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Impact of Kidney Disease on Drug Pharmacokinetics

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Background: Kidney failure dramatically alters the pharmacokinetics of drugs by decreasing the organ's ability to filter, reabsorb, and eliminate molecules. The kidneys in significant part control eliminating water-soluble drugs and metabolites. Decline in renal function can lead to reduced pharmacological efficacy, accumulation of medications, and increased toxicity. Moreover, affected by kidney disease are drug absorption, distribution (because of changes in plasma protein binding), metabolism (especially in severe cases), and renal clearance. Reducing adverse effects in affected persons and optimizing therapy dosage depend on an awareness of these changes.
Aim: Emphasizing changes in absorption, distribution, metabolism, and excretion, one can investigate how renal illness affects the pharmacokinetics of different medications. This work also seeks to shed light on dosage modification techniques and factors related to safe pharmacological control for individuals with compromised renal function.
Conclusion: Mostly by lowering renal clearance and changing plasma protein binding, kidney illness greatly influences the pharmacokinetics of medications, hence increasing the free (active) drug concentration. These alterations need for customized medication dosage depending on degree of renal damage. Renal function tests include glomerular filtration rate (GFR) and drug level monitoring where relevant help healthcare professionals prevent toxicity while maintaining therapeutic efficacy. Improving patient outcomes calls for more study and development of renal-safe medications and policies.
Keywords: Kidney Disease, Pharmacokinetics, Drug Absorption, Drug Distribution, Drug Metabolism.

Kidney

Al-Naimi and Al-Kuraishy released their findings in 2019. The term "nephrotoxicity" describes the harmful effects of chemicals and medications on the kidneys. The consequences of nephrotoxins, or compounds that demonstrate nephrotoxicity, are more severe in patients who already have renal failure. The risk of drug-induced nephrotoxicity increases to about 20% in the elderly due to poly-medication and prolonged life expectancy. The megalin multi-ligand receptor is involved in the selective endocytosis and accumulation of aminoglycosides, making the proximal tubule epithelial cells particularly susceptible to their nephrotoxic effects. Recently reported and based on consensus are the phenotypic criteria for induced nephrotoxicity. Although there has been some encouraging evidence for new kidney biomarkers such as kidney damage molecule 1 in observational studies, there has not been enough evidence to draw any firm conclusions about a link to clinically significant outcomes. It will be possible to put these biomarkers into clinical practice only after that.

THE ROLE OF DRUG-INDUCED NEPHROTOXICITY

As stated by Lawrence et al. (2019). Damage to the glomeruli, inflammation, thrombotic microangiopathy, crystal nephropathy, and other mechanisms are among the many that can lead to nephrotoxicity. The hormones renal prostaglandin and angiotensin II regulate the pressure in the afferent and efferent arterioles, which maintains a constant glomerular filtration rate (GFR) in healthy kidneys. It follows that prostaglandin antagonists, including NSAIDs, ACEIs, and ARBs, can cause glomerular dysfunction.

Medications reach cells in the renal proximal tubules via tubular reabsorption and delayed concentration mechanisms. The tubular mitochondria are susceptible to damage from toxicity and drug-induced oxidative stress, which compromises the tubular transport mechanism. Damage to the tubules can be caused by antivirals such adefovir and foscarnet, aminoglycosides, and amphotericin B (Al-Naimi et al.; 2019)

In 2019, Sudjarwo et al. So, the primary ways in which drugs cause kidney damage are as follows: Variations in the glomeruli's pulse

Normal glomerular filtration, which filters about 120 mL of plasma per minute, is maintained by an intraglomerular pressure that is reliant on the pressure differential between afferent and efferent arterioles. Circulating prostaglandins control the pressure in afferent arterioles, while angiotensin II mediates vasoconstriction to control the pressure in efferent arterioles and intraglomerular regions. As a result, ACEIs such as diclofenac, an ARB, valsartan, and captopril considerably reduce GFR and exacerbate intraglomerular hypertension. In addition, tacrolimus and cyclosporine produce afferent arteriole vasoconstrictions in a dose-dependent manner.

Renal tubule cytotoxicity

The renal proximal tubules aid in the excretion of various waste products, including drugs and their metabolites. Proximal tubule cells undergo biotransformation, actively secrete, and reabsorb substances, making them especially vulnerable to acute kidney injury and drug-induced toxicity. Furthermore, many transporters and metabolic enzymes are consistently expressed by the epithelium lining the proximal tubules, which aids in the kidneys' ability to remove medications. The proximal tubules of the kidneys are particularly susceptible to cisplatin and antiretroviral drugs due to the diminutive size of the renal drug transporters (Qu et al. 2018)

Nephropathy in the interstitial space with glomerulonephritis

Glomerulonephritis, an inflammation of the glomeruli, can be caused by a variety of nephrotoxic chemicals, including gold, interferon, NSAIDs, lithium, hydralazine, and pamidronate. Quinolones, allopurinol, rifampicin, sulfonamide, and lansoprazole are among the drugs that might produce interstitial nephritis as an adverse effect. Chronic interstitial nephritis can be caused by two years of Cyclosporine, some Chinese herbal therapies, and nonsteroidal anti-inflammatory medications (>1 g/day). It is crucial to detect this issue at an early stage because it can progress to end-stage kidney disease. Just what Frazier et al. (2018) stated.

Toxic crystal nephropathy

Many drugs can produce the precipitation of insoluble crystals, which can lead to an interstitial reaction and obstruction in the distal renal tubules. Most commonly, crystals can be seen in the following drug classes: ampicillin, sulfonamides, acyclovir, ciprofloxacin, methotrexate, and triamterene. When these drugs are precipitated in acidic urine, they can cause crystal nephropathy, which is more common in patients with renal impairment. Lymphoma proliferative problems and tumor lysis during chemotherapy induction both contribute to acute renal failure due to the buildup of uric acid and calcium. On November 20, 2023. Microangiopathy brought on by medication and thrombosis Quinine, ticlopidine, and cyclosporine are among the medications that might induce microangiopathy. This is because these medications elicit platelet activations and thrombotic thrombocytopenic purpura,which lead to endothelial cytotoxicity (Rosen et al. 2019).

Muscle atrophy caused by drugs

Both the direct toxic effects of some medications on myocytes and the propensity of myocytes to the toxic effects of exercise can cause damage to the skeletal muscles. Myocytes rupture in reaction to this damage, releasing intracellular myoglobin and creatine kinase. Myoglobin mostly harms the kidneys by direct toxicity and tubular obstructions. Numerous substances have been discovered to induce rhabdomyolysis, including cocaine, ketamine, heroin, alcohol, etc. (Matsubara et al. 2018).

Blood Markers for Nephrotoxicity

That happened in 2018 according to Campos et al. Renal failure and nephrotoxicity have long been indicated by blood urea and serum creatinine. These tests are sensitive enough to identify advanced renal disease, but they are not foolproof. Hence, to detect the early kidney injury and pinpoint its site, new biomarkers were required that were more sensitive and specific. A sign of both the short-term and long-term renal damage produced by nephrotoxic drugs can be a urine protein. The glomeruli in normal kidneys block the passage of some big-molecular-weight proteins into the nephron lumen. On the other hand, these proteins can accumulate in the urine when the nephrons aren't functioning correctly.

In terms of early detection of structural glomerular damage, glomerular dysfunction, and glomerular damage, high-molecular-weight proteins albumin, transferrin, and immunoglobulin G are more sensitive, correspondingly. The proximal renal tubules are normally responsible for protein reabsorption, but nephron overload happens when the concentration of low-molecular-weight proteins surpasses their reabsorbing capacity. Zhalaliddin et al. (2024) states that damage to the proximal renal tubules causes the reabsorption ability to fail, leading to low-molecular-weight proteinuria.

Vijayasimha and Jha (2019) state that In nephrotoxicity, low-molecular-weight proteins such α1-microglobulin, β2-microglobulin, Cystatin C (Cys C), retinol-binding protein, and kidney injury molecule-1 (KIM-1) are important indicators of the underlying damage to the renal glomeruli and tubules. Nephrotoxic medications, such as cisplatin, NSAIDs, and aminoglycosides, raise KIM-1 expression due to ischemia reperfusion damage. Therefore, the immune response to damage to the renal proximal tubules in nephrotoxicity is correlated with blood KIM-1 levels. In addition, injured kidneys have an increased production of KIM-1 mRNA, which causes its release into the lumen and subsequent excretion in urine. In addition, KIM-1 is stable and easily detectable, therefore it can be identified in blood.

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein linked to granulocytes and nephrotoxicity; it causes the inflammation that happens after acute renal injury and renal ischemia. In cases of drug-induced nephrotoxicity, cytokines such as interleukin (IL), interferon, and colony-stimulating factors can be employed as markers of kidney injury because of their roles in both the damage and healing of renal tubules. Romejko and colleagues released their findings in 2023.
The presence of these markers in blood and urine can be used to estimate drug-induced nephrotoxicity. As a result, quantifying proteins in urine can provide a general estimate of nephrotoxicity and renal impairment. There is a correlation between nephrotoxic chemicals and

both acute kidney damage and chronic renal failure. However, conventional assessments of blood urea and serum creatinine cannot ascertain the extent to which nephrotoxic drugs inflict kidney impairment.

A study conducted in 2018 by Andankar et al. In addition, interferon gamma is activated by caspase-1 during apoptosis, and IL-18 was initially discovered to stimulate this protein. The receptors on certain cell types are bound by IL-18. These cell types include mast, dendritic, T-cell, and basophil cells. A role for IL-18 in the pathogenesis of obesity, IBD, and chronic kidney disease has been identified. Elevated IL-18 blood levels are also linked to renal tubular atrophy and interstitial fibrosis. Elevated levels of IL-18 in the urine are also linked to drug-induced nephrotoxicity and acute kidney injury. Elevated IL-18 levels are linked to acute kidney injury; these levels may either indicate renal impairment or act as a factor that slows the progression of the disease. The authors Dinarello and Kaplanski make this claim (2018).

According to Coksal and colleagues (2019); The presence of cystatin C as a trace protein in the cerebrospinal fluid and urine of individuals with renal failure was initially documented in 1961. Based on this, it predicted renal failure in 1985. When combined with blood urea and serum creatinine, Cys C provides a more comprehensive evaluation of renal function and glomerular filtration rate (GFR). There is a link between increased Cys C levels and decreased GFR and glomerular filtration because these processes remove low-molecular-weight proteins like Cys C. Cys C serum levels may be able to predict when kidney diseases would occur, according to the available evidence. Atherosclerosis, cancer, neurological problems, and cigarette smoking are all linked to higher levels of Cys C in the blood.

A 2011 publication by Mesnard and colleagues was... The 70-83 kDa glycoprotein called vitronectin (VTN) is produced by hepatocytes and is found in plasma. It was first identified in 1967 as serum spreading factor. It may have a role in either enhancing or decreasing fibrogenesis in reaction to renal interstitial injury, given its near proximity to C5b-9, the active complement cascade, and the immune glomerular deposit. The presence of fibrosis is associated with elevated VTN serum levels in patients with renal diseases. Plasminogen activator inhibitor-1 half-life lengthening and VTN binding both lead to an increase in plasmin production, which in turn reduces the severity of acute kidney damage.

Fuchs and Hewitt (2011) state that... The α- and β-subunits that make up the transmembrane receptor Integrin (ITN) help with adherence to the extracellular matrix. Thanks to its antifibrotic effect, ITN significantly protects the glomeruli after glomerular injury by regulating vital cell processes and homeostasis. In contrast, inhibitors of ITN $\alpha 2\beta 1$ may be very useful in minimizing kidney damage because they forestall glomerular injury by decreasing collagen production. In addition, the reduction of cyclosporine-induced nephrotoxicity is achieved by ITN $\alpha 2\beta 1$ inhibitors through the inhibition of mesangial collagen production. It was stated by Cano et al. (2016). In Figure 1, we can observe how the disease has progressed and what clinical outcomes might be anticipated by utilizing novel biomarkers that help estimate kidney damage.

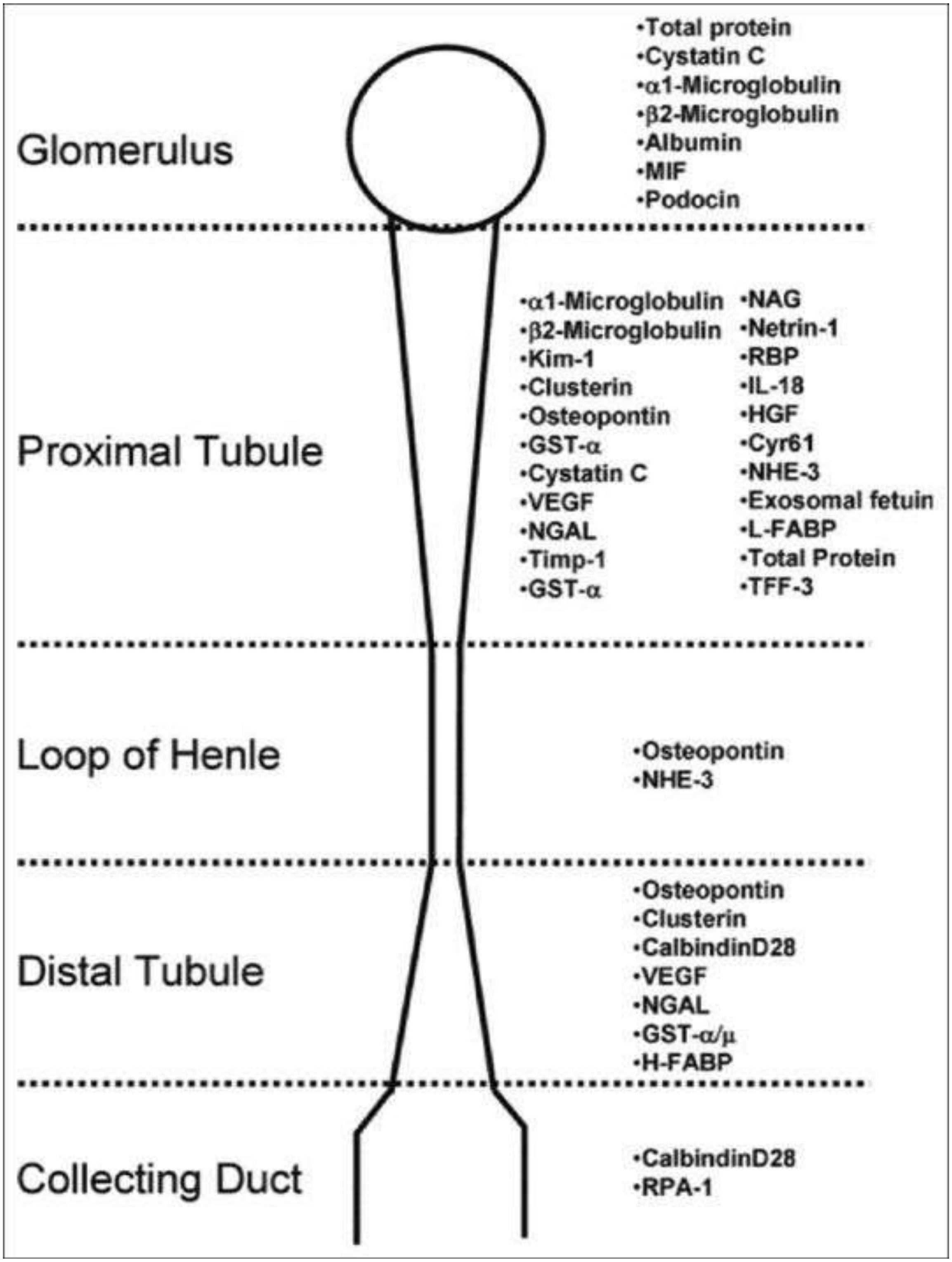

Figure 1 (Fuchs and Hewitt, 2011) shows the predicted locations of acute injury damage biomarkers.

Reducing the Probability of Adverse Drug Reactions

Being alert to and taking measures to avoid the following risk factors is crucial to avoid drug-induced nephrotoxicity:

Questions concerning the patient

A publication by Prasaja and colleagues was made in 2015. Heart failure, dehydration, diabetes mellitus, and chronic renal insufficiency are major risk factors for acute kidney injury in people older than 60 years old. Heredity is a factor in determining susceptibility to drug-induced nephrotoxicity, and hormonal differences make men more vulnerable than women to these effects. Medications can also compromise kidney function if the patient is dehydrated, has heart failure, or has hepatic insufficiency.

Potential pharmacological factors

In 2015, Zununi et al. published it, Aminoglycosides and cyclosporine are among the many drugs that might harm the kidneys. Furthermore, certain drugs, like allopurinol, can cause chronic interstitial nephritis and crystal nephropathy if exposed to them for an extended period. Combinations of nephrotoxic medications, such as aminoglycosides and diuretics, further raise the risk of renal impairment.

Taking measures to avoid

Just as Whiting et al. (2017) reported. The use of effective medications that are safe for renal function. Finding and minimizing the sources of risk finding out how well the kidneys are functioning beforehand Changing one's diet according to one's renal function. In high-risk people, monitoring GFR is essential before treatment starts. Using pharmaceuticals in conformity with standards established by the FDA Getting enough water and taking care of any acute or chronic diseases that may already be present. It is important for the expert physician and room pharmacists to communicate well so that they can track medication dosages and study the dose-response curve.

Publication on the topic may be found in Elsby et al. (2017), Early Diagnosis and Treatment of Renal Impairment, Reversible renal dysfunctions induced by nephrotoxic medications are the most common, so stopping the offending drugs is the first line of defense. It is possible that trimethoprim and cimetidine compete with creatinine for renal tubular secretion, which causes serum creatinine levels to rise before the nephrotoxic effects of these medicines begin to take effect. Nevertheless, most nephrotoxic drugs fall into this category. Unlike blood urea, which is altered by diet, serum creatinine remains constant and hence serves as a better measure of renal function. Thus, a 50% rise, or greater than 2 mg/dL, from baseline in creatinine is a precursor to acute renal failure. Reviewing all prescriptions for affected patients is crucial to identify the causative nephrotoxic medication.

Methotrexate medication ordered

As Weinblatt (2018) indicates Methotrexate is a folic acid antagonist that has been licensed by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis and is also helpful for those with juvenile idiopathic arthritis. Methotrexate was recommended for rheumatoid arthritis by Gubner after he studied it in a placebo-controlled, double-blind clinical experiment. At first, aminoopterin was considered the progenitor molecule for methotrexate; it was first successfully used to treat juvenile leukemia.

Bedoui et al. published their findings in 2019. Methotrexate is a potent chemotherapeutic drug that is currently in use to treat a wide variety of cancers. This drug is a safe and effective treatment for numerous connective tissue ailments, such as psoriasis, vasculitis, inflammatory bowel disease, systemic lupus erythematosus, and many more. The drug's efficacy and safety in treating blood dyscrasia have not been established, and it is not recommended for use by pregnant women. The immunomodulatory and anti-inflammatory properties of the drug are also helpful for organ transplant patients.

Researchers Chande et al. Some cancers, including ulcerative colitis, non-Hodgkin's lymphoma, breast carcinoma, small-cell lung carcinoma, ovarian carcinoma, and epidermal malignancies of the head and neck, have responded well to a combination of methotrexate and anti-TNF medicines. Like cyclosporin, the medicine is beneficial against graft-versus-host disease. Methotrexate is given to patients with a variety of illnesses, including eczema, sarcoidosis, fungus-related irritations, advanced non-Hodgkin lymphoma, and non-metastatic osteosarcoma.

What Methotrexate Does and How It Works

As per the research conducted by Singh et al. (2019). Methotrexate has a highly particular mechanism of action when it comes to immunosuppression in autoimmune diseases and chemotherapy. One antifolate antimetabolite that has found value in cancer treatment is methotrexate. The enzyme methotrexate-polyglutamate is produced when the human reduced folate carriers (SLC19A1) absorb methotrexate into the cell. One enzyme that transforms dihydrofolate to the active form of folic acid in the body is dihydrofolate reductase, which methotrexate and methotrexate-polyglutamate both inhibit. Tetrahydrofolate is a fundamental component for the synthesis of DNA and RNA. Not only does methotrexate-polyglutamate prevent DNA synthesis, but it also blocks thymidylate synthase and purine de novo synthesis. This method is beneficial in the therapy of cancer due to its cytotoxic effect.

As stated by Hanoodi and Mittal (2023). Multiple factors contribute to methotrexate's status as the drug of choice for autoimmune diseases. Adenosine and guanine metabolism are slowed down, leading to a buildup of adenosine, since it hinders the enzyme AICAR transformylase. The anti-inflammatory actions of adenosine are multifaceted: it decreases B-cell activity, boosts the sensitivity of activated CD-95 T cells, and inhibits methyltransferase activity, which in turn stops beta-1 interleukin from attaching to its receptor on cell surfaces. Because of its strong binding to plasma proteins, methotrexate levels in the blood can be increased by medications that deplete these proteins. An example of this would be a medication interaction. Medication that decreases the renal clearance of methotrexate may also cause its concentration to rise.

Tukukino et al. (2020) is cited. Blood MTX treducesy can be increased by cyclosporin, cisplatin, valproate, proton pump inhibitors, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), penicillin, warfarin, and aminoglycosides; aminoglycosides and probenecid reduce MTX absorption. Due to their widespread use, NSAIDs and PPIs also have the most significant and potentially harmful interactions.

Administration

This is according to Yeng (2019). Methotrexate medicine must be started after a comprehensive examination. A complete blood count with differential, as well as tests for kidney and liver function, are part of this evaluation. The kidney tests include serum creatinine, blood urea nitrogen, and urinalysis, while the liver tests include testing for bilirubin, AST, ALT, serum albumin, and hepatitis serology. In addition, getting tested for HIV is crucial, and if the doctor thinks it's necessary, they should request a chest radiograph. Methotrexate can be administered orally or directly into a muscle, organ, or subcutaneous tissue via intravenous injections.

As stated by Lawrence et al. (2019). The prescribed dosage for this medicine, when taken orally, is usually a weekly "pulse," which may consist of a single dose, or three smaller doses spaced eight hours apart on consecutive days. Take folic acid (1 mg daily or 5–7 mg once weekly) to prevent bone marrow suppression; it's something all patients should consider. In humans, the rate of oral absorption varies with dosage. Peak serum levels are achieved in just one to two hours. Using a single-dose auto-injector, MTX can be administered intravenously in amounts of 7.5 mg to 30 mg. Levels of 10, 15, 25, 25, 27, and 30 mg are all that are on the market.

In their 2014 study, Patel et al. For the first four weeks after starting methotrexate, patients should have their CBC, RBFT, and LFT examined weekly; after that, they should be monitored at least every two months.

Negative Outcomes

(The 1994 research by Bannwarth et al.), Even with a low dose of methotrexate, side effects may still develop. The most common negative effects are those that affect the digestive system, including nausea, vomiting, mucosal ulcers, and a lack of appetite. These can be successfully addressed and are experienced by most people. The most serious side effect of methotrexate is hepatotoxicity. Taking folic acid supplements while taking methotrexate can help prevent these adverse effects, which are like folate deficiency. Rare adverse effects of low-dose methotrexate include steatosis, fibrosis, and cirrhosis of the liver, however a little rise in aminotransferases levels is usual. Ultrasonography and liver biopsies are necessary tools for determining the severity of liver damage following intensive treatment.

Methotrexate, being a member of group X, is absolutely forbidden to be used during pregnancy. Before prescribing this medication to any woman of reproductive age, the doctor must advise her of the treatment's potential for teratogenesis and insist that she use two forms of birth control. Those taking high doses may also get mucosal ulceration. In such a case, methotrexate toxicity could be just around the corner. Hair loss, listlessness, fever, decreased white blood cell count, gastrointestinal hemorrhage, pancreatitis, suppression of bone marrow (aplastic anemia), infections, lymphoproliferative disorders in cancer, and renal failure are other possible deadly side effects. Based on what Gohar (2019) says.

Poor choice

Do not give this medication to anyone who has ever had an unfavorable response to methotrexate. Avoid using methotrexate if you are pregnant or nursing since it increases the risk of teratogenicity and is excreted into breast milk. For patients who have experienced severe anemia, leukopenia, thrombocytopenia, or bone marrow hypoplasia in the past, methotrexate should be administered with caution. Avoid using methotrexate for psoriasis or rheumatoid arthritis if you have a history of liver illness, cirrhosis, alcoholic hepatitis, or chronic drinking. In addition to HIV/AIDS, blood dyscrasias, renal insufficiency, and radiation therapy, methotrexate should not be used in these conditions (Kremer et al., 1995).

Always be aware

Based on what Gohar (2019) says. Vital signs should be monitored weekly during the first four weeks of methotrexate treatment, and then every two months thereafter. Keeping your whole list of prescriptions up to date is the best way to avoid drug interactions. Liver function tests and liver biopsies are diagnostic tools for hepatotoxicity. It is necessary to monitor creatinine clearance to avoid nephrotoxicity. Patients should also be monitored for pulmonary toxicity because they may experience symptoms such as dry cough, fever, or dyspnea. Baseline chest radiographs can detect lung fibrosis, infiltrates, pleural effusions, and hilar adenopathy. In countries where tuberculosis is common, testing for the disease is crucial because methotrexate has the potential to bring it back to life. Bone marrow toxicity is closely monitored due to the possibility of myelosuppression caused by folate deficiency.

Toxicity

According to Shetty et al. (2017), A high-dose methotrexate (HDMTX) dose is one that exceeds 500 mg/ml. Lymphoproliferative diseases can cause a wide range of symptoms in patients, including nausea, alopecia, mucosal ulceration, fatigue, fever, leukopenia, gastrointestinal bleeding, infections, interstitial pneumonitis, renal impairment, teratogenesis, and cancer. To combat MTX toxicity, administer leucovorin right away. Patients suffering from renal failure must be adequately hydrated and their urine must be alkalinized with sodium bicarbonate.

Last year, Van et al. Glucarpidase, thymidine, and leucovorin are the three antidotes for methotrexate poisoning. Leucovorin, a reduced active form of folic acid, is administered to patients receiving methotrexate so that they do not have myelosuppression, gastrointestinal toxicity, or neurotoxicity. To prevent cell damage from MTX, the chemical thymidine is being studied. Glucarpidase rapidly breaks down methotrexate into inert metabolites in individuals with renal failure, allowing for its rapid elimination from the body. As a therapy for MTX toxicity, the combination of leucovorin and glucarpidase can decrease plasma methotrexate concentrations by 97% or more in less than 15 minutes. Leucovorin should be continued for a minimum of 48 hours after glucarpidase administration.

Hemodialysis and hemoperfusion are two more potential causes of low MTX levels. The treatment for an intrathecal overdose includes draining and exchanging cerebrospinal fluid (CSF), giving steroids and antidotes, and stopping the use of any medications that make it harder for the body to remove methotrexate, like salicylates, cisplatin, valproate, NSAIDs, penicillin, warfarin, and TMP (Ghannoum et al., 2022).

Conclusion

Mostly by reducing renal clearance and altering plasma protein binding, kidney disease significantly affects the pharmacokinetics of drugs, hence raising the free (active) drug concentration. These changes depend on the degree of renal impairment and call for tailored treatment dosage. Renal function tests include drug level monitoring where relevant and glomerular filtration rate (GFR), which helps medical professionals avoid toxicity while preserving therapeutic efficacy. Enhanced patient outcomes demand more research and development of renal-safe drugs and regulations.

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