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DOSE ADJUSTMENT IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT: Chronic Kidney Disease (CKD) is a progressive condition affecting the kidneys, resulting in a decline in their functionality over time. It affects millions of individuals worldwide. CKD affects renal drug elimination and other pharmacokinetic processes involved in drug disposition (Eg; absorption, drug distribution, nonrenal clearance [metabolism]). 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 rate (GFR) and should be calculated using online or electronic calculators. Recommended methods for maintenance dosing adjustments are dose reductions, lengthening the dosing interval or both. Physicians should be familiar with commonly used medications that require dosage adjustments. Resources are available to assist in dosing decisions for patients with CKD.

Key words: Chronic Kidney Disease (CKD), Dose Adjustment, Medication dose adjustment, Chronic renal failure.

INTRODUCTION:

Chronic Kidney Disease (CKD) necessitates a comprehensive approach to medication management. Determining the appropriate dosage for CKD patients is crucial to ensuring both efficacy and safety. CKD refers to the progressive deterioration of kidney function over time.[1] The severity of CKD is categorized into 5 - stages, with Stage - I being the mildest and Stage – V representing End-Stage Renal Disease (ESRD). As kidney function declines, the clearance of drugs and their metabolites also diminishes, posing challenges for effective drug therapy. Responsible medication management in CKD patients is critical to preventing toxicity and optimizing treatment outcomes.[2]

One crucial aspect of managing CKD is dose adjustment, ensuring that it is tailored to the specific needs of patients with impaired kidney function. In CKD patients, the kidneys are unable to filter and eliminate medications from the body efficiently. This impaired drug clearance can lead to potential toxicity if standard doses are administered. Therefore, dose adjustment is necessary to prevent adverse effects and optimize treatment outcomes in all CKD patients. Various factors must be taken into account when adjusting medication doses for CKD patients. These include the stage of kidney disease, the patients age, weight, co-morbidities and the pharmacokinetic properties of the drug. All these factors play a crucial role in determining the appropriate medication dosage for each individual. Adjusting medication doses for CKD patients can be challenging due to the variability in individual responses to medications. Renal function fluctuates in CKD patients, requiring constant monitoring and dose adjustments to ensure optimal therapeutic effects without causing harm. Additionally, the lack of standardized guidelines for dose adjustment further complicates the process. Individualized dose adjustment is essential for all CKD patients to achieve optimal treatment outcomes. By tailoring medication doses to each patients specific renal function and other individual characteristics, healthcare providers can minimize the risk of adverse effects and maximize the benefits of treatment.[3, 4, 5] **Dosing Adjustments** - Loading doses usually do not need to be adjusted in patients with chronic kidney disease. Published guidelines suggest methods for maintenance dosing adjustments: dose reduction, lengthening the dosing interval, or both.[3, 4] Dose reduction involves reducing each dose while maintaining the normal dosing interval. This approach 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.[6]

Dosing recommendations for individual drugs can be found in Drug Prescribing in Renal Failure: Dosing Guidelines for Adults. The guidelines are divided into three broad GFR categories (less than 10 mL/minute/1.73 m^2, 10 - 50 mL/minute/1.73 m^2 and more than 50 mL/minute/1.73 m^2), encompassing an up to 10-fold range in renal function. The guidelines do not correspond with the K/DOQI staging system; therefore, although they can be used for initial dosages, regimens must be individualized further based on patient response and serum drug concentrations.[7]

Resources for More Information About Dosing Adjustments in Patients with CKD[8]

Drug Prescribing in Renal Failure: Dosing Guidelines for Adults Publisher: American College of Physicians PDA download:http://acp.pdaorder.com/pdaorder/-/605920537541/item?oec-catalog-item-id=1028
FDA Center for Food Safety and Applied Nutrition Web site: http://www.fda.gov/food
FDA MedWatch Web site: http://www.fda.gov/medwatch/index.html
Medline Plus (herbal medicine) Web site: http://www.nlm.nih.gov/medlineplus/herbalmedicine.html
National Center for Complementary and Alternative Medicine Web site: http://www.nccam.nih.gov/
National Kidney Disease Education Program Web site: http://www.nkdep.nih.gov
National Kidney Foundation Web site: http://www.kidney.org/

PDA = personal digital assistant; FDA = U.S. Food and Drug Administration.

Dose Adjustment Principles in CKD Patients[3, 4]

Individualized Assessment: Each CKD patient is unique, necessitating an individualized approach to medication management. Factors such as kidney function, comorbidities, drug interactions and patient characteristics should be carefully evaluated before determining the optimal dosage.

Renal Clearance: Drugs that are primarily eliminated by the kidneys require dose adjustment in CKD patients due to reduced renal clearance. Adjustments are typically based on the estimated glomerular filtration rate (eGFR), which measures kidney function. Other parameters like serum creatinine levels and proteinuria, may also influence dosage adjustments.

Drug Pharmacokinetics: Understanding a drug pharmacokinetic profile is crucial in determining its appropriate dosage. Alterations in absorption, distribution, metabolism and elimination may occur in CKD patients, necessitating dose adjustments to maintain therapeutic levels.

Nephrotoxicity: Certain medications have nephrotoxic potential, meaning they can further impair kidney function in CKD patients. Careful consideration of these drugs is vital and their use may be limited or avoided altogether.

Dose Adjustment in Different Stages of CKD[5, 6, 7]

Stage - I and II CKD: In these early stages, dosage adjustments are generally unnecessary since kidney function is relatively well preserved. However, close monitoring and periodic reassessment of medication regimens are essential.

Stage - III CKD: As kidney function declines, dose adjustments are warranted, especially for renally cleared drugs. Reducing the dose or increasing the dosing interval helps prevent drug accumulation and potential toxicity.

Stage - IV CKD: Further dose reductions or extended dosing intervals are often required in Stage IV CKD due to significantly impaired renal function.

Stage - V CKD/(ESRD): ESRD necessitates tailored dosing strategies as the kidneys are no longer able to adequately eliminate drugs from the system. Careful medication selection, alternative routes of administration and monitoring of drug levels may be necessary.

Study Methodology: A comprehensive literature review search was performed through google in various reputed journals for 3 - months to identify relevant articles for the study of 'Dose Adjustment in Chronic Kidney Disease Patients'. We collected an electronic database search from different articles published in different journals. The search strategy included the use of terms or text words related to CKD, Dose adjustments, Medication dose adjustment, Medication Adherence, Disease Management etc., The method of analysis and inclusion criteria for this review were specified in advance and documented.

To be included in this review, the articles had to meet the following criteria: (i) be an original article (i.e., randomized controlled trials, non-randomized controlled studies, cohort studies, cross-over studies, before-and-after studies); (ii) be published in any national or international journals in English; (iii) have evaluated the dose adjustment in CKD patients; (iv) report possible changes over time in outcome measures and (v) include adult CKD patients using polypharmacy. Studies without a clear description of Dosage adjustment; with multiprofessional interventions not led by the pharmacist; patients with other diseases than cancer in which the relevance to the population of interest could not be appraised were excluded. The full-text articles were reviewed to determine whether they met the prespecified inclusion criteria. Any disagreements were resolved by consensus through discussion.[10, 11, 12]

The studied articles were summarized as;

DISCUSSION:

STUDY – 1: Abdulrahman M Alahdal *et al.*,[12] conducted a retrospective study on the evaluation of applying drug dose adjustment by physicians to patients with renal impairment, which consisted of 98 patients, was reduced to 80 due to insufficient recorded data available for 17 patients and the transfer of one patient to another hospital. Recorded patient data includes, baseline demographics, medical history, laboratory outcomes (such as serum creatinine levels and creatinine clearance), renal state (such as the extent of renal impairment and dialysis), treatment advice and medication data (such as drug labels, dosages, concurrent drug use and dose modifications). With an average dose of 6 - medications per patient, a total of 502 substances were examined in 80 patients, the average age of patients was 60 years, with 55% male and 45% female. The majority of patients (40%) are suffering from multiple disorders including diabetes, hypertension and other conditions. Additionally, 5% of patients have had renal transplants. The highest number of patients was in stage - III (4%). Out of 502 medications, 196 (39%) needed dose adjustment, 92 (46.9%) were adjusted and 104 (53.1%) were not adjusted. The results revealed that antibiotics contributed to the majority of medications that required dose adjustments (39.8%). Among the antibiotics advised for renal dosage adjustment, Vancomycin was the most often prescribed and ranked highest. Moreover, of all the medications advised for renal dosage modification, Ranitidine, Atenolol and Furosemide ranked highest.

STUDY - 2: Yahaya Hassan *et al.*,[13] conducted a comparative study with a preintervention and postintervention design. The preintervention phase (prospective and observational only) was conducted from the beginning of February to the end of May 2007. The intervention phase was conducted from the beginning of March to the end of June 2008. There were 2 - randomized groups of 300 patients, each with an estimated creatinine clearance of ≤ 50 mL/min. Dialysis was provided to the majority of patients who had stage - V CKD. Out of 2814 prescriptions dispensed in the preintervention group, 607 (21.6%) required a change in dosage or avoidance of the medication due to renal function. Out of them, 322 (53.0%) did not follow dosing guidelines and 285 (47.0%) did. A total of 640 prescriptions (21.5%) out of 2981 in the intervention group required dosage adjustments or avoidance due to renal function. Of the prescriptions, 464 (72.5%) were modified in accordance with suggestions made by the collaborative renal medication dosing service. The percentage of prescriptions for the medications under study that deviated from the specified doses declined to 176 (27.5%) ($p < 0.001$). During the intervention phase, 212 (54.6%) of the 388 pharmacist recommendations were accepted by the prescribers. Medications that are frequently prescribed inappropriately for patients with impaired renal function include antibacterials, Ranitidine, Metoclopramide, angiotensin converting enzyme (ACE) inhibitors, Tramadol, Atenolol, Chlorothiazide and Allopurinol. This can involve prescribing these medications at higher doses or frequencies than recommended or when it is not appropriate.

Suspected ADEs were present in 64 (21.3%) of the 300 patients in the preintervention group, accounting for 73 occurrences in all. In the intervention group, there were 49 incidents in 48 (16.0%) patients, a significant decrease

from this number ($p < 0.05$). The drug classes that were most commonly associated with ADEs were diuretics, antithrombotic agents, medications for diabetic mellitus and antibiotics. In the preintervention group, there were 20 (27.4%) serious ADEs, 42 (57.5%) significant ADEs and 11 (15.1%) insignificant ADEs. There were 5 - (10.2%) serious cases, 36 (73.5%) significant cases and 8 (16.3%) insignificant cases in the intervention group.

STUDY – 3: Sepideh Emami *et al.*,[14] conducted research on evaluation of drug dose adjustment in patients with kidney disease, total of 142 patients were evaluated. The majority of patients (84.9%) were admitted to wards for infectious and general internal illnesses. The mean age ± SD was 62.7 ± 16.4 years, the male:female ratio was 86:56 and the mean serum creatinine ± SD was 2.3 ± 2.0 mg/dl. Following the removal of 11 dialysis patients, 131 patients remained, with 44, 75 and 12 patients in each of the AKI, CKD and unidentified groups (due to inadequate information) categories. Dose adjustment was necessary in 193 (23.2%) of the 830 prescriptions that were analyzed. In 88 (45.5%) orders, these modifications were made correctly, in 105 (54.4%) orders, they were not. The most frequently inappropriate medications were Ranitidine, Digoxin (PO) and Midazolam, which were given inappropriate dosages in 79.5%, 73.5% and 28.5% of instances, respectively. Once factor corrections were applied, the highest percentage of inappropriate dosages were found for Atenolol, Metformin and Digoxin (IV), with 49.0 (100%), 48.2 (98.3%) and 42.8 (87.3%) respectively. Additionally, 81% of patients required at least one prescription medication dose change. There were also 19 orders that were contraindicated. Among these orders were those suggesting that Phenazopyridine, Glyburide, Metformin and Spironolactone were prohibited in 47.6%, 83.3%, 66.6% and 100% of cases respectively.

STUDY – 4: Kidu Gidey *et al.*,[15] conducted a cross-sectional study to assess the drug dose adjustment practices in patients with renal impairments, consisted of 422 patients. Of the participants, 59.2% were male and the remaining were female, with a greater ratio of male to female (86:56). The study participants ranged in age from 16 - 93 years old, with a mean age SD of 42.90 ± 17.340. A large proportion of patients (32%) belonged to the 46 – 65 age group. The patients with renal impairment had a mean S_{cr} level of 3.94 ± 3.02 (range: 1.4 – 14.4) and a mean Cr_{Cl} of 28.84 ± 14.5 ml/min (range: 5 – 50). Among the 231 patients suffering from renal impairment, 849 prescription entries were recorded. For individuals with renal impairment, 42.5% of the recommended medications needed to have their doses adjusted. Out of all the medications that need to have their dosage adjusted, 51% were ordered incorrectly (46.6% were prescribed at the wrong dosage and 4.4% were contraindicated). Ciprofloxacin was the most often prescribed medication in the antimicrobial drug group (59.2%) that required dose modification.

STUDY – 5: Yuki Kondo *et al.*,[16] conducted a web-based questionnaire on awareness and current implementation of drug dosage adjustment by pharmacists in patients with CKD in Japan. A total of 284 pharmacists, comprising 190 community-based pharmacists (66.9%) and 94 hospital pharmacists (33.1%) contributed to the survey. The percentage (%) of pharmacists with 20 years of experience was 45 (15.8%), 73 (25.7%), 101 (35.6%) and 65 (22.9%). Prescriptions were regularly filled by the community pharmacists for an average of 3 - hospital departments. Prescriptions from nephrologists were regularly filled by 80 pharmacists (39.2%). They focused on

the pharmacists encounters with adverse medication events resulting from prescribing the wrong dosage for patients with CKD. The % of hospital pharmacists (n = 47, 50.0%) who had experienced such adverse medication events was significantly higher than that of community pharmacists (n = 22, 11.6%). The drugs that cause adverse drug events most frequently cited by hospital and community pharmacists were antivirals and Pregabalin. Implementing ADR has been affected by difficulty in obtaining information on patient renal function, according to more community pharmacists (n = 168, 88.4%) than hospital pharmacists (n = 13, 13.8%). The final logistic regression model determined that regularly receiving prescriptions from nephrologists, experience with adverse drug events caused by inappropriate dosage for CKD patients and awareness of needing pharmacists to check dosage of renally excreted drugs were the factors influencing community pharmacist's implementation of ADR.

STUDY - 6: Rayane Saad *et al.,*[17] conducted a retrospective cross-sectional study on the evaluation of renal drug dosing adjustment in CKD patients at 2 - university hospitals, in 12 month, 2138 CKD patients were identified. A total of 223 patients (10.4% of screened subjects) were considered for assessment based on the inclusion criteria. 578 orders of the research drugs were prescribed to those patients. There were 99 (44.4%) females and 124 (55.6%) males in the study population. A total of 27 individuals (12.1%) were admitted for renal-related reasons. The mean age was 65.78 years (ranging from 19 - 96); the mean body weight was 76.3 kg. Of the 104 patients (46.6%) admitted to the internal medicine (IM) floor, 84 (37.7%) and 94 (42.2%) were in the G4 and G5 phases of CKD. 95 patients (42.6%) in the study group were hemodialysis patients.

Out of 578 orders, 215 orders (37%) had appropriate adjustments, 284 (49%), corresponding to the majority, had inappropriate adjustments and 79 orders (14%) had no adjustments at all. When type of medication and dose adjustment were evaluated, Bisoprolol was the most frequently prescribed drug that required dose adjustment, it was appropriately adjusted in 24/196 (12.2%) and inappropriately adjusted in 168/196 (85.8%) of cases, followed by Ranitidine, Metoclopramide, Ramipril and Simvastatin, which were adequately adjusted in 42/68 (61.7%), 22/45 (48.8%), 22/35 (62.9%) and 30/31 (96.8%) patients. Fenofibrate was associated with the highest proportion of not adjusted doses 19/20 (95%), followed by Oseltamivir and Captopril, which were not adjusted in 5/8 (62.5%) and 3/5 (60%) of cases.

STUDY – 7: Sarah Seiberth *et al.,*[18] conducted a retrospective observational study of patients at the time of hospital admission to 2 - urology wards, on correct use of non-indexed eGFR for drug dosing and renal drug-related problems (DRPs). 1341 patients were admitted over the 6 - month trial period. Medication reconciliation led by a pharmacist was completed for 1320 (98%) of the patients. The majority of all patients were male (82.6%) and the mean age was 67 (18 – 94) years. A total of 277 patients (20.5%) had an $eGFR_{indexed}$ between 15 and 59 ml/min/1.73 m^2, whereas 16 patients (1.2%) had an $eGFR_{indexed}$ less than 15 ml/min/1.73 m^2. Among all patients, the median BSA was significantly greater than 1.73 m^2. Upon recalculating $eGFR_{non\text{-}indexed}$ using the patients actual BSA, 67 (5.1%) of the patients were found to be not within the crucial range of 15 – 59 ml/min. Compared to patients with eGFR ≥ 60 ml/min, the remaining 203 (15.4%) patients in the critical $eGFR_{non\text{-}indexed}$ range of 15 – 59 ml/min were older and significantly more likely to have co-morbidities like arterial hypertension (HTN),

cardiovascular disease or hypercholesterolemia. Male patients had a higher BMI and BSA when compared to female patients with $eGFR_{non\text{-}indexed}$ 15 – 59 ml/min; however, there was no significant difference in age (p = 0.31), number of medications (p = 0.62) or $eGFR_{non\text{-}indexed}$ (p = 0.69). When patients below the age of 65 and above the age of 65 were compared, there was no significant difference in $eGFR_{non\text{-}indexed}$ values (p = 0.88). However, older patients had higher drug usage ($p < 0.05$).

STUDY - 8: Abid Mubashir Sheikh *et al.*,[19] conducted a retrospective study to determine prescribing practices among patients with renal impairment in medical departments to enhance patient care at a tertiary care hospital. Renal impairment was present in 29% (233/804) of the patients. The final study comprised 184 of these patients who had renal impairment. The patient's interquartile range (IQR) was 25 – 75 years, with a median age of 53.0 years. A total of 54.3% of the patients were male. Among the co-morbidities, 71.2% (n = 131) included conditions like diabetes, congestive heart failure and HTN. Diabetes mellitus (DM) and HTN were found in 43/184 (23.4%) and 92/184 (50.0%) of the cases. While 38.0% (n = 70) of people were HIV negative and 47.3% (n = 87) of people were HIV positive, 14.7% (n = 27) of people did not know their status. Out of the 184 patients, 61.9% (n = 112) had at least one prescription that needed to be adjusted in dosage due to the patients degree of renal impairment. Out of 1143 prescription entries, 20.5% (n = 234) need a dosage adjustment; however, only 45.7% (n = 107) are appropriately adjusted. According to the logistic regression model, there was no correlation between drug dosing errors and the patient's age, gender, history of DM, HTN, co-morbidities or grade of renal impairment. There was a strong correlation between the number of prescription medications requiring renal adjustment and their frequency of use. The probability of inappropriate dosage modifications not being performed increases with the number of prescribed medications, specifically 3 or more (p-value = 0.003).

STUDY - 9: Zair Hassan *et al.*,[20] conducted a retrospective study on the assessment of medication dosage adjustment in hospitalized patients with CKD at the nephrology department of the Institute of Kidney Disease (IKD) Pakistan. 1,537 patient medical charts were studied throughout the study period. Final analysis contained 231 patients (15.03% of the screened patients). Among the 231 patients, 184 (79.7%) were male. The average age of the patients was 46.14 (±15.90) years. Of the patients, 209 [90.5%] were in the stage - V of CKD, while 14 (6.1%) were at the stage - IV. More than 5 - prescriptions were written for about 85.3% of patients. Antibiotics (95.23%) are the most commonly prescribed drugs in this study. The majority of patients (77.92%) had co-morbidities, with the most common conditions being obstructive nephropathy (36 [15.58%]), DM (57 [24.67%]) and HTN (148 [64%]). A total of 1,549 prescription medications were written, 480 (30.99%) of them needed dose adjustment, 196 (40.42%) of those doses were correctly adjusted, while the rest, 286 (59.58%) were not. The most frequently unadjusted medications were Meropenem (100%), Cefepime (100%), Ciprofloxacin (100%), Rosuvastatin (100%), Cefoperazone/Sulbactam (91.33%), Ranitidine (65.71%) and Piperacillin/Tazobactam (85.71%). The most properly adjusted medications were Aspirin (100%), Captopril (100%), Bisoprolol (100%), Pregabalin (100%), Levofloxacin (100%), Vancomycin (87.5%), Domperidone (80.7%), Cefotaxime (78.12%), Furosemide (69%), Sodium bicarbonate (53.65%) and Spironolactone (50%). Based on univariate analysis, the

total number of prescribed drugs (p = 0.01), GFR category G5 (p = 0.041) and drugs that require dose adjustment (p = 0.001) were found to be significantly associated with dosing error. After various confounding factors were taken into account, it was discovered that the presence of obstructive nephropathy (p = 0.041) was substantially linked with medication errors.

STUDY – 10: Tirsit Kestela Zeleke *et al.*,[21] conducted a cross-sectional study to assess medicine dose adjustment practice and associated factors among adult patients with renal impairment admitted to medical departments at referral hospitals. Out of 2850 patients, 424 (19.7%) patients with a GFR ≤60 were considered for evaluation. The participants mean age was 47.5 years, with a standard deviation of ±16.6. Half of the patients were male, 227 (53.5%) and the mean weight was 60.35 kg. 374 (88.2%) patients have co-morbidities. 158 (37.3%) of them were HTN, 124 (29.2%) were DM and 99 (23.3%) of participants had congestive heart failure. Out of the 1581 prescriptions for medications, 815 (51.5%) required dose adjustments. Among them, 398 (48.8%) were adjusted appropriately and Cimetidine was the most commonly inappropriately adjusted medicine. 63 (70.7%) followed by Atenolol, Ciprofloxacin and Ceftazidime, while Metformin was the least with inappropriate dose adjustment. However, the practice of dose adjustment was substantially correlated with the number of prescription medications, that is, the probability of an inappropriate dose adjustment increased by 3.20 times with an increase in the total number of prescribed medications. In terms of employment status, the probability of an inappropriate dose adjustment practice increases by 3.18 when one is unemployed compared to one who is employed. Additionally, the odds of an inappropriate dose adjustment improve by 1.65 with an increase in co-morbidities.

CONCLUSION: In managing CKD patients, dose adjustment plays a vital role in ensuring safe and effective therapy. Optimized dosage regimens must consider individual patient characteristics, stage of CKD, renal clearance, pharmacokinetic profiles of medications and nephrotoxicity potential. Achieving the right balance in medication management for CKD patients benefits overall patient well-being and contributes to favorable treatment outcomes.

Inappropriate dosing in patients with CKD can cause toxicity or ineffective therapy. In particular, older patients are at a higher risk of developing advanced disease and related adverse events caused by age-related decline in renal function and the use of multiple medications to treat comorbid conditions. CKD can affect glomerular blood flow and filtration, tubular secretion and reabsorption and renal bioactivation and metabolism. Drug absorption, bioavailability, protein binding, distribution volume and nonrenal clearance (metabolism) also can be altered in these patients. Physicians should pay careful attention when considering drug therapies with active or toxic metabolites that can accumulate and contribute to exaggerated pharmacologic effects or ADRs in patients with CKD.

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