In the intensive care unit (ICU) numerous medications are prescribed to critically ill patients. Besides the acute illness, these patients suffer from many underlying chronic diseases which mandates the administration of multiple drugs simultaneously. Comorbid conditions, altered drug pharmacokinetics, and drug–drug interactions further increases the risk for both drug overdosing and underdosing and adverse medication effects. Underdosing is complicated by reduced efficacy, whereas overdosing results in various end-organ toxicities.The end organ toxicities include acute kidney injury (AKI), hepatotoxicity, neurological dysfunction, cardiopulmonary toxicity, and other end-organ disturbances.

AKI in ICU: AKI occurs frequently in the ICU in upto two thirds of patients which is often multifactorial and can be severe enough to require renal replacement therapy (RRT) in about 6% of patients.[1-5] The main causes of AKI in the ICU are sepsis and septic shock, systemic inflammatory response syndrome, cardiac, hepatic and multiorgan dysfunction and volume depletion.These events prime the kidney for injury by causing renal hypoperfusion and promoting oxidative stress.[6] Importantly, nephrotoxic drugs contribute to AKI in 19–25% of cases in the ICU.[4,7] In fact, 22.2% of the top 100 drugs used in an adult ICU at a tertiary care center were considered potentially nephrotoxic.[8]

So ICU patients are very prone to develop AKI. AKI is again associated with its attendant adverse consequences like prolonged hospital length of stay, hospital related morbid events, development of chronic kidney disease (CKD) and requirement of acute/chronic RRT and most importantly its contribution to hospital and overall mortality.[9] So the critical care clinician should be well aware of all the drugs that can cause nephrotoxicity and take into account the altered pharmacokinetics of the drugs in these diseases for optimal drug dosing to maximize efficacy and minimize toxicity.

Pharmacokinetic alterations in kidney dysfunction in ICU patients

Derangement of kidney function affects the pharmacokinetics of drugs. Some of the common causes of kidney failure are disease, injury and drug intoxication. Acute diseases or trauma to the kidney can cause uremia in which glomerular filtration is impaired or reduced leading to accumulation of excessive fluid and blood nitrogenous waste products in the body.Uremic patients may exhibit pharmacokinetic change in bioavailability, volume of distribution and clearance.

Bioavailability: The oral bioavailability of a drug in severe uremia may be decreased as a result of disease related changes in gastrointestinal motility, increased gastric pH (alters the drug-ionized state), formation of insoluble drug complexes in the intestines, nutrient–drug interactions, and bowel edema.[10]

Volume of distribution (V_D): In critical illness, V_D may be increased or decreased depending on the level of total body water, level of renal function, and changes in drug protein binding.[10-12] Increased drug V_D often develops from early goal-directed therapy for sepsis, edematous states, such as cirrhosis and acute hepatic failure, nephrotic syndrome, right and left heart failure, and many illnesses associated with shock requiring aggressive volume repletion to maximize end-organ perfusion. Efficacy can suffer if drug dosing is not adjusted to these changes. Reduced V_D may be seen with older age and volume depletion from vomiting, diarrhea, blood loss, and diuretics. AKI and CKD may also reduce the V_D of certain drugs by altering tissue binding.[10,13] Drug therapy that does not account for this will lead to excessive dosing and end-organ toxicity.

Clearance: Total body clearance of drugs in uremic patients is also decreased by either a decrease in glomerular filtration rate (GFR) and possibly active tubular secretion and reduced hepatic clearance.

Nephrotoxic drugs:

These are therapeutic agents that have the potential to cause adverse effects on kidney function as a result of direct toxicity or compromised renal perfusion. The type of kidney dysfunction that are induced by nephrotoxic drugs include acute tubular necrosis, glomerular and tubulointerstitial injury, hemodynamically mediated damage and obstructive nephropathy. Potential adverse effects can be prevented by reducing the dose, extending the dose interval or by prescribing an alternative medicine that is less likely to accumulate.

Common forms of drug induced AKI

- Hemodynamic AKI: Nonsteroidal anti-inflammatory drugs (NSAIDs) RAAS inhibitors, Calcineurin inhibitors (cyclosporine, tacrolimus), Vasopressors
- Acute tubular necrosis: Radiocontrast, Nephrotoxic antimicrobials (aminoglycosides, amphotericin B)
- Osmotic nephropathy: Hydroxyethyl starch (HES), Intravenous immunoglobulin (IVIG containing sucrose)

- Crystal nephropathy: Highly active anti-retroviral therapy (HAART), Acyclovir Ciprofloxacin, Sodium phosphate purgatives
- Acute interstitial nephritis: Antibiotics (b-lactams, sulfa-based, quinolones), Proton pump inhibitors, H2 antagonists, Anti-convulsants

Adjustment of drug dosages in renal dysfunction:

Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes. Dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration and should be calculated using online or electronic calculators. The Cockcroft and Gault formula and Modification of Diet in Renal Disease (MDRD) are the most widely used formula to estimate renal function.

Drug dosing in Acute kidney injury:

Loading dose: Many patients with AKI are overhydrated and the volume of distribution is much larger than under normal conditions. So the volume of distribution of many hydrophilic drugs like B- lactams , cephalosporins and carbapenems are significantly increased in the presence of AKI. The loading dose need to be higher by almost 25% than the starting dose for persons with normal kidney function.

Maintenance dose: The rate of change of kidney function and fluid volume status in AKI is very dynamic. So the maintenance doses of many drugs, especially antimicrobial agents should be initiated at normal or near normal dosage regimens and adjustments made thereafter based on the relationship between drug pharmacokinetic characteristics and kidney function.

Drug dosing in Chronic kidney disease:

Loading dose: A loading dose should be used for most patients with stage 4 or 5 CKD to achieve the desired steady state concentration as the volume of distribution is significantly increased in patients with AKI and CKD relative to those with normal kidney function.In patients with impaired kidney function and physical examination revealing normal ECF volume , a loading dose equivalent to a patient with normal kidney function should be given.In patients with marked volume expansion, a higher loading dose may need to be given.

Maintenance dose: The primary reference for information regarding the maintenance dose for patients with CKD should be the FDA and / or EMA official product labeling. Either the dose should be reduced or the interval extended.

Extracorporeal drug losses:

Failure to consider dialysis drug clearance will significantly reduce drug efficacy.

Hemodialysis: The efficiency of drug removal depends on physicochemical properties. As molecular size decreases (<500d) and water solubility increases, the drug removal increases. Conversely as protein binding and V_D increase, dialysis clearance decreases. HD factors include membrane type and surface area, blood flow rates and dialysis frequency and duration. Drugs known to be significantly cleared by dialysis should be administered after dialysis. Maintenance drug dosing with intermittent hemodialysis should be guided by published dosing recommendations based on creatinine clearance <10ml/min with postdialysis administration. Peritoneal Dialysis: Peritoneal dialysis does not enhance drug removal to a degree that would require special dosage regimen modification. CRRT: Maintenance drug dosing in patients on CRRT is best estimated using total creatinine clearance (patientþtherapy). With high-volume CRRT (>25ml/kg per h), most drugs should be dosed based on a creatinine clearance between 25 and 50ml/min.[14]

Conclusion:

The proper dosing of medication for patients with renal impairment can maximize therapeutic efficacy and minimize toxicity. Proper dosing can also have an economic impact on the health system. Dosage adjustment can result in avoidance of costs associated with drug related toxicity and cost saving in terms of drugs cost.

References:

1. Dennen P, Douglas IS, Anderson R. Acute kidney injury in the intensive care unit: an update and primer for the intensivist. Crit Care Med 2010; 38: 261–275.
2. Uchino S. The epidemiology of acute renal failure in the world. Curr Opin Crit Care 2006; 12: 538–543.
3. Bagshaw SM, George C, Bellomo R. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care

2007; 11: R68.
4. Uchino S, Kellum JA, Bellomo R et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294: 813–818.
5. Uchino S, Bellomo R, Goldsmith D et al. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006; 34: 1913–1917.
6. Joannidis M, Druml W, Forni LG et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit. Intensive Care Med 2010; 36: 392–411.
7. Mehta RL, Pascual MT, Soroko S et al. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. Kidney Int 2004; 66: 1613–1621.
8. Taber SS, Mueller BA. Drug-associated renal dysfunction. Crit Care Clin 2006; 22: 357–374
9. Chertow GM, Burdick E, Honour M et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005; 16: 3365–3370.
10. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin 2006; 22: 255–271.
11. Vilay AM, Churchwell MD, Mueller BA. Drug metabolism and nonrenal clearance in acute kidney injury. Crit Care 2008; 12: 235–243. 27.
12. Schmith VD, Foss JF. Inflammation: planning for a source of pharmacokinetic/pharmacodynamic variability in translational studies. Clin Pharmacol Ther 2010; 87: 488–491.
13. Olyaei AJ, Bennett WM. Drug dosing in the elderly patients with chronic kidney disease. Clin Geriatr Med 2009; 25: 459–527. Schetz M. Drug dosing in continuous renal replacement therapy: general rules. Curr Opin Crit Care 2007; 13: 645–651.

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