JMS 2023;Vol 6 (2):179-188
UDC:616-056.7-085.33.015.3
DOI: 10.55302/JMS2362179n

THERAPEUTIC DRUG MONITORING AND EVALUATION OF SAFETY OF INTRAVENOUS INFUSION OF AMIKACIN IN PATIENTS WITH CYSTIC FIBROSIS

Aleksandar Nikodinovski[1], Stojka Naceva Fushtikj[2], Jasmina Trojachanec-Pavlovska[1], Krume Jakjovski[1], Bojan Labachevski[1], Nikola Kolovchevski[1], Marija Bujaroska Perkovikj[3], Zorica Bozhinoska[3], Dijana Grupche[4], Nikola Labachevski[1]

[1]Department of Preclinical and Clinical Pharmacology and Toxicology, Faculty of Medicine, Ss.Cyril and Methodius University in Skopje, North Macedonia

[2]JZU University Clinic of Pediatric Diseases, Faculty of Medicine, Ss.Cyril and Methodius University in Skopje, North Macedonia

[3]Institute of Forensic Medicine, Criminology and Medical Deontology, Faculty of Medicine, Ss.Cyril and Methodius University in Skopje, North Macedonia

[4]General hospital Ohrid, Ohrid, North Macedonia

Abstract

Therapeutic drug monitoring (TDM) involves measuring drug concentrations in plasma, serum or blood. This information is used to individualize dosage so that drug concentrations can be maintained within a target range and to make dose adjustments. Amikacin is a kanamycin-derived semisynthetic aminoglycoside antibiotic and one of the important antimicrobial agent against Gram-negative pathogens. Aminoglycoside antibiotics have a small therapeutic index and therapeutic range due to monitoring of amikacin concentrations is necessary. For optimal antimicrobial effect of amikacin therapy and prevent toxicity, it is recommended monitoring of amikacin concentrations during therapy with this drug.

The study for evaluation of safety of the therapy with amikacin intravenous infusion included 12 patients (7 male and 5 female) with cystic fibrosis. Amikacin was infused over 1 h in the dose of 30 mg/kg (maximum 1.5 g) one time daily during 10-14 days. Blood samples for determination concentrations of amikacin were obtained at the following times: immediately before administration of third dose of amikacin, at the end of infusion, 30 min. and 6 h after infusion. The concentrations of amikacin in the sample before administration of third dose of amikacin was <2 μg/ml in all treated patients. Safety of the therapy was evaluated from the results of laboratory analyses, creatinine clearance (estimated according to the Cockroft-Gault equation), anamnestic symptoms of ototoxicity or vestibular toxicity, evaluation of the whisper test and other adverse events.

From the results of our study, we suggest that the dose of 30 mg/kg once daily amikacin infusion administered for 10-14 days is safety in patients with cystic fibrosis.

Keywords: amikacin, therapeutic drug monitoring (TDM), cystic fibrosis, intravenous infusion, safety, creatinine clearance (CCr), ototoxicity, vestibular toxicity.

Introduction

Therapeutic drug monitoring involves measuring the concentration of drugs or their metabolites and interpreting them by a doctor with appropriate education (clinical pharmacologist or clinical pharmacist). The drugs being monitored have a narrow therapeutic index, which represents the ratio between the toxic and effective dose of the drug [1,2,3,4].

Therapeutic drug monitoring aims to individualize the therapeutic regimen, which is necessary due to the variable response of individuals to the drug. The goal is to achieve the desired response from the patient to the therapy and to avoid the toxic effects of the drug itself.

The variability in the patient's response to therapy depends on several factors, some originating from the drug itself, and some from the patient. Reasons for the different patient response to the drug include: race, gender, age, body weight, disease characteristics, and genetic polymorphism.

Reasons for different drug responses originating from the drug itself include: the use of multiple drugs simultaneously and their interactions, inappropriate dosing, inadequate response based on the duration of therapy, and specific pharmacokinetic characteristics of the drug.

Indications for therapeutic drug monitoring include:

a) drugs with a narrow therapeutic range,

b) drugs for which the optimal dose cannot be determined solely based on clinical observation,

c) drugs for which there is a correlation between the level of drug concentration in plasma/serum and pharmacological effects and/or toxicity,

d) drugs that exhibit significant interindividual pharmacokinetic variability when administered at the standard dose, while the pharmacokinetic characteristics of the drug are relatively stable in the same patient,

e) for drugs where, due to the duration of treatment and the clinical condition of the patient, an effort should be made to determine the optimal dose of the drug,

f) to diagnose that drug toxicity is the cause of the patient's symptoms,

g) if the patient's cooperation during treatment is unsatisfactory, based on the concentrations of the drug in the blood/plasma/serum, to determine whether the patient regularly takes the medication.

Medications Requiring Therapeutic Monitoring [1,2,3,5]:

Drug category	Drugs	Treatment
Cardiovascular drugs	digoxin, digitoxin, amiodarone, lidocaine, quinidine, procainamide, N-acetyl-procainamide	congestive heart failure, angina pectoris, arrhythmia
Antibiotics	Aminoglycosides (gentamicin, tobramycin, amikacin), vancomycin, chloramphenicol	Bacterial infections resistant to less toxic antibiotics
Antiepileptics	phenobarbital, phenytoin, valproic acid, carbamazepine, ethosuximide, gabapentin, lamotrigine, levetiracetam, topiramate, zonisamide, eslicarbazepine acetate, felbamate, lacosamide, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, vigabatrin;	Epilepsy, seizure prevention, mood stabilizer
Immunosuppressants	cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, azathioprine	azathioprine Prevention of transplant rejection;autoimmune diseases
Anti-cancer drugs	Methotrexate, all cytotoxic agents	Psoriasis, rheumatoid arthritis, various types of cancer, non-Hodgkin lymphoma, osteosarcoma
Bronchodilators	Theophylline, caffeine	Asthma, chronic obstructive pulmonary disease (COPD), neonatal apnea
Psychiatric Drugs	Lithium, valproic acid, some antidepressants (imipramine, amitriptyline, nortriptyline, doxepin, desipramine)	Bipolar disorder (manic depression), depression

Amikacin

Amikacin is a semi-synthetic antibiotic that belongs to the group of aminoglycoside antibiotics and is a derivative of kanamycin A. The drug was patented in 1971, and its discovery was published by the research institute Bristol-Banyu in Japan in 1976.

Amikacin acts on a wide range of infections caused by Gram-negative bacteria [6,7].

Its action is bactericidal, resulting from the inhibition of bacterial protein synthesis by binding to the ribosomal subunit 30S of the bacterial cell. Amikacin is effective against many strains that are resistant to other aminoglycosides within the same group. It is used in the treatment of bone and joint infections, intra-abdominal infections, pneumonia, bronchiectasis, meningitis, urinary tract infections, sepsis, in cases of acute exacerbation of pneumonia in patients with cystic fibrosis, and in cases of multi-drug resistant tuberculosis.

Gram-negative bacteria susceptible to Amikacin include *Pseudomonas species, Escherichia coli, Proteus spp, Klebsiella, Enterobacter, Shigella, Salmonella, Serratia spp, Minea-Herralae, Citrobacter freundii, Acinetobacter* and *Providencia spp*. Gram-positive bacteria sensitive to the action of amikacin include *Staphylococcus aureus, MRSA, Streptococcus pyogenes, Enterococcus,* and *Diplococcus pneumoniae*.

Amikacin is also used in severe infections caused by Gram-negative anaerobic bacteria such as mycobacterial strains, *Nocardia*, and life-threatening infections in newborns. It is administered intravenously, intramuscularly, and via nebulization, and in certain cases, it can also be given intrathecally and intraventricularly.

The typical duration of treatment is 7-10 days. The total daily dose, regardless of the method of administration, should not exceed the dose of 15-20 mg/kg/day. In severe and complicated cases where treatment needs to extend beyond 10 days, the use of amikacin should be reevaluated.

Before initiating amikacin treatment, an evaluation of kidney function is required. Like other aminoglycosides in the group, amikacin induces auditory, vestibular, and renal toxicity. Toxicity most often results from the administration of higher doses than the recommended therapeutic doses of amikacin or due to synergistic effects in combination with drugs similar to amikacin.

- Neurotoxicity - ototoxicity: the toxic effect of amikacin on the eighth (VIII) cranial nerve damages the cochlea by inducing forced apoptosis of the cells and excessive production of oxidative free radicals, leading to a reduction in high-frequency hearing. Symptoms of dizziness, paresthesia, nausea, vomiting, headache, blurred vision when moving the head, as well as neuromuscular blockade with the onset of acute muscle paralysis and apnea.
- Nephrotoxicity: the concentration of amikacin in the renal cortex becomes ten times higher than in the plasma, interfering with phospholipids in lysosomes and causing the release of proteolytic enzymes into the cell cytoplasm. Nephrotoxicity results in increased serum creatinine levels, albuminuria, hematuria, leukocyturia, azotemia, and oliguria. Most patients experience reversible changes in renal function upon discontinuation of therapy.
- Rare Adverse Effects: skin rash, tremor, nausea and vomiting, headache, eosinophilia, arthralgia, anemia, hypotension, hypomagnesemia, macular infarction (when applied to the eye) with vision loss.

The best way to administer amikacin is parenterally since it is not absorbed orally. After absorption, amikacin binds to plasma proteins, about 20% of the administered dose. The elimination half-life of amikacin is 2-3 hours in patients with normal kidney function, and 94-98% of the given dose is eliminated unchanged within 24 hours [7,8,9,10].

Bactericidal concentrations are found in pleural fluid, amniotic fluid, and the peritoneal cavity after intravenous administration. Peak concentrations in plasma are achieved 1 hour after a 500 mg dose administered intramuscularly and amount to approximately 20 μg/ml. Approximately 10-12 hours after the dose, amikacin's plasma concentration decreases to 2 μg/ml. When the drug is administered

intramuscularly, the bactericidal range of amikacin is maintained for 10-12 hours. With intravenous administration of 500 mg of amikacin over 30 minutes as an infusion, a plasma concentration of 38 μg/ml is achieved. The doses that achieve the best bactericidal effects are those that result in maximal concentrations of amikacin in the plasma or serum, typically 8-10 times higher than the minimum inhibitory concentrations for the bacteria (MIC).

Therapeutic monitoring of amikacin is important for the individualized therapy of each patient to achieve the best balance between the drug's benefits and risks. To achieve optimal drug concentration and avoid underdosing, it is necessary to monitor the drug's concentration in serum or plasma. The maximum concentration of amikacin in plasma that needs to be reached is 35 μg/ml in serum, with a concentration greater than 10 μg/ml before the next dose of the drug. To prevent the possibility of amikacin being underdosed or causing ototoxicity and nephrotoxicity, monitoring is essential [6,10,11,12,13].

The concentrations of amikacin need to be monitored in the kidneys throughout its use. Pharmacokinetic parameters that are monitored include Cmax, representing the maximum concentration of the antibiotic at the site of antibiotic activity, Tmax, which is the time value at which Cmax is achieved, and AUC, which denotes the area under the curve of plasma or serum antibiotic concentrations obtained at different time points from the time of its administration to its elimination from the body. Pharmacodynamic parameters are used to determine the relationship between serum concentration and the toxic effects of the drug. Before administering the drug, it is necessary to determine the sensitivity of the causative agent of the disease to the antibiotic. MIC (Minimum Inhibitory Concentration) and MBC (Minimum Bactericidal Concentration) are used as parameters for sensitivity. When determining the dosage and dosing regimen, individual patient characteristics such as height, weight, age, and kidney function should also be taken into account.

To determine if the dose and dosing regimen have been correctly chosen, pharmacodynamic parameters referred to as PK/PD are used. The most commonly used parameters are C max/MIC, T max/MIC, and AUC/MIC. The most commonly used parameter for assessment when using aminoglycoside antibiotics and fluoroquinolones is C max/MIC. For aminoglycosides, it has been established that the maximum concentration should be achieved at least 10 times higher than the minimum inhibitory concentration.

To determine the effectiveness of amikacin, it is necessary to measure the concentration before and after the administration of the third dose of therapy when the so-called “steady-state” is considered to be achieved. To adjust the dose of amikacin most effectively, it is best to measure the concentration 30 minutes before the next dose is administered. In order to achieve optimal effects and minimize toxic effects, several studies have been conducted in which amikacin is administered once a day or in three separate doses.

The most common adverse effects of amikacin, as with all aminoglycosides, are nephrotoxicity and ototoxicity (vestibular and auditory toxicity). Nephrotoxicity in amikacin is associated with maintaining high concentrations of the drug over an extended period of time rather than the size of the maximum concentrations in the serum. Nephrotoxicity is common in patients with pre-existing kidney damage, as well as in patients with reduced fluid intake. Adequate hydration during amikacin therapy has been found to reduce amikacin toxicity. In patients in whom dose modification has been performed during the course of therapy, a reduction in kidney toxicity has also been observed.

To determine the extent of nephrotoxicity, it is necessary to assess kidney function before the start of therapy and then on a daily basis during the treatment. In several studies, it has been found that concurrent use of nephrotoxic drugs such as cisplatin, bacitracin, and colistin increases the toxicity of amikacin.

The neurotoxicity of amikacin manifests as audio-vestibular and auditory toxicity, most commonly bilateral. Ototoxicity is more pronounced in patients with impaired kidney function. The neurotoxicity of amikacin depends on the duration of amikacin therapy as well as the maximum concentration in the serum. Ototoxicity is not dependent on the dosing regimen. Typically, ototoxicity presents as high-frequency hearing loss, which is determined through audiometric examination, rarely conducted before the start of therapy, and with a whisper test. Hearing loss is a reversible change that normalizes after discontinuation of amikacin administration or dose adjustment.

Optimal therapeutic effects in the treatment of infections are achieved in patients in whom amikacin concentrations in the serum/plasma are measured during treatment and in whom dose adjustment of the drug has been performed. During amikacin treatment, concentrations of 15 to 40 μg/ml are achieved, measured 20-30 minutes after intramuscular injection or 20-30 minutes after the start of intravenous infusion. Low concentrations of amikacin are a result of underdosing. Amikacin concentrations in plasma/serum are measured using a closed analytical system and commercial reagents. To properly dose the drug, it is necessary to measure the minimum and maximum serum (plasma) concentrations. The required dose is determined as the quotient of the product of the given dose and the theoretically desired concentration, with the obtained concentration of the drug. In addition to calculation, it can also be obtained by entering the values into specialized computer software. To determine the dose correctly, the MIC (Minimum Inhibitory Concentration) needs to be determined as well.

Material and methods

The open, single center clinical study was performed on 12 patients of both sexes (7 male and 5 female) with cystic fibrosis who have egzacerbations of disease or come for regular treatment with Amikacin i.v. infusion for at least 7 days to 14 days in the dose 30 mg/kg/day (maximum 1.5 g/day). Other criteria for inclusion in the study were:

- subjects aged ≥ 4 to 65 years;
- patients who agreed to participate in the research and signed an informed consent (himself or his parent or legal representative);
- able to communicate and co-operate with the investigator and his staff.

Patients with a positive answer to any of the following were not eligible to enter the study:

- -history of positive allergic reaction on amikacin or other aminoglycoside antibiotics,
- -patients with myasthenia gravis,
- -patients with clearance of creatinine ≤30 ml/min,
- -patients with history of drug and alcohol abuse during 12 months,
- -participating in other clinical trials previous two months,
- -patients who are on hemodialysis,
- -patients in whom it is necessary to apply therapy with drugs that interfere with creatinine clearance, leading to increase in amikacin concentrations or have nephrotoxic, neurotoxic and ototoxic effect,
- subjects aged <4 or > 65 years;

Treatment during the study

During the clinical trial, the patients receive therapy with amikacin at dose of 30 mg/kg per day, once a day, in the form of infusion (maximum 1.5 g/day).

During the study, patients may receive other medications to treat their underlying disease.

Methods

Therapeutic monitoring of amikacin concentrations is performed by determining amikacin concentrations in blood samples taken immediately after the end of intravenous infusion and after 30 minutes, 6h, 12h and 1h before the next dose of the drug. The first blood sample to determine the concentration of amikacin was taken 1h before the administration of the third dose of the drug. Serum amikacin concentrations were determined on an Architect c4000 instrument, ABBOTT, USA by fluorescence polarization immunological method and using commercial kits for calibration, control and determination of amikacin serum concentrations.

Evaluation of the safety of amikacin therapy was performed by evaluating the following parameters:

a) anamnestic data with special attention to the occurrence of side effects/events,
b) vital signs measuring (blood pressure and heart rate),
c) physical examination, whisper test (Whispered-voice test),

d) concentration of creatinine and urea in serum and clearance of creatinine,

e) other examinations that are performed during the examination (microbiological analyses, hematological and biochemical laboratory analyses, urinalysis, spirometry, x-ray examinations, audiometry etc.).

Results

The demographics and clinical characteristics of the subjects participating in this study are summarized in Table 1 and 2.

Table 1. Demographics characteristics of subjects with cystic fibrosis treated with Amikacin

	Age	**Weight**	**Height**	**BMI**
Average	16.73	46.92	157.87	18.6
±SD	3.98	11.17	14.03	2.43
Minimum	7	23.9	127	14.8
Maximum	22	61.5	172	21.8
N	12	12	12	12

Table 2. Clinical characteristics of subjects with cystic fibrosis treated with Amikacin

Number of patients	***Diagnosis***
1	Pneumopathia chr., *Pseudomonas aeruginosa* pneumonia
1	Pneumopathia chr., *Streptococcus viridans B* pneumonia
4	Pneumopathia chr.,*Pseudomonas aeruginosa* inf. chr., Insufitientio pancreatis, Haepatopathia(Cirrhosis Hepatis)
1	Pneumopathia chr., *Pseudomonas aeruginosa* inf. chr., Insufitientio pancreatis, *MRSA infection*
2	Pneumopathia chr., Insufitientio pancreatis, Cirrhosis Hepatis
1	Pneumopathia chr., *Pseudomonas aeruginosa* inf. chr., *Staphylococcus aureus* inf.chr., Insufitientio pancreatis
1	Pneumopathia chr., *Pseudomonas aeruginosa* inf. chr., Insufitientio pancreatis
1	Pneumopathia chr., Insufitientio pancreatis

All patients who participated in the study (12) had Pneumopathy chr., chronic infection with *Pseudomonas aeruginosa* was presented in 7 patients, chronic infection with *Staphylococcus aureus* in 1 patient, insufitientio pancreatis had 8 patients, and Haepatopathy including Cirrhosis hepatis 6 patients.

Blood samples for determination concentrations of amikacin were obtained at the following times: immediately before administration of third dose of amikacin, at the end of infusion, 30 min. and 6 h after infusion and 1 h before administration of the next dose of amikacin. Amikacin was administered in the dose of 30 mg/kg (max.1.5 g). Amikacin was infused intravenously once daily for 30 minutes. The concentrations of amikacin were presented in Table 3.

Table 3. Serum concentrations of Amikacin in the subjects

	Day 3 - 1h before infusion	0.5 h after infusion	6 h after infusion	1 h before next dose
Average	< 2 µg/ml	79.59	9.66	< 2 µg/ml
±SD	/	16.31	4.89	/
Minimum	/	58.30	2.50	/
Maximum	/	99.50	17.10	/
N	12	12	12	12

Serum concentrations of amikacin showed a significant decrease in the sample taken 6 hours after the end of the infusion, and after 12 hours in all patients they were less than 2 µg/ml.
Vitals signs (body temperature, blood pressure and heart rate) were measured every day during the study, in the morning prior to medications administrations. Results from systolic and diastolic blood pressure and heart rate are presented in Figure 1.

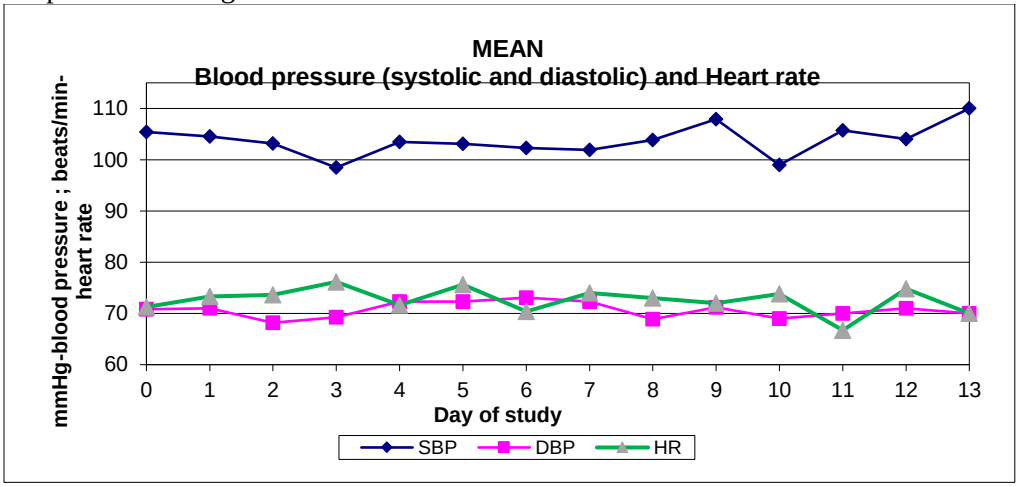

Figure 1. Systolic and diastolic blood pressure and heart rate values during the study

There are no significant differences for values of systolic and diastolic blood pressure and heart rate measured at the start of the study (before medications administrations) and values measured during the study and at the end of study.

Concentrations of creatinine and urea in serum and clearance creatinine (estimated according Cockroft-Gault equation) (11) are summarized in Table 4, 5 and 6.

Table 4. Serum concentrations of creatinine (µmol/L)

	Day-1	Day-4	Day-7	Day-10	End of study
Average	61.37	57.54	56.83	58.20	60.56
±SD	9.80	9.91	11.62	12.31	13.13
Minimum	52.90	46.20	46.10	45.20	49.80
Maximum	78.60	81.20	80.50	82.20	80.40
N	12	12	12	12	7

Table 5. Clearance of creatinine (ml/min)

	Day-1	**Day-4**	**Day-7**	**Day-10**	**End of study**
Average	111.54	119	121.91	119.64	121.71
±SD	18.45	19.01	25.87	25.48	21.75
Minimum	71	80	84	86	93
Maximum	140	147	164	158	156
N	12	12	12	12	7

Table 6. Serum concentrations of urea (μmol/L)

	Day-1	**Day-4**	**Day-7**	**Day-10**	**End of study**
Average	4.39	4.44	5.44	5.36	5.79
±SD	1.26	1.16	1.65	0.83	0.92
Minimum	2.8	2.9	3.7	3.7	4.6
Maximum	7	6.4	9.3	6.3	7.1
N	12	12	12	12	7

There is no significant differences for values of creatinine in serum, clearance of creatinine and systolic and urea in serum (before medications administrations) and values measured during the study and at the end of study. Also, there is not significant differences for values of creatinine in serum, clearance of creatinine and urea in serum in each patient individually at the different measurement points (1, 4, 7, 10 days and at the end of the study).

There is no adverse event reported during the study.

There are no significant differences for values of laboratory (biochemical and hematology) results before administrations of therapy and at the end of study.

Discussion

The inappropriate use of antimicrobial agents is one of the most important factors inducing microbial resistance, can prolong the duration of hospitalization and increase patients' mortality rates. Previous studies have demonstrated that up to 50% of antibiotics prescriptions in hospitals are inappropriate [15,16,17,18]. In our study, the adherence of amikacin usage to the guideline was 100%.

Amikacin was infused over 30 minutes in our patients in accordance with the standard guideline in order to prevent nephrotoxicity and ototoxicity.

The amikacin serum concentrations obtained in the blood sample taken 1 h before administration of the third dose and 1h before administration of the next dose of the drug are < 2 μg/ml and indicate that amikacin therapy should be continued at the same dose of the drug. In other studies, twenty-eight percent of the patients received an underdose and 47% received an overdose of amikacin. Also, in 52.5% of the patients, peak serum concentrations were under the therapeutic range (15-30 μg/mL) (27,28).

All parameters through which the toxicity of amikacin was determined during the study (anamnestic data with special attention to the occurrence of adverse effects/events, vital signs measuring, physical examination, whisper test, laboratory analyzes including urinalysis and concentration of creatinine and urea in serum and clearance of creatinine) show that there are no changes during the duration of the study. These parameters are in correlation with amikacin concentrations obtained by Therapeutic Drug Monitoring (TDM). No signs of nephrotoxicity and neurotoxicity (ototoxicity and/or vestibular toxicity)

were registered in any patient in the study. In other clinical studies, kidney toxicity is particularly pronounced during treatment with amikacin for a duration longer than 10 days.

Regarding the toxicity on the kidneys, it was determined that it is not related to the size of the maximum concentrations of amikacin in the plasma (serum) but to the maintenance of higher concentrations of the drug over a longer period of time, during repeated therapy with the drug, as well as in patients with previous impaired renal function. In some studies, by modifying the dose (its reduction) after determining amikacin concentrations, smaller toxic effects on the kidneys were determined.

Neurotoxicity of amikacin manifests itself as auditory and vestibular toxicity, which in clinical studies is mostly bilateral. The risk of ototoxicity was higher in patients who had impaired renal function and in whom the duration of amikacin therapy was longer than 7 days. In addition to prolonged maintenance of higher amikacin concentrations, ototoxicity is also associated with the magnitude of peak amikacin plasma (serum) concentrations. Hearing loss at high frequencies can hardly be noticed, except in cases where an audiometric examination is carried out before the onset of damage.

However, audiometry is difficult to perform in critically ill patients. Therefore, clinicians diagnose hearing impairment by detecting signs and symptoms suggestive of ototoxicity or the whisper test.

Audiotoxicity symptoms are tinnitus, feeling of pressure in the ears, and vestibular symptoms are loss of balance, headache, nausea (nausea), vomiting, dizziness, nystagmus, ataxia.

Our study did not purpose monitor the therapeutic efficacy of amikacin and other therapy given during the study. However, it was reported that a good general condition, microbiological eradication and improvement of spirometric analyses (FVC, FEV1, FEV1-FVC, PEF and FEF 25%-75%) was achieved in 11 out of 12 (91.67%) patients. Only in 1 patient it was necessary to change the antibiotic therapy after 10 days due to poor therapeutic efficiency of the therapy. This rate is acceptable in comparison to those reported by previous investigators who reported that 80%-92% of their patients were cured with amikacin therapy.

Conclusion

From the results obtained in our study, we conclude that amikacin given by infusion at a dose of 30 mg/kg once daily for a period of 10-14 days achieves blood concentrations that are within the therapeutic range and has excellent safety in patients with cystic fibrosis.

References

1. Kang JS and Lee MH: Overview of Therapeutic Drug monitoring. Review. DOI: 10.3904/kjim.2009.24.1.1.
2. Ghiculescu RA: Therapeutic Drug monitoring: which drugs, why, when and how to do it. Aust Prescr 2008, 31:42-44.
3. Xu L, Cheng X, Guanhua Z, Hu J, Li Q, Fan G: Therapeutic Drug monitoring of amikacin: quantification in plasma by liquid chromatography-tandem mass spectrometry and work experience of clinical pharmacists. Eur J Hosp Pharm 2022, e77-e82.doi:10.1136/ejhpharm-2021-003-049.
4. Zylbersztajn B, Barraza M, Torres JP, Morales J: Therapeutic monitoring of antimicrobial agents un pediatrics. Review based on Latin American experiences. Rev.chil.infectol. 2018, vol 35 (1).
5. Pacifici GM and Marchini G: Clinical Pharmacology of amikacin in infants and children. Clin Med Invest 2020, 5:1-14. doi:10.15761/CMI.1000199.
6. Jenkins A, Thomson HA, Brown MN, Semple Y, Sluman C, MacGowanA, Lovering MA and Wiffen JP: Amikacin use and therapeutic drug monitoring in adults: do dose regimens and drug exposures affects either outcome or adverse events? A systematic review. J.Antimicrob Chemother 2016, 71:2754-2759.
7. Amikacin 250 mg/ml & 500 mg/ml SmPC: https://www.medicines.org.uk/emc/product/3784/smpc #gref.
8. Sumpter A, Anderson BJ: Pediatric Pharmacology in the first year of life. Curr. Opin. Anesthesiol. 2009, 22(4):469-475.

9. Zaske D.: Applied Pharmacokinetics. Principles of therapeutic Drug Monitoring. 3rd ed.Vancouver: Applied Pharmacokinetics:1992.
10. Toit M, Burger JR, Rakumakoe MD and Rheeders M: Standars of aminoglycoside therapeutic drug monitoring in a South Africa private hospital: perspectives and implications. Ghana Med J:2019, 53(1):8-12.
11. Lenoir M, Puel J.: Dose dependent changes in the rat cochlea following aminoglycoside intoxication. II. Histological study : Hear Res 1987; 26:199-209.
12. Abdul -Aziz HM : Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper. Intensive Care Med 2020, 46:1127-1153.
13. Buclin T, Thoma Y, Widmer N, Andre P, Guidi M, Csajka C, Decosterd AL: The steps to Therapeutic Drug Monitoring: A structured Approach Illustrated with Imatinib. Front Pharmacol 2020, https://doi.org/10.3389/fphar.202000177.
14. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron, 1976; 16:31-41.
15. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest. 2000;118:146–55.doi: 10.1378/chest.118.1.146.
16. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med. 1998;244:379–86.doi: 10.1046/j.1365-2796.1998.00379.x.
17. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a riskfactor for hospital mortality among critically ill patients. Chest. 1999;115:462–74.doi: 10.1378/chest.115.2.462.
18. Fraser A, Paul M, Almanasreh N, Tacconelli E, Frank U, Cauda R, et al. Benefit of appropriate empirical antibiotic treatment: thirty-day mortality and duration of hospital stay. Am J Med.2006;119:970–6. doi: 10.1016/j.amjmed.2006.03.034.
19. Franson TR, Quebbeman EJ, Whipple J, Thomson R, Bubrick J, Rosenberger SL, et al. Prospective comparison of traditional and pharmacokinetic aminoglycoside dosing methods. Crit Care Med.1988; 16:840–3. doi: 10.1097/00003246-198809000-00004.
20. Bartal C, Danon A, Schlaeffer F, Reisenberg K, Alkan M, Smoliakov R, et al. Pharmacokinetic dosing of aminoglycosides: a controlled trial. Am J Med. 2003; 114:194–8. doi: 10.1016/S0002-9343(02)01476-6.
21. DeMaria A, Jr, Treadwell TL, Saunders CA, Porat R, McCabe WR. Randomized clinical trial of aztreonam and aminoglycoside antibiotics in the treatment of serious infections caused by gram-negative bacilli. Antimicrob Agents Chemother. 1989;33:1137–43. doi: 10.1128/AAC.33.8.1137.
22. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS., Jr Optimizing aminoglycoside therapy fornosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother.1999;43:623–9.