Bjornsson[b]	MALE: $\frac{[27-(0.173\times age)]\times weight\times 0.07}{S_{cr}}$ FEMALE: $\frac{[25-(0.175\times age)]\times weight\times 0.07}{S_{cr}}$
Gates[b]	MALE: $(89.4 \times S_{cr}^{-1.2})$ + (55 — age) x $(0.447 \times S_{cr}^{-1.1})$ FEMALE: $(60 \times S_{cr}^{-1.1})$ + (56 — age) x $(0.3 \times S_{cr}^{-1.1})$

[a] S_{cr}, Serum creatinine concentration (mg/dL); S_u, serum urea concentration (mg/dL); alb, serum albumin concentration (g/dL); age in years; weight in kilograms

[b] Creatinine clearance estimation (ml/min)

[c] GFR estimation (ml/min per 1.73 m^2) by the six-variable or four-variable Modification of Diet in Renal Disease formulas (MDRD 1 and MDRD 2, respectively)

[d] S_{cr}, Serum creatinine concentration in mmol/L; S_u, serum urea concentration in mmol/L; height in meters

[e] Times body surface area/1.73 m^2

Sources of error for the determination of GFR from serum creatinine are, in addition to the problems of standardizing the analytical method, variation in production rate and tubular secretion [15]. Cystatin C, a small, non-glycosylated 13-kDa basic protein, has been proposed as an alternative filtration marker to creatinine [5, 15]. Cystatin C is produced at a constant rate with renal elimination occurring solely by glomerular filtration. There is no tubular secretion, and only minimal extrarenal elimination. Therefore, the blood concentration of cystatin C depends almost entirely on the GFR and is not substantially affected by diet, nutritional status, or inflammatory or malignant diseases [16]. Cystatin C facilitates the recognition of incipient CKD without the need for correction for age and anthropometric data. Specific equations also based on serum creatinine concentrations have been developed to estimate the GFR in children, such as the Schwartz formula, but these are no substitute for an accurate determination of GFR by markers such as iohexol [17].

Identifying and stratifying patients at risk for renal disease and for dosage adjustment purposes are extremely important. The selection of the most appropriate measurement of renal function depends on the clinical question being asked, the accuracy required, and the inconvenience to the patient. Serum creatinine concentration and calculated CL_{CR} yield a reasonable estimation of renal function with minimal cost and inconvenience. Glomerular filtration rate should be corrected for body surface area and interpreted in the context of physiological effects such as pregnancy, high blood pressure, liver cirrhosis, etc. [18]. The isotopic measurement of GFR can be used when a greater accuracy is required, when renal function is poor, or when muscle mass is significantly outside the normal range. The question of whether the use of calculated CL_{CR} or eGFR instead of measured CL_{CR} for dosage adjustment in patients with renal impairment is sufficiently accurate remains unresolved [19]. There is a considerable debate as to the best method to measure or estimate renal function in the course of a pharmacokinetic study in patients with renal dysfunction. Indeed, there is a growing body of literature suggesting that measured or calculated CL_{CR} does not always predict renal drug clearance for the individualization of drug dosage in a variety of clinical settings and patient groups [5, 20]. An interesting approach that has already been applied to investigate simultaneously various drug metabolizing pathways may be the use of a cocktail of markers [5, 21, 22]. A proposed cocktail to assess renal drug handling consists of sinistrin to measure GFR, para-aminohippuric acid to measure renal plasma flow and net tubular anion secretion, pindolol to measure net tubular cation secretion, and fluconazole as an indicator of passive reabsorption [22]. However, more research is needed to

confirm that measuring the different renal pathways using a cocktail approach does improve the prediction of drug clearance [5].

Renal drug clearance

Three processes can potentially contribute to the renal clearance of a drug: glomerular filtration, tubular secretion, and tubular reabsorption. Approximately 20–25% of cardiac output, or 1.1 L of blood per minute, goes to the kidneys. Of this volume, approximately 10% is filtered at the glomerulus. The glomerular filtration rate, i.e. the rate at which plasma water is filtered, is generally considered to be around 120 mL min^{-1} in a 70-kg, 20-year-old, healthy man. Large circulating molecules, such as albumin and α_1-acid glycoprotein, to which many drugs are reversibly bound, are normally not filtered to any appreciable extent at the glomerulus. Consequently, only unbound drug in plasma water is excreted by glomerular filtration. Glomerular filtration is a low clearance process. Indeed, it can be shown that the renal extraction ratio of a substance which is only filtered and not secreted nor reabsorbed by the tubules, and which is totally unbound in plasma (fu=1), is only 0.11 [23].

In addition to glomerular filtration, the kidney can extract substances from the blood by active secretion into the tubular lumen. The renal proximal tubule is the primary site of active transport for a wide variety of substrates, including organic anions/cations, peptides, and nucleosides [24–26]. The proximal tubule cells are equipped with separate transport systems for organic anions and cations, each consisting of multiple transporters localized in the plasma membranes at the basolateral and luminal membranes of the cells and with overlapping substrate specificities. Organic anion transporters belong to various transporter families, including the organic anion transporters (OATs), organic anion transporter polypeptides (OATPs), and multidrug resistance-associated proteins (MRPs) transporter families. Certain members of these transporter families have been shown to play critical roles in the renal excretion of a number of drugs (e.g., β-lactam antibiotics, anticancer agents, diuretics, nonsteroidal anti-inflammatory drugs, anti-human immunodeficiency virus drugs, antidiabetics, and angiotensin-converting enzyme inhibitors) and drug metabolites (e.g. glucuronide and glutathione conjugates). The renal organic cation transport systems, i.e. organic cation transporters (OCTs) and MDR1/P-glycoprotein (P-gp) mediate the excretion process of numerous drugs, such as cimetidine, procainamide, quinidine, anthracyclines, digoxine, etc. [24]. Drug substances secreted by the same transporters can compete with each other; in doing so, they may affect their renal clearances and can cause drug–drug interactions. Although it is generally assumed that these transporters significantly contribute to renal drug excretion and are the cause of variability in renal drug elimination, knowledge regarding the specific roles of these transporters in renal drug elimination and drug–drug interactions remains rather limited.

Active tubular secretion is an efficient mechanism for extracting substances from the circulation and secreting them into the tubular lumen. Some drugs are excellent substrates for these transporters and, consequently, they are completely removed from the blood within the time they are in contact with the active transport site, even when they are bound to plasma proteins or located in blood cells. As is the case for hepatic clearance, renal clearance by tubular secretion can be perfusion rate limited or capacity rate limited [27]. When renal clearance is perfusion rate limited, the extraction ratio is not limited to the unbound fraction of drug. Inversely, when renal drug clearance is capacity rate limited, as, for example, in the case of excretion by glomerular filtration or when the affinity of the drug is not high for the active site on the transporter, the extraction ratio is limited by the reversible binding of the drug to plasma proteins or its location in red blood cells [23].

Tubular reabsorption is the third mechanism which may influence the renal excretion of drugs. For the majority of drugs and drug metabolites, tubular reabsorption takes place by passive diffusion. The extensive reabsorption of filtered water along the renal tubule—from 120 ml of plasma water filtered per minute to only 1–2 ml min^{-1} arriving in the collecting tubules and bladder as urine—is the driving force for tubular reabsorption. Urine pH, by modulating the degree of ionization of drugs and their metabolites, and urinary flow rate, by influencing the concentration gradient, control the tubular reabsorption of drugs. Consequently, depending on the physico–chemical characteristics of the drug substances, especially lipophilicity, pKa, and molecular weight, tubular reabsorption may vary from being negligible to being virtually complete. Extensive reabsorption is seen for lipophilic drugs which readily pass across the luminal membrane back into the blood perfusing the nephron. Accordingly, their renal clearances are very low. In addition, peptide transporters (PEPT1, PEPT2) are expressed on the apical membrane of renal epithelial cells that mediate the tubular reabsorption of peptide-like drugs such as β-lactam antibiotics and angiotensin-converting enzyme inhibitors [24].

The kidneys also play an important role in the clearance of therapeutic proteins [28]. Many peptides and proteins with molecular weight <30 kDa are filtered by the glomerulus and then excreted via the urine. As the molecular weight increases (>30 kDa), the capacity of a protein for glomerular filtration decreases, and proteins such as albumin (69 kDa) and immunoglobulin (Ig)G (160 kDa) are virtually not filtered at the glomerulus. Since

the glomerular filter is negatively charged due to the presence of glycosaminoglycans, anionic proteins such as interferon-alpha (IFN-α) and tumor necrosis factor-alpha (TNFα) are repelled and not filtered. After glomerular filtration, peptides can be excreted unchanged in the urine or degraded to products that are excreted in the urine [29]. Polypeptides and proteins can also be actively reabsorbed by the proximal tubules through luminal endocytosis, followed by hydrolysis by the digestive enzymes in the lysosomes to peptide fragments and amino acids [30]. The amino acids are then reabsorbed by a carrier-mediated, energy-dependent transport mechanism. The net result is that only a small fraction of intact protein is detected unchanged in urine. Examples of proteins that undergo tubular reabsorption are oxytocin, vasopressin, calcitonin, insulin, and growth hormone.

Low-molecular-weight proteins (lysozyme, insulin, and growth hormone) are extensively filtered by the kidneys, reabsorbed from the luminal side by renal tubular cells, and released back into the circulation either as intact molecules or as catabolic products, i.e., amino acids and polypeptides. Renal tubular cells also have an active transport mechanism for di- and tripeptides [24, 30]. Many circulating peptides can undergo peritubular extraction and hydrolysis, which is another renal mechanism of elimination for peptides. This mode of renal elimination has been demonstrated for calcitonin, oxytocin, vasopressin, parathyroid hormone, angiotensin II, insulin, and interleukin (IL)-2 [31].

Effect of renal dysfunction on pharmacokinetic processes

Absorption

Drugs are most frequently administered orally. Both the rate and extent of absorption from the gastrointestinal tract influence the drug plasma concentration–time profile. The gastrointestinal absorption of a drug is usually not studied in detail in patients with renal dysfunction. The rate of absorption is, in most clinical pharmacokinetic studies, assessed by measuring Tmax, the time at which the maximum plasma concentration (Cmax) occurs. Tmax has been shown to be slightly increased for a number of drugs when administered orally to patients with severe renal dysfunction. However, this is certainly not true for all drugs, and the clinical consequences are in most cases negligible. The longer Tmax may be due to reduced gastric emptying in these patients or simply to a longer plasma elimination half-life of the drug. Extent of oral absorption (absolute bioavailability, F) is best assessed by comparing the area under the plasma drug concentration–time curve (AUC) following oral and intravascular administration. Most pharmacokinetic studies in patients with renal dysfunction do not measure absolute oral bioavailability but simply determine pharmacokinetic parameters such as plasma clearance (CL), volume of distribution (V) and plasma half-life (t½) following oral administration of the drug. Changes in AUC following oral drug administration may not only be due to altered extent of absorption but also to altered plasma clearance and volume of distribution and, consequently, are not always easy to interpret. Drugs undergoing significant presystemic elimination (gut wall, liver) will have a moderate to low oral bioavailability [32]. Impaired drug metabolism has been shown in patients with severe renal dysfunction (see below) and may be the cause of a significant increase in oral bioavailabity in these patients due to reduced presystemic elimination [33, 34]. One of the first well-documented examples of increased plasma drug concentrations due to decreased first-pass metabolism is propoxyphene [35, 36]. Propoxyphene is subject to pronounced pre-systemic biotransformation after oral administration. In functionally anephric patients, the AUC of propoxyphene and its major metabolite, norpropoxyphene, was shown to be approximately twofold higher than that of healthy control subjects. The increase in the AUC of propoxyphene is very likely the result of reduced pre-systemic metabolism in the anephric patients. Norpropoxyphene is normally eliminated renally and, therefore, accumulates when renal function is impaired. Like propoxyphene, norpropoxyphene can depress cardiac conduction, and its accumulation can contribute to the cardiac toxicity associated with propoxyphene intoxication. Other drugs with reduced oral bioavailability due to pronounced presystemic elimination, such as propranolol, dihydrocodeine, and sildenafil, have been shown to have a significant increase in AUC when administered orally to patients with severe renal dysfunction [33, 34, 37–39].

Patients with renal disease are treated with many medications, some of which may alter the absorption of other concomitantly administered drugs. For example, hyperphosphatemia is an important component of the bone disease seen in chronic renal failure, and many of these patients take phosphate binders, such as calcium carbonate, lanthanum carbonate, and sevelamer hydrochloride. These phosphate binders may interact with certain drugs (e.g., many fluoroquinolones) in the gastrointestinal tract, thereby reducing their extent of absorption [40, 41].

Distribution

The plasma protein binding of many acidic drugs is decreased in patients with renal dysfunction [33, 34, 42]. Several mechanisms have been proposed to explain this decreased plasma binding, including hypoalbuminemia, the

accumulation of endogenous substances which competitively displace acidic drugs from their binding sites on albumin, and a conformational change of the binding sites on the albumin molecule. While acidic drugs usually only bind to plasma albumin, basic drugs in general have a high affinity for α_1-acid glycoprotein but often also bind to albumin and lipoproteins. Although the plasma binding of basic drugs appears to be generally unaffected in patients with chronic renal disease, it may be increased for some drugs (e.g., bepridil, disopyramide) because α_1-acid glycoprotein is an acute phase protein that is elevated in certain patients with renal disease, such as in renal transplant patients and patients on hemodialysis [33, 34, 42].

The unbound fraction in plasma is an important determinant of the oral clearance of blood flow-limited drugs and of the oral and systemic clearance of capacity-limited drugs [27, 32]. In these cases, reduced plasma protein binding will lead to an increase in the total plasma clearance, which should not be misinterpreted as an increased capacity of the patient to eliminate the drug. For example, the oral drug clearance will change in direct proportion to its unbound fraction in plasma (fu) if the intrinsic capacity of the eliminating processes to remove the drug from the body (i.e. intrinsic clearance CL_{int}) is not affected:

$$CL_{oral} = fu \cdot CL_{int} \quad (1)$$

Therefore, to correctly interpret the effect of renal dysfunction on the oral drug clearance, one should take alterations of fu into account. For example, suppose the unbound fraction in the plasma of a drug administered orally is doubled in a patient with renal dysfunction. Assuming CL_{int} is unaffected, the plasma clearance (CL_{oral}) will then double, and total plasma drug concentration will decrease to half its normal value. However, the unbound plasma concentration of the drug Cu (i.e., Cp × fu), which is the therapeutically active moiety, will remain unchanged, and despite lower total plasma drug concentrations, the dose will not have to be adjusted. As a consequence, for therapeutic drug monitoring purposes of therapeutic agents, such as phenytoin and valproic acid, whose unbound plasma fraction may be significantly increased in patients with renal dysfunction, unbound rather than total plasma concentrations should be determined [42].

The volume of distribution of several drugs is significantly increased in patients with severe renal dysfunction [33, 34]. An increased volume of distribution may be the result of fluid overload, decreased protein binding, or altered tissue binding. The volume of distribution of a few drugs, such as digoxin, pindolol, and ethambutol, is decreased in patients with ESRD probably due to a decrease in their tissue binding [34]. V_{area} represents the volume of distribution during the terminal plasma elimination phase when a distribution equilibrium between the drug in plasma and all tissues is achieved. V_{ss} is the volume of distribution that applies at steady state when the drug is infused at a constant rate [32]. V_{area} varies when drug elimination changes (e.g., in a patient with renal dysfunction) even though there is no change in the distribution space. It is therefore preferable to define a drug's distribution volume in terms of V_{ss}, a parameter that is theoretically independent of changes in the drug's rate of elimination. Knowing the volume of distribution of a drug is important in case a loading dose has to be administered to rapidly achieve plasma drug concentrations within the therapeutic window (see below).

Elimination

Metabolism is the major mechanism for the elimination of drugs from the body. Relatively few drugs are eliminated almost entirely unchanged by the kidneys. The plasma clearance of a drug is the pharmacokinetic parameter that best describes the capacity of a patient to eliminate that drug substance. Drug plasma clearance (CL) is generally considered to be the sum of a renal and non-renal component:

$$CL = CL_R + CL_{NR} = fe \cdot CL + (1 - fe) \cdot CL \quad (2)$$

where CL_R and CL_{NR} denote renal and non-renal plasma clearance, respectively, and fe is the fraction of the (intravenous) dose excreted unchanged in the urine by a healthy kidney and indicates the contribution of the kidney to the overall elimination of the drug. We will now briefly discuss how the processes involved in the renal and non-renal clearance of drugs may be altered in patients with renal dysfunction.

Renal excretion

Depending on the etiology of renal dysfunction, the normal histology of the glomeruli and the tubules may be differentially affected. However, according to the intact nephron hypothesis, the function of all segments of a diseased nephron are assumed to be equally affected [43]. Consequently, it is assumed that, regardless of the intrarenal pathways of excretion, i.e., filtration, secretion, and reabsorption, the loss of excretory function in the diseased kidney can be quantified by GFR, a measure of glomerular function. Although it has been shown in rat models of acute renal failure that glomerular filtration and tubular secretion by the anionic and cationic pathways are not equally affected, the renal clearance of most drugs in patients appears to vary in direct proportion to GFR or to a measure of GFR, such as estimated creatinine clearance, regardless

of the intrarenal mechanism involved in their urinary excretion. For example, the plasma clearance of memantine has been shown to increase in direct proportion to CL_{CR}, as estimated by the Cockroft–Gault method (Fig. 1) [44]. When there is no renal function (*y*-intercept, $CL_{CR}=0$), some plasma clearance remains: this is the non-renal clearance. Dosage adjustment of memantine in patients with impaired renal function will be based on the relationship between memantine plasma clearance and CL_{CR} in the studied patient sample (Table 2). As pointed out before, the intact nephron hypothesis has been questioned by some researchers who believe that a better method to quantify renal function for dosage adjustment purposes may be based on the cocktail approach [5, 20].

Drug metabolism

There is overwhelming experimental evidence that, both in laboratory animals and in patients, the non-renal clearance of many drugs can also be altered in renal dysfunction. It has long been known that even drugs which are mostly or completely eliminated from the body by non-renal mechanisms may accumulate in patients with renal dysfunction if their dosage regimen is not adjusted [45–47]. Pharmacokinetic studies in patients with renal dysfunction have shown that non-renal clearance is reduced for many drugs, especially in ESRD, providing indirect evidence that the metabolism of these drugs is impaired in these patients. Recently, the effect of renal dysfunction on drug-metabolizing enzymes has been more directly demonstrated. Dowling et al. used the erythromycin breath test (EBT)

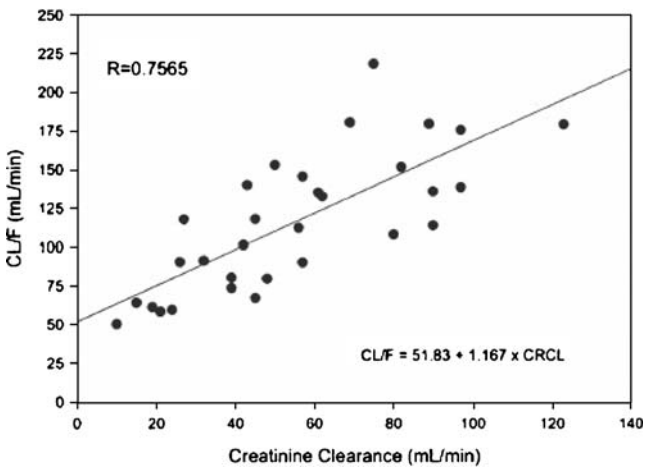

Fig. 1 The plasma clearance (*CL/F*) of memantine, following oral administration of 20 mg memantine to healthy subjects and patients with varying degrees of renal dysfunction, varies linearly with creatinine clearance. The plasma clearance of memantine in a patient with no renal function, i.e. $CL_{CR}=0$, is due to non-renal clearance (metabolism). (Reprinted with permission of the American Society for Clinical Pharmacology and Therapeutics from Periclou et al. [44])

to assess hepatic CYP3A activity in patients with ESRD undergoing long-term hemodialysis three times weekly [48]. The EBT following intravenous administration of ^{14}C-erythromycin has been extensively used to measure in vivo hepatic cytochrome 450 (CYP)3A activity, although the outcome of the test may also be affected by the activity of hepatic uptake and efflux transporters such as OATP and P-gp [49]. The results of this study showed that patients with ESRD had a 28% lower baseline hepatic EBT value despite adequate dialysis compared to age-matched healthy control subjects. In another study, Dreisbach et al. measured the plasma warfarin S/R ratio in patients with ESRD undergoing hemodialysis three times weekly and in healthy controls [50]. S-warfarin is metabolized almost exclusively by CYP2C9 and R-warfarin by multiple CYP (CYP1A2, CYP2C19, CYP3A) and non-CYP pathways [51]. Consequently, the plasma warfarin S/R ratio may be a useful indicator of relative CYP2C9 activity. The plasma S/R warfarin ratio was increased by approximately 50% in ESRD patients compared to healthy controls, indicating that CYP2C9 activity in these patients was reduced more than the activity of the other enzymes contributing to the metabolism of warfarin. The idea that renal dysfunction could differentially affect the activity of various drug-metabolizing enzymes, similar to what has been described in liver cirrhosis, is not new [52, 53]. Indeed, Teunissen et al. showed that although the overall plasma clearance of antipyrine, a marker substance completely eliminated by metabolism catalyzed by several CYP450 isoenzymes, was not different in patients with chronic renal failure compared to healthy control subjects, the formation clearance of one of the metabolites, norantipyrine, was decreased on average by 50% in the renal patients [54].

Many in vivo and in vitro studies using rat models of acute and chronic renal failure spanning several decades have shown a down-regulation of the activity of not only CYP450 enzymes but also other drug-metabolizing enzymes, such as N-acetyltransferase [55–65]. In contrast, the activity of UDP-glucuronosyltransferases 1A and 2B seem to be preserved [66]. Uremic toxins that accumulate in the body in chronic renal failure have been implicated in these alterations in drug-metabolizing enzyme activity [60, 61]. Nolin et al., for example, showed that hemodialysis acutely improves erythromycin breath test results in patients with ESRD [67]. Because intravenously administered erythromycin is not only a substrate for hepatic CYP3A, but also for hepatic uptake (OATP) and efflux (P-gp) transporters, these observations may indicate that uremia alters the activity of CYP3A and transporters simultaneously or independently.

Many drugs and/or their phase I metabolites are eliminated by glucuronidation [68]. These glucuronides are very polar and are efficiently excreted by renal

Table 2 Plasma clearance (CL/F) of memantine in patients with varying degrees of renal dysfunction [44]. Patients were classified according to their renal function as recommended by FDA and EMEA guidelines

Group	Description	GFR (mL min^{-1} per $1.73m^{-2}$)	CL/F of memantine (mL min^{-1})[a]
1	Normal renal function	>80	147.8±28.6 (n=8)
2	Mild renal impairment	50–80	146.0±39.7 (n=8)
3	Moderate renal impairment	30–50	93.9±24.7 (n=8)
4	Severe renal impairment	<30	71.7±23.9 (n=7)
5	End-stage renal disease	Requiring dialysis	-

FDA, Federal Drug Administration; EMEA, European Medicines Agency; GFR, glomerular filtration rate

[a] Values are the mean ± standard deviation

mechanisms such as tubular secretion. Acyl glucuronides, i.e., glucuronide conjugates of compounds containing a carboxylic acid group, are not stable at physiological pH and are susceptible to hydrolysis by a myriad of catalysts, including β-glucuronidases, non-specific esterases, serum albumin, and hydroxide ions [69]. In patients with renal dysfunction, glucuronide conjugates generally accumulate in the plasma. In the case of plasma accumulation of acyl glucuronides of carboxylic acid drugs, this will inevitably lead to their systemic hydrolysis and, consequently, reduced plasma clearance of the parent compound. Systemic hydrolysis of acyl glucuronides has been shown to be the cause of accumulation of several carboxylic acid drugs in patients with renal dysfunction [69, 70]. For example, the arylpropionic acid non-steroidal anti-inflammatory drug ketoprofen has a significantly reduced plasma clearance in patients with renal dysfunction because of the compromised capacity to excrete ketoprofen acyl glucuronide in urine which results in enhanced regeneration of the parent drug by hydrolysis [71–73].

The kidney also expresses many of the same drug-metabolizing enzymes as those found in the liver. In vitro studies with human kidney and liver microsomes have shown that many drugs can be metabolized at comparative rates in both organs [74–76]. In addition, studies in patients undergoing liver transplantation have clearly shown that drugs such as propofol and morphine are glucuronidated during the anhepatic phase of the surgery, presumably in the kidney and possibly in other organs as well [77–79]. An interesting example illustrating how renal drug metabolism may be impaired in patients with reduced kidney function is provided by imipenem, an antibiotic that is partly eliminated by metabolism by renal brush border dehydropeptidase and by renal excretion. A study in patients with varying degrees of renal dysfunction demonstrated that its renal metabolism decreased with decreasing renal function [80]. The total weight of the kidneys, however, is much less than the weight of the liver and, therefore, the contribution of the kidneys to the overall in vivo drug metabolic clearance is, in most cases, probably relatively low.

Drug transport

Most studies to date have focused on the role of drug-metabolizing enzymes as key determinants of the pharmacokinetic processes of absorption (presystemic metabolism) and elimination (metabolism). During the last decade, however, it has become increasingly apparent that carrier-mediated processes, or transporters, may have a significant impact on drug pharmacokinetics through their targeted expression in organs such as the intestine, the kidney, and the liver [81]. Although reduced metabolic enzyme activity can be responsible for the decrease in the non-renal clearance of drugs in patients with renal dysfunction, it has increasingly become evident that other mechanisms, such as alterations in the activity of transporters, may also be involved. Recent work by Benet and colleagues has clearly shown that metabolic enzyme and transporter activities are interdependent and that this interplay significantly affects the systemic exposure of drugs cleared through non-renal routes [49, 82–85]. For example, inhibition of hepatic OATP1B-mediated uptake of atorvastatin, a substrate of both OATP1B and CYP3A, resulted in a more than fourfold increase in the AUC of atorvastatin and its two primary metabolites, 2-OH- and 4-OH-atorvastatin [85]. This means that inhibition of the hepatic OATP-mediated uptake of drugs, such as atorvastatin, could translate into significant clinical changes in drug efficacy and toxicity. Very little information is available to date on the effect of renal dysfunction on the activity of drug transporters in patients. However, results of several studies in rat models have shown that the activity of uptake and efflux transporters, expressed in the small intestine, the kidney, and the liver, is altered in chronic renal failure [60, 86, 87]. For example, the protein expression of the intestinal efflux transporters P-gp and MRP2 is decreased

in rats with chronic renal failure, whereas the expression of the influx transporters Oatp2 and Oatp3 is not affected. In the liver, however, protein expression of P-gp and Oatp2 is reduced, whereas MRP2 expression is not affected by chronic renal failure. These results indicate that chronic renal failure can affect the expression of drug transporters differently in the liver compared to the intestine.

A consequence of chronic renal failure is the accumulation in the body of molecular breakdown products normally eliminated by the kidneys, such as urea, parathyroid hormone, indoxyl sulfate, and cytokines. These breakdown products, referred to as uremic toxins, have been implicated in a number of problems in patients with chronic renal failure, including bleeding tendencies from platelet dysfunction, hypertension, cardiac failure, neuropathy, irregularities in thyroid function, altered protein binding of drugs, decreased renal tubular secretion of organic ions, and inhibition of hepatic drug metabolism [88, 89]. The prevailing explanation is that accumulated uremic toxins are also responsible for altered transporter activity in patients with chronic renal failure by either transcriptional or translational modifications, or acute post-translational modifications of the transporter function in question. The latter explanation is supported by findings in experimental chronic renal failure models and in patients with ESRD that the plasma clearance of CYP450 and transporter substrates is increased by dialysis, which reduces the concentrations of these uremic toxins [67, 90, 91].

Accumulation of active metabolites

Many drugs are eliminated from the body by metabolism. The metabolites thus formed are often thought of as inactive waste products, which is certainly not always the case. Numerous examples exist of substances, so-called prodrugs, which rely on in vivo biotransformation into one or more active metabolites to exert their pharmacological effects. In many other cases, both the parent compound and its metabolite(s) are active. The duration and intensity of the pharmacological responses are dependent on the time courses of all active substances in the body. Drug metabolites are usually eliminated by further metabolism and/or renal excretion. Consequently, metabolites, especially polar phase II conjugates such as glucuronides and sulfates, often accumulate in patients with renal dysfunction. When adjusting the dosage of a drug in these patients, the altered pharmacokinetics of all active species of the drug molecule has to be considered [33, 92].

Morphine is a good example illustrating the significance of the accumulation of drug metabolites in patients with renal dysfunction. Morphine is eliminated by metabolism to five metabolites: morphine-3-glucuronide, morphine-6-glucuronide, normorphine, codeine, and morphine-N-oxide [38]. Renal excretion of morphine itself only accounts for approximately 4% of its overall elimination. However, when given standard doses of morphine, patients with renal dysfunction showed typical signs of morphine intoxication, i.e., respiratory depression, mental obtundation, and hypotension [38, 93, 94]. Subsequent studies showed that the major morphine metabolites, i.e., morphine-3-glucuronide and morphine-6-glucuronide, which are normally excreted by renal mechanisms, extensively accumulate in patients with renal dysfunction [95, 96]. Unexpectedly, it was also shown that morphine-6-glucuronide is a stronger opioid analgesic than morphine itself and that the prolonged respiratory depression in renal failure patients receiving morphine if due to high plasma levels of morphine-6-glucuronide [97–99]. However, transporters may also be involved in the altered pharmacokinetics and toxicity of morphine and its active glucuronide in patients with renal dysfunction. Morphine-6-glucuronide does not easily cross the blood-brain barrier in patients with normal renal function [100]. However, even after a single dose of morphine given orally to renal patients requiring hemodialysis, the concentration of morhine-6-glucuronide in plasma dramatically increases and its cerebrospinal fluid (CSF) concentration 24 h following morphine administration is 15 times higher than that found in patients with normal kidney function [101]. P-glycoprotein and other transporters expressed at the blood–brain barrier have been shown to modulate the transport of morphine-6-glucuronide into the brain [102, 103]. The activity of these transporters could be altered in renal failure. In addition, the situation is even more complex because mutations in the μ-opioid receptor may play a protective role against morphine-6-glucuronide-related opioid toxicity [104]. The morphine example illustrates that multiple factors, pharmacokinetic and pharmacodynamic, may be responsible for the increased sensitivity of certain drug substances and their active metabolites in patients with renal dysfunction.

Effect of dialysis on drug pharmacokinetics

Hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), and automated peritoneal dialysis are established treatments for patients with ESRD [105, 106]. High-flux dialysis and hemodiafiltration are more recently introduced renal replacement therapies in ESRD patients [107, 108]. All of these procedures are designed to remove toxic waste products that accumulate in patients with ESRD. However, they also remove drugs and active drug metabolites and, consequently, dosage adjustment may be necessary in patients treated with these dialysis techniques.

The efficiency of a dialysis system to remove drugs from the body depends on many factors, including the character-

istics of the drug substance (molecular weight, plasma protein binding, volume of distribution), the properties (membrane type, surface area, thickness etc) and geometry (countercurrent or concurrent blood and dialysate flow) of the dialysis system, and dialysis conditions (e.g., blood and dialysate flow rates, duration of the dialysis treatment) [32, 34]. As a result, quantitative extrapolation of drug dialyzability from one study to another may be complicated.

One approach to dosage adjustment in dialyzed patients is to replace the amount of drug lost in the dialysate during the treatment period. The fraction of the drug in the body at the start of dialysis that is eliminated by the dialysis procedure depends on the fraction of total elimination that dialysis represents and the fraction of drug lost by all routes of elimination [32]:

$$\text{fraction of drug initially in body eliminated by dialysis} = f_D \cdot \left[1 - e^{k_D \cdot \theta}\right] \quad (3)$$

where f_D is the fraction of total elimination occurring by dialysis, k_D is the overall elimination rate constant during dialysis, and θ is the duration of the dialysis period. Kinetic parameters characterizing the efficacy of a dialysis procedure, such as f_D, k_D, and dialysis clearance, for drugs that are likely to be administered to ESRD patients are determined during the drug development process or in the years shortly after introduction of the drug onto the market [109, 110]. Specific information on drug dosage in patients with ESRD undergoing regular dialysis treatment can be found in specialized scientific journals and books [see, for example, 111–115].

Dosage adjustment in patients with renal dysfunction

Adjustment of the usual drug dosage regimen may be necessary in patients with renal dysfunction to avoid excessive accumulation of the drug and/or its active metabolite(s) which could result in serious adverse reactions. A dosage regimen is characterized by the maintenance dose (D_M) and the dosing interval (τ). The goal is to derive an equation that allows estimation of the maintenance dosing regimen in a patient with renal dysfunction based on a measure of his/her kidney function (KF). The objective is to adjust the usual dosage regimen, by reducing the maintenance dose and/or prolonging the dosing interval, to avoid accumulation of the drug (and/or its active metabolites) in the patient with impaired kidney function. Despite the complexity of the mechanisms underlying the alterations in drug pharmacokinetics in patients with renal dysfunction, a general approach can be developed.

The aim of dosage adjustment in patients with renal dysfunction is to maintain the same average unbound plasma concentrations at steady state ($Cu_{ss,\ ave}$) in the renal patient compared to the typical patient (55 years old, 70 kg) with normal kidney function:

$$Cu_{ss,ave} = \frac{F \cdot [D_M/\tau]}{CLu} = \frac{F^* \cdot [D_M/\tau]^*}{CLu^*} \quad (4)$$

where F is the oral bioavailability, CLu is the plasma clearance of unbound drug, and D_M/τ is the oral dosage regimen in a patient with normal kidney function. A superscripted asterisk is used to indicate parameters for a patient with renal dysfunction. The adjusted dosage regimen for the renal patient, i.e. $[D_M/\tau]^*$, can then be calculated as follows:

$$[D_M/\tau]^* = \frac{CLu^*/F^*}{CLu/F} \cdot [D_M/\tau] \quad (5)$$

When oral bioavailability is not altered in the patient with renal dysfunction, F and F^* can be omitted from the equation. CLu represents the overall plasma clearance of unbound drug, i.e., it consists of a renal and a non-renal clearance. The unbound clearance ratio, CLu^*/CLu, can be estimated using the following relationship [32, 34]:

$$\frac{CLu^*}{CLu} = KF \cdot fe + [1 - fe] \cdot \frac{\left[(140 - age) \cdot BW^{0.7}\right]}{1660} \quad (6)$$

where KF is kidney function, and fe is the fraction of the (intravenous) dose excreted as unchanged drug in the urine in a patient with normal renal function. Age and body weight (BW) of the renal patient are expressed in years and kilograms, respectively. The second part of the left side of Eq. 10 represents a factor by which the non-renal plasma clearance of the drug deviates from that in the typical 55-year-old, 70-kg patient without renal disease. The kidney function (KF) in a particular patient can be estimated as the ratio of the patient's creatinine clearance to a presumed normal creatinine clearance of 120 ml min^{-1} per 1.73 m^{-2}.

For this general approach to be applicable, a number of conditions have to be fulfilled: (1) the renal clearance of the drug is directly proportional to the measure of kidney function, for example, creatinine clearance, used to establish the relationship; (2) renal function does not affect the metabolic (non-renal) elimination of the drug; (3) renal and non-renal elimination of the drug are linear; (4) the pharmacodynamic response to the drug is not altered in renal dysfunction. To take potential differences in plasma protein binding between renal patients and patients with normal kidney function into account, these equations are based on unbound drug clearance. This is important for

those drugs that show altered plasma protein binding in patients with renal dysfunction.

Many drugs have a markedly prolonged plasma half-life in patients with renal dysfunction. The time required to reach steady state by the administration of a maintenance dose at a constant dosing interval is approximately five half-lives [32]. Therefore, administration of a loading dose is sometimes required in these patients when it is important to rapidly achieve plasma drug concentrations within the therapeutic window. Calculation of the loading dose of a particular drug is based on the volume of distribution, the bioavailability F, and the target drug concentration in plasma:

$$D_L = \frac{Cp_{target} \cdot V}{F} \quad (7)$$

where D_L is the initial dose or loading dose, Cp_{target} is the drug's target concentration in plasma, and V is its distribution volume.

Altered pharmacodynamics in renal disease

Chronic renal failure can affect multiple organ systems and, consequently, the response to a given drug may change even though the drug's pharmacokinetics are not dramatically altered. For example, furosemide reaches its site of action, the luminal side of the ascending limb of the loop of Henle, via tubular secretion. Patients with chronic renal failure exhibit an increased maximal response when the dose is adjusted to the functional status of the kidneys [116, 117]. To achieve an adequate diuretic response in these patients, plasma furosemide concentrations must be increased by administering larger doses so that adequate amounts of drug reach the site of action. Adjusting the furosemide dose in a patient with renal dysfunction to maintain normal plasma concentrations would not be appropriate because of the altered pharmacodynamic response of furosemide in chronic renal failure.

Several studies of enoxaparin in patients with varying degrees of renal failure have shown that anti-Xa clearance decreases with the degree of renal function [118, 119]. As a result, dosage reduction is recommended in patients with severe renal impairment (i.e., CL_{CR}<30 ml min^{-1}). However, the accumulation of uremic toxins in chronic renal failure causes complex disturbances of the coagulation system. Uremia can lead to an increased bleeding tendency, for example, due to platelet dysfunction, which is further enhanced by the use of anticoagulants during extracorporeal blood purification procedures [120, 121]. In major clinical trials, enoxaparin has been associated with increased bleeding rates in patients with chronic renal failure [122]. It seems that dosage adjustment based on measures of kidney function, such as CL_{CR}, may not always lead to optimal anticoagulation in patients with chronic renal failure [123]. Further studies with enoxaparin may therefore be necessary to define and determine the need for dosage adjustments based on pharmacokinetic/pharmacodynamic (PK/PD) studies in patients with chronic renal failure.

The effect of renal dysfunction on the pharmacodynamic responses of drugs has not been well studied. However, the examples of furosemide and enoxaparin show that ideally integrated PK/PD studies are needed to evaluate the necessity of dosage adjustment in renal dysfunction.

Drug development and regulatory implications

The clinical efficacy and safety profile of a new medicinal product is established in phase III studies, which are usually restricted to a well-defined patient population. This population may not fully represent the patient population in which the drug will be used once it is on the market. Therefore, pharmacokinetic and pharmacodynamic studies in special populations are performed to estimate drug exposure in subpopulations of patients with characteristics that may affect drug exposure, such as children, elderly patients, and patients with renal or hepatic impairment. The clinical consequences of altered exposure are then assessed, taking PK/PD relationships into consideration. If needed, specific treatment recommendations can then be developed [124].

Recommendations regarding the pharmacokinetic characterization of drugs in patients with renal dysfunction are published by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) [109, 110]. These guidelines recommend that a pharmacokinetic study be carried out during the development of a drug which is likely to be used in patients with impaired renal function and when renal dysfuncton is likely to significantly alter the pharmacokinetics of the drug substance and/or its active metabolite(s). As described before, renal dysfunction has not only been shown to decrease the renal clearance of drugs and their metabolites, but it has also been associated with altered absorption, plasma protein binding, distribution, biotransformation and, in some cases, pharmacodynamics in patients with impaired renal function. Therefore, it should be mandatory to study the impact of renal dysfunction on PK/PD of all drugs that will be used in these patients, for the simple reason that it is difficult to predict the impact kidney function may have on the PK/PD of a particular drug [125].

According to the FDA and EMEA guidelines, the pharmacokinetics of the drug should be characterized in patients with various degrees of renal dysfunction versus patients typical of "the usual patient population", thus not necessarily normal healthy young volunteers, to assess whether a dosage adjustment is required in patients with renal dysfunction. These guidelines recommend that a measure of

GFR be used to assess renal function and to classify patients into five groups: (1) normal renal function (CL_{CR} >80 mL min^{-1}); (2) mild renal impairment (CL_{CR} 50–80 mL min^{-1}); (3) moderate renal impairment (CL_{CR} 30–49 mL min^{-1}); (4) severe renal impairment (CL_{CR} <30 mL min^{-1}); (5) ESRD (patients requiring dialysis) (see also Table 2). This classification recommended by the FDA and EMEA is slightly different from the classification of The National Kidney Foundation Kidney Disease Outcomes Quality Initiative to stage chronic renal disease [6]. Estimated creatinine clearance, based on serum creatinine levels and the Cockroft–Gault formula, is widely used in patient care settings as a measure of renal function because it is more practical than most other kidney function tests. The EMEA guideline recommends that renal function be determined by measuring GFR using accurate well-established methods, such as iohexol clearance.

The traditional two-stage method is most often used to assess whether dosage adjustment is required for patients with impaired renal function, and if so, to develop dosing recommendations based on measures of renal function. In the two-stage approach, a detailed pharmacokinetic (data-rich) study is carried out in carefully selected subjects to minimize interindividual variability in order to obtain estimates of individual pharmacokinetic parameters, such as plasma clearance, distribution volume, plasma half-life, etc. Subsequently, relationships between patient characteristics (e.g., CL_{CR}) and the estimated pharmacokinetic parameters are established by categorization or regression techniques, and these may be useful for recommending dosage adjustment for certain patient categories. An example of this two-stage approach is the study mentioned above on the *N*-methyl-D-aspartate receptor antagonist memantine carried out by Periclou et al. in patients with varying degrees of renal impairment [44] . Based on the results of this study, the authors concluded that no dosage adjustments are needed for patients with mild or moderate renal impairment. In patients with severe renal impairment, however, a target dose of 5 mg twice daily is recommended compared to the normal dosage regimen of 10 mg twice daily (Fig. 1; Table 2). This specific dosing recommendation should then be included in the Summary of Product Characteristics of the medicinal product. Both the FDA and EMEA guidelines also recommend that, when possible, pharmacodynamic assessment should be included in these pharmacokinetic studies in patients with renal impairment [109, 110].

Population pharmacokinetics in patients with renal dysfunction

Population pharmacokinetics is the study of the sources and correlates of the variability in drug plasma concentrations among individuals, who constitute the target patient population, receiving clinically relevant doses of a drug of interest [126–128]. Over the past two decades, the population pharmacokinetic approach has gained tremendous importance and has become the new standard in drug development. Population pharmacokinetics has increasingly been applied for the evaluation of new treatment regimens and for dose individualization [see 129–131]. Population PK/PD models assist in the selection of the optimal dose for individual patients or for patient subgroups by identifying patient characteristics related to drug exposure or treatment outcome. Nonlinear mixed-effects modeling, which is a parametric one-stage method, has been used most frequently to perform population analyses. The mixed effects that are simultaneously estimated comprise fixed effects (typical parameter estimates and covariate effects) and random effects (variability between individuals and residual error).

It is clear that a population PK/PD study in patients participating in phase II/phase III clinical trials can be used to assess the impact of renal function on the PK/PD of a drug. Both the FDA and EMEA guidelines for evaluating the effect of renal impairment on the pharmacokinetics of medicinal products discuss the possibility of using the population pharmacokinetic approach as an acceptable alternative, or for confirming the dosing recommendations derived from a traditional two-stage pharmacokinetic study in renal impairment patients. For example, enoxaparin, a low-molecular-weight heparin, is partially degraded by the liver to inactive fragments and partially eliminated by the kidneys in forms retaining biological activity [123]. Several pharmacokinetic studies have shown that enoxaparin clearance is significantly related to determinants of renal function [118, 119]. Consequently, enoxaparin accumulates in patients with renal impairment, resulting in an increased level of anticoagulation assessed by anti-factor Xa activity. These studies have suggested that a dose adjustment should be considered in patients with renal impairment. The FDA subsequently recommended a decrease of enoxaparin dosage by reducing the frequency of administration, i.e. from 1 mg kg^{-1} 12 h^{-1} (the recommended dosage in non-renal failure patients) to 1 mg kg^{-1} 24 h^{-1} in patients with severe renal impairment [132]. Hulot et al. conducted a population pharmacokinetic analysis using 532 patients receiving subcutaneous (s.c.) enoxaparin for the treatment of non-ST-segment elevation of acute coronary syndrome and having normal renal function (34%), mild renal impairment (36%), moderate renal impairment (20%), and severe renal impairment (10%) [133]. Population pharmacokinetic modeling and simulations were carried out by using NONMEM, the standard software package for nonlinear mixed-effects modeling. The results of their analyses indicate that the following enoxaparin dosage adjustments should be implemented in renal dysfunction:

0.8 mg kg^{-1} 12 h^{-1} in patients with moderate renal impairment, and 0.66 mg kg^{-1} 24 h^{-1} in patients with severe renal impairment. Their analyses also suggest that an initial s.c. dose of 1 mg kg^{-1} could be administered regardless of kidney function to avoid subtherapeutic anti-Xa activities in the first hours following the start of enoxaparin therapy. This example illustrates how population pharmacokinetic modeling is useful to confirm or further improve dosing guidelines recommended on the basis of data obtained from the traditional two-stage approach.

Concluding remarks

Renal dysfunction affects more than just the renal clearance of drugs and/or active drug metabolites. Other important pharmacokinetic processes, such as plasma protein binding and the distribution and metabolism of drug substances, may be altered, especially in patients with severe renal impairment or ESRD. Even when the dosage adjustments recommended for patients with renal dysfunction are carefully followed, adverse drug reactions remain common. The following are general guidelines to take into account when administering drugs to patients with renal dysfunction:

- When fe (fraction of the intravenous dose excreted unchanged in the urine) is >0.3, a dosage adjustment is most likely required at least in patients with severe renal impairment (CL_{CR}<30 mL min^{-1}) and patients with ESRD. For drugs whose fe approaches 1.0, dosage adjustment will probably be necessary when the CL_{CR} < 50 ml min^{-1}, or even for patients having a CL_{CR} between 50 and 80 mL min^{-1}.
- When the fe is <0.3, elimination of the drug from the body occurs to a large extent by non-renal mechanisms, in most cases by metabolism. Since it has been shown that drug metabolism may be altered in patients with chronic renal failure, dosage adjustment may also be necessary for these drugs to avoid excessive accumulation of the drug.
- Estimation of GFR based on serum creatinine level and using the Cockroft–Gault equation is still the most widely used approach for drug dosage adjustment, although it is known to have limitations in certain classes of patients, such as critically ill patients with burns and patients with the hepato-renal syndrome.
- Patients with ESRD require regular treatment by extracorporeal techniques (hemodialysis, peritoneal dialysis, hemofiltration) to remove endogenous toxic substances that would otherwise accumulate. These techniques may increase drug elimination, thereby complicating drug therapy in these patients.
- The plasma protein binding of several drugs (especially weak acids) may be significantly decreased in patients with renal impairment. Although a change in drug dosage may not be necessary if only the plasma protein binding of the drug is altered, interpretation of drug plasma concentrations (therapeutic drug monitoring) should be based on unbound plasma concentrations.
- Because the plasma half-life may be considerably longer in a patient with renal impairment, a loading dose may be required when it is important to rapidly achieve target plasma drug concentrations.
- Many examples exist of active drug metabolites that accumulate in patients with renal dysfunction if the dosage of the parent drug is not properly adjusted. In addition, the pharmacodynamics of certain drugs may be altered in patients with renal impairment. The assumption, therefore, that equal or similar drug plasma concentrations in patients with renal impairment and in patients with normal kidney function will result in similar drug responses may not always be correct.
- Severe hepatic dysfunction is usually accompanied by some renal impairment (hepato-renal syndrome). Reduced renal excretion has been reported in patients with severe cirrhosis (Child–Pugh class C) for a number of drugs mainly eliminated by renal excretion in unchanged form [53]. Extra caution should therefore be exercised when treating these patients.
- Patients with chronic renal failure have serious health problems and require multiple medications. Drug interactions can complicate the application of recommendations for dosage adjustment.
- Obviously, extra caution is warranted when prescribing drugs with a narrow therapeutic index in patients with renal dysfunction.

Taking the above points into account, the final decision regarding what dosage regimen to use in an individual patient with renal dysfunction should be based on quantitative recommendations on dosages and dosing intervals derived from traditional two-stage pharmacokinetic studies and/or population PK/PD studies. Secondary sources of drug information regarding dosage adjustment in patients with renal dysfunction should be used with caution, as recently shown by Vidal et al. [134]. They compared the advice given on dosage adjustment by four commonly used secondary pharmacotherapeutic sources: British National Formulary, Martindale, American Hospital Formulary System Drug Information, and the 1999 edition of the handbook *Drug Prescribing in Renal Failure* [135–138]. They concluded that "the remarkable variation in definitions and recommendations, along with scarce details of the methods used to reach this advice, makes the available sources of drug information ill suited for clinical use". In

their response to the article by Vidal et al., the editors of the respective secondary sources agree that major difficulties are encountered when trying to find and compile the important information on which clear dosing guidelines could be formulated in patients with renal disease [139].

Obviously, advice on drug prescription, dose and dosing interval, contraindications, and adverse effects should be evidence-based. For all drugs intended to be used in patients with renal dysfunction, the manufacturer should carry out at least one traditional two-stage pharmacokinetic study in patients with varying degrees of renal impairment. Dosing recommendations should be based on the results of such a study and should be described in the Summary of Product Characteristics following the FDA and EMEA guidelines [109, 110]. Ideally, these dosing recommendations should be confirmed by a PD/PK study in a much larger patient population.

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