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REVIEW ARTICLE

Pharmacokinetic and bioavailability variations in renal disease

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Abstract

The mammal's kidney demonstrates a high degree of complexity both structurally and functionally and as a consequence plays a vital role in homeostatic functions which include reuptake, secretion, metabolism and endocrine. Chronic kidney diseases, an example of uremia, has an effect on both morphology and physiology of the kidney which may alter the pharmacokinetics of the drugs. Uremia can affect drug pharmacokinetics by modifying drug elimination directly. Bioavailability of the drug during severe uremia is diminished. Observed volume of distribution (Vd) is dependent on protein binding characteristics in plasma, body tissues and water. In a state of disease due to reduction of drug and protein complexes, Vd increases. Also half-life increases due a reduced glomerular filtration rate (GFR). Renal abnormalities cause reduction in binding of plasma proteins with numerous drugs and as consequence metabolic clearance of such drug molecules will increase. So we can conclude that dosing adjustments are necessary for patients with abnormal renal functioning. These adjustments can include reduction in recommended dosage levels and/or increase of subsequent dosage intervals to reach therapeutic goals of safety and efficacy. During drug development, studies must be carried out to assess the effect of impaired renal function on the drug. Such studies are not required for monoclonal antibodies, gaseous and volatile drugs which are eliminated via the lungs. For drugs to be used by end stage renal diseases (ESRD), treated by dialysis, pharmacokinetics must be studied and the related conditions with and without dialysis should be studied in order to discover which magnitude dialysis is responsible for the purging of both the drug or its dynamic metabolites which may be potentially active. Appropriate dosage adjustments are based on creatinine levels alone. An extensive evaluation on pharmacokinetics of various drugs in patients with renal diseases suggests the dosage adjustments are necessary to achieve the targeted therapeutic outcome and prevent drug serum levels crossing the toxic threshold. The purpose of review is to investigate the pharmacokinetic and bioavailability variations and its effect on patients with renal impairments.

Keywords

Chronic kidney disease
Glomerular filtration rate
Kidneys
Pharmacokinetics

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Introduction

Kidneys are the structures which are shaped like a bean. Their location is near to the center of the back. Inside the kidney are found about a million tiny structures known as the nephron they have a function to filter the blood. They remove toxic waste and also excessive water as urine. Renal insufficiency is a reduced function of the kidney contributing factors to renal artery disease and various other kidney diseases. Some patients with this disease experience little or no symptoms. While other patients may develop severe symptoms which include high blood pressure, reduced kidney function or even kidney failure which requires dialysis to treat. Renal artery disease is usually diagnosed with duplex ultrasound scan or other noninvasive tests which include angiograms with both the computerized tomography (CT) and magnetic resonance imaging (MRI) sources. Acute renal failure (ARF) is a common occurrence in neonatal intensive care units. In most cases underlying causes for ARF include sepsis, metabolic disease, perinatal asphyxia or premature birth.

Renal insufficiency leads to an increased risk of developing serious and non-renal complications that can cause death. These complications should not be confused with the treatable complications of a serious disease. Renal insufficiency has complicated clinical courses characterized by sepsis, delirium, hemorrhage and respiratory failure. Most of these problems established after the onset of renal failure (Levy et al., 1996). A large number of kidney diseases affect the nephrons. The damage to nephrons produces the damage to kidneys and impair their function of removing the waste resulting in host problems including genetic problems, injuries or medication (Walden et al., 2012). Hypertension is alarming predisposing factor of end stage renal disease and its treatment needs to take serious considerations (Klag et al., 1996).

Impairment or degeneration of kidney function affects the pharmacokinetics of drug. Acute diseases or trauma to the kidney can cause uremia, in which GFR is impaired, leading to accumulation of excessive fluid and nitrogenous waste products in the blood. Uremia reduces GFR as well as active secretions which as a result reduces drug excretion resulting in a longer half-life of the drug (Shargel et al., 2007). Changes in half-life are marked as indicator of changed drug disposition. Half-life is dependent upon volume of distribution (Vd) and total body clearance indirectly (Gibson, 1986). Uremia can affect drug pharmacokinetics directly an example of it is uremia causing change in the levels of electrolytes resulting in the altered metabolism as well as physiological conditions. These changes may affect both pharmacokinetics and dynamics while the drug elimination may be effected by the impairment. Therapeutic along with toxic response could possibly be changed as a consequence of changing the drug sensitivity at the site of the receptor (Shargel et al., 2007). Changes in pharmacokinetics can be caused by age related physiological changes. As a result dosage is modified for elderly patients especially for those drugs which are eliminated via renal route (Cusack, 2004). Captopril forced renal function reduction leading to nephrotoxicity directly causing allergic reactions and renal blood flow reduction due to a drop in the systemic blood flow (Hricik et al., 1983). Metformin, involved in type 2 diabetes treatment, has half-life of 5 hours in patient with proper renal function. Both CLR and CLF diminish in approximate proportionate relationship with CLCR, as a result its dose should be reduced proportionately with the CLCR (Graham et al., 2011). Chronic disease of the kidney (CKD), also sometimes referred to as chronic renal disease, is a continual drop in renal functionality over a prolonged duration of time which may be months to years. Diagnosis of CKD is made on the basis of screening of individuals that have high risk factors for kidney problem. Examples of these factors include diabetes, high blood pressure and family history with a one of its widely accepted complications include CV diseases, anemia, pericarditis and renal dystrophy (Eknoyan et al., 2004; Martínez-Castelao et al., 2014). Identifying trait of CKD is a creatinine blood level test which is a muscle metabolic byproduct. High creatinine levels mean an inversely proportionate GFR as a consequence diminished capacity of renal elimination of waste. Creatinine concentration may be near average level in the earlier stages of the disease. However it can still be discovered by analysis of urine showing a presence of protein or RBCs in the sample. To completely investigate the main cause of damage to kidneys, many medical imaging techniques, blood analysis and if required kidney tissue biopsy are employed to find out whether the causative factor is reversible or not (National, 2002). Status of patients not representing severe symptoms can be figured out by monitoring blood pressure as well as kidney function tests.

Effects of renal disease on pharmacokinetics: Uremic patients may exhibit pharmacokinetic changes in bioavailability, volume of distribution and clearance.

Bioavailability (F): Bioavailability encompasses two vital attributes i.e. how rapidly the drug enter systemic circulation known as rate of circulation and the magnitude of average strength that enters the body known as the extent of absorption (Food & Administration, 2000). The bioavailability via oral route of a drug during severe uremia is reduced as a consequence of affiliated changes in the gastrointestinal tract (GIT) motility and pH as a result of nausea, vomiting, diarrhea. Intestinal blood flow may be altered as well, e.g. bioavailability of propranolol which

demonstrates a high first pass effect may be above average in patient that has renal disease as result of decreased metabolism by the liver (Shargel et al., 2007). Contributing patient factors include type of meals, timing of taking meals, age of the patient, genetic attributes and the conditions that prevail in the GIT. Factors related to the dosage form include the chemical nature of the drug (salt or acid), its physical characteristics including crystalline structure, size of the drug particle and the formulating factors which include the excipients and manufacturing processes involved (Food & Administration, 2000). Experimental evidence suggests that metabolism of some drugs is diminished compared to healthy kidney e.g. paracetamol and p-aminobenzoic acid (Gibson, 1986).

Apparent volume of distribution (Vd): Vd is largely dependent upon plasma protein binding or protein binding in tissues and total volume of water within the body. Renal failure may change drug distribution as a consequence of changes in the balance of fluids or binding of drug protein. Protein binding in plasma proteins with weekly acidic drugs in patients having uremia is reduced while binding of basic drugs is altered to a lesser extent. Reduction in protein binding causes an accumulation of large number of free drug molecules in the blood as a result VD is increased. However half-life is prolonged due to significantly reduced GFR (Shargel et al., 2007).

Since several renal diseases causes a decrease in the plasma protein binding of numerous drugs, the metabolic sanction of such drugs will be enhanced (Levy, 1977). Protein binding may be further compromised due to accumulation of various biochemical metabolites such as free fatty acid & urea, which may compete with active drug for the protein binding sites (Shargel et al., 2007).

Total body clearance: Complete body clearance of medication in patients with uremia is reduced by different factors such as a reduction in GFR, due to active tubular secretion or a diminished clearance via hepatic route by a reduction in intrinsic hepatic clearance. During clinical practice required dose, in patients having renal disease, is deduced by the renal function and an estimate of body clearance levels. CIT is the abbreviation used in the description of drug elimination (Shargel et al., 2007). CIT is described as both total renal (CIR) and total non-renal (CNIR) or metabolic removal of a drug. Renal failure is notorious for changing enzyme system of microsomal mixed function oxidase. As a result in end stage renal diseases (ESRD) there is chance for an alteration in disposition of drugs that are metabolized in the liver (Gibson, 1986).

An in depth analysis of pharmacokinetics in patients with uremia is deemed impossible. Also uremic patients may not be stable enough consequently their condition may shift too rapidly for pharmacokinetics analysis (Shargel et al., 2007).

Examples of some drugs in renal impaired patients:

Rivaroxaban: It is an orally administered directly acting Factor Xa inhibitor which has been approved for use in over 90 countries to prevent venous thrombo-embolism in patients undergone an elected knee or hip replacement surgical procedure. Removal of rivaroxban is reduced with renal disease leading to increased effects with both plasma exposure and pharma-codynamics which are expected for a drug partially excreted via renal route.Renal effect on rivaroxban clearance was minimal, which was also included in patients with a renal disease (Kubitza et al., 2010).

Prednisolone: It is used in patients who were perpetrated with liver failure, renal impairment or kidney transplant. Subjects having age > 65 years, females orally administered estrogen containing steroid based contraceptives and in patients using ketoconazole have shown an elevated unbound levels of the drug prednisolone (Frey & Frey, 1990).

Morphine: Removal of the drug morphine differs in renal impaired patients yet glucoronide metabolites are still excreted via renal route in patients with renal impairment. The by- products may be retained and will gradually accumulate. High levels of morphine 6 glucoronide (M6G) have been found in patients with reduced renal activity, crossing the blood brain barrier (BBB) gradually and produces increased duration of their effect on the CNS (Dean, 2004).

Opioids: They are conventionally used in patients with renal disease for pain management. However management of morphine, dextropropxyphene and pethidine is rendered complex by the accumulation of active metabolites which are removed via the renal route (Davies et al., 1996).

β-blockers: They have a rapid uptake from the GIT. However reduced uptake rates have been observed in the elderly and young patients with a renal impairment. Highly lipophilic beta blockers are broken down almost exclusively however those with a less lipophilic nature are removed via the renal route. A reduction in the renal and hepatic function has been observed to effect the removal of those beta blocking drugs which are removed with these organs (Johnsson & Regårdh, 1976).

Tacrolimus (TAC): It is an immunosuppressant of macrolide type which is commonly used following a kidney, heart or liver transplant. Blood concentration of TAC is monitored and constantly adjusted towards therapeutic levels. Myco-phenolate motefill is a precursor drug which is quickly absorbed and broken down to the pharmacologically active compound known as mycophernolic acid (MPA Administrating an extract of the plant known as St. Johns wort to a patient being treated with TAC can result in serious consequences including reduced blood TAC concentration leading to increased chances of organ rejection (Mai et al., 2003).

Metoprolol: Its pharmacokinetics were studied in patients of varying stages of renal failure as well as control group. The patients were administered with 20 mg of metoprolol tartrate via I.V. route and 50 mg of the same drug via oral route both in a single dose and during mostly controlled conditions. There were no large difference observed in the bioavailability between the two groups as well as the rate of elimination. The patient administered the drug through the oral route demonstrated bioavailability of 59% with a variation of 9% in patients with renal disease while those in the control was found to be 55% with a variation of 7%. Rate of clearance in patients with renal failure was found to be 1 liter per minute with variation of 0.1 liters while in patients of control group were found to be 0.8 liters per minute with a variation of 0.1 liter. Half-life was found to be similar in both at 4.6 hours with a variation of 1.2 hours (Jordö et al., 1980).

Furosemide: In healthy individuals, it has an average half-life of about 30 to 120 minutes. However the values exceed up to about 9.6 hour in individual with a renal disease such as ESRD which demonstrates that renal abnormality have a significant effect (Ponto & Schoenwald, 1990).

Lamivudine (3TC): It is a nucleoside having a high potency and is deemed effective against both in vitro and newly in vivo HIV as demonstrated in research studies. Its pharmacokinetic activity is altered in patients with renal impairment. An adjustment either by reducing the dose or increasing subsequent dosage interval is found to be necessary. The highest concentration of 3TC grows with diminished renal function. Pharmacokinetic models demonstrate that for the hospitalized patients having renal failure, a dose of 25 mg shows equivalent therapeutic effect as of 150 mg dose in a normal patient (Bohjanen et al., 2002).

Fibrates: They have been utilized clinically for the treatment of dyslipidemias. All drugs belonging to this classification are mainly eliminated via the renal route since they demonstrate a high protein binding, some increase in half life has been observed among patients having severe kidney disease (Miller & Spence, 1998).

Atenolol: It is utilized as anti-arrhythmic. Its half-life in five renal impaired patients was demonstrated to be increased (Wan et al., 1979).

Naproxen: In normal individuals the half-life of naproxen was establish to be 17.7 hours with a variation of almost 3.0 hours and it was not altered in a meaningful way in patients with a renal disease at almost 18.1 hours with a variation of 5.3 hours. Naproxen levels did not rise to above average levels in the serum in patients having uremia. Interestingly the levels were discovered to be below normal in manner found to be significant in patients that had a renal disease. These findings suggest increased drug breakdown and a higher observed volume of distribution of the drug during the diseased state. It's probable cause is a reduction in binding with proteins found in the blood serum. However it is suggested that dosage adjustment is not obligatory in patients having renal disease or impairment (Anttila et al., 1980).

Renal dysfunction effects on drug usage

- Drugs may be accumulated which are normally excreted.
- Active metabolites are accumulated.
- Distribution of drugs and their binding to proteins maybe altered.
- Reduction in renal metabolism may occur (Matzke et al., 2011).

Various drugs have been developed to combat diseases. These diseases influence the metabolism of the drugs which in turn alters the way patient responds to therapy. Critical information would be establish by using both PK and PD studies within specific populations in combination with large, third phase clinical trials (Atkinson & Reidenberg, 2002).

The physiological stress that has been linked to renal impairment can affect the elimination attributes to drugs and metabolites from the patients. Normally drugs are removed from the subject via various routes which are characterized by their clearance values (Levy, 1977). In certain situations, relevant statistics has also been discovered by use of pharmacokinetic methods for the interpretation of data that has been generated from phase III clinical trials. Diseased state and the patient age, among other factors, have a significant part to play in the removal of drug, its distribution and absorption within the body (Piergies et al., 1994).

Renal patients are those that are relatively stable even after undergoing extensive dialysis and various pharmacokinetic studies have been executed on such patients. Patients with moderately diminished renal function have not studied using the same scale however research on such patients has been advised in the present guidelines set by FDA (Food & Administration, 1998).

Table 1: Pharmacokinetic parameters exaggerated by Age/GFR.

Parameter (abbreviation)	Clinical Application
Bioavailability (F)	Regulates the quantity of drug accomplishing the systemic circulation and hence amount at action site.
Volume of Distribution (VD)	Defines the extent of a loading dose
Clearance (Cl)	Defines the maintenance dose
Half-life (T1/2)	Governs the amount of needed time to attain steady state serum concentrations or remove the drug (four times the T1/2)

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Mechanisms of renal excretion or drugs elimination

Glomerular filtration: The process of glomerular filtration affects almost all drugs which have a smaller molecular size and is limited by virtue of drug binding to the plasma proteins. Oppositely secretion by renal tubules is non-limiting since a combination of protein bound and free drug molecules are found in the plasma that can be removed. As observed, the secretion by renal tubules of paraaminohippurate is fast enough that its clearance can be utilized in the estimation of the flow of blood in the kidneys. Competitiveness among the drugs rendering renal secretion is a vital factor in drug-drug type ADRs (Brenner, 1985).

The scale of GFR can be accomplished by the utilization of many exogenous chemicals. The insulin cleared through urination, marked as the gold standard, is rarely executed other than research purposes due to the lack of availability of chemicals and the time consuming process. The metabolic clearance, also known as biotransformation, in predominately drugs that are bound to plasma protein, varies in proportion to their free fraction. Free fraction of drug is also known as the ratio between the free to total drug molecules that are found in the plasma. Since serious renal disease roots a drop in the plasma protein binding with various drugs so breakdown and removal of such drugs increases (Levy, 1977).

Generalized conclusions by using renal clearance values: If renal clearance is more than the rate of drug filtration the drug is being secreted by the renal tubules as demonstrated in (Table1). If renal removal is lesser than the rate of drug filtration, there is reabsorption of the drug by the tubules (Atkinson & Reidenberg, 2002).

Estimated GFR–MDRD Formula: (MDRD = Modification of Diet in Renal Disease)

eGFR (mL/min/1.73 m2) = 175 [Serum Creatinine (umol/L) x 0.0113]-1.154 x age (years)-0.203

• Multiply the result by 0.742, if female
• Multiply the result by 1.21, If African American
• Not valid for e GFR > 60
• Not valid for very thin, very fat, elderly or paraplegics (Matzke et al., 2011).

The effects of decreased renal function on drug elimination have been examined most widely. This is suitable, since only elimination clearance (CLE) and drug dose are expressed as amount/time, (I) determine the average steady state concentration of drug in the body (Css):

$$Css = \frac{I}{CLE} \quad \ldots\ldots\ldots\ldots\ldots 1$$

For many drugs, CLE actually consists of additive renal (CLR) and non-renal (CLNR) components, as indicated by the following equation:

$$CLE = CLR + CLNR \ldots\ldots 2$$

Non-renal clearance is usually equated with drug metabolism but could also include hemodialysis and other methods of drug removal. The involvement of hemodialysis to the total clearance of a drug rest on degree of the clearance acquired by hemodialysis virtual to the extent of the body clearance of drug on a day between dialysis (Levy, 1977). In fact, metabolic clearance of a drug frequently comprises of additive assistances from numerous equivalent metabolic pathways. The description of metabolism of drug by a clearance term is typically suitable since metabolism of most drugs can be frequently defined by first order kinetics within therapeutic drug concentrations range (Atkinson & Reidenberg, 2002). Renal disease has the prospective to change not only the renal clearance of unchanged drug but may also considerably adapt the metabolic alteration of drugs in both the kidneys and liver. It can no longer be presumed that the drug pharmacokinetics which are disposed primarily by metabolism will be unchanged in renal failure (Gibson, 1986).

Table 2: Mechanisms involve in renal excretion.

Sr. No	Mechanisms	Affects	Influenced by	Examples
1	Glomerular Filtration	All drugs or metabolites having same molecule size	Drug filtration rate, Protein binding	----------
2	Renal tubular Secretion	By competition with other drugs	Not influenced by Protein binding,	Active drugs: Pencillin, Procaine Amide Metabolites: Glucuronides
3	Reabsorption by Non-Ionic Diffusion	Weak acids and bases	Only important, if excretion of free drug is major elimination path.	WeakAcids: Phenobarbital Weak bases: Quinidine
4	Active Reabsorption	Affects ions, not proved for other drugs	----------	Halides: Bromides, Flourides Alkaline Earth Metals: Lithium

Table 3: Effect of renal disease on drug metabolism.

Sr. No.	Process	Effect	Examples
1	Oxidations	Normal Or Increase	Phenytoin
2	Hydrolases	Plasma Estrase: Slowed	Procaine
		Plasma Peptidase: Normal	Angiotensin
3	Reduction	Slowed	Hydrocortisone
4	Synthesis	Glucuronide Formation: Normal	Hydrocortisone
		Acetylation: Slowed	Procainamide
		Sulfate Conjugation: Normal	Methyldopa

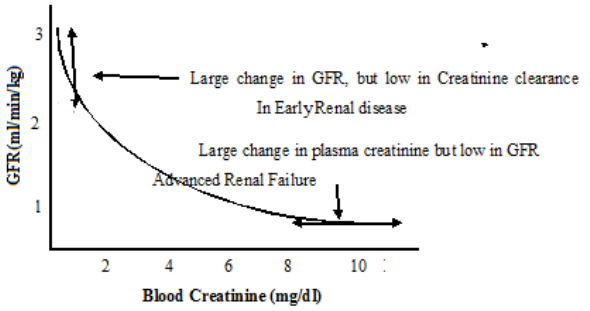

Figure 1: GFR vs Creatinine.

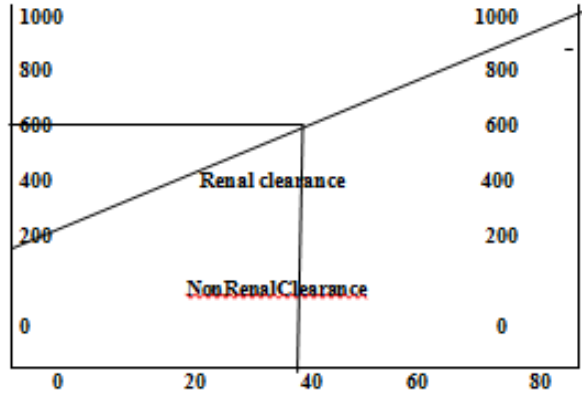

Figure 2: Elimination clearance on Y-axis & Creatinine clearance on X-axis Nomogram for estimating Cimetidine clearance for a 70 kg patient with impair renal function (Dettli, 1974).

Detti thought the additional properties of elimination rate constants demonstrating similar removal pathways pave way for making nomograms which are used to estimate the dose adjustments deemed suitable for patients having renal disease. It may also be used to compute with approximate elimination clearance as demonstrated in Figure 1 (Dettli, 1974).

- In implementing this approach, creatinine clearance (CLCR) usually is estimated from the Cockcroft and Gault equation (Matzke et al., 2011).

Cockroft-Gault Equation: 140-age x (lean body weight) x 0.85 (if female) 72 x serum creatinine.

Cimetidine demonstrates a slightly lower levels or renal clearance in normal individuals and in individuals with CLE besides duodenal ulceration and in elderly healthy individuals than demonstrated on Figure, based on reports by previous investigators who only conducted tests on younger subjects (Grahnen et al., 1979).

Interestingly there is a change in the labelling of cimetidine which under the heading of " dosage adjustment for renal impaired patients" suggests that " patients having creatinine clearance less than 30 cc per minute, being treated for prevention of upper GI hemorrhage, should be given half of the suggested dose" but under the heading of " pharmacokinetics" it is suggested that afterward administration via I.M. or I.V. route 75% of drug is recovered in urine unchanged after a duration of 24 hours.

As only a quarter of the drug is removed by non-renal routes, the information shows that functionally anaphoric individuals who are administered half the normal cimetidine dose could have possibly noxious blood concentrations which are twice as the recommended levels for individuals with relatively normal renal activity. Cimetidine was the first antihistamine H2 receptor blocker that has a wider range of clinical uses. It is weakly basic and has high water solubility. In individuals with later stage renal impairments, total plasma clearance of the drug cimetidine is dropped from an average value of 500 ml/min to less than 200 ml/min. Main cause of this is a drop in renal removal to 50 ml per minute or in some cases even lesser. Removal half-life rises from 2 to 4-5 hours in patients having renal impairment. The absolute bioavailability in patients with renal impairment remains similar or just a little higher in comparison with control individuals. A drop in dose of cimetidine is advised with degree of severity of renal disease so a dose of 400 mg being advised in patients with very low levels of renal activity (Somogyi & Gugler, 1983) when dose alterations are required for individuals with a renal disease it can be done by reduction in dosage or by increasing the interval of subsequent dose. An example would be once the CLE value has been estimated. The daily dose of the drug can be dropped in proportion to the quotient of the expected clearance which is to be divided by clearance in normal individuals. This will prolong the average concentration of the drug at

required levels regardless the drug is infused intermittently or continuously (Atkinson & Reidenberg, 2002).

It is noteworthy that it is usually easier to dose the subjects given the drugs with a short half-life to dose them with a multiple of the half-life of the drug's multiple which is calculated by the mathematical equation given below and is dependent upon the therapeutic index of the drug. The half -life can be estimated from the following equation:

$$t\frac{1}{2} = \frac{0.693Vd(\ area)}{CLE} \quad \ldots\ldots\ldots\ldots 3$$

The normal dose can be administered at multiple of the lengthened half-life. The adjustment of dosage interval is especially important if plasma peak levels and normal plasma levels need to be maintained below a certain point due to reasons of safety (Atkinson & Reidenberg, 2002).

The accuracy of Dettli's process of antedating drug removal is dependent on two important factors:

1- The removal via non renal routes remains more or less the same during renal disease.

2- CLE drops linearly in proportion with CLCR.

Pharmacokinetics in patients having impaired renal function: Study design, impact on dosing and labelling and data analysis

Introduction: This help is proposed to available by certain sponsors during the investigation phase of the drug molecule, under development plan, to launch studies to determine the effect of renal disease on the pharmacokinetics of the drug being investigated.

Background: After undergoing circulation, the drug is removed via either excretion or by break down from the kidney or the liver. Apparent change that will be caused by renal disease is diminution in renal removal or likely renal breakdown of the drug molecule or its products. However it has also been related to fluctuations including hepatic breakdown, binding with proteins in the plasma and the circulation of the drug (Food & Administration, 1998).

For most therapeutics which are intended for patients with renal impairments, including those drugs for which primary route of removal is not through the kidney, PK must be investigated in patients with a renal disease and dose adjustments for those patients should be provided (Food et al., 2010).

Decision about conducting study among impaired renal function patients

When studies may be important: A study in renal disease patients may be required when the drug,

(1) May change the PK of the drug itself and or its active and toxic metabolites.

(2) A dosage change is necessitated in such patient to ensure drug safety and efficacy.

(3) If the drug has a narrow therapeutic index and the drug (either direct or its metabolites) is excreted via renal route (Food & Administration, 1998).

When a study may not be required? For various drugs renal disease is not a significant factor for changing the PK of the drug sufficiently to warrant a dosage change.

1. For drugs that are volatile or gaseous in nature and primary route of excretion is via lungs.
2. Drugs for which a single dose of administration is required lest clinically some circumstances arise which may alter this requirement
3. For monoclonal antibodies

Other facts to consider: Also if a renal disease may have little or no influence on the PK of the drug, the effect of hemodialysis must be taken to consider as larger doses of the drug maybe required for patients with an ongoing treatment with hemodialysis than those with normal renal function (Food & Administration, 1998).

Study design: The main purpose of the recommended study in patients with a renal disease is to investigate if the pharmacokinetics are changed to a significant level that warrant a change in the recommended dosage or doses that have been determined from the phase 3 clinical trials.

The investigation should primarily focus on a comparison between renal impaired patients and individuals representing the mean renal functionality levels which may not be considered healthy people (Food & Administration, 1998; Food et al., 2010).

Basic design of the complete investigation: Could be used on numerous drugs of which pharmacodynamics, which includes the relationship between concentration and its response, are established to be unchanged by a renal disease or drugs having wide therapeutic index and presenting no concern for safety of the patient (Food & Administration, 1998).

Study Participants: Particularly it should not comprise of young and healthy male volunteers if the majority of the population comprises of the elderly inclusive of female. An acceptable method would be to study volunteers who are similar to the average population of patients in their renal functions and other characteristics including gender, weight and age. The investigation may also include a group of individuals demonstrating above average renal function than the control group i.e. group of healthy young subjects (Food & Administration, 1998; Food et al., 2010).

A large variety of renal function levels increases the chances to detect and characterize the influence of renal functionality levels on PK. Exogenous markers including EDTA, iohexol, diethyl triamine and pancreatic acid provide a close reading of the GFR however usually these methods aren't utilized clinically (Food et al., 2010).

Table 4: An Example of dosing recommendation in numerous renal function groups based on or estimated creatinine clearance (CLcr) or estimated GFR (eGFR) (Atkinson & Reidenberg, 2002).

Stage	Description	eGFR(mL/min/ 1.73m2)	Dose	Frequency	CLcr c (mL/min)	Dose	Frequency
1	Control (normal) GFR	>90	200	Every 12 hours	>90	200	Every 12 hours
2	Mild decrease in GFR	60-89	200	Every 12 hours	60-89	200	Every 12 hours
3	Moderate decrease in GFR	30-59	100	Every 12 hours	30-59	100	Every 12 hours
4	Severe decrease in GFR	15-29	100	Every 24 hours	15-29	100	Every 24 hours
5	End stage renal disease (EDRSD)	<15 not on dialysis Requiring dialysis	50	Every 24 hours Supplemental dose, if appropriate, should be given after dialysis	<15 not on dialysis Requiring dialysis	50	Every 24 hours Supplemental dose, if adequate, must be administered after dialysis

Serum-creatinine based equations used to estimate renal function:

1) Estimation of the rate of creatinine clearance (Clor) by the use of Cockcroft-gault(C-G) equation

2) Estimated glomerular filteration rate (eGFR) by Modification of diet in renal disease (MDRD)

eGFR (mL/min/1.73 m2) = 175 x (Scr, std)-1.154 x (Age)-0.203 x (0.742 if female) x 260 (1.212 if African American Scr, std: serum creatinine measured with a standardized assay.

Reduced pharmacokinetic study: If renal disease does not modify PK sufficiently, requiring a change in dosage, then the scale of the study may have a larger scale along with its complexity than required. Another method utilizes a dual staged approach, in the initial stage patients with extreme levels of renal function are investigated which include a control group (Group 1) and subjects with severe levels of renal impairment (Group 4). If there results support that renal impairment does not modify PK to the magnitude which requires a dosage adjustment, no further investigations are required. If the evidence isn't strong enough to prove this assumption then in the second stage the remaining renal functional level groups, including individuals with mild to moderate levels of renal disease, should be investigated. The data of these stages should be mixed for all following investigations (Food & Administration, 1998).

Drug administration: An investigation with a single dose sufficient to describe with accuracy the PK of the drug is being carried out. Drug and its products demonstrate linear and time independent PK at the levels predictable in the subjects to be investigated. An investigation with several doses is usually advised when the drug or an active product exhibits either a nonlinear or PK which are time dependent (Food et al., 2010).

Sample collection: Plasma or a complete blood sample, if required along with urine samples, should be tested for both an unmodified drug and any products with a pharmacological activity including both therapeutic and adverse. The sample collection should be done with sufficient frequency and duration of time to ensure an accurate estimation of the PK activity of the primary drug and its active products (Food & Administration, 1998; Food et al., 2010).

For drugs and products with a comparatively low levels of plasma protein binding e.g. degree of binding is less than 80%, modification in binding due to renal disease are miniscule. In such circumstances investigation and description of PK as total concentration levels should be sufficient (Food & Administration, 1998; Food et al., 2010).

Dialysis effect on pharmacokinetics: Hemodialysis can modify the PK of drug to a sufficient degree which warrants a dose adjustment. Requirement of dose adjustment may arise due to a pharmacologically relevant levels of drugs are removed by the process. So a modification in the recommended doses such as an extra dose may be suitable for the drugs being administered to patients with ESRD undergoing treatment with dialysis. PK should be investigated in such individuals within conditions of dialysis and without it to observe the degree with which hemodialysis modifies the removal of the drug and its active products (Food et al., 2010).

i- If the drug and or its products are removed primarily by non-renal means then the dialysis contributes to a small degree to the overall removal.

ii- In case of large Vd of drug or its metabolites, only a miniscule percentage of drug within the system will be removed via dialysis.

Data analysis: The data analysis classically comprises of the following steps:

- ✓ An estimate regarding pharmacokinetic (PK) characteristics.
- ✓ Forming of mathematical model which relate the levels of renal function with the pharmacokinetic characteristics.

- ✓ Creation of dosage advice including a review if dosage modification is required in patients with renal impairment (Food & Administration, 1998).

Dose recommendations development: Dose recommendation should be drafted founded on the results of the investigation by utilizing model narrating RF and relevant characteristics of PK. Normally doses are modified to produce similar ranges of unbound plasma levels of drug or its active product in both patients with normal renal function and patients with a renal disease. Simulations are supported as method to recognize the doses and dose duration attaining the aim for individuals having varying degrees of renal function (Food et al., 2010). For some substances such as those removed primarily by breakdown or via secretion in to the bile, even severe levels of renal disease may not modify the PK significantly to require a change in doses. A sponsor could also provide evidence for this conclusion by analyzing the data to prove the pharmacokinetic measurements particularly important to the therapeutic result among subjects with severe renal disease are almost close to the subjects having average renal function (Food & Administration, 1998).

Labeling: The labeling should redirect the clinically significant information relating to the outcome of renal function on pharmacodynamics and pharmacokinetics (if known) of the drug.

- ✓ Highlights of Prescribing Information
- ✓ (e.g., Dosage and administration, precautions and warnings, contraindications and use in particular populations).
- ✓ Doses and administering
- ✓ If there is requirement of a modification is dosage with a renal disease it should be written and changes should be elaborated (Food & Administration, 1998; Food et al., 2010).

Contraindications, precautions and warnings

- ✓ If renal impairment effects the pharmacokinetics of drug that render the drug unsafe for patients use having renal impairment, this information should be counted in the contraindications section, with reference to Dosage And Administration section (Food et al., 2010).

Over dosage: Primary target of dialysis investigation is to discover the requirement for dosage adjustments in ESRD patients, more information about the importance of dialysis in overdose circumstances may be reasonably obtained from the results of the investigation. In circumstances in which the information remains unknown (Food & Administration, 1998; Food et al., 2010).

Conclusion: Drugs may be prove unsafe or toxic due to their narrow therapeutic index, less elimination rate from the body, high serum/plasma levels of drugs, long t1/2, reduced glomerular filtration rate & decreased creatinine clearance in renal disease patients. So, dose adjustments is necessary due to pharmacokinetic changes in dialysis/renal disease patients for prevention of abnormal or toxic plasma level of drugs by using already established investigational drug study designs.

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References

Anttila M, Haataja M and Kasanen A 1980. Pharmacokinetics of naproxen in subjects with normal and impaired renal function. *European journal of clinical pharmacology*, **18**, 263-268.

Atkinson AJ and Reidenberg M 2002. Effects of renal disease on pharmacokinetics. National Institutes of Health Clinical Center.

Bohjanen PR, Johnson MD, Szczech LA, Wray DW, Petros WP, Miller CR and Hicks CB 2002. Steady-state pharmacokinetics of lamivudine in human immunodeficiency virus-infected patients with end-stage renal disease receiving chronic dialysis. *Antimicrobial agents and chemotherapy*, **46**, 2387-2392.

Brenner B 1985. Nephron adaptation to renal injury or ablation. *American Journal of Physiology-Renal Physiology*, **249**, F324-F337.

Cusack BJ 2004. Pharmacokinetics in older persons. *The American journal of geriatric pharmacotherapy*, **2**, 274-302.

Davies G, Kingswood C and Street M 1996. Pharmacokinetics of opioids in renal dysfunction. *Clinical pharmacokinetics*, **31**, 410-422.

Dean M 2004. Opioids in renal failure and dialysis patients. *Journal of pain and symptom management*, **28**, 497-504.

Dettli L 1974. Individualization of drug dosage in patients with renal disease. *Medical Clinics of North America*, **58**, 977-985.

Eknoyan G, Lameire N, Barsoum R, Eckardt K-U, Levin A, Levin N, Locatelli F, Macleod A, Vanholder R and Walker R 2004. The burden of kidney disease: improving global outcomes. *Kidney International*, **66**, 1310-1314.

Food and Administration D 1998. Guidance for industry: pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling. *Rockville, MD: US Department of Health and Human Services*.

Food and Administration D 2000. Guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. *Food and Drug Administration, Rockville, MD*.

Food, Administration D, Health UDo and Services H 2010. Guidance for industry. Pharmacokinetics in patients with impaired renal function-Study design, data analysis, and impact on dosing and labeling. *Available at: www. fda. gov/ downloads/ Drugs/ GuidanceComplian ceRegulatoryInfo rmation/ Guidances/ UCM72127. pdf. Accessed*, **5**.

Frey BM and Frey FJ 1990. Clinical pharmacokinetics of prednisone and prednisolone. *Clinical pharmacokinetics*, **19**, 126-146.

Gibson TP 1986. Renal disease and drug metabolism: an overview. *American Journal of Kidney Diseases*, **8**, 7-17.

Graham GG, Punt J, Arora M, Day RO, Doogue MP, Duong J, Furlong TJ, Greenfield JR, Greenup LC and Kirkpatrick CM 2011. Clinical pharmacokinetics of metformin. *Clinical pharmacokinetics*, **50**, 81-98.

Grahnen A, Von Bahr C, Lindström B and Rosen A 1979. Bioavailability and pharmacokinetics of cimetidine. *European journal of clinical pharmacology*, **16**, 335-340.

Hricik DE, Browning PJ, Kopelman R, Goorno WE, Madias NE and Dzau VJ 1983. Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenoses or renal-artery stenosis in a solitary kidney. *New England Journal of Medicine*, **308**, 373-376.

Johnsson G and Regårdh C-G 1976. Clinical pharmacokinetics of β-adrenoceptor blocking drugs. *Clinical pharmacokinetics*, **1**, 233-263.

Jordö L, Attman P, Aurell M, Johansson L, Johnsson G and Regårdh C-G 1980. Pharmacokinetic and pharmacodynamic properties of metoprolol in patients with impaired renal function. *Clinical pharmacokinetics*, **5**, 169-180.

Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB and Stamler J 1996. Blood pressure and end-stage renal disease in men. *New England Journal of Medicine*, **334**, 13-18.

Kubitza D, Becka M, Mueck W, Halabi A, Maatouk H, Klause N, Lufft V, Wand DD, Philipp T and Bruck H 2010. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. *British journal of clinical pharmacology*, **70**, 703-712.

Levy EM, Viscoli CM and Horwitz RI 1996. The effect of acute renal failure on mortality: a cohort analysis. *JAMA*, **275**, 1489-1494.

Levy G 1977. Pharmacokinetics in renal disease. *The American journal of medicine*, **62**, 461-465.

Mai I, Störmer E, Bauer S, Krüger H, Budde K and Roots I 2003. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. *Nephrology Dialysis Transplantation*, **18**, 819-822.

Martínez-Castelao A, Górriz JL, Segura-De La Morena J, Cebollada J, Escalada J, Esmatjes E, Fácila L, Gamarra J, Gràcia S and Hernánd-Moreno J 2014. Consensus document for the detection and management of chronic kidney disease. *Nefrologia*, **34**, 243-262.

Matzke GR, Aronoff GR, Atkinson AJ, Bennett WM, Decker BS, Eckardt K-U, Golper T, Grabe DW, Kasiske B and Keller F 2011. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney International*, **80**, 1122-1137.

Miller DB and Spence JD 1998. Clinical pharmacokinetics of fibric acid derivatives (fibrates). *Clinical pharmacokinetics*, **34**, 155-162.

National KF 2002. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *American journal of kidney diseases: the official journal of the National Kidney Foundation*, **39**, S1.

Piergies AA, Worwag EM and Atkinson AJ 1994. A concurrent audit of high digoxin plasma levels. *Clinical Pharmacology & Therapeutics*, **55**, 353-358.

Ponto LLB and Schoenwald RD 1990. Furosemide (frusemide) a pharmacokinetic/pharmacodynamic review (part I). *Clinical pharmacokinetics*, **18**, 381-408.

Shargel L, Wu-Pong S and Yu AB 2007. Applied biopharmaceutics & pharmacokinetics. McGraw-Hill.

Somogyi A and Gugler R 1983. Clinical pharmacokinetics of cimetidine. *Clinical pharmacokinetics*, **8**, 463-495.

Walden P, Ellis D and Hicks R 2012. Know the flow: Kidney disease. *Nursing made Incredibly Easy*, **10**, 18-28.

Wan S, Koda R and Maronde R 1979. Pharmacokinetics, pharmacology of atenolol and effect of renal disease. *British journal of clinical pharmacology*, **7**, 569-574.