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Pharmacovigilance of Furosemide in Chronic Kidney Failure.

Author's Name(s):
1. Deep R. Tope
2. Namrata N. Dhote
3. Dnyaneshwari S. Gaigole
4. Prof. Nikita V. Mahalle
5. Dr. Harigopal S. Sawarkar
Dr. Rajendra Gode College of Pharmacy, Amravati.

Abstract:

This study focuses on the evaluation of adverse drug reactions (ADRs) associated with furosemide use in patients with chronic kidney failure (CKF). Furosemide, a high-ceiling loop diuretic, remains central in managing fluid overload and hypertension in CKF; however, its clinical benefits are frequently offset by a significant risk of ADRs, especially in individuals with compromised renal function. Through careful observation, the study identified common adverse effects such as electrolyte imbalances (hypokalemia, hyponatremia, hypomagnesemia), dehydration, volume depletion, hypotension, and polyuria. Severe outcomes including ototoxicity, acute kidney injury, and life-threatening arrhythmias were also reported, particularly in high-dose or rapid intravenous administration settings.

Rare but critical adverse events like Stevens-Johnson Syndrome (SJS), pancytopenia, hepatic encephalopathy, interstitial nephritis, and acute pancreatitis were documented, underscoring the necessity of vigilant patient monitoring. Drug interactions with agents such as aminoglycosides, NSAIDs, ACE inhibitors, and digoxin further amplified the risk profile. The findings emphasize that personalized dosing strategies, regular electrolyte and renal function monitoring, and heightened pharmacovigilance are vital for minimizing adverse outcomes.

In conclusion, while furosemide remains indispensable in the symptomatic management of CKF, its safe use demands a patient-specific, closely supervised approach. Enhanced awareness of its potential risks and proactive management of ADRs can significantly improve patient safety and therapeutic success in chronic kidney failure treatment.

INTRODUCTION

MODULE 1

Chapter 1: Introduction to Clinical Trials

1.1 Definition of Clinical Trials

A clinical trial is a carefully designed research study conducted with human participants to evaluate the safety, efficacy, or effectiveness of a medical intervention, which can range from pharmaceuticals and medical devices to procedures or behavioural treatments. Clinical trials provide the evidence necessary to determine whether a new treatment is safe and effective for public use. These trials are an essential part of medical research and contribute significantly to advances in healthcare.

According to the U.S. National Library of Medicine (2022), a clinical trial involves a series of structured tests and evaluations under controlled conditions to gather data on the health effects of the intervention being studied. The overarching goal is to generate reliable and valid results that inform clinical practice and regulatory decisions.

1.2 Phases of Clinical Trials

Clinical trials are typically divided into four distinct phases, each serving a specific purpose in the assessment of a new treatment. These phases help ensure the safety and efficacy of the drug or procedure before it is made widely available.

1.2.1 Phase 1: Safety and Dosage

Phase 1 trials are the first step in testing a new treatment. The primary objective is to assess the safety of the intervention, including determining the maximum tolerated dose and identifying potential side effects.

- **Participants:** Small group of healthy volunteers (20-100 individuals).
- **Objectives:** Establish the pharmacokinetics of the drug (how it is absorbed, metabolized, and excreted in the body), monitor adverse effects, and determine an appropriate dosage range.

- **Duration:** Typically lasts several months.

1.2.2 Phase 2: Efficacy and Side Effects

Phase 2 trials involve a larger group of participants who have the condition the treatment is intended to address. The focus shifts to evaluating the treatment's efficacy while continuing to monitor safety.

1. **Participants:** Typically, 100-300 patients.
2. **Objectives:** Determine whether the intervention is effective and refine the optimal dose.
3. **Duration:** Can range from several months to a couple of years.

1.2.3 Phase 3: Confirmatory Trials

Phase 3 trials are pivotal as they involve a large number of participants and are designed to confirm the drug's effectiveness and safety in a real-world population. These trials often compare the new drug with a placebo or existing standard treatment.

- **Participants:** 1,000-3,000 or more patients.
- **Objectives:** Provide definitive evidence regarding the drug's effectiveness, assess long-term side effects, and gather data to support regulatory approval.
- **Duration:** Typically, 1-4 years.

1.2.4 Phase 4: Post-Marketing Surveillance

Phase 4 trials, also known as post-marketing surveillance, take place after a drug has been approved by regulatory authorities and is made available to the public. The purpose of Phase 4 trials is to monitor the long-term effects, safety, and efficacy of the drug in a broader population and detect any rare or long-term adverse effects that were not identified in earlier trials.

- **Participants:** A diverse patient population across various settings.
- **Objectives:** Monitor the drug's performance in the general population, detect uncommon side effects, and explore additional uses or applications.
- **Duration:** Ongoing, depending on the need for surveillance.

1.2 Functions of Drug Controller General of India (DCGI) and Central Drug Standard Control Organization (CDSCO)

1.2.1 DCGI:

Regulation and Approval: Oversees the approval of new drugs, clinical trials, and manufacturing practices.
Monitoring Drug Safety: Ensures drug safety by monitoring adverse drug reactions and maintaining drug quality.
Licensing: Issues licenses for the manufacturing, sale, and import of drugs and medical devices in India.

1.2.2 CDSCO:

Regulation and Enforcement: Enforces the Drugs and Cosmetics Act to ensure the safety, efficacy, and quality of drugs and cosmetics in India.
Approval of Drugs and Clinical Trials: Regulates the approval of drugs, medical devices, and clinical trials to ensure their compliance with safety standards.
Control and Surveillance: Controls and monitors the import, export, and manufacturing of drugs and cosmetics, ensuring public health safety.

1.3 Types of Regulatory Applications

1. Investigational New Drug Application (IND):

Submitted to regulatory authorities to gain approval for initiating clinical trials of a new drug in humans. It provides information on preclinical data, proposed protocols, and manufacturing details.

2. New Drug Application (NDA):
Required for the approval of a new drug to be marketed and sold in the general population. It includes data from clinical trials demonstrating the drug's safety and efficacy.

3. Abbreviated New Drug Application (ANDA):
Used for the approval of generic drugs. It ensures the generic product is bioequivalent to the brand-name drug without requiring extensive clinical trials.

4. Biologics License Application (BLA):
Submitted for the approval of biological products, such as vaccines, blood products, and monoclonal antibodies. It ensures compliance with regulatory requirements for safety and efficacy.

5. Market Authorization Application (MAA):
Required in regions such as the European Union to gain approval for marketing drugs or biological products.

6. Post-Marketing Applications:
Includes applications for label expansions, additional indications, or changes in manufacturing processes after a drug is approved and marketed.

Module 2: Good Clinical Practice

1) **Objectives and Scope of ICH-Good Clinical Practice (GCP):**

Objectives:

Ensure the rights, safety, and well-being of clinical trial participants.

Establish standards for designing, conducting, recording, and reporting clinical trials.

Facilitate mutual acceptance of clinical trial data by regulatory authorities worldwide.

Scope:

Applies to clinical trials involving human participants globally. Covers ethical considerations, investigator responsibilities, sponsor obligations, and protocol adherence.

2) **Objectives and Scope of New Drugs and Clinical Trials Rules, 2019 (India):**

Objectives:

Streamline clinical trial approval processes in India.

Promote transparency and accountability in clinical research.

Ensure timely approval of new drugs while maintaining participant safety.

Scope:

Regulates clinical trials, ethics committee approvals, and compensation for trial-related injuries.
Applies to new drugs, investigational new drugs, and orphan drugs in India.

3) Protocol Designing for Clinical Trials

A clinical trial protocol is a detailed document that outlines the rationale, objectives, design, methodology, and statistical framework of a clinical research study. According to ICH Good Clinical Practice (GCP) guidelines, the protocol should cover the following key elements:

- General Information: Includes title and basic details of the trial.
- Background: Provides context and rationale for the study.
- Objectives: Defines the primary and secondary goals of the trial.
- Study Design: Describes the trial's structure (e.g., randomized, controlled).
- Subject Selection: Specifies inclusion and exclusion criteria for participant selection.
- Treatment Plan: Details the interventions, dosages, and treatment protocols for subjects.
- Efficacy Assessment: Defines how the treatment's effectiveness will be measured.
- Safety Assessment: Outlines how the safety of participants will be monitored.
- Adverse Events: Details reporting and handling of any side effects.
- Study Discontinuation: Explains criteria for stopping the trial.
- Statistical Methods: Describes the approach to data analysis and sample size calculation.
- Quality Control: Ensures data accuracy and consistency throughout the trial.
- Ethical Considerations: Ensures compliance with ethical standards and participant rights.
- Data Management: Outlines procedures for data handling and record-keeping.
- Publication Policy: Defines plans for publishing the trial results.
- Timeline: Provides an overall timeline or flowchart of the study's phases.
- References and Appendices: Lists relevant studies and additional supporting material.

Module 3: Concept of Pharmacovigilance

3.1Definition of Pharmacovigilance:

Pharmacovigilance is the science and activities related to the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) or any other drug-related problems.

- Objectives of Pharmacovigilance:

Ensure the safety of pharmaceutical products post-marketing.

Detect, evaluate, and prevent adverse drug reactions (ADRs).

Improve patient safety and promote rational use of medications.

- Types of Pharmacovigilance:

Spontaneous Reporting: Collection of ADR reports from healthcare professionals and consumers.

Targeted Surveillance: Monitoring of specific drugs or groups of patients for safety concerns.

Cohort Studies and Case-Control Studies: Observational studies to assess risk and benefit profiles of drugs.

- Components of Pharmacovigilance:

Adverse Drug Reaction Monitoring: Continuous collection and analysis of ADR data.

Signal Detection: Identifying potential risks associated with drugs.

Risk Management: Developing strategies to mitigate identified risks.

Regulatory Actions: Implementing changes to drug labelling, distribution, or marketing based on findings.

3.2 Constitution and Objectives of Pharmacovigilance Program of India (PvPI)

Constitution of PvPI:

The Pharmacovigilance Program of India (PvPI) was established by the Central Drugs Standard Control Organization (CDSCO) under the Ministry of Health and Family Welfare. The program is implemented by the Indian Pharmacopoeia Commission (IPC), which is the National Coordinating Center for PvPI.

➢ **Objectives of PvPI:**

4. ADR Monitoring: Monitor and assess the safety of medicines used in India by collecting and analyzing adverse drug reactions (ADRs).
5. Patient Safety: Ensure the safety of patients by detecting, understanding, and preventing ADRs and other drug-related problems.
6. Public Awareness: Educate healthcare professionals and the public about the importance of reporting ADRs.
7. Regulatory Support: Provide regulatory authorities with ADR data to inform decision-making related to drug approval and market surveillance.
8. Risk Management: Develop risk management strategies for identified safety concerns.

➢ **List of National Adverse Drug Monitoring Centers (AMCs) and Their Functions**

In India, Pharmacovigilance Program of India (PvPI) operates through a network of National Adverse Drug Monitoring Centers (AMCs) located across various regions. These centres are responsible for collecting, analyzing, and reporting adverse drug reactions (ADRs).

Here is a list of the AMCs along with their functions:

1. Indian Pharmacopoeia Commission (IPC), Ghaziabad

Function: Acts as the National Coordinating Centre for PvPI. Collects ADR data, analyzes, and disseminates findings. It provides recommendations to regulatory authorities.

2. All India Institute of Medical Sciences (AIIMS), New Delhi

Function: A major center for monitoring ADRs in hospitalized patients. Provides support in ADR training and awareness for healthcare professionals.

3. Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh

Function: Collects ADR reports, analyzes them, and supports research in pharmacovigilance. It plays an important role in educating health professionals about ADR monitoring.

4. King Edward Memorial (KEM) Hospital, Mumbai

Function: Monitors ADRs in both outpatient and inpatient settings. Provides guidance to local healthcare providers on ADR identification and reporting.

5. Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram

Function: Acts as a regional ADR monitoring center and helps in the detection and analysis of ADRs.

6. National Institute of Pharmaceutical Education and Research (NIPER), Mohali Function: Provides ADR monitoring and contributes to drug safety research.

Module 4: International Conference on Harmonization (ICH) E2 Guidelines

➢ Elements of the Non-Clinical and Clinical Safety Specification

The ICH E2e Guidelines outline the requirements for non-clinical and clinical safety specifications of a new pharmaceutical product. These specifications are essential to assess and ensure the safety of a drug before and during clinical trials.

- **Non-Clinical Safety Specification:**

Toxicology Data: Includes acute, sub-acute, and chronic toxicity data, genotoxicity, and carcinogenicity studies to assess potential harmful effects.

Pharmacokinetics: Information on how the drug is absorbed, distributed, metabolized, and excreted in animals to predict human responses.

Reproductive Toxicity: Data from animal studies to evaluate the impact on fertility, embryonic development, and birth defects.

Safety Pharmacology: Assesses effects on vital organs, including the cardiovascular and respiratory systems.

- **Clinical Safety Specification:**

Adverse Drug Reactions (ADR): Monitors and categorizes adverse reactions based on clinical trials and post-marketing surveillance.

Risk Management: Develops strategies to minimize identified risks during clinical development and post-marketing phases.

Clinical Monitoring: Includes structured assessments for safety during clinical trials, ensuring timely identification and management of adverse events.

➢ Identification and Evaluation of Risks Including Drug-Drug and Drug-Food Interactions

- **Drug-Drug Interactions (DDIs):**

Identification: DDIs occur when two or more drugs interact, affecting their efficacy or safety. These interactions can be identified through preclinical studies, clinical trials, and post-marketing surveillance.

Evaluation: Risk evaluation involves monitoring therapeutic outcomes, understanding the pharmacokinetic (e.g., metabolism) or pharmacodynamics (e.g., synergistic effects) mechanisms, and utilizing databases and reports on ADRs to assess the significance of interactions.

- **Drug-Food Interactions:**

Identification: These interactions happen when food affects the absorption, metabolism, or action of a drug. Identified through clinical trials, laboratory studies, and spontaneous reporting systems.

Evaluation: Evaluation includes determining the effect of food on drug bioavailability (e.g., the presence of food altering the absorption of certain medications) and using clinical monitoring to detect any adverse outcomes.

Both DDIs and drug-food interactions are critical for ensuring patient safety, and regulatory bodies require their thorough evaluation during clinical trials and post-marketing phases.

➢ Design and Conduct of Observational Studies

1. Design of Observational Studies:

Types: Includes cohort studies, case-control studies, and cross-sectional studies. These studies do not involve experimental manipulation but observe real-world patient behaviours or outcomes.

Objective: To assess associations between exposures (e.g., drugs) and outcomes (e.g., adverse reactions) without intervening.

Data Collection: Involves gathering data through patient records, surveys, or registries.

2. Conduct of Observational Studies:

Sampling: Participants are selected based on specific inclusion/exclusion criteria and observed over a period.

Analysis: Statistical methods are used to identify correlations or associations, but causality is not established.

Ethics: Must adhere to ethical guidelines, ensuring informed consent and patient confidentiality.

Literature Review:

Literature Review:

1. **Becker et.al. [1978],** according to Becker approximately 39.8% of 533 hospitalized patients experienced ADRs due to furosemide, predominantly dose-related, with common effects like electrolyte disturbances (23.5%), extracellular volume depletion (9%), and hepatic coma (3.6%).

2. **Bennett et.al. [1978],** as per Bennett a clinical evaluation of 204 patients receiving furosemide revealed significant electrolyte imbalances, including hypokalaemia (25%), hypochloraemia (35.8%), and hyponatremia (24.5%), with some cases of hyperkalaemia due to concomitant potassium-sparing agents.

3. **Luhdorf et.al. [1977],** Luhdorf reported an ADR incidence of 10.1% among 2,367 hospitalized patients, mainly intravascular volume depletion (4.6%) and hypokalaemia (3.6%).

4. **Chittenden and Kamath [1978],** Chittenden and Kamath observed that 21% of 585 hospital inpatients on furosemide developed ADRs, such as hyperuricemia, hypovolemia, and renal function disturbances, especially when daily doses exceeded 80 mg.

5. **Ellison [1994],** Ellison highlighted the risk of ototoxicity with high-dose intravenous furosemide, particularly when combined with aminoglycosides in patients with chronic kidney failure (CKF).

6. **Iseki et.al. [2006],** according to Iseki haemodialysis patients using loop diuretics like furosemide had a higher incidence of minor bleeding events, suggesting a possible procoagulant effect.

7. **Singri et.al. [2004],** Singri discussed that furosemide promotes vitamin and electrolyte losses, indirectly impairing coagulation function by affecting vitamin K–dependent clotting factors.

8. **Humes [1991],** Humes detailed that furosemide reduces renal prostaglandin synthesis, leading to altered renal hemodynamic and potential impacts on platelet aggregation and bleeding tendencies.

9. **FAERS Database Reports [2010–2020],** FAERS Database Reports revealed several cases linking furosemide to increased prothrombin time and easy bruising, although these events were rare compared to other ADRs.

10. **BMC Pharmacology [2024],** according to BMC Pharmacology long-term use of furosemide is associated with thiamine and magnesium depletion, which may worsen metabolic or vascular dysfunction in CKF.

11. **Elliott and Tullett [1992],** Elliott and Tullett noted that furosemide's impact on vascular endothelium integrity could explain its procoagulant effects, especially in patients with chronic renal insufficiency.

12. **Segarra et.al. [1997],** Segarra confirmed that furosemide-induced hypoalbuminemia can alter drug binding, increasing the risk of toxicity and bleeding complications in CKF patients.

13. **Tonshoff et.al. [1992],** Tonshoff emphasized the need for careful dose adjustment and electrolyte monitoring to prevent ADRs in pediatric CKF patients treated with loop diuretics.

14. **The National Kidney Foundation NKF [2022],** according The National Kidney Foundation NKF close monitoring of coagulation parameters in advanced CKD patients receiving furosemide due to heightened vascular and hematologic side effect risks.

15. **The KDOQI Guidelines [2023],** the KDOQI Guidelines reinforced that while furosemide remains a first-line treatment for volume overload in CKF, clinicians should be alert to rare but significant ADRs related to bleeding and coagulation.

AIM AND OBJECTIVE

Aim:

The aim of this study is to monitor and analyse the adverse effects and safety profiles of furosemide, ensuring their optimal use and minimizing potential risks to patients.

Objectives:

- To collect and analyse data on adverse drug reactions (ADRs)
- To identify the frequency and severity of ADRs in different patient populations.
- To compare the safety profiles.
- To provide recommendations for healthcare professionals on the safe use of these
- medications.
- To raise awareness about the importance of pharmacovigilance in clinical
- practice.
- To improve patient care and safety.
- To improve public health and safety.
- To contribute to the assessment of benefits, harm, effectiveness and risk of
- medicines.
- To promote education and clinical training.
- To promote effective communication with the public.
- To promote rational and safe use of medicines.

CASE STUDY

Module 5: Case Study

Chronic Kidney Disease (CKD)

1. INTRODUCTION:

Kidney failure (renal failure) means one or both of your kidneys no longer function well on their own. Kidney failure is sometimes temporary and develops quickly (acute). Other times it's a chronic (long-term) condition that slowly gets worse. Kidney failure is the most severe stage of kidney disease. It's fatal without treatment. If you have kidney failure, you may survive a few days or weeks without treatment.

Chronic kidney disease (CKD) is characterized from a progressing reduction in renal function, and end-stage renal disease (ESRD) patients end up requiring renal replacement therapy (RRT). CKD is an important health issue worldwide with high morbidity and mortality rates among the non-communicable diseases. The all-cause mortality due to CKD or to CKD-attributable cardiovascular diseases is estimated to account for 5% globally, and its prevalence is growing.

Considering ESRD patients, demographics data from severe studies reveal a tendency to increase the size of the patient population as well as their age, highlighting the importance of advanced nephrological healthcare.

- **Functions of kidney:**

- Electrolyte and volume regulation
- Excretion of nitrogenous waste
- Elimination of exogenous molecules, for example, many drugs
- Synthesis of a variety of hormones, for example, erythropoietin
- Metabolism of low molecular weight proteins, for example, insulin.
- Remove waste products from the body.
- Remove drug from the body
- Control the production of red blood cell.
- Make urine and purify blood.

1.1. Pathophysiology of Chronic Kidney Failure

Chronic Kidney Failure (CKF), also known as chronic kidney disease (CKD), is a progressive and irreversible deterioration of renal function lasting for more than three months. It is typically classified into five stages based on the glomerular filtration rate (GFR), with end-stage renal disease (ESRD) representing the final stage where dialysis or transplantation is required. The pathophysiological process of CKF begins with an initial insult to the nephrons—whether due to diabetes, hypertension, glomerulonephritis, or other causes. In response, the remaining nephrons undergo adaptive hyperfiltration and hypertrophy to compensate for the lost function. Although initially beneficial, this adaptive response leads to glomerular hypertension, increased capillary permeability, and ultimately glomerulosclerosis and tubulointerstitial fibrosis.

- **Key mechanisms involved in CKF progression include:**

➢ Glomerular hypertension and hyperfiltration: Increase intraglomerular pressure, damaging the filtration barrier.
➢ Inflammation and oxidative stress: Stimulate profibrotic cytokines like TGF-β, promoting fibrosis.
➢ Proteinuria: Causes direct toxicity to tubular cells and promotes inflammatory responses.
➢ Renin-Angiotensin-Aldosterone System (RAAS) activation: Leads to vasoconstriction, sodium retention, and further nephron injury.

- **As kidney function declines, the body accumulates uremic toxins, leading to systemic complications such as:**

➢ Anaemia (due to decreased erythropoietin production),
➢ Electrolyte imbalances (like hyperkalaemia, hypocalcaemia),
➢ Acid-base disturbances (mainly metabolic acidosis),
➢ Cardiovascular complications (hypertension, left ventricular hypertrophy).

Over time, this creates a vicious cycle of nephron loss, leading to ESRD if not managed properly.

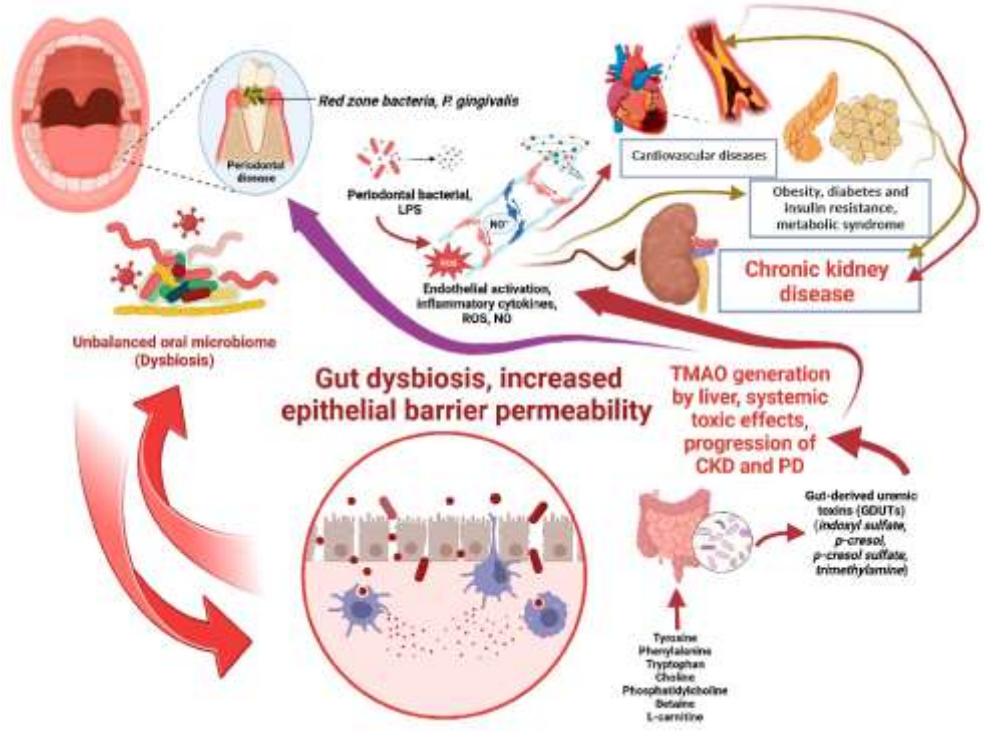


Diagram No.1: Pathophysiology of kidney failure.

1.2. ANATOMY OF KIDNEY:

- **Location:**

The kidneys are located on either side of the spine, in the retroperitoneal space. The left kidney is situated a little higher than the right one, because of the liver on the right side of the abdominal cavity, above the right kidney.

- **Structure:**

Each of the two bean-shaped organs weighs about 125 to 175 grams and 115 to 155 grams in males and females respectively. The kidney typically measures approximately 11 to 14 centimetres in length, 6 centimetres in width and is about 4 centimetres thick. The kidneys are protected by fat, muscles, and ribs of the back. Perirenal fat, also called the renal fat pad, protects the kidneys from external force or damage. The kidneys have a medial dimple called the renal helium, which is the entry and exit point for structures that supply or drain the kidneys such as the nerves, ureters, vessels, and lymphatics.

- **Glomeruli:**

Glomeruli are groups of tiny blood vessels that perform the first stage of filtering your blood. They then pass filtered substances to the renal tubules. The name for this process is Glomerular filtration.

- **Renal tubules**:

These tiny tubes reabsorb and return water, nutrients and minerals your body needs (including sodium and potassium). The tubules remove waste, including excess acid and fluids through a process called diffusion.

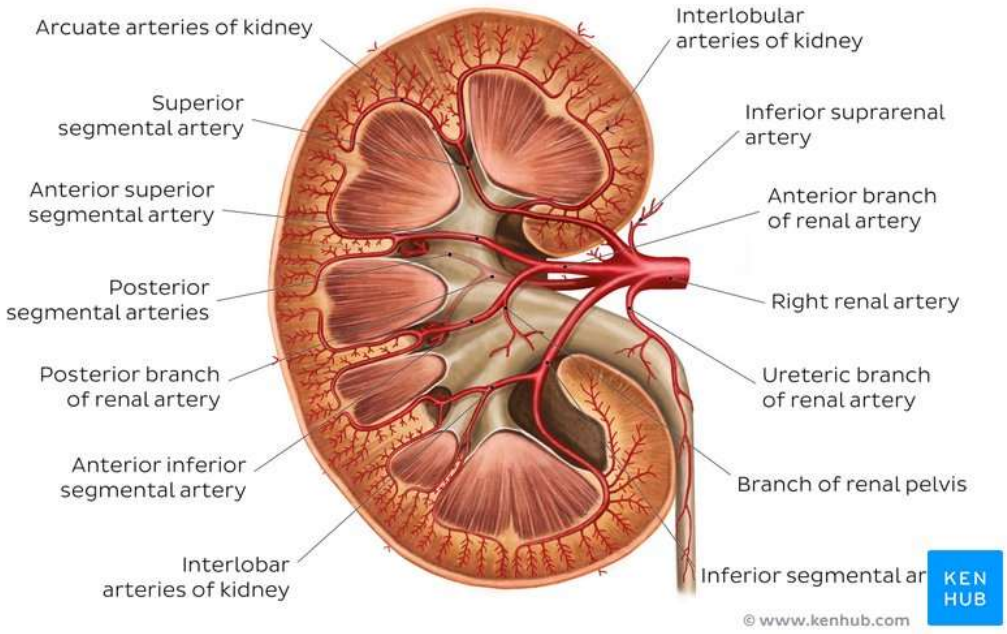


Diagram No.2: Anatomy of kidney

1.3. TYPES OF RENAL FAILURE:

Acute and chronic renal failure is the two kinds of kidney failure.

1. Acute Renal Failure (ARF):

ARF is the syndrome in which glomerular filtration declines abruptly (hours to days) and is usually reversible. According to the KDIGO criteria in 2012, AKI can be diagnosed with any one of the following: (1) creatinine increase of 0.3 mg/dL. in 48 hours, (2) creatinine increases to 1.5 times baseline within last 7 days, or (3) urine volume less than 0.5 mL/kg per hour for 6 hours. Recently the term acute kidney injury (AKI) has replaced ARF because AKI denotes the entire clinical spectrum from a mild increase in serum creatinine to overt renal failure,

2. Chronic Renal Failure (CRF):

CRF or chronic kidney disease (CKD) is defined as a persistent impairment of kidney function, in other words, abnormally elevated serum creatinine for more than 3 months or calculated glomerular filtration rate (GFR) less than 60 ml per minute/1.73m2. It often involves a progressive loss of kidney function necessitating renal replacement therapy (dialysis or transplantation). When a patient needs renal replacement therapy, the condition is called end-stage renal disease (ESRD)

- **Kidney Failure Indication**

- Diabetes
- high blood pressure
- heart disease
- family history of kidney disease
- Over 60 years of age

- long history of taking pain reliever including over the counter products such as non-steroidal anti-inflammatory drugs (NSAID)
- **Early features of kidney failure:**

There are kidney disease stages according to your estimated glomerular filtration rate (eGFR). Your eGFR is a calculation of how well your kidneys filter substances. A normal eGFR is about 100. The lowest eGFR is 0, which means there's no remaining kidney function. 1.2 for women and more than 14 for male.

The formula for estimating glomerular filtration rate (GFR) is often calculated using the serum creatinine level, age, race, and gender. The most commonly used equation for estimating GFR is the Modification of Diet in Renal Disease (MDRD).

Epidemiology Collaboration (CKD-EPI) equation is often preferred because it's more accurate, especially at higher GFRs: GFR 141 min (Scr/x, 1) a max (Ser /κ, 1) ^ (-1.209) x 0.993 (Age) 1.018 (if female) 1.159 (if black).

Where:

- ✓ Scr is serum creatinine in mg/dl.
- ✓ κ is 0.7 for females and 0.9 for males
- ✓ α is-0.329 for females and -0.411 for males
- ✓ min indicates the minimum of Ser/xor 1
- ✓ max indicates the maximum of Scr/kor 1.9

- **The stages of any kidney disease include:**

Stage I: Your GFR is higher than 90 but below 100. At this stage, your kidneys have mild damage but still function normally.

Stage II: Your GFR may be as low as 60 or as high as 89. You have more damage to your kidneys than in stage I, but they still function well.

Stage III: Your GFR may be as low as 30 or as high as 59. You may have mild or severe loss of kidney function.

Stage IV: Your GFR may be as low as 15 or as high as 29. You have severe loss of kidney function.

Stage V: Your GFR is below 15. Your kidneys are nearing or at complete failure.

1.4. EPIDEMIOLOGY:

Every Year about 209 patients per million population per year, with 30% of AKI patients with requiring renal replacement therapy. 10 CRF is known to be more prevalent in men than in women, this gender disparity extends to ESPD. The incidence of Akl has been cited as on 1% on hospital admission 2% to 5% during hospitalization 31% patient treated to intensive care units (ICUS) and in 4% to 15% of patients after cardiovascular surgery, 20.22 24. A multinational study surveying the burden of kidney disease, from 2023 approximately 850 million people affected by chronic kidney disease (CKD) worldwide, people of every age and race are affected, and people from disadvantaged populations are at higher risk."

1.5. ETIOLOGY:

1.5.1 First warning signs of kidney failure:

Many people experience few or no symptoms in the early stages of kidney disease. However chronic kidney disease (CKD) may still cause damage even though you feel fine. CKD and kidney failure symptoms vary between people. If your kidneys aren't working properly, you may notice one or more of the following signs:

1. Extreme tiredness (fatigue).
2. Nausea and vomiting
3. Confusion or trouble concentrating.
4. Swelling (edema), particularly around your hands, ankles or face.
5. Peeing more often.
6. Cramps (muscle spasms).
7. Dry or itchy skin, Poor appetite or food may taste metallic.
8. Diabetes mellitus
9. Hypertension
10. Glomerulonephritis.

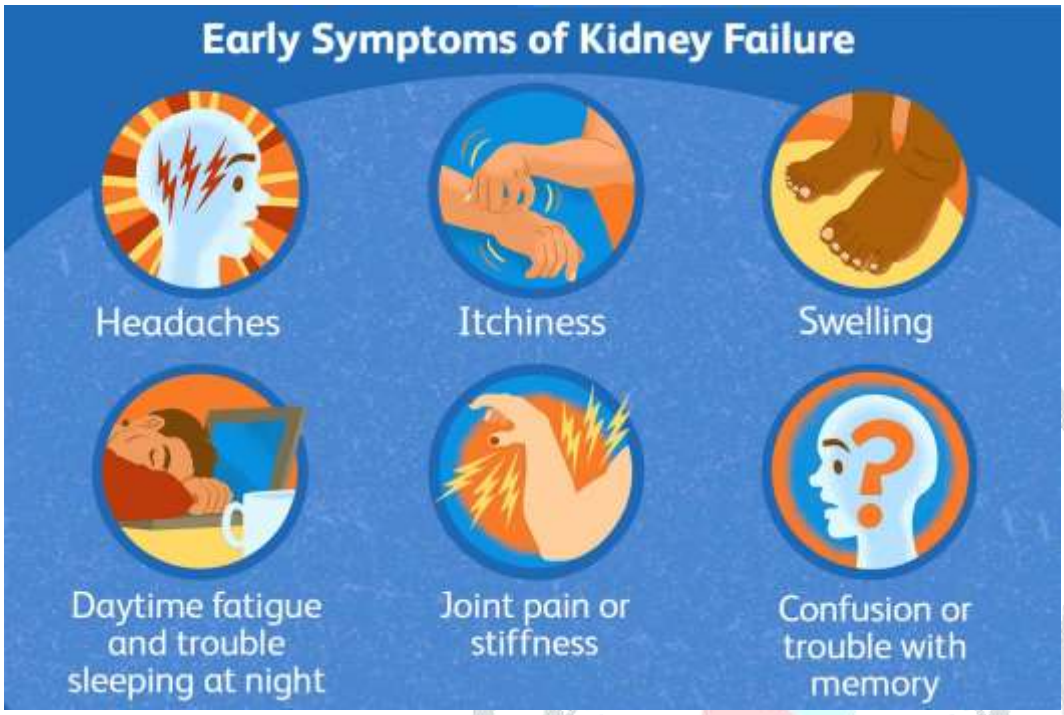


Diagram No. 3: Early symptoms of kidney failure

1.5.2 Common causes of kidney failure:

Diabetes and high blood pressure are the most common causes of chronic kidney disease and kidney failure.

Unmanaged diabetes can lead to high blood sugar levels (hyperglycaemia). Consistently high blood sugar can damage your kidneys as well as other organs.

High blood pressure means blood travels forcefully through your body's blood vessels. Over time and without treatment, the extra force can damage your kidneys' tissue.

Kidney failure usually doesn't happen quickly. Other (CKD) causes that may lead to kidney failure include:

Polycystic kidney disease (PKD). PKD is a condition you inherit from one of your parents (inherited condition) that causes fluid-filled sacs (cysts) to grow inside your kidneys. Glomerular diseases affect how well your kidneys filter waste. Lupus is an autoimmune disease that can cause organ damage, joint pain, fever and skin rashes.

1.6. DIAGNOSIS:

Overall kidney function is judged by the level of filtration that occurs. Filtration is accomplished by the tiny blood vessels in the kidney called "glomeruli". So overall kidney function is called the "glomerular filtration rate" (GFR),

Diagnosis of kidney failure typically involves a combination of medical history review, physical examination, blood tests (such as serum creatinine and blood urea nitrogen), urine tests (such as urine albumin-to-creatinine ratio), imaging studies (such as ultrasound or CT scan), and sometimes a kidney biopsy. These help determine the cause, severity, and appropriate treatment plan for the kidney failure it's crucial to consult with a healthcare professional for accurate diagnosis and management.

1.6.1 Tests:

A healthcare provider may use a variety of kidney function tests to evaluate your kidneys and diagnose kidney failure. If the provider suspects you're at risk of kidney failure, common tests include:

➢ **Blood test:**

Blood tests show how well kidneys remove waste from blood. For these use a thin needle to withdraw a small amount of blood from a vein of the arm, then analyse blood sample.

➢ **Urine test:**

Urine tests measure specific substances in a pee, such as protein or blood.

➢ **Special labs:**

- Creatinine Kinase (CK)
- Immunology antibodies based on the clinical scenario

➢ **Imaging Test:**

- Renal ultrasound
- Doppler-flow kidney US, depending upon the clinical scenario
- An abdominal x-ray (KUB) to evaluate for renal calculi (not all calculi will be present on KUB)

1.7. MEDICATION:

Depending on the cause of your kidney disease, a healthcare provider may prescribe one or more of the following medications:

- Angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB). These medications help lower your blood pressure.
- Diuretic help to remove extra fluid from the body.
- Statins: help to lower cholesterol levels.
- Erythropoietin-stimulating agent: build red blood cells cause anaemia.
- Vitamin D and calcitriol: Prevent bone loss.
- Phosphate binders: Help to move extra phosphorus in blood.

All ESRD patients wees prescribed with phosphate-binding agents, drugs for bone structure and mineralization as well as lipid-lowering medications (a 60, 100.09%). In addition, almost all of them Were receiving therapies for anaemia (n-58, 97%) analgesics or nonsteroidal anti-inflammatory drugs (n 57,95%) for pain management related to the ESRD. Overall, patients received average of 103 different medications (minimum four and maximum 18 different drugs). The prevalence of hypertension (and generally CVD) resulted in recording an increased member of patients (54, 9014) receiving relative medications, as well as antiplatelet/anticoagulant therapies (34, 57%). CVD drugs referred to antihypertensive agent (75%), mostly B blockers (50%) and statins (45%). Patients were often prescribed with CNS drugs such as antidepressants (36, 60%) and antipsychotics (n 12, 20%). Oder medications recorded among ESRD patients warm related with type 1 or type II diabetes and thyroid medications. All medications were administered following the relative clinical guidance for duos adjustment According to GFR and RRT data. Regarding water Emiction, all patients followed a diet with approximately 250 ml. water per day and 250-500 est. from diet (food, juices, coffee etc) This the average recommendation adjusted based on personalized asides and characteristics such laboratory test results, diet, and quality of life. comorbidities, monthly

1.7.1 TREATMENT:

By Dialysis help your body filter blood.

Two types of dialysis:

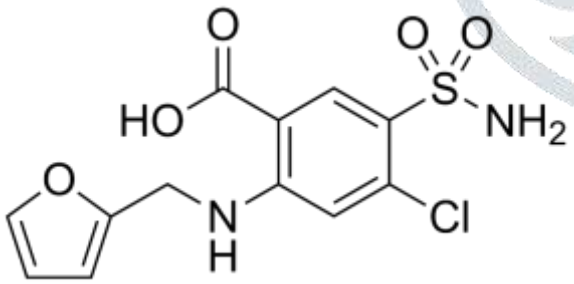
A) Haemodialysis: a machine regularly clears your blood for you. Most people get haemodialysis three to four days a well at a hospital or dialysis clinic status.

B) Peritoneal dialysis: In peritoneal dialysis, a provides attaches a bag a dialysis solution to a catheter in your abdominal lining. The solution flows from the bags into your abdominal lining, alicycles I drained back into the bag sometime people can receive peritoneal dialysis at home.

1.7.2 Kidney transplant: A surgeon places a healthy kidney in your body during a kidney transplant to take over for your damaged kidney. The healthy kidney (Donar regent may come from Donar. you can live well with one a decreased Donar organ healthy kidney.

Module 6: Selection of Drug.

- **Drug:** Furosemide
- **Class:** Loop Diuretics.
- **Chemical formula:** C12H11ClN2O5S.
- **Chemical Structure:**



- **Molecular weight**: 330.74 g/mol
- **IUPAC Name**: 4-chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid.
- **Synonym**: Frusemide, Lasix, Disemide, Promide, Radisemide, and Zafurida.
- **Brand Name:**
- **India**: Lasix, Frasix, Furotal, Furomide, Diuromide, Diurapid, Frusid.
- **International Non-proprietary Name (INN):** Furosemide.

❖ Introduction:

Furosemide is a widely used loop diuretic, especially valuable for managing fluid overload in patients with chronic kidney disease (CKD). CKD involves a progressive loss of renal function, often leading to sodium and water retention, resulting in edema, hypertension, and in severe cases, pulmonary congestion. As kidney function declines, maintaining fluid balance becomes challenging, making diuretics essential.

In CKD, furosemide promotes diuresis, reducing extracellular fluid volume, alleviating edema, and controlling blood pressure. It is especially useful in stage 3 to 5 CKD, where fluid retention worsens cardiovascular risks. Furosemide also helps manage hyperkalaemia by increasing urinary potassium excretion in patients who still produce urine.

However, its effectiveness may decrease in advanced CKD due to poor drug delivery to the nephron. Overuse can lead to hypovolemia, electrolyte imbalances, and worsening renal function. Therefore, dose adjustment and close monitoring are crucial.

Despite limitations, furosemide remains central in relieving symptoms and improving comfort in CKD when used judiciously.

❖ Pharmacology of Furosemide in Chronic Kidney Failure (CKF):

Furosemide is a widely used **loop diuretic** that plays a critical role in the management of fluid overload, edema, and hypertension in patients with **chronic kidney failure (CKF)**. It is particularly important in the **early and middle stages of CKF**, but its effectiveness diminishes in **advanced stages** of the disease due to the decline in kidney function. Understanding its pharmacology is essential for optimizing its use in CKF, where impaired renal clearance can lead to complications in dosing and drug efficacy.

1. Pharmacokinetics Parameters of Furosemide:

Parameter	**Details**
Absorption	Oral bioavailability: 10–100% (average ~50%), reduced in CKD
Time to peak (Tmax)	Oral: 1–2 hours; IV: within 30 minutes
Protein Binding	~95% (mainly to albumin)
Volume of Distribution	0.2 L/kg
Metabolism	Minimal hepatic metabolism
Elimination	Primarily renal (65–70% excreted unchanged in urine)
Half-life (t½)	0.5–2 hours (may be prolonged in renal or hepatic impairment)
Excretion	Mainly via kidneys; tubular secretion into the proximal tubule is essential

2. Pharmacodynamics

Therapeutic Class	Loop diuretic
Main Action	Inhibits reabsorption of sodium, chloride, and potassium, promoting diuresis
Onset of Action	Oral: ~30–60 minutes IV: ~5 minutes
Duration of Action:	Oral: ~6–8 hours IV: ~2 hours
Effects:	Strong natriuresis and diuresis Reduction in blood volume and preload Mild antihypertensive effect Management of edema, hyperkalaemia, and hypertension

3. Mechanism of Action (MOA)

Furosemide acts on the **thick ascending limb of the loop of Henle** by inhibiting the **Na^+-K^+-$2Cl^-$ (NKCC2) cotransporter** on the luminal (apical) membrane of tubular epithelial cells. This results in:

- Decreased reabsorption of **Na^+, K^+, and Cl^-**
- Increased excretion of **Ca^{2+}, Mg^{2+}, H_2O**
- Decreased medullary hypertonicity → impaired water reabsorption
- Ultimately leads to **increased urine output and natriuresis**

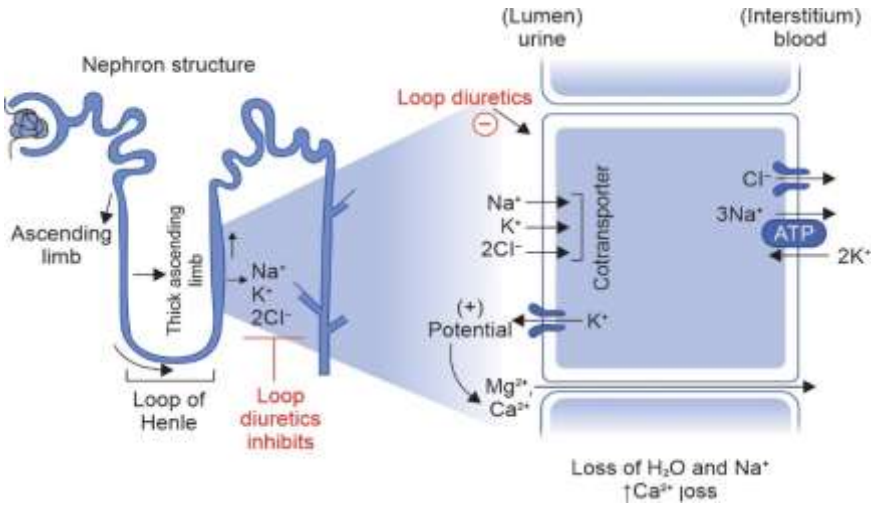


Diagram No. 4: MOA of Furosemide in CKF

❖ The Effect of Furosemide in Chronic Kidney Disease (CKD) on Various Systems and Organs:

Furosemide, a potent loop diuretic, is commonly used to manage fluid overload and edema, particularly in chronic kidney disease (CKD). It works by inhibiting sodium, chloride, and potassium reabsorption in the loop

of Henle, leading to increased urine production. However, in CKD, it can have various effects on several organ systems.

1. Renal System

Diuresis and Fluid Balance:
Furosemide increases urine output, helping to reduce edema and fluid retention. However, in CKD, its effect may be reduced, and higher doses may be needed. Electrolyte imbalances like hypokalaemia and hypocalcaemia are common, requiring careful monitoring.

Risk of AKI:
Excessive diuresis can cause hypovolemia, leading to acute kidney injury (AKI) in CKD patients, necessitating close monitoring of renal function.

2. Cardiovascular System

Blood Pressure and Fluid Overload:
Furosemide helps lower blood pressure in CKD patients by reducing fluid volume and preload. However, in severe CKD, it can cause hypotension.

Electrolyte Imbalances and Arrhythmias:
Potassium loss from furosemide can increase the risk of arrhythmias, especially ventricular arrhythmias. Hypomagnesemia may also contribute to these issues, requiring careful electrolyte monitoring

3. Respiratory System

Pulmonary Edema:
Furosemide is effective in managing pulmonary edema in CKD and heart failure, providing relief from dyspnea (shortness of breath) by decreasing fluid accumulation in the lungs.

4. Gastrointestinal System

Nausea and Vomiting:
Furosemide may cause gastrointestinal discomfort, such as nausea and vomiting, particularly in patients with electrolyte disturbances.

Drug Interactions:
Furosemide can alter the renal clearance of other drugs, so careful monitoring is needed to avoid adverse drug interactions.

5. Endocrine System

RAAS Activation:

Furosemide can activate the renin-angiotensin-aldosterone system (RAAS) due to fluid depletion, leading to increased aldosterone and sodium retention, which may reduce the efficacy of the diuretic.

6. Musculoskeletal System

Electrolyte Imbalance and Muscle Weakness:

Loss of potassium and calcium may cause muscle weakness, cramps, and tetany. Long-term use of furosemide can also increase the risk of osteoporosis due to calcium loss.

7. Nervous System

Cognitive Impairment:

Severe electrolyte imbalances like hyponatremia and hypokalaemia can lead to confusion and delirium, especially in elderly CKD patients.

Ototoxicity:
High doses or rapid administration of furosemide can lead to ototoxicity, causing hearing loss.

8. Dermatologic System

Rashes and Photosensitivity:
Furosemide may cause photosensitivity, making patients more prone to sunburn, along with skin rashes in some cases.

❖ **Therapeutic Uses in the context of Chronic Kidney Failure:**

1. **Edema Associated with Chronic Kidney Failure (CKF)**

- Primary Use in CKF: Furosemide is used to manage fluid retention caused by declining kidney function. In CKF, the kidneys fail to excrete excess sodium and water, leading to edema, ascites, and sometimes pulmonary congestion.
- Mechanism: Furosemide promotes diuresis by inhibiting sodium and chloride reabsorption in the thick ascending limb of the loop of Henle.
- Goal: Helps in reducing fluid overload, preventing respiratory distress, and improving quality of life in CKF patients.

2. Acute Kidney Injury (AKI)

- Though more controversial, furosemide may be used in volume-overloaded AKI patients to promote urine output and prevent complications from fluid accumulation.
- Used to distinguish between oliguric and non-oliguric AKI by observing the diuretic response.

3. Nephrotic Syndrome

- In nephrotic syndrome, massive proteinuria leads to hypoalbuminemia and severe edema.
- Furosemide is used, often with albumin infusion, to mobilize fluid and relieve swelling.
- It helps restore hemodynamic stability and improve renal perfusion.

4. Congestive Heart Failure (CHF)

- Furosemide is first-line therapy in patients with fluid retention and pulmonary edema due to CHF.
- In patients with combined CHF and CKD (cardiorenal syndrome), furosemide helps balance the fluid status and reduce cardiac workload.

5. Liver Cirrhosis with Ascites

- In patients with hepatorenal syndrome or cirrhosis-related edema, furosemide is used alongside spironolactone.
- It helps manage ascites, pleural effusion, and peripheral edema by promoting salt and water excretion.

6. Hypertension (Resistant Cases)

- In patients with chronic kidney disease and volume-dependent hypertension, furosemide is useful to control blood pressure by reducing plasma volume.
- Particularly beneficial in stage 4 and 5 CKD, where thiazide diuretics are less effective.

7.

Clinical Situation	Route	Initial Dose	Maximum Dose	Frequency	Remarks
Edema in CKD Stage 3–4	Oral	40–80 mg	Up to 160 mg/day	Once or twice daily	Adjust dose based on urine output and weight change.
Severe Edema / CKD Stage 5 (non-dialysis)	Oral	80–120 mg	Up to 240–320 mg/day (in divided)	Once or twice daily	High doses may be needed due to reduced renal function.
Volume Overload in Haemodialysis Patients	IV	80–120 mg	Up to 250 mg IV bolus	Once or twice weekly (pre-HD)	Usually administered before or during dialysis sessions.
Pulmonary Edem in CKD	IV Bolus	40–80 mg IV	Up to 200 mg IV	Every 6–8 hrs or as needed	Monitor BP, electrolytes, and urine output.
Continuous IV Infusion (in resistant cases)	IV Infusion	10–20 mg/hour	Up to 40 mg/hour	Continuous	Reserved for severe volume overload nonresponsive to bolus.

Hypercalcemia

- Furosemide increases urinary calcium excretion.
- Used in acute management of hypercalcemia, especially when combined with intravenous saline to prevent volume depletion.

8. Hyperkalaemia (with Caution)

- Can assist in the temporary management of hyperkalaemia by promoting urinary potassium excretion.
- It is not a first-line treatment, but can be helpful in combination with other therapies.

9. Acute Pulmonary Edema

- Rapid IV administration of furosemide provides quick relief from pulmonary congestion in emergency settings.
- Reduces preload, improving oxygenation and respiratory status.

❖ **Dose of Furosemide in CKF:**

❖ **Side Effects of Furosemide:**

1. Common Side Effects

- Hypokalaemia (↓ potassium)
- Hyponatremia (↓ sodium)
- Hypomagnesemia (↓ magnesium)
- Hypocalcaemia (↓ calcium)
- Dehydration
- Hypotension
- Increased urination (polyuria)
- Dizziness

2. Less Common Side Effects

- Hyperuricemia
- Hearing disturbances (ototoxicity)
- Photosensitivity reactions
- Hyperglycaemia

3. Rare but Serious Adverse Effects (ADRs)

- Severe electrolyte imbalance
- Pancreatitis
- Aplastic anaemia, agranulocytosis- (hematologic toxicity)
- Interstitial nephritis
- Hepatic encephalopathy- in liver-compromised patients.

❖ **Contraindications of furosemide:**

1. **Anuria:** Furosemide is ineffective when urine output is absent and may worsen fluid overload without clinical benefit.
2. **Severe hypokalaemia:** The drug can further lower potassium levels, increasing the risk of life-threatening arrhythmias.
3. **Severe hyponatremia:** Further sodium loss can lead to neurological complications, including confusion and seizures.
4. **Hypovolemia or dehydration:** Excessive diuretic action can cause circulatory collapse, hypotension, and acute kidney injury.
5. **Hepatic coma or hepatic encephalopathy:** Furosemide-induced electrolyte disturbances may precipitate or worsen hepatic encephalopathy.
6. **Known hypersensitivity to Furosemide or sulphonamide derivatives**: May lead to serious allergic reactions, including rash, bronchospasm, or anaphylaxis.
7. **Neonates with jaundice or hyperbilirubinemia:** Furosemide may displace bilirubin from albumin, increasing the risk of kernicterus.
8. **Gout (use with caution):** Furosemide can increase serum uric acid levels, potentially triggering gout attacks.
9. **Pregnancy (caution advised):** Use only if clearly needed, as it may affect fetal electrolyte balance and renal development.

❖ **Drug Interactions of Furosemide in Chronic Kidney Failure (CKF):**

1. Aminoglycosides (e.g., Gentamicin, Amikacin)

- Interaction: Increased risk of ototoxicity and nephrotoxicity.
- Mechanism: Both drugs affect the cochlea and renal tubules. The risk is higher in CKF where drug clearance is reduced.
- Management: Avoid concurrent use or monitor renal function and hearing closely.

2. ACE Inhibitors / ARBs (e.g., Enalapril, Losartan)

- Interaction: Increased risk of hypotension and worsening renal function.
- Mechanism: Combined effect of vasodilation and diuresis may decrease renal perfusion.
- Management: Start with low doses, monitor blood pressure and renal function regularly.

3. NSAIDs (e.g., Ibuprofen, Diclofenac)

- Interaction: Reduced diuretic effect and increased risk of renal impairment.
- Mechanism: NSAIDs inhibit prostaglandin synthesis, reducing renal blood flow and antagonizing Furosemide's natriuretic action.
- Management: Avoid long-term NSAID use in CKF; use acetaminophen if analgesia is needed.

4. Digoxin

- Interaction: Increased risk of digitalis toxicity due to Furosemide-induced hypokalaemia.
- Mechanism: Low potassium levels enhance digoxin binding to cardiac tissue.
- Management: Monitor serum potassium and digoxin levels; correct electrolytes as needed.

5. Lithium

- Interaction: Increased serum lithium levels, leading to toxicity.
- Mechanism: Furosemide reduces lithium clearance by the kidneys.
- Management: Avoid concurrent use or monitor lithium levels frequently.

6. Corticosteroids (e.g., Prednisolone)

- Interaction: Enhanced risk of hypokalaemia.
- Mechanism: Both drugs cause potassium loss through different mechanisms.
- Management: Monitor potassium, consider potassium supplements if needed.

7. Antihypertensive Agents (e.g., Beta-blockers, Calcium channel blockers)

- Interaction: Additive hypotensive effect.
- Mechanism: Combined vasodilation and volume depletion may cause symptomatic hypotension.
- Management: Adjust doses carefully; monitor blood pressure regularly.

8. Sulfonylureas and Insulin

- Interaction: Altered glucose tolerance.
- Mechanism: Diuretic-induced electrolyte changes may affect insulin action.
- Management: Monitor blood glucose levels closely in diabetic CKF patients.

9. Cisplatin

- Interaction: Enhanced ototoxicity and nephrotoxicity.
- Mechanism: Additive toxic effects on kidneys and auditory system.
- Management: Avoid or ensure rigorous monitoring of renal and auditory function.

10. Theophylline

- Interaction: Increased risk of toxicity due to electrolyte disturbances.
- Mechanism: Hypokalaemia may enhance the arrhythmogenic potential of theophylline.
- Management: Monitor serum potassium and theophylline levels.

Module No. 7: Identification of Adverse effects of a selected drug

❖ **Adverse Drug Reactions (ADRs) of Furosemide –**

Furosemide, a high-ceiling loop diuretic, is commonly employed to manage fluid overload in conditions such as congestive heart failure, liver cirrhosis, and chronic kidney failure (CKF). While its therapeutic efficacy is well-established, the safety profile of Furosemide necessitates ongoing clinical vigilance. This is due to the wide range of potential adverse drug reactions (ADRs), especially in CKF patients, where impaired renal function can significantly alter the drug's pharmacokinetics and pharmacodynamics. The pharmacovigilance approach to Furosemide therapy focuses on the identification, prevention, and management of these ADRs, ensuring optimal therapeutic outcomes and minimizing risks, particularly in patients with compromised renal function.

1. Common ADRs

a. **Electrolyte Imbalances**
Furosemide inhibits the Na^+-K^+-$2Cl^-$ symporter in the thick ascending loop of Henle, leading to increased excretion of sodium, potassium, calcium, and magnesium. In both CKF and non-CKF patients, this can cause hypokalaemia, hyponatremia, hypomagnesemia, and hypocalcaemia. These imbalances can lead to fatigue, arrhythmias, cramps, and neuromuscular symptoms.

b. **Dehydration and Volume Depletion**
Excessive diuresis, especially in high doses or in CKF patients with reduced adaptive capacity, may result in hypovolemia. Clinical manifestations include hypotension, dizziness, dry mucosa, and postural instability. Volume depletion also risks further reduction in glomerular filtration in CKF patients.

c. **Hypotension**
Orthostatic or symptomatic hypotension is commonly reported, especially when Furosemide is co-administered with antihypertensives. In CKF, where blood pressure regulation is already compromised, the risk is amplified.

d. **Polyuria**
A predictable diuretic effect that can be bothersome to patients. In CKF, response to Furosemide may be diminished due to reduced nephron sensitivity, necessitating higher doses, which increases ADR risk.

2. Severe ADRs

a. **Ototoxicity**
High-dose or rapid IV administration of Furosemide, especially in CKF where renal clearance is impaired, can cause dose-related ototoxicity. This may present as reversible or irreversible hearing loss, tinnitus, or vertigo. Risk is higher when combined with other ototoxic drugs such as aminoglycosides.

b. **Acute Kidney Injury (AKI)**
Aggressive diuresis in volume-depleted or elderly CKF patients can lead to prerenal azotemia or AKI due to decreased renal perfusion. Monitoring renal parameters is crucial, especially during initiation or dose adjustment.

c. **Severe Electrolyte Disturbances**
Profound hypokalaemia and hypomagnesemia can lead to life-threatening arrhythmias, particularly in patients on digitalis or antiarrhythmic drugs.

d. **Hyperuricemia and Gout**
Furosemide decreases uric acid excretion, potentially precipitating gout in predisposed individuals. This is often dose-related and may require monitoring and urate-lowering therapy.

3. Rare but Serious ADRs

a. **Aplastic Anemia and Agranulocytosis**
Though rare, Furosemide has been associated with severe haematological reactions including pancytopenia, requiring discontinuation and supportive care.

b. **Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)**
Hypersensitivity reactions such as SJS or TEN are rare but life-threatening and require immediate drug cessation and intensive care.

c. **Pancreatitis**
Reports exist of acute pancreatitis associated with Furosemide use, though causality remains uncertain. The mechanism may involve ischemia or hypersensitivity.

d. **Hepatic Encephalopathy**
In patients with hepatic cirrhosis and CKF, Furosemide-induced electrolyte shifts can precipitate hepatic encephalopathy. This is due to ammonia retention and altered blood-brain barrier permeability.

e. **Interstitial Nephritis**
Immunologically mediated interstitial nephritis may occur, usually presenting with fever, rash, and eosinophilia. Withdrawal of the drug often leads to recovery.

❖ **ADR causes and management of furosemide:**

Sr No.	**Adverse Drug Reaction (ADR)**	**Causes**	**Management**
1.	Hypokalaemia (Low potassium levels)	Furosemide promotes potassium excretion in urine, especially in high doses or prolonged use	Monitor serum potassium levels, supplement potassium orally or intrave

			nously, adjust Furosemide dose.
2.	Hyponatremia (Low sodium levels)	Increased renal sodium loss due to the diuretic effect	Monitor serum sodium levels, restrict fluid intake, adjust dose or discontinue Furosemide if necessary
3.	Hypomagnesemia (Low magnesium levels)	Increased renal excretion of magnesium	Monitor serum magnesium levels, supplement magnesiu

			m as nee ded, adj ust dos age of Fur ose mid e
4.	Deh ydra tion and Hyp ovol emia	Excessive diuresis leading to volume depletion, particularly in CKF	Mai ntai n ade qua te flui d inta ke, slo w the rate of ad min istr atio n, mo nito r ren al fun ctio n and elec trol ytes
5.	Otot oxici ty (Hea ring loss, tinni tus)	High doses or rapid IV administration, especially in patients with renal impairment	Lim it the dos e and rate of IV ad min istr

			ation, consider alternative diuretics if risk is high
6.	Acute Kidney Injury (AKI)	Decreased renal perfusion due to excessive diuresis in volume-depleted states	Monitor renal function (creatinine, GFR), adjust dose, use the lowest effective dose, consider alternative diuretics
7.	Gout (Hyperuricemia)	Reduced uric acid excretion due to Furosemide's effect on renal function	Monitor uric acid levels,

			avoid Furosemide in gout-prone patients, use urate-lowering therapy if necessary
8.	Rash (Allergic Reactions)	Hypersensitivity or allergic reaction to Furosemide	Discontinue Furosemide, provide antihistamines or corticosteroids if necessary
9.	Stevens-Johnson Syndrome	Rare, idiosyncratic reaction in susceptible individuals	Immediate discontinuation

	(SJS)		of Furosemide, hospitalization, symptomatic treatment, and referral to a specialist
10.	Pancytopenia (Agranulocytosis)	Rare, immune-mediated reaction leading to bone marrow suppression	Discontinue Furosemide, supportive care including blood transfusion, if necessary, monitor blood counts

11.	Pancreatitis	Rare, mechanism unclear but may involve ischemic injury to the pancreas	Immediate discontinuation of Furosemide, symptomatic management, and possible hospitalization

RESULTS

Result:

In this study, we monitored and analysed the adverse drug reactions (ADRs) associated with the use of furosemide in patients with chronic kidney failure (CKF).

The analysis revealed that the most commonly observed adverse effects were electrolyte imbalances such as hypokalaemia, hyponatremia, hypomagnesemia, and hypocalcaemia. Additionally, significant incidences of dehydration, volume depletion, hypotension, and polyuria were documented, especially in patients receiving higher doses.

Severe adverse effects noted included ototoxicity (manifesting as hearing loss and tinnitus), acute kidney injury (AKI), profound hypokalaemia leading to life-threatening arrhythmias, and hyperuricemia resulting in gout attacks.

Rare but serious reactions observed included pancytopenia, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), acute pancreatitis, hepatic encephalopathy, and interstitial nephritis.

The study highlighted that patient with impaired renal function exhibited a higher incidence and severity of ADRs, emphasizing the necessity for dose adjustment, close monitoring of electrolytes and renal function, and careful evaluation of drug interactions.

Discussion:

Furosemide, a high-ceiling loop diuretic, plays an essential role in the management of fluid overload, hypertension, and electrolyte disturbances in CKF patients. However, its therapeutic benefits are significantly limited by its high potential for adverse drug reactions, particularly in the setting of impaired renal clearance.

Electrolyte imbalances emerged as the most frequent adverse effects, attributed to the inhibition of the Na^+-K^+-$2Cl^-$ transporter at the thick ascending limb of Henle's loop. Hypokalaemia, hyponatremia, hypocalcaemia, and hypomagnesemia contributed to clinical symptoms such as muscle cramps, weakness, arrhythmias, and cognitive disturbances, which were more pronounced in patients with advanced CKD stages.

Dehydration and hypovolemia, secondary to excessive diuresis, posed a significant risk for acute kidney injury. The additive hypotensive effects, particularly when used concomitantly with antihypertensives, further complicated the clinical management.

High-dose or rapid intravenous administration of furosemide led to a notable incidence of ototoxicity, with reports of reversible and irreversible hearing loss. The co-administration of nephrotoxic and ototoxic drugs, such as aminoglycosides, further augmented this risk.

The study also revealed rare but life-threatening reactions such as Stevens-Johnson Syndrome, pancytopenia, hepatic encephalopathy, and interstitial nephritis, underscoring the need for vigilant monitoring and early recognition of clinical warning signs.

Drug interactions were found to significantly enhance the risk of ADRs, particularly with agents like NSAIDs, ACE inhibitors, aminoglycosides, digoxin, and lithium, necessitating careful review of concurrent medications.

Overall, while furosemide remains a mainstay in symptom management for CKF patients, its narrow therapeutic index and adverse reaction profile demand a personalized, closely supervised therapeutic approach to minimize risks and optimize clinical outcomes.

Conclusion:

The study concludes that while furosemide is a cornerstone in the management of fluid overload and hypertension in chronic kidney failure, it is associated with a considerable risk of adverse drug reactions.

Electrolyte imbalances, dehydration, ototoxicity, and acute kidney injury were the predominant adverse events observed. Rare but severe reactions, including Stevens-Johnson Syndrome, pancytopenia, and hepatic encephalopathy, emphasize the critical need for pharmacovigilance.

Close monitoring of renal function, serum electrolytes, and careful dose titration are essential to enhance the safety of furosemide therapy. Special attention must be given to potential drug interactions, which can further exacerbate adverse outcomes.

Healthcare providers should adopt a patient-centred approach, integrating regular monitoring, patient education, and individualized treatment adjustments to mitigate risks. Pharmacovigilance activities must be strengthened to ensure early detection, reporting, and management of ADRs, thereby improving therapeutic outcomes and ensuring patient safety in the use of furosemide among CKF patients.

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