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International Journal of Pharmacognosy and Phytochemical Research 2024; 16(4); 01-05

eISSN: 0975-4873, pISSN: 2961-6069

Review Article

An Overview of Drug Therapies Affecting Renal Function

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Received: 21st Oct, 24; Accepted: 9th Nov, 24; Revised: 15th Nov, Available Online: 30th Nov, 24

ABSTRACT

Undesirable side effects of medication are inevitable. Due to the role of the kidneys in clearance and filtration, the renal system faces a unique situation regarding the side effects of drugs. It has an important role for different classes of drugs to be excreted, and drugs are a key factor for this system to be at risk. Many drug classes cause renal insults. The top six classes were pain killers, antibiotics, proton pump inhibitors, antidiabetics, antihyperlipidemics, and agents for erectile dysfunction. Renal insults caused by these agents could vary in severity. Some drugs could cause nephrotoxicity from one dose, while others may only need continuous monitoring. Different populations also operate under different rules, as some people need dose adjustments while others who are medically free of major illnesses do not. A variety of unfavorable outcomes for the kidney could take place, such as acute kidney injury, chronic kidney disease, and end-stage renal disease, and unfortunately, some of these issues could lead to the need for renal replacement therapies. The outcome of this review paper will help multidisciplinary physicians to understand the renal side effects of the most used drug classes in the Kingdom of Saudi Arabia, their destructive mechanisms, and most importantly, the clinical presentations of renal dysfunction in relation to each class. Emphasizing these adverse effects will prevent future unfavorable outcomes, especially in commonly used drugs that are frequently prescribed for different age groups. Moreover, some of these drugs are considered to be over-the-counter medications, which makes them a serious problem that needs to be handled cautiously.

Keywords*: drugs, adverse effect, renal failure, renal impairment, nephrotoxic*

INTRODUCTION

Renal Failure:

Renal hindrance or kidney failure is an ailment, wherein kidney capacities are impeded. This prompts failure in sufficiently filtering the metabolic wastes from the blood. It is a common disease worldwide and is associated with high rates of morbidity and mortality. Kidney disease is a widespread and increasingly prevalent problem.[1]

Acute kidney injury (AKI) is defined as an abrupt (within hours) decrease in kidney function; it affects approximately 1 in 5 adults admitted to hospital with acute illness. AKI frequently occurs in critically ill patients, for whom dosing regimens are complicated by multiorgan dysfunction, significant changes in volume status and often very rapid changes in renal function. In these circumstances, there is a significant risk of over- and underdosing of medications.

Chronic kidney disease (CKD) is defined as impaired renal function lasting longer than 3 months and is often characterized by a slow progressive decline in renal function over years. It is thought to affect >10% of the general population, equating to >800 million people worldwide, and is associated with other chronic conditions such as hypertension, diabetes mellitus and heart disease.

Whether kidney disease is acute or chronic, renal dysfunction can have significant implications for the safe prescribing of medicines. Reductions in renal function impair the renal excretion of many drugs and their metabolites, leading to accumulation and increased risks of toxicity and adverse events. In addition, altered drug absorption, protein binding and drug distribution can increase risk of toxicity, or impair the effectiveness of some medications.1,2 It is therefore important that prescribers have a good understanding of the altered pharmacokinetics associated with renal disease, enabling them to tailor the dosage regimen to maximize effectiveness and minimize the risk of adverse effects in this patient group.[2]

Altered pharmacokinetics in renal disease

The pharmacokinetic handling of drugs is often altered in patients with renal disease.

Absorption: increased gastric pH is common in CKD, driven, in part, by increased ammonia formation in the gut. This increased pH can enhance the absorption of some medications (e.g. aspirin, digoxin), while the absorption of other drugs (e.g. ketoconazole, furosemide) can be reduced. Furthermore, several medications commonly prescribed in renal disease can alter the absorption of other drugs. Of note, phosphate binders, which are commonly

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prescribed in CKD, can chelate and significantly reduce the absorption of many drugs including quinolones, bisphosphonates and tetracyclines.[2]

Distribution: the volume of distribution (Vd) is defined as the total amount of a drug in the body divided by its peak concentration in the plasma (Cmax). There is an inverse relationship between plasma concentration and Vd. For example, drugs that are highly lipid soluble, or have low plasma protein binding, have a higher Vd and therefore a lower post-dose plasma concentration; hydrophilic compounds and those that are highly protein bound have a low Vd and a high post-dose plasma concentration. In renal disease, fluid balance can significantly alter. Fluid overload can lead to an expansion of both the intravascular and extracellular fluid compartments. This causes an increase in Vd and a reduction in post-dose plasma concentrations; conversely, volume depletion, often seen in the initial stages of AKI or after aggressive diuretic therapy, decreases Vd and increases plasma concentrations. Protein binding of acidic drugs (e.g. furosemide, warfarin, phenytoin) is reduced in renal impairment. This is caused by several factors including reductions in serum proteins (particularly in nephrotic syndrome), structural changes to binding sites and the direct displacement of drugs from albumin binding sites by acidic compounds that accumulate in renal disease. This leads to an increase in the unbound (or free) fraction of drug. This not only increases the Vd, but also increases the potential pharmacological action of the drug, so dose adjustments can be required. Importantly, most drug assays give a total concentration rather than differentiating between bound and free drug, so these may not reflect the increased tissue drug exposure.[3]

Renal metabolism: the kidney is a site of metabolism of some drugs and expresses many of the same drug-metabolizing enzymes as are found in the liver. The most notable example is the conversion of 25-(OH) vitamin D3 to its active form 1,25-(OH)2 vitamin D3. The kidney also plays a central role in the clearance of insulin from the systemic circulation; insulin is freely filtered at the glomerulus and then almost completely reabsorbed by the proximal tubular cells, where it is degraded by proteolytic enzymes.

Non-renal metabolism: most drugs are excreted unchanged or as more water-soluble compounds after metabolism in the liver. In general, as renal function worsens, phase I hydrolysis and reduction reactions slow, as do many phase II metabolic reactions (acetylation, glycine conjugation), resulting in reduced elimination. Some hepatically metabolized drugs also have active metabolites that are excreted renally, which can accumulate in renal impairment, leading to drug toxicity. For example, morphine is metabolized in the liver to morphine-3-glucuronide (55%) and morphine-6-glucuronide (10%). Morphine-6- glucuronide is a potent mu-opioid agonist and is highly dependent on renal excretion; the half-life (t½) increases from 2.1 hours in normal renal function, to 27 hours in patients with severe renal failure.

Elimination: renal excretion is the major route of elimination for most drugs and/or their metabolites; it depends on the glomerular filtration rate (GFR), active renal tubular secretion and active or passive tubular reabsorption. In the glomerulus all molecules <60,000 Da are freely filtered out of the blood. Therefore, most drugs are readily filtered unless they are bound to large molecules such as albumin or have been incorporated into blood cells. Drugs that are highly protein bound are actively secreted into the proximal convoluted tubules and excreted. As urine continues to pass through the renal tubule and becomes more concentrated, lipid-soluble drugs and their metabolites tend to be reabsorbed passively down their increased concentration gradient while water-soluble drugs, and their metabolites, are not. All aspects of renal elimination are affected in patients with renal impairment. As the GFR falls there is a reduction in free drug elimination leading to an increase in free drug t½. Tubular secretion is also generally reduced through a combination of reduced tubular numbers and, as drug concentrations increase, saturation of the capacity of the transporters responsible for tubular secretion; this ultimately leads to an increased elimination t½. Reabsorption of drugs from the distal portion of the nephron can also be reduced, leading to increased drug concentrations within the urine as renal function declines.

Clearance of drugs in haemodialysis and peritoneal dialysis

Patients on dialysis usually have a GFR of <10 ml/minute, meaning that renal drug elimination is severely impaired.[4]

The efficacy of dialysis in removing drugs from the body depends on many factors including the:

- properties of the drug (e.g. Vd, protein binding)
- delivery of drug to the filter (dialysis blood flow, time on dialysis)
- filter properties (surface area, pore size).

In haemodialysis and haemodiafiltration, clearance follows first-order kinetics and, for low molecular weight drugs that are not heavily protein bound, generally provides efficient clearance. High-flux dialysers are increasingly used, which are capable of removing moderate-sized molecules of 10,000e15,000 Da. Heavily protein-bound drugs are not successfully filtered, even if they have a low molecular mass, and drugs with a larger Vd are also less efficiently removed. In general, the efficiency of drug removal with peritoneal dialysis is substantially lower than that of haemodialysis and patients should be dosed as if they have a GFR <10 ml/ minute.[5]

Types of Renal Impairment

The two primary types of kidney disease are acute kidney injury (AKI) and chronic kidney disease (CKD). Acute kidney disease is often reversible with adequate treatment, whereas CKD is often not reversible. In both cases, there is usually an underlying cause.

A decrease in the glomerular filtration rate (GFR) can determine kidney failure. Based on the GFR rate, renal impairment can be classified into five stages.

- Stage 1: If the GFR is average or above 90 ml/min, which is associated with albuminuria, blood abnormalities, and abnormal urine tests
- Stage 2: If the GFR is slightly reduced, that is in kidney damage which can be studied by imaging, abnormality in urine and blood
- Stage 3: If the GFR is moderately reduced, that is in the range of 30– 59 ml/min, which is associated with the need for screening and physician reference, and it is also divided into: Stage 3a: Moderate reduction in GFR of 45 ml/min/1.73 m2
- Stage 3b: GFR of 30 ml/min/1.73 m2).
- Stage 4: If the GFR is highly reduced, that is in the range of 15–29 ml/min, requiring renal replacement therapy.
- Stage 5: When GFR reduced to < 15 ml/min/1.73 m2 called as established kidney failure, or end-stage kidney disease (ESRD).

Renal impairment is characterized by a progressive decline in glomerular filtration rate, a significant public health issue worldwide associated with high morbidity and mortality. In most cases, renal impairment is associated with comorbidities such as hypertension and diabetes, which require multiple drug therapy during a course of treatment, leading to polypharmacy. The stages of kidney failure is shown in Figure 1.

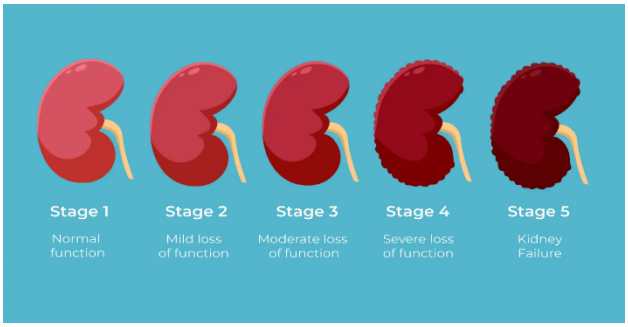

Figure 1: Stages of kidney failure

Assessing renal function

Assessing renal function, and adjusting medication dosages as required, is vital in individuals with impaired renal function. The most important measure of renal function that might influence prescribing is the GFR. Serum creatinine, a by-product of muscle metabolism, is widely used as a surrogate to estimate GFR because it is generally released at a constant rate by the body, is freely filtered at the glomerulus and is not reabsorbed. However, it is not a perfect marker and, if considered in isolation, can overestimate (e.g. elderly, low body weight) or underestimate (e.g. high muscle mass) renal function. Approximately 15% of serum creatinine is also actively secreted by the renal tubule, which can be inhibited by certain drugs (e.g. trimethoprim, cimetidine), leading to an increase in serum creatinine even though the GFR remains unchanged. Finally, in advanced renal failure, creatinine is actively secreted into the gastrointestinal tract, leading to an overestimation of renal function this patient group.[6]

Estimated GFR (eGFR) can be made more reliable by adjustment for factors such as body weight, age and gender using a mathematical formula; two commonly used examples are the Modification of Diet in Renal Disease (MDRD) equation and the CKD Epidemiology Collaboration (CKD-EPI) equation.[7] For drug dosing, however, creatinine clearance (CrCl) using the Cockcroft eGault formula is generally preferred. While the eGFR and CrCl are not interchangeable, for most adults of normal height and weight, eGFR can be used to determine dose adjustments. Exceptions to this include patients at the extremes of body weight, elderly individuals and drugs with significant toxicity. eGFR and CrCl are only accurate in patients with CKD and should not be relied on in those with rapidly changing renal function (e.g. AKI).[8]

Reviewing medications

All individuals with CKD should have regular medication reviews to ensure that their drug doses are appropriate for their degree of renal impairment. This is particularly important in patients with CKD who have an eGFR of <60 ml/minute, especially if renal function is rapidly declining.[9] Prescribers should also be aware of emerging drug adverse effects, which can be an early indication of the development of more serious adverse events. As renal function declines, the kidney can become more susceptible to nephrotoxicity, so every effort should be made to limit the use of nephrotoxic medications. In patients who require nephrotoxic drugs, regular therapeutic drug monitoring should be used when possible (e.g. for aminoglycosides), alongside regular monitoring of renal function.[10]

Drug dosing

For drugs that are excreted by the kidney, the main concern is that there could be a prolongation of their t½ and significant drug accumulation. Clinically, this often means that single doses or loading doses of a drug are often the same as for individuals with normal renal function.[11] However, a dose reduction can be required for drugs that are given as regular repeated doses. A steady-state concentration is reached after 5 t½ and, for renally excreted drugs, both the t½ and time to achieve steady state will be extended when renal function is impaired. The plasma concentration at that time will also rise because a smaller proportion of the previous dose will have been excreted by the time of the subsequent dose.

When a drug with significant renal excretion is prescribed to a person with renal impairment the dosing regimen can be adjusted in three ways:

- reducing the dose
- extending the dose interval
- a combination of the two.

For drugs with a narrow therapeutic index or serious adverse effects, monitoring of plasma drug concentrations is an important guide. In addition to altered

pharmacokinetics, the pharmacodynamic response to some drugs can be reduced as renal function declines (i.e. reduced therapeutic efficacy).[12]

Examples include:

- sodium-glucose co-transporter 2 SGLT2 inhibitors e the amount of glucose that can be eliminated in the urine is reduced at an eGFR < 45 ml/minute, impairing their effectiveness at lowering blood glucose.[13]
- nitrofurantoin e at an eGFR < 45 ml/minute, the kidney is unable to concentrate nitrofurantoin sufficiently in the urine to be effective at treating urinary infection
- thiazide diuretics e these can be less effective in advanced CKD because of changes in sodium concentration in the distal tubules.[14]

Recommendations for adjusting drug regimens can be obtained from regularly updated drug information references such as the British National Formulary, Renal Drug Database or Electronic Medicines Compendium, some of the examples shown in Table 1.

Table 1: Class of drug impact of renal impairment

Class	Drug	Contraindicated or to be avoided if possible when:	Reason
Analgesics	Pethidine	GFR <60	Convulsions
Antibiotics	Cefepime	GFR <30	CNS toxicity
Phase-prophylactic psychotropic drugs	Lithium	GFR <60	Nephro- and neurotoxicity
Antidiabetic drugs	Glibenclamide, gimepiride	GFR <60	Hypoglycemia
	Metformin	GFR <60	Lactic acidosis
Diuretics	Spironolactone, eplerenone	GFR <30	Hyperkalemia
Immune suppressants	Methotrexate	GFR <60	Myelotoxicity
Radiological contrast media	Gadolinium	GFR <30	Nephrogenic systemic fibrosis
LMW-heparin	Enoxaparin	GFR <60	Risk of hemorrhage

Clinical Significance[15,16]

Factors and conditions that may worsen the renal injury and thus should be either avoided or resolved include the following:

- Nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs, aminoglycosides, and iodinated contrast
- Uncontrolled diabetes
- Systemic hypertension
- Proteinuria
- Dehydration
- Smoking
- Hyperlipidemia
- Hyperphosphatemia

Based on several studies, 34% to 53% of the drugs requiring adjustment were not considered in physicians' instructions. There are various explanations for the inadequacy of medication dose regulation.[17] The most frequent reason is that physicians often underestimate the impact of mild and intermediate renal insufficiency or that they have inadequate knowledge of the medications that require dose adjustment in renal insufficiency. Although the serum creatinine level is a widely used value in everyday practice, this is a late biomarker of decreased renal function (rising only after significant loss of renal function), thus leading to underestimating renal impairment, especially among older patients.[18]

Another possible explanation is that physicians do not calculate the creatinine clearance using one of the three existing formulas due to insufficient time, which leads to underestimating the necessity of adjusting medication dosage.[19] The Food and Drug Administration and European Medicines Agency have particular guidelines about pharmacokinetics regarding patients with impaired renal function that should be followed when developing new drugs. Physicians should consider the potential

adverse effects, drug interactions, and treatment failures or discontinuations due to nephrotoxicity before administering any drug.[20]

Conclusions

The results of this study state that these classes of drugs have many side effects on renal function. In some classes, a particular drug can be the only renal insulting agent. The results also showed how various drugs could increase renal insult when combined together, as was seen with NSAIDs and vancomycin. In different classes, the mechanisms leading to renal injury varied between clear, unclear, and a hypothesis. A single dose is enough for some drugs to be acutely nephrotoxic, which was seen in gentamicin, or nephrotoxicity can be chronic with long-term usage of some drugs, like NSAIDs. Others are sufficiently nephrotoxic when used in the long term and in a high dosage, which is the case for VIN. The definition of long-term usage for different drugs is different. For the same drug, nephrotoxicity may or may not occur for different populations, a phenomenon manifested with the antihyperlipidemic statin, which is considered a contributing factor to AKI in older people. The results showed that kidney function assessments before the administration of a nephrotoxic drug should not be limited to assessing only serum creatinine; this was proved true in metformin administration. Solutions to reverse or inhibit renal complications were also discussed. However, in some cases, the solution could only be to avoid the insulting agent for a certain population or to ensure continuous clinical monitoring in a healthcare facility, especially with the long-term use of a drug. The results of this study should encourage physicians to study a drug's mechanism of action and its effects on kidney function in a patient before any administration of a drug that probably affects the kidney (or not) to prevent unwelcomed outcomes that can lead to a lower quality of life or increased mortality. Effective communication between physicians, pharmacists, and nurses is essential for safe and appropriate drug administration in patients with renal impairment.

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