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Dose Adjustment in Renal Failure

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Abstract
The effect of a drug can be altered due to renal diseases. This is usually due to inefficient clearance of renally excreting drugs from the body. Pharmacokinetic parameters such as bioavailability, volume of distribution, protein binding, and biotransformation of a drug can also be altered in kidney diseases. Hence adjustment of dose according to renal clearance is important .Creatinine clearance is one of those parameters that help to assess the renal function. It can be estimated with Cockcroft- gault equation. Thus following proper dose adjustment for renally excreting drugs, wecan reduce the chances of drug induced nephrotoxicity.

Introduction

Errors related to drug dosing is common in renally impaired patients and may lead to adverse effects and poor outcome. Hence it is important to make appropriate dose adjustments[1]. Clinical pharmacist plays a major role in controlling progression of chronic kidney disease, by identifying drug related problems and by adjusting the dose, thus the progression of CKD can be prevented[2]. Creatinine clearance and eGFR are the most commonly used parameters for the evaluation of renal function[1].

The incidence of acute kidney injury during hospital admission due to drug nephrotoxicity is about 19%.This can be reduced by adjusting the dose of renally cleared drugs according to the patient's estimated glomerular filtration rate (eGFR)[3]

Pharmacokinetic Parameters in CKD

Bioavailability

The bioavailability of a medication is the fraction of the total dose of a drug that reaches systemic circulation[4]. Route of drug delivery and the rate of administration are the major variables contributing to bioavailability. Kidney disease and commonly associated co-morbid conditions have a combined effect on various aspects of Absorption. Uraemia-induced vomiting may prevent drug from getting fully absorbed. Patients with congestive heart failure or cirrhosis combined with renal failure leads to fluid over load in the body causing decreased oral bioavailability[5]

Volume of distribution

The Vd is a proportion of the volume of pharmacological agent in the body compared to the amount of drug in the serum[4]. Kidney

impairment can lead to change in volume of distribution and protein binding of medications. Volume of distribution is increased in patient with oedematous condition.

Extracellular fluid volume imbalance have the greatest effect on hydrophilic compounds or those with low Vd (<0.7 ml/kg). When dosing this category of medications, fluid status has to be considered[5]

Protein Binding

On distribution phase many of the pharmacologic agents bind with plasma protein to a varying extend. In kidney failure, Uremic molecules and other organic wastes accumulate and they have the ability to bind to plasma proteins displacing the pharmacological agent. The rise in unbound drug molecule, increases the potential pharmacologic action of the medication.

For example,

Phenytoin, a highly protein-bound (98%) drug, based on the extent of available protein binding and due to its narrow therapeutic index, dosage adjustments may be required.[5]

Biotransformation

The process of chemical change to a pharmacologically active agent from a parent compound to a drug metabolite. Patients with CKD have slower renal drug clearance and prolonged half-life compared to patients with normal renal function. Many drugs produce therapeutically active metabolite which may accumulate in these patients. Example, morphine 3 glucuronide, morphine 6 glucuronide are the metabolites of morphine, plasma concentration of these agent are higher in CKD patients[5]

Elimination

Elimination t1/2 is the time needed for the plasma concentration of the drug to get reduced by 50%[4]

Acute or chronic kidney injury, loss of nephrons and reduced renal function can be indicated with a decrease in glomerular function and tubular secretions. GFR is useful in determining renal function and dosage adjustments in CKD patients. Creatinine clearance (Clcr) is the most common practical method to estimate GFR.[5]

Estimation of Renal Function

In practice serum creatinine concentration is used for renal function assessment .even though it has limitations it remains as a robust and practical parameter for most clinical situations.

Serum creatinine

Serum creatinine and renal function are inversely related, doubling of serum creatinine represent halving of GFR. The normal range of serum creatinine level is 50 to 120 micromol/litter. Renal function declines with age and it has linear relation with lean body mass. When we consider a woman and a man with same serum creatinine, woman's serum creatinine represents approxi-mately 0.85 of the renal function of man.[6]

Creatinine clearance

It is the rate at which creatinine is removed from the blood by the kidneys, it roughly approximates the GFR[7]

Direct determination of creatinine clearance need simultaneous measurement of creatinine concentration in serum and in a timed urine specimen usually 24 hours. But this is labour some procedure.

Hence other equations were evolved to estimate creatinine clearance. Which only require serum creatinine concentration.[6]

Cockcroft- Gault Equation[8]

Creatinine clearance (mL/min) = (140 – age) x lean body weight (kg) (x 0.85 for females)

Serum creatinine (micromol/L) x 0.815

Dose Alterations in Renal Impairment

Once the creatinine clearance is estimated the need for dose adjustment for renally cleared drug must be determined. Usually dose adjustment is required when the creatinine clearance is below 60 ml /min .adjustments can be made by reducing the dose or by extending dosing interval.

1). Reducing each dose while maintaining the normal dosing interval

Risk

Risk of toxicity if the interval is not adequate for drug elimination

2.) Normal doses are maintained with extended interval

Risk

Chance for sub therapeutic drug levels in blood, especially towards the end of the dosing interval

Knowledge about appropriate dosage adjustment is important to ensure the effectiveness of drug, thus accumulation and further kidney damage by the medications can be avoided. Antihypertensive, hypoglycemics, antimicrobials analgesics and NSAID are some classes of drugs which require adjustments [1]

Drugs Requiring Renal Dose Adjustment[9], [10]

Drug	Indication	Normal dose	GFR ml/min	Recommended Dose
Acyclovir IV	H.simplex H.zoster	5-10 mg/kg	25-50 10-25 <10	5-10mg/kgQ12H 5-10mg/kgQ24H 2.5-5mg/kgQ24H
Alendronic acid	Osteoporosis	5-16mg daily or 70mgonceweekly	<35	Not recommended
Allopurinol	Gout	100-900mg/day 300mg usually	20-50 10-20	200-300mg daily 100-200mg daily
Amikacin	Antibacterial	15mg/kg/day divided Max:1.5g/day	20-50 10-20	5-6mg/kgQ12H 3-4mg/kgQ24H
AmilorideHCl	Oedema	5-10mg daily Max:20mgdaily	20-50,10-20 <10	50%of dose Avoid
Baclofen	Chronic severe sapasticity of voluntary muscle	5mgTID increase gradually	10-20	5mgBD
Metformin	Noninsulin dependent DM PCOD	500mg ,TID 1.5-1.7g daily	40-50 10-40	25-50% of dose 25%of dose
Nitrofurantoin	UTI	50-100 mg ,Q6H	<60	Contra-indicated
Tobramycin	Antibacterial	3-6mg/kg/day IV/IM divided Q8H	40-60 20-40 10-20	Q12H Q24H Q48H

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