Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i5.2792

AMINOGLYCOSIDE INDUCED KIDNEY INJURY AND ITS PHARMACOLOGICAL TREATMENT – OVERVIEW

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Abstract
The semi-synthetic or natural antibiotics known as aminoglycosides are produced by actinomycetes. They were some of the first antibiotics to be created for clinical use, and some of them have been approved for use in patients. Strong antibiotics like aminoglycosides work to stop the synthesis of new proteins, which is the main goal of all antibiotics. Aminoglycosides are used in the treatment of a wide range of illnesses, including bone infections, external burns, cystic fibrosis, diarrhoea, endocarditis, febrile neutropenia, fish tapeworm infections, hepatic encephalopathy, intra-abdominal infections, joint infections, kidney infections, meningitis, pelvic inflammatory disease, peritonitis, skin or soft tissue infections, and urinary tract infections. However, reduced renal function and hearing loss are the most frequent side effects of aminoglycosides. Aminoglycosides must be supplied intravenously because oral administration results in inadequate absorption. When other antibiotics are either ineffective or inappropriate, aminoglycosides are frequently utilised. The following aminoglycoside resistance mechanisms exist: (a) deactivating aminoglycosides through N-acetylation, adenylylation, or O-phosphorylation; (b) lowering the intracellular concentration of aminoglycosides through changes to the flexibility of the outer membrane; (c) inhibiting active efflux; and (d) drug trapping; and (e) mutating the 30S ribosomal subunit target. These are all examples of resistance mechanisms. As antibiotic resistance grows around the world, aminoglycosides are becoming more crucial in medical therapy. In this essay, I will examine which aminoglycoside antibiotic damages kidney cells most severely and examine the pharmacological therapy paradigm that is currently in use. Everything revolves around improving patient safety and results.

Keyword: Aminoglycoside, Treatment, kidney injury, Drugs, Patients, GFR

INTRODUCTION

Actinomycetes are the source of aminoglycosides, which are both natural or semi-synthetic antibiotics. They were some of the first antibiotics to be developed for clinical use, and some have

received approval for use in patient. Aminoglycosides are powerful antibiotic and the general purpose of antibiotics is preventing the formation of new protein. [1]

Children are frequently taken aminoglycosides, which are bactericidal, broad-spectrum antibiotics, primarily for illnesses induced by Gram-negative organisms. Aminoglycosides are effective against both Gram-positive and Gram-negative microorganisms. Gentamicin, amikacin, tobramycin, neomycin, and streptomycin are some of the aminoglycosides. [2]

The most widely used aminoglycoside is gentamicin, however amikacin may be very effective against resistant species. Aminoglycosides commonly prescribed for the treatment of bacteremia, endocarditis, and serious infections of the urinary tract and abdomen. Sometime aminoglycoside is used to treat serious infections of the heart, lungs, blood, eye, cervix, abdomen, urinary system, skin, and soft tissues. [3]

Aminoglycoside use in many medical condition for example bone infection, burns external, cystic fibrosis, diarrhoea, endocarditis, febrile neutropenia, fish tapeworm infection, hepatic encephalopathy, intra-abdominal infection, joint Infection, kidney infections, meningitis, pelvic inflammatory disease, peritonitis, skin or soft tissue infection, urinary tract infection. but the most common adverse reactions of aminoglycosides are impaired renal function and hearing loss. Healthcare professionals must administer aminoglycosides intravenously because they are poorly absorbed when administered orally. Aminoglycosides are often used when other antibiotics are ineffective or contraindicated. [4]

Aminoglycoside antibiotic are not use for long period because its produce toxicity in body and also when more use aminoglycoside antibiotic then fully chances to cause nephrotoxicity and ototoxicity. Aminoglycoside antibiotic one of the reason that cause nephrotoxicity because aminoglycosides freely pass through the glomerulus and are subsequently accumulated in the proximal tubular cells, where they are mainly taken up and cause injury. [5]

When the blood urea nitrogen (BUN) and serum creatinine increases, which are signs of reduction in glomerular filtration rate (GFR), that are the most common clinical indications of renal injury related to aminoglycoside therapy. Other symptoms of functional impairment, such as polyuria and urine hypo osmolality, are also present in aminoglycoside nephrotoxicity. The second reason is management of hospitalised patients is complicated by kidney impairment caused due to aminoglycoside treatment, which is a significant financial burden for patient. the burden of drug also causes kidney impairment and the reason of burden is take more aminoglycoside drug that also chances to cause resistance. [6]

Aminoglycoside resistance mechanisms include: (a) deactivating aminoglycosides through Nacetylation, adenylylation, or O-phosphorylation, (b) decreasing the intracellular concentration of aminoglycosides through modifications to the flexibility of the outer membrane, reduced inner membrane transport, active efflux, and drug trapping, (c) the 30S ribosomal subunit target is modified by mutation, and (d) the aminoglycoside binding site is methylated. these all are the mechanism of resistance. Aminoglycosides are becoming more and more important in medical treatment, but as the issue of antibiotic resistance spreads across the world. [7]

In this paper I will review which aminoglycoside antibiotic is causing more kidney cell injury and also review the current concept of pharmacological treatment. It's all about work of patient safety and better outcome.

MECHANISM OF ACTION

The FDA-approved indications for the various aminoglycoside medications differ from one another. For example:

DRUGS	MOSTLY USE IN	COMMON SIDE EFFECT
Gentamicin	Meningitis	Hearing loss, kidney damage
Tobramycin	Pseudomonas aeruginosa	Nerve problem
Amikacin	Meningitis	Hearing loss, kidney damage
Neomycin	Hepatic coma	Hearing loss, kidney damage
Plazomicin	UTI	Blood in urine
Streptomycin	TB	Black, tarry stools

The professionals team members who want to prescribe aminoglycosides will benefit from this activity's review of the indications, contraindications, mechanism of action, adverse event profile, and other important aspects (such as off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, and relevant interactions). [8]

[1]GENTAMICIN

Gentamicin is an aminoglycoside antibiotic, this is the bactericidal, but the oxygen-dependent active transport of gentamicin allows it to pass through the gram-negative membrane. Aminoglycosides are ineffective against anaerobic bacteria since oxygen is necessary for their growth. Gentamicin and other aminoglycosides disrupt mRNA translation by binding to the 16s rRNA at the 30s ribosomal subunit once they have entered the cytoplasm. This results in the creation of non-functional proteins. [9]

[2]TOBRAMYCIN

Tobramycin works by preventing the production of protein in bacterial cells. Tobramycin is bactericidal, according to in vitro experiments. After parenteral dosing tobramycin is quickly absorbed and tobramycin can be found in tissues and bodily fluids. [10]

[3]AMIKACIN

Amikacin can be given parenterally or by nebulization. Amikacin interferes with the reading of the genetic code and inhibits protein synthesis when it binds to the 30 S bacterial ribosome subunit. For example, it causes premature protein termination and the inclusion of the wrong amino acid. [11]

[4]NEOMYCIN

Neomycin is a component of the aminoglycoside class of antibiotics. Neomycin also the cause bactericidal effects by preventing the synthesis of bacterial proteins. Neomycin has specific benefits for the GI tract because it is not well absorbed into the systemic circulation. Similar to most aminoglycosides, neomycin inhibits bacterial protein synthesis by binding to the 30s ribosomal subunit. [12]

[5]PLAZOMICIN

Plazomicin attaching to the bacterial 30S ribosomal subunit, plazomicin has an antibacterial effect on sensitive bacteria. Typically, aminoglycosides bind to the ribosomal aminoacyl-tRNA site (A-site) and cause a conformational shift to help in the binding of the antibiotic to the rRNA. [13]

[6]STREPTOMYCIN

Streptomycin is a bactericidal, its inhibits the production of ribosomal peptides and proteins. It attaches to a portion of the 16S rRNA on the smaller 30S component of the bacterial ribosome, affect the function and stopping additional protein synthesis by preventing the formation of peptide bonds. [14]

RESISTANCE

Small compounds like aminoglycosides are naturally blocked the bacterial cell wall, which can be enhanced further by acquired mutations. [15] When aminoglycosides attach to the aminoacyl-tRNA recognition site (A-site) of the 16S rRNA, which makes up the 30S ribosomal subunit, polypeptide synthesis is inhibited, which results in cell death. Numerous mechanisms can lead to resistance to aminoglycosides, including: (1) enzymatic modification and inactivation of the aminoglycosides, which is frequently seen in gram-positive and negative bacteria (2) decreased permeability (3) increased efflux and (4) modifications of the 30S ribosomal subunit that prevent the aminoglycosides from binding to the ribosome. [16]

TYPE OF KIDNEY INJURY

[1]ACUTE KIDNEY INJURY

The reason of acute kidney injury is a rise in the plasma creatinine concentration of more than 0.5 to 1 mg/dL (44 to 88 micromol/L) or a 50% increase in plasma creatinine from baseline occurs in 10 to 20% of patients, and acute kidney injury is a relatively common side effect of treatment with aminoglycoside antibiotics. Acute renal injury caused by aminoglycosides can occur in up to 20 to 33% of children, who get the treatment. [17]

[2]CHRONIC KIDNEY INJURY

Aminoglycosides (AGs) are essential medications for treating Gram-negative infections because they have two effects: they quickly kill bacteria and they restrict bacterial development for a long time after plasmatic levels are reduced to sub inhibitory levels. In regular use of aminoglycoside antibiotics may result in chronic kidney disease (CKD) and subclinical renal damage. The second reason is the mayo clinic antimicrobial therapy; Quick Guide advises delaying 2 hours after infusion to allow for the end of the distribution phase of AG in CKD patients. [18]

DISCUSSION

In our study explore the outcome of renal injury and discuss about the treatment of kidney injury cause by aminoglycoside antibiotic. We are finding the most of the risky drug in past that cause kidney injury. Also we see the level of damage and explore the control of that damage caused by AG.

In this study also describe about function of AGs drugs and how they cause effect on kidney. As a result, the Kidney Disease Improving Global Outcomes (KDIGO) AKI guidelines recommended avoiding AGs in patients who were at risk of (or already had) AKI and using less nephrotoxic treatment alternatives to AGs if available. AG one of the most common class that cause AKI [Acute Kidney Injury] [19]. Aminoglycosides (AGs) should be avoided in individuals at risk for acute kidney damage (AKI), according to recent guidelines. These suggestions were based on studies done a few years ago [20].

When once the produce nephrotoxicity in body then chances to causes proteinuria, enzymuria, a decline in glomerular filtration rate, an increase in blood urea levels, a slow increase in serum creatinine levels, and hyposmolar urine output in humans, all of which cause acute renal failure (ARF). [21]

Additionally, there is growing evidence that the effects of AKI go beyond the acute stage, leading to CKD, an increased risk of cardiovascular issues, repeated episodes of AKI, and longterm mortality. [22]

However, regeneration already takes place during therapy, and the newly produced tubular cells appear to be more resistant to aminoglycosides. This could be one of the causes for the relatively uncommon occurrence of clinically significant renal function impairment. [23]

Depending on the nomogram developed by Hartford Hospital, the AG drug concentration monitoring for once-daily dosing is timed between 6 and 14 hours after the end of the first dosage infusion and the next dose depend on the timed drug level falls on the reference of nomogram. [24]

TREATMENT

Recent research has shown that newer drugs, such as third-generation cephalosporins and aztreonam, may frequently be similarly therapeutic and economical as aminoglycosides without the nephrotoxicity. [25]

There are two key factors in health care that must be taken into account when choosing the right dose. The volume of distribution and clearance rate of an aminoglycoside. While the latter is related to creatinine clearance, which measures renal function, the former is related to plasma volume and specific tissue compartments. In some cases, the drug was change or we give the alternate with the proper care of the patient. and we also calculate every single dose because they have already facing the kidney problem. [26]

Calculation part is very important for better treatment. These treatments are happening in both condition acute kidney injury [AKI] and chronic kidney disease [CKD]. GFR [glomerular filtration rate] also involve here because all the treatment continues according to GFR. These are the all about pharmacological treatment of aminoglycoside toxicity.

CONCLUSION

In this study conclusion are reviewed the riskiest aminoglycosides is a gentamicin that cause sever kidney injury and we observed in this study also the many aminoglycosides are cause acute kidney injury or we can say acute renal disease. The study showing current concept of pharmacological treatment of kidney injury that cause by aminoglycoside antibiotics.

Our main motive of the paper, that is the patient safety by proper treatment because patient safety is the first priority of every health care professional and also patient have rights to take proper treatment. This review also helpful for many healthcare professional and medical reader because here just try to give basic information about the kidney injury and their treatment.

RESULT

The final result is found the drug [gentamicin], which is highly cause renal toxicity or injury. Use the alternate is better treatment of renal toxicity and also if gentamicin is important for the patient then give with under the supervision and with more especial care. These are the some more important point for helpful in medical sector. Motive of this paper also try to encourage for right treatment in health sector and also helpful to the provide updated knowledge to healthcare professional.

Reference :

1. Krause KM, Serio AW, Kane TR, Connolly LE. Aminoglycosides: An Overview. *Cold Spring Harbor Perspectives in Medicine*. 2016;6(6):a027029. doi:https://doi.org/10.1101/cshperspect.a027029
2. Germovsek E, Barker CI, Sharland M. What do I need to know about aminoglycoside antibiotics? *Archives of disease in childhood Education and practice edition*. 2017;102(2):89-93. doi:https://doi.org/10.1136/archdischild-2015-309069
3. Uis S. Gonzalez I, Spencer JP. Aminoglycosides: A Practical Review. *American Family Physician*. 1998;58(8):1811-1820. https://www.aafp.org/pubs/afp/issues/1998/1115/p1811.html#:~:text=Ge ntamicin%20is%20the%20most%20commonly
4. List of Aminoglycosides. Drugs.com. https://www.drugs.com/drugclass/aminoglycosides.html
5. UpToDate. www.uptodate.com. Accessed July 10, 2023. https://www.uptodate.com/contents/manifestations-of-and-risk-factorsfor-aminoglycoside-nephrotoxicity#:~:text=Aminoglycosides%20are%20freely%20filtered%20a cross
6. Laurent G, Kishore BK, Tulkens PM. Aminoglycoside-induced renal phospholipidosis and nephrotoxicity. *Biochemical Pharmacology*. 1990;40(11):2383-2392. doi:https://doi.org/10.1016/0006-2952(90)90078y
7. Shakil S, Khan R, Zarrilli R, Khan AU. Aminoglycosides versus bacteria – a description of the action, resistance mechanism, and nosocomial battleground. *Journal of Biomedical Science*. 2007;15(1):5-14. doi:https://doi.org/10.1007/s11373-007-9194-y
8. Block M, Blanchard DL. Aminoglycosides. PubMed. Published 2023.

https://www.ncbi.nlm.nih.gov/books/NBK541105/#:~:text=There%20are%20several%20drugs%20within
9. Chaves BJ, Tadi P. Gentamicin. PubMed. Published 2022. https://www.ncbi.nlm.nih.gov/books/NBK557550/#:~:text=Go%20to%3A-
10. tobramycin injection, USP Clinical Pharmacology | Pfizer Medical Information - US. www.pfizermedicalinformation.com. Accessed July 28, 2023. https://www.pfizermedicalinformation.com/enus/tobramycin/clinical-pharmacology
11. Sizar O, Rahman S, Sundareshan V. Amikacin. PubMed. Published 2022. https://www.ncbi.nlm.nih.gov/books/NBK430908/#:~:text=Go%20to%3A-
12. Veirup N, Kyriakopoulos C. Neomycin. PubMed. Published 2023. Accessed July 28, 2023. https://www.ncbi.nlm.nih.gov/books/NBK560603/#:~:text=Indicatio ns-
13. Plazomicin. go.drugbank.com. https://go.drugbank.com/drugs/DB12615
14. Waters M, Tadi P. Streptomycin. PubMed. Published 2022. https://www.ncbi.nlm.nih.gov/books/NBK555886/
15. Garneau-Tsodikova S, Labby KJ. Mechanisms of resistance to aminoglycoside antibiotics: overview and perspectives. *MedChemComm*. 2016;7(1):11-27. doi:https://doi.org/10.1039/c5md00344j
16. Doi Y, Wachino J, Arakawa Y. Aminoglycoside Resistance. *Infectious Disease Clinics of North America*. 2016;30(2):523-537. doi:https://doi.org/10.1016/j.idc.2016.02.011
17. UpToDate. www.uptodate.com. Accessed July 30, 2023. https://www.uptodate.com/contents/manifestations-of-and-riskfactors-for-aminoglycoside-nephrotoxicity#H8
18. Halouzková BA, Hartinger JM, Krátký V, Tesař V, Slanař O. Dosing of Aminoglycosides in Chronic Kidney Disease and End-Stage Renal Disease Patients Treated with Intermittent Hemodialysis. *Kidney and Blood Pressure Research*. Published online April 20, 2022:1-11. doi:https://doi.org/10.1159/000523892
19. Chou CL, Chuang NC, Chiu HW, Liao CT, Hsu YH, Chang TH. Aminoglycosides use has a risk of acute kidney injury in patients without prior chronic kidney disease. *Scientific Reports*. 2022;12(1):17212. doi:https://doi.org/10.1038/s41598-022-21074-x
20. Paquette F, Bernier-Jean A, Brunette V, et al. Acute Kidney Injury and Renal Recovery with the Use of Aminoglycosides: A Large Retrospective Study. *Nephron*. 2015;131(3):153-160. doi:https://doi.org/10.1159/000440867
21. Nenad Stojiljkovic, Stoiljkovic M, Mihailovic D, et al. Beneficial Effects of Calcium Oral Coadministration in Gentamicin-Induced Nephrotoxicity in Rats. 2012;34(5):622-627. doi:https://doi.org/10.3109/0886022x.2012.664809
22. Pickkers P, Darmon M, Hoste E, et al. Acute kidney injury in the critically ill: an updated review on pathophysiology and management. *Intensive Care Medicine*. 2021;47(8):835-850. doi:https://doi.org/10.1007/s00134-021-06454-7
23. Mattie H. Efficacy and nephrotoxicity of aminoglycosides. Published online January 1, 1991:55-63. doi:https://doi.org/10.1007/978-94011-3798-0_6
24. Oup.com. Published 2023. https://academic.oup.com/jac/article/71/11/3250/2399419
25. Appel GB. Aminoglycoside nephrotoxicity. *The American Journal of Medicine*. 1990;88(3):S16-S20. doi:https://doi.org/10.1016/00029343(90)90082-o
26. Kotler Donald P, Sordillo Emilia M. Nutritional Status and Aminoglycoside Dosing. *Clinical Infectious Diseases*. 1998;26(1):249250. doi:https://doi.org/10.1086/517047