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Rational Use of Amikacin in Children

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Abstract

Amikacin, an aminoglycoside, is used against Gram –ive and Gram +ive microorganisms for treating Sepsis, Meningitis, Jaundice neonatum, Respiratory diseases and Urinary Tract Infections. A retrospective study on Rational use of Amikacin in children was carried out to review the rationality of prescribing Amikacin, evaluating the dose, route, timing, duration of the drug, Drug interactions, therapeutic drug monitoring , Adverse Drug Reaction monitoring and reporting, awareness of nurses and other paramedical staff, role of pharmacist in the treatment and in providing pharmaceutical care to the patient and the collaboration amongst the health care professionals for carrying out the whole treatment. A total of 130 children were involved in this study from Children Hospital Lahore, Services Institute of Medical Sciences Lahore and renowned general physicians. 94.61% patients had been receiving Amikacin therapy empirically, 80.76% patients had completed their therapy within 10 days, and 86.15% of patients had their culture sensitivity reports attached to their profiles. Resistance was seen in 11.53% patients. 90.77% patients had been irrationally prescribed with Cephalosporins and amongst 24.95% patients, the drug interactions were observed. 59.23% cases were only supervised by the pharmacist. Amikacin had been rationally prescribed as an empiric therapy with duration of less than 10 days but it had been irrationally prescribed when given alongwith interacting drugs. It had been rationally stored and administered by the nursing staff with a little supervision of pharmacist and a little provision of pharmaceutical care. Proper therapeutic drug monitoring and consequent dosage adjustment were provided rarely.

Key words: Amikacin use, Aminoglycosides, Children, Rational use.

Introduction

WHO (1985), defines rational use of medicines as: "Patients receiving medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community". Rational drug use promotes quality of care and cost-effective therapy. It helps to ensure that drugs are used only when they are needed, and that people understand what the medicines are for and how to use them.

While rationally prescribing an Antibacterial agent, one must consider factors like site of infection, type of infection, severity of infection, isolate and its sensitivity, source of infection, host factors and drug related factors. Drug therapy in pediatric patients demands special care, as children are not small adults. The patient's age, weight and surface area need to be accurate to ensure proper dosing, and special care must be provided as the weight and surface area may change significantly in a small period of time.

Amikacin is an aminoglycoside that is widely used in treating many gram negative bacterial infections and other problems. It stands as an empirical therapy in treating meningitis, sepsis, burns, respiratory tract infections etc. Its extensive and rational use in children is seen due to its safety and efficacy as compared to other agents. It is a protein synthesis inhibitor and binds to 30s ribosomal subunit inhibiting the ribosomal translocation and thus disrupting the integrity of the bacterial cell membrane. [1]

Pharmacokinetically, in children and adults, the drug shows a mean plasma clearance of 120ml/min/1.73m; major route of elimination is renal (82%); volume of distribution is 32%; half life is 1.6 hrs; inulin clearance shows that 64% of drug filtered by kidneys is excreted in urine. [2]

Amikacin sulfate injection is a sterile solution of Amikacin Sulfate in water for injection or of Amikacin in water for injection prepared with the aid of sulfuric acid. It contains not less than 90.0 % and not more than 120.0% of the labeled amount of amikacin. It contains not more than 0.33 USP Endotoxin Unit per mg of

Amikacin.[3]Amikacin is effective against aerobic organisms like gram negative enteric rods, enterobacter aerogenes, Escherichia Coli, Klebsiella pneumoniae, Proteus (indole positive), Serratia marcescens, and other gram negative bacilli like Pseudomonas aeruginosa, Vibrio cholera, Yersinia pestis, Francisella tularensis. It is ineffective against anaerobic bacteria, fungi and viruses. [4]The use of amikacin as a first-line aminoglycoside is associated with a decrease in resistance to other aminoglycosides and a slight increase in overall resistance to amikacin among aerobic gram-negative bacilli. [5] The resistance to amikacin of nosocomial infections may also increase with continuous use of the drug. [6] In neonatal intensive care unit, use of Amikacin does not cause an increase in Amikacin resistance and even if some resistance in gram negative bacteria is seen, that is also due to decreased permeability of the drug. [7]Pediatric patients especially at risk are premature infants, infants of low birth weight, patients requiring invasive procedures and those who are immunocompromised. To date, Amikacin is being used for the treatment of infection in a variety of sites; respiratory tract, urinary tract, blood, skin and soft tissues, abdomen, central nervous system, bone and joints. Satisfactory levels have been demonstrated in blood, viscera, soft tissue, joint spaces, bone, the peritoneal space and urine. Cerebrospinal fluid levels have been erratic when the parenteral route is employed alone. [8] Pediatric Amikacin usage includes therapy of neonatal infections, cystic fibrosis, febrile neutropenic episodes in patients with cancer, abdominal surgery, bacterial endocarditis, and gram-negative central nervous system infections. [9]The Amikacin is frequently prescribed for newborn infants with suspected or documented sepsis or meningitis. Amikacin treated patients face ototoxicity, however the rate of nephrotoxicity caused by Amikacin is less as compared to Gentamicin. [10]Patients were monitored for ototoxicity by following serial audiograms, serum creatinine, and Amikacin blood levels. Some may develop tinnitus, nystagmus or vertigo. Patients with a “peak” serum level exceeding 32 μg/ml and with “trough” levels exceeding 10 μg/ml developed cochlear damage. Both monitoring of blood levels and limiting duration of therapy may prevent amikacin ototoxicity [11]Amikacin antibiotics cause transient, usually nonoliguric, renal failure in up to 10–30% of patients treated with these drugs, and are the cause of the largest proportion of drug-induced acute nephrotoxicities. The toxic mechanism includes (i) uptake of the drug by proximal tubular cells, where it is first sequestered within lysosomes and (ii) development of a lysosomal phospholipidosis, which is rapidly associated with cell necrosis and various alterations to subcellular structure and function. Because the uptake of Amikacin by the kidney is saturable, administration of daily doses of these drugs as one or two injections, rather than as multiple injections or by continuous infusion, may also decrease the risk for toxicity. [12]Amikacin cannot be delivered orally probably due to efflux of drug by P-glycoprotein pump in the brush border of intestine. [13] The intravenous administration of amikacin when given in a dose of 7.5 mg/kg over one hour every 12 hours consistently producing peak blood concentrations within the therapeutic range during the first two weeks of life of neonates. [14]A dosing chart is maintained for the neonates based on gestational age (GA) and body weight giving once-a-day amikacin dosage regimen involving an injection every 24 hrs and it confirms the use of individualizing the Amikacin therapy in neonates. [15]Co-administration of Ceftazidime, Imipenem or Aztreonam with Amikacin in healthy volunteers might affect C_{max} and AUC without influencing any other pharmacokinetic parameter. [16]Extract of Ginkgo Biloba 761 is regarded as a facilitating drug for the development of Amikacin ototoxicity. [17] A patient with normal renal function who receives a potentially toxic dose of amikacin can be appropriately managed by careful hydration and maintenance of a generous diuresis. Amikacin is not detected in the peritoneal

dialysate. There are no apparent toxic effects from the overdose. [18]

Pharmacist is in the most suitable position to provide pharmaceutical care to the patient. Pharmaceutical care is the responsible provision of drug therapy for achieving definite therapeutic outcomes that improve patient's quality of life. These outcomes are 1) Cure of a disease, 2) Elimination or reduction of a patient's symptomatology, 3) Arresting or slowing of a disease process 4) Preventing a disease or symptomatology. [19]

This is a comparative study conducted in pediatric ward of different hospitals to evaluate the rationality in using Amikacin in children. The decision for prescribing Amikacin in children by the physician and the role of pharmacist in drug storage, administration, Drug interactions, reporting of ADR, therapeutic drug monitoring and consequent dose adjustment has been judged through this study.

Material and Method:

A data collection form had been well formulated which included questions that could well evaluate the prescribing criteria of physicians, the nurse's administration of the medicine, the pharmacist's involvement in the whole procedure and patient's attitude towards the therapy. Data had been collected from 55 patients of Services Institute of Medical Sciences and Children Hospital of Lahore, 25 patient of some renowned General Physicians outside Lahore and 50 patients from the hospital records, making a total of 130 patients. The data had been tabulated and the results are shown graphically. Amikacin is a drug that develops resistance after a long time even if it is being administered with medicines that potentiate its adverse effects. It was prescribed as an empiric therapy for infants and neonates, thus precautionary measures were taken in prescribing the proper dosage and frequency. Nurses must administer the Intravenous injection according to Standard Operating Procedures and the pharmacist must keep a check over the whole process right from the beginning to the end. Patient's attitude towards the therapy should be compliant so that he does not quit the therapy at any time. This rationality can be evaluated under different factors like checking the Drug interactions and Adverse Drug Reactions, Therapeutic drug monitoring, consequent dose adjustment etc. throughout the treatment.

Results:

The results are represented graphically explaining various factors judged to evaluate the rationality in prescribing Amikacin. Amongst, 80.77% patients, the drug were being given for duration of less than 10 days whereas only 13.85% were receiving the therapy for more than 10 days.(Fig 1)

Figure 1
Duration of Amikacin Therapy

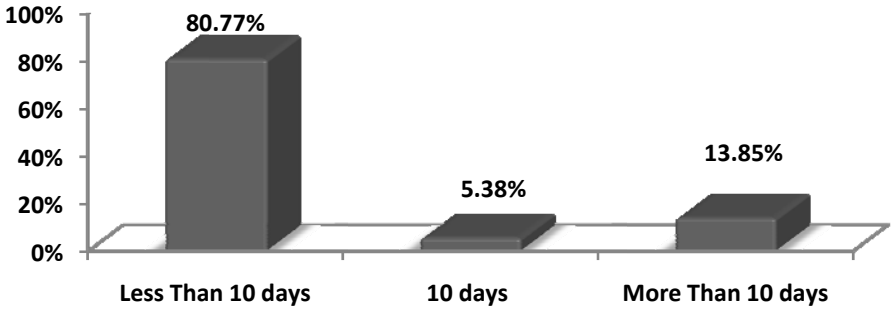
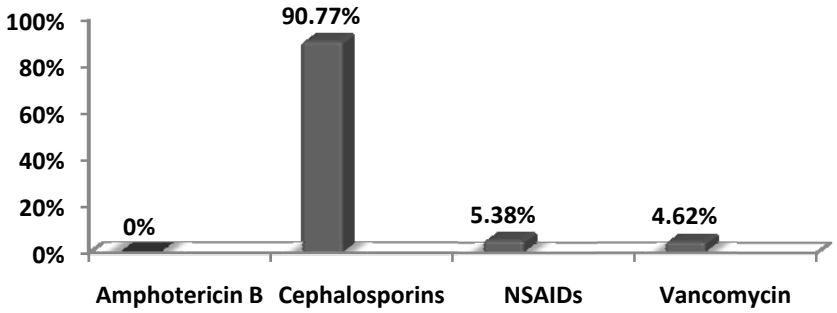


Figure 2 Drugs Prescribed Alongwith Amikacin



About 90.77% of the patients were being co-administered with Cephalosporins with little percentages of NSAIDs and Vancomycin(Fig 2)

About 65.39% patients did not face the Adverse Drug Reactions associated with Amikacin, however, only 26.15% came across nephrotoxicity and only 10 % had to bear ototoxicity.(Fig 3)

The first graph explaining different parameters suggested that 94.61% patients received Amikacin as an empiric therapy, 86.25% got the culture sensitivity test performed using blood specimen and only 11.53% patients showed resistance towards Amikacin and thus then switched over to some other antibiotic.(Fig 4)

Figure 3 Adverse Drug Reactions

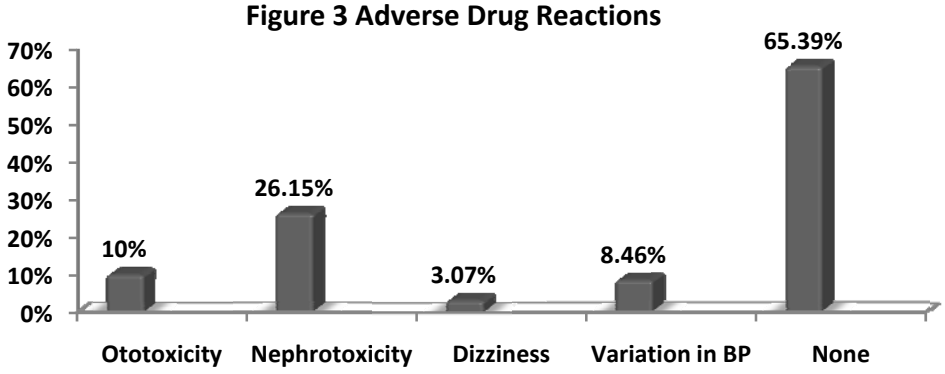
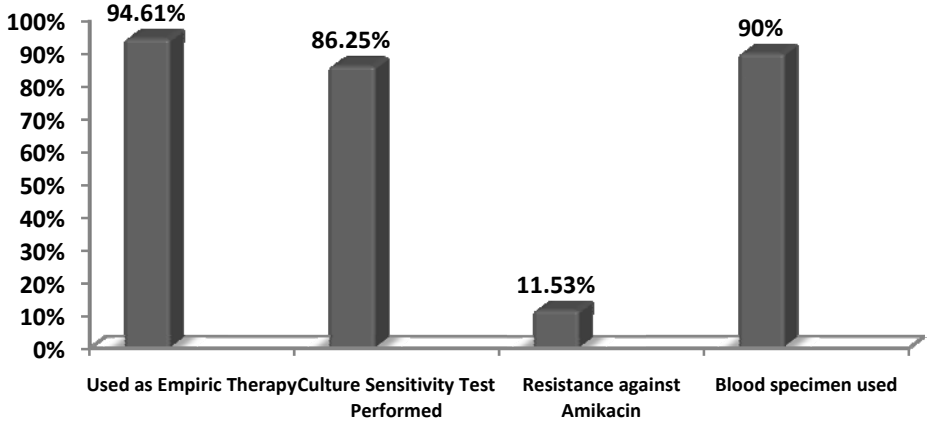
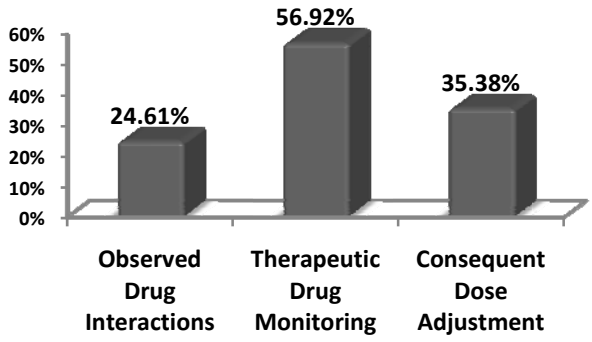


Figure 4 Different Parameters 1



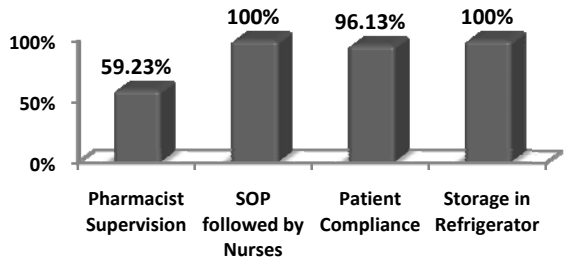
The second graph suggesting different parameters explained the rate of observed drug interactions to be 24.61%, therapeutic drug monitoring carried out amongst 56.92% of the patients and consequent dose adjustment being provided only to 35.38% patients.(Fig 5)

Figure 5 : Different Parameters 2



The third graph of different parameters explained that 59.23% of the patient cases were only being supervised by the pharmacist. It also suggested that 100% of the nurses followed the SOP for administration of the medicine and the medicine is stored in refrigerator for all of the patients. It gives a good percentage of 96.13% patients who were compliant to the therapy.(Fig 6)

Figure 6 : Different Parameters 3



The ADRs being reported by the patients were 9.23% whereas those by the health care professionals were 28.46%(Fig 7).

The overall patient's mindset during and after the therapy is stated to be excellent amongst 40.76%, good amongst 39.23%, satisfactory amongst 16.92% and poor amongst 3.07% of the patients(Fig 8).

Figure 7 : ADR reporting

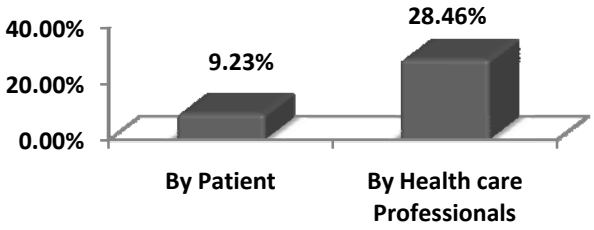
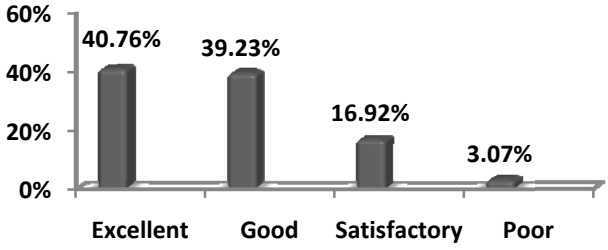


Figure 8 :Patient's mindset



Discussion

Amikacin is a drug that is indicated for a short term treatment of serious infections caused due to Gram Negative strains of bacteria for a period of 7-10 days. After 10 days, After 10 days, the adverse effects of Amikacin potentiate and Amikacin does not remain as effective as before. Therefore, the shorter is the therapy with Amikacin, the more effective it is. Cephalosporin is amongst the class of drugs that potentiate the nephrotoxicity and ototoxicity associated with Amikacin. However, it is amongst the drugs that are administered as an empiric therapy. Co-administration of Cephalosporins with Amikacin in healthy volunteers might affect C_{max} and AUC without influencing any other pharmacokinetic parameter. Plasma half life and clearance rate remains unchanged [20]. Culture sensitivity test is a good tool for determining the type of bacteria and to determine which antibiotics can successfully fight an infection. Although in emergency cases

the physician has to start the therapy immediately, prior to getting the results of the tests, yet it is better to see the results and then start the treatment. As the therapy is usually discontinued before 10 days, therefore the adverse effects do not become prominent during this period. Most of the patients come across the adverse effects only when the drug is being administered for more than 10 days. Patients were monitored for ototoxicity by following serum creatinine, and Amikacin blood levels. [11]

Therapeutic drug monitoring (TDM) of aminoglycoside antibacterials with the goal of minimising toxicity and maximising effectiveness has become routine. Successful management of serious infections requires the ability to achieve therapeutic peak concentrations, while maintaining low trough concentrations will assist in avoiding nephrotoxicity. TDM services have been shown to reduce Amikacin nephrotoxicity [21]. These data indicate that a TDM program can markedly reduce the total dose of Amikacin, which can potentially reduce tissue accumulation and toxicity [22]. Pharmaceutical Care involves the process through which a pharmacist cooperates with a patient and other professionals in designing, implementing, and monitoring a therapeutic plan that will produce specific therapeutic outcomes for the patient. He must identify potential and actual drug related problems, resolve actual drug-related problems and prevent potential drug-related problems [19]. He should always keep a check over the dose and the drugs prescribed to provide the quality care to the patients. Once daily administration has resulted in a small reduction in nephrotoxicity but continuous therapeutic drug monitoring is required [23]. Adequate hydration provided by fluids, proper storage of medication and any signs of adverse effects should be responded as soon as possible. Thus, it is necessary that the pharmacist supervises every patient rather than just keeping an eye over a few cases. He must check prescriptions to ensure that there are no errors and that they are appropriate and safe for the individual patient, provide advice on the dosage of medicines and the most appropriate form of medication, participate in ward rounds, take patient drug histories and be involved in decision-making on appropriate treatments. He should supervise the work of less experienced and less qualified staff so that their inefficiency may in no way affect patient's health and quality of life. The nurses must be well trained to follow the Standard Operating Procedures to administer the Intravenous injections without risking the patient to phlebitis. The ADRs are rarely reported by the patients and their guardians because they do not know that the effect they are coming across is an adverse effect or a part of the therapy. However, the health care professionals are to keep a check on the adverse effects being faced by the patients through proper monitoring and finding the cause leading to the adversity. Amikacin is a drug that has a small duration of therapy. For this reason it is the drug of choice of the physicians with a great satisfaction seen amongst the patients.

Conclusion: Amikacin is being widely used as an empiric therapy amongst the neonates and infants. It is used in the treatment of Jaundice Neonatum, Respiratory Distress Syndrome, Meconium Aspirate Syndrome, Early onset Sepsis, Late onset Sepsis and Asphyxia Neonatum. The therapy is effective in neonates and children when given through an Intravenous route, usually prescribed once or twice daily along with fluids. The co-administered drugs help Amikacin in performing its function but also potentiate the adverse effects. Thus a close therapeutic drug monitoring has to be done to avoid the adverse effects like Nephrotoxicity and ototoxicity to develop, and consequent dose adjustment should be provided. Pharmacist's supervision and provision of pharmaceutical care is required at every step of the treatment. In a nutshell, Amikacin, if used rationally, is a drug that can create wonders in the field of medicine.

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