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MEDICATIONS IN THE KIDNEY

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Medications in the kidney

Summary

Patients with chronic kidney disease constitute a population at high risk for adverse drug reactions and/or drug-drug-interactions. Renal dysfunction-induced pathophysiological changes may alter both medication pharmacodynamics and handling. Most pharmacokinetic parameters are adversely affected by impaired kidney function, among which reduced glomerular filtration and altered tubular secretion and reabsorption lead to the most specific alterations. Dosages of drugs cleared by the kidney should usually be adjusted according to creatinine clearance. Recommended methods for maintenance dosing adjustments are dose reductions, lengthening the dosing interval, or both. Appropriate drug selection and dosing in patients with chronic kidney disease is imperative to avoid drug adverse events and to ensure optimal patient outcomes.

Résumé

Les patients avec une insuffisance rénale chronique représentent une population à haut risque vis-à-vis des manifestations indésirables et/ou des interactions médicamenteuses. Les modifications physiopathologiques associées à une altération de la fonction rénale peuvent altérer à la fois la pharmacodynamie et la pharmacocinétique de nombreux médicaments. La plupart des paramètres pharmacocinétiques sont modifiés en présence d'une insuffisance rénale, parmi lesquels la diminution de la filtration glomérulaire et une altération de la sécrétion et de la réabsorption tubulaire conduisent aux altérations les plus spécifiques. Les dosages des médicaments éliminés par le rein doivent généralement être ajustés en fonction de la clairance de la créatinine. Les méthodes habituellement recommandées pour ajuster les doses de maintenance sont la diminution posologique de chaque dose administrée, l'augmentation de l'intervalle entre deux doses successives ou une combinaison des deux. Une sélection judicieuse des médicaments et un ajustement approprié de leur dosage sont indispensables pour éviter les manifestations indésirables et garantir le meilleur pronostic des patients avec insuffisance rénale.

1) Introduction

People with chronic kidney disease (CKD) often live with many illnesses and complex drug treatment regimens. It is of common knowledge, since several decades, that renal function can modify the relationship between drug dose and clinical effect in a variety of ways (1,2). The effects of CKD on both pharmacokinetics (drug absorption, distribution, metabolism and elimination) and pharmacodynamics (drug's effect at the target site) increase the potential for adverse drug reactions and drug toxicity. Indeed, renal insufficiency has been associated with an increased risk of adverse effects with many classes of medications (3). The risk of some, but not all, adverse effects has been linked to the patient's degree of residual renal function. This may be the result of inappropriate individualization of those agents that are primarily eliminated by the kidney, or an alteration in the pharmacodynamic responses as a result of renal insufficiency (4). One aspect of renal excretion that is often overlooked is the elimination of biologically active or toxic metabolites of parent compounds.

Physicians managing patients with CKD are faced with difficult decisions about starting or continuing treatment with drugs that are handled by, or potentially toxic to, the kidney (5). Inappropriate dosing in patients with CKD can cause toxicity or ineffective therapy (6). In particular, older patients, an increasingly prevalent population, are at higher risk of development advanced disease and related adverse events caused by age-related decline in renal function and the use of multiple medications to treat comorbid conditions (7,8). Since renal function can affect drug disposition by a wide variety of mechanisms, the astute clinician must be aware of these potential mechanisms to make best use of his/her clinical skills and laboratory armamentarium for the patient's benefit (9,10). In the present review, we do not aim to give detailed guidance on every drug, but rather to highlight general principles of drug handling by the kidney and give advice for drug therapy in patients with CKD.

2) Role of the kidney in drug elimination

Almost all pharmacokinetic parameters could be adversely affected by CKD, including drug oral absorption and bioavailability, protein binding and distribution volume, nonrenal clearance (metabolism) and renal elimination (6,11). For instance, drug distribution may be altered in renal insufficiency due to pH-dependent protein binding and reduced protein (primarily albumin) levels. Interestingly, renal disease may also affect hepatic metabolism, although the exact underlying mechanisms are not well understood (9). All these changes could potentially require appropriate drug dosing in CKD patients. Here we will only focus on the role of the kidney in drug elimination because the most important pharmacokinetic change in CKD is

excretion. Renal excretion of drugs occurs through glomerular filtration and tubular secretion and reabsorption (12). It is influenced by renal blood flow, glomerular filtration rate (GFR) and urinary flow rate (11). CKD can affect glomerular blood flow and filtration, tubular secretion and reabsorption, as well as renal bioactivation and metabolism. Glomerular filtration and tubular process may both be affected in CKD, but not to the same extent, and the type of renal disease may differentially affect filtration and excretion (9). Methods that measure all renal handling pathways would allow informed dosage individualisation using an understanding of renal excretion pathways and patient characteristics (13).

a) Glomerular filtration

Drug elimination is highly dependent on prevailing level of kidney function. Therefore measurement (or accurate estimation) of GFR is crucial to appropriate drug dosing. The glomerular elimination of drugs depends on several factors, including the molecular weight and protein binding characteristics of the medication. Drugs bound to albumin are not filtered. Therefore, the filtration rate of these drugs is directly proportional to their free plasma concentrations, ie the fraction of the drug that actually gets filtered. In CKD, medication elimination by glomerular filtration is decreased, resulting in a prolonged free drug elimination half-life (6). It is a well-known principle that endogenous creatinine clearance correlates well with the renal elimination of most medications. However, it is a common oversight for health care practitioners to fail to take estimates of creatinine clearance into account before dosing medications. The lack of dose adjustments in patients with renal insufficiency is an often overlooked, yet preventable, cause of drug dosing errors (see below) (6). Although the most practical and commonly used clinical measure of renal function is estimated creatinine clearance as a marker for glomerular filtration, it is noteworthy that this simple marker may be misleading in two important at-risk populations, neonates and the elderly (9). Finally, using estimated creatinine clearance as the lone measure of medication handling and then only adjusting those medications that are filtered by the kidney during CKD may be inappropriate, because several other factors could also play an important role in establishing an appropriate dosing regimen (6,13).

b) Tubular secretion

As the kidney plays an important role in the elimination of numerous endobiotics and xenobiotics, renal tubular epithelial cells express a variety of transporter proteins with diverse substrate specificities (14). Such transporters are predominantly localized to the proximal

tubules and utilize ATP or transmembrane ion gradients to drive the vectorial movements of substrate compounds. Thus, the renal proximal tubule is the primary site of carrier-mediated drug transport from blood to urine. Based on their preferential substrate selectivity, the renal transport systems have often been classified as either organic anion (OAT) or cation (OCT) transport systems. Many renal transporter proteins, including those for organic ions, peptides, and nucleosides, have been shown to directly transport or interact with a number of clinically utilized drugs. Focused studies of drug transporters in the kidney have significantly enhanced our understanding of the cellular and molecular basis of transporter-mediated drug elimination (14).

Although protein binding decreases the glomerular filtration of some drugs, the renal tubular secretion of these medications may be increased. Indeed, highly protein-bound medications are actively secreted into the proximal convoluted tubules, ensuring they are excreted via transporters (14). However, with advanced kidney disease, drug clearance is significantly impaired despite tubular secretion. Indeed, in CKD, the secretion of most drugs eliminated by this active transport system is also reduced. Another factor affecting active tubular secretion of drugs is that this is a transport-mediated process so that, with higher drug levels, the secretion reaches a limit leading to an increased elimination half-life. Also, competition between drugs for active secretion can reduce their excretion (see below : drug-drug interactions). Both endogenous substances and drugs are secreted and reabsorbed by these transporters. Patients with renal failure may develop toxicity due to competition for these pathways of secretion due to endogenous substances and medications that compete for these transporters (11). A better insight into the molecular mechanisms and transporters governing renal drug elimination is required to better predict the in vivo kinetic profile of substrate drugs, especially in presence of CKD.

c) Tubular reabsorption

In healthy kidneys, the renal clearance of many drugs is slow because they are substantially reabsorbed from the distal portion of the nephron, despite glomerular filtration and active secretion (6). This is a passive process, which is, however, affected by several factors, including protein binding, medication lipophilicity, urine concentrating activities and pH. Only drugs in an uncharged (more lipid soluble form) state may freely cross cell membranes and thus the tubular barrier to be passively reabsorbed. Weak acids gain protons in an acidic environment and become uncharged whereas weak bases gain protons in an acidic environment and become charged (and vice versa). As expected, reductions in medication

reabsorption are observed in patients with CKD, resulting in increased urinary concentrations of renally eliminated medications, such as aspirin and lithium (6).

c) Renal metabolism

A factor of drug biotransformation that cannot be overlooked is the kidney as a site for drug metabolism. Normally, the kidneys have nearly 15% of the metabolic function of the liver, with most of the metabolic enzymes located in the renal cortex (15). Some drugs are more extensively metabolized via the kidney (6). Renal metabolism is obviously reduced in CKD. This results in increased parent compound concentrations, potentially increasing the prevalence of adverse effects.

3) Drug-drug interactions in the kidney

Patients with CKD frequently require multiple pharmaceutical agents to manage both the underlying renal dysfunction and frequent comorbid disease states. Given the propensity for polypharmacy in this population, the potential for adverse events and drug-drug interactions is high (16). Many drugs are dependent on renal transporters for their ultimate urinary elimination (14). Combined use of drugs that interact with renal transporters may increase the risk for drug interactions.

Drug-drug interactions due to competitive inhibition of renal organic anion or cation secretion systems have been noticed clinically for a long time (17). Medications can interact with either organic anion (OAT) or cation (OCT) transporters in proximal tubular cells (11,14). In both cases, drug elimination is impaired. A classical example is probenecid that inhibits renal secretion of other anionic drugs through inhibition of the organic anion transport system. Renal excretion of penicillin derivatives and various other drugs (e.g. cisplatin, ciprofloxacin, …) is also decreased by coadministration of probenecid. Similarly, nonsteroidal anti-inflammatory drugs may inhibit the renal excretion of methotrexate via specific transporters so that coadministration may result in severe methotrexate toxicity (bone marrow depression, renal insufficiency, hepatitis). Other drugs, such as cimetidine and trimethoprim, appear to be potent inhibitors of the renal tubular secretion of a number cationic drugs, which also results in adverse drug side effects (14). When coadministered with compounds that inhibit P-glycoprotein renal transport activity (e.g. quinidine, clarithromycin, ritonavir, …), tubular secretion of digoxin is markedly diminished, thereby leading to an increase in plasma digoxin concentrations and potential cardiac toxicity (14). The risk of severe adverse events due to such drug-drug interactions is even greater in patients with CKD. A better insight into the molecular mechanisms

governing renal drug elimination is likely to aid in the design or use of drugs with greater safety profiles (14).

4) Drug dosing adjustments in kidney disease

Drug dosing in patients with CKD requires knowledge of the pharmacologic alterations that occur with renal dysfunction (see above). Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes (4,5). Physicians should pay careful attention when considering drug therapies with active or toxic metabolites that can accumulate and contribute to exaggerated pharmacologic effects or adverse drug reactions in patients with CKD. Dosages of drugs cleared renally should be adjusted based on the patient's renal function, calculated as creatinine clearance or GFR. A common oversight in prescribing medications to patients with CKD is inherently to reduce the drug doses or prolong the dosing intervals at the initiation of therapy. Initial dosages should be determined using published guidelines and adjusted based on patient's response (4). Serum drug concentrations should be used to monitor effectiveness and toxicity when appropriate. This is the case for many drugs such as digoxin, ciclosporin, aminoglycosides, … (6).

Dosing theories in the CKD population may concern both loading (initial) dose and maintenance dose (4,6). The purpose of a loading dose is to produce rapidly a therapeutic plasma concentration. In clinical practice, loading doses usually do not need to be adjusted in patients with CKD. Digoxin is one medication exception to this general rule. After the initiation of therapy with a loading dose, a maintenance dose is required to maintain steady-state plasma concentrations. Recommended methods for maintenance dosing adjustments are dose reductions, lengthening the dosing interval, or both. Dose reduction maintains more constant drug concentrations, but it is associated with a higher risk of toxicities if the dosing interval is inadequate to allow for drug elimination. Normal doses are maintained with the extended interval method, but the dosing interval is lengthened to allow time for drug elimination, before redosing. Lengthening the dosing interval has been associated with a lower risk of toxicities but a higher risk of subtherapeutic drug concentrations, especially toward the end of the dosing interval. Nevertheless, this expanded interval method generally corresponds well with CKD-induced delays in medication excretion, allowing more time for the drug to be eliminated before redosing. To calculate an extended dosing interval, one must calculate the patient's creatinine clearance and know the normal dosing interval of the medication to be administered. Using the following equation, one can determine the appropriate dosing interval on a patient-by-patient basis : new expanded dosing interval = (normal creatinine clearance per the patient's calculated creatinine

clearance) x the normal dosing interval (6). The method works particularly well with medications that have a broad therapeutic window and a long half-life.

5. Extracorporeal removal of drugs

Drugs are eliminated to some degree by the various forms of dialysis, including hemodialysis, peritoneal dialysis, and continuous renal replacement therapies (11). However, extracorporeal removal of drugs is difficult to predict and influenced by various factors, among which molecular weight of drug, distribution volume of drug, drug solubility, protein binding, poor size and surface area of hemodialysis membrane, blood and dialysate flow rates, … Several drugs require dosing after hemodialysis. Guidelines are available in books on subject on drug prescribing in dialysis (18). The difficulties related to extracorporeal removal of drugs will not be further covered as this topic is outside that of the present review dealing more specifically with medications in the kidney.

6. Conclusions

Although optimization of the desired therapeutic outcomes are of paramount importance, additional therapeutic issues for patients with reduced renal function are the prevention or minimization of future acute or chronic nephrotoxic insults, as well as the severity and occurrence of adverse effects on other organ systems. Indeed, the incidence of adverse events is much higher in patients with CKD than in those without renal insufficiency. The general principles to enhance the safety of drug therapy in patients with CKD include knowledge of the pharmacokinetics, interactions and potential toxicities of the therapeutic agent, consideration of possible alternative therapies and individualization of drug dosing based on patient level of renal function. Some medications need to be avoided all together in CKD either because of lack of efficacy or more importantly risk of toxicity. Numerous other medications require appropriate dosing adjustments, either by reducing the individual dose, or lengthening the dosing interval, or both. It is important to understand how to appropriately prescribe medications to patients with various levels of acute renal failure and CKD, including those undergoing some form of renal replacement therapy. Application of the pharmacotherapeutic principles into clinical practice, especially appropriate drug dosing adjustments, will hopefully enhance the safety of these agents and optimize patient outcomes.

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